



Clinical trial results:

Phase II trial of durvalumab (Medi4736) plus tremelimumab with concurrent radiotherapy in patients with localized muscle invasive bladder cancer treated with a selective bladder preservation approach

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2017-003159-44 |
| Trial protocol | ES |
| Global end of trial date | 16 August 2022 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 26 October 2023 |
| First version publication date | 26 October 2023 |

Trial information

Trial identification

| | |
|-----------------------|-------------------------|
| Sponsor protocol code | SOGUG-2017-A-IEC(VEJ)-1 |
|-----------------------|-------------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03702179 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Spanish Oncology Genitourinary Group (SOGUG) |
| Sponsor organisation address | C/ Velazquez 7 3ª planta, Madrid, Spain, 28001 |
| Public contact | Federico Nepote, MFAR Clinical Research, investigacion@mfar.net |
| Scientific contact | Federico Nepote, MFAR Clinical Research, investigacion@mfar.net |

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 | 16 August 2023 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 16 August 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 16 August 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of durvalumab plus tremelimumab with concurrent radiotherapy in terms of pathological response rate in patients with localized muscle invasive bladder cancer treated with bladder preservation intent.

Protection of trial subjects:

The protocol already includes all measures required to protect the patients.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 04 February 2019 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Spain: 32 |
| Worldwide total number of subjects | 32 |
| EEA total number of subjects | 32 |

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 | 25 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details:

Patients diagnosed with urothelial carcinoma of the bladder, in clinical stages T2-4a N0 M0, who are not candidates for radical cystectomy by medical reasons, refusal or patient's choice.

Pre-assignment

Screening details:

Screening procedures will be performed up to 28 days before Day 1 of Week 1, unless otherwise specified. All patients must first read, understand, and sign the IEC-approved ICF before any study-specific screening procedures are performed.

Period 1

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

Blinding implementation details:

single-arm study

Arms

| | |
|-----------|------------------|
| Arm title | Experimental arm |
|-----------|------------------|

Arm description:

Durvalumab) (1500mg Q4W) in combination with tremelimumab (75 mg IV Q4W) for up to 3 doses/cycles each, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

Radiotherapy 46 Gy to the minor pelvis and 64-66 Gy to the bladder.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Durvalumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

1500mg every 4 weeks for up to 3 cycles, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met

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

Dosage and administration details:

75mg every 4 weeks for up to 3 cycles, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met

| Number of subjects in period 1 | Experimental arm |
|---------------------------------------|------------------|
| Started | 32 |
| Completed | 32 |

Baseline characteristics

Reporting groups

| Reporting group title | Study period |
|--------------------------------|--------------|
| Reporting group description: - | |

| Reporting group values | Study period | Total | |
|---|--------------|-------|--|
| Number of subjects | 32 | 32 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | | 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) | | 0 | |
| From 65-84 years | | 0 | |
| 85 years and over | | 0 | |
| Age continuous | | | |
| Units: years | | | |
| median | 71 | | |
| full range (min-max) | 49 to 91 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 7 | 7 | |
| Male | 25 | 25 | |
| Eastern Cooperative Oncology Group Performance Status (ECOG-PS) | | | |
| Measure Description: Describes a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (walking, working...). The scale ranges from 0 (Fully active, able to carry on all pre-disease performance without restriction) to 5 (Dead). | | | |
| Units: Subjects | | | |
| ECOG 0 | 25 | 25 | |
| ECOG 1 | 7 | 7 | |
| Histology | | | |
| Measure Description: Describes the histology subtype of tumor, the type of cells from which the tumor has arisen | | | |
| Units: Subjects | | | |
| Urothelial carcinoma | 31 | 31 | |
| Mixed urothelial carcinoma | 1 | 1 | |
| Clinical T stage | | | |
|] Measure Description: T stage according to AJCC criteria. Describes the extent of tumor spread and size. T ranges from T1 (The tumor has spread to the connective tissue but it does not involve the bladder wall muscle) to T4 (The tumor has spread to any of the following: the abdominal wall, the pelvic wall, the prostate or seminal vesicle, or the uterus or vagina). | | | |
| Units: Subjects | | | |
| T2 | 28 | 28 | |
| T3 | 3 | 3 | |

| | | | |
|---|----|----|--|
| T4 | 1 | 1 | |
| Previous bladder cancer non muscle invasive | | | |
| Measure Description: Describes the history of bladder cancer for patients, the presence or not of previous local bladder cancer that may have occurred earlier before inclusion and that may be treated with resection of local treatments | | | |
| Units: Subjects | | | |
| Yes | 14 | 14 | |
| No | 18 | 18 | |
| Previous treatment | | | |
| Measure Description: Type of previous treatments for bladder cancer before patient inclusion | | | |
| Units: Subjects | | | |
| Bacillus CalmetteGuérin (BCG) | 9 | 9 | |
| Mitomycin | 1 | 1 | |
| Transurethral Resection of Bladder Tumor (TURBT) | 1 | 1 | |
| No treatment | 21 | 21 | |
| PD-L1 expression | | | |
| Measure Description: Programmed death-1 ligand 1 (PD-L1) expression levels in tumor tissue samples has been described as correlated with response to immunotherapy such as the experimental treatment studied in this trial. PD-L1 expression is measured by immunohistochemistry in tumor sample and could be positive (high expression) or negative (low expression). | | | |
| Units: Subjects | | | |
| Positive | 15 | 15 | |
| Negative | 12 | 12 | |
| Unknown | 5 | 5 | |

End points

End points reporting groups

| | |
|--|------------------|
| Reporting group title | Experimental arm |
| Reporting group description: Durvalumab) (1500mg Q4W) in combination with tremelimumab (75 mg IV Q4W) for up to 3 doses/cycles each, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Radiotherapy 46 Gy to the minor pelvis and 64-66 Gy to the bladder. | |

Primary: Proportion of Patients With Pathological Response

| | |
|---|--|
| End point title | Proportion of Patients With Pathological Response ^[1] |
| End point description: Pathological response is defined as the absence of muscle- invasive bladder cancer at post-treatment biopsy (\leq cT1). Cystoscopy and bladder biopsy six weeks since the end of radiotherapy | |
| End point type | Primary |
| End point timeframe: 12 weeks | |

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: This is a single arm trial. No comparisons were scheduled as only one group of patients is evaluated. the trial results are discussed and compared to previous data in scientific publications.

| End point values | Experimental arm | | | |
|--------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 ^[2] | | | |
| Units: Patients | | | | |
| Complete Response (\leq T1) | 26 | | | |
| Non-response (MIBC) | 2 | | | |

Notes:

[2] - 4 patients not evaluated: 2 died, 1 withdrawn and 1 clinical deterioration before evaluation

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Patients With Bladder Preserved

| | |
|--|---|
| End point title | Rate of Patients With Bladder Preserved |
| End point description: Number of patients whom bladder has been preserved after cystoscopic evaluation. | |
| End point type | Secondary |
| End point timeframe: 24 months | |

| | | | | |
|-----------------------------|-------------------|--|--|--|
| End point values | Experimental arm | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 28 ^[3] | | | |
| Units: Patients | | | | |
| Preserved bladder | 28 | | | |
| Not preserved bladder | 0 | | | |

Notes:

[3] - 4 patients not evaluated: 2 died, 1 withdrawn and 1 clinical deterioration before evaluation

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Immediate Salvage Cystectomies

| | |
|--|--|
| End point title | Rate of Immediate Salvage Cystectomies |
| End point description: | |
| Number of patients with indication of salvage cystectomies after first trial-related cystoscopic evaluation. | |
| End point type | Secondary |
| End point timeframe: | |
| 24 months | |

| | | | | |
|---------------------------------|------------------|--|--|--|
| End point values | Experimental arm | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 32 | | | |
| Units: Patients | | | | |
| Radical cystectomy performed | 1 | | | |
| Radical cystectomy not required | 31 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Late Salvage Cystectomies

| | |
|---|-----------------------------------|
| End point title | Rate of Late Salvage Cystectomies |
| End point description: | |
| Number of patients with indication of salvage cystectomies based on follow-up cystoscopic evaluation. | |
| End point type | Secondary |
| End point timeframe: | |
| 24 months | |

| | | | | |
|------------------------------|------------------|--|--|--|
| End point values | Experimental arm | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 32 | | | |
| Units: Patients | | | | |
| Required late cystectomy | 2 | | | |
| Not required late cystectomy | 30 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Survival With Bladder Preserved Free of Tumor

| | |
|---|---|
| End point title | Survival With Bladder Preserved Free of Tumor |
| End point description: | |
| Time from the start of immunotherapy to either the date of cystectomy or the date of recurrence of muscle- invasive bladder carcinoma or metastasis. Here we report the estimated rate of patients free of event at 24 months after the start of immunotherapy. Estimation by kaplan meier method. | |
| End point type | Secondary |
| End point timeframe: | |
| 24 months | |

| | | | | |
|---|-------------------|--|--|--|
| End point values | Experimental arm | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 32 | | | |
| Units: percentage of patients (%) free of event | | | | |
| arithmetic mean (confidence interval 95%) | 65 (50.3 to 84.1) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-free Survival

| | |
|---|-----------------------|
| End point title | Disease-free Survival |
| End point description: | |
| Time from treatment start to tumour relapse or distant progression (without Salvage cystectomy). Bladder relapse with salvage cystectomy is not considered as an event. Deaths are also considered as events. Here we report the estimated rate of patients free of events at 24 months after the start of the immunotherapy. Estimation by kaplan meier method | |
| End point type | Secondary |
| End point timeframe: | |
| 24 months | |

| | | | | |
|---|---------------------|--|--|--|
| End point values | Experimental arm | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 32 | | | |
| Units: percentage of patients (%) free of event | | | | |
| arithmetic mean (confidence interval 95%) | 71.4 (57.2 to 89.1) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

| | |
|--|------------------|
| End point title | Overall Survival |
| End point description: | |
| Time from the start of immunotherapy to the date of death due to any cause. The reported outcome is the estimated ratio of patients alive at 24 months after start of immunotherapy using kaplan meier method. | |
| End point type | Secondary |
| End point timeframe: | |
| 24 months | |

| | | | | |
|---|---------------------|--|--|--|
| End point values | Experimental arm | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 32 | | | |
| Units: percentage of patients (%) alive | | | | |
| arithmetic mean (confidence interval 95%) | 84.3 (72.5 to 97.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-related Adverse Events as Assessed by CTCAE v4.0

| | |
|---|--|
| End point title | Number of Participants With Treatment-related Adverse Events as Assessed by CTCAE v4.0 |
| End point description: | |
| Frequency, nature and number of patients developing adverse events throughout follow up | |
| End point type | Secondary |

End point timeframe:

24 months

| | | | | |
|--|------------------|--|--|--|
| End point values | Experimental arm | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 32 | | | |
| Units: Patients | | | | |
| Had treatment-related adverse events | 31 | | | |
| Had not treatment-related adverse events | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-related Adverse Event Grade ≥ 3

| | |
|-----------------|--|
| End point title | Number of Participants With Treatment-related Adverse Event Grade ≥ 3 |
|-----------------|--|

End point description:

Frequency, nature and number of patients developing high grade adverse events throughout follow up

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

24 months

| | | | | |
|--|------------------|--|--|--|
| End point values | Experimental arm | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 32 | | | |
| Units: Patients | | | | |
| Had treatment-related adverse events | 10 | | | |
| Had not treatment-related adverse events | 22 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout the study period, approximately a median of 24 months follow up.

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

Dictionary used

| | |
|-----------------|----------|
| Dictionary name | NCICTCAE |
|-----------------|----------|

| | |
|--------------------|---|
| Dictionary version | 4 |
|--------------------|---|

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Full dataset |
|-----------------------|--------------|

Reporting group description:

All patients who received at least one dose of study treatment.

| Serious adverse events | Full dataset | | |
|--|------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 11 / 32 (34.38%) | | |
| number of deaths (all causes) | 7 | | |
| number of deaths resulting from adverse events | 1 | | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Fever | | | |
| subjects affected / exposed | 3 / 32 (9.38%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Other, specify | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 32 (3.13%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Diarrhea | | | |
| subjects affected / exposed | 5 / 32 (15.63%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fecaloid peritonitis | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Immunomediated colitis | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| other specify | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute pyelonephritis | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cystitis noninfective | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Other specify | | | |
| subjects affected / exposed | 2 / 32 (6.25%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Full dataset | | |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 32 / 32 (100.00%) | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 5 / 32 (15.63%) | | |
| occurrences (all) | 5 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 4 / 32 (12.50%) | | |
| occurrences (all) | 4 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 3 / 32 (9.38%) | | |
| occurrences (all) | 3 | | |
| Blood and lymphatic system disorders | | | |
| Anemia | | | |
| subjects affected / exposed | 4 / 32 (12.50%) | | |
| occurrences (all) | 4 | | |
| Hematuria | | | |
| subjects affected / exposed | 4 / 32 (12.50%) | | |
| occurrences (all) | 4 | | |
| General disorders and administration site conditions | | | |

| | | | |
|---|----------------------|--|--|
| Edema limbs subjects affected / exposed occurrences (all) | 3 / 32 (9.38%) 3 | | |
| Fatigue subjects affected / exposed occurrences (all) | 7 / 32 (21.88%) 7 | | |
| Other specify subjects affected / exposed occurrences (all) | 3 / 32 (9.38%) 3 | | |
| Insomnia subjects affected / exposed occurrences (all) | 3 / 32 (9.38%) 3 | | |
| Gastrointestinal disorders | | | |
| Constipation subjects affected / exposed occurrences (all) | 3 / 32 (9.38%) 3 | | |
| Diarrhea subjects affected / exposed occurrences (all) | 9 / 32 (28.13%) 9 | | |
| Other specify subjects affected / exposed occurrences (all) | 7 / 32 (21.88%) 7 | | |
| Nausea subjects affected / exposed occurrences (all) | 3 / 32 (9.38%) 3 | | |
| Vomiting subjects affected / exposed occurrences (all) | 3 / 32 (9.38%) 3 | | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus subjects affected / exposed occurrences (all) | 7 / 32 (21.88%) 7 | | |
| Rash maculo-papular subjects affected / exposed occurrences (all) | 3 / 32 (9.38%) 3 | | |
| Other specify | | | |

| | | | |
|--|------------------------|--|--|
| subjects affected / exposed occurrences (all) | 5 / 32 (15.63%) 5 | | |
| Renal and urinary disorders Other specify subjects affected / exposed occurrences (all) | 15 / 32 (46.88%) 15 | | |
| Urinary frequency subjects affected / exposed occurrences (all) | 11 / 32 (34.38%) 11 | | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 5 / 32 (15.63%) 5 | | |
| Urinary tract pain subjects affected / exposed occurrences (all) | 4 / 32 (12.50%) 4 | | |
| Musculoskeletal and connective tissue disorders Other specify subjects affected / exposed occurrences (all) | 4 / 32 (12.50%) 4 | | |
| Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all) | 4 / 32 (12.50%) 4 | | |
| Hyperthyroidism subjects affected / exposed occurrences (all) | 8 / 32 (25.00%) 8 | | |
| Hypothyroidism subjects affected / exposed occurrences (all) | 4 / 32 (12.50%) 4 | | |
| Other specify subjects affected / exposed occurrences (all) | 3 / 32 (9.38%) 3 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 24 May 2019 | Substantial amendment No. 1 is requested as a result of: <ul style="list-style-type: none">- Substantial amendment of part II of the trial with EudraCT 2017-003159-44 due to expansion of centers (IVO) and change of principal investigator at the Hospital Universitari i Politècnic La Fe.- The possibility of collecting urine samples from patients included in the Catalan Institute of Oncology L'Hospitalet is also included, for which changes are applied both in the protocol and by generating a specific patient information sheet for this purpose.- References to personal data protection are updated to current legislation. |
| 20 November 2019 | Substantial amendment No. 2 is requested as a result of: Due to problems with the stock of tremelimumab vials by the laboratory supplying the AstraZeneca molecule, the doses of the vials are modified, changing to 25 mg/mL of liquid solution at a concentration of 20 mg/mL with an expiration date. longer |
| 16 October 2020 | Substantial amendment No. 3 is requested as a result of: <ul style="list-style-type: none">- Safety changes due to the update of the investigator brochure from version 14 of Durvalumab to version 15 and from version 9 of Tremelimumab to version 10. These changes must be recorded in the Trial Protocol as well as in the Information Sheet. Patient Information.- Change of Principal Investigator at the ICO Hospital Germans Trias i Pujol Hospital, Badalona, Dr Olatz Etzaniz will replace Dr Alberto Font Pous. |
| 21 June 2021 | Substantial amendment No. 4 is requested as a result of: <ul style="list-style-type: none">- Update of the safety aspects of Imfinzi (Durvalumab) due to the new update of the Investigator's Brochure. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported