Clinical trial results:
Phase II multicenter study to analyze the predictive value of fusion gene TMPRSS2-ETS in response to enzalutamide in patients with metastatic CRPC no previously treated with chemotherapy

Summary

EudraCT number	2014-003192-28
Trial protocol	ES
Global end of trial date	18 July 2019

Results information

Result version number	v1 (current)
This version publication date	27 November 2020
First version publication date	27 November 2020

Trial information

Trial identification

Sponsor protocol code	SOG-MIE-2014-04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02288936
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Spanish Oncology Genito-Urinary Group
Sponsor organisation address	Velázquez, 7, 3rd floor, Madrid, Spain, 28001
Public contact	Spanish Oncology Genito-Urinary Group, SOGUG, 0034 610286915,
Scientific contact	Spanish Oncology Genito-Urinary Group, SOGUG, 0034 610286915,

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	21 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 July 2019
Global end of trial reached?	Yes
Global end of trial date	18 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

PSA progression free survival (PCWG2 criteria) depending on the presence of TMPRSS2-ETS fusion gene rearrangements

Protection of trial subjects:

All patients have been treated according to GCP criteria.
Patients were entitled to withdraw from the study at any time and for any reason without prejudice of their future medical care on the part of the doctor or the center.
Any medication that patients needed for their correct clinical control (except prohibited therapies), according to investigator's criteria were allowed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 January 2015
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: 98
Worldwide total number of subjects	98
EEA total number of subjects	98

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)	9
From 65 to 84 years	80
85 years and over	9

Subject disposition

Recruitment

Recruitment details:

Patients initiated enzalutamide as first line treatment between February and November 2015 at 16 Spanish institutions

Pre-assignment

Screening details:

Patients had to sign an informed consent for biomarkers study. A physical examination, serology, hematology, biochemistry, ECG and a tumor evaluation and biopsy were performed to participating patients.

Period 1

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

Arms

Arm title	Study treatment

Arm description:

Treatment with enzalutamide 160 mg/day until progression disease, unacceptable toxicity, protocol non-compliance or withdrawal of consent.

Arm type	Experimental
Investigational medicinal product name	Enzalutamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Enzalutamida dose will be 160 mg/day (Four capsules of 40 mg each)

Number of subjects in period 1	Study treatment
Started	98
Completed	98

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	98	98	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	9	9	
From 65-84 years	80	80	
85 years and over	9	9	
Age continuous Units: years			
median	77		
full range (min-max)	57 to 95	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	98	98	
Bone metastases Units: Subjects			
Yes	80	80	
No	18	18	
Number of bone metastases Units: Subjects			
<4	50	50	
>=4	30	30	
No	18	18	
ECOG Units: Subjects			
ECOG-0	53	53	
ECOG-1	45	45	
Pain Units: Subjects			
No pain	45	45	
Mild (<= BPI score	52	52	
NA	1	1	
CTC status Units: Subjects			

Positive	35	35	
Negative	63	63	
AR status Units: Subjects			
Gain	11	11	
Without changes	87	87	
ALP ratio Units: Subjects			
high	28	28	
Normal values	70	70	
LDH ratio Units: Subjects			
High	31	31	
Normal ranges	67	67	
TMPRSS-ERG-RT_PCR Units: Subjects			
Negative	66	66	
Positive	32	32	
ERG - IHC Units: Subjects			
Negative	63	63	
Positive	35	35	
Visceral metastases Units: Subjects			
Yes	17	17	
No	81	81	
Liver metastases Units: Subjects			
Yes	4	4	
No	94	94	
Lymph nodes metastases Units: Subjects			
Yes	47	47	
No	51	51	
PSA Units: ng/dL			
median	24.95		
full range (min-max)	0.59 to 4319	-	
Albumin Units: ug/dL			
median	4.15		
full range (min-max)	3.29 to 5.00	-	
Haemoglobin Units: g/dL			
median	13.2		
full range (min-max)	7.5 to 17.3	-	
ALP ratio Units: Not applicable			
median	0.71		
full range (min-max)	0.24 to 17.46	-	
LDH ratio			

Units: Not applicable			
median	0.84		
full range (min-max)	0.29 to 3.36	-	
Neutrophil to lymphocyte ratio			
Units: Not applicable			
median	2.14		
full range (min-max)	0.52 to 12.33	-	
Plasma DNA			
Units: ng/mL			
median	18.64		
full range (min-max)	0.00 to 1585.00	-	

Subject analysis sets	
Subject analysis set title	TMPRSS2-ERG Negative
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with TMPRSS2-ERG gen negative	
Subject analysis set title	TMPRSS2-ERG Positive
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with TMPRSS2-ERG gen positive	

Reporting group values	TMPRSS2-ERG Negative	TMPRSS2-ERG Positive	
Number of subjects	66	32	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	5	4	
From 65-84 years	57	23	
85 years and over	4	5	
Age continuous			
Units: years			
median	76	80	
full range (min-max)	57 to 87	60 to 95	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	66	32	
Bone metastases			
Units: Subjects			
Yes	53	27	
No	13	5	
Number of bone metastases			
Units: Subjects			

<4	34	16	
>=4	19	11	
No	13	5	
ECOG Units: Subjects			
ECOG-0	32	21	
ECOG-1	34	11	
Pain Units: Subjects			
No pain	30	15	
Mild (<= BPI score	35	17	
NA	1	0	
CTC status Units: Subjects			
Positive	23	12	
Negative	43	20	
AR status Units: Subjects			
Gain	5	6	
Without changes	61	26	
ALP ratio Units: Subjects			
high	16	12	
Normal values	40	20	
LDH ratio Units: Subjects			
High	21	10	
Normal ranges	45	22	
TMPRSS-ERG-RT_PCR Units: Subjects			
Negative			
Positive			
ERG - IHC Units: Subjects			
Negative			
Positive			
Visceral metastases Units: Subjects			
Yes	12	5	
No	54	27	
Liver metastases Units: Subjects			
Yes	3	1	
No	63	31	
Lymph nodes metastases Units: Subjects			
Yes	28	19	
No	38	13	
PSA Units: ng/dL			
median	24.36	29.53	

full range (min-max)	2.5 to 4318.78	0.59 to 870.58	
Albumin Units: ug/dL median full range (min-max)	 4.11 3.29 to 5.00	 4.18 3.50 to 4.90	
Haemoglobin Units: g/dL median full range (min-max)	 13.15 7.50 to 16.40	 13.35 9.10 to 17.30	
ALP ratio Units: Not applicable median full range (min-max)	 0.70 0.24 to 11.85	 0.77 0.31 to 17.46	
LDH ratio Units: Not applicable median full range (min-max)	 0.84 0.29 to 3.36	 0.84 0.61 to 2.51	
Neutrophil to lymphocyte ratio Units: Not applicable median full range (min-max)	 2.10 0.52 to 6.17	 2.33 0.61 to 12.33	
Plasma DNA Units: ng/mL median full range (min-max)	 17.84 0.06 to 1585.00	 20.44 0.5 to 164.09	

End points

End points reporting groups

Reporting group title	Study treatment
Reporting group description:	
Treatment with enzalutamide 160 mg/day until progression disease, unacceptable toxicity, protocol non-compliance or withdrawal of consent.	
Subject analysis set title	TMPRSS2-ERG Negative
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with TMPRSS2-ERG gen negative	
Subject analysis set title	TMPRSS2-ERG Positive
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with TMPRSS2-ERG gen positive	

Primary: PSA progression free survival

End point title	PSA progression free survival
End point description:	
End point type	Primary
End point timeframe:	
Time from study entry to an increase of >= 25% or an absolute increase >= 2ng/mL	

End point values	Study treatment	TMPRSS2-ERG Negative	TMPRSS2-ERG Positive	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	98	66	32	
Units: months				
median (confidence interval 95%)	14.1 (10.2 to 20.2)	14.7 (10.68 to 20.5)	12.8 (7.36 to 20.5)	

Statistical analyses

Statistical analysis title	PSA progression free survival
Comparison groups	TMPRSS2-ERG Negative v TMPRSS2-ERG Positive
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.8
Method	Fisher exact
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.58

Secondary: PSA response rate

End point title	PSA response rate

End point description:

End point type	Secondary

End point timeframe:

From patient inclusion to the lowest result of PSA subsequent basal status.

End point values	Study treatment	TMPRSS2-ERG Negative	TMPRSS2-ERG Positive	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	98	66	30	
Units: Patients				
Decline >= 50%	79	55	24	
Decline < 50%	19	11	6	

Statistical analyses

Statistical analysis title	PSA response rate
Comparison groups	TMPRSS2-ERG Negative v TMPRSS2-ERG Positive
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.69
Method	Fisher exact

Secondary: Radiographic response rate

End point title	Radiographic response rate

End point description:

End point type	Secondary

End point timeframe:

From patient start to the lowest PSA level subsequent basal status.

End point values	Study treatment	TMPRSS2-ERG Negative	TMPRSS2-ERG Positive	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	43	30	13	
Units: Patients				
Objective response	21	14	7	
Stable disease	17	13	4	
Progressive disease	5	2	2	

Statistical analyses

Statistical analysis title	Radiographic response
Comparison groups	TMPRSS2-ERG Negative v TMPRSS2-ERG Positive
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.5
Method	Fisher exact

Secondary: Radiographic progression free survival

End point title	Radiographic progression free survival
End point description:	
End point type	Secondary
End point timeframe:	
Time from study entry to radiographic progression	

End point values	Study treatment	TMPRSS2-ERG Negative	TMPRSS2-ERG Positive	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	98	66	32	
Units: months				
median (confidence interval 95%)	25.2 (21.7 to 33.1)	23.9 (20.3 to 24.0)	27.9 (17.9 to 30.0)	

Statistical analyses

Statistical analysis title	Radiographic progression free survival
Comparison groups	TMPRSS2-ERG Negative v TMPRSS2-ERG Positive
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.857
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.96

Secondary: Overall survival	
End point title	Overall survival
End point description:	
End point type	Secondary
End point timeframe:	
From study entry to patient exitus.	

End point values	Study treatment	TMPRSS2-ERG Negative	TMPRSS2-ERG Positive	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	98	66	32	
Units: months				
median (confidence interval 95%)	37.5 (33.7 to 39.0)	38.1 (33.7 to 39.0)	36.9 (27.6 to 37.3)	

Statistical analyses

Statistical analysis title	Overall Survival
Comparison groups	TMPRSS2-ERG Negative v TMPRSS2-ERG Positive
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.4873
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.23

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	2.21

Secondary: PSA rate >=90%

End point title	PSA rate >=90%

End point description:

End point type	Secondary

End point timeframe:

From patient inclusion to the lowest result of PSA subsequent basal status

End point values	Study treatment	TMPRSS2-ERG Negative	TMPRSS2-ERG Positive	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	98	66	30	
Units: Patients				
Decline >=90%	51	36	15	
Decline < 90%	47	30	15	

Statistical analyses

Statistical analysis title	PSA decline >=90%
Comparison groups	TMPRSS2-ERG Negative v TMPRSS2-ERG Positive
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.83
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From patient informed consent signature to last dose of study treatment

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	All patients

Reporting group description: -

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 98 (35.71%)		
number of deaths (all causes)	50		
number of deaths resulting from adverse events	2		
Vascular disorders			
Ischemic stroke			
subjects affected / exposed	4 / 98 (4.08%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Cognitive disorder			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	6 / 98 (6.12%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	5 / 98 (5.10%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Back pain			

subjects affected / exposed	3 / 98 (3.06%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Fracture			
subjects affected / exposed	4 / 98 (4.08%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	98 / 98 (100.00%)		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 98 (2.04%)		
occurrences (all)	2		
Vascular disorders			
Hypertension			
subjects affected / exposed	37 / 98 (37.76%)		
occurrences (all)	37		
Flushing			
subjects affected / exposed	23 / 98 (23.47%)		
occurrences (all)	23		
Peripheral swelling			
subjects affected / exposed	19 / 98 (19.39%)		
occurrences (all)	19		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	6 / 98 (6.12%)		
occurrences (all)	6		
Cardiac failure			
subjects affected / exposed	4 / 98 (4.08%)		
occurrences (all)	4		
Atrioventricular block			

subjects affected / exposed occurrences (all)	1 / 98 (1.02%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Cognitive disorder subjects affected / exposed occurrences (all) Spinal cord compression subjects affected / exposed occurrences (all)	 10 / 98 (10.20%) 10 5 / 98 (5.10%) 5 2 / 98 (2.04%) 2		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	 70 / 98 (71.43%) 70		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all)	 16 / 98 (16.33%) 16 15 / 98 (15.31%) 15		
Renal and urinary disorders Renal failure subjects affected / exposed occurrences (all)	 3 / 98 (3.06%) 3		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Fracture	 38 / 98 (38.78%) 38 23 / 98 (23.47%) 23 		

subjects affected / exposed occurrences (all)	6 / 98 (6.12%) 6		
Metabolism and nutrition disorders Anorexia nervosa subjects affected / exposed occurrences (all) Hepatic enzyme increased subjects affected / exposed occurrences (all) Weight decreased subjects affected / exposed occurrences (all)	 23 / 98 (23.47%) 23 5 / 98 (5.10%) 5 2 / 98 (2.04%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2018	Recruitment period increased.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported