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. Manoteras, 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:

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)	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
Arm title	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/m² 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/m² 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/m² 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/m² 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/m² 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/m² 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.

Arm title	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/m² 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/m² 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/m² 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/m² 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/m² 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/m² 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.

Arm title	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.

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

Reporting group values	Total		
Number of subjects	73		
Age categorical Units: Subjects			
Adults (18-64 years)	29		
From 65-84 years	44		
Age continuous Units: years arithmetic mean inter-quartile range (Q1-Q3)	- -		
Gender categorical Units: Subjects			
Female	7		
Male	66		
Race 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 therapiess	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	

Reporting group values	Overall		
Number of subjects	73		
Age categorical Units: Subjects			
Adults (18-64 years)	29		
From 65-84 years	44		
Age continuous Units: years			
arithmetic mean	65.7		
inter-quartile range (Q1-Q3)	61.0 to 72.0		
Gender categorical Units: Subjects			
Female	7		
Male	66		
Race 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 therapiess	64		
Cystectomy performed 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)[1]

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: STANDARD	HOT: STANDARD	HOT: 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:

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:

20 weeks

End point values	COLD: STANDARD	HOT: STANDARD	HOT: 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:

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:

2 years

End point values	COLD: STANDARD	HOT: STANDARD	HOT: 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 %

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