Clinical trial results:
An open label biomarker pilot study of the antitumoral acrivity of denosumab in the pre-operative setting of early breast cancer

Summary

EudraCT number	2016-002678-11
Trial protocol	ES
Global end of trial date	25 January 2022

Results information

Result version number	v1 (current)
This version publication date	06 July 2023
First version publication date	06 July 2023
Summary attachment (see zip file)	ICO_Final Report (ICO_DBIOMARK FINAL REPORT 13.06.2023.pdf)

Trial information

Trial identification

Sponsor protocol code	ICO-13-001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Institut Catala d'Oncologia
Sponsor organisation address	Av. Gran Via 199-203, L'Hospitalet de Llobregat, Spain, 08908
Public contact	Gestora de proyectos, Institut Catala d'Oncologia, 34 932607139, cmoreno2@iconcologia.net
Scientific contact	Gestora de proyectos, Institut Catala d'Oncologia, 34 932607139, cmoreno2@iconcologia.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	28 February 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 January 2022
Global end of trial reached?	Yes
Global end of trial date	25 January 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the antiproliferative and/or pro-apoptotic activity of denosumab in early breast cancer. If the Hypothesis of this study is proven right it will substantiate and provide rationale to the development of denosumab as an ant-cancer drug in breast cancer.

Protection of trial subjects:

N/A

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 April 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: 58
Worldwide total number of subjects	58
EEA total number of subjects	58

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)	42
From 65 to 84 years	15
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Subjects diagnosed with early, resectable, Her-2 negative breast cancer are candidates to this study. Once the informed consent form of this study is signed by the patients, a tumor biopsy and blood sample will be obtained (biopsy A).

Pre-assignment

Screening details:

Subjects meeting the study eligibility criteria as assessed during the screening period should be randomized 2:1 into the two described cohorts within 7 days of planned initiation of study treatment.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

This study will be a biomarker finding study. Laboratory investigators will be blinded to the randomization of the subject. The study team not involved in laboratory investigations will have access to the randomization of the subjects.

Arms

Are arms mutually exclusive?	No
Arm title	Arm A Denosumab

Arm description:

Subjects are planned to be randomized into two cohorts (arm A and arm B) in a 2:1 fashion.
Only those patients allocated to arm A will receive the study treatment with two doses of 120 mg sc of Deno-sumab on days 1 and 8, prior to surgery.

Arm type	Experimental
Investigational medicinal product name	Denosumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Injection

Dosage and administration details:

If the patients are considered eligible, after the screening period, two doses of subcutaneous Denosumab (120 mg) (d1, 8) will be administered.

Arm title	Arm B Observational

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Arm A Denosumab	Arm B Observational
Started	39	21
Completed	37	21
Not completed	2	0
Consent withdrawn by subject	1	-
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	58	58	
Age categorical Units: Subjects			
Adults (18-64 years)	57	57	
85 years and over	1	1	
Gender categorical Units: Subjects			
Female	58	58	

End points

End points reporting groups

Reporting group title	Arm A Denosumab

Reporting group description:

Subjects are planned to be randomized into two cohorts (arm A and arm B) in a 2:1 fashion.
Only those patients allocated to arm A will receive the study treatment with two doses of 120 mg sc of Deno-sumab on days 1 and 8, prior to surgery.

Reporting group title	Arm B Observational

Reporting group description: -

Primary: Endpoints to evaluate the primary Objective

End point title	Endpoints to evaluate the primary Objective

End point description:

Changes in the percentage of tumor cells expressing Ki67 and/or cleaved caspase 3 between Biopsy A (pre-treatment) and Biopsy B (post-treatment).

End point type	Primary

End point timeframe:

Only subjects assigned to arm A will receive two doses of denosumab 120 mg sc, administered on days 1 and 8 stating 21 days (±7 days) prior to scheduled surgery.

End point values	Arm A Denosumab	Arm B Observational		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[1]	21		
Units: percentage	37	21		

Notes:

[1] - 60 patients were included as planned, however, only 58 patients were evaluable.

Statistical analyses

Statistical analysis title	Ki67
Comparison groups	Arm A Denosumab v Arm B Observational
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.894
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)

Notes:

[2] - Denosumab did not reduce tumor cell proliferation compared with control arm. Quantifications were performed blindly by two independent pathologists specialized in breast cancer. The percentage of tumor cells that express Ki67 increased in the experimental arm, but also in the control arm.

Statistical analysis title	Cleaved_Caspase 3
Comparison groups	Arm A Denosumab v Arm B Observational

Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.038
Method	t-test, 2-sided

Notes:

[3] - No increase in Cleaved-Caspase 3 were observed after denosumab. The findings are statistically significant, although marginally, and not clinically relevant.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse events occurring out to 30 days following the completion of study treatment phase was reported. All "related" adverse events was reported within the period between 30 days after completion of study treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.3

Reporting groups

Reporting group title	Experimental

Reporting group description: -

Serious adverse events	Experimental		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 37 (2.70%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Experimental		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 37 (8.11%)		
General disorders and administration site conditions			
Discomfort at the injection			
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 June 2018	Change of an excipient (sorbitol) in the study drug formulation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported