NOVARTIS

Clinical Trial Results Database

Sponsor

Novartis

Generic Drug Name

Capmatinib

Trial Indication(s)

Advanced solid tumors

Protocol Number

CINC280X1101

Protocol Title

A Phase I study of INC280 in Japanese patients with advanced solid tumors

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase II

Study Start/End Dates

10-Feb-2012 (first patient first visit) to 22-Jan-2016 (last patient last visit)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This study was a first-in Japanese study of INC280 and was designed as an open-label, multicenter dose escalation with an expansion part.

The study enrolled Japanese patients with advanced solid tumors who were refractory to currently available therapies or have tumors for which no effective treatment was available. Patients received treatment in 28-day cycles as long as there was no evidence of disease progression, intolerable toxicity, withdrawal of consent, or discontinuation for any other reason.

In the dose escalation part, the patients received doses of INC280 (capsule formulation at dose levels of 100 mg QD, 200 mg QD, 400 mg QD, 500 mg QD, 600 mg QD, 800 mg QD, 400 mg BID, and 600 mg BID; tablet formulation at dose levels of 200 mg BID, and 400 mg BID) until the MTD and/or highest studied dose to be safe was determined.

Centers

2 centers in Japan

Publication

None

Objectives:

Primary objective

- To determine the maximum tolerated dose (MTD) and/or highest studied dose determined to be safe of INC280 as a single agent when administered orally to Japanese patients with advanced solid tumors.

Secondary objective(s)

- To characterize the safety and tolerability of INC280.
- To evaluate the pharmacokinetics (PK) of INC280.
- To evaluate the preliminary anti-tumor activity of INC280.

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

The test product, INC280 capsules or tablets were administrated once a day or twice a day orally to all patients. (see 'Study Design/Methodology')

Statistical Methods

An adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle was used in the dose-escalation to determine MTD and / or highest studied dose being safe.

Data was summarized using descriptive statistics (continuous data) and/or contingency tables (categorical data) for demographic and baseline characteristics, efficacy measurements, safety measurements, and all relevant PK and PD measurements.

No formal interim analysis was planned. However, the design in the dose-escalation part of the study foresaw that decisions based on the current data were taken before the end of the study.

Study Population: Key Inclusion/Exclusion Criteria

Key inclusion Criteria:

- Male and female patients aged ≥ 18.
- Patients with advanced solid tumors that are refractory to currently available therapies or for whom no effective treatment is available.
- Patients with Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 2.
- Patients with the following baseline laboratory values were allowed: hemoglobin >9 g/dL (without transfusion support or growth factors), platelet count ≥ 100×10^9/L, absolute neutrophil count (ANC) ≥ 1.5×10^9/L (without growth factor support), total bilirubin level ≤ 1.5 × upper limit of normal (ULN), AST/SGOT and/or ALT/SGPT levels ≤ 2.5 × ULN or ≤ 5.0 × ULN (if HCC was primary disease

or liver metastasis was present), serum creatinine ≤ 1.5 × ULN, creatinine clearance > 45 mL/min, asymptomatic serum amylase ≤ grade 2 (per CTCAE v4.0) , serum lipase ≤ ULN and fasting serum triglyceride level ≤ 500 mg/dL.

Key exclusion criteria:

- Patients with symptomatic CNS metastases that are neurologically unstable or requiring increasing doses of steroids to control CNS disease.
- Patients with impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of INC280.
- Patients who have undergone a bone marrow or solid organ transplant.
- Women who are pregnant or breast feeding.

Participant Flow Table

Patient disposition, by treatment group (full analysis set)

	INC280 100 mg QD capsule N=3 n (%)	INC280 200 mg QD capsule N=4 n (%)	INC280 400 mg QD capsule N=3 n (%)	INC280 500 mg QD capsule N=4 n (%)	INC280 600 mg QD capsule N=4 n (%)	INC280 800 mg QD capsule N=4 n (%)	INC280 400 mg BID capsule N=4 n (%)	INC280 600 mg BID capsule N=3 n (%)	INC280 200 mg BID tablet N=3 n (%)	INC280 400 mg BID tablet N=12 n (%)	All patients N=44 n (%)
Patients treated											
Treatment discontinued	3 (100)	4 (100)	3 (100)	4 (100)	4 (100)	4 (100)	4 (100)	3 (100)	3 (100)	12 (100)	44 (100)
Primary reason for end of treatment											
Adverse event	0	0	0	0	0	1 (25.0)	0	1 (33.3)	1 (33.3)	1 (8.3)	4 (9.1)
Lost to follow-Up	0	0	0	0	1 (25.0)	0	0	0	0	0	1 (2.3)
Progressive disease	3 (100)	4 (100)	3 (100)	4 (100)	3 (75.0)	3 (75.0)	4 (100)	2 (66.7)	2 (66.7)	10 (83.3)	38 (86.4)
Subject/guardian decision	0	0	0	0	0	0	0	0	0	1 (8.3)	1 (2.3)
Study evaluation after completion of treatment											

	INC280 100 mg QD capsule N=3 n (%)	INC280 200 mg QD capsule N=4 n (%)	INC280 400 mg QD capsule N=3 n (%)	INC280 500 mg QD capsule N=4 n (%)	INC280 600 mg QD capsule N=4 n (%)	INC280 800 mg QD capsule N=4 n (%)	INC280 400 mg BID capsule N=4 n (%)	INC280 600 mg BID capsule N=3 n (%)	INC280 200 mg BID tablet N=3 n (%)	INC280 400 mg BID tablet N=12 n (%)	All patients N=44 n (%)
Patients no longer being followed for study evaluation completion	3 (100)	4 (100)	3 (100)	4 (100)	4 (100)	4 (100)	4 (100)	3 (100)	3 (100)	12 (100)	44 (100)
Primary reason for study evaluation completion											
Completed	1 (33.3)	3 (75.0)	3 (100)	3 (75.0)	3 (75.0)	3 (75.0)	3 (75.0)	3 (100)	2 (66.7)	9 (75.0)	33 (75.0)
Death	0	0	0	1 (25.0)	0	0	0	0	0	0	1 (2.3)
New therapy for study indication	2 (66.7)	1 (25.0)	0	0	0	1 (25.0)	1 (25.0)	0	1 (33.3)	3 (25.0)	9 (20.5)
Missing	0	0	0	0	1 (25.0)	0	0	0	0	0	1 (2.3)

Baseline Characteristics

Demographics at baseline, by treatment group (full analysis set)

Demographic variable	INC280 100 mg QD capsule N=3	INC280 200 mg QD capsule N=4	INC280 400 mg QD capsule N=3	INC280 500 mg QD capsule N=4	INC280 600 mg QD capsule N=4	INC280 800 mg QD capsule N=4	INC280 400 mg BID capsule N=4	INC280 600 mg BID capsule N=3	INC280 200 mg BID tablet N=3	INC280 400 mg BID tablet N=12	All patients N=44
Age (years, at Screening)											
n	3	4	3	4	4	4	4	3	3	12	44
Mean	69.7	52.3	53.7	61.5	58.3	58.5	59.3	62.3	54.3	59.8	59.0
SD	7.51	14.38	21.39	7.94	6.65	9.81	9.64	7.64	11.37	15.44	12.08
Median	74.0	57.0	65.0	60.5	60.0	62.5	61.0	64.0	51.0	66.0	62.0
Minimum	61	32	29	53	49	44	46	54	45	26	26
Maximum	74	63	67	72	64	65	69	69	67	73	74

Demographic variable	INC280 100 mg QD capsule N=3	INC280 200 mg QD capsule N=4	INC280 400 mg QD capsule N=3	INC280 500 mg QD capsule N=4	INC280 600 mg QD capsule N=4	INC280 800 mg QD capsule N=4	INC280 400 mg BID capsule N=4	INC280 600 mg BID capsule N=3	INC280 200 mg BID tablet N=3	INC280 400 mg BID tablet N=12	All patients N=44
Age category (years, at Screening) –n (%)											
< 65	1 (33.3)	4 (100)	1 (33.3)	3 (75.0)	4 (100)	3 (75.0)	3 (75.0)	2 (66.7)	2 (66.7)	5 (41.7)	28 (63.6)
≥ 65	2 (66.7)	0	2 (66.7)	1 (25.0)	0	1 (25.0)	1 (25.0)	1 (33.3)	1 (33.3)	7 (58.3)	16 (36.4)
Sex -n (%)											
Female	2 (66.7)	2 (50.0)	1 (33.3)	2 (50.0)	2 (50.0)	1 (25.0)	1 (25.0)	2 (66.7)	0	4 (33.3)	17 (38.6)
Male	1 (33.3)	2 (50.0)	2 (66.7)	2 (50.0)	2 (50.0)	3 (75.0)	3 (75.0)	1 (33.3)	3 (100)	8 (66.7)	27 (61.4)
Weight (kg, at baseline)											
n	3	4	3	4	4	4	4	3	3	12	44
Mean	49.12	59.60	63.23	62.35	59.33	64.20	57.00	55.00	61.33	61.28	59.80
SD	2.973	16.455	3.855	13.853	8.059	5.846	9.832	6.245	3.691	14.928	10.992
Median	48.50	55.55	61.80	66.70	59.90	66.35	57.00	53.00	60.70	58.60	60.25
Minimum	46.5	45.0	60.3	43.0	49.0	55.6	45.0	50.0	58.0	42.0	42.0
Maximum	52.4	82.3	67.6	73.0	68.5	68.5	69.0	62.0	65.3	97.7	97.7
Height (cm, at Screening)											
n	3	4	3	4	4	4	4	3	3	12	44
Mean	155.30	165.38	161.27	158.60	162.88	162.18	165.00	155.37	169.13	161.53	161.77
SD	5.205	7.010	12.351	5.485	8.171	10.559	3.651	8.532	3.695	6.855	7.492
Median	154.10	163.95	161.10	160.20	165.50	165.35	165.00	154.00	167.00	161.75	163.00
Minimum	150.8	158.6	149.0	151.0	151.0	147.0	161.0	147.6	167.0	153.0	147.0
Maximum	161.0	175.0	173.7	163.0	169.5	171.0	169.0	164.5	173.4	175.1	175.1
Body mass index (kg/m^2)											
n	3	4	3	4	4	4	4	3	3	12	44
Mean	20.44	21.53	24.72	24.61	22.29	24.43	20.85	22.74	21.43	23.41	22.81
SD	2.193	4.122	5.147	4.432	1.638	1.157	2.780	0.337	0.546	4.775	3.556

Demographic variable	INC280 100 mg QD capsule N=3	INC280 200 mg QD capsule N=4	INC280 400 mg QD capsule N=3	INC280 500 mg QD capsule N=4	INC280 600 mg QD capsule N=4	INC280 800 mg QD capsule N=4	INC280 400 mg BID capsule N=4	INC280 600 mg BID capsule N=3	INC280 200 mg BID tablet N=3	INC280 400 mg BID tablet N=12	All patients N=44
Median	21.33	21.10	23.23	25.46	21.56	24.54	20.94	22.91	21.72	23.12	22.24
Minimum	17.9	17.1	20.5	18.9	21.3	22.9	17.4	22.3	20.8	14.4	14.4
Maximum	22.0	26.9	30.4	28.6	24.7	25.7	24.2	23.0	21.8	31.9	31.9
ECOG performance status -n (%)											
0	0	3 (75.0)	2 (66.7)	2 (50.0)	2 (50.0)	2 (50.0)	1 (25.0)	1 (33.3)	2 (66.7)	4 (33.3)	19 (43.2)
1	3 (100)	1 (25.0)	1 (33.3)	2 (50.0)	2 (50.0)	2 (50.0)	3 (75.0)	2 (66.7)	1 (33.3)	8 (66.7)	25 (56.8)

Summary of Efficacy

Primary Outcome Result

Determination MTD and/or highest studied dose determined to be safe of INC280 as a single agent

Highest studied dose determined to be safe	400 mg BID with tablet in Japanese patients with advanced solid tumors.
MTD	Not determined

Secondary Outcome Results

Best response

	All patients N=44 n
Complete Response (CR)	0

	All patients N=44 n
Partial Response (PR)	0
Stable Disease (SD)	8
Progressive Disease (PD)	32
UNKNOWN (UNK)	2
Non-CR/Non-PD,	2

Summary of primary PK parameters of INC280 by treatment group (pharmacokinetic analysis set) - Profile day: Cycle 1 Day 15

Treatment	Statistics	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	AUCtau (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)
INC280 100 mg QD capsule (N=3)	**n**	**3**	**NA**	**3**	**3**	**3**
	Mean (SD)	2770 (1040)		2770 (1040)	395 (53.1)	N/A
	CV% mean	37.5		37.3	13.4	N/A
	Geo-mean	2630		2640	393	N/A
	CV% Geo-mean	41.6		41.4	14.1	N/A
	Median	2790		2800	425	3.98
	[Min; Max]	[1720; 3800]		[1730; 3800]	[334; 427]	[1.02; 4.07]
INC280 200 mg QD	**n**	**3**	**NA**	**3**	**3**	**3**
	Mean (SD)	9900 (1960)		9910 (1960)	2160 (760)	N/A
	CV% mean	19.8		19.7	35.2	N/A

Treatment	Statistics	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	AUCtau (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)
capsule (N=4)	Geo-mean	9760		9770	2070	N/A
	CV% Geo-mean	21.2		21.1	38.3	N/A
	Median	10500		10500	2160	1.00
	[Min; Max]	[7710; 11500]		[7720; 11500]	[1400; 2920]	[0.983; 2.00]
INC280 400 mg QD capsule (N=3)	**n**	**3**	**NA**	**3**	**3**	**3**
	Mean (SD)	26400 (18400)		26400 (18400)	5060 (4010)	N/A
	CV% mean	69.6		69.6	79.2	N/A
	Geo-mean	20600		20600	3550	N/A
	CV% Geo-mean	121.5		121.5	173.0	N/A
	Median	28500		28500	5290	2.00
	[Min; Max]	[7060; 43600]		[7060; 43600]	[944; 8950]	[1.95; 2.05]
INC280 500 mg QD capsule (N=4)	**n**	**3**	**NA**	**3**	**3**	**3**
	Mean (SD)	43700 (7690)		43700 (7680)	7960 (952)	N/A
	CV% mean	17.6		17.6	12.0	N/A
	Geo-mean	43300		43300	7930	N/A
	CV% Geo-mean	17.9		17.9	11.6	N/A
	Median	43700		43700	7480	1.97
	[Min; Max]	[36000; 51400]		[36100; 51400]	[7350; 9060]	[1.03; 2.00]

Treatment	Statistics	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	AUCtau (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)
INC280 600 mg QD capsule (N=4)	**n**	**4**	**NA**	**4**	**4**	**4**
	Mean (SD)	39000 (7140)		39000 (7140)	7180 (897)	N/A
	CV% mean	18.3		18.3	12.5	N/A
	Geo-mean	38500		38500	7140	N/A
	CV% Geo-mean	18.4		18.4	13.1	N/A
	Median	38400		38400	7340	1.48
	[Min; Max]	[31900; 47500]		[31900; 47500]	[5950; 8100]	[0.967; 2.03]
INC280 800 mg QD capsule (N=4)	**n**	**4**	**NA**	**4**	**4**	**4**
	Mean (SD)	39400 (7690)		39400 (7700)	6450 (3550)	N/A
	CV% mean	19.5		19.5	55.0	N/A
	Geo-mean	38900		38900	5740	N/A
	CV% Geo-mean	18.2		18.2	60.9	N/A
	Median	35900		36000	5760	3.00
	[Min; Max]	[34900; 50900]		[34900; 50900]	[3400; 10900]	[2.00; 4.08]
INC280 400 mg BID capsule (N=4)	**n**	**3**	**NA**	**3**	**3**	**3**
	Mean (SD)	11100 (8850)		11000 (8750)	1980 (1740)	N/A
	CV% mean	79.6		79.2	88.0	N/A
	Geo-mean	8990		8960	1540	N/A
	CV% Geo-mean	93.4		92.8	102.5	N/A

Treatment	Statistics	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	AUCtau (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)
	Median	7770		7750	1180	3.95
	[Min; Max]	[4430; 21100]		[4430; 21000]	[777; 3970]	[2.00; 3.98]
INC280 600 mg BID capsule (N=3)	**n**	**2**	**NA**	**2**	**2**	**2**
	Mean (SD)	62600 (656)		62500 (645)	16500 (2190)	N/A
	CV% mean	1.0		1.0	13.3	N/A
	Geo-mean	62600		62500	16400	N/A
	CV% Geo-mean	1.0		1.0	13.4	N/A
	Median	62600		62500	16500	1.99
	[Min; Max]	[62200; 63100]		[62000; 62900]	[14900; 18000]	[1.97; 2.02]
INC280 200 mg BID tablet (N=3)	**n**	**3**	**NA**	**3**	**3**	**3**
	Mean (SD)	12000 (6180)		12000 (6150)	3140 (1620)	N/A
	CV% mean	51.3		51.2	51.7	N/A
	Geo-mean	11000		11000	2850	N/A
	CV% Geo-mean	56.2		56.2	59.6	N/A
	Median	10800		10800	2960	0.967
	[Min; Max]	[6580; 18800]		[6540; 18700]	[1610; 4840]	[0.967; 2.00]
INC280 400 mg BID	**n**	**9**	**NA**	**9**	**9**	**9**
	Mean (SD)	31500 (19800)		31400 (19700)	7570 (4460)	N/A
	CV% mean	63.0		62.8	58.9	N/A

Treatment	Statistics	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	AUCtau (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)
tablet (N=12)	Geo-mean	26400		26300	6450	N/A
	CV% Geo-mean	70.4		70.2	67.0	N/A
	Median	25600		25600	6060	1.00
	[Min; Max]	[10600; 63800]		[10600; 63300]	[2750; 15200]	[0.500; 2.00]

n: number of patients with non-missing values.
CV% mean = coefficient of variation (%) = sd/mean*100.
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.

Summary of Safety

Safety Results

Dose limiting toxicities occurring during cycle 1 by primary system organ class, preferred term, and treatment group (dose determining set)

Primary system organ class Preferred term	INC280 100 mg QD capsule N=3 n (%)	INC280 200 mg QD capsule N=3 n (%)	INC280 400 mg QD capsule N=3 n (%)	INC280 500 mg QD capsule N=3 n (%)	INC280 600 mg QD capsule N=4 n (%)	INC280 800 mg QD capsule N=4 n (%)	INC280 400 mg BID capsule N=3 n (%)	INC280 600 mg BID capsule N=3 n (%)	INC280 200 mg BID tablet N=3 n (%)	INC280 400 mg BID tablet N=10 n (%)	All patients N=39 n (%)
Any DLT	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1 (33.3)**	**0**	**1 (10.0)**	**2 (5.1)**

Primary system organ class Preferred term	INC280 100 mg QD capsule N=3 n (%)	INC280 200 mg QD capsule N=3 n (%)	INC280 400 mg QD capsule N=3 n (%)	INC280 500 mg QD capsule N=3 n (%)	INC280 600 mg QD capsule N=4 n (%)	INC280 800 mg QD capsule N=4 n (%)	INC280 400 mg BID capsule N=3 n (%)	INC280 600 mg BID capsule N=3 n (%)	INC280 200 mg BID tablet N=3 n (%)	INC280 400 mg BID tablet N=10 n (%)	All patients N=39 n (%)
Psychiatric Disorders	0	0	0	0	0	0	0	1 (33.3)	0	1 (10.0)	2 (5.1)
Depression	0	0	0	0	0	0	0	0	0	1 (10.0)	1 (2.6)
Suicidal Ideation	0	0	0	0	0	0	0	1 (33.3)	0	0	1 (2.6)

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

Primary system organ class	INC280 100 mg QD capsule N=3 n (%)	INC280 200 mg QD capsule N=4 n (%)	INC280 400 mg QD capsule N=3 n (%)	INC280 500 mg QD capsule N=4 n (%)	INC280 600 mg QD capsule N=4 n (%)	INC280 800 mg QD capsule N=4 n (%)	INC280 400 mg BID capsule N=4 n (%)	INC280 600 mg BID capsule N=3 n (%)	INC280 200 mg BID tablet N=3 n (%)	INC280 400 mg BID tablet N=12 n (%)	All patients N=44 n (%)
Any AE	**3 (100)**	**3 (75.0)**	**2 (66.7)**	**4 (100)**	**4 (100)**	**4 (100)**	**4 (100)**	**3 (100)**	**3 (100)**	**12 (100)**	**42 (95.5)**
Gastrointestinal Disorders	1 (33.3)	3 (75.0)	1 (33.3)	4 (100)	3 (75.0)	3 (75.0)	2 (50.0)	2 (66.7)	2 (66.7)	11 (91.7)	32 (72.7)
Investigations	1 (33.3)	2 (50.0)	1 (33.3)	4 (100)	3 (75.0)	1 (25.0)	4 (100)	1 (33.3)	2 (66.7)	12 (100)	31 (70.5)
Metabolism and nutrition disorders	2 (66.7)	2 (50.0)	0	1 (25.0)	4 (100)	2 (50.0)	3 (75.0)	2 (66.7)	1 (33.3)	8 (66.7)	25 (56.8)
General Disorders And Administration Site Conditions	0	0	0	3 (75.0)	2 (50.0)	2 (50.0)	3 (75.0)	2 (66.7)	2 (66.7)	8 (66.7)	22 (50.0)
Skin and subcutaneous tissue disorders	1 (33.3)	2 (50.0)	1 (33.3)	0	2 (50.0)	2 (50.0)	2 (50.0)	1 (33.3)	0	9 (75.0)	20 (45.5)

Primary system organ class	INC280 100 mg QD capsule N=3 n (%)	INC280 200 mg QD capsule N=4 n (%)	INC280 400 mg QD capsule N=3 n (%)	INC280 500 mg QD capsule N=4 n (%)	INC280 600 mg QD capsule N=4 n (%)	INC280 800 mg QD capsule N=4 n (%)	INC280 400 mg BID capsule N=4 n (%)	INC280 600 mg BID capsule N=3 n (%)	INC280 200 mg BID tablet N=3 n (%)	INC280 400 mg BID tablet N=12 n (%)	All patients N=44 n (%)
Nervous System Disorders	0	0	0	1 (25.0)	0	2 (50.0)	1 (25.0)	2 (66.7)	1 (33.3)	4 (33.3)	11 (25.0)
Infections and infestations	1 (33.3)	0	0	0	2 (50.0)	1 (25.0)	0	2 (66.7)	1 (33.3)	4 (33.3)	11 (25.0)
Respiratory, thoracic and mediastinal disorders	0		0	1 (25.0)	1 (25.0)	2 (50.0)	1 (25.0)	1 (33.3)	0	3 (25.0)	9 (20.5)
Blood And Lymphatic System Disorders	1 (33.3)	0	0	1 (25.0)	1 (25.0)	1 (25.0)	0	0	1 (33.3)	3 (25.0)	8 (18.2)
Neoplasms Benign, Malignant and unspecified (incl cysts and polyps)	0	0	0	0	2 (50.0)	3 (75.0)	0	0	0	2 (16.7)	7 (15.9)
Musculoskeletal and connective tissue disorders	1 (33.3)	1 (25.0)	0	2 (50.0)	1 (25.0)	0	0	0	1 (33.3)	0	6 (13.6)
Psychiatric disorders	0	0	1 (33.3)	0	0	0	0	1 (33.3)	0	2 (16.7)	4 (9.1)
Hepatobiliary Disorders	0	1 (25.0)	0	0	1 (25.0)	1 (25.0)	0	0	0	1 (8.3)	4 (9.1)
Vascular Disorders	0	0	0	2 (50.0)	0	0	1 (25.0)	0	0	0	3 (6.8)
Reproductive system and breast disorders	1 (33.3)	0	0	0	0	0	0	0	0	1 (8.3)	2 (4.5)
Cardiac Disorders	0	0	0	0	0	0	2 (50.0)	0	0	0	2 (4.5)
Renal and urinary disorders	0	0	0	0	1 (25.0)	0	0	0	0	0	1 (2.3)
Immune System	0	0	0	0	1 (25.0)	0	0	0	0	0	1 (2.3)

Primary system organ class	INC280 100 mg QD capsule N=3 n (%)	INC280 200 mg QD capsule N=4 n (%)	INC280 400 mg QD capsule N=3 n (%)	INC280 500 mg QD capsule N=4 n (%)	INC280 600 mg QD capsule N=4 n (%)	INC280 800 mg QD capsule N=4 n (%)	INC280 400 mg BID capsule N=4 n (%)	INC280 600 mg BID capsule N=3 n (%)	INC280 200 mg BID tablet N=3 n (%)	INC280 400 mg BID tablet N=12 n (%)	All patients N=44 n (%)
Disorders											
Eye Disorders	0	0	1 (33.3)	0	0	0	0	0	0	0	1 (2.3)

Adverse events, regardless of study treatment relationship, by preferred term and treatment group (with a frequency cut off of 5% in all patients) (safety set)

	INC280 100 mg QD capsule N=3		INC280 200 mg QD capsule N=4		INC280 400 mg QD capsule N=3		INC280 500 mg QD capsule N=4		INC280 600 mg QD capsule N=4		INC280 800 mg QD capsule N=4	
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 (%)	All grades n (%)	Grade 3/4 n (%)
Any AE	**3 (100)**	**0**	**3 (75.0)**	**1 (25.0)**	**2 (66.7)**	**0**	**4 (100)**	**2 (50.0)**	**4 (100)**	**4 (100)**	**4 (100)**	**0**
Blood Creatinine Increased	1 (33.3)	0	1 (25.0)	0	1 (33.3)	0	3 (75.0)	0	3 (75.0)	0	1 (25.0)	0
Nausea	1 (33.3)	0	2 (50.0)	0	1 (33.3)	0	0	0	3 (75.0)	0	2 (50.0)	0
Decreased Appetite	1 (33.3)	0	2 (50.0)	1 (25.0)	0	0	0	0	3 (75.0)	1 (25.0)	2 (50.0)	0
Vomiting	1 (33.3)	0	3 (75.0)	0	0	0	0	0	3 (75.0)	0	1 (25.0)	0
Diarrhoea	0	0	0	0	1 (33.3)	0	4 (100)	0	1 (25.0)	0	0	0
Hypoalbuminaemia	1 (33.3)	0	1 (25.0)	0	0	0	1 (25.0)	0	1 (25.0)	1 (25.0)	1 (25.0)	0

	INC280 100 mg QD capsule N=3		INC280 200 mg QD capsule N=4		INC280 400 mg QD capsule N=3		INC280 500 mg QD capsule N=4		INC280 600 mg QD capsule N=4		INC280 800 mg QD capsule N=4	
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 (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Oedema Peripheral	0	0	0	0	0	0	1 (25.0)	0	2 (50.0)	0	0	0
Malaise	0	0	0	0	0	0	0	0	1 (25.0)	0	0	0
Pyrexia	0	0	0	0	0	0	2 (50.0)	0	1 (25.0)	0	2 (50.0)	0
Anaemia	1 (33.3)	0	0	0	0	0	1 (25.0)	0	1 (25.0)	0	1 (25.0)	0
Constipation	1 (33.3)	0	1 (25.0)	0	0	0	1 (25.0)	0	0	0	2 (50.0)	0
Fatigue	0	0	0	0	0	0	1 (25.0)	0	1 (25.0)	0	0	0
Headache	0	0	0	0	0	0	1 (25.0)	0	0	0	1 (25.0)	0
Cough	0	0	0	0	0	0	1 (25.0)	0	1 (25.0)	0	1 (25.0)	0
Dry Skin	1 (33.3)	0	0	0	1 (33.3)	0	0	0	0	0	0	0
Amylase Increased	0	0	0	0	0	0	0	0	0	0	0	0
Gamma-Glutamyltransferase Increased	0	0	0	0	0	0	2 (50.0)	0	1 (25.0)	1 (25.0)	0	0
Hyponatraemia	0	0	0	0	0	0	0	0	1 (25.0)	1 (25.0)	0	0
Hypophosphataemia	0	0	0	0	0	0	0	0	1 (25.0)	1 (25.0)	0	0
Cancer Pain	0	0	0	0	0	0	0	0	1 (25.0)	0	2 (50.0)	0
Ascites	0	0	1 (25.0)	1 (25.0)	0	0	0	0	1 (25.0)	0	0	0
Alanine Aminotransferase Increased	0	0	0	0	0	0	1 (25.0)	1 (25.0)	1 (25.0)	0	0	0
Aspartate Aminotransferase Increased	0	0	0	0	0	0	1 (25.0)	1 (25.0)	1 (25.0)	0	0	0

	INC280 100 mg QD capsule N=3		INC280 200 mg QD capsule N=4		INC280 400 mg QD capsule N=3		INC280 500 mg QD capsule N=4		INC280 600 mg QD capsule N=4		INC280 800 mg QD capsule N=4	
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 (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Weight Decreased	0	0	1 (25.0)	0	0	0	0	0	0	0	0	0
Hyperkalaemia	1 (33.3)	0	0	0	0	0	0	0	1 (25.0)	0	0	0
Tumour Pain	0	0	0	0	0	0	0	0	1 (25.0)	0	1 (25.0)	0
Dyspnoea	0	0	0	0	0	0	1 (25.0)	0	0	0	1 (25.0)	0
Pruritus	0	0	0	0	0	0	0	0	0	0	0	0
Rash	0	0	1 (25.0)	0	0	0	0	0	0	0	1 (25.0)	0
Hypotension	0	0	0	0	0	0	2 (50.0)	0	0	0	0	0

	INC280 400 mg BID capsule N=4		INC280 600 mg BID capsule N=3		INC280 200 mg BID tablet N=3		INC280 400 mg BID tablet N=12		All patients N=44	
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 (%)**
Any AE	**4 (100)**	**2 (50.0)**	**3 (100)**	**0**	**3 (100)**	**1 (33.3)**	**12 (100)**	**5 (41.7)**	**42 (95.5)**	**15 (34.1)**
Blood Creatinine Increased	4 (100)	0	1 (33.3)	0	1 (33.3)	0	7 (58.3)	0	23 (52.3)	0
Nausea	2 (50.0)	0	2 (66.7)	0	0	0	8 (66.7)	0	21 (47.7)	0
Decreased Appetite	2 (50.0)	1 (25.0)	2 (66.7)	0	1 (33.3)	0	5 (41.7)	0	18 (40.9)	3 (6.8)
Vomiting	0	0	2 (66.7)	0	1 (33.3)	0	6 (50.0)	0	17 (38.6)	0

	INC280 400 mg BID capsule N=4		INC280 600 mg BID capsule N=3		INC280 200 mg BID tablet N=3		INC280 400 mg BID tablet N=12		All patients N=44	
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 (%)**
Diarrhoea	0	0	0	0	1 (33.3)	0	4 (33.3)	0	11 (25.0)	0
Hypoalbuminaemia	2 (50.0)	1 (25.0)	0	0	0	0	3 (25.0)	0	10 (22.7)	2 (4.5)
Oedema Peripheral	1 (25.0)	0	0	0	0	0	5 (41.7)	1 (8.3)	9 (20.5)	1 (2.3)
Malaise	2 (50.0)	0	1 (33.3)	0	2 (66.7)	0	2 (16.7)	0	8 (18.2)	0
Pyrexia	1 (25.0)	0	1 (33.3)	0	0	0	1 (8.3)	0	8 (18.2)	0
Anaemia	0	0	0	0	0	0	3 (25.0)	0	7 (15.9)	0
Constipation	0	0	0	0	0	0	2 (16.7)	0	7 (15.9)	0
Fatigue	1 (25.0)	0	1 (33.3)	0	0	0	3 (25.0)	0	7 (15.9)	0
Headache	1 (25.0)	0	1 (33.3)	0	0	0	1 (8.3)	0	5 (11.4)	0
Cough	0	0	0	0	0	0	2 (16.7)	0	5 (11.4)	0
Dry Skin	1 (25.0)	0	0	0	0	0	2 (16.7)	0	5 (11.4)	0
Amylase Increased	1 (25.0)	0	0	0	1 (33.3)	0	2 (16.7)	1 (8.3)	4 (9.1)	1 (2.3)
Gamma-Glutamyltransferase Increased	0	0	0	0	0	0	1 (8.3)	1 (8.3)	4 (9.1)	2 (4.5)
Hyponatraemia	2 (50.0)	2 (50.0)	0	0	0	0	1 (8.3)	1 (8.3)	4 (9.1)	4 (9.1)
Hypophosphataemia	1 (25.0)	0	0	0	0	0	2 (16.7)	1 (8.3)	4 (9.1)	2 (4.5)
Cancer Pain	0	0	0	0	0	0	1 (8.3)	0	4 (9.1)	0
Ascites	1 (25.0)	1 (25.0)	0	0	0	0	0	0	3 (6.8)	2 (4.5)
Alanine Aminotransferase Increased	0	0	0	0	0	0	1 (8.3)	0	3 (6.8)	1 (2.3)

	INC280 400 mg BID capsule N=4		INC280 600 mg BID capsule N=3		INC280 200 mg BID tablet N=3		INC280 400 mg BID tablet N=12		All patients N=44	
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 (%)
Aspartate Aminotransferase Increased	0	0	0	0	0	0	1 (8.3)	0	3 (6.8)	1 (2.3)
Weight Decreased	0	0	0	0	0	0	2 (16.7)	0	3 (6.8)	0
Hyperkalaemia	0	0	1 (33.3)	0	0	0	0	0	3 (6.8)	0
Tumour Pain	0	0	0	0	0	0	1 (8.3)	1 (8.3)	3 (6.8)	1 (2.3)
Dyspnoea	0	0	0	0	0	0	1 (8.3)	0	3 (6.8)	0
Pruritus	0	0	1 (33.3)	0	0	0	2 (16.7)	0	3 (6.8)	0
Rash	1 (25.0)	0	0	0	0	0	0	0	3 (6.8)	0
Hypotension	1 (25.0)	0	0	0	0	0	0	0	3 (6.8)	0

All patients including all cohorts (INC280 capsule 100 mg through 800 mg QD cohorts, 400 mg and 600 mg BID cohorts, and INC280 tablet 200 mg and 400 mg BID cohorts).

Overall summary of frequencies of deaths, serious adverse events, and other important adverse events by treatment group (safety set)

	INC280 100 mg QD capsule N=3	INC280 200 mg QD capsule N=4	INC280 400 mg QD capsule N=3	INC280 500 mg QD capsule N=4	INC280 600 mg QD capsule N=4	INC280 800 mg QD capsule N=4	INC280 400 mg BID capsule N=4	INC280 600 mg BID capsule N=3	INC280 200 mg BID tablet N=3	INC280 400 mg BID tablet N=12	All patients N=44

Category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All deaths	0	0	0	1 (25.0)	0	0	0	0	0	0	1 (2.3)
On-treatment deaths	0	0	0	0	0	0	0	0	0	0	0
SAEs	0	1 (25.0)	0	1 (25.0)	1 (25.0)	1 (25.0)	1 (25.0)	0	1 (33.3)	1 (8.3)	7 (15.9)
Suspected to be drug-related	0	0	0	0	1 (25.0)	0	0	0	1 (33.3)	0	2 (4.5)
AEs leading to discontinuation	0	0	0	0	0	1 (25.0)	0	1 (33.3)	1 (33.3)	1 (8.3)	4 (9.1)
Suspected to be drug-related	0	0	0	0	0	1 (25.0)	0	1 (33.3)	1 (33.3)	1 (8.3)	4 (9.1)
AEs requiring dose interruption and/or reduction	2 (66.7)	2 (50.0)	1 (33.3)	3 (75.0)	4 (100)	2 (50.0)	2 (50.0)	2 (66.7)	0	8 (66.7)	26 (59.1)
Suspected to be drug-related	1 (33.3)	0	1 (33.3)	2 (50.0)	3 (75.0)	1 (25.0)	1 (25.0)	1 (33.3)	0	7 (58.3)	17 (38.6)

Other Relevant Findings

N/A

The data support the further clinical development of INC280;

- The highest studied dose determined to be safe of INC280 tablet formulation as single agent was 400 mg BID, which had been declared as the recommended phase II dose for INC280 as single agent and in combination with gefitinib in the future studies.
- Overall, INC280 was well tolerated with a manageable safety profile.
- Eight patients (18.18%) had a best overall response of stable disease.

Date of Clinical Trial Report

6 September 2016