Clinical trial results:
An Open-Label Study of Regorafenib in Combination with Pembrolizumab in Patients with Advanced or Metastatic Hepatocellular Carcinoma (HCC) after PD-1/PD-L1 Immune Checkpoint Inhibitors

Summary

EudraCT number	2020-003555-16
Trial protocol	FR DE IT ES
Global end of trial date	23 April 2024

Results information

Result version number	v1 (current)
This version publication date	10 April 2025
First version publication date	10 April 2025

Trial information

Trial identification

Sponsor protocol code	BAY73-4506/21469

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04696055
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, +49 30 300139003, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, +49 30 300139003, 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	23 April 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 April 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the objective anti-tumor activity of regorafenib in combination with pembrolizumab as a second line treatment for advanced HCC

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 (or their legally authorized representative according to local legislation). Participating subjects (or their legally authorized representative according to local legislation) 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	03 February 2021
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	9 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 63
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	United States: 25
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Japan: 5
Country: Number of subjects enrolled	Korea, Republic of: 16
Worldwide total number of subjects	136
EEA total number of subjects	84

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)	57
From 65 to 84 years	78
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted between 03 February 2021 (first subject first visit) and 23 April 2024 (last subject last visit) at multi-centers in 9 countries.

Pre-assignment

Screening details:

A total of 136 participants were screened, of whom 41 were screening failures. A total of 95 participants were assigned to treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Regorafenib + Pembro [1L: Atezolizumab + Bevacizumab]

Arm description:

Cohort 1 with subjects after one systemic line of therapy consisting of atezolizumab plus bevacizumab treatment combination only. Pembrolizumab 400 mg was administered as an intravenous (IV) infusion every 6 weeks. Regorafenib was given orally at a starting dose of 90 mg once daily for 3 weeks of every 4 weeks (i.e., 3 weeks on, 1 week off). If the starting dose of 90 mg daily was well tolerated the dose was escalated to 120 mg starting after the first 4-week cycle of regorafenib.

Arm type	Experimental
Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY 73-4506
Other name	Stivarga
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

At a starting dose of 90 mg once daily for 3 weeks of every 4 weeks (i.e., 3 weeks on, 1 week off), oral. If the starting dose of 90 mg daily was well tolerated the dose was escalated to 120 mg starting after the first 4-week cycle.

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	MK-3475
Other name	Keytruda
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

400 mg, IV infusion, every 6 weeks

Arm title	Regorafenib + Pembro [1L: Any other IO containing treatment]

Arm description:

Cohort 2 with subjects after one systemic line of therapy consisting of any PD-1/PD-L1 immune oncology (IO) containing first line treatment (excluding atezolizumab with or without bevacizumab) in monotherapy or combination regimens. Pembrolizumab 400 mg was administered as an IV infusion every 6 weeks. Regorafenib was given orally at a starting dose of 90 mg once daily for 3 weeks of every 4 weeks (i.e., 3 weeks on, 1 week off). If the starting dose of 90 mg daily was well tolerated the dose was escalated to 120 mg starting after the first 4-week cycle of regorafenib.

Arm type	Experimental

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	MK-3475
Other name	Keytruda
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

400 mg, IV infusion, every 6 weeks

Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY 73-4506
Other name	Stivarga
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

At a starting dose of 90 mg once daily for 3 weeks of every 4 weeks (i.e., 3 weeks on, 1 week off), oral. If the starting dose of 90 mg daily was well tolerated the dose was escalated to 120 mg starting after the first 4-week cycle.

Number of subjects in period 1[1]	Regorafenib + Pembro [1L: Atezolizumab + Bevacizumab]	Regorafenib + Pembro [1L: Any other IO containing treatment]
Started	68	27
Completed	0	0
Not completed	68	27
Physician decision	3	-
Subject Decision	1	2
Adverse Event	10	2
Progressive Disease - Radiological Progression	42	20
Death	4	-
Unspecified	7	2
Progressive Disease - Clinical Progression	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 136 subjects were screened, of whom 41 were screening failures. Only 95 subjects were assigned to treatment.

Baseline characteristics

Reporting groups

Reporting group title	Regorafenib + Pembro [1L: Atezolizumab + Bevacizumab]

Reporting group description:

Cohort 1 with subjects after one systemic line of therapy consisting of atezolizumab plus bevacizumab treatment combination only. Pembrolizumab 400 mg was administered as an intravenous (IV) infusion every 6 weeks. Regorafenib was given orally at a starting dose of 90 mg once daily for 3 weeks of every 4 weeks (i.e., 3 weeks on, 1 week off). If the starting dose of 90 mg daily was well tolerated the dose was escalated to 120 mg starting after the first 4-week cycle of regorafenib.

Reporting group title	Regorafenib + Pembro [1L: Any other IO containing treatment]

Reporting group description:

Cohort 2 with subjects after one systemic line of therapy consisting of any PD-1/PD-L1 immune oncology (IO) containing first line treatment (excluding atezolizumab with or without bevacizumab) in monotherapy or combination regimens. Pembrolizumab 400 mg was administered as an IV infusion every 6 weeks. Regorafenib was given orally at a starting dose of 90 mg once daily for 3 weeks of every 4 weeks (i.e., 3 weeks on, 1 week off). If the starting dose of 90 mg daily was well tolerated the dose was escalated to 120 mg starting after the first 4-week cycle of regorafenib.

Reporting group values	Regorafenib + Pembro [1L: Atezolizumab + Bevacizumab]	Regorafenib + Pembro [1L: Any other IO containing treatment]	Total
Number of subjects	68	27	95
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	61.7	70.9	
standard deviation	± 13.1	± 7.3	-
Gender categorical Units: Subjects			
Female	15	7	22
Male	53	20	73
Race Units: Subjects			
Asian	19	3	22
Black or African American	2	0	2
White	37	20	57
Multiple	1	0	1
Not reported	9	4	13
Ethnicity Units: Subjects			
Hispanic or Latino	7	3	10
Not Hispanic or Latino	50	17	67
Not reported	11	7	18

End points

End points reporting groups

Reporting group title	Regorafenib + Pembro [1L: Atezolizumab + Bevacizumab]

Reporting group description:

Cohort 1 with subjects after one systemic line of therapy consisting of atezolizumab plus bevacizumab treatment combination only. Pembrolizumab 400 mg was administered as an intravenous (IV) infusion every 6 weeks. Regorafenib was given orally at a starting dose of 90 mg once daily for 3 weeks of every 4 weeks (i.e., 3 weeks on, 1 week off). If the starting dose of 90 mg daily was well tolerated the dose was escalated to 120 mg starting after the first 4-week cycle of regorafenib.

Reporting group title	Regorafenib + Pembro [1L: Any other IO containing treatment]

Reporting group description:

Cohort 2 with subjects after one systemic line of therapy consisting of any PD-1/PD-L1 immune oncology (IO) containing first line treatment (excluding atezolizumab with or without bevacizumab) in monotherapy or combination regimens. Pembrolizumab 400 mg was administered as an IV infusion every 6 weeks. Regorafenib was given orally at a starting dose of 90 mg once daily for 3 weeks of every 4 weeks (i.e., 3 weeks on, 1 week off). If the starting dose of 90 mg daily was well tolerated the dose was escalated to 120 mg starting after the first 4-week cycle of regorafenib.

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects who took at least 1 dose of study intervention were included in the efficacy and safety evaluation

Primary: Overall response rate (ORR) per RECIST 1.1 by central assessment

End point title	Overall response rate (ORR) per RECIST 1.1 by central assessment[1]

End point description:

Overall response rate (ORR) is defined as the percentage of subjects with best overall response of confirmed complete response (CR) or partial response (PR). ORR per RECIST 1.1 by independent central assessment is reported). RECIST 1.1: response evaluation criteria in solid tumors version 1.1

End point type	Primary

End point timeframe:

Up to 15 months. Data up to 38 months are now available and are also reported for full transparency.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the nature of this trial, only descriptive statistics were performed. Neither confirmatory nor exploratory inferential statistical analyses were pre-specified. Thus those analyses were not performed.

End point values	Regorafenib + Pembro [1L: Atezolizumab + Bevacizumab]	Regorafenib + Pembro [1L: Any other IO containing treatment]		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68[2]	27[3]		
Units: Percentage				
number (confidence interval 95%)				
Up to 15 months (primary outcome)	5.9 (1.6 to 14.4)	11.1 (2.4 to 29.2)		
Up to 38 months (as of study completion)	7.4 (2.4 to 16.3)	14.8 (4.2 to 33.7)		

Notes:

[2] - FAS

[3] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR) per RECIST 1.1 by central assessment and investigator assessment

End point title	Duration of response (DOR) per RECIST 1.1 by central assessment and investigator assessment

End point description:

Duration of response (DOR) for partial response (PR) and complete response (CR) was defined as the time from the first documented objective response of PR or CR, whichever noted earlier, to disease progression or death (if death occurs before progression was documented). DOR was defined for confirmed responders only, i.e., subjects with a CR or PR. RECIST 1.1: response evaluation criteria in solid tumors version 1.1

End point type	Secondary

End point timeframe:

Up to 38 months

End point values	Regorafenib + Pembro [1L: Atezolizumab + Bevacizumab]	Regorafenib + Pembro [1L: Any other IO containing treatment]		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[4]	5[5]		
Units: day				
median (full range (min-max))				
Central assessment	210 (158 to 937)	195 (83 to 280)		
Investigator assessment	431 (82 to 893)	364 (117 to 839)		

Notes:

[4] - Confirmed responders in FAS

[5] - Confirmed responders in FAS. 4 / 5 subjects analyzed by central/investigator assessment respectively

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR) per RECIST 1.1 by investigator assessment

End point title	Overall response rate (ORR) per RECIST 1.1 by investigator assessment

End point description:

Overall response rate (ORR) is defined as the percentage of subjects with best overall response of confirmed complete response (CR) or partial response (PR). ORR by RECIST 1.1 investigator review is reported. RECIST 1.1: response evaluation criteria in solid tumors version 1.1

End point type	Secondary

End point timeframe:

Up to 38 months

End point values	Regorafenib + Pembro [1L: Atezolizumab + Bevacizumab]	Regorafenib + Pembro [1L: Any other IO containing treatment]		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68[6]	27[7]		
Units: Percentage				
number (confidence interval 95%)	7.4 (2.4 to 16.3)	18.5 (6.3 to 38.1)		

Notes:

[6] - FAS

[7] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with adverse events (AEs) and serious adverse events (SAEs)

End point title	Number of subjects with adverse events (AEs) and serious adverse events (SAEs)

End point description:

An AE was considered as treatment-emergent (TEAE) if arising or worsening after start of first study intervention administration until 30 days after administration of any study intervention. In addition, any AEs qualifying as a serious adverse event (SAE) were collected for 90 days after the last dose of pembrolizumab, unless a new anti-cancer therapy had been initiated.

End point type	Secondary

End point timeframe:

Up to 38 months

End point values	Regorafenib + Pembro [1L: Atezolizumab + Bevacizumab]	Regorafenib + Pembro [1L: Any other IO containing treatment]		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68[8]	27[9]		
Units: subject				
Any TEAE	68	27		
Any SAE	37	11		

Notes:

[8] - FAS

[9] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with safety-relevant changes in clinical parameters

End point title	Number of subjects with safety-relevant changes in clinical parameters

End point description:

Number of subjects with clinically relevant trends observed in laboratory data, ECG data, or ECOG performance status is reported.

End point type	Secondary

End point timeframe:

Up to 38 months

End point values	Regorafenib + Pembro [1L: Atezolizumab + Bevacizumab]	Regorafenib + Pembro [1L: Any other IO containing treatment]		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68[10]	27[11]		
Units: subject	0	0		

Notes:

[10] - FAS

[11] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with dose modification

End point title	Percentage of subjects with dose modification

End point description:

Dose modification included dose interruption, dose reduction, dose discontinuation.

End point type	Secondary

End point timeframe:

Up to 38 months

End point values	Regorafenib + Pembro [1L: Atezolizumab + Bevacizumab]	Regorafenib + Pembro [1L: Any other IO containing treatment]		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68[12]	27[13]		
Units: Percentage				
number (not applicable)				
Regorafenib - drug interruptions or delays	63.2	70.4		
Regorafenib - dose reductions	41.2	63.0		
Regorafenib - drug withdrawal	16.2	25.9		

Pembrolizumab - dose interruptions or delays	14.7	25.9		
Pembrolizumab - drug withdrawal	4.4	11.1		

Notes:

[12] - FAS

[13] - FAS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After start of first study intervention administration until 30 days after administration of any study intervention. Serious adverse events were collected for 90 days after the last dose of pembrolizumab unless a new anti-cancer therapy had been initiated

Adverse event reporting additional description:

Adverse event reporting for the the deaths (all causes) considers all deaths that occurred at any time during the study before the last contact

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Regorafenib+Pembrolizumab [Any other IO containing treatment]

Reporting group description:

Cohort 2 with participants after one systemic line of therapy consisting of any PD-1/PD-L1 immune oncology (IO) containing first line treatment (excluding atezolizumab with or without bevacizumab) in monotherapy or combination regimens. Pembrolizumab 400 mg was administered as an intravenous (IV) infusion every 6 weeks (Q6W). Regorafenib was given orally (p.o.) at a starting dose of 90 mg once daily (QD) for 3 weeks of every 4 weeks (i.e., 3 weeks on, 1 week off). If the starting dose of 90 mg daily was well tolerated the dose was escalated to 120 mg starting after the first 4-week cycle of regorafenib.

Reporting group title	Regorafenib+Pembrolizumab [1L: Atezolizumab + Bevacizumab]

Reporting group description:

Cohort 1 with participants after one systemic line of therapy consisting of atezolizumab plus bevacizumab treatment combination only. Pembrolizumab 400 mg was administered as an intravenous (IV) infusion every 6 weeks (Q6W). Regorafenib was given orally (p.o.) at a starting dose of 90 mg once daily (QD) for 3 weeks of every 4 weeks (i.e., 3 weeks on, 1 week off). If the starting dose of 90 mg daily was well tolerated the dose was escalated to 120 mg starting after the first 4-week cycle of regorafenib.

Serious adverse events	Regorafenib+Pembrolizumab [Any other IO containing treatment]	Regorafenib+Pembrolizumab [1L: Atezolizumab + Bevacizumab]	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 27 (40.74%)	37 / 68 (54.41%)	
number of deaths (all causes)	20	53	
number of deaths resulting from adverse events	0	5	
Vascular disorders			
Lymphoedema			
subjects affected / exposed	1 / 27 (3.70%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Capillary leak syndrome			

subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 27 (3.70%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site haematoma			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fatigue			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	1 / 27 (3.70%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Lung disorder			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	2 / 27 (7.41%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	3 / 5	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

SARS-CoV-2 test positive			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 27 (3.70%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	1 / 27 (3.70%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningorrhagia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 27 (0.00%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric ulcer perforation			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoperitoneum			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			

subjects affected / exposed	0 / 27 (0.00%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 27 (3.70%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary obstruction			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			

subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cytolysis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot			

subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 27 (0.00%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 27 (3.70%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 27 (3.70%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sepsis			
subjects affected / exposed	1 / 27 (3.70%)	3 / 68 (4.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 3	
Biliary sepsis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
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	1 / 27 (3.70%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection pseudomonal			
subjects affected / exposed	1 / 27 (3.70%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperlipasaemia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 68 (1.47%)	
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	Regorafenib+Pembrolizumab [Any other IO containing treatment]	Regorafenib+Pembrolizumab [1L: Atezolizumab + Bevacizumab]	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 27 (100.00%)	63 / 68 (92.65%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 27 (33.33%)	15 / 68 (22.06%)	
occurrences (all)	20	23	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	18 / 27 (66.67%)	23 / 68 (33.82%)	
occurrences (all)	54	52	
Fatigue			
subjects affected / exposed	4 / 27 (14.81%)	14 / 68 (20.59%)	
occurrences (all)	6	21	
Mucosal inflammation			
subjects affected / exposed	4 / 27 (14.81%)	9 / 68 (13.24%)	
occurrences (all)	6	9	
Oedema peripheral			
subjects affected / exposed	1 / 27 (3.70%)	8 / 68 (11.76%)	
occurrences (all)	1	9	
Pyrexia			
subjects affected / exposed	5 / 27 (18.52%)	13 / 68 (19.12%)	
occurrences (all)	9	16	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 27 (3.70%)	5 / 68 (7.35%)	
occurrences (all)	1	6	
Dyspnoea exertional			
subjects affected / exposed	2 / 27 (7.41%)	0 / 68 (0.00%)	
occurrences (all)	3	0	
Dyspnoea			

subjects affected / exposed	2 / 27 (7.41%)	4 / 68 (5.88%)	
occurrences (all)	3	4	
Dysphonia			
subjects affected / exposed	5 / 27 (18.52%)	13 / 68 (19.12%)	
occurrences (all)	7	16	
Cough			
subjects affected / exposed	3 / 27 (11.11%)	6 / 68 (8.82%)	
occurrences (all)	4	6	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 27 (14.81%)	6 / 68 (8.82%)	
occurrences (all)	4	7	
Investigations			
Weight decreased			
subjects affected / exposed	4 / 27 (14.81%)	7 / 68 (10.29%)	
occurrences (all)	8	8	
Alanine aminotransferase increased			
subjects affected / exposed	3 / 27 (11.11%)	4 / 68 (5.88%)	
occurrences (all)	8	4	
Lipase increased			
subjects affected / exposed	2 / 27 (7.41%)	3 / 68 (4.41%)	
occurrences (all)	2	7	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	2 / 27 (7.41%)	2 / 68 (2.94%)	
occurrences (all)	3	2	
Blood bilirubin increased			
subjects affected / exposed	6 / 27 (22.22%)	9 / 68 (13.24%)	
occurrences (all)	23	13	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 27 (11.11%)	9 / 68 (13.24%)	
occurrences (all)	7	16	
Transaminases increased			
subjects affected / exposed	1 / 27 (3.70%)	4 / 68 (5.88%)	
occurrences (all)	1	4	
Blood alkaline phosphatase increased			

subjects affected / exposed	0 / 27 (0.00%)	4 / 68 (5.88%)	
occurrences (all)	0	8	
Nervous system disorders			
Sciatica			
subjects affected / exposed	2 / 27 (7.41%)	1 / 68 (1.47%)	
occurrences (all)	2	1	
Headache			
subjects affected / exposed	2 / 27 (7.41%)	5 / 68 (7.35%)	
occurrences (all)	2	6	
Dizziness			
subjects affected / exposed	2 / 27 (7.41%)	2 / 68 (2.94%)	
occurrences (all)	3	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 27 (7.41%)	11 / 68 (16.18%)	
occurrences (all)	12	22	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	4 / 27 (14.81%)	4 / 68 (5.88%)	
occurrences (all)	6	6	
Abdominal pain			
subjects affected / exposed	5 / 27 (18.52%)	15 / 68 (22.06%)	
occurrences (all)	9	17	
Stomatitis			
subjects affected / exposed	1 / 27 (3.70%)	5 / 68 (7.35%)	
occurrences (all)	3	9	
Vomiting			
subjects affected / exposed	3 / 27 (11.11%)	9 / 68 (13.24%)	
occurrences (all)	4	10	
Nausea			
subjects affected / exposed	5 / 27 (18.52%)	13 / 68 (19.12%)	
occurrences (all)	8	15	
Constipation			
subjects affected / exposed	5 / 27 (18.52%)	14 / 68 (20.59%)	
occurrences (all)	6	17	
Diarrhoea			

subjects affected / exposed	13 / 27 (48.15%)	23 / 68 (33.82%)	
occurrences (all)	34	37	
Dry mouth			
subjects affected / exposed	3 / 27 (11.11%)	6 / 68 (8.82%)	
occurrences (all)	3	6	
Dyspepsia			
subjects affected / exposed	3 / 27 (11.11%)	3 / 68 (4.41%)	
occurrences (all)	3	3	
Ascites			
subjects affected / exposed	3 / 27 (11.11%)	5 / 68 (7.35%)	
occurrences (all)	3	9	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 27 (0.00%)	4 / 68 (5.88%)	
occurrences (all)	0	7	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 27 (3.70%)	5 / 68 (7.35%)	
occurrences (all)	1	5	
Eczema			
subjects affected / exposed	2 / 27 (7.41%)	0 / 68 (0.00%)	
occurrences (all)	2	0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	14 / 27 (51.85%)	27 / 68 (39.71%)	
occurrences (all)	24	64	
Pruritus			
subjects affected / exposed	5 / 27 (18.52%)	7 / 68 (10.29%)	
occurrences (all)	6	9	
Rash			
subjects affected / exposed	6 / 27 (22.22%)	10 / 68 (14.71%)	
occurrences (all)	12	16	
Alopecia			
subjects affected / exposed	4 / 27 (14.81%)	3 / 68 (4.41%)	
occurrences (all)	4	4	
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	0 / 27 (0.00%)	5 / 68 (7.35%)	
occurrences (all)	0	5	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	2 / 27 (7.41%)	8 / 68 (11.76%)	
occurrences (all)	3	8	
Muscle spasms			
subjects affected / exposed	2 / 27 (7.41%)	3 / 68 (4.41%)	
occurrences (all)	2	4	
Arthralgia			
subjects affected / exposed	10 / 27 (37.04%)	13 / 68 (19.12%)	
occurrences (all)	20	14	
Back pain			
subjects affected / exposed	2 / 27 (7.41%)	7 / 68 (10.29%)	
occurrences (all)	3	12	
Infections and infestations			
COVID-19			
subjects affected / exposed	6 / 27 (22.22%)	3 / 68 (4.41%)	
occurrences (all)	7	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	13 / 27 (48.15%)	21 / 68 (30.88%)	
occurrences (all)	22	32	
Hypoalbuminaemia			
subjects affected / exposed	1 / 27 (3.70%)	6 / 68 (8.82%)	
occurrences (all)	2	19	
Hyponatraemia			
subjects affected / exposed	1 / 27 (3.70%)	7 / 68 (10.29%)	
occurrences (all)	1	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 June 2021	Key modifications were: • Duration of contraception use was clarified to align with wording of Investigator's Brochure (IB). • Exclusion criteria and dose modification sections adapted to align with wording from regorafenib Summary of Product Characteristics (SmPC). • Guidance for regorafenib non-hematologic toxicities and liver toxicities added. • Guidance for Grade 3 immune-related adverse events (irAEs) added. • HCV serotyping added if genotyping was not available for hepatitis C virus (HCV) infection.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported