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Clinical Trial Results Database

Sponsor

Novartis

Generic Drug Name

Ceritinib

Trial Indication(s)

Locally advanced or metastatic tumors characterized by genetic alterations in anaplastic lymphoma kinase (ALK)

Protocol Number

CLDK378X1101

Protocol Title

A phase I, multicenter, open-label dose escalation study of LDK378, administered orally in Japanese patients with tumors characterized by genetic alterations in anaplastic lymphoma kinase (ALK)

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase III

Study Start/End Dates

27-Jun-2012 (first patient first visit) to 28-Jan-2016 (last patient last visit)

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Reason for Termination (If applicable)

Patient recruitment to the expansion phase was terminated by Sponsor due to the slow enrollment status before reaching the targeted number of patients. Importantly, the recruitment termination was not a consequence of any safety or efficacy concerns.

Study Design/Methodology

This was a phase I, multicenter, open-label, dose-escalation study of LDK378, in Japanese patients with tumors characterized by genetic alterations in ALK, investigating the safety, PK, and preliminary anti-tumor activity. LDK378 was administered orally, once-daily, as continuous dosing preceded by a 3-day single dose PK run-in period. At least 3 but not more than 6 patients were to be enrolled per dose cohort, with at least 6 patients at the MTD (Maximum Tolerated Dose)/RD (Recommended Dose). In addition, in order to further characterize safety, anti-tumor activity, and single and multiple-dose PK of LDK378 at the MTD/RD, at least 6 additional patients were to be enrolled in a dose-expansion phase after determination of the MTD/RD.

Dose-escalation was guided by an adaptive Bayesian logistic regression model (BLRM) employing the escalation with overdose control (EWOC) principle.

After amendment 4 (28-Feb-2014), the patient population in the dose-expansion part was changed to the patients with non-small cell lung cancers (NSCLC) that had progressed since alectinib therapy.

Centers

5 centers in Japan

Publication

None

Objectives:

[Primary objective]

- To estimate the MTD/ RD of LDK378 as a single agent when administered orally to Japanese patients with tumors characterized by genetic alterations in ALK

[Secondary objectives]

- To characterize the safety and tolerability of LDK378, including both acute and chronic toxicities
- To characterize single and multiple-dose pharmacokinetics (PK) of LDK378
- To assess preliminary anti-tumor activity of LDK378 as a single agent when administered orally to Japanese patients with tumors characterized by genetic alterations in ALK at MTD / RD by CT/MRI

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

LDK378 was administered orally, once-daily, as continuous dosing. Novartis supplied LDK378 as 50 mg and 150 mg hard gelatin capsules. The study drug was supplied in bottles.

Statistical Methods

The primary objective of this study was to estimate the MTD/RD of LDK378 as a single agent when administered orally to Japanese patients with tumors characterized by genetic alterations in ALK. The corresponding primary analysis was based on an adaptive BLRM guided by the EWOC principle.

Data analyses in this study were generally based on the descriptive summaries for demographic and other baseline characteristics, safety, efficacy and pharmacokinetic measurements. Qualitative data were summarized by frequency counts and percentages. Continuous data were summarized by appropriate descriptive statistics such as mean, standard deviation, median, minimum, and maximum.

The full analysis set (FAS) consisted of all patients (NSCLC or non-NSCLC) who had received at least one dose of LDK378, which was identical with the safety set. The efficacy analysis set (EAS) consisted of NSCLC patients who had received the first dose of LDK378 at least 18 weeks prior to the analysis cut-off date. Dose-Determining Set (DDS) consisted of all patients (NSCLC or non-NSCLC) from the safety set who were enrolled in the dose-escalation phase and either met the minimum exposure criterion and had sufficient safety evaluations (as determined by the Investigators and Novartis), or had experienced a DLT during cycle 1 (including the PK run-in period).

The pharmacokinetic analysis set (PAS) consisted of all patients (NSCLC or non-NSCLC) who had received at least one dose of LDK378 and had at least one evaluable pharmacokinetic sample.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:

- Patients had to be histologically diagnosed with a locally advanced or metastatic malignancy that has progressed despite standard therapy, or for which no effective standard therapy exists.
- Enrollment was limited to those patients with tumors that have a genetic alteration in ALK. In patients with NSCLC, the tumor had to carry an ALK translocation in ≥15% of positive cells, as measured by the fluorescent in situ hybridization (FISH) test. In patients with diseases other than NSCLC, ALK translocation was not required, and overexpression of ALK protein was considered indicative of a genetic alteration in ALK.
- Patients could have received prior treatment with crizotinib.
- Measurable disease or non-measurable disease.
- Age ≥ 18 years
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
- Demonstrated the following hematological/blood chemistry laboratory values within 14 days prior to the first dose of study drug (Day 1 of PK run-in): Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, Hemoglobin (Hgb) ≥ 9 g/dL (≥ 90 g/L), Platelets ≥ 100 x 10^9/L Serum total bilirubin ≤ 1.5 x upper limit of normal (ULN), AST (SGOT) and ALT (SGPT) ≤ 2.5 x ULN, Calculated creatinine clearance (CrCL) ≥ 50 mL/min (≥ 0.835 mL/s), Serum amylase ≤ ULN.

Key Exclusion Criteria:

- Patients with symptomatic central nervous system (CNS) metastases who were neurologically unstable or require increasing doses of steroids to control their CNS disease.
- Patients with uncontrolled nausea, vomiting or diarrhea > CTCAE grade 1.
- History of pancreatitis or history of increased amylase or lipase that was due to pancreatic disease.
- Acute or chronic liver disease. Evidence of active viral hepatitis, including Hepatitis A, B or C.
- Impaired cardiac function or clinically significant cardiac disease.
- Patients with a prior or current history of interstitial lung disease (ILD) or interstitial pneumonitis.
- Other concurrent severe and/or uncontrolled medical conditions.
- Pregnant or nursing (lactating) women.
- 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 of study treatment through the 28 days of follow-up period after stopping study drug.

Participant Flow Table

Disposition Reason	LDK378 300 mg N=3 n (%)	LDK378 450 mg N=6 n (%)	LDK378 600 mg N=4 n (%)	LDK378 750 mg N=9 n (%)	All patients N=22 n (%)
Patients treated					
Treatment ongoing	0	0	0	0	0
Treatment discontinued	3 (100)	6 (100)	4 (100)	9 (100)	22 (100)
Primary reason for treatment discontinuation					

Disposition Reason	LDK378 300 mg N=3 n (%)	LDK378 450 mg N=6 n (%)	LDK378 600 mg N=4 n (%)	LDK378 750 mg N=9 n (%)	All patients N=22 n (%)
Adverse event	0	0	1 (25.0)	1 (11.1)	2 (9.1)
Death	0	1 (16.7)	0	0	1 (4.5)
Lack of efficacy	2 (66.7)	3 (50.0)	3 (75.0)	6 (66.7)	14 (63.6)
New therapy for study indication	0	1 (16.7)	0	0	1 (4.5)
Physician decision	0	1 (16.7)	0	0	1 (4.5)
Study terminated by sponsor	0	0	0	1 (11.1)	1 (4.5)
Subject/guardian decision	1 (33.3)	0	0	1 (11.1)	2 (9.1)
Study evaluation after end of treatment					
Patients no longer being followed for study evaluation completion	3 (100)	6 (100)	4 (100)	9 (100)	22 (100)
Patients continuing to be followed for study evaluation completion	0	0	0	0	0
Primary reason for study evaluation completion					
Completed	1 (33.3)	2 (33.3)	4 (100)	2 (22.2)	9 (40.9)
Death	0	2 (33.3)	0	0	2 (9.1)
Lost to follow-up	0	0	0	1 (11.1)	1 (4.5)
New therapy for study indication	2 (66.7)	2 (33.3)	0	5 (55.6)	9 (40.9)
Study terminated by sponsor	0	0	0	1 (11.1)	1 (4.5)

Baseline Characteristics

Demographics (FAS)

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Demographic variable	LDK378 300 mg N=3	LDK378 450 mg N=6	LDK378 600 mg N=4	LDK378 750 mg N=9	All patients N=22
Age (years)					
n	3	6	4	9	22
Mean (SD)	50.7 (5.51)	42.2 (13.89)	43.3 (12.18)	48.8 (10.93)	46.2 (11.29)
Median	51.0	37.0	39.0	43.0	43.0
Min-Max	45 – 56	29 - 67	34 - 61	38 - 68	29 – 68
Age category (years) - n (%)					
<65	3 (100)	5 (83.3)	4 (100)	8 (88.9)	20 (90.9)
≥ 65	0	1 (16.7)	0	1 (11.1)	2 (9.1)
Sex - n (%)					
Male	0	1 (16.7)	2 (50.0)	8 (88.9)	11 (50.0)
Female	3 (100)	5 (83.3)	2 (50.0)	1 (11.1)	11 (50.0)
Predominant race - n (%)					
Asian	3 (100)	6 (100)	4 (100)	9 (100)	22 (100)
Ethnicity - n (%)					
Japanese	3 (100)	6 (100)	4 (100)	9 (100)	22 (100)
Weight (kg, at baseline)					
n	3	6	4	9	22
Mean (SD)	52.433 (8.9612)	52.975 (6.9449)	55.063 (9.4452)	69.000 (6.3166)	59.836 (10.4252)
Median	50.200	53.025	55.650	70.300	60.600
Min-Max	44.80 - 62.30	44.70 - 62.00	42.95 - 66.00	59.20 - 79.10	42.95 - 79.10
Height (cm, at screening)					
n	3	6	4	9	22

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Demographic variable	LDK378 300 mg N=3	LDK378 450 mg N=6	LDK378 600 mg N=4	LDK378 750 mg N=9	All patients N=22
Mean (SD)	157.10 (8.180)	166.52 (10.704)	158.80 (9.127)	167.13 (5.759)	164.08 (8.727)
Median	161.00	165.05	158.85	166.60	165.05
Min-Max	147.7 - 162.6	152.1 - 184.3	150.6 - 166.9	159.9 - 175.0	147.7 - 184.3
Body mass index (kg/m^2)					
n	3	6	4	9	22
Mean (SD)	21.610 (6.0793)	19.120 (1.9658)	21.768 (2.7031)	24.742 (2.4859)	22.241 (3.6608)
Median	18.990	19.285	21.995	23.350	22.170
Min-Max	17.28 - 28.56	16.83 - 21.24	18.79 - 24.29	22.05 - 28.97	16.83 - 28.97
Baseline ECOG performance status - n (%)					
0	2 (66.7)	2 (33.3)	1 (25.0)	5 (55.6)	10 (45.5)
1	1 (33.3)	2 (33.3)	3 (75.0)	4 (44.4)	10 (45.5)
2	0	2 (33.3)	0	0	2 (9.1)
>2	0	0	0	0	0
Smoking history - n (%)					
Never	2 (66.7)	3 (50.0)	3 (75.0)	5 (55.6)	13 (59.1)
Current	0	0	0	2 (22.2)	2 (9.1)
Former	1 (33.3)	3 (50.0)	1 (25.0)	2 (22.2)	7 (31.8)

Prior antineoplastic medications (FAS)

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Characteristics	LDK378 300 mg N=3 n (%)	LDK378 450 mg N=6 n (%)	LDK378 600 mg N=4 n (%)	LDK378 750 mg N=9 n (%)	All patients N=22 n (%)
Prior antineoplastic medications					
No	0	0	0	0	0
Yes	3 (100)	6 (100)	4 (100)	9 (100)	22 (100)
Setting at last medication					
Adjuvant	0	0	0	0	0
Neoadjuvant	0	0	0	0	0
Therapeutic	3 (100)	6 (100)	4 (100)	9 (100)	22 (100)
Prevention	0	0	0	0	0
Palliative	0	0	0	0	0
Other	0	0	0	0	0
Number of prior regimens					
0	0	0	0	0	0
1	0	1 (16.7)	0	4 (44.4)	5 (22.7)
2	0	1 (16.7)	1 (25.0)	2 (22.2)	4 (18.2)
3	2 (66.7)	2 (33.3)	1 (25.0)	3 (33.3)	8 (36.4)
>3	1 (33.3)	2 (33.3)	2 (50.0)	0	5 (22.7)
Prior ALK inhibitor					
No	1 (33.3)	1 (16.7)	0	2 (22.2)	4 (18.2)
Yes	2 (66.7)	5 (83.3)	4 (100)	7 (77.8)	18 (81.8)
Reason for discontinuation of last prior ALK inhibitor					
Adverse event	0	0	0	0	0
Disease progression	2 (66.7)	4 (66.7)	2 (50.0)	7 (77.8)	15 (68.2)

Characteristics	LDK378 300 mg N=3 n (%)	LDK378 450 mg N=6 n (%)	LDK378 600 mg N=4 n (%)	LDK378 750 mg N=9 n (%)	All patients N=22 n (%)
Completed prescribed regimen	0	0	0	0	0
Unknown	0	1 (16.7)	2 (50.0)	0	3 (13.6)
Other	0	0	0	0	0
Last prior ALK inhibitor discontinued due to PD	2 (100)	4 (80.0)	2 (50.0)	7 (100)	15 (83.3)
Last prior ALK inhibitor discontinued due to reasons other than PD	0	1 (20.0)	2 (50.0)	0	3 (16.7)
Prior anticancer medications					
Alectinib	1 (33.3)	0	2 (50.0)	4 (44.4)	7 (31.8)
ASP3026	0	1 (16.7)	0	1 (11.1)	2 (9.1)
Bevacizumab	0	0	0	2 (22.2)	2 (9.1)
Carboplatin	2 (66.7)	0	0	1 (11.1)	3 (13.6)
Cisplatin	1 (33.3)	6 (100)	4 (100)	6 (66.7)	17 (77.3)
Crizotinib	1 (33.3)	5 (83.3)	3 (75.0)	2 (22.2)	11 (50.0)
Docetaxel	1 (33.3)	2 (33.3)	3 (75.0)	1 (11.1)	7 (31.8)
Erlotinib	0	1 (16.7)	0	0	1 (4.5)
Gefitinib	0	0	0	0	0
Gemcitabine	2 (66.7)	0	0	0	2 (9.1)
Paclitaxel	1 (33.3)	0	0	1 (11.1)	2 (9.1)
Pemetrexed	3 (100)	5 (83.3)	4 (100)	5 (55.6)	17 (77.3)
Vinorelbine	1 (33.3)	1 (16.7)	0	1 (11.1)	3 (13.6)

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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 based on investigator assessment by treatment group (FAS – NSCLC)

	LDK378 300 mg N=3	LDK378 450 mg N=6	LDK378 600 mg N=4	LDK378 750 mg N=8
Best overall response – n (%)				
Complete response (CR)	0	0	0	0
Partial response (PR)	3 (100)	3 (50.0)	2 (50.0)	3 (37.5)
Stable disease (SD)	0	1 (16.7)	0	3 (37.5)
Progressive disease (PD)	0	1 (16.7)	2 (50.0)	0
Unknown	0	1 (16.7)	0	2 (25.0)
Overall response rate (ORR) (CR or PR)-n(%)	3 (100)	3 (50.0)	2 (50.0)	3 (37.5)
95% CI	(29.2-100.0)	(11.8-88.2)	(6.8-93.2)	(8.5-75.5)
Disease control rate (DCR) (CR or PR or SD)-n (%)	3 (100)	4 (66.7)	2 (50.0)	6 (75.0)
95% CI	(29.2-100.0)	(22.3-95.7)	(6.8-93.2)	(34.9-96.8)

Pharmacokinetic parameters (PAS)

Dose	Day	n	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)	$T_{1/2}$ (h)
LDK378 300 mg	PK run-in	2	5.10	168 (3)	2760 (33)	22.1 (3.4)
	Cycle 1 day 8	3	3.00	537 (208)	10700 (4950)	N/A

Dose	Day	n	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)	$T_{1/2}$ (h)
n=3	Cycle 2 day 1	2	5.98	867 (59)	N/A	N/A
LDK378 450 mg n=6	PK run-in	5	5.88	76 (68)	1030 (963)	26.0 (6.3)[a]
	Cycle 1 day 8	5	3.97	858 (215)	18400 (4010)[b]	N/A
	Cycle 2 day 1	5	5.95	982 (102)	20900 (3990)[c]	N/A
LDK378 600 mg n=4	PK run-in	4	5.97	215 (196)	3710 (3590)	30.7 (3.6)
	Cycle 1 day 8	4	3.44	1060 (633)	16600 (10500)[c]	N/A
	Cycle 2 day 1	4	4.93	1150 (592)	21400 (15300)[a]	N/A
LDK378 750 mg n=6	PK run-in	6	5.98	206 (75)	3590 (1680)	33.4 (4.3)[d]
	Cycle 1 day 8	6	6.96	1220 (212)	25700 (4440)[d]	N/A
	Cycle 2 day 1	3	1.93	1470 (375)	26400 (5810)[a]	N/A

[a]n=2; [b]n=4; [c]n=3; [d]n=5.

Values represent median for T_{max}, and mean (standard deviation) for C_{max}, AUC_{0-24}, and $T_{1/2}$.

Summary of Safety

Safety Results

Dose limiting toxicities (Dose-determining set)

Preferred term	LDK378 300 mg N=3 n (%)	LDK378 450 mg N=5 n (%)	LDK378 600 mg N=4 n (%)	LDK378 750 mg N=6 n (%)	All patients N=18 n (%)

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Preferred term	LDK378 300 mg N=3 n (%)	LDK378 450 mg N=5 n (%)	LDK378 600 mg N=4 n (%)	LDK378 750 mg N=6 n (%)	All patients N=18 n (%)
-Total	0	0	1(25.0)	1(16.7)	2(11.1)
Drug-induced liver injury	0	0	0	1(16.7)	1 (5.6)
Lipase increased	0	0	1(25.0)	0	1 (5.6)

Summary of posterior distribution of DLT rates from BLRM (Dose-determining set)

	Posterior probabilities that Pr (DLT) is in interval					Quantiles		
Dose level (mg)	Under-dosing 0-0.16	Targeted toxicity 0.16-0.33	Excessive toxicity 0.33-1	Mean	SD	2.5%	50%	97.5%
150	0.995	0.005	0.000	0.024	0.030	0.000	0.013	0.107
300	0.974	0.026	0.000	0.049	0.043	0.003	0.037	0.162
450	0.907	0.091	0.002	0.083	0.055	0.014	0.070	0.219
600	0.736	0.252	0.012	0.125	0.070	0.027	0.112	0.293
750	0.510	0.417	0.073	0.175	0.096	0.040	0.157	0.407
900	0.353	0.455	0.192	0.228	0.132	0.051	0.201	0.558
1050	0.258	0.432	0.311	0.279	0.165	0.060	0.243	0.698
1200	0.197	0.400	0.403	0.325	0.191	0.069	0.282	0.800

Adverse Events by System Organ Class

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Primary system organ class	LDK378 300 mg N=3 n (%)	LDK378 450 mg N=6 n (%)	LDK378 600 mg N=4 n (%)	LDK378 750 mg N=9 n (%)	All patients N=22 n (%)
-Any primary system organ class	3(100)	6(100)	4(100)	9(100)	22(100)
Gastrointestinal disorders	3(100)	6(100)	4(100)	9(100)	22(100)
Investigations	3(100)	4(66.7)	4(100)	7(77.8)	18(81.8)
General disorders and administration site conditions	1(33.3)	5(83.3)	3(75.0)	8(88.9)	17(77.3)
Metabolism and nutrition disorders	0	3(50.0)	3(75.0)	8(88.9)	14(63.6)
Skin and subcutaneous tissue disorders	2(66.7)	4(66.7)	2(50.0)	6(66.7)	14(63.6)
Infections and infestations	2(66.7)	3(50.0)	3(75.0)	4(44.4)	12(54.5)
Nervous system disorders	3(100)	4(66.7)	1(25.0)	2(22.2)	10(45.5)
Respiratory, thoracic and mediastinal disorders	2(66.7)	4(66.7)	1(25.0)	2(22.2)	9(40.9)
Hepatobiliary disorders	0	0	2(50.0)	5(55.6)	7(31.8)
Musculoskeletal and connective tissue disorders	3(100)	0	1(25.0)	3(33.3)	7(31.8)
Blood and lymphatic system disorders	2(66.7)	3(50.0)	0	1(11.1)	6(27.3)
Eye disorders	1(33.3)	0	1(25.0)	2(22.2)	4(18.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1(33.3)	2(33.3)	0	0	3(13.6)
Renal and urinary disorders	0	1(16.7)	0	2(22.2)	3(13.6)
Ear and labyrinth disorders	1(33.3)	0	0	1(11.1)	2(9.1)
Injury, poisoning and procedural complications	1(33.3)	1(16.7)	0	0	2(9.1)
Psychiatric disorders	0	1(16.7)	0	1(11.1)	2(9.1)
Vascular disorders	0	1(16.7)	0	1(11.1)	2(9.1)
Cardiac disorders	0	1(16.7)	0	0	1(4.5)
Immune system disorders	0	1(16.7)	0	0	1(4.5)

Most Frequently Reported AEs Overall by Preferred Term n (%)

	LDK378 300 mg N=3		LDK378 450 mg N=6		LDK378 600 mg N=4		LDK378 750 mg N=9		All patients N=22	
Preferred term	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 (%)	Grade 3/4 n (%)
-Total	3 (100)	2 (66.7)	6 (100)	5 (83.3)	4 (100)	4 (100)	9 (100)	8 (88.9)	22 (100)	19 (86.4)
Nausea	3 (100)	0	6 (100)	0	4 (100)	0	7 (77.8)	1 (11.1)	20 (90.9)	1 (4.5)
Diarrhoea	3 (100)	0	2 (33.3)	0	4 (100)	0	8 (88.9)	1 (11.1)	17 (77.3)	1 (4.5)
Vomiting	1 (33.3)	0	6 (100)	0	4 (100)	0	5 (55.6)	0	16 (72.7)	0
Blood creatinine increased	3 (100)	0	4 (66.7)	0	1 (25.0)	0	6 (66.7)	0	14 (63.6)	0
Decreased appetite	0	0	3 (50.0)	0	3 (75.0)	0	4 (44.4)	1 (11.1)	10 (45.5)	1 (4.5)
Fatigue	0	0	2 (33.3)	0	3 (75.0)	0	4 (44.4)	0	9 (40.9)	0
Hyperuricaemia	0	0	0	0	1 (25.0)	0	6 (66.7)	2 (22.2)	7 (31.8)	2 (9.1)
Abdominal pain	2 (66.7)	0	1 (16.7)	0	1 (25.0)	0	2 (22.2)	0	6 (27.3)	0
Alanine aminotransferase increased	0	0	2 (33.3)	0	1 (25.0)	1 (25.0)	3 (33.3)	3 (33.3)	6 (27.3)	4 (18.2)
Aspartate aminotransferase increased	0	0	2 (33.3)	0	1 (25.0)	1 (25.0)	3 (33.3)	1 (11.1)	6 (27.3)	2 (9.1)
Constipation	1 (33.3)	0	3 (50.0)	1 (16.7)	0	0	1 (11.1)	0	5 (22.7)	1 (4.5)
Headache	1 (33.3)	0	3 (50.0)	0	1 (25.0)	0	0	0	5 (22.7)	0
Hepatic function abnormal	0	0	0	0	1 (25.0)	0	4 (44.4)	1 (11.1)	5 (22.7)	1 (4.5)
Pyrexia	0	0	2 (33.3)	0	0	0	3 (33.3)	0	5 (22.7)	0
Rash	0	0	3 (50.0)	0	1 (25.0)	0	1 (11.1)	0	5 (22.7)	0

Serious Adverse Events and Deaths

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Category	LDK378 300 mg N=3 n (%)	LDK378 450 mg N=6 n (%)	LDK378 600 mg N=4 n (%)	LDK378 750 mg N=9 n (%)	All patients N=22 n (%)
All deaths [a]	0	2 (33.3)	0	0	2 (9.1)
On-treatment deaths [b]	0	2 (33.3)	0	0	2 (9.1)
Serious adverse event	1 (33.3)	5 (83.3)	2 (50.0)	5 (55.6)	13 (59.1)
Discontinued due to SAE(s)	0	0	1 (25.0)	1 (11.1)	2 (9.1)

- [a] All deaths including those >28 days after last dose of study drug.
- [b] Deaths occurring >28 days after last dose of study drug are not included.
- Only AEs occurring during treatment or within 28 days of the last dose of study drug are reported.

Conclusion:

The MTD for LDK378 was determined to be 750 mg/day in Japanese patients in this phase I study considering the safety and PK profile of LDK378.

LDK378 has an acceptable tolerability profile in Japanese patients with tumors characterized by genetic alterations in ALK. The most common AEs were gastrointestinal (nausea, diarrhea, vomiting). Elevated transaminases were also common. These AEs were managable with symptomatic treatment and/or dose reductions or interruptions when needed.

Although data was too limited to draw firm conclusions on dose-proportionality or pharmacokinetic linearity, exposures generally increased in a linear manner with increasing dose.

LDK378 has potent and clinically meaningful anti-tumor activity in patients with ALK-positive NSCLC in Japan regardless of the prior treatment of ALK inhibitors.

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Clinical Trial Results Database

Date of Clinical Trial Report

28 October 2016