



## Clinical trial results:

### Phase IIa open-label clinical study of intratumoural administration of BO-112 in combination with pembrolizumab in subjects with liver metastasis from colorectal cancer or gastric/gastro-oesophageal junction cancer

#### Summary

EudraCT number	2019-004624-38
Trial protocol	BE ES IT DE
Global end of trial date	02 December 2022

#### Results information

Result version number	v1 (current)
This version publication date	16 December 2023
First version publication date	16 December 2023

#### Trial information

##### Trial identification

Sponsor protocol code	BOT112-02
-----------------------	-----------

##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	Highlight Therapeutics, S.L.
Sponsor organisation address	Parc Científic de la Universitat de València, c/ Catedrático Agustín Escardino, 9, 46980 Paterna (Valencia), Spain,
Public contact	Clinical operations, Pivotal S.L., +34 917081250, maria.moreno@pivotalcr.com
Scientific contact	Clinical operations, Pivotal S.L., +34 917081250, maria.moreno@pivotalcr.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	14 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 February 2021
Global end of trial reached?	Yes
Global end of trial date	02 December 2022
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

Investigation of the anti-tumour efficacy and safety of repeated IT administrations of BO-112 in metastatic liver lesions in combination with IV pembrolizumab

Protection of trial subjects:

To limit the number of patients exposed to a potentially non-effective treatment, a Simon's 2-stage design was applied with a Data Monitoring Committee (DMC) review of available safety and efficacy data of the Stage 1 patients for each cohort separately.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 July 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: 15
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Italy: 1
Worldwide total number of subjects	18
EEA total number of subjects	18

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)	11
From 65 to 84 years	7

85 years and over	0
-------------------	---

## Subject disposition

### Recruitment

Recruitment details:

First patient gave informed consent on 08 July 2020 and last patient gave informed consent on 21 December 2020.

Type of location was medical hospital.

### Pre-assignment

Screening details:

Patients were approved by the sponsor's Medical Director before entering the treatment phase.

Approval was given after reviewing of the eligibility package, checking the inclusion/exclusion criteria and, if needed, after discussion with the PIs. 25 patients were enrolled in the study and 18 patients were included in the treatment phase.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Cohort A

Arm description:

Cohort A consisted of 11 patients with CRC (microsatellite stable [MSS]) with nonresectable liver metastases suitable for IT injection and who had received at least 2 prior standard of care systemic anticancer therapies for advanced/metastatic disease. Patients who had resection of hepatic metastases and had hepatic recurrence, needed to have 1 or more prior standard of care systemic anticancer therapies in order to be eligible for this study.

Arm type	Experimental
Investigational medicinal product name	BO-112
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Injection

Dosage and administration details:

1 mg of 0.6 mg/mL administered in 1.7 mL volume as an IT injection on Day 1 or 2 and Day 8 of Cycle 1, then Day 1 or 2 of each subsequent cycle

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Injection

Dosage and administration details:

200mg IV administered on Day 1 of each 3-week cycle

<b>Arm title</b>	Cohort B
------------------	----------

Arm description:

Cohort B consisted of 7 patients with gastric or GC/GEJ with nonresectable liver metastases suitable for IT injection and who had received at least 1 prior standard of care systemic anticancer therapy for advanced/metastatic disease.

Arm type	Experimental
----------	--------------

Investigational medicinal product name	BO-112
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Injection

Dosage and administration details:

1 mg of 0.6 mg/mL administered in 1.7 mL volume as an IT injection on Day 1 or 2 and Day 8 of Cycle 1, then Day 1 or 2 of each subsequent cycle

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Injection

Dosage and administration details:

200mg IV administered on Day 1 of each 3-week cycle

<b>Number of subjects in period 1</b>	Cohort A	Cohort B
Started	11	7
Completed	0	0
Not completed	11	7
Adverse event, serious fatal	1	-
Consent withdrawn by subject	-	1
Adverse event, non-fatal	1	2
Protocol specified withdrawal criteria met	-	1
Progressive disease	9	3

## Baseline characteristics

### Reporting groups

Reporting group title	Cohort A
-----------------------	----------

Reporting group description:

Cohort A consisted of 11 patients with CRC (microsatellite stable [MSS]) with nonresectable liver metastases suitable for IT injection and who had received at least 2 prior standard of care systemic anticancer therapies for advanced/metastatic disease. Patients who had resection of hepatic metastases and had hepatic recurrence, needed to have 1 or more prior standard of care systemic anticancer therapies in order to be eligible for this study.

Reporting group title	Cohort B
-----------------------	----------

Reporting group description:

Cohort B consisted of 7 patients with gastric or GC/GEJ with nonresectable liver metastases suitable for IT injection and who had received at least 1 prior standard of care systemic anticancer therapy for advanced/metastatic disease.

Reporting group values	Cohort A	Cohort B	Total
Number of subjects	11	7	18
Age categorical			
Units: Subjects			
Adults (18-64 years)	7	4	11
From 65-84 years	4	3	7
Age continuous			
Units: years			
arithmetic mean	55.6	56.1	
full range (min-max)	37 to 74	37 to 71	-
Gender categorical			
Units: Subjects			
Female	4	1	5
Male	7	6	13

## End points

### End points reporting groups

Reporting group title	Cohort A
Reporting group description: Cohort A consisted of 11 patients with CRC (microsatellite stable [MSS]) with nonresectable liver metastases suitable for IT injection and who had received at least 2 prior standard of care systemic anticancer therapies for advanced/metastatic disease. Patients who had resection of hepatic metastases and had hepatic recurrence, needed to have 1 or more prior standard of care systemic anticancer therapies in order to be eligible for this study.	
Reporting group title	Cohort B
Reporting group description: Cohort B consisted of 7 patients with gastric or GC/GEJ with nonresectable liver metastases suitable for IT injection and who had received at least 1 prior standard of care systemic anticancer therapy for advanced/metastatic disease.	

### Primary: Determination of the objective response rate (ORR) based on best overall response (all time points) using RECIST 1.1

End point title	Determination of the objective response rate (ORR) based on best overall response (all time points) using RECIST 1.1 <sup>[1]</sup>
End point description:	
End point type	Primary
End point timeframe: Overall study duration dependent on the duration of achieved clinical benefit; expected to be in the range of 24-36 months. Individual subject study duration depended on maintenance of clinical benefit and tolerability; expected to range from 2-12 months.	

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: Statistical analysis was not appropriate for this end point, so was therefore not performed.

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	7		
Units: Objective response rate (ORR)				
number (not applicable)	0	0		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All AEs from ICF signing to end of study (follow up) visit recorded.

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	NCI CTCAE
-----------------	-----------

Dictionary version	4.03
--------------------	------

### Reporting groups

Reporting group title	Cohort A
-----------------------	----------

Reporting group description:

Cohort A consisted of 11 patients with CRC (microsatellite stable [MSS]) with nonresectable liver metastases suitable for IT injection and who had received at least 2 prior standard of care systemic anticancer therapies for advanced/metastatic disease. Patients who had resection of hepatic metastases and had hepatic recurrence, needed to have 1 or more prior standard of care systemic anticancer therapies in order to be eligible for this study.

Reporting group title	Cohort B
-----------------------	----------

Reporting group description:

Cohort B consisted of 7 patients with gastric or GC/GEJ with nonresectable liver metastases suitable for IT injection and who had received at least 1 prior standard of care systemic anticancer therapy for advanced/metastatic disease.

Serious adverse events	Cohort A	Cohort B	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 11 (45.45%)	2 / 7 (28.57%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events	1	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 11 (27.27%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 11 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			



subjects affected / exposed	2 / 11 (18.18%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Infections and infestations</b>			
Alpha haemolytic streptococcal infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Bacteraemia</b>			
subjects affected / exposed	0 / 11 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>COVID-19 pneumonia</b>			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

<b>Non-serious adverse events</b>	Cohort A	Cohort B	
<b>Total subjects affected by non-serious adverse events</b>			
subjects affected / exposed	11 / 11 (100.00%)	7 / 7 (100.00%)	
<b>Vascular disorders</b>			
Hypertension			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Hypotension			
subjects affected / exposed	2 / 11 (18.18%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
<b>General disorders and administration site conditions</b>			
Asthenia			
subjects affected / exposed	3 / 11 (27.27%)	2 / 7 (28.57%)	
occurrences (all)	6	2	
Chills			

subjects affected / exposed	5 / 11 (45.45%)	0 / 7 (0.00%)	
occurrences (all)	9	0	
Fatigue			
subjects affected / exposed	2 / 11 (18.18%)	1 / 7 (14.29%)	
occurrences (all)	2	2	
Injection site pain			
subjects affected / exposed	0 / 11 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	5	
Pyrexia			
subjects affected / exposed	8 / 11 (72.73%)	4 / 7 (57.14%)	
occurrences (all)	20	8	
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	2 / 11 (18.18%)	1 / 7 (14.29%)	
occurrences (all)	4	3	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 11 (9.09%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 11 (18.18%)	2 / 7 (28.57%)	
occurrences (all)	2	2	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 11 (9.09%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 11 (9.09%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 11 (18.18%)	1 / 7 (14.29%)	
occurrences (all)	2	1	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 11 (18.18%)	0 / 7 (0.00%)	
occurrences (all)	2	0	

Neuropathy Peripheral subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 7 (14.29%) 1	
Presyncope subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 7 (0.00%) 0	
Tremor subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 7 (0.00%) 0	
Syncope subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 7 (14.29%) 1	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 7 (14.29%) 1	
Eye disorders Eczema eyelids subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 7 (0.00%) 0	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	4 / 11 (36.36%) 5	1 / 7 (14.29%) 1	
Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 7 (14.29%) 2	
Constipation subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2	0 / 7 (0.00%) 0	
Diarrhoea subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 2	2 / 7 (28.57%) 2	
Dyspepsia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 7 (14.29%) 1	
Dysphagia			

subjects affected / exposed	0 / 11 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	4 / 11 (36.36%)	1 / 7 (14.29%)	
occurrences (all)	12	1	
Vomiting			
subjects affected / exposed	2 / 11 (18.18%)	2 / 7 (28.57%)	
occurrences (all)	7	3	
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	1 / 11 (9.09%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Hepatomegaly			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Haematuria			
subjects affected / exposed	1 / 11 (9.09%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 11 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 11 (9.09%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Back pain			

subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 2	1 / 7 (14.29%) 1	
Groin pain subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 7 (0.00%) 0	
Muscle spasms subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 7 (14.29%) 1	
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 7 (0.00%) 0	
Infections and infestations Asymptomatic COVID-19 subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 7 (0.00%) 1	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2	1 / 7 (14.29%) 1	
Hypercalcemia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 7 (0.00%) 0	
Hyperglycemia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 7 (0.00%) 0	
Hypoalbuminaemia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 7 (14.29%) 1	
Hyponatraemia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 7 (14.29%) 1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 May 2020	<ul style="list-style-type: none"><li>- The epidemiological situation at the time forced the introduction of COVID-19 infection as a specific risk. Based on that, the protocol and the ICF were amended to include some recommendations for the investigators and specific information in this regard for the patients.</li><li>- Administratively, the names of the sponsor and CRO were changed, and personnel changes were documented.</li><li>- Addition of site as releaser of BO-112 and site as releaser of pembrolizumab, and updated pembrolizumab IB.</li></ul>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
19 January 2021	Cohort B (GC/GEJ cancer patients with liver metastasis) was put on hold due to low recruitment in 2021; 7 patients were analyzed.	-

Notes:

### Limitations and caveats

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

It was planned to enrol 25 patients in Germany but no patients were subsequently enrolled.

Notes: