



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 |
|-----------------------|------------|

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 |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 25 |
|--------------------|----|

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