Science For A Better Life

Clinical Study Synopsis

This Clinical Study Synopsis is provided for patients and healthcare professionals to increase the transparency of Bayer's clinical research. This document is not intended to replace the advice of a healthcare professional and should not be considered as a recommendation. Patients should always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labelling information approved for the patient's country or region. Data in this document or on the related website should not be considered as prescribing advice.
The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Date of study report:	19-Jun-2018
Study title:	An open label, Phase I study to evaluate the safety, tolerability, pharmacokinetics and efficacy of BAY 1163877 in Japanese subjects with refractory, locally advanced or metastatic solid tumors
Sponsor's study number:	16958
NCT number:	NCT02592785
EudraCT number:	Not applicable
Sponsor:	Bayer Yakuhin
Clinical phase:	Phase 1
Study objectives:	**Primary objectives:** • Safety • Tolerability • Pharmacokinetics (PK) **Secondary objectives:** • Biomarker status, • Pharmacodynamic parameters, • Tumor response …of BAY 1163877 in Japanese subjects with refractory, locally advanced or metastatic solid tumors.
Test drug:	Rogaratinib (BAY1163877)
Name of active ingredient(s):	Rogaratinib
Dose:	600 mg bid (1200 mg/day, cohort 1), 800 mg bid (1600 mg/day, cohort 2) Single dose on Cycle 1, Day 1/ twice daily from Cycle 1, Day 3 and beyond
Route of administration:	Oral
Duration of treatment:	Single-administration of BAY 1163877 was done in the morning of Cycle 1, Day 1. Starting on Cycle 1, Day 3, BAY 1163877 was administered twice daily for the remaining 19 days of Cycle 1. For subsequent cycles,

	BAY 1163877 was administered twice daily for 21 days each cycle. Subjects continued dosing until tumor progression, unacceptable toxicity, consent withdrawal, or withdrawal from the study at the discretion of the investigator.
Reference drug:	Not applicable
Indication:	Refractory, locally advanced or metastatic solid tumors
Diagnosis and main criteria for inclusion:	**Inclusion criteria:** • Japanese male or female subjects must be 20 years at the first time of informed consent • Subjects with histologically or cytologically confirmed, refractory, locally advanced or metastatic solid tumors who are not amenable to any standard therapy or candidates for standard therapy at discretion of investigators. • Ability to understand and willingness to sign the written subject information sheet / informed consent form for fibroblast growth factor receptor (FGFR)1/2/3 expression (all subjects) / FGFR3 mutation testing (only bladder cancer subjects). Signed informed consent has to be obtained before any study specific procedure regarding FGFR1/2/3 expression / FGFR3 mutation testing. • Ability to understand and willingness to sign the written subject information sheet / informed consent form for study enrollment eligibility (excluding FGFR1/2/3 expression / FGFR3 mutation testing) Signed informed consent obtained before any (further) study. • Existence of archival or fresh tumor tissue for FGFR1/2/3 expression (all subjects) / FGFR3 mutation testing (only bladder cancer subjects). • Subjects enrolled must present high FGFR expression levels based on archival or fresh tumor biopsy specimen analysis. Bladder cancer subjects with low overall FGFR expression levels can be included if activating FGFR3 mutations are confirmed. • Subjects must have at least one measurable or evaluable lesion according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). • Subjects with resected primary tumors who have documented metastases are eligible. • Life expectancy of at least 3 months. • Recovery to National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.03 (CTCAE v4.03) Grade < 2 level or recovery to baseline preceding the prior treatment from any previous drug / procedure-related toxicity (subjects with persistent alopecia, anemia, and/or hypothyroidism can be included). • Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0, 1, or 2.

- Adequate bone marrow, liver and renal function as assessed by laboratory requirements below:
  - Hemoglobin (Hb) ≥ 9.0 g/dL
  - Absolute neutrophil count (ANC) ≥ 1,500/mm3
  - Platelet count ≥ 75,000/mm3
  - Total bilirubin ≤ 1.5 times the upper limit of normal (ULN).
- Documented or diagnosed constitutional jaundice such as Gilbert syndrome is allowed if total bilirubin is mildly elevated (< 6 mg/dL).
- Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≤ 2.5 times ULN (≤ 5 times ULN for subjects with liver involvement of their cancer)
- Alkaline phosphatase ≤ 2.5 times ULN (≤ 5 times ULN for subjects with liver involvement of their cancer)
- Amylase and/or lipase ≤ 2.5 times ULN
- Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m2, according to the Modified Diet in Renal Disease (MDRD) abbreviated formula
- Prothrombin time-International normalized ratio (PT-INR) and activated partial thromboplastin time (APTT) ≤ 1.5 times ULN.
- Subjects being treated with anticoagulant, e.g. warfarin or heparin, was allowed to participate provided no prior evidence of an underlying abnormality in these parameters exists.
- Women of childbearing potential regardless of menorrhea or amenorrhea and men must agree to use adequate birth control measures from the time of signing of the informed consent form until at least 3 months after the last study drug administration.
- Women of childbearing non potential are defined as:
  - Age >50 years with amenorrhea for at least 12 months
  - Age ≤50 years with 6 months of spontaneous amenorrhea and follicle stimulating hormone level within postmenopausal range (>40 mIU/mL)
  - Bilateral oophorectomy
- Negative serum and/or urine pregnancy test in women of childbearing potential.

Exclusion criteria:

- Impaired cardiac function or clinically significant cardiac disease (i.e., congestive heart failure (CHF) New York Heart Association (NYHA) Class III or IV), unstable angina (symptoms of angina at rest) or newonset angina (within last 3 months) or myocardial infarction within past 6 months and cardiac arrhythmias requiring anti-arrhythmic therapy (beta-blockers or digoxin are permitted).
- Left ventricular ejection fraction (LVEF) < 50% as assessed by echocardiography performed

	• Subjects with history and/or current evidence of endocrine alteration of calcium phosphate homeostasis (e.g. parathyroid disorder, history of parathyroidectomy, tumor lysis, tumoral calcinosis). Calcium (Ca) x (time) phosphate (PO4) should be < 70 mg^2/dL^2. • Current evidence of corneal disorder / keratopathy including but not limited to bullous / band keratopathy, corneal abrasion, inflammation / ulceration, keratoconjunctivitis etc. (to be confirmed by ophthalmologic examination). Pre-existing cataract is not an exclusion criterion. • Moderate or severe hepatic impairment requiring therapy (subjects with Child-Pugh score B or C cannot be included.) • Known human immunodeficiency virus (HIV) infection • Subjects with an active hepatitis B and/or C infection requiring treatment • Anticancer chemotherapy or immunotherapy during the study or within 5-half-lives of anticancer chemotherapy or immunotherapy before start of study treatment. • Systolic blood pressure ≤ 110 and pulse rate ≥ 100/min, or diastolic blood pressure ≤ 60 mmHg and pulse rate ≥ 100/min • Uncontrolled hypertension as indicated by a systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg
Study design:	The study is an open-label, non-randomized, dose-escalation study of BAY 1163877 (as hydrochloride) orally given twice daily at 600 mg and 800 mg in sequential cohorts of subjects with refractory, locally advanced or metastatic solid tumors.
Methodology:	The study was composed of 2 cohorts. The dose of Cohort 1 was 600 mg BID, followed by 800 mg BID in Cohort 2. Three to 6 and 6 Japanese subjects were planned to be enrolled in Cohorts 1 and 2, respectively. The decision to proceed to Cohort 2 was based on safety variables during Cycle 1 (21 days) of 3 subjects in Cohort 1. As no doselimiting toxicity (DLT) was seen in these 3 subjects, all subsequent subjects were enrolled in Cohort 2. Safety and tolerability evaluations included: physical examinations, vital signs, electrocardiograms (ECGs), left ventricular ejection fraction (LVEF) assessment, eye examinations, adverse events (AEs), concomitant medications and laboratory tests. Each subject was regularly assessed during each cycle for potential AEs and disease related signs and symptoms according to CTCAE, v4.03. The PK of rogaratinib was evaluated on Day 1 in Cycle 1 after single-dose administration, and on Day 15 in Cycle 1 during multiple-dose administration of BID rogaratinib in Cohorts 1 and 2. In addition, PK blood sampling was performed for long-term PK assessment on Day 1 through Cycles 2 to 5. Tumor response was evaluated by the site investigator using RECIST v1.1

	at every 2nd cycle. For biomarker evaluations, FGFR1/2/3 expression was examined in all subjects using fresh or archival tumor tissue. The testing was performed prospectively. Subjects tested to have high FGFR1/2/3 expression were enrolled. FGFR3 mutations were examined in bladder cancer subjects; bladder cancer subjects with FGFR3 mutation could be enrolled even if they had low overall FGFR expression levels. Serum levels of fibroblast growth factor (FGF)23 and phosphate were measured as pharmacodynamic parameters.
Study center(s):	The study was conducted at 2 study centers in Japan.
Publication(s) based on the study (references):	None at the time of report creation
Study period:	**Study Start Date:** 15-Dec-2015 **Study Completion Date:** 06-Dec-2017
Early termination:	Not aplicable
Number of subjects:	**Planned:** 12 **Analyzed:** 09

Criteria of evaluation:	The primary endpoints of the study were the number and intensity of all treatment-emergent AEs (TEAEs) and PK parameters **Primary Endpoints:** *Safety parameters - Treatment-emergent Adverse Events* • Number of TEAEs • Intensity of TEAEs *PK parameters:* • Cycle 1, Day 1 single dose: Cmax, Cmax,norm, Cmax/D, AUC(0-12), AUC(0-12)norm, AUC(0-12)/D, AUC(0-tlast), AUC(0-tlast)norm, AUC(0-tlast)/D, AUC, AUCnorm, and AUC/D • Cycle 1, Day 15 multiple dose: Cmax,md, Cmax,norm, md, Cmax/Dmd, AUC(0-12)md, AUC(0-12) norm,md, AUC(0-12)/Dmd, AUC(0-tlast)md, AUC(0-tlast) norm,md, and AUC(0-tlast)/Dmd. *(AUC may not have been calculated if it was not possible to estimate half-life.)* **Secondary Endpoints:** *PK parameters:* • tmax, tlast, t1/2 in Cycle 1, Day 1 • tmax,md and tlast,md in Cycle 1, Day 15. *Pharmacodynamic parameters:* • Serum phosphate concentrations • Serum FGF23 concentrations *Biomarkers:* • FGFR1/2/3 mRNA expression in fresh or archival tumor tissue *Efficacy parameters:* • Tumor response based on RECIST 1.1 criteria
Statistical methods:	Statistical analysis was performed using SAS; the version used is specified in the statistical analysis plan. All data were listed and study summary tables provided where appropriate. Quantitative data were described using summary statistics. Summary statistics were provided for the original data as well as for the change versus baseline, where appropriate. Frequency tables were provided for qualitative data. **Adverse events** Individual listings of DLT and AEs were provided. The incidence of TEAEs and drug-related TEAEs, respectively, were summarized by cohort in frequency tables using worst CTCAE v4.03 grade. Serious AEs (SAEs) were also summarized and listed. The analysis was also done

	using Medical Dictionary for Regulatory Activities (MedDRA) terms. **Pharmacokinetic analyses** The concentration-times courses of all analytes were tabulated for each cohort. The following statistics were calculated for each of the sampling points: arithmetic mean, standard deviation and coefficient of variation (CV), geometric mean, geometric standard deviation (re-transformed standard deviation of the logarithms) and geometric CV, minimum, median, maximum value and the number of measurements Individual and geometric mean concentration vs. time curves of all analytes were plotted by treatment using both linear and semi-logarithmic scale. Pharmacokinetic characteristics (tmax and tlast excluded) were summarized by the statistics mentioned above. tmax and tlast were described by minimum, maximum and median as well as frequency counts.
Substantial protocol changes:	There was one global amendment to the original study protocol, Version 1.0, dated 27 Aug 2015: Protocol Amendment 01 (global amendment), forming integrated protocol Version 2.0, dated 16 SEP 2015, introduced the following clinically relevant/major change: • The duration of the hospitalization period was modified.

Subject disposition and baseline

Disposition

After pre-screening for FGFR1/2/3 mRNA expression, 9 subjects with advanced malignancies were enrolled (screened) sequentially at 2 study centers in Japan. All 9 subjects were treated with rogaratinib and were valid for all analyses. Three subjects (33.3%) were treated in Cohort 1 at 600 mg rogaratinib, and 6 subjects (66.6%) were treated in Cohort 2 at 800 mg rogaratinib.
All 9 subjects discontinued treatment. The primary reason for termination of treatment was radiological disease progression (6 subjects, 66.7%); the other reason was the occurrence of AE(s) not associated with clinical disease progression (3 subjects, 33.3%).

Results

Clinical pharmacology evaluation

Interpretation of these results should take into account the small sample size and the difference in sample size between the 2 cohorts (3 versus 6 subjects) and the heterogeneity of the treated population.

Pharmacokinetic evaluation

Single oral (tablet) doses of 600 mg and 800 mg rogaratinib reached peak plasma concentrations approximately 1 to 6hours after administration (tmax ranges: 1.78 - 5.95 hours and 0.95 - 2.02 hours, respectively), and after multiple twice-daily dosing, peak plasma concentrations were reached

between 1 and 4 hours (with tmax ranges: 0.967 - 3.93 hours and 1.02 - 2.98 hours, respectively). Maximum (peak) plasma concentrations (Cmax) and AUC of rogaratinib increased with dose. Dose-normalized AUC showed no relevant differences between the 2 doses following both single and multiple dosing, indicating that exposure of rogaratinib showed dose proportionality in this dosing range in general.

Table 1 and Table 2 provide the results for selected PK parameters for rogaratinib.

Table 1: Summary statistics (geometric mean [G-CV%]) of PK parameters of rogaratinib in plasma up to 48 hours following a single dose on Cycle 1, Day 1 (PKS)

		Cohort 1			Cohort 2	
Parameter	Unit	n	Geom. Mean	Geom. CV (%)	n	Geom. Mean	Geom. CV (%)
AUC	ug*h/L	3	44072	88.7	6	60793	46.9
AUC(0-t_{last})	ug*h/L	3	43665	87.7	6	60130	46.9
AUC(0-12)	ug*h/L	3	32321	75.7	6	51906	39.8
%AUC($t_{last-inf}$)	%	3	0.586	226	6	0.841	124
AUC(0- t_{last})/D	h/L	3	0.0728	87.7	6	0.0752	46.9
AUC(0-12)/D	h/L	3	0.0539	75.7	6	0.0649	39.8
AUC/D	h/L	3	0.0735	88.7	6	0.0760	46.9
AUC(0- t_{last})$_{norm}$	kg*h/L	3	4.44	98.6	6	4.88	43.5
AUC(0-12)$_{norm}$	kg*h/L	3	3.29	80.2	6	4.21	38.1
AUC$_{norm}$	kg*h/L	3	4.48	99.9	6	4.935	43.3
C_{max}	ug/L	3	5396	87.8	6	12492	27.7
C_{max}/D	/L	3	0.00899	87.8	6	0.0156	27.7
$C_{max,norm}$	kg/L	3	0.549	74.8	6	1.014	25.6
$t_{1/2}$	hours	3	7.120	12.7	6	7.67	51.0
CL/F	L/h	3	13.6	88.7	6	13.2	46.9
t_{max}	hours	3	3.83[a]	1.78 - 5.95[b]	6	1.91[a]	0.95 - 2.02[b]

a = median; b = range
%AUC($t_{last-inf}$) = AUC from tlast to infinity in %; AUC = area under the plasma concentration vs time curve from zero to infinity; AUC/D = AUC divided by dose; AUC$_{norm}$ = area under the curve divided by dose per kg body weight; AUC(0-12) = AUC from time zero to 12 hours; AUC(0-12)/D = AUC(0-12) divided by dose; AUC(0-12)$_{norm}$ = AUC(0-12) divided by dose per kg body weight; AUC(0-t_{last}) = AUC from time zero to the last concentration > LLOQ; AUC(0- t_{last})/D = AUC(0-t_{last}) divided by dose; AUC(0- t_{last})$_{norm}$ = AUC(0-t_{last}) divided by dose per kg body weight; CL/F = apparent oral clearance; C_{max} = maximum observed drug concentration in plasma; C_{max}/D = C_{max} divided by dose; $C_{max,norm}$ = C_{max} divided by dose per kg body weight; Geom. = geometric; Geom. CV = geometric coefficient of variation; LLOQ = lower limit of quantification; $t_{1/2}$ = half-life associated with the terminal slope; t_{last} = time of last plasma concentration above LLOQ; t_{max} = time to reach maximum drug concentration in plasma

Table 2: Summary statistics (geometric mean [G-CV%]) of PK parameters of rogaratinib in plasma up to 12 hours following multiple doses on Cycle 1, Day 15 (PKS)

		Cohort 1			Cohort 2		
Parameter	Unit	n	Geom. Mean	Geom. CV (%)	n	Geom. Mean	Geom. CV (%)
$AUC(0\text{-}t_{last})_{md}$	ug*h/L	2	51070	8.30	3	62325	38.5
$AUC(0\text{-}12)_{md}$	ug*h/L	2	51042	8.22	3	62538	37.8
$AUC(0\text{-}t_{last})/D_{md}$	h/L	2	0.0851	8.30	3	0.0779	38.5
$AUC(0\text{-}12)/D_{md}$	h/L	2	0.0851	8.22	3	0.0782	37.8
$AUC(0\text{-}t_{last})_{norm,md}$	kg*h/L	2	5.62	6.15	3	5.64	10.2
$AUC(0\text{-}12)_{norm,md}$	kg*h/L	2	5.61	6.07	3	5.66	10.04
$C_{max,md}$	ug/L	2	7582	16.8	3	11586	40.5
C_{max}/D_{md}	/L	2	0.0126	16.8	3	0.0145	40.5
$C_{max,norm,md}$	kg/L	2	0.834	14.6	3	1.048	9.66
$t_{max,md}$	hours	2	2.45	0.967 - 3.93	3	2.05	1.02 - 2.98

a = median; b = range
AUC = area under the plasma concentration vs time curve from zero to infinity;
AUC(0-12) = AUC from time zero to 12 hours; $AUC(0\text{-}12)/D_{md}$ = AUC(0-12) after multiple administrations divided by dose; $AUC(0\text{-}12)_{md}$ = AUC(0-12) after multiple administrations; $AUC(0\text{-}12)_{norm,md}$ = AUC(0-12) after multiple administrations divided by dose per kg body weight; $AUC(0\text{-}t_{last})_{md}$ = $AUC(0\text{-}t_{last})$ after multiple administrations; $AUC(0\text{-}t_{last})/D_{md}$ = $AUC(0\text{-}t_{last})$ after multiple administrations divided by dose; $AUC(0\text{-}t_{last})_{norm,md}$ = $AUC(0\text{-}t_{last})$ after multiple administrations divided by dose per kg body weight; C_{max}/D_{md} = C_{max} after multiple administrations divided by dose; $C_{max,md}$ = C_{max} after multiple administrations; $C_{max,norm,md}$ = C_{max} divided by dose per kg body weight; Geom. = geometric; Geom. CV = geometric coefficient of variation; LLOQ = lower limit of quantification; t_{last} = time of last plasma concentration above LLOQ; $t_{max,md}$ = time to reach maximum drug concentration in plasma after multiple administrations

Pharmacodynamic evaluation
Following administration of rogaratinib, serum phosphate levels increased from baseline with a similar maximum mean increase at Cycle 2, Day 1 regardless of dose (approximate 2-fold increase from baseline).
There were no clear changes in FGF23 levels in response to rogaratinib administration in this study.

Safety evaluation
All 9 subjects (100.0%) included in the SAF reported at least 1 TEAE, and 8 subjects (88.9%) reported at least 1 drug-related TEAE, irrespective of seriousness, severity and causality classification (Table 3). Most TEAEs were Grade 1 or 2 (mild or moderate).
There were no deaths, and no DLTs during the study. One subject in Cohort 2 (800 mg bid) experienced TESAEs of pharyngeal haemorrhage and dysphagia; these were not considered to be related to study treatment.
Common TEAEs (MedDRA preferred term [PT]) were hyperphosphataemia (88.9%), constipation (44.4%), diarrhea (33.3%), stomatitis (33.3%), and dysgeusia (33.3%). All other TEAEs were reported by 2 subjects or fewer (22.2%).
Two out of 9 subjects (22.2%) reported at least 1 TEAE of CTCAE Grade 3 (severe) (1 subject in each cohort), and 2/9 subjects (22.2%) reported at least 1 TEAE of CTCAE Grade 4 (life-threatening) (both in Cohort 2) (Table 4).

Drug-related TEAEs were reported for 8 out of 9 subjects (88.9%). Six subjects (66.7%) had at least 1 drug-related TEAE with a worst CTCAE toxicity of Grade 2, and 2 subjects (22.2%) had drug-related Grade 3 TEAEs: alanine aminotransferase increased and hyponatraemiano drug-related SAEs.
Treatment with rogaratinib was interrupted in 8 out of 9 subjects (88.9%); 3 subjects in Cohort 1 (100.0%) and 5 subjects in Cohort 2 (83.3%). There were dose reductions in 4 out of 9 subjects (44.4%); 1 subject in Cohort 1 (33.3%) and 3 subjects in Cohort 2 (50.0%).
Treatment with rogaratinib was permanently discontinued in 3 out of 9 subjects (33.3%); 1 subject in Cohort 1 (33.3%) and 2 subjects in Cohort 2 (33.3%). The most common reason for study drug interruption was hyperphosphataemia, occurring in 7 of the 8 subjects who had interruptions. Hyperphosphataemia was also the reason for dose reductions in 3 subjects (33.3%), and discontinuation in 1 subject (11.1%).

No AEs of retinal disorders were reported.

Table 3: Overview of treatment-emergent adverse events (Safety analysis set)

		Cohort 1 N=3 (100%)	Cohort 2 N=6 (100%)	Total N=9 (100%)
Number (%) of subjects				
Any AE		3 (100.0%)	6 (100.0%)	9 (100.0%)
Worst grade	Grade 1	0	0	0
	Grade 2	2 (66.7%)	3 (50.0%)	5 (55.6%)
	Grade 3	1 (33.3%)	1 (16.7%)	2 (22.2%)
	Grade 4	0	2 (33.3%)	2 (22.2%)
	Grade 5 (death)	0	0	0
Serious		0	1 (16.7%)	1 (11.1%)
Leading to dose modification[a]		3 (100.0%)	5 (83.3%)	8 (88.9%)
Leading to permanent discontinuation of study drug		1 (33.3%)	2 (33.3%)	3 (33.3%)
Any drug-related AE		3 (100.0%)	5 (83.3%)	8 (88.9%)
Worst grade	Grade 1	0	0	0
	Grade 2	2 (66.7%)	4 (66.7%)	6 (66.7%)
	Grade 3	1 (33.3%)	1 (16.7%)	2 (22.2%)
	Grade 4	0	0	0
	Grade 5 (death)	0	0	0
Serious		0	0	0
Leading to dose modification[a]		3 (100.0%)	5 (83.3%)	8 (88.9%)
Leading to permanent discontinuation of study drug		1 (33.3%)	1 (16.7%)	2 (22.2%)

Any AE also includes subjects with grade not available for all adverse events.
a Modifications include interruptions and reductions
CTCAE Version 4.03

Table 4: Treatment-emergent adverse events by MedDRA Version 20.1, only CTCAE Grade ≥3 events (SAF)

Primary system organ class (SOC) Preferred term (PT) (alphabetical order)	CTCAE grade	Cohort 1 N=3 (100%)	Cohort 2 N=6 (100%)	Total N=9 (100%)
Number (%) of subjects				
All system organ classes	Any Grade ≥3	1 (33.3%)	3 (50.0%)	4 (44.4%)
	Grade 3	1 (33.3%)	1 (16.7%)	2 (22.2%)
	Grade 4	0	2 (33.3%)	2 (22.2%)
	Grade 5 (death)	0	0	0
Gastrointestinal disorders		0	1 (16.7%)	1 (11.1%)
Dysphagia	Grade 3	0	1 (16.7%)	1 (11.1%)
Investigations		0	2 (33.3%)	2 (22.2%)
Alanine aminotransferase increased	Grade 3	0	1 (16.7%)	1 (11.1%)
Lipase increased	Grade 4	0	1[a] (16.7%)	1 (11.1%)
White blood cell count increased	Grade 3	0	1 (16.7%)	1 (11.1%)
Metabolism and nutrition disorders		1 (33.3%)	2 (33.3%)	3 (33.3%)
Hypertriglyceridaemia	Grade 4	0	1[b] (16.7%)	1 (11.1%)
Hyponatraemia	Grade 3 or 4			2 (22.2%)
	Grade 3	1 (33.3%)		
	Grade 4		1[a] (16.7%)	
Hypophosphataemia	Grade 3	0	1 (16.7%)	1 (11.1%)
Respiratory, thoracic and mediastinal disorders		0	1 (16.7%)	1 (11.1%)
Pharyngeal haemorrhage	Grade 3	0	1 (16.7%)	1 (11.1%)

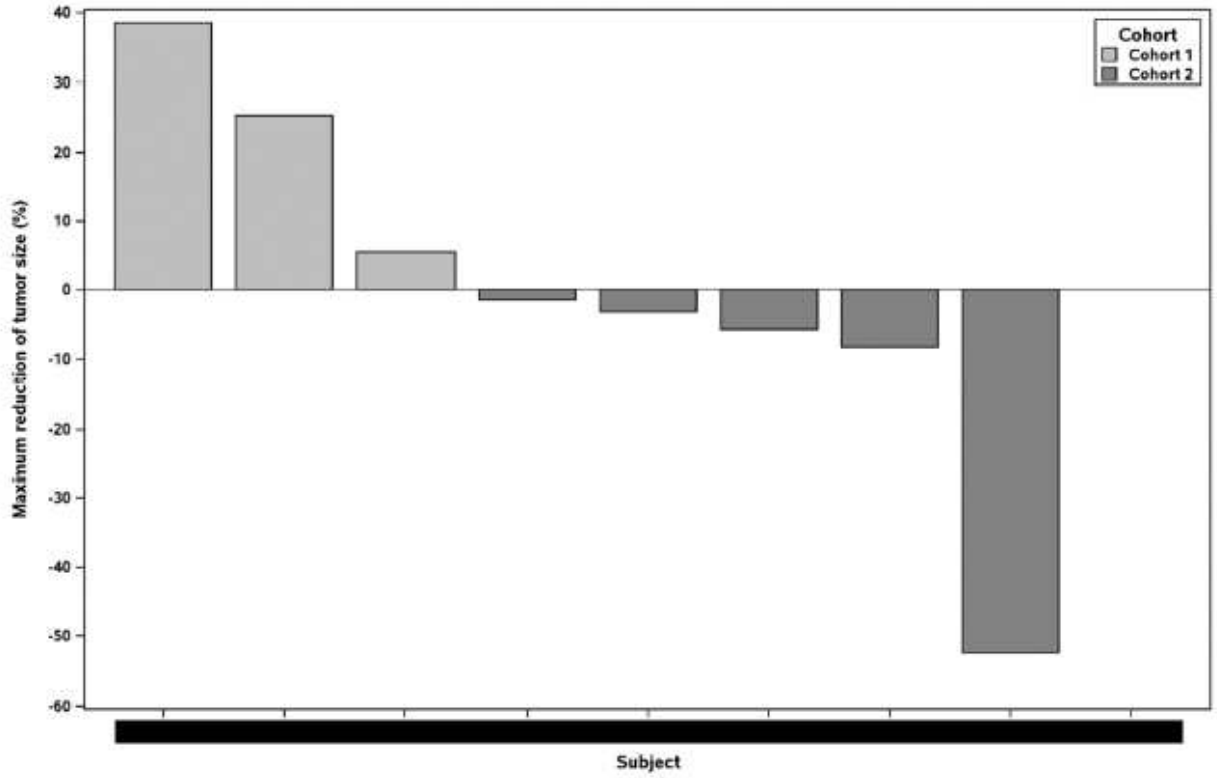
a
b [redacted]
MedDRA Version 20.1
CTCAE Version 4.03

Efficacy evaluation

All 9 subjects were evaluable for the assessment of tumor response based on the RECIST 1.1 criteria. No complete responses (CR) were reported during the study. One subject receiving 800 mg bid rogaratinib had a best response rating of partial response (PR) after 4 cycles of treatment (which continued through his 13 cycles of treatment), 5 subjects had a best response rating of stable disease (SD), and 3 subjects had a best response rating of progressive disease (PD). The disease control rate, i.e. CR, PR or SD was 83.3% in subjects receiving the 800 mg dose and 33.3% in subjects receiving the 600 mg dose.
The median time to progression was 199 days (range 6-324) in subjects receiving the 800 mg dose and 38 days (range 35-38) in subjects receiving the 600 mg dose.

The change in size of target lesions is shown in Figure 1.

Figure 1: Maximum percent reduction in the size of target lesions (FAS)



Biomarkers evaluation

The biomarker data are summarized in Table 5.

All 9 subjects had high levels of expression of at least one of the FGFR types.

Table 5: Biomarker investigations (FAS)

Subject	Location	Origin	FGFR1[a]	FGFR2[a]	FGFR3[a]
Cohort 1					
[redacted]	Lymph node	Metastasis	96.02	289.12	867.90
	Nasal cavity	Metastasis	886.42	58.46	4243.72
	Lymph node	Lymph node	142.09	442.01	1480.46
Cohort 2					
[redacted]	Nasopharynx	Primary tumor	170.87	547.91	2204.28
	Middle lobe lung	Metastasis	2526.21	1065.04	130.44
	Liver	Primary tumor	1.43	151.30	1504.22
	Cervical lymph node	Lymph node	923.75	1490.00	6657.35
	Ear	Primary tumor	928.10	1307.71	7.58
	Lung	Primary tumor	1198.37	308.65	1474.03

a Result or finding in original units. All values are given in normalized Nanostring fluorescence signal intensity counts; 800 counts were defined as a cut-off for eligibility based on preclinical response data.

Nine FGFR mRNA-positive subjects were enrolled into the study after pre-screening for FGFR1/2/3 mRNA expression.

Overall conclusions

- Multiple (bid) oral doses of 600 and 800 mg rogaratinib were well tolerated in Japanese subjects with refractory, locally advanced or metastatic solid tumors.
- Overall, the toxicities observed in Japanese subjects were consistent with the known safety profile of rogaratinib.
- Peak plasma concentrations of rogaratinib were achieved by 4 hours after single and multiple (bid) doses of 600 mg and 800 mg. The Cmax and AUC of rogaratinib increased with dose.
- The exposure of rogaratinib was dose proportional following both single and multiple (bid) dosing at 600 and 800 mg.
- Regarding the levels of pharmacodynamic variables, serum phosphate was clearly increased at Cycle 2, Day 1 (approximately 2-fold versus baseline) in both cohorts, whereas there was no clear trend in the changes observed in FGF23 following administration of rogaratinib.
- The best tumor response was PR in one subject in Cohort 2. A better tumor response was observed in subjects receiving 800 mg bid rogaratinib, with 5 subjects (83.3%) having controlled disease (CR, PR or SD; RECIST 1.1) at this dose, compared to 1 subject at the 600 mg dose (33.3%). The median time to progression in subjects receiving 800 mg bid rogaratinib was 199 days (range 6-324).