Clinical trial results:
The GOING Study: Regorafenib followed by nivolumab in patients with Hepatocellular Carcinoma progressing under sorafenib or after discontinuation of atezolizumab plus bevacizumab

Summary

EudraCT number	2019-003108-10
Trial protocol	ES
Global end of trial date	09 July 2024

Results information

Result version number	v1 (current)
This version publication date	25 July 2025
First version publication date	25 July 2025

Trial information

Trial identification

Sponsor protocol code	GOING

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04170556
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	FRCB-IDIBAPS (Fundació de Recerca Clínic Barcelona - Institut d'Investigacions Biomèdiques August Pi i Sunyer)
Sponsor organisation address	C/Roselló149-153, Barcelona, Spain, 08036
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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	27 April 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 July 2024
Global end of trial reached?	Yes
Global end of trial date	09 July 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of regorafenib in combination with Nivolumab.

Protection of trial subjects:

All patients including in Safety set signed informed consent and meet the selection criteria. To ensure patient safety, the following procedures were performed at all study visits during treatment: Physical examination, ECOG performance status, ECG, Vital signs, Assessment of AEs/SAEs, Concomitant medications, Serum chemistry, Hematology, Coagulation and Urinalysis.
Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 January 2020
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	Spain: 67
Worldwide total number of subjects	67
EEA total number of subjects	67

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)	32
From 65 to 84 years	35

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The screened patients were 85 and 16 of them were screening failure. Two additional patients who signed the informed consent form did not start study treatment.
Finally 67 patients received study treatment, 53 in cohort A (previous sorafenib) and 14 in cohort B (previous atezolizumab+bevacizumab).

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	67
Number of subjects completed	67

Period 1

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

Arms

Arm title	Experimental

Arm description:

Regorafenib + Nivolumab

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

Dosage and administration details:

Regorafenib was initiated at full dose (160 mg/day; 3 weeks on and 1 week off) in monotherapy for the first 8 weeks and the dose was modified upon development of adverse events according to the manufacturer’s recommendations. After week 8, regorafenib was continued in combination with nivolumab, until symptomatic tumor progression, unacceptable adverse events, patient decision or death. Further regorafenib dose modifications were allowed in the combination phase, according to the development of adverse events.

Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nivolumab started in combination with regorafenib after 8 weeks of regorafenib monotherapy. Nivolumab (30-minutes IV infusion every 2 weeks) was administered in the first 5 enrolled patients at the dose of 3 mg/kg to define the tolerance and, if no severe adverse event was reported, the following 5 patients received 3 mg/Kg. If no severe adverse event was reported, the following patients received 240 mg/infusion. Treatment continued until symptomatic tumor progression, unacceptable adverse events, patient decision or death. The dose of nivolumab was not modified during the treatment of each patient.

Number of subjects in period 1	Experimental
Started	67
Completed	67

Baseline characteristics

Reporting groups	
Reporting group title	Overall

Reporting group description: -

Reporting group values	Overall	Total	
Number of subjects	67	67	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	32	32	
From 65-84 years	35	35	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	65.4		
standard deviation	± 8.19	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	59	59	
Etnicity Units: Subjects			
Asian	1	1	
Latin or Hispanic	2	2	
White	64	64	
Tumor burden Units: Subjects			
Extrahepatic spread	22	22	
Multinodular	23	23	
Portal invasion	14	14	
Single ≤ 2 cm	1	1	
Single or up to 3 nodules ≤ 3 cm	7	7	
Cirrhosis Units: Subjects			
No	28	28	
Yes	39	39	
Vascular invasion Units: Subjects			
No	41	41	
Yes	26	26	

ECOG Units: Subjects			
ECOG 0	60	60	
ECOG 1	7	7	
HIV infection Units: Subjects			
No	66	66	
Yes	1	1	
First line treatment Units: Subjects			
Sorafenib	53	53	
Atezolizumab plus bevacizumab	14	14	
Worst type of progression to first line treatment Units: Subjects			
Extrahepatic Growth	18	18	
Intrahepatic Growth	25	25	
New Extrahepatic Lesion	12	12	
New Intrahepatic Lesion	12	12	
Weight Units: Kg			
arithmetic mean	74.9		
standard deviation	± 14.2	-	
Body mass index Units: kg/m2			
arithmetic mean	25.9		
standard deviation	± 4.4	-	

End points

End points reporting groups

Reporting group title	Experimental
Reporting group description:	
Regorafenib + Nivolumab	

Primary: Adverse event

End point title	Adverse event[1]
End point description:	
Patients with at least one adverse event	
End point type	Primary
End point timeframe:	
At each study visit until end of treatment.	

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: Single arm study. No statistical analyses for this end point.

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Patients				
Yes	67			
No	0			

Statistical analyses

No statistical analyses for this end point

Primary: Treatment-related adverse event

End point title	Treatment-related adverse event[2]
End point description:	
Patients with at least one treatment-realted adverse event	
End point type	Primary
End point timeframe:	
At each study visit until end of treatment.	

Notes:

[2] - 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: Single arm study. No statistical analyses for this end point.

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Patients				
Yes	64			
No	3			

Statistical analyses

No statistical analyses for this end point

Primary: Adverse event with death

End point title	Adverse event with death[3]

End point description:

Patients with at least one adverse event leading to death

End point type	Primary

End point timeframe:

At each study visit until end of treatment.

Notes:

[3] - 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: Single arm study. No statistical analyses for this end point.

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Patients				
Yes	6			
No	61			

Statistical analyses

No statistical analyses for this end point

Primary: Serious adverse event

End point title	Serious adverse event[4]

End point description:

Patients with at least one serious adverse event

End point type	Primary

End point timeframe:

At each study visit until end of treatment.

Notes:

[4] - 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: Single arm study. No statistical analyses for this end point.

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Patients				
Yes	38			
No	29			

Statistical analyses

No statistical analyses for this end point

Primary: Treatment-related serious adverse event

End point title	Treatment-related serious adverse event[5]

End point description:

Patients with at least one treatment-related serious adverse event

End point type	Primary

End point timeframe:

At each study visit until end of treatment.

Notes:

[5] - 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: Single arm study. No statistical analyses for this end point.

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Patients				
Yes	14			
No	53			

Statistical analyses

No statistical analyses for this end point

Primary: Adverse event leading to discontinuation

End point title	Adverse event leading to discontinuation[6]

End point description:

Patients with at least one adverse event leading to discontinuation of regorafenib and/or nivolumab

End point type	Primary

End point timeframe:

At each study visit until end of treatment.

Notes:

[6] - 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: Single arm study. No statistical analyses for this end point.

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Patients				
Yes	28			
No	39			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate

End point title	Overall Response Rate

End point description:

Patients with partial or complete response at any time, i.e. the best response from inclusion along all follow-up.

End point type	Secondary

End point timeframe:

Every 8 weeks

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: Percentage				
number (confidence interval 95%)	16.4 (8.5 to 27.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

The time from the inclusion date to death from any cause

End point type	Secondary

End point timeframe:

From start of treatment to death or last follow up

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: month				
median (confidence interval 95%)	20 (11 to 37)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression

End point title	Time to progression

End point description:

The time from the inclusion date to progression

End point type	Secondary

End point timeframe:

Every 8 weeks

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	67			
Units: month				
median (confidence interval 95%)	4 (2 to 6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progresion pattern

End point title	Progresion pattern

End point description:

o Intrahepatic growth: increased size of intrahepatic target lesions or progression of intrahepatic "non-target" lesions at baseline.
o New intrahepatic lesion: emergence of new intrahepatic lesions
o Extrahepatic growth: increased size of extrahepatic target lesions, progression of extrahepatic "non-target" lesions at baseline or progression of the existing vascular invasion.
o New extrahepatic lesion: emergence of new extrahepatic lesions
Only for the 45 patients with available radiological progression.

End point type	Secondary

End point timeframe:

Every 8 weeks

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	48[7]			
Units: Patients				
New extrahepatic lesion	14			
Extrahepatic growth	6			
New intrahepatic lesion	13			
Intrahepatic growth	15			

Notes:

[7] - Only for patients with available radiological progression.

Statistical analyses

No statistical analyses for this end point

Secondary: Post-progression survival

End point title	Post-progression survival

End point description:

For those patients who progressed, the time from the progression date to death from any cause

End point type	Secondary

End point timeframe:

From progression disease to death or last follow up

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: month				
median (confidence interval 95%)	12 (5 to 19)			

Statistical analyses

No statistical analyses for this end point

Secondary: New extrahepatic spread

End point title	New extrahepatic spread

End point description:

Rate of patients who develop new extra-hepatic spread. Only for patients with available radiological progression.

End point type	Secondary

End point timeframe:

Every 8 weeks

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: percent				
number (confidence interval 95%)				
Yes	29.2 (17.0 to 44.1)			
No	70.8 (55.9 to 83.0)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Every study visit until end of treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Experimental

Reporting group description: -

Serious adverse events	Experimental		
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 67 (56.72%)		
number of deaths (all causes)	42		
number of deaths resulting from adverse events	6		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Lung neoplasm			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

Pyrexia			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Disease progression			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax spontaneous			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax traumatic			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Conduction disorder			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic encephalopathy			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Neuropathy peripheral			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Haemoperitoneum				
subjects affected / exposed	4 / 67 (5.97%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	1 / 1			
Diarrhoea				
subjects affected / exposed	2 / 67 (2.99%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholangitis acute				
subjects affected / exposed	2 / 67 (2.99%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatic failure				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperbilirubinaemia				

subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Toxic epidermal necrolysis			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Immune-mediated myositis			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pyelonephritis			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			

subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonitis bacterial			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
COVID-19 pneumonia			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Experimental		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 67 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	32 / 67 (47.76%)		
occurrences (all)	69		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	35 / 67 (52.24%)		
occurrences (all)	86		
Chest pain			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	6		
Discomfort			

subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	6		
Fatigue			
subjects affected / exposed	10 / 67 (14.93%)		
occurrences (all)	19		
Influenza like illness			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	6		
Mucosal inflammation			
subjects affected / exposed	8 / 67 (11.94%)		
occurrences (all)	16		
Oedema			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	7		
Oedema peripheral			
subjects affected / exposed	13 / 67 (19.40%)		
occurrences (all)	19		
Pyrexia			
subjects affected / exposed	14 / 67 (20.90%)		
occurrences (all)	28		
Decreased appetite			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Aphonia			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	5		
Cough			
subjects affected / exposed	8 / 67 (11.94%)		
occurrences (all)	10		
Dysphonia			
subjects affected / exposed	10 / 67 (14.93%)		
occurrences (all)	12		
Dyspnoea			

subjects affected / exposed	7 / 67 (10.45%)		
occurrences (all)	9		
Rhinorrhoea			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Oropharyngeal pain			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	5		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	19 / 67 (28.36%)		
occurrences (all)	37		
Amylase increased			
subjects affected / exposed	7 / 67 (10.45%)		
occurrences (all)	16		
Aspartate aminotransferase increased			
subjects affected / exposed	21 / 67 (31.34%)		
occurrences (all)	48		
Blood bilirubin increased			
subjects affected / exposed	10 / 67 (14.93%)		
occurrences (all)	21		
Blood creatinine increased			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	8		
Blood lactate dehydrogenase increased			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	7		
Gamma-glutamyl transferase increased			
subjects affected / exposed	6 / 67 (8.96%)		
occurrences (all)	6		
Lipase increased			

subjects affected / exposed occurrences (all)	11 / 67 (16.42%) 24		
Weight decreased subjects affected / exposed occurrences (all)	10 / 67 (14.93%) 12		
Blood alkaline phospatase increased subjects affected / exposed occurrences (all)	4 / 67 (5.97%) 4		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	7 / 67 (10.45%) 7		
Headache subjects affected / exposed occurrences (all)	6 / 67 (8.96%) 7		
Paraesthesia subjects affected / exposed occurrences (all)	4 / 67 (5.97%) 4		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	16 / 67 (23.88%) 28		
Eosinophilia subjects affected / exposed occurrences (all)	4 / 67 (5.97%) 6		
Lymphopenia subjects affected / exposed occurrences (all)	5 / 67 (7.46%) 12		
Thrombocytopenia subjects affected / exposed occurrences (all)	6 / 67 (8.96%) 9		
Leukocytosis subjects affected / exposed occurrences (all)	5 / 67 (7.46%) 7		
Gastrointestinal disorders			

Abdominal discomfort subjects affected / exposed occurrences (all)	4 / 67 (5.97%) 4		
Abdominal pain subjects affected / exposed occurrences (all)	21 / 67 (31.34%) 26		
Abdominal pain upper subjects affected / exposed occurrences (all)	10 / 67 (14.93%) 16		
Ascites subjects affected / exposed occurrences (all)	8 / 67 (11.94%) 16		
Constipation subjects affected / exposed occurrences (all)	11 / 67 (16.42%) 15		
Diarrhoea subjects affected / exposed occurrences (all)	32 / 67 (47.76%) 70		
Dyspepsia subjects affected / exposed occurrences (all)	5 / 67 (7.46%) 7		
Nausea subjects affected / exposed occurrences (all)	7 / 67 (10.45%) 14		
Vomiting subjects affected / exposed occurrences (all)	8 / 67 (11.94%) 30		
Hepatobiliary disorders Hyperbilirrubinaemia subjects affected / exposed occurrences (all)	14 / 67 (20.90%) 33		
Hypertransaminaemia subjects affected / exposed occurrences (all)	9 / 67 (13.43%) 21		
Immune-mediated hepatitis			

subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
Hyperkeratosis			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	5		
Palmar-plantar erythrdysaesthesia syndrome			
subjects affected / exposed	28 / 67 (41.79%)		
occurrences (all)	65		
Pruritus			
subjects affected / exposed	9 / 67 (13.43%)		
occurrences (all)	11		
Rash			
subjects affected / exposed	9 / 67 (13.43%)		
occurrences (all)	11		
Skin lesion			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	6		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	9 / 67 (13.43%)		
occurrences (all)	22		
Endocrine disorders			
Hypothyriodism			
subjects affected / exposed	8 / 67 (11.94%)		
occurrences (all)	9		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	14 / 67 (20.90%)		
occurrences (all)	24		
Back pain			
subjects affected / exposed	12 / 67 (17.91%)		
occurrences (all)	17		
Muscle spasm			
subjects affected / exposed	6 / 67 (8.96%)		
occurrences (all)	11		

Myalgia			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Musculoskeletal chest pain			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	5		
Infections and infestations			
Pneumonia			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Urinary tract infection			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	8		
Respiratory tract infection			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	6		
COVID-19			
subjects affected / exposed	9 / 67 (13.43%)		
occurrences (all)	11		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Hyperkalaemia			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Hypoalbuminaemia			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Hypomagnesaemia			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	5		
Hyponatraemia			
subjects affected / exposed	8 / 67 (11.94%)		
occurrences (all)	14		
Decreased appetite			

subjects affected / exposed occurrences (all)	22 / 67 (32.84%) 39		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 August 2020	To add a new objective: "Serum and Tissue marker characterization". To add an exclusion criteria: "Concomitant anticoagulation…are permitted" To add the quality of life: HCC18, QCQ-30, ISS Pruritus and Microbiota questionnaries.
15 April 2021	To include an additional cohort (B) of patients treated with first line of Atezolizumab plus bevacizumab
03 March 2022	To extend the trial recruitment period for 9 months till 31st of December 2022 Other changes includes change of the study finalization definition, some changes on inclusion and exclusion criteria. Also, admin changes were included.
10 August 2023	To shorten the follow-up period of Cohort A and B from 18 to 10 months. The study end date was updated and admin changes were included.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported