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

Summary

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

Results information

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

Trial information

Trial identification

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

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 August 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 August 2022
Global end of trial reached?	Yes
Global end of trial date	16 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	5
From 65 to 84 years	25
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Blinding implementation details:

single-arm study

Arms

Arm title	Experimental arm

Arm description:

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

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

Dosage and administration details:

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

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

Dosage and administration details:

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

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

Baseline characteristics

Reporting groups

Reporting group title	Study period

Reporting group description: -

Reporting group values	Study period	Total	
Number of subjects	32	32	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	71		
full range (min-max)	49 to 91	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	25	25	
Eastern Cooperative Oncology Group Performance Status (ECOG-PS)			
Measure Description: Describes a patient’s level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (walking, working...). The scale ranges from 0 (Fully active, able to carry on all pre-disease performance without restriction) to 5 (Dead).			
Units: Subjects			
ECOG 0	25	25	
ECOG 1	7	7	
Histology			
Measure Description: Describes the histology subtype of tumor, the type of cells from which the tumor has arisen			
Units: Subjects			
Urothelial carcinoma	31	31	
Mixed urothelial carcinoma	1	1	
Clinical T stage			
] Measure Description: T stage according to AJCC criteria. Describes the extent of tumor spread and size. T ranges from T1 (The tumor has spread to the connective tissue but it does not involve the bladder wall muscle) to T4 (The tumor has spread to any of the following: the abdominal wall, the pelvic wall, the prostate or seminal vesicle, or the uterus or vagina).			
Units: Subjects			
T2	28	28	
T3	3	3	

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

End points

End points reporting groups

Reporting group title	Experimental arm

Reporting group description:

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

Primary: Proportion of Patients With Pathological Response

End point title	Proportion of Patients With Pathological Response[1]

End point description:

Pathological response is defined as the absence of muscle- invasive bladder cancer at post-treatment biopsy (≤cT1).
Cystoscopy and bladder biopsy six weeks since the end of radiotherapy

End point type	Primary

End point timeframe:

12 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This is a single arm trial. No comparisons were scheduled as only one group of patients is evaluated. the trial results are discussed and compared to previous data in scientific publications.

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Patients With Bladder Preserved

End point title	Rate of Patients With Bladder Preserved

End point description:

Number of patients whom bladder has been preserved after cytoscopic evaluation.

End point type	Secondary

End point timeframe:

24 months

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Immediate Salvage Cystectomies

End point title	Rate of Immediate Salvage Cystectomies

End point description:

Number of patients with indication of salvage cystectomies after first trial-related cystoscopic evaluation.

End point type	Secondary

End point timeframe:

24 months

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

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Late Salvage Cystectomies

End point title	Rate of Late Salvage Cystectomies

End point description:

Number of patients with indication of salvage cystectomies based on follow-up cystoscopic evaluation.

End point type	Secondary

End point timeframe:

24 months

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

Statistical analyses

No statistical analyses for this end point

Secondary: Survival With Bladder Preserved Free of Tumor

End point title	Survival With Bladder Preserved Free of Tumor

End point description:

Time from the start of immunotherapy to either the date of cystectomy or the date of recurrence of muscle- invasive bladder carcinoma or metastasis.
Here we report the estimated rate of patients free of event at 24 months after the start of immunotherapy. Estimation by kaplan meier method.

End point type	Secondary

End point timeframe:

24 months

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

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-free Survival

End point title	Disease-free Survival

End point description:

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

End point type	Secondary

End point timeframe:

24 months

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

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Time from the start of immunotherapy to the date of death due to any cause. The reported outcome is the estimated ratio of patients alive at 24 months after start of immunotherapy using kaplan meier method.

End point type	Secondary

End point timeframe:

24 months

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

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants With Treatment-related Adverse Events as Assessed by CTCAE v4.0

End point description:

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

End point type	Secondary

End point timeframe:

24 months

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

24 months

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Throughout the study period, approximately a median o 24 months follow up.	
Assessment type	Systematic

Dictionary used	
Dictionary name	NCICTCAE
Dictionary version	4

Reporting groups	
Reporting group title	Full dataset
Reporting group description:	
All patients who received at least one dose of studry treatment.	

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 May 2019	Substantial amendment No. 1 is requested as a result of: - Substantial amendment of part II of the trial with EudraCT 2017-003159-44 due to expansion of centers (IVO) and change of principal investigator at the Hospital Universitari i Politècnic La Fe. - The possibility of collecting urine samples from patients included in the Catalan Institute of Oncology L'Hospitalet is also included, for which changes are applied both in the protocol and by generating a specific patient information sheet for this purpose. - References to personal data protection are updated to current legislation.
20 November 2019	Substantial amendment No. 2 is requested as a result of: Due to problems with the stock of tremelimumab vials by the laboratory supplying the AstraZeneca molecule, the doses of the vials are modified, changing to 25 mg/mL of liquid solution at a concentration of 20 mg/mL with an expiration date. longer
16 October 2020	Substantial amendment No. 3 is requested as a result of: - Safety changes due to the update of the investigator brochure from version 14 of Durvalumab to version 15 and from version 9 of Tremelimumab to version 10. These changes must be recorded in the Trial Protocol as well as in the Information Sheet. Patient Information. - Change of Principal Investigator at the ICO Hospital Germans Trias i Pujol Hospital, Badalona, Dr Olatz Etxaniz will replace Dr Alberto Font Pous.
21 June 2021	Substantial amendment No. 4 is requested as a result of: - Update of the safety aspects of Imfinzi (Durvalumab) due to the new update of the Investigator's Brochure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported