



## Clinical trial results:

### The DUTRENEO Trial: A Prospective Study to Individualize the Approach with DURvalumab (MEDI4736) and TREmelimumab in NEOadjuvant Bladder Cancer patients.

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2017-002246-68 |
| Trial protocol           | ES             |
| Global end of trial date | 12 April 2023  |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 12 February 2025 |
| First version publication date | 12 February 2025 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | DUTRENEO |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03472274 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Fundación CRIS de investigación para vencer el cáncer                                   |
| Sponsor organisation address | Avda. Manóteras, 22, 3º - Office 109, Madrid, Spain, 28050                              |
| Public contact               | Fundación CRIS contra el Cáncer, Fundación CRIS contra el Cáncer, alopez@criscancer.org |
| Scientific contact           | Enrique Grande, MD Anderson cancer Center Madrid, 0034 917878600, info@mdanderson.es    |

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                       | 02 October 2023 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 12 April 2023   |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 12 April 2023   |
| Was the trial ended prematurely?                     | No              |

Notes:

---

**General information about the trial**

---

Main objective of the trial:

To assess the antitumor activity measured as pT0 rate of durvalumab plus tremelimumab in comparison with the activity shown by standard chemo-based approach in selected patients with locally advanced urothelial bladder tumors with a pro-inflammatory composite biomarker selection.

Protection of trial subjects:

The patient signed the informed consent before carrying out any procedure related to the study. Physical examination, hematology, biochemistry, ECG, vital signs, pregnancy test, evaluation of adverse events and evaluation of the tumor were made before the inclusion of the patient in the study and during the study.

All adverse events that occur during the period comprehended from the time of enrollment of the patient in the study to 100 days after discontinuation of the investigational products were recorded.

---

Background therapy: -

Evidence for comparator:

The comparator selected for this study is standard cisplatin-based neoadjuvant chemotherapy, which is the recommended treatment for patients with muscle-invasive bladder cancer (MIBC) who are eligible for cisplatin.

Key studies and meta-analyses, have shown an improvement in survival rates with cisplatin-based chemotherapy compared to surgery alone. The regimens included in this trial (Gemcitabine/Cisplatin, ddMVAC, and others) represent current standards of care as recommended by major clinical guidelines. Moreover, cisplatin-based chemotherapy serves as a robust benchmark for evaluating the efficacy of novel therapeutic approaches, such as the immunotherapy combination (durvalumab + tremelimumab) being tested in this trial. Its inclusion ensures the validity and comparability of study outcomes within the established standard of care.

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 16 August 2018 |
| 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: 73 |
| Worldwide total number of subjects   | 73        |
| EEA total number of subjects         | 73        |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| 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)                      | 29 |
| From 65 to 84 years                       | 44 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Of the 101 patients that signed the informed consent, 28 were screening failures. 21 patients were assigned to the COLD: STANDARD arm, and 52 patients were randomized, 22 to the HOT: STANDARD arm and 30 to the HOT: DUTRENEO arm. All patients included in the analysis received study treatment.

### Pre-assignment

Screening details:

All patients with a negative pro-inflammatory signature who met the selection criteria and signed the informed consent were assigned to the control group.

All patients with a positive pro-inflammatory signature who met the selection criteria and signed the informed consent were randomly assigned to either the control or experimental group.

### Period 1

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

Blinding implementation details:

Patients were randomised centrally through an Interactive Voice/Web Response System (IXRS).

### Arms

|                              |                |
|------------------------------|----------------|
| Are arms mutually exclusive? | Yes            |
| <b>Arm title</b>             | COLD: STANDARD |

Arm description:

Patients in this arm received standard neoadjuvant chemotherapy based on their clinical evaluation and eligibility:

-Regimen 1: Combination of Gemcitabine + Cisplatin

-Regimen 2: Combination of ddMVAC (Methotrexate + Vinblastine + Doxorubicin + Cisplatin)

|  |                                       |
|--|---------------------------------------|
| Arm type                               | Active comparator                     |
| Investigational medicinal product name | Gemcitabine                           |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Gemcitabine 1,000-1,200 mg/m<sup>2</sup> was administered intravenously on days 1 and 8 of each 21-day cycle as part of Regimen 1 in combination with Cisplatin.

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name | Cisplatin                             |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Cisplatin 70 mg/m<sup>2</sup> was administered intravenously on day 1 of each 21-day treatment cycle for 3 cycles as part of as part of Regimen 1 in combination with Gemcitabine.

|  |  |
|--|--|
| Investigational medicinal product name | Methotrexate                                 |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |

|                          |                 |
|--------------------------|-----------------|
| Routes of administration | Intravenous use |
|--------------------------|-----------------|

Dosage and administration details:

Methotrexate 30 mg/m<sup>2</sup> was administered intravenously on day 1 as part of the combined treatment in Regimen 2.

|  |                                   |
|--|-----------------------------------|
| Investigational medicinal product name | Vinblastine                       |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Powder for solution for injection |
| Routes of administration               | Intravenous use                   |

Dosage and administration details:

Vinblastine 3 mg/m<sup>2</sup> was administered intravenously on day 2 of each 14-day cycle, in combination with Doxorubicin and Cisplatin, followed by Granulocyte Colony-Stimulating Factor (G-CSF) for 7 consecutive days (days 4 through 10) as part of the combined treatment in Regimen 2.

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name | Doxorubicin                           |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Doxorubicin 30 mg/m<sup>2</sup> was administered intravenously on day 2 of each 14-day cycle, in combination with Vinblastine and Cisplatin, followed by Granulocyte Colony-Stimulating Factor (G-CSF) for 7 consecutive days (days 4 through 10) as part of the combined treatment in Regimen 2.

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name | Cisplatin                             |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Cisplatin 70 mg/m<sup>2</sup> was administered intravenously on day 2 of each 14-day cycle, in combination with Vinblastine and Doxorubicin, followed by Granulocyte Colony-Stimulating Factor (G-CSF) for 7 consecutive days (days 4 through 10) as part of the combined treatment in Regimen 2.

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | HOT: STANDARD |
|------------------|---------------|

Arm description:

Patients in this arm received standard neoadjuvant chemotherapy based on their clinical evaluation and eligibility:

-Regimen 1: Combination of Gemcitabine + Cisplatin

-Regimen 2: Combination of ddMVAC (Methotrexate + Vinblastine + Doxorubicin + Cisplatin)

|  |                                       |
|--|---------------------------------------|
| Arm type                               | Active comparator                     |
| Investigational medicinal product name | Gemcitabine                           |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Gemcitabine 1,000-1,200 mg/m<sup>2</sup> was administered intravenously on days 1 and 8 of each 21-day cycle as part of Regimen 1 in combination with Cisplatin.

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name | Cisplatin                             |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |

|                          |                 |
|--------------------------|-----------------|
| Routes of administration | Intravenous use |
|--------------------------|-----------------|

Dosage and administration details:

Cisplatin 70 mg/m<sup>2</sup> was administered intravenously on day 1 of each 21-day treatment cycle for 3 cycles as part of as part of Regimen 1 in combination with Gemcitabine.

|  |  |
|--|--|
| Investigational medicinal product name | Methotrexate                                 |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Intravenous use                              |

Dosage and administration details:

Methotrexate 30 mg/m<sup>2</sup> was administered intravenously on day 1 as part of the combined treatment in Regimen 2.

|  |                                   |
|--|-----------------------------------|
| Investigational medicinal product name | Vinblastine                       |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Powder for solution for injection |
| Routes of administration               | Intravenous use                   |

Dosage and administration details:

Vinblastine 3 mg/m<sup>2</sup> was administered intravenously on day 2 of each 14-day cycle, in combination with Doxorubicin and Cisplatin, followed by Granulocyte Colony-Stimulating Factor (G-CSF) for 7 consecutive days (days 4 through 10) as part of the combined treatment in Regimen 2.

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name | Doxorubicin                           |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Doxorubicin 30 mg/m<sup>2</sup> was administered intravenously on day 2 of each 14-day cycle, in combination with Vinblastine and Cisplatin, followed by Granulocyte Colony-Stimulating Factor (G-CSF) for 7 consecutive days (days 4 through 10) as part of the combined treatment in Regimen 2.

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name | Cisplatin                             |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Cisplatin 70 mg/m<sup>2</sup> was administered intravenously on day 2 of each 14-day cycle, in combination with Vinblastine and Doxorubicin, followed by Granulocyte Colony-Stimulating Factor (G-CSF) for 7 consecutive days (days 4 through 10) as part of the combined treatment in Regimen 2.

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | HOT: DUTRENEO |
|------------------|---------------|

Arm description:

Patients in this arm received the combination of Durvalumab + Tremelimumab. Initially, a safety run-in was conducted with a small group of patients to assess the safety and tolerability of the combination therapy. This early phase was crucial to ensure that the treatment regimen was well-tolerated before proceeding with full recruitment. If no significant safety concerns were observed, recruitment would continue as planned.

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

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name | Durvalumab                            |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Durvalumab 1500 mg was administered intravenously every 4 weeks for 3 months as part of the combined treatment.

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

Dosage and administration details:

Tremelimumab 75 mg was administered intravenously every 4 weeks for 3 months as part of the combined treatment.

| <b>Number of subjects in period 1</b> | COLD: STANDARD | HOT: STANDARD | HOT: DUTRENEO |
|---------------------------------------|----------------|---------------|---------------|
| Started                               | 21             | 22            | 30            |
| Completed                             | 16             | 19            | 23            |
| Not completed                         | 5              | 3             | 7             |
| Consent withdrawn by subject          | 1              | 1             | -             |
| Death                                 | 3              | 2             | 6             |
| Lost to follow-up                     | -              | -             | 1             |
| Incorrectly enrolled                  | 1              | -             | -             |

## Baseline characteristics

### Reporting groups

|                       |                |
|-----------------------|----------------|
| Reporting group title | COLD: STANDARD |
|-----------------------|----------------|

Reporting group description:

Patients in this arm received standard neoadjuvant chemotherapy based on their clinical evaluation and eligibility:

-Regimen 1: Combination of Gemcitabine + Cisplatin

-Regimen 2: Combination of ddMVAC (Methotrexate + Vinblastine + Doxorubicin + Cisplatin)

|                       |               |
|-----------------------|---------------|
| Reporting group title | HOT: STANDARD |
|-----------------------|---------------|

Reporting group description:

Patients in this arm received standard neoadjuvant chemotherapy based on their clinical evaluation and eligibility:

-Regimen 1: Combination of Gemcitabine + Cisplatin

-Regimen 2: Combination of ddMVAC (Methotrexate + Vinblastine + Doxorubicin + Cisplatin)

|                       |               |
|-----------------------|---------------|
| Reporting group title | HOT: DUTRENEO |
|-----------------------|---------------|

Reporting group description:

Patients in this arm received the combination of Durvalumab + Tremelimumab. Initially, a safety run-in was conducted with a small group of patients to assess the safety and tolerability of the combination therapy. This early phase was crucial to ensure that the treatment regimen was well-tolerated before proceeding with full recruitment. If no significant safety concerns were observed, recruitment would continue as planned.

| Reporting group values              | COLD: STANDARD | HOT: STANDARD | HOT: DUTRENEO |
|-------------------------------------|----------------|---------------|---------------|
| Number of subjects                  | 21             | 22            | 30            |
| Age categorical                     |                |               |               |
| Units: Subjects                     |                |               |               |
| Adults (18-64 years)                | 7              | 10            | 12            |
| From 65-84 years                    | 14             | 12            | 18            |
| Age continuous                      |                |               |               |
| Units: years                        |                |               |               |
| arithmetic mean                     | 66.3           | 66.4          | 64.9          |
| inter-quartile range (Q1-Q3)        | 62.0 to 72.0   | 61.0 to 73.0  | 60.0 to 72.0  |
| Gender categorical                  |                |               |               |
| Units: Subjects                     |                |               |               |
| Female                              | 3              | 1             | 3             |
| Male                                | 18             | 21            | 27            |
| Race                                |                |               |               |
| Units: Subjects                     |                |               |               |
| Caucasian                           | 21             | 21            | 30            |
| Asian                               | 0              | 1             | 0             |
| ECOG-PS                             |                |               |               |
| Units: Subjects                     |                |               |               |
| ECOG-PS 0                           | 12             | 18            | 19            |
| ECOG-PS 1                           | 9              | 4             | 11            |
| Number of patients in each location |                |               |               |
| Units: Subjects                     |                |               |               |
| Bladder                             | 16             | 17            | 24            |
| Lymph nodes                         | 1              | 1             | 6             |



|   |                   |                   |                   |
|---|-------------------|-------------------|-------------------|
| No location   | 4                 | 4                 | 0                 |
| Treatment type by group<br>Units: Subjects  |                   |                   |                   |
| DUTRENEO  | 0                 | 0                 | 30                |
| Regimen 1   | 10                | 14                | 0                 |
| Regimen 2   | 11                | 8                 | 0                 |
| Previous surgery<br>Units: Subjects   |                   |                   |                   |
| Yes   | 21                | 22                | 30                |
| No  | 0                 | 0                 | 0                 |
| Previous radiotherapy<br>Units: Subjects  |                   |                   |                   |
| Yes   | 0                 | 0                 | 1                 |
| No  | 21                | 22                | 29                |
| Previous chemotherapy<br>Units: Subjects  |                   |                   |                   |
| Yes   | 0                 | 1                 | 1                 |
| No  | 21                | 21                | 29                |
| Other previous anticancer therapies<br>Units: Subjects  |                   |                   |                   |
| BCG   | 1                 | 4                 | 3                 |
| Homeopathic treatment (oral)  | 0                 | 0                 | 1                 |
| No previous anticancer therapies  | 20                | 18                | 26                |
| Cystectomy performed<br>Units: Subjects   |                   |                   |                   |
| No  | 0                 | 1                 | 3                 |
| Yes   | 20                | 20                | 26                |
| Not available   | 1                 | 1                 | 1                 |
| Number of cycles by Group<br>Units: Number of cycles<br>arithmetic mean<br>inter-quartile range (Q1-Q3) | 2.4<br>2.0 to 3.0 | 2.4<br>2.0 to 3.0 | 2.7<br>2.0 to 3.0 |

|   |       |  |  |
|---|-------|--|--|
| <b>Reporting group values</b>   | Total |  |  |
| Number of subjects  | 73    |  |  |
| Age categorical<br>Units: Subjects  |       |  |  |
| Adults (18-64 years)  | 29    |  |  |
| From 65-84 years  | 44    |  |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>inter-quartile range (Q1-Q3) | -     |  |  |
| Gender categorical<br>Units: Subjects   |       |  |  |
| Female  | 7     |  |  |
| Male  | 66    |  |  |
| Race<br>Units: Subjects   |       |  |  |
| Caucasian   | 72    |  |  |
| Asian   | 1     |  |  |

|                                     |    |  |  |
|-------------------------------------|----|--|--|
| ECOG-PS                             |    |  |  |
| Units: Subjects                     |    |  |  |
| ECOG-PS 0                           | 49 |  |  |
| ECOG-PS 1                           | 24 |  |  |
| Number of patients in each location |    |  |  |
| Units: Subjects                     |    |  |  |
| Bladder                             | 57 |  |  |
| Lymph nodes                         | 8  |  |  |
| No location                         | 8  |  |  |
| Treatment type by group             |    |  |  |
| Units: Subjects                     |    |  |  |
| DUTRENEO                            | 30 |  |  |
| Regimen 1                           | 24 |  |  |
| Regimen 2                           | 19 |  |  |
| Previous surgery                    |    |  |  |
| Units: Subjects                     |    |  |  |
| Yes                                 | 73 |  |  |
| No                                  | 0  |  |  |
| Previous radiotherapy               |    |  |  |
| Units: Subjects                     |    |  |  |
| Yes                                 | 1  |  |  |
| No                                  | 72 |  |  |
| Previous chemotherapy               |    |  |  |
| Units: Subjects                     |    |  |  |
| Yes                                 | 2  |  |  |
| No                                  | 71 |  |  |
| Other previous anticancer therapies |    |  |  |
| Units: Subjects                     |    |  |  |
| BCG                                 | 8  |  |  |
| Homeopathic treatment (oral)        | 1  |  |  |
| No previous anticancer therapies    | 64 |  |  |
| Cystectomy performed                |    |  |  |
| Units: Subjects                     |    |  |  |
| No                                  | 4  |  |  |
| Yes                                 | 66 |  |  |
| Not available                       | 3  |  |  |
| Number of cycles by Group           |    |  |  |
| Units: Number of cycles             |    |  |  |
| arithmetic mean                     |    |  |  |
| inter-quartile range (Q1-Q3)        | -  |  |  |

---

### Subject analysis sets

|                                   |               |
|-----------------------------------|---------------|
| Subject analysis set title        | Overall       |
| Subject analysis set type         | Full analysis |
| Subject analysis set description: |               |
| Received study medication         |               |

---

|   |                      |  |  |
|---|----------------------|--|--|
| <b>Reporting group values</b>   | Overall              |  |  |
| Number of subjects  | 73                   |  |  |
| Age categorical<br>Units: Subjects  |                      |  |  |
| Adults (18-64 years)  | 29                   |  |  |
| From 65-84 years  | 44                   |  |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>inter-quartile range (Q1-Q3) | 65.7<br>61.0 to 72.0 |  |  |
| Gender categorical<br>Units: Subjects   |                      |  |  |
| Female  | 7                    |  |  |
| Male  | 66                   |  |  |
| Race<br>Units: Subjects   |                      |  |  |
| Caucasian   | 72                   |  |  |
| Asian   | 1                    |  |  |
| ECOG-PS<br>Units: Subjects  |                      |  |  |
| ECOG-PS 0   | 49                   |  |  |
| ECOG-PS 1   | 24                   |  |  |
| Number of patients in each location<br>Units: Subjects                            |                      |  |  |
| Bladder   | 57                   |  |  |
| Lymph nodes   | 8                    |  |  |
| No location   | 8                    |  |  |
| Treatment type by group<br>Units: Subjects  |                      |  |  |
| DUTRENEO  | 30                   |  |  |
| Regimen 1   | 24                   |  |  |
| Regimen 2   | 19                   |  |  |
| Previous surgery<br>Units: Subjects   |                      |  |  |
| Yes   | 73                   |  |  |
| No  | 0                    |  |  |
| Previous radiotherapy<br>Units: Subjects  |                      |  |  |
| Yes   | 1                    |  |  |
| No  | 72                   |  |  |
| Previous chemotherapy<br>Units: Subjects  |                      |  |  |
| Yes   | 2                    |  |  |
| No  | 71                   |  |  |
| Other previous anticancer therapies<br>Units: Subjects                            |                      |  |  |
| BCG   | 8                    |  |  |
| Homeopathic treatment (oral)  | 1                    |  |  |
| No previous anticancer therapies  | 64                   |  |  |
| Cystectomy performed<br>Units: Subjects   |                      |  |  |

|                              |            |  |  |
|------------------------------|------------|--|--|
| No                           | 4          |  |  |
| Yes                          | 66         |  |  |
| Not available                | 3          |  |  |
| Number of cycles by Group    |            |  |  |
| Units: Number of cycles      |            |  |  |
| arithmetic mean              | 2.5        |  |  |
| inter-quartile range (Q1-Q3) | 2.0 to 3.0 |  |  |

## End points

### End points reporting groups

|                       |                |
|-----------------------|----------------|
| Reporting group title | COLD: STANDARD |
|-----------------------|----------------|

Reporting group description:

Patients in this arm received standard neoadjuvant chemotherapy based on their clinical evaluation and eligibility:

-Regimen 1: Combination of Gemcitabine + Cisplatin

-Regimen 2: Combination of ddMVAC (Methotrexate + Vinblastine + Doxorubicin + Cisplatin)

|                       |               |
|-----------------------|---------------|
| Reporting group title | HOT: STANDARD |
|-----------------------|---------------|

Reporting group description:

Patients in this arm received standard neoadjuvant chemotherapy based on their clinical evaluation and eligibility:

-Regimen 1: Combination of Gemcitabine + Cisplatin

-Regimen 2: Combination of ddMVAC (Methotrexate + Vinblastine + Doxorubicin + Cisplatin)

|                       |               |
|-----------------------|---------------|
| Reporting group title | HOT: DUTRENEO |
|-----------------------|---------------|

Reporting group description:

Patients in this arm received the combination of Durvalumab + Tremelimumab. Initially, a safety run-in was conducted with a small group of patients to assess the safety and tolerability of the combination therapy. This early phase was crucial to ensure that the treatment regimen was well-tolerated before proceeding with full recruitment. If no significant safety concerns were observed, recruitment would continue as planned.

|                            |         |
|----------------------------|---------|
| Subject analysis set title | Overall |
|----------------------------|---------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Received study medication

### Primary: Pathological complete response (pT0)

|                 |   |
|-----------------|---|
| End point title | Pathological complete response (pT0) <sup>[1]</sup> |
|-----------------|---|

End point description:

The antitumor activity is measured as pT0 rate (defined as no evidence of residual disease based on pathological review of the surgical specimen) of durvalumab plus tremelimumab in comparison with the activity shown by standard chemo-based approach in selected patients with locally advanced urothelial bladder cancer with a pro-inflammatory composite biomarker selection.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

20 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: Statistical analysis is not included for this primary endpoint according to the study design.

| End point values            | COLD:<br>STANDARD | HOT:<br>STANDARD | HOT:<br>DUTRENEO | Overall              |
|-----------------------------|-------------------|------------------|------------------|----------------------|
| Subject group type          | Reporting group   | Reporting group  | Reporting group  | Subject analysis set |
| Number of subjects analysed | 21                | 22               | 30               | 73                   |
| Units: Patients             | 11                | 6                | 10               | 27                   |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Response Rate (ORR)

|  |                             |
|--|-----------------------------|
| End point title  | Overall Response Rate (ORR) |
| End point description:<br>ORR is defined as the number of subjects with a best overall response (BOR) of a complete response (CR) or partial response (PR) divided by the number of randomized subjects for each treatment group. The BOR is defined as the best response designation, as determined investigator assessment, recorded between the date of randomization and the date of cystectomy, as assessed by investigator per RECIST 1.1. |                             |
| End point type   | Secondary                   |
| End point timeframe:<br>20 weeks   |                             |

| End point values                 | COLD:<br>STANDARD   | HOT:<br>STANDARD   | HOT:<br>DUTRENEO   | Overall              |
|----------------------------------|---------------------|--------------------|--------------------|----------------------|
| Subject group type               | Reporting group     | Reporting group    | Reporting group    | Subject analysis set |
| Number of subjects analysed      | 21                  | 22                 | 30                 | 73                   |
| Units: percent                   |                     |                    |                    |                      |
| number (confidence interval 95%) | 42.9 (21.7 to 64.0) | 18.8 (2.1 to 34.3) | 13.3 (1.2 to 25.5) | 23.3 (13.6 to 33.0)  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Disease Free Survival (DFS)

|   |                             |
|---|-----------------------------|
| End point title   | Disease Free Survival (DFS) |
| End point description:<br>Disease Free Survival (DFS) is defined as the time (in months) elapsed between the start of treatment with durvalumab and tremelimumab or cisplatin-based chemotherapy until the documentation of disease recurrence according to RECIST v1.1 or death due to any cause, whichever occurs first. For subjects who are alive and disease-free at the time of data cut-off for analysis, DFS has been censored at the last tumor assessment date. |                             |
| End point type  | Secondary                   |
| End point timeframe:<br>2 years   |                             |

| End point values                 | COLD:<br>STANDARD        | HOT:<br>STANDARD          | HOT:<br>DUTRENEO         | Overall                  |
|----------------------------------|--------------------------|---------------------------|--------------------------|--------------------------|
| Subject group type               | Reporting group          | Reporting group           | Reporting group          | Subject analysis set     |
| Number of subjects analysed      | 21                       | 22                        | 30                       | 73                       |
| Units: month                     |                          |                           |                          |                          |
| median (confidence interval 95%) | 14.671 (0.000 to 32.230) | 27.632 (27.632 to 27.632) | 26.480 (1.992 to 50.968) | 14.737 (6.932 to 22.541) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival (OS)

|                 |                       |
|-----------------|-----------------------|
| End point title | Overall Survival (OS) |
|-----------------|-----------------------|

End point description:

Overall survival (OS) is defined as the time (in months) from the start of treatment with the combination of durvalumab and tremelimumab or cisplatin-based chemotherapy until death due to any cause. For subjects who are alive at the time of data cut-off, OS has been censored on the last date when subjects are known to be alive.

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

End point timeframe:

2 years

| End point values                 | Overall                   |  |  |  |
|----------------------------------|---------------------------|--|--|--|
| Subject group type               | Subject analysis set      |  |  |  |
| Number of subjects analysed      | 73                        |  |  |  |
| Units: month                     |                           |  |  |  |
| median (confidence interval 95%) | 41.809 (26.674 to 56.945) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All adverse events were documented during study treatment at each study visit and for minimum of 100 days after the last dose of study medications.

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 27.0 |
|--------------------|------|

### Reporting groups

|                       |                |
|-----------------------|----------------|
| Reporting group title | COLD: STANDARD |
|-----------------------|----------------|

Reporting group description: -

|                       |               |
|-----------------------|---------------|
| Reporting group title | HOT: STANDARD |
|-----------------------|---------------|

Reporting group description: -

|                       |               |
|-----------------------|---------------|
| Reporting group title | HOT: DUTRENEO |
|-----------------------|---------------|

Reporting group description: -

| Serious adverse events  | COLD: STANDARD   | HOT: STANDARD   | HOT: DUTRENEO    |
|---|------------------|-----------------|------------------|
| Total subjects affected by serious adverse events                   |                  |                 |                  |
| subjects affected / exposed   | 10 / 21 (47.62%) | 4 / 22 (18.18%) | 15 / 30 (50.00%) |
| number of deaths (all causes)                                       | 3                | 3               | 6                |
| number of deaths resulting from adverse events                      | 1                | 0               | 0                |
| Investigations  |                  |                 |                  |
| Blood creatine phosphokinase increased                              |                  |                 |                  |
| subjects affected / exposed   | 0 / 21 (0.00%)   | 0 / 22 (0.00%)  | 1 / 30 (3.33%)   |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 0           | 1 / 1            |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0           | 0 / 0            |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                 |                  |
| Follicular lymphoma   |                  |                 |                  |
| subjects affected / exposed   | 1 / 21 (4.76%)   | 0 / 22 (0.00%)  | 0 / 30 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 1            | 0 / 0           | 0 / 0            |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0           | 0 / 0            |
| Tumour pain   |                  |                 |                  |
| subjects affected / exposed   | 0 / 21 (0.00%)   | 0 / 22 (0.00%)  | 1 / 30 (3.33%)   |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 0           | 0 / 1            |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0           | 0 / 0            |
| Cardiac disorders   |                  |                 |                  |



|  |                |                |                |
|--|----------------|----------------|----------------|
| Myocardial infarction                                |                |                |                |
| subjects affected / exposed                          | 1 / 21 (4.76%) | 0 / 22 (0.00%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all      | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Myocarditis  |                |                |                |
| subjects affected / exposed                          | 0 / 21 (0.00%) | 0 / 22 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                             |                |                |                |
| Coma   |                |                |                |
| subjects affected / exposed                          | 0 / 21 (0.00%) | 0 / 22 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |                |                |                |
| Asthenia   |                |                |                |
| subjects affected / exposed                          | 0 / 21 (0.00%) | 0 / 22 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Pyrexia  |                |                |                |
| subjects affected / exposed                          | 1 / 21 (4.76%) | 0 / 22 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all      | 1 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                           |                |                |                |
| Gastrointestinal toxicity                            |                |                |                |
| subjects affected / exposed                          | 0 / 21 (0.00%) | 1 / 22 (4.55%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Hernial eventration                                  |                |                |                |
| subjects affected / exposed                          | 0 / 21 (0.00%) | 0 / 22 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Reproductive system and breast disorders             |                |                |                |
| Pelvic fluid collection                              |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 21 (0.00%) | 0 / 22 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Prostatitis                                     |                |                |                |
| subjects affected / exposed                     | 0 / 21 (0.00%) | 0 / 22 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatobiliary disorders                         |                |                |                |
| Liver disorder                                  |                |                |                |
| subjects affected / exposed                     | 1 / 21 (4.76%) | 0 / 22 (0.00%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| Aspiration                                      |                |                |                |
| subjects affected / exposed                     | 1 / 21 (4.76%) | 0 / 22 (0.00%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pulmonary embolism                              |                |                |                |
| subjects affected / exposed                     | 0 / 21 (0.00%) | 1 / 22 (4.55%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |
| Acute kidney injury                             |                |                |                |
| subjects affected / exposed                     | 0 / 21 (0.00%) | 0 / 22 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Autoimmune nephritis                            |                |                |                |
| subjects affected / exposed                     | 0 / 21 (0.00%) | 0 / 22 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Urinoma   |                |                |                |
| subjects affected / exposed                     | 0 / 21 (0.00%) | 0 / 22 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Musculoskeletal and connective tissue disorders |                |                |                |
| Myositis  |                |                |                |
| subjects affected / exposed                     | 0 / 21 (0.00%) | 0 / 22 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Bacteraemia                                     |                |                |                |
| subjects affected / exposed                     | 0 / 21 (0.00%) | 1 / 22 (4.55%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| COVID-19  |                |                |                |
| subjects affected / exposed                     | 1 / 21 (4.76%) | 0 / 22 (0.00%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Peritonitis                                     |                |                |                |
| subjects affected / exposed                     | 1 / 21 (4.76%) | 0 / 22 (0.00%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pyelonephritis                                  |                |                |                |
| subjects affected / exposed                     | 1 / 21 (4.76%) | 0 / 22 (0.00%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Pyelonephritis acute                            |                |                |                |
| subjects affected / exposed                     | 0 / 21 (0.00%) | 0 / 22 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Sepsis  |                |                |                |
| subjects affected / exposed                     | 1 / 21 (4.76%) | 0 / 22 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Septic shock                                    |                |                |                |
| subjects affected / exposed                     | 1 / 21 (4.76%) | 0 / 22 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

|   |                 |                 |                |
|---|-----------------|-----------------|----------------|
| Urinary tract infection                         |                 |                 |                |
| subjects affected / exposed                     | 3 / 21 (14.29%) | 3 / 22 (13.64%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 4           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Urosepsis                                       |                 |                 |                |
| subjects affected / exposed                     | 1 / 21 (4.76%)  | 0 / 22 (0.00%)  | 2 / 30 (6.67%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 3          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |

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

| <b>Non-serious adverse events</b>                     | COLD: STANDARD    | HOT: STANDARD     | HOT: DUTRENEO    |
|---|-------------------|-------------------|------------------|
| Total subjects affected by non-serious adverse events |                   |                   |                  |
| subjects affected / exposed                           | 21 / 21 (100.00%) | 22 / 22 (100.00%) | 26 / 30 (86.67%) |
| General disorders and administration site conditions  |                   |                   |                  |
| Asthenia  |                   |                   |                  |
| subjects affected / exposed                           | 14 / 21 (66.67%)  | 18 / 22 (81.82%)  | 14 / 30 (46.67%) |
| occurrences (all)                                     | 25                | 32                | 24               |
| Mucosal inflammation                                  |                   |                   |                  |
| subjects affected / exposed                           | 4 / 21 (19.05%)   | 2 / 22 (9.09%)    | 1 / 30 (3.33%)   |
| occurrences (all)                                     | 5                 | 3                 | 1                |
| Pyrexia   |                   |                   |                  |
| subjects affected / exposed                           | 3 / 21 (14.29%)   | 0 / 22 (0.00%)    | 3 / 30 (10.00%)  |
| occurrences (all)                                     | 3                 | 0                 | 3                |
| Respiratory, thoracic and mediastinal disorders       |                   |                   |                  |
| Cough   |                   |                   |                  |
| subjects affected / exposed                           | 1 / 21 (4.76%)    | 1 / 22 (4.55%)    | 3 / 30 (10.00%)  |
| occurrences (all)                                     | 1                 | 1                 | 3                |
| Psychiatric disorders                                 |                   |                   |                  |
| Insomnia  |                   |                   |                  |
| subjects affected / exposed                           | 1 / 21 (4.76%)    | 3 / 22 (13.64%)   | 1 / 30 (3.33%)   |
| occurrences (all)                                     | 1                 | 4                 | 2                |
| Investigations  |                   |                   |                  |
| Alanine aminotransferase increased                    |                   |                   |                  |

|                                      |                  |                  |                 |
|--------------------------------------|------------------|------------------|-----------------|
| subjects affected / exposed          | 3 / 21 (14.29%)  | 0 / 22 (0.00%)   | 2 / 30 (6.67%)  |
| occurrences (all)                    | 3                | 0                | 2               |
| Aspartate aminotransferase increased |                  |                  |                 |
| subjects affected / exposed          | 3 / 21 (14.29%)  | 0 / 22 (0.00%)   | 1 / 30 (3.33%)  |
| occurrences (all)                    | 3                | 0                | 3               |
| Lipase increased                     |                  |                  |                 |
| subjects affected / exposed          | 1 / 21 (4.76%)   | 0 / 22 (0.00%)   | 2 / 30 (6.67%)  |
| occurrences (all)                    | 2                | 0                | 2               |
| Neutrophil count decreased           |                  |                  |                 |
| subjects affected / exposed          | 4 / 21 (19.05%)  | 2 / 22 (9.09%)   | 0 / 30 (0.00%)  |
| occurrences (all)                    | 8                | 4                | 0               |
| Platelet count decreased             |                  |                  |                 |
| subjects affected / exposed          | 4 / 21 (19.05%)  | 2 / 22 (9.09%)   | 0 / 30 (0.00%)  |
| occurrences (all)                    | 8                | 6                | 0               |
| Weight decreased                     |                  |                  |                 |
| subjects affected / exposed          | 1 / 21 (4.76%)   | 0 / 22 (0.00%)   | 2 / 30 (6.67%)  |
| occurrences (all)                    | 2                | 0                | 2               |
| Nervous system disorders             |                  |                  |                 |
| Dysgeusia                            |                  |                  |                 |
| subjects affected / exposed          | 8 / 21 (38.10%)  | 2 / 22 (9.09%)   | 0 / 30 (0.00%)  |
| occurrences (all)                    | 13               | 2                | 0               |
| Blood and lymphatic system disorders |                  |                  |                 |
| Anaemia                              |                  |                  |                 |
| subjects affected / exposed          | 11 / 21 (52.38%) | 7 / 22 (31.82%)  | 5 / 30 (16.67%) |
| occurrences (all)                    | 13               | 14               | 7               |
| Neutropenia                          |                  |                  |                 |
| subjects affected / exposed          | 9 / 21 (42.86%)  | 8 / 22 (36.36%)  | 0 / 30 (0.00%)  |
| occurrences (all)                    | 12               | 12               | 0               |
| Thrombocytopenia                     |                  |                  |                 |
| subjects affected / exposed          | 7 / 21 (33.33%)  | 12 / 22 (54.55%) | 0 / 30 (0.00%)  |
| occurrences (all)                    | 8                | 18               | 0               |
| Gastrointestinal disorders           |                  |                  |                 |
| Abdominal pain                       |                  |                  |                 |
| subjects affected / exposed          | 0 / 21 (0.00%)   | 1 / 22 (4.55%)   | 2 / 30 (6.67%)  |
| occurrences (all)                    | 0                | 1                | 4               |
| Constipation                         |                  |                  |                 |

|  |                  |                  |                 |
|--|------------------|------------------|-----------------|
| subjects affected / exposed            | 7 / 21 (33.33%)  | 6 / 22 (27.27%)  | 3 / 30 (10.00%) |
| occurrences (all)                      | 12               | 8                | 3               |
| Diarrhoea                              |                  |                  |                 |
| subjects affected / exposed            | 4 / 21 (19.05%)  | 3 / 22 (13.64%)  | 4 / 30 (13.33%) |
| occurrences (all)                      | 5                | 4                | 9               |
| Dyspepsia                              |                  |                  |                 |
| subjects affected / exposed            | 4 / 21 (19.05%)  | 1 / 22 (4.55%)   | 0 / 30 (0.00%)  |
| occurrences (all)                      | 4                | 1                | 0               |
| Nausea                                 |                  |                  |                 |
| subjects affected / exposed            | 10 / 21 (47.62%) | 15 / 22 (68.18%) | 2 / 30 (6.67%)  |
| occurrences (all)                      | 17               | 26               | 2               |
| Vomiting                               |                  |                  |                 |
| subjects affected / exposed            | 5 / 21 (23.81%)  | 4 / 22 (18.18%)  | 1 / 30 (3.33%)  |
| occurrences (all)                      | 5                | 5                | 2               |
| Skin and subcutaneous tissue disorders |                  |                  |                 |
| Alopecia                               |                  |                  |                 |
| subjects affected / exposed            | 6 / 21 (28.57%)  | 5 / 22 (22.73%)  | 1 / 30 (3.33%)  |
| occurrences (all)                      | 6                | 5                | 1               |
| Pruritus                               |                  |                  |                 |
| subjects affected / exposed            | 1 / 21 (4.76%)   | 1 / 22 (4.55%)   | 7 / 30 (23.33%) |
| occurrences (all)                      | 1                | 1                | 10              |
| Rash                                   |                  |                  |                 |
| subjects affected / exposed            | 0 / 21 (0.00%)   | 2 / 22 (9.09%)   | 6 / 30 (20.00%) |
| occurrences (all)                      | 0                | 3                | 6               |
| Renal and urinary disorders            |                  |                  |                 |
| Dysuria                                |                  |                  |                 |
| subjects affected / exposed            | 1 / 21 (4.76%)   | 0 / 22 (0.00%)   | 3 / 30 (10.00%) |
| occurrences (all)                      | 1                | 0                | 3               |
| Haematuria                             |                  |                  |                 |
| subjects affected / exposed            | 1 / 21 (4.76%)   | 1 / 22 (4.55%)   | 5 / 30 (16.67%) |
| occurrences (all)                      | 2                | 1                | 5               |
| Nocturia                               |                  |                  |                 |
| subjects affected / exposed            | 0 / 21 (0.00%)   | 1 / 22 (4.55%)   | 1 / 30 (3.33%)  |
| occurrences (all)                      | 0                | 2                | 3               |
| Endocrine disorders                    |                  |                  |                 |

|   |                       |                       |                      |
|---|-----------------------|-----------------------|----------------------|
| Hyperthyroidism<br>subjects affected / exposed<br>occurrences (all)   | 0 / 21 (0.00%)<br>0   | 0 / 22 (0.00%)<br>0   | 4 / 30 (13.33%)<br>5 |
| Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)  | 0 / 21 (0.00%)<br>0   | 1 / 22 (4.55%)<br>1   | 1 / 30 (3.33%)<br>3  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 0 / 21 (0.00%)<br>0   | 0 / 22 (0.00%)<br>0   | 3 / 30 (10.00%)<br>4 |
| Infections and infestations<br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)        | 5 / 21 (23.81%)<br>8  | 4 / 22 (18.18%)<br>6  | 8 / 30 (26.67%)<br>9 |
| Urosepsis<br>subjects affected / exposed<br>occurrences (all)   | 1 / 21 (4.76%)<br>1   | 0 / 22 (0.00%)<br>0   | 2 / 30 (6.67%)<br>3  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all)      | 9 / 21 (42.86%)<br>15 | 8 / 22 (36.36%)<br>10 | 2 / 30 (6.67%)<br>2  |
| Hypomagnesaemia<br>subjects affected / exposed<br>occurrences (all)   | 3 / 21 (14.29%)<br>4  | 0 / 22 (0.00%)<br>0   | 0 / 30 (0.00%)<br>0  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 18 December 2018 | Durvalumab Investigator Brochure has been updated from 12th version to 13th version. New AESIs have been described. Protocol and Patient Information Sheet have been updated according to new IB safety information.   |
| 14 October 2019  | AstraZeneca will provide for this study 25 mg vials in addition to the initially foreseen 400 mg vials in order to avoid stock issues.   |
| 22 December 2020 | This relevant amendment modifies the protocol due to the latest update of the durvalumab investigator's brochure. The changes apply mainly to adverse events of special interest and durvalumab-associated toxicity management guidelines. The FUNDACION CRIS address has been updated in the protocol. This change has not been detailed in the amendment document. |

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

|               |
|---------------|
| None reported |
|---------------|

Notes: