Clinical trial results:
A phase I/IIa trial to evaluate the safety and efficacy of the combination of the oncolytic immunotherapy Pexa-Vec with the PD-1 receptor blocking antibody nivolumab in the first-line treatment of advanced hepatocellular carcinoma (HCC)

Summary

EudraCT number	2016-000085-32
Trial protocol	IT
Global end of trial date	03 February 2021

Results information

Result version number	v1 (current)
This version publication date	22 October 2021
First version publication date	22 October 2021

Trial information

Trial identification

Sponsor protocol code	TG6006.01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03071094
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	TRANSGENE
Sponsor organisation address	400 boulevard Gonthier d'Andernach, CS80166, Parc d'Innovation, Illkirch-Graffenstaden, France, 67405
Public contact	Medical Affairs Secretariat, TRANSGENE, 33 388279155, clinical.trials@transgene.fr
Scientific contact	Associate Medical Director, TRANSGENE, 33 388279100, clinical.trials@transgene.fr

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	30 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2020
Global end of trial reached?	Yes
Global end of trial date	03 February 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Phase I part: To evaluate the safety profile of intratumoral (IT) Pexa-Vec combined with intravenous (IV) nivolumab in patients with advanced HCC.
Phase IIa part: To evaluate the anti-tumor activity and efficacy of IT Pexa-Vec combined with IV nivolumab in patients with advanced hepatocellular carcinoma (HCC) with respect to Overall Response Rate (ORR) (RECIST 1.1).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy:

Not applicable.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	04 July 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Regulatory reason
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Italy: 3
Worldwide total number of subjects	14
EEA total number of subjects	14

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)	5
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First participant signed informed consent on 04 July 2017. Last participant last visit occurred on 03 February 2021.

Pre-assignment

Screening details:

Of 14 screened participants, 12 were included in the trial (one subject did not fulfill all eligibility criteria and one subject could not be included due to study early termination).

Pre-assignment period milestones

Number of subjects started	14
Number of subjects completed	12

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Subject did not fulfill all eligibility criteria: 1
Reason: Number of subjects	Study terminated early by the Sponsor: 1

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	Pexa-Vec combined with nivolumab - Phase I

Arm description:

Phase I part of the trial: single cohort of 6 patients assessing the safety of standard Pexa-Vec and nivolumab doses.

Arm type	Experimental
Investigational medicinal product name	Pexastimogene devacirepvec
Investigational medicinal product code	Pexa-Vec
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intratumoral use

Dosage and administration details:

Participants were administered Pexa-Vec as 3 bi-weekly intratumoral (IT) injections of 10e9 plaque-forming units (pfu) at day 1, week 2 and week 4.

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

Dosage and administration details:

Participants were administered 240 mg of nivolumab intravenously every 2 weeks (from week 2).

Arm title	Pexa-Vec combined with nivolumab - Phase IIa

Arm description:

Phase IIa part of the trial: extension of the Phase I part to up to 30 patients, assessing the efficacy and safety of Pexa-Vec and nivolumab.

Arm type	Experimental
Investigational medicinal product name	Pexastimogene devacirepvec
Investigational medicinal product code	Pexa-Vec
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intratumoral use

Dosage and administration details:

Participants were administered Pexa-Vec as 3 bi-weekly intratumoral (IT) injections of 10e9 plaque-forming units (pfu) at day 1, week 2 and week 4.

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

Dosage and administration details:

Participants were administered 240 mg nivolumab intravenously every 2 weeks (from week 2).

Number of subjects in period 1[1]	Pexa-Vec combined with nivolumab - Phase I	Pexa-Vec combined with nivolumab - Phase IIa
Started	7	5
Completed	5	4
Not completed	2	1
Adverse event, serious fatal	-	1
Disease progression	1	-
Adverse event, non-fatal	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: Of 14 screened participants, 12 were included in the trial (one subject did not fulfill all eligibility criteria and one subject could not be included due to study early termination).

Baseline characteristics

Reporting groups	
Reporting group title	Pexa-Vec combined with nivolumab - Phase I
Reporting group description:	
Phase I part of the trial: single cohort of 6 patients assessing the safety of standard Pexa-Vec and nivolumab doses.	
Reporting group title	Pexa-Vec combined with nivolumab - Phase IIa
Reporting group description:	
Phase IIa part of the trial: extension of the Phase I part to up to 30 patients, assessing the efficacy and safety of Pexa-Vec and nivolumab.	

Reporting group values	Pexa-Vec combined with nivolumab - Phase I	Pexa-Vec combined with nivolumab - Phase IIa	Total
Number of subjects	7	5	12
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)	2	2	4
From 65-84 years	5	3	8
85 years and over	0	0	0
Age continuous Units: years			
median	67.7	62.8	
standard deviation	± 8.1	± 18.0	-
Gender categorical Units: Subjects			
Female	2	1	3
Male	5	4	9
Stage of HCC per BCLC (Barcelona Clinic Liver Cancer) Units: Subjects			
Stage 0	0	0	0
Stage A	0	0	0
Stage B	0	0	0
Stage C	7	5	12
Stage D	0	0	0
ECOG performance status Units: Subjects			
Score 0	4	5	9
Score 1	3	0	3
Score 2	0	0	0
Score 3	0	0	0

Score 4	0	0	0

End points

End points reporting groups

Reporting group title	Pexa-Vec combined with nivolumab - Phase I
Reporting group description:	
Phase I part of the trial: single cohort of 6 patients assessing the safety of standard Pexa-Vec and nivolumab doses.	
Reporting group title	Pexa-Vec combined with nivolumab - Phase IIa
Reporting group description:	
Phase IIa part of the trial: extension of the Phase I part to up to 30 patients, assessing the efficacy and safety of Pexa-Vec and nivolumab.	
Subject analysis set title	Safety population (phase I)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants who received at least one dose of either study drug.	
Subject analysis set title	DLT (dose-limiting toxicity) population (phase I)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants who received all 3 Pexa-Vec and 2 nivolumab administrations and completed the 4 weeks from the first study drug administration and/or participants having exhibited a dose-limiting toxicicty (DLT) after at least one dose of either study drug (excluding one patient who did not complete the 4 week-period from the first study drug administration).	
Subject analysis set title	Safety population (phase I and phase IIa)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants who received at least one dose of either study drug.	
Subject analysis set title	Intent to treat population (phase I and phase IIa)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Participants who received at least one dose of either study drug.	

Primary: Number of participants with dose limiting toxicities (DLTs)

End point title	Number of participants with dose limiting toxicities (DLTs)[1]
End point description:	
DLTs are occurrence of any following AE related to study drugs occurring during 4 weeks after 1st Pexa-Vec injection: 1. Grade 3-4 non-hematologic toxicity representing a 2-grade increase over baseline, excluding: nausea, vomiting, diarrhea, fever >40.0°C lasting less than 24h (grade 3), alopecia, grade 3 fatigue* and grade 3 laboratory/metabolic abnormalities* (*returning to grade 2 or less within 72h) 2. Grade ≥ 3 acute immune-related AE involving major organs 3. Grade ≥ 3 injection site reaction 4. AST or ALT ≥ 10xULN unless related to liver metastases progression; AST or ALT doubling concurrent with total bilirubin doubling 5. Any toxicity resulting in treatment delay of 2 or more weeks 6. Grade ≥ 3 or ≥ 2-grade neutropenia increase over baseline lasting >7 days, neutropenic fever, grade 4 thrombocytopenia (or grade 3 with bleeding) 7. Association of LVEF less than LLN, blood troponin T or I increase above ULN and any ECG abnormality indicating grade 3 cardiac disorder.	
End point type	Primary
End point timeframe:	
4 weeks from the first study drug administration	
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: Data for this end point were analyzed descriptively.	

End point values	DLT (dose-limiting toxicity) population (phase I)			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: Participants	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with serious adverse events (SAEs)

End point title	Number of participants with serious adverse events (SAEs)[2]

End point description:

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence or effect in a patient, whether or not considered related to the protocol treatment, that at any dose: (i) results in death, (ii) is lifethreatening, (iii) requires inpatient's hospitalization or prolongation of existing inpatients´ hospitalization, (iv) results in persistent or significant disability or incapacity, (v) is a congenital anomaly or birth defect, (vi) results in any other medically important condition.

End point type	Primary

End point timeframe:

4 weeks from the first study drug administration

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: Data for this end point were analyzed descriptively.

End point values	Safety population (phase I)			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: Participants	6			

Statistical analyses

No statistical analyses for this end point

Primary: Overall response rate (ORR) according to RECIST 1.1.

End point title	Overall response rate (ORR) according to RECIST 1.1.[3]

End point description:

Overall Response Rate (ORR): proportion of patients, whose best overall response is either complete response (CR) or partial response (PR), confirmed at least 4 weeks after initial documentation.

End point type	Primary

End point timeframe:

6 months from the first study drug administration

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: Efficacy data were analyzed descriptively and presented for phase I + phase IIa.

End point values	Intent to treat population (phase I and phase IIa)			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: Percentage of participants				
number (confidence interval 95%)	33.3 (9.9 to 65.1)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (and serious adverse events) were recorded from the first study drug administration up to 28 days after the last study drug dose.

Adverse event reporting additional description:

Adverse event information was collected by regular investigator assessment and regular laboratory testing.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Pexa-Vec combined with nivolumab - Phase I

Reporting group description:

Participants who received at least one dose of either study drug.

Reporting group title	Pexa-Vec combined with nivolumab - Phase IIa

Reporting group description:

Participants who received at least one dose of either study drug.

Reporting group title	Safety population (phase I and phase IIa)

Reporting group description:

Participants who received at least one dose of either study drug.

Serious adverse events	Pexa-Vec combined with nivolumab - Phase I	Pexa-Vec combined with nivolumab - Phase IIa	Safety population (phase I and phase IIa)
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 7 (85.71%)	4 / 5 (80.00%)	10 / 12 (83.33%)
number of deaths (all causes)	2	1	3
number of deaths resulting from adverse events	1	1	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour necrosis	Additional description: Tumour necrosis		
subjects affected / exposed	0 / 7 (0.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Spinal compression fracture	Additional description: Spinal compression fracture		
subjects affected / exposed	0 / 7 (0.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Hypertension	Additional description: Hypertension		
subjects affected / exposed	2 / 7 (28.57%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences causally related to treatment / all	3 / 6	0 / 0	3 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General physical health deterioration	Additional description: General physical health deterioration		
subjects affected / exposed	1 / 7 (14.29%)	1 / 5 (20.00%)	2 / 12 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 2
Inflammation	Additional description: Inflammation		
subjects affected / exposed	0 / 7 (0.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness	Additional description: Influenza like illness		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	2 / 7 (28.57%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences causally related to treatment / all	3 / 3	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury	Additional description: Acute kidney injury		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Device related infection	Additional description: Device related infection		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetic ketoacidosis	Additional description: Diabetic ketoacidosis		

subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia	Additional description: Hypercalcaemia		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia	Additional description: Hypokalaemia		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Pexa-Vec combined with nivolumab - Phase I	Pexa-Vec combined with nivolumab - Phase IIa	Safety population (phase I and phase IIa)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	5 / 5 (100.00%)	12 / 12 (100.00%)
Vascular disorders			
Haematoma	Additional description: Haematoma		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Hypertension	Additional description: Hypertension		
subjects affected / exposed	4 / 7 (57.14%)	2 / 5 (40.00%)	6 / 12 (50.00%)
occurrences (all)	6	8	14
Hypotension	Additional description: Hypotension		
subjects affected / exposed	2 / 7 (28.57%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	5	0	5
Peripheral venous disease	Additional description: Peripheral venous disease		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Asthenia	Additional description: Asthenia		
subjects affected / exposed	2 / 7 (28.57%)	5 / 5 (100.00%)	7 / 12 (58.33%)
occurrences (all)	2	6	8

Chest pain	Additional description: Chest pain		
subjects affected / exposed	0 / 7 (0.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Chills	Additional description: Chills		
subjects affected / exposed	2 / 7 (28.57%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	2	0	2
Fatigue	Additional description: Fatigue		
subjects affected / exposed	2 / 7 (28.57%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	4	0	4
Influenza like illness	Additional description: Influenza like illness		
subjects affected / exposed	1 / 7 (14.29%)	3 / 5 (60.00%)	4 / 12 (33.33%)
occurrences (all)	3	5	8
Injection site pain	Additional description: Injection site pain		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Oedema peripheral	Additional description: Oedema peripheral		
subjects affected / exposed	5 / 7 (71.43%)	0 / 5 (0.00%)	5 / 12 (41.67%)
occurrences (all)	6	0	6
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	7 / 7 (100.00%)	1 / 5 (20.00%)	8 / 12 (66.67%)
occurrences (all)	16	1	17
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: Cough		
subjects affected / exposed	2 / 7 (28.57%)	1 / 5 (20.00%)	3 / 12 (25.00%)
occurrences (all)	3	1	4
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	2 / 7 (28.57%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	2	0	2
Epistaxis	Additional description: Epistaxis		
subjects affected / exposed	0 / 7 (0.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Psychiatric disorders			
Insomnia	Additional description: Insomnia		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Nervousness	Additional description: Nervousness		

subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Investigations			
C-reactive protein	Additional description: C-reactive protein		
subjects affected / exposed	0 / 7 (0.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Electrocardiogram QT prolonged	Additional description: Electrocardiogram QT prolonged		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Liver function test increased	Additional description: Liver function test increased		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Lymphocyte count decreased	Additional description: Lymphocyte count decreased		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Neutrophil count decreased	Additional description: Neutrophil count decreased		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Transaminases increased	Additional description: Transaminases increased		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Troponin I increased	Additional description: Troponin I increased		
subjects affected / exposed	0 / 7 (0.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Weight decreased	Additional description: Weight decreased		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
White blood cell count increased	Additional description: White blood cell count increased		
subjects affected / exposed	0 / 7 (0.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Cardiac disorders			
Arrhythmia	Additional description: Arrhythmia		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Sinus tachycardia	Additional description: Sinus tachycardia		

subjects affected / exposed	1 / 7 (14.29%)	1 / 5 (20.00%)	2 / 12 (16.67%)
occurrences (all)	4	1	5
Nervous system disorders			
Headache	Additional description: Headache		
subjects affected / exposed	1 / 7 (14.29%)	2 / 5 (40.00%)	3 / 12 (25.00%)
occurrences (all)	1	3	4
Hepatic encephalopathy	Additional description: Hepatic encephalopathy		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	2
Neuropathy peripheral	Additional description: Neuropathy peripheral		
subjects affected / exposed	0 / 7 (0.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Paraesthesia	Additional description: Paraesthesia		
subjects affected / exposed	0 / 7 (0.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Abdominal distension	Additional description: Abdominal distension		
subjects affected / exposed	0 / 7 (0.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	2 / 7 (28.57%)	1 / 5 (20.00%)	3 / 12 (25.00%)
occurrences (all)	2	4	6
Abdominal pain upper	Additional description: Abdominal pain upper		
subjects affected / exposed	1 / 7 (14.29%)	2 / 5 (40.00%)	3 / 12 (25.00%)
occurrences (all)	1	3	4
Ascites	Additional description: Ascites		
subjects affected / exposed	2 / 7 (28.57%)	1 / 5 (20.00%)	3 / 12 (25.00%)
occurrences (all)	4	1	5
Constipation	Additional description: Constipation		
subjects affected / exposed	2 / 7 (28.57%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	4	0	4
Diarrhoea	Additional description: Diarrhoea		

subjects affected / exposed	2 / 7 (28.57%)	2 / 5 (40.00%)	4 / 12 (33.33%)
occurrences (all)	2	2	4
Dry mouth	Additional description: Dry mouth		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Haemorrhoids	Additional description: Haemorrhoids		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	3	0	3
Hiatus hernia	Additional description: Hiatus hernia		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Melaena	Additional description: Melaena		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Nausea	Additional description: Nausea		
subjects affected / exposed	1 / 7 (14.29%)	2 / 5 (40.00%)	3 / 12 (25.00%)
occurrences (all)	1	4	5
Oesophagitis	Additional description: Oesophagitis		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Stomatitis	Additional description: Stomatitis		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Toothache	Additional description: Toothache		
subjects affected / exposed	0 / 7 (0.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Vomiting	Additional description: Vomiting		
subjects affected / exposed	1 / 7 (14.29%)	1 / 5 (20.00%)	2 / 12 (16.67%)
occurrences (all)	1	2	3
Skin and subcutaneous tissue disorders			
Pruritus	Additional description: Pruritus		
subjects affected / exposed	3 / 7 (42.86%)	1 / 5 (20.00%)	4 / 12 (33.33%)
occurrences (all)	7	1	8
Rash	Additional description: Rash		
subjects affected / exposed	1 / 7 (14.29%)	1 / 5 (20.00%)	2 / 12 (16.67%)
occurrences (all)	1	1	2

Rash erythematous	Additional description: Rash erythematous		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Skin mass	Additional description: Skin mass		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Renal and urinary disorders			
Renal failure	Additional description: Renal failure		
subjects affected / exposed	0 / 7 (0.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Renal impairment	Additional description: Renal impairment		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	2
Strangury	Additional description: Strangury		
subjects affected / exposed	0 / 7 (0.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: Arthralgia		
subjects affected / exposed	1 / 7 (14.29%)	1 / 5 (20.00%)	2 / 12 (16.67%)
occurrences (all)	1	3	4
Back pain	Additional description: Back pain		
subjects affected / exposed	1 / 7 (14.29%)	2 / 5 (40.00%)	3 / 12 (25.00%)
occurrences (all)	1	2	3
Myalgia	Additional description: Myalgia		
subjects affected / exposed	0 / 7 (0.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Pain in extremity	Additional description: Pain in extremity		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Spinal pain	Additional description: Spinal pain		
subjects affected / exposed	0 / 7 (0.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Infections and infestations			
Fungal infection	Additional description: Fungal infection		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1

Nasopharyngitis	Additional description: Nasopharyngitis		
subjects affected / exposed	2 / 7 (28.57%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	3	0	3
Rash pustular	Additional description: Rash pustular		
subjects affected / exposed	3 / 7 (42.86%)	2 / 5 (40.00%)	5 / 12 (41.67%)
occurrences (all)	3	2	5
Tooth infection	Additional description: Tooth infection		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Metabolism and nutrition disorders			
Decreased appetite	Additional description: Decreased appetite		
subjects affected / exposed	5 / 7 (71.43%)	2 / 5 (40.00%)	7 / 12 (58.33%)
occurrences (all)	6	2	8
Diabetes mellitus	Additional description: Diabetes mellitus		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Hyperglycaemia	Additional description: Hyperglycaemia		
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Hypomagnesaemia	Additional description: Hypomagnesaemia		
subjects affected / exposed	0 / 7 (0.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Type 2 diabetes mellitus	Additional description: Type 2 diabetes mellitus		
subjects affected / exposed	0 / 7 (0.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 June 2017	Protocol amendment 1 dated 26 June 2017: reinforcement of the cardiac monitoring with addition of cardiac echography, electrocardiogram and measurement of blood troponin T or I levels at baseline and at various timepoints after Pexa-Vec/nivolumab administrations. Cardiac toxicities were added to the list of dose-limiting toxicities (DLT).
19 October 2017	Protocol amendment 2 dated 19 October 2017: introduction of a clearance for study participation after a cardiology consultation and increase of the frequency of the cardiac echography, electrocardiogram and measurements of blood troponin T or I levels. Change in the prophylactic antipyretic medication by introduction of intakes of oral ibuprofen alternating with paracetamol. Addition of the prophylactic antiemetic medication with esomeprazole.
22 December 2017	Protocol amendment 3 dated 22 December 2017: introduction of the ability to temporarily suspend concomitant anti-hypertensive medications in case of hypertension. Precision that ibuprofen may be contra-indicated in case of underlying advanced cirrhosis. Exclusion of grade 3 fever from the dose limiting toxicities. Precision of the severity (grade ≥ 3) in the definition of the DLT neutropenia.
04 May 2018	Protocol amendment 4 dated 04 May 2018: additional contact for reporting serious adverse events (SAE), pregnancy and overdose.
20 March 2019	Protocol amendment 5 dated 20 March 2019: no substantial changes introduced, only administrative changes and re-phrasings for sake of clarity.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
18 September 2019	The trial was terminated prematurely during the Phase IIa due to the failure of Pexa-Vec and nivolumab in their respective pivotal trials in HCC.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated early as per Sponsor's decision based on the failure of Pexa-Vec and nivolumab in their respective pivotal trials in HCC. Consequently, the enrollment in Phase IIa was not completed. The number of patients analysed is small.

Notes: