Clinical trial results:
SPOTLIGHT 203: Phase 2 single arm clinical study to evaluate the efficacy and safety of intratumoral administration of BO-112 in combination with pembrolizumab in subjects that have progressed on anti-PD-1-based therapy in refractory unresectable malignant melanoma stage III or IV

Summary

EudraCT number	2020-003921-51
Trial protocol	FR
Global end of trial date	03 October 2023

Results information

Result version number	v1 (current)
This version publication date	06 February 2025
First version publication date	06 February 2025

Trial information

Trial identification

Sponsor protocol code	BOT112-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04570332
WHO universal trial number (UTN)	-
Other trial identifiers	KEYNOTE: B77

Notes:

Sponsors

Sponsor organisation name	Highlight Therapeutics, S.L.
Sponsor organisation address	Parque Científico Universidad de Valencia Calle Catedrático Agustín Escardino, 9, Paterna (Valencia), Spain, 46980
Public contact	Marisol Quintero Ortiz, Highlight Therapeutics, S.L., +34 682544814, mquintero@highlighttherapeutics.com
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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	17 October 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 October 2023
Global end of trial reached?	Yes
Global end of trial date	03 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the anti-tumor activity of intratumoral (IT) BO-112 in combination with intravenous (IV) pembrolizumab in advanced melanoma patients

Protection of trial subjects:

The study was conducted in accordance with the protocol and with the following:
- Guidelines of the Declaration of Helsinki.
- International Council for Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations (including the European Union [EU] Clinical Trials Directive and the Code of Federal Regulations).

Background therapy: -

Evidence for comparator:

Not applicable.

Actual start date of recruitment	18 January 2021
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Spain: 25
Worldwide total number of subjects	42
EEA total number of subjects	42

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)	18
From 65 to 84 years	21
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Recruitment countries: France and Spain
Special populations: patients with advanced and/or metastatic unresectable stage III or stage IV melanoma that has progressed on anti-PD-1-containing treatment, either as monotherapy, or in combination with other checkpoint inhibitors or therapies.
Stage III tumor: 4 subjects
Stage IV tumor: 38 subjects

Pre-assignment

Screening details:

From a total of 54 patients screened, 42 were enrolled in the study (17 patients enrolled from 6 sites in France and 25 patients enrolled from 10 sites in Spain) and treated. The majority of screening failures were due to not meeting eligibility criteria relating to prior lines of therapy.

Period 1

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

Arms

Arm title	BO-112 + Pembrolizumab

Arm description:

Multicenter, phase 2, open-label, single-arm, adaptive design study to determine the preliminary anti-tumor activity and confirm the safety of IT BO-112 in combination with IV pembrolizumab.
Study treatments were administered until disease progression, unacceptable toxicity, death, withdrawal of consent, study termination or up to 2 years

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

Dosage and administration details:

Dose of BO-112 was based on lesion size as specified below. The minimum number of lesions injected per study visit was 1 and the maximum was 8. The maximum volume to be injected was 3.4 mL per visit, distributed over different injectable tumors.

Lesion size	Max Dose / Max Volume to be administered
≤ 0.5 cm	Up to 0.06 mg / 0.1 mL
> 0.5 cm & < 1.5 cm	Up to 0.3-0.6 mg / 0.5-1.0 mL
≥ 1.5 cm	Up to 1.0 mg / 1.7 mL

BO-112 was administered IT once weekly for the first 7 weeks and then once every three weeks.

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

Dosage and administration details:

Pembrolizumab was administered at a dose of 200 mg by IV infusion every 3 weeks.

Number of subjects in period 1	BO-112 + Pembrolizumab
Started	42
Completed	24
Not completed	18
Consent withdrawn by subject	1
Death	17

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	42	42	
Age categorical Units: Subjects			
Adults (18-64 years)	18	18	
From 65-84 years	21	21	
85 years and over	3	3	
Gender categorical Units: Subjects			
Female	18	18	
Male	24	24	
Pathological diagnosis			
Pathological subtype of melanoma			
Units: Subjects			
Cutaneous melanoma	30	30	
Acral melanoma	9	9	
Mucosal melanoma	3	3	
Advanced/metastatic disease Units: Subjects			
Yes	14	14	
No	28	28	
Current AJCC8 Tumor Stage Units: Subjects			
Stage III	4	4	
Stage IV	38	38	
BRAF Status Units: Subjects			
Mutated	7	7	
Not mutated	35	35	
Baseline tumor size Units: Subjects			
<30 mm	8	8	
30-50 mm	6	6	
50-100 mm	15	15	
≥ 100 mm	13	13	
Baseline Lactate Dehydrogenase (LDH) values Units: Subjects			
Normal LDH values	26	26	
High LDH values	16	16	
ECOG performance status Units: Subjects			
ECOG performance status 0	33	33	

ECOG performance status 1	9	9	
Liver metastases Units: Subjects			
Yes	8	8	
No	34	34	
Bone metastases Units: Subjects			
Yes	5	5	
No	37	37	
Lung metastases Units: Subjects			
Yes	17	17	
No	25	25	
Skin metastases Units: Subjects			
Yes	5	5	
No	37	37	
Prior line of treatment (adjuvant only)			
Patients who received only adjuvant treatment prior to the clinical trial			
Units: Subjects			
Nivolumab	4	4	
Pembrolizumab	6	6	
No adjuvant treatment	32	32	
Prior line of treatment (advanced)			
Patients who received advanced treatment prior to the trial			
Units: Subjects			
Nivolumab	10	10	
Pembrolizumab	12	12	
Nivolumab + Ipilimumab	6	6	
Other anti-PD1 combinations	4	4	
No advanced treatment	10	10	
PD-L1 expression			
Patients with negative or positive PD-L1 expression			
Units: Subjects			
Negative	9	9	
Positive	23	23	
Not evaluable	10	10	
Weight Units: Kg			
arithmetic mean	71.60		
standard deviation	± 15.68	-	
Time since initial diagnosis Units: Months			
arithmetic mean	39.71		
standard deviation	± 52.63	-	
Number of metastatic lesions Units: Lesions			
median	6.00		
inter-quartile range (Q1-Q3)	4.00 to 9.00	-	
Number of target metastatic lesions Units: Lesions			

median	3.00		
inter-quartile range (Q1-Q3)	2.00 to 4.00	-	

Subject analysis sets

Subject analysis set title	Intention-to-treat population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-to-treat (ITT) population was defined as those participants who were enrolled into the study (i.e. received at least one dose of the study drug(s), and was used to analyze the secondary efficacy endpoints, including subgroup analyses. In this trial, the ITT population was the same as the Safety population.

Subject analysis set title	Modified intention-to-treat population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Modified intention-to-treat (mITT) population was defined as all participants who were included, had at least one dose of trial treatment and underwent baseline and at least one post-baseline tumor response assessment by Independent Radiological Central Review (IRCR). The mITT population was used to analyze the primary endpoint.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population was defined as all participants who received at least one dose of study treatment, and was used to analyze the secondary endpoint of safety and tolerability of IT BO-112 + IV pembrolizumab. Safety population was used for all safety related analysis. In this trial, the ITT population was the same as the Safety population.

Reporting group values	Intention-to-treat population	Modified intention-to-treat population	Safety population
Number of subjects	42	40	42
Age categorical Units: Subjects			
Adults (18-64 years)	18	18	18
From 65-84 years	21	19	21
85 years and over	3	3	3
Gender categorical Units: Subjects			
Female	18	18	18
Male	24	22	24
Pathological diagnosis			
Pathological subtype of melanoma			
Units: Subjects			
Cutaneous melanoma	30	29	30
Acral melanoma	9	8	9
Mucosal melanoma	3	3	3
Advanced/metastatic disease Units: Subjects			
Yes	14	14	14
No	28	26	28
Current AJCC8 Tumor Stage Units: Subjects			
Stage III	4	4	4
Stage IV	38	36	38

BRAF Status Units: Subjects			
Mutated	7	7	7
Not mutated	35	33	35
Baseline tumor size Units: Subjects			
<30 mm	8	8	8
30-50 mm	6	5	6
50-100 mm	15	14	15
≥ 100 mm	13	13	13
Baseline Lactate Dehydrogenase (LDH) values Units: Subjects			
Normal LDH values	26	25	26
High LDH values	16	15	16
ECOG performance status Units: Subjects			
ECOG performance status 0	33	32	33
ECOG performance status 1	9	8	9
Liver metastases Units: Subjects			
Yes	8	7	8
No	34	33	34
Bone metastases Units: Subjects			
Yes	5	3	5
No	37	37	37
Lung metastases Units: Subjects			
Yes	17	16	17
No	25	24	25
Skin metastases Units: Subjects			
Yes	5	5	5
No	37	35	37
Prior line of treatment (adjuvant only)			
Patients who received only adjuvant treatment prior to the clinical trial			
Units: Subjects			
Nivolumab	4	3	4
Pembrolizumab	6	5	6
No adjuvant treatment	32	32	32
Prior line of treatment (advanced)			
Patients who received advanced treatment prior to the trial			
Units: Subjects			
Nivolumab	10	10	10
Pembrolizumab	12	12	12
Nivolumab + Ipilimumab	6	6	6
Other anti-PD1 combinations	4	4	4
No advanced treatment	10	8	10
PD-L1 expression			
Patients with negative or positive PD-L1 expression			

Units: Subjects			
Negative	9	8	9
Positive	23	22	23
Not evaluable	10	10	10
Weight			
Units: Kg			
arithmetic mean	71.60	71.60	71.60
standard deviation	± 15.68	± 15.68	± 15.68
Time since initial diagnosis			
Units: Months			
arithmetic mean	39.71	39.71	39.71
standard deviation	± 52.63	± 52.63	± 52.63
Number of metastatic lesions			
Units: Lesions			
median	6.00	6.00	6.00
inter-quartile range (Q1-Q3)	4.00 to 9.00	4.00 to 9.00	4.00 to 9.00
Number of target metastatic lesions			
Units: Lesions			
median	3.00	3.00	3.00
inter-quartile range (Q1-Q3)	2.00 to 4.00	2.00 to 4.00	2.00 to 4.00

End points

End points reporting groups

Reporting group title	BO-112 + Pembrolizumab

Reporting group description:

Multicenter, phase 2, open-label, single-arm, adaptive design study to determine the preliminary anti-tumor activity and confirm the safety of IT BO-112 in combination with IV pembrolizumab.
Study treatments were administered until disease progression, unacceptable toxicity, death, withdrawal of consent, study termination or up to 2 years

Subject analysis set title	Intention-to-treat population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-to-treat (ITT) population was defined as those participants who were enrolled into the study (i.e. received at least one dose of the study drug(s), and was used to analyze the secondary efficacy endpoints, including subgroup analyses. In this trial, the ITT population was the same as the Safety population.

Subject analysis set title	Modified intention-to-treat population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Modified intention-to-treat (mITT) population was defined as all participants who were included, had at least one dose of trial treatment and underwent baseline and at least one post-baseline tumor response assessment by Independent Radiological Central Review (IRCR). The mITT population was used to analyze the primary endpoint.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population was defined as all participants who received at least one dose of study treatment, and was used to analyze the secondary endpoint of safety and tolerability of IT BO-112 + IV pembrolizumab. Safety population was used for all safety related analysis. In this trial, the ITT population was the same as the Safety population.

Primary: Primary Efficacy Endpoint

End point title	Primary Efficacy Endpoint[1]

End point description:

Overall response rate (ORR) using RECIST 1.1, defined as the percentage of patients achieving a complete response (CR) or partial response (PR) as best overall response, by independent radiological central review (IRCR).

End point type	Primary

End point timeframe:

Until all participants with post-baseline imaging had achieved a best overall response during the treatment period.

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: The scope of this study was to evaluate the efficacy and safety of BO-112 in combination with pembrolizumab. The study was a single arm trial and had no comparison groups. Therefore the study was not amenable to comparative statistical analyses. However, the null hypothesis was H0: ORR=10% (p0) and was tested against H1: ORR>10% at one-sided 5% significance level. 4 (10%) participants achieved CR and 6 (15%) participants achieved PR, yielding an ORR of 25% (95% CI: 12.69%, 41.20%, p=0.0008).

End point values	BO-112 + Pembrolizumab			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: Overall Response Rate (ORR)				
number (confidence interval 95%)				
ORR	25 (12.69 to 41.2)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Safety

End point title	Safety

End point description:

End point type	Other pre-specified

End point timeframe:

The total duration for each participating subject was up to 2 years of treatment and up to 90 days for a safety follow up after last dose of study drug. The mean cumulative dose was 2223.81 ± 2173.10 mg for pembrolizumab and 18.30 ± 13.01 mg for BO-112.

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	42			
Units: Doses and duration				
Number of subjects reporting any TEAEs	42			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

TEAE (Treatment Emergent Adverse Event) was defined as an AE that occurred after the first administration of study treatment until 90 days after last dose in this trial.

Adverse event reporting additional description:

TEAEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0. AEs were coded with the Preferred Term (PT) level, and System Organ Class (SOC) term using the Medical Dictionary for Regulatory Activities (MedDRA dictionary).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Safety population

Reporting group description: -

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 42 (35.71%)		
number of deaths (all causes)	17		
number of deaths resulting from adverse events	7		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphangiosis carcinomatosa			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Cerebral haematoma				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Epilepsy				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
General physical health deterioration				
subjects affected / exposed	3 / 42 (7.14%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 3			
Asthenia				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Condition aggravated				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Disease progression				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Vomiting			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Tracheal compression			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Arthralgia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 42 (2.38%)		
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	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 42 (97.62%)		

Vascular disorders Hypertension subjects affected / exposed occurrences (all)	 5 / 42 (11.90%) 7		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Chills subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Influenza like illness subjects affected / exposed occurrences (all) Injection site pain subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 29 / 42 (69.05%) 74 12 / 42 (28.57%) 25 3 / 42 (7.14%) 5 5 / 42 (11.90%) 12 10 / 42 (23.81%) 12 7 / 42 (16.67%) 9 19 / 42 (45.24%) 90		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 6 / 42 (14.29%) 6		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 6 / 42 (14.29%) 6		
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	6		
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	6		
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	4		
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 42 (26.19%)		
occurrences (all)	17		
Tremor			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	5		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	4		
Eye disorders			
Eye pruritus			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Vision blurred			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	6 / 42 (14.29%)		
occurrences (all)	7		
Diarrhoea			

subjects affected / exposed	18 / 42 (42.86%)		
occurrences (all)	30		
Dry mouth			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	4		
Nausea			
subjects affected / exposed	13 / 42 (30.95%)		
occurrences (all)	32		
Stomatitis			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	4		
Vomiting			
subjects affected / exposed	12 / 42 (28.57%)		
occurrences (all)	26		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	9 / 42 (21.43%)		
occurrences (all)	17		
Rash			
subjects affected / exposed	7 / 42 (16.67%)		
occurrences (all)	11		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	5		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 42 (16.67%)		
occurrences (all)	12		
Back pain			
subjects affected / exposed	8 / 42 (19.05%)		
occurrences (all)	13		
Myalgia			
subjects affected / exposed	6 / 42 (14.29%)		
occurrences (all)	9		
Pain in extremity			

subjects affected / exposed occurrences (all)	10 / 42 (23.81%) 13		
Infections and infestations COVID-19 subjects affected / exposed occurrences (all)	 5 / 42 (11.90%) 7		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 10 / 42 (23.81%) 13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 November 2020	Spain Protocol Substantial Amendment #1: Contraception inclusion criteria updated, Schedule of Assessments (SoA) timing updated.
23 March 2021	Spain Protocol Substantial Amendment #2 BO-112 administration was updated (not relevant); PK analysis was updated to a subset of participants instead of whole population; serum albumin was removed from incl criteria, Excl. criteria ALT/AST from normal to >2.5 ULN; Excl hepatitis was updated, Excl. HCV was updated, AE reporting was updated to start from first dose rather than from screening initiation, SoA was updated, Serum chemistry was reduced.
23 March 2021	France Protocol Substantial modification #1 BO-112 administration was updated, PK analysis was updated from all to a subset of participants, Incl # 4 was updated to histologically OR cytolgically confirmed diagnosis, serum albumin was removed, Excl. 4 ALT/AST from normal to > 2.5 ULN, Excl. # 14 interstitial lung disease was added, Excl # 18 hepatitis was updated, Excl. #19 HCV was updated, AE reporting was updated, SoA was updated.
08 August 2021	Spain Protocol Substantial modification #3 Update on INCL #7 prior anti-PD1 therapy; Excl # 18 was updated with 72 hour wash out for COVID vaccines; handling of participants with skin lesions was only updated to allow for surgical resection in case of pCR.
18 August 2021	France Protocol Substantial modification #2 Some changes were implemented, mainly to update BO-112 stability data, but also for clarifying how response assessments for participants with only skin lesions and pathological complete response (pCR) were done. Besides, safety wording was updated for BO-112, based on current DSUR and IB. Informed consent form was also updated accordingly.
18 July 2022	France and Spain Protocol Substantial modification #4 Sponsor personnel was updated, OS shortened to 1 year; the safety profile of BO-112 in section 5.1.2 (Rationale) was updated Some changes have been implemented, mainly to update long term follow up, as secondary endpoint Overall Survival (OS) was only followed up to 1 year (it was 2 years per prior protocol versions). This has been decided once all, primary endpoint and rest of secondary endpoints have been met. Participants who were on treatment, continued on treatment per protocol. This follow up OS assessment update was only applicable to those participants who had discontinued treatment and were still alive at least one year after first study treatment visit. In addition, BO-112 safety and efficacy data were updated to align with the most recent IB and DSUR versions. As minor changes, all references to the updated protocol version and date were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported