Clinical trial results:
A randomized, open label, multicenter Phase 2/3 study to evaluate the efficacy and safety of rogaratinib (BAY 1163877) compared to chemotherapy in patients with FGFR-positive locally advanced or metastatic urothelial carcinoma who have received prior platinumcontaining-chemotherapy

Summary

EudraCT number	2016-004340-11
Trial protocol	GB IE NL FR AT CZ ES PT FI SK HU DK BE SE PL IT
Global end of trial date	27 October 2020

Results information

Result version number	v1 (current)
This version publication date	30 October 2021
First version publication date	30 October 2021

Trial information

Trial identification

Sponsor protocol code	17403

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03410693
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser Wilhelm Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 December 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective for the Phase 2 part of the study was to demonstrate the efficacy of rogaratinib over chemotherapy (docetaxel, paclitaxel, or vinflunine) in terms of ORR of urothelial carcinoma patients with FGFR positive tumors. The original objective of the Phase 3 part of the study was to demonstrate the superiority of rogaratinib over chemotherapy in terms of prolonging the overall survival (OS) of urothelial carcinoma patients with FGFR positive tumors. Once the decision was made to not conduct the Phase 3 part of the study, OS was then considered an exploratory efficacy variable for Phase 2.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 May 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	China: 4
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Ireland: 6
Country: Number of subjects enrolled	Israel: 4

Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Japan: 14
Country: Number of subjects enrolled	Korea, Republic of: 15
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Portugal: 5
Country: Number of subjects enrolled	Russian Federation: 6
Country: Number of subjects enrolled	Slovakia: 4
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Taiwan: 14
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	175
EEA total number of subjects	96

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	55
From 65 to 84 years	119
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This study enrolled participants at 111centers in 28 countries from 31 MAY 2018 (first participant first visit) to 27 OCT 2020 (last participant last visit).

Pre-assignment

Screening details:

A total of 718 participants signed the informed consent for prescreening, of which 256 participants completed the prescreening, while 462 participants discontinued the prescreening. The discontinuations were due to screening failure (322), other reasons (98), withdrawal by the participant (22), and death (20).

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Rogaratinib (BAY1163877)_overall population

Arm description:

Participants who were randomized to this group following a 1:1 ratio received rogaratinib 600 mg orally twice a day (b.i.d.) continuously, during a 21-day treatment cycle.

Arm type	Experimental
Investigational medicinal product name	Rogaratinib
Investigational medicinal product code	BAY1163877
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Rogaratinib 600 mg (consisting of 3 tablets à 200 mg) was taken orally (p.o.) twice a day (b.i.d.), continuously, during a 21-day treatment cycle.

Arm title	Chemotherapy_overall population

Arm description:

Participants who were randomized to this group following a 1:1 ratio received chemotherapy (docetaxel, paclitaxel or vinflunine) at the discretion of the investigator, as intravenous (i.v.) infusion once every three weeks (on day 1 of a 21-day cycle).

Arm type	Active comparator
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

The starting dose for docetaxel was 75 mg/m² given as i.v. infusion, once every three weeks (on day 1 of a 21-day cycle).

Investigational medicinal product name	Vinflunine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details: The starting dose for vinflunine was 320 mg/m² given as i.v. infusion, once every three weeks (on day 1 of a 21-day cycle).	
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: The starting dose for paclitaxel was 175 mg/m² given as i.v. infusion, once every three weeks (on day 1 of a 21-day cycle).	

Number of subjects in period 1	Rogaratinib (BAY1163877)_overall population	Chemotherapy_overall population
Started	87	88
Started treatment	86	82
Active follow-up performed	61	56
Entered long term follow-up	56	69
Completed	0	0
Not completed	87	88
Disc trt: Lost to follow up	-	1
Disc trt: Withdrawal by participant	6	4
Disc trt: radiological progression	58	50
Disc trt:AE not asso. w/ clinical disease progress	1	4
Discontinued (disc) treatment (trt): Death	6	4
Study drug never administered	1	6
Disc trt: clinical progression	1	5
Disc trt: Physician decision	-	5
Disc trt: Adverse Event (AE)	13	9
Disc trt: Other	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Rogaratinib (BAY1163877)_overall population
Reporting group description:	
Participants who were randomized to this group following a 1:1 ratio received rogaratinib 600 mg orally twice a day (b.i.d.) continuously, during a 21-day treatment cycle.	
Reporting group title	Chemotherapy_overall population
Reporting group description:	
Participants who were randomized to this group following a 1:1 ratio received chemotherapy (docetaxel, paclitaxel or vinflunine) at the discretion of the investigator, as intravenous (i.v.) infusion once every three weeks (on day 1 of a 21-day cycle).	

Reporting group values	Rogaratinib (BAY1163877)_overall population	Chemotherapy_overall population	Total
Number of subjects	87	88	175
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	23	32	55
From 65-84 years	64	55	119
85 years and over	0	1	1
Age continuous Units: years			
arithmetic mean	67.7	66.4	
standard deviation	± 8.3	± 10.3	-
Gender categorical Units: Subjects			
Female	75	70	145
Male	12	18	30
Race Units: Subjects			
White	55	55	110
Black or African American	1	0	1
Asian	23	25	48
Not reported	8	8	16
Ethnicity Units: Subjects			
Not Hispanic or Latino	76	78	154
Hispanic or Latino	1	0	1
Not reported	10	10	20
Cancer Category Units: Subjects			

Location of primary cancer: bladder	56	45	101
Location of primary cancer: Ureter	17	14	31
Location of primary cancer: Renal pelvis	12	28	40
Location of primary cancer: Proximal urethra	2	1	3
Cancer stage at study entry Units: Subjects			
Stage III B	1	3	4
Stage IV	5	12	17
Stage IV A	13	24	37
Stage IV B	67	48	115
Unknown	1	1	2
PIK3CA and/or RAS activating mutations			
PIK3CA: Phosphoinositide 3 kinase, catalytic subunit alpha isoform RAS: Rat sarcoma			
Units: Subjects			
Absent	65	69	134
Present	10	10	20
Unknown	12	9	21
FGFR expression from Targos			
FGFR: Fibroblast growth factor receptor			
Units: Subjects			
Negative	13	14	27
Positive	69	69	138
Not assessed	5	5	10

End points

End points reporting groups

Reporting group title	Rogaratinib (BAY1163877)_overall population
Reporting group description:	
Participants who were randomized to this group following a 1:1 ratio received rogaratinib 600 mg orally twice a day (b.i.d.) continuously, during a 21-day treatment cycle.	
Reporting group title	Chemotherapy_overall population
Reporting group description:	
Participants who were randomized to this group following a 1:1 ratio received chemotherapy (docetaxel, paclitaxel or vinflunine) at the discretion of the investigator, as intravenous (i.v.) infusion once every three weeks (on day 1 of a 21-day cycle).	
Subject analysis set title	Rogaratinib_WT population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Wild type population	
Subject analysis set title	Chemotherapy_WT population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Wild type population	

Primary: Objective response rate (ORR) - central assessment

End point title	Objective response rate (ORR) - central assessment
End point description:	
ORR is defined as the percentage of participants with complete response (CR) or partial response (PR). participants for whom overall best response is not CR or PR, as well as participants without any post-baseline tumor assessment will be considered non-responders.	
End point type	Primary
End point timeframe:	
From start of treatment up to end of active follow-up	

End point values	Rogaratinib (BAY1163877)_overall population	Chemotherapy_overall population	Rogaratinib_WT population	Chemotherapy_WT population
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	87	88	62	63
Units: percentage				
number (confidence interval 95%)	19.5 (11.8 to 29.4)	21.6 (13.5 to 31.6)	19.4 (10.4 to 31.4)	23.8 (14.0 to 36.2)

Statistical analyses

Statistical analysis title	ORR difference_overall population
Comparison groups	Rogaratinib (BAY1163877)_overall population v Chemotherapy_overall population

Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6991
Method	Fisher exact
Parameter estimate	ORR difference (R-C)
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14
upper limit	9.9

Statistical analysis title	ORR difference_WT Population
Comparison groups	Chemotherapy_WT population v Rogaratinib_WT population
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7944
Method	Fisher exact
Parameter estimate	ORR difference (R − C)
Point estimate	-4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.9
upper limit	9.9

Secondary: Disease-control rate (DCR) - central assessment

End point title	Disease-control rate (DCR) - central assessment

End point description:

DCR was defined as the percentage of participants whose overall best response was not a progressive disease (i.e., CR, PR, stable disease [SD] or Non CR/Non PD).

End point type	Secondary

End point timeframe:

From start of treatment till end of active follow-up

End point values	Rogaratinib (BAY1163877) _overall population	Chemotherapy _overall population	Rogaratinib_WT population	Chemotherapy _WT population
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	87	88	62	63
Units: percentage				
number (confidence interval 95%)	50.6 (39.6 to	55.7 (44.7 to	53.2 (40.1 to	63.5 (50.4 to

61.5)	66.3)	66.0)	75.3)

Statistical analyses

Statistical analysis title	DCR difference_Overall Population
Comparison groups	Rogaratinib (BAY1163877)_overall population v Chemotherapy_overall population
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7962
Method	Fisher exact
Parameter estimate	DCR difference (R-C)
Point estimate	-5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.9
upper limit	9.7

Statistical analysis title	DCR difference_WT population
Comparison groups	Rogaratinib_WT population v Chemotherapy_WT population
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9109
Method	Fisher exact
Parameter estimate	DCR difference (R-C)
Point estimate	-10.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.5
upper limit	6.9

Secondary: Progression-free survival (PFS) - central assessment

End point title	Progression-free survival (PFS) - central assessment

End point description:

Progression free survival (PFS) was defined as the time (days) from randomization to date of first observed disease progression (radiological or clinical assessment or both) or death due to any cause (if death occurred before progression was documented).

End point type	Secondary

End point timeframe:
From start of treatment till end of active follow-up

End point values	Rogaratinib (BAY1163877)_overall population	Chemotherapy_overall population	Rogaratinib_WT population	Chemotherapy_WT population
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	87	88	62	63
Units: months				
median (confidence interval 95%)	2.7 (1.6 to 4.6)	3.2 (2.7 to 4.4)	2.8 (2.6 to 5.1)	4.0 (2.8 to 6.1)

Statistical analyses

Statistical analysis title	Hazard ratio (R/C)_Overall population
Comparison groups	Rogaratinib (BAY1163877)_overall population v Chemotherapy_overall population
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8672
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.226
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.853
upper limit	1.762

Statistical analysis title	Hazard ratio (R/C)_WT population
Comparison groups	Rogaratinib_WT population v Chemotherapy_WT population
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9171
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.341
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	2.043

Secondary: Duration of response (DOR)- central assessment

End point title	Duration of response (DOR)- central assessment

End point description:

DOR (for patients with PR and CR only) was defined as the time from the first documented objective response of PR or CR, whichever was noted earlier, to disease progression (including symptomatic deterioration) or death, whichever was earlier

End point type	Secondary

End point timeframe:

From start of treatment till end of active follow-up

End point values	Rogaratinib (BAY1163877)_overall population	Chemotherapy_overall population	Rogaratinib_WT population	Chemotherapy_WT population
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	87	88	62	63
Units: months				
median (confidence interval 95%)	4.9 (2.2 to 7.0)	5.8 (3.5 to 7.7)	5.1 (1.5 to 9.2)	7.0 (2.7 to 8.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with treatment emergent adverse events

End point title	Number of participants with treatment emergent adverse events

End point description:

A treatment-emergent event is defined as any event arising or worsening after the start of study drug administration until 30 days after the last administration of study treatment.

End point type	Secondary

End point timeframe:

From start of treatment up to 30 days after the last administration of study treatment

End point values	Rogaratinib (BAY1163877)_overall population	Chemotherapy_overall population		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	82		
Units: participants				
Any TEAE	86	82		
Any drug related TEAE	81	76		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the start of study drug administration until 30 days after the last administration of study treatment

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Rogaratinib (BAY1163877)

Reporting group description:

Participants who were randomized to this group following a 1:1 ratio received rogaratinib 600 mg orally twice a day (b.i.d.) continuously, during a 21-day treatment cycle.

Reporting group title	Chemotherapy

Reporting group description:

Participants who were randomized to this group following a 1:1 ratio received chemotherapy (docetaxel, paclitaxel or vinflunine) at the discretion of the investigator, as intravenous (i.v.) infusion once every three weeks (on day 1 of a 21-day cycle).

Serious adverse events	Rogaratinib (BAY1163877)	Chemotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 86 (45.35%)	33 / 82 (40.24%)	
number of deaths (all causes)	47	45	
number of deaths resulting from adverse events	16	5	
Surgical and medical procedures			
Ureteral stent insertion			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Condition aggravated			
subjects affected / exposed	2 / 86 (2.33%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	

Death			
subjects affected / exposed	4 / 86 (4.65%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 4	0 / 2	
Mucosal inflammation			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 86 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 86 (1.16%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	4 / 86 (4.65%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	1 / 6	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 1	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 86 (3.49%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	

Emphysema			
subjects affected / exposed	0 / 86 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 86 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 86 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 86 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biopsy liver			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	2 / 86 (2.33%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	3 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lipase increased			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 86 (1.16%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 86 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic fracture			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Epilepsy			

subjects affected / exposed	0 / 86 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neurotoxicity			
subjects affected / exposed	0 / 86 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 86 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 86 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 86 (0.00%)	4 / 82 (4.88%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 86 (0.00%)	4 / 82 (4.88%)	
occurrences causally related to treatment / all	0 / 0	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	3 / 86 (3.49%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 86 (0.00%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intussusception			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			

subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 86 (1.16%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			
Anuria			
subjects affected / exposed	0 / 86 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 86 (1.16%)	3 / 82 (3.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			

subjects affected / exposed	0 / 86 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephritis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oliguria			
subjects affected / exposed	0 / 86 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage urinary tract			
subjects affected / exposed	0 / 86 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postrenal failure			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 86 (1.16%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	3 / 86 (3.49%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	3 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			

subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 86 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 86 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 86 (1.16%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 86 (0.00%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Relapsing fever			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 86 (0.00%)	3 / 82 (3.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 86 (1.16%)	4 / 82 (4.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 86 (1.16%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin infection			
subjects affected / exposed	0 / 86 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	0 / 86 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 86 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Device related infection			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 86 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia pyelonephritis			

subjects affected / exposed	0 / 86 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 86 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 86 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Rogaratinib (BAY1163877)	Chemotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 86 (98.84%)	77 / 82 (93.90%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	6 / 86 (6.98%)	1 / 82 (1.22%)	
occurrences (all)	6	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	25 / 86 (29.07%)	19 / 82 (23.17%)	
occurrences (all)	52	40	

Mucosal inflammation			
subjects affected / exposed	7 / 86 (8.14%)	8 / 82 (9.76%)	
occurrences (all)	20	12	
Fatigue			
subjects affected / exposed	21 / 86 (24.42%)	28 / 82 (34.15%)	
occurrences (all)	32	41	
Oedema peripheral			
subjects affected / exposed	8 / 86 (9.30%)	10 / 82 (12.20%)	
occurrences (all)	9	13	
Pyrexia			
subjects affected / exposed	12 / 86 (13.95%)	10 / 82 (12.20%)	
occurrences (all)	15	14	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 86 (4.65%)	6 / 82 (7.32%)	
occurrences (all)	6	7	
Dyspnoea			
subjects affected / exposed	3 / 86 (3.49%)	5 / 82 (6.10%)	
occurrences (all)	3	6	
Epistaxis			
subjects affected / exposed	10 / 86 (11.63%)	1 / 82 (1.22%)	
occurrences (all)	10	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 86 (5.81%)	4 / 82 (4.88%)	
occurrences (all)	5	4	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	13 / 86 (15.12%)	2 / 82 (2.44%)	
occurrences (all)	22	4	
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 86 (11.63%)	2 / 82 (2.44%)	
occurrences (all)	16	3	
Blood creatinine increased			
subjects affected / exposed	11 / 86 (12.79%)	3 / 82 (3.66%)	
occurrences (all)	18	6	

Gamma-glutamyltransferase increased			
subjects affected / exposed	5 / 86 (5.81%)	0 / 82 (0.00%)	
occurrences (all)	6	0	
Lipase increased			
subjects affected / exposed	9 / 86 (10.47%)	3 / 82 (3.66%)	
occurrences (all)	25	11	
Neutrophil count decreased			
subjects affected / exposed	0 / 86 (0.00%)	14 / 82 (17.07%)	
occurrences (all)	0	22	
Weight decreased			
subjects affected / exposed	10 / 86 (11.63%)	6 / 82 (7.32%)	
occurrences (all)	11	7	
White blood cell count decreased			
subjects affected / exposed	0 / 86 (0.00%)	5 / 82 (6.10%)	
occurrences (all)	0	5	
Blood alkaline phosphatase increased			
subjects affected / exposed	12 / 86 (13.95%)	2 / 82 (2.44%)	
occurrences (all)	14	3	
Calcium phosphate product increased			
subjects affected / exposed	8 / 86 (9.30%)	0 / 82 (0.00%)	
occurrences (all)	10	0	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	13 / 86 (15.12%)	5 / 82 (6.10%)	
occurrences (all)	14	6	
Headache			
subjects affected / exposed	6 / 86 (6.98%)	4 / 82 (4.88%)	
occurrences (all)	7	5	
Neuropathy peripheral			
subjects affected / exposed	3 / 86 (3.49%)	10 / 82 (12.20%)	
occurrences (all)	4	12	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 86 (1.16%)	10 / 82 (12.20%)	
occurrences (all)	1	14	
Blood and lymphatic system disorders			

Neutropenia			
subjects affected / exposed	3 / 86 (3.49%)	19 / 82 (23.17%)	
occurrences (all)	6	30	
Anaemia			
subjects affected / exposed	11 / 86 (12.79%)	28 / 82 (34.15%)	
occurrences (all)	17	66	
Eye disorders			
Dry eye			
subjects affected / exposed	5 / 86 (5.81%)	3 / 82 (3.66%)	
occurrences (all)	5	3	
Detachment of retinal pigment epithelium			
subjects affected / exposed	7 / 86 (8.14%)	0 / 82 (0.00%)	
occurrences (all)	16	0	
Subretinal fluid			
subjects affected / exposed	7 / 86 (8.14%)	0 / 82 (0.00%)	
occurrences (all)	8	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	15 / 86 (17.44%)	13 / 82 (15.85%)	
occurrences (all)	18	27	
Constipation			
subjects affected / exposed	25 / 86 (29.07%)	29 / 82 (35.37%)	
occurrences (all)	31	54	
Diarrhoea			
subjects affected / exposed	48 / 86 (55.81%)	18 / 82 (21.95%)	
occurrences (all)	92	19	
Dry mouth			
subjects affected / exposed	10 / 86 (11.63%)	2 / 82 (2.44%)	
occurrences (all)	15	2	
Mouth ulceration			
subjects affected / exposed	5 / 86 (5.81%)	3 / 82 (3.66%)	
occurrences (all)	7	3	
Nausea			
subjects affected / exposed	27 / 86 (31.40%)	20 / 82 (24.39%)	
occurrences (all)	38	38	
Vomiting			

subjects affected / exposed	15 / 86 (17.44%)	18 / 82 (21.95%)	
occurrences (all)	19	26	
Stomatitis			
subjects affected / exposed	10 / 86 (11.63%)	10 / 82 (12.20%)	
occurrences (all)	15	14	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	20 / 86 (23.26%)	24 / 82 (29.27%)	
occurrences (all)	23	26	
Dry skin			
subjects affected / exposed	7 / 86 (8.14%)	2 / 82 (2.44%)	
occurrences (all)	9	2	
Nail discolouration			
subjects affected / exposed	6 / 86 (6.98%)	0 / 82 (0.00%)	
occurrences (all)	8	0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	7 / 86 (8.14%)	0 / 82 (0.00%)	
occurrences (all)	10	0	
Rash			
subjects affected / exposed	7 / 86 (8.14%)	3 / 82 (3.66%)	
occurrences (all)	9	5	
Onychomadesis			
subjects affected / exposed	7 / 86 (8.14%)	0 / 82 (0.00%)	
occurrences (all)	8	0	
Nail toxicity			
subjects affected / exposed	7 / 86 (8.14%)	0 / 82 (0.00%)	
occurrences (all)	12	0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	9 / 86 (10.47%)	6 / 82 (7.32%)	
occurrences (all)	13	8	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 86 (10.47%)	7 / 82 (8.54%)	
occurrences (all)	12	7	
Back pain			

subjects affected / exposed	8 / 86 (9.30%)	8 / 82 (9.76%)	
occurrences (all)	8	9	
Myalgia			
subjects affected / exposed	5 / 86 (5.81%)	10 / 82 (12.20%)	
occurrences (all)	6	12	
Pain in extremity			
subjects affected / exposed	7 / 86 (8.14%)	4 / 82 (4.88%)	
occurrences (all)	10	4	
Infections and infestations			
Influenza			
subjects affected / exposed	5 / 86 (5.81%)	0 / 82 (0.00%)	
occurrences (all)	5	0	
Conjunctivitis			
subjects affected / exposed	5 / 86 (5.81%)	3 / 82 (3.66%)	
occurrences (all)	8	3	
Paronychia			
subjects affected / exposed	7 / 86 (8.14%)	0 / 82 (0.00%)	
occurrences (all)	8	0	
Urinary tract infection			
subjects affected / exposed	12 / 86 (13.95%)	8 / 82 (9.76%)	
occurrences (all)	12	13	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	8 / 86 (9.30%)	6 / 82 (7.32%)	
occurrences (all)	11	14	
Hyperphosphataemia			
subjects affected / exposed	39 / 86 (45.35%)	0 / 82 (0.00%)	
occurrences (all)	79	0	
Hyponatraemia			
subjects affected / exposed	6 / 86 (6.98%)	5 / 82 (6.10%)	
occurrences (all)	9	7	
Decreased appetite			
subjects affected / exposed	36 / 86 (41.86%)	21 / 82 (25.61%)	
occurrences (all)	55	25	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 May 2019	• The maximum planned dose was reduced to 600 mg BID from 800 mg BID; • The requirement of cytological confirmation of urothelial carcinoma was removed from the inclusion criteria; • A roll over study was introduced; • Post dose 12 lead ECG beyond cycle 5 was removed.
12 November 2019	• Clarifications were added to explain that due to the stop of enrollment, the study was not to move forward to its Phase 3 and remain Phase 2; • The primary efficacy variable was updated as ORR for the Phase 2 part, and OS was considered an exploratory efficacy variable for the Phase 2 part; • A post trial access program was added as an option for patients to continue receiving rogaratinib treatment and LPLV to be reached based on the last patient changing to a post trial access program.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported