



Clinical trial results:

A multicenter phase II study evaluating denosumab (XGEVA®) in combination with nivolumab (OPDIVO®) as second-line therapy for patients with stage IV non-small-cell lung cancer (squamous and non-squamous) with bone metastases

Summary

EudraCT number	2018-001105-85
Trial protocol	FR
Global end of trial date	19 October 2023

Results information

Result version number	v1 (current)
This version publication date	20 March 2025
First version publication date	20 March 2025
Summary attachment (see zip file)	DENIVOS CSR Synopsis (DENIVOS_CSR Synopsis_V1.0_en_20250304.pdf)

Trial information

Trial identification

Sponsor protocol code	P_2017_007
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03669523
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Centre Hospitalier Annecy Genevois
Sponsor organisation address	1 avenue de l'Hopital, EPAGNY METZ TESSY, France, 74370
Public contact	Marion GHIDI, Centre Hospitalier Annecy Genevois, +33 (0)4 50 63 70 31, mghidi@ch-annecygenevois.fr
Scientific contact	Marion GHIDI, Centre Hospitalier Annecy Genevois, +33 (0)4 50 63 70 31, mghidi@ch-annecygenevois.fr

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	30 September 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 October 2023
Global end of trial reached?	Yes
Global end of trial date	19 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the Objective Response Rate (Complete Responses and Partial Responses) according to the PD-L1-expression rate (determined by immunohistochemistry and considered positive when $\geq 1\%$ of the tumor cells are labeled) in Non-Small Cell Lung Cancer patients with bone metastases treated with the second-line denosumab-nivolumab combination.

Protection of trial subjects:

The study was performed in accordance with the current version of the declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013). The trial was conducted in agreement with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP).

During the pre-inclusion visit, the investigator informed the patient and answered all questions concerning the objective, constraints, foreseeable risks and expected benefits of the trial. The investigator also specified the patient's rights within the framework of biomedical research and verifies eligibility criteria. Copies of the information note and the consent form were given to the patient by the investigator. The patient information note detailed the procedures involved in the study (aims, methodology, potential risks, anticipated benefits) and the investigator explained these to each patient. After this information session, the patient had a minimum 2-day reflection period. During the inclusion visit, the patient's inclusion and non-inclusion criteria were validated by the investigating physician and, if the patient gave his/her written consent, the investigator could proceed to include the patient. When the patient agreed to participate, the doctor and patient wrote their names and surnames, dated and signed the consent form.

The different copies of the information note and the consent form were distributed as follows:

- Copies of the information note and signed consent form were given to the patient.
- The original was saved by the investigator (even if the patient changes residence during the trial) in a safe place not accessible to third parties, for a duration of 30 years after the end of the trial.

All patients provided written informed consent to participate in the study prior to being screened.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 November 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 82
Worldwide total number of subjects	82
EEA total number of subjects	82

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)	33
From 65 to 84 years	48
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

National, multicenter, prospective, open phase II trial, single arm, testing the Denosumab–Nivolumab combination as second-line therapy for patients with stage IV NSCLCs and bone metastases. It was planned to include a total of 86 patients during a 36 months inclusion period.

Date of first enrolment: 2018/11/08

Date of last completed : 2023/10/19

Pre-assignment

Screening details:

Patients were recruited among those managed in consultations or hospitalization in 20-30 participating GFPC centers.

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	Denosumab + Nivolumab combination
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	DENOSUMAB
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Injection

Dosage and administration details:

120 mg every 4 weeks

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

Dosage and administration details:

240 mg, IV infusion over 30 minutes, every 2 weeks

Number of subjects in period 1	Denosumab + Nivolumab combination
Started	82
Completed	82

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	82	82	
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)	33	33	
From 65-84 years	48	48	
85 years and over	1	1	
Age continuous			
Units: years			
median	67		
inter-quartile range (Q1-Q3)	61 to 73	-	
Gender categorical			
Units: Subjects			
Female	17	17	
Male	65	65	
PDL-1 status			
Units: Subjects			
PDL-1 negative	39	39	
PDL-1 positive	43	43	
Body Mass Index			
Units: kg/m ²			
median	23.7		
inter-quartile range (Q1-Q3)	21 to 25.8	-	

Subject analysis sets

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set (FAS) was comprised of the 82 included patients who had at least one tumoral evaluation at inclusion, and as the trial is conducted in Intention-To-Treat (ITT).	
Subject analysis set title	Per protocol set
Subject analysis set type	Per protocol

Subject analysis set description:

Four patients were excluded from Full analysis set because of major deviations, leaving 78 patients in the Per Protocol (PP) population.

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population was comprised a total of 82 patients and correspond to ITT population

Reporting group values	Full analysis set	Per protocol set	Safety analysis set
Number of subjects	82	78	82
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	33	33	33
From 65-84 years	48	44	48
85 years and over	1	1	1
Age continuous			
Units: years			
median	67	66	67
inter-quartile range (Q1-Q3)	61 to 73	61 to 72	61 to 73
Gender categorical			
Units: Subjects			
Female	17	16	17
Male	65	62	65
PDL-1 status			
Units: Subjects			
PDL-1 negative	39	36	39
PDL-1 positive	43	42	43
Body Mass Index			
Units: kg/m ²			
median	23.7	23.7	23.7
inter-quartile range (Q1-Q3)	21 to 25.8	21.2 to 25.8	21 to 25.8

End points

End points reporting groups

Reporting group title	Denosumab + Nivolumab combination
Reporting group description: -	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description: The Full Analysis Set (FAS) was comprised of the 82 included patients who had at least one tumoral evaluation at inclusion, and as the trial is conducted in Intention-To-Treat (ITT).	
Subject analysis set title	Per protocol set
Subject analysis set type	Per protocol
Subject analysis set description: Four patients were excluded from Full analysis set because of major deviations, leaving 78 patients in the Per Protocol (PP) population.	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description: The safety population was comprised a total of 82 patients and correspond to ITT population	

Primary: Overall Response Rate (ORR) by PD-L1 status

End point title	Overall Response Rate (ORR) by PD-L1 status
End point description:	
End point type	Primary
End point timeframe:	
Overall study duration	

End point values	Denosumab + Nivolumab combination	Full analysis set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	82	82		
Units: %				
number (confidence interval 95%)				
Overall	12 (6.3 to 22)	12 (6.3 to 22)		
PDL-1 negative	8 (2 to 22)	8 (2 to 22)		
PLD-1 positive	16 (7.3 to 31)	16 (7.3 to 31)		

Statistical analyses

Statistical analysis title	Overall Response Rate by PDL-1 status
Comparison groups	Denosumab + Nivolumab combination v Full analysis set

Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	other ^[1]
Parameter estimate	Risk ratio (RR)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	2.14

Notes:

[1] - Descriptive analysis

Secondary: Overall Response Rate (ORR) by histological type

End point title	Overall Response Rate (ORR) by histological type
End point description:	
End point type	Secondary
End point timeframe:	
Overall study duration	

End point values	Denosumab + Nivolumab combination	Full analysis set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	82	82		
Units: %				
number (confidence interval 95%)				
Overall	12 (4.5 to 20)	12 (4.5 to 20)		
Non-squamous	10 (4.5 to 20)	10 (4.5 to 20)		
Squamous	23 (6.2 to 54)	23 (6.2 to 54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

End point title	Progression free survival
End point description:	
End point type	Secondary
End point timeframe:	
Overall study duration	

End point values	Denosumab + Nivolumab combination	Full analysis set	Per protocol set	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	82	82	78	
Units: HR				
number (confidence interval 95%)				
Overall	0.8 (0.54 to 1.19)	0.8 (0.54 to 1.19)	0.81 (0.54 to 1.22)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival
End point description:	
End point type	Secondary
End point timeframe:	
Overall study duration	

End point values	Denosumab + Nivolumab combination	Full analysis set	Per protocol set	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	82	82	78	
Units: HR				
number (confidence interval 95%)				
Overall	0.78 (0.52 to 1.16)	0.78 (0.52 to 1.16)	0.79 (0.52 to 1.19)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Overall study duration

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25
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Frequency threshold for reporting non-serious adverse events: 0 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Listing of adverse displayed by patient is available on demand.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 February 2018	<ul style="list-style-type: none">- Modification of Inclusion/Non-inclusion Criteria- Protocol update based on Nivolumab and Denosumab PCRs- Grade correction for AST, ALT and total bilirubin for Nivolumab dose shifts or permanent discontinuation- Change in the calculation formula for creatinine clearance.- Correction of the interval between two cycles- Protocol updated to the latest NCI CTCAE version- Correction of the first meeting of the Independent Monitoring Committee
05 September 2018	Investigator list update
16 May 2019	<ul style="list-style-type: none">- Modification of Inclusion/Non-inclusion criteria- Protocol update with definition of pseudoprogression- Addition of a bibliographic reference- Update Investigators List (V4.0)
12 September 2019	<ul style="list-style-type: none">- Change of Project Manager and Statistician- Modification of Non-inclusion criteria- Investigators list update (V5.0)
10 February 2020	Investigator list update (V6.0)
03 August 2020	<ul style="list-style-type: none">- Extension of recruitment period to 30/06/2021- Modification of Inclusion/Non-Inclusion criteria
12 May 2021	<ul style="list-style-type: none">- Extension of recruitment period to 31/12/2021

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported