# 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 |
| Scientific contact | Marisol Quintero Ortiz, Highlight Therapeutics, S.L., +34 682544814, mquintero@highlighttherapeutics.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 | 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<br>Units: Subjects | | | |
| Adults (18-64 years) | 18 | 18 | |
| From 65-84 years | 21 | 21 | |
| 85 years and over | 3 | 3 | |
| Gender categorical<br>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<br>Units: Subjects | | | |
| Yes | 14 | 14 | |
| No | 28 | 28 | |
| Current AJCC8 Tumor Stage<br>Units: Subjects | | | |
| Stage III | 4 | 4 | |
| Stage IV | 38 | 38 | |
| BRAF Status<br>Units: Subjects | | | |
| Mutated | 7 | 7 | |
| Not mutated | 35 | 35 | |
| Baseline tumor size<br>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<br>Units: Subjects | | | |
| Normal LDH values | 26 | 26 | |
| High LDH values | 16 | 16 | |
| ECOG performance status<br>Units: Subjects | | | |
| ECOG performance status 0 | 33 | 33 | |

| | | | |
|---|---|---|---|
| ECOG performance status 1 | 9 | 9 | |
| Liver metastases<br>Units: Subjects | | | |
| Yes | 8 | 8 | |
| No | 34 | 34 | |
| Bone metastases<br>Units: Subjects | | | |
| Yes | 5 | 5 | |
| No | 37 | 37 | |
| Lung metastases<br>Units: Subjects | | | |
| Yes | 17 | 17 | |
| No | 25 | 25 | |
| Skin metastases<br>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<br>Units: Kg | | | |
| arithmetic mean | 71.60 | | |
| standard deviation | ± 15.68 | - | |
| Time since initial diagnosis<br>Units: Months | | | |
| arithmetic mean | 39.71 | | |
| standard deviation | ± 52.63 | - | |
| Number of metastatic lesions<br>Units: Lesions | | | |
| median | 6.00 | | |
| inter-quartile range (Q1-Q3) | 4.00 to 9.00 | - | |
| Number of target metastatic lesions<br>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<br>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<br>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<br>Units: Subjects | | | |
| Yes | 14 | 14 | 14 |
| No | 28 | 26 | 28 |
| Current AJCC8 Tumor Stage<br>Units: Subjects | | | |
| Stage III | 4 | 4 | 4 |
| Stage IV | 38 | 36 | 38 |

| | | | |
|---|---|---|---|
| BRAF Status<br>Units: Subjects | | | |
| Mutated | 7 | 7 | 7 |
| Not mutated | 35 | 33 | 35 |
| Baseline tumor size<br>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<br>Units: Subjects | | | |
| Normal LDH values | 26 | 25 | 26 |
| High LDH values | 16 | 15 | 16 |
| ECOG performance status<br>Units: Subjects | | | |
| ECOG performance status 0 | 33 | 32 | 33 |
| ECOG performance status 1 | 9 | 8 | 9 |
| Liver metastases<br>Units: Subjects | | | |
| Yes | 8 | 7 | 8 |
| No | 34 | 33 | 34 |
| Bone metastases<br>Units: Subjects | | | |
| Yes | 5 | 3 | 5 |
| No | 37 | 37 | 37 |
| Lung metastases<br>Units: Subjects | | | |
| Yes | 17 | 16 | 17 |
| No | 25 | 24 | 25 |
| Skin metastases<br>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<br>Hypertension<br>subjects affected / exposed<br>occurrences (all) | <br><br>5 / 42 (11.90%)<br>7 | | |
| General disorders and administration site conditions<br>Asthenia<br>subjects affected / exposed<br>occurrences (all)<br><br>Chills<br>subjects affected / exposed<br>occurrences (all)<br><br>Fatigue<br>subjects affected / exposed<br>occurrences (all)<br><br>Influenza like illness<br>subjects affected / exposed<br>occurrences (all)<br><br>Injection site pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)<br><br>Pyrexia<br>subjects affected / exposed<br>occurrences (all) | <br><br>29 / 42 (69.05%)<br>74<br><br>12 / 42 (28.57%)<br>25<br><br>3 / 42 (7.14%)<br>5<br><br>5 / 42 (11.90%)<br>12<br><br>10 / 42 (23.81%)<br>12<br><br>7 / 42 (16.67%)<br>9<br><br>19 / 42 (45.24%)<br>90 | | |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all) | <br><br>6 / 42 (14.29%)<br>6 | | |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all) | <br><br>6 / 42 (14.29%)<br>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<br>occurrences (all) | 10 / 42 (23.81%)<br>13 | | |
| Infections and infestations<br>COVID-19<br>subjects affected / exposed<br>occurrences (all) | <br><br>5 / 42 (11.90%)<br>7 | | |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | <br><br>10 / 42 (23.81%)<br>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:<br>Contraception inclusion criteria updated, Schedule of Assessments (SoA) timing updated. |
| 23 March 2021 | Spain Protocol Substantial Amendment #2<br>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<br>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<br>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<br>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<br>Sponsor personnel was updated, OS shortened to 1 year; the safety profile of BO-112 in section 5.1.2 (Rationale) was updated<br>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.<br>In addition, BO-112 safety and efficacy data were updated to align with the most recent IB and DSUR versions.<br>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