Clinical trial results:
Abrogation of chronic monoclonal antibody treatment-induced T-cell exhaustion with DURVALUMAB (MEDI4736) in advanced HER-2 negative breast cancer: a pilot proof-of-concept trial

Summary

EudraCT number	2015-005609-34
Trial protocol	ES
Global end of trial date	09 July 2019

Results information

Result version number	v1 (current)
This version publication date	30 November 2020
First version publication date	30 November 2020

Trial information

Trial identification

Sponsor protocol code	CNIO-BR-008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02802098
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fundación CRIS de investigación para vencer el cáncer
Sponsor organisation address	Princesa de Eboli, 9, Madrid, Spain, 28050
Public contact	Marta Cardona, Fundación CRIS de investigación para vencer el cáncer, +34 911161312, mcardona@criscancer.org
Scientific contact	Marta Cardona, Fundación CRIS de investigación para vencer el cáncer, +34 911161312, mcardona@criscancer.org

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 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 July 2019
Global end of trial reached?	Yes
Global end of trial date	09 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the immunodynamics in peripheral blood and in the tumor of combined administration of DURVALUMAB and the monoclonal antibody bevacizumab in advanced HER-2- negative breast cancer patients that have progressed to bevacizumab-based treatment.

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	03 May 2016
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: 25
Worldwide total number of subjects	25
EEA total number of subjects	25

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)	19
From 65 to 84 years	6

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patient were recruited in the study from June 13th 2016 until July 9th 2018

Pre-assignment

Screening details:

The patients underwent PDL-1 analysis before signing the study informed consent form in order to check if the patient was elegible. 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	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Study treatment

Arm description:

Treatment with DURVALUMAB, if ≥ 30 kg, commences on day 1 following confirmation of eligibility into the study and continues on a Q2W schedule + Bevacizumab 15 mg/ Kg Q3W or 10 mg/ Kg Q2W, IV infusion for a maximum duration of treatment of 12 months. Study treatment should be discontinued prior to 12 months if there is confirmed PD (unless the investigator considers the subject to continue to receive benefit from treatment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or if other reasons to discontinue study treatment occur.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

15 mg/kg administrated once every 3 weeks or 10 mg/kg administrated once every 2 weeks.

Investigational medicinal product name	Durvalumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Patients with ≥ 30 kg, a fixed dose of 750 mg of DURVALUMAB was administered every 2 weeks (Equivalent dose of 10 mg/kg Q2W).

Number of subjects in period 1	Study treatment
Started	25
Completed	25

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	25	25	
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)	19	19	
From 65-84 years	6	6	
85 years and over	0	0	
Age continuous Units: years			
median	54.1		
full range (min-max)	34.5 to 77.4	-	
Gender categorical Units: Subjects			
Female	24	24	
Male	1	1	
Race Units: Subjects			
Caucasian	23	23	
Arabian	1	1	
Latin	1	1	
ECOG-PS at baseline Units: Subjects			
ECOG-PS 0	15	15	
ECOG-PS 1	10	10	
TNM at diagnosis			
T			
Units: Subjects			
Tx	2	2	
T1	4	4	
T2	10	10	
T3	5	5	
T4	2	2	
ND	2	2	
TNM at diagnosis			
N			

Units: Subjects			
Nx	2	2	
N0	6	6	
N1	11	11	
N2	1	1	
N3	3	3	
ND	2	2	
TNM at diagnosis			
M			
Units: Subjects			
M0	16	16	
M1	8	8	
ND	1	1	
Stage at diagnosis			
Stage			
Units: Subjects			
IA	2	2	
IIA	4	4	
IIB	5	5	
IIIC	4	4	
IV	7	7	
ND	3	3	
TNM at study inclusion			
T			
Units: Subjects			
Tx	2	2	
T0	1	1	
T1	1	1	
T2	4	4	
T3	1	1	
T4	2	2	
ND	14	14	
TNM at study inclusion			
N			
Units: Subjects			
Nx	2	2	
N0	3	3	
N1	4	4	
N2	2	2	
N3	1	1	
ND	13	13	
TNM at study inclusion			
M			
Units: Subjects			
M1	24	24	
ND	1	1	
Stage at study inclusion Units: Subjects			
IV	24	24	
ND	1	1	
Histology			

Units: Subjects			
Ductal	18	18	
Lobular	4	4	
Others	3	3	
Differentation grade Units: Subjects			
G1	3	3	
G2	10	10	
G3	7	7	
ND	5	5	
Estrogen hormonal receptors Units: Subjects			
Positive	16	16	
Negative	9	9	
Previous surgery Units: Subjects			
Yes	21	21	
No	4	4	
Sentinel node biopsy result Units: Subjects			
Positive	7	7	
Negative	2	2	
Not biopsied	16	16	
Previous local chemotherapy Units: Subjects			
Yes	16	16	
No	9	9	
Previous treatments: monotherapy and radiotherapy Units: Subjects			
Yes	18	18	
No	7	7	
Number of previous lines to advanced/metastatic disease Units: Subjects			
One	4	4	
Two	8	8	
Three	4	4	
Four	6	6	
Five	2	2	
Seven	1	1	
Number of locations Units: Subjects			
One	4	4	
Two	8	8	
Three	3	3	
Four	3	3	
Five	4	4	
Six	1	1	
Seven	1	1	
Eight	1	1	
Number of cycles administered			

Units: Subjects			
One	2	2	
Two	5	5	
Three	9	9	
Four	2	2	
Five	1	1	
Six	1	1	
Eight	2	2	
Thirteen	2	2	
Fourteen	1	1	
Number of durvalumab infusion interruptions			
Non-hematological toxicity (N=4)			
Units: Subjects			
None	22	22	
One	2	2	
Two	1	1	
Number of bevacizumab infusion interruptions			
Non-hematological toxicity (N=6), treatment not related (1), not related AE (1)			
Units: Subjects			
None	18	18	
One	6	6	
Two	1	1	
Number of durvalumab infusions delayed			
Not related AE (N=3), Treatment not related reason (N=1)			
Units: Subjects			
None	21	21	
One	4	4	
Number of bevacizumab infusions delayed			
Not related AE (N=3), Treatment not related reason (N=2)			
Units: Subjects			
None	20	20	
One	5	5	
Progesterone receptors			
Units: Subjects			
Positive	10	10	
Negative	15	15	
Previous radiotherapy			
Units: Subjects			
Yes	14	14	
No	11	11	
PDL-1 Expression			
Units: Subjects			
Positive	4	4	
Negative	16	16	
Unknow	5	5	
Cardiac frequency			
Units: bpm			
median	75.0		

full range (min-max)	58.0 to 96.0	-	
Temperature Units: celsius temperature median full range (min-max)	 36.1 35.1 to 36.7	 -	
Sistolic blood pressure Units: mmHg median full range (min-max)	 125.0 77.0 to 162.0	 -	
Diastolic blood pressure Units: mmHg median full range (min-max)	 75.0 61.0 to 90.0	 -	
Respiratory frequency Units: breaths per minute median full range (min-max)	 16.0 12.0 to 22.0	 -	
Weight Units: Kg median full range (min-max)	 57.0 47.0 to 75.2	 -	
Height Units: cm median full range (min-max)	 160.0 150.0 to 179.0	 -	
Time from initial diagnosis Units: months median full range (min-max)	 43.2 4.7 to 116.0	 -	
Time from metastatic diagnosis Units: months median full range (min-max)	 18.1 0.2 to 116.0	 -	
Time from intial diagnosis to metastatic diagnosis Units: months median full range (min-max)	 4.6 0.0 to 97.2	 -	
Time of previous treatment with bevacizumab Units: months median full range (min-max)	 7.9 1.6 to 24.7	 -	
Time on treatment Units: Weeks median full range (min-max)	 18.6 4.1 to 57.3	 -	
Bevacizumab dose intensity Units: mg/Kg/week median full range (min-max)	 4.5 2.4 to 4.95	 -	
Durvalumab dose intensity			

Units: mg/week			
median	332.7		
full range (min-max)	181.03 to 375.0	-	
Bevacizumab related dose intensity			
Units: NA			
median	0.90		
full range (min-max)	0.48 to 0.99	-	
Durvalumab related dose intensity			
Units: NA			
median	0.89		
full range (min-max)	0.48 to 1.0	-	

End points

End points reporting groups

Reporting group title	Study treatment

Reporting group description:

Treatment with DURVALUMAB, if ≥ 30 kg, commences on day 1 following confirmation of eligibility into the study and continues on a Q2W schedule + Bevacizumab 15 mg/ Kg Q3W or 10 mg/ Kg Q2W, IV infusion for a maximum duration of treatment of 12 months. Study treatment should be discontinued prior to 12 months if there is confirmed PD (unless the investigator considers the subject to continue to receive benefit from treatment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or if other reasons to discontinue study treatment occur.

Primary: Peripheral Blood Mononuclear Cells (PBMCS) differences after treatment between responders and non-responders

End point title	Peripheral Blood Mononuclear Cells (PBMCS) differences after treatment between responders and non-responders[1]

End point description:

Differences in CD4+, CD8+ and Treg cells

End point type	Primary

End point timeframe:

From treatment initiation to first evaluation (8 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: One arm clinical trial. Only descriptive analyses performed. No comparisons.

End point values	Study treatment			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: p-value				
number (not applicable)				
CD4+ Naïve	0.87			
CD4+ Effector	0.01			
CD4+ Central memory	0.09			
CD4+ Effector Memory	0.04			
CD8+ Naive	0.1			
CD8+ Effector	0.02			
CD8+ Central memory	0.02			
CD8+ Effector memory	0.78			
T-reg	0.11			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit rate at 4 months

End point title	Clinical Benefit rate at 4 months

End point description:

End point type	Secondary

End point timeframe:

From treatment initiation to 4 months follow-up.

End point values	Study treatment			
Subject group type	Reporting group			
Number of subjects analysed	25[2]			
Units: Patients				
Partial response	2			
Stable disease	5			
Not follow-up available	18			

Notes:

[2] - Only 7 patients have a follow-up >=4 months

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the end of first treatment dose to 90 days after last dose of durvalumab.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Bevacizumab and Durvalumab treatment

Reporting group description: -

Serious adverse events	Bevacizumab and Durvalumab treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 25 (28.00%)		
number of deaths (all causes)	12		
number of deaths resulting from adverse events	1		
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			

subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Bevacizumab and Durvalumab treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 25 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	14 / 25 (56.00%)		
occurrences (all)	14		
General physical health deterioration			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Pain			

subjects affected / exposed occurrences (all) Peripheral swelling subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Mucosal dryness subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2 2 / 25 (8.00%) 2 3 / 25 (12.00%) 3 2 / 25 (8.00%) 2		
Respiratory, thoracic and mediastinal disorders Chest pain subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all)	 2 / 25 (8.00%) 2 2 / 25 (8.00%) 2 5 / 25 (20.00%) 5		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all)	 2 / 25 (8.00%) 2 2 / 25 (8.00%) 2		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	 5 / 25 (20.00%) 5 2 / 25 (8.00%) 2		
Blood and lymphatic system disorders			

Anaemia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all)	 2 / 25 (8.00%) 2 2 / 25 (8.00%) 2		
Eye disorders Xerophthalmia subjects affected / exposed occurrences (all)	 2 / 25 (8.00%) 2		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 7 / 25 (28.00%) 7 5 / 25 (20.00%) 5 4 / 25 (16.00%) 4 3 / 25 (12.00%) 3 4 / 25 (16.00%) 4		
Hepatobiliary disorders Hypoalbuminaemia subjects affected / exposed occurrences (all)	 2 / 25 (8.00%) 2		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 2 / 25 (8.00%) 2		
Renal and urinary disorders Urinary tract infection			

subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Proteinuria			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	4		
Musculoskeletal pain			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Bone pain			
subjects affected / exposed	5 / 25 (20.00%)		
occurrences (all)	5		
Musculoskeletal chest pain			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 25 (20.00%)		
occurrences (all)	5		
Hyperglycaemia			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Hypothyroidism			

subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 January 2017	Modification toxicity management guidelines
26 October 2017	Inclusion criteria modified
18 December 2018	Updating protocol safety information according to new Investigator Brochure.

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.

The pilot design of the study and the sample size analyzed do not allow to detail a definitive conclusions. Only 7 patients of 25 could be followed up for 4 months.

Notes: