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

DENIVOS

Clinical Study Report Synopsis Version 1.0 of 2025-03-04

Full study title	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
Study Acronym	DENIVOS
Name of Product / Active Ingredient	XGEVA® Denosumab
Phase of development / Brief study design	Phase II, single-arm, multicenter 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.
EudraCT / ID RCB Number	2018-001105-85
ClinicalTrials.gov Identifier	NCT03669523
Internal Study Code / Protocol identification	CHANGE: 16-50 / P_2017_007 GFPC: 06-2017 AMGEN: 20177225
Sponsor	Centre Hospitalier Annecy Genevois
Project management	**Centre Hospitalier Annecy Genevois** Délégation à la Recherche Clinique et à l'Innovation Biostatistics : Tristan DELORY / Mélissa PETRIER Clinical Project Manager : Marion GHIDI Data Management : Mathieu LENORMAND

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Studied period (year)	**Date of first enrolment: 2018/11/08** **Date of last completed: 2023/10/19**
Scientific justification	Bone metastases are common in Non-Small Cell Lung Cancer (NSCLC), affecting 30–65% of the patients, depending on the series [1, 2]. They most often occur during disease progression (59.7% in the GFPC trial) [3]. The frequency of skeletal-related events (SREs) (pathological fractures, medullary compression, analgesic radiotherapy, preventive and/or analgesic surgery and hypercalcemia) is high. It is thought that more than half of the patients with bone metastases will have at least 1 SRE, with rates ranging from 55% to 62% [3–5]. Expert and medical Society guidelines, notably European Society for Medical Oncology (ESMO) in 2014, then in 2016, recommended using anti-resorptive agents (bisphosphonates or Denosumab) to prevent SREs, attenuate pain and improve the quality of life, and decrease the medical–economic impact of this major metastatic site [6–11]. Denosumab is a humanized monoclonal antibody. It mimics the action of osteoprotegerin (OPG), thereby inhibiting osteoclastogenesis by blocking the binding of the receptor activator of nuclear factor-κB (RANK) to its ligand (RANKL), and thus interrupts the vicious circle between tumor cells and bone [12]. RANK is a transmembrane protein expressed on osteoclasts, and its ligand, RANKL, is soluble and secreted by osteoblasts. Denosumab was accorded marketing authorization in France in 2011 as an anti-resorptive agent for bone metastases to delay the occurrence of SREs in lung-cancer patients. The results of 3 phase III studies evaluating the place of Denosumab vs. zoledronic acid have been published. Lung cancers were included in the

	trial examining solid tumors (other than breast and prostate) and multiple myelomas, and represented 40% of the population [13]. In a non-inferiority analysis, the primary objective was reached with Denosumab prolonging by approximately 4 months the time to the first SRE (20.6 vs. 16.3 months, hazard ratio (HR) 0.84 [95% confidence interval (CI) 0.71–0.98] p=0.0007). In the lung-cancer subgroup, this difference did not reach significance (HR 0.85 [95% CI 0.65–1.12]). In contrast, the exploratory analysis of that subgroup [14] showed overall survival (OS) prolonged by 1.2 months for the Denosumab arm vs. zoledronic acid (8.9 vs. 7.7 months, HR 0.8 [95% CI 0.67–0.95] p=0.01). Immunotherapy, notably immune-checkpoint inhibitors (ICPIs), like Nivolumab (anti-programed death-1 (PD-1)), has recently become an integral part of the therapeutic arsenal against NSCLCs. Nivolumab was accorded marketing authorization based on the phase III CHECKMATE 017 (squamous cell NSCLCs) and CHECKMATE 057 (non-squamous cell NSCLCs) trials vs docetaxel, after the phase II CHECKMATE 063 trial 15–17. The search for a biomarker predictive of the response to immunotherapy is becoming more-and-more crucial, so as not to expose patients who risk early cancer hyperprogression [18]. Immunohistochemical labeling of PD-1 ligand (PD-L1) on tumor cells (± infiltrating the stroma) is the most studied and reliable biomarker. Knowing its status has become indispensable in immunotherapy trials because an elevated PDL-1 has been correlated to a better response [19]. Prescribing second-line Nivolumab is not conditioned by the PD-L1 status because those trials had not foreseen stratification according to this criterion's status. However, post-hoc analysis of PD-L1 in the CHECKMATE 057 trial on non-squamous cell NSCLCs showed prolonged OS for patients with PD-L1–positive tumors, whether the positivity threshold was 1%, 5% or 10% [16]. Thus, knowing the PD-L1 status is necessary to interpret the results of immunotherapy trials. The RANK–RANKL system was studied in preclinical osteoimmunology models. It is expressed by certain cells, notably antigen-presenting cells, such as dendritic cells or lymphocytes, essential for the adaptive immunity function solicited by immunotherapy 20–24. It is part of the tumor necrosis factor (TNF)–TNF-receptor (TNF-R) family and is implicated in the interactions between dendritic cells and lymphocytes. The RANK–RANKL role in the development and function of regulatory T cells (Tregs) remains poorly elucidated. Information on the interaction of the RANK–RANKL system and adaptive immunity obtained with the preclinical models is discordant and rare. A case report on a patient with melanoma bone metastases treated with Denosumab and ipilimumab (ICPI of the anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) type) obtained a promising cancerological outcome, without any sign of deleterious interaction 25. The aim of this trial is to evaluate the combination of Denosumab and Nivolumab in second line of NSCLC with bone metastases.
Main objective and primary endpoint	Objective: To evaluate the ORR (CRs and PRs) according to the PD-L1–expression rate (determined by immunohistochemistry and considered positive when ≥1% of the tumor cells are labeled) in NSCLC patients with bone metastases treated with the second-line Denosumab–Nivolumab combination. Endpoint: The main judgment criterion is the ORR according to the PD-L1 expression rate, defined as the number of treated patients having a CR or PR

	(according to RECIST criteria 1.1, Appendix 2) to treatment divided by the number of patients included.
Secondary objectives and endpoints	Objectives: 1. To evaluate, for the entire population, the disease-control rate (DCR) (CR, PR, SD), the ORR, the OS and progression-free survival (PFS); 2. To evaluate according to the PD-L1–expression level, the disease-control rate (DCR) (CR, PR, SD), OS and progression-free survival (PFS); 3. To evaluate according to the histological type (adenocarcinoma vs. squamous cell), the disease-control rate (DCR) (CR, PR, SD), the ORR, the OS and progression-free survival (PFS); 4. To evaluate the time to the first SRE for the entire population and according to the history of anti-resorptive treatment; 5. To evaluate the toxicities of the association of Denosumab with Nivolumab. Endpoints: 1. 2. and 3.: - DCR: percentage of patients with a CR or PR and SD, evaluated for the entire population, then according to the PD-L1–expression rate and histological type (adenocarcinoma vs squamous cell). - ORR: percentage of patients with a CR or PR, evaluated for the entire population, then according to the histological type (adenocarcinoma vs squamous cell). - OS at 24 months evaluated for the entire population, then according to the PD-L1–expression rate and histological type (adenocarcinoma vs squamous cell). - PFS at 24 months evaluated for the entire population, then according to the PD-L1–expression rate and histological type (adenocarcinoma vs squamous cell). 4. Time to the first SRE in months for the entire population and according to the history of anti-resorptive treatment. 5. The incidence of AEs, severe AEs (SAEs), deaths and biological abnormalities scored according to NCI CTCAE V5.0 terminology. The collection of AEs will be completed as soon as consent is signed.
Methodology	Phase II multicenter single-arm French study
Study population	Number of patients planned: 86 evaluable subjects Number of patients included: 82 patients Number of patients analyzed: • Intention to treat: 82 patients • Per protocol: 78 patients
Inclusion criteria	- ≥18 years old; - Cytologically or histologically proven stage IV NSCLC; - ECOG PS 0/1 (Appendix 3); - For non-squamous cell NSCLC, patients without known activating EGFR mutation, ALK or ROS-1 translocation, or BRAF V600 mutation. - Patients who had received first-line platin salt-based chemotherapy and will be given second-line Nivolumab;

	- Patients with bone metastases, symptomatic or not, confirmed by X-rays, CT scan, MRI, PET–CT scan or technetium bone scintigraphy; - Presence of at least 1 measurable target lesion, according to RECIST criteria 1.1 (Appendix 2), in a non-irradiated site; - PD-L1 status known and expressed as a percentage of tumor cells; assessed at the diagnosis or the more recent PD-L1 expression status available. - Estimated life-expectancy ≥12 weeks; - No prior malignant tumor during the previous 5 years, except for adequately treated in situ carcinomas of the cervix or basal or squamous cell carcinomas of the skin; - Adequate organ function determined by laboratory analyses less than 7 days before inclusion: o Normal hepatic function: bilirubin < 1.5× normal (N), ALAT and ASAT <2.5× N or <5× N if hepatic metastases are present; o Renal function (calculation of renal clearance and creatininemia at least ≥ 45 mL/min); o Hematological function: absolute number of neutrophils ≥ 1.5×109/L and/or platelets ≥ 100×109/L, hemoglobin ≥ 8 g/dL; - Women of child-bearing age must use an highly effective contraceptive method and mechanical contraception during and up to 6 months after the end of treatment; - The men must use effective contraception during and up to 6 months after the treatment period; - Patient with asymptomatic brain metastases (treated or not) OR symptomatic brain metastases but adequately treated and controlled at the time of enrolment (without or with corticotherapy ≤ 10mg/day) , can be included. Carcinomatous meningitis is excluded regardless of clinical stability; - Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines; - Patient affiliated or benefitting from the French national health insurance program (Sécurité Sociale).
Exclusion criteria	- Patients previously treated with immunotherapy; - Patients with symptomatic cerebral metastases not treated and not controlled; - Contraindication to Nivolumab use: o Prior autoimmune disease(s), define as disease required systemic treatment in the past (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. o Prior diffuse interstitial pneumopathy, o Systemic immunosuppressive therapy; define as steroid medication at a dose greater than Prednisone 10 mg/day or equivalent. For patients with MMR-deficient high-grade

	gliomas, concurrent steroid medication at a dose greater than Prednisone 20mg/day or equivalent.
	- Contraindication for Denosumab use:
	  o Poor dental status requiring immediate specialized management, like oral surgery,
	  o Prior or current signs of osteonecrosis of the jaw/osteomyelitis,
	  o Invasive dental intervention schedule during the study or not yet healed;
	- Subject has known sensitivity to any of the products to be administered during the study
	- Concomitant administration of bisphosphonates;
	- Hypocalcemia;
	- Medical or psychological condition preventing informed consent;
	- Pregnant or breastfeeding woman;
	- PD-L1–status results unavailable.
	- Simultaneous participation of the patients in another clinical research trial

Test product, dose, mode of administration, batch number	**Denosumab XGEVA®**
	- Therapeutic class: treatment for bone diseases; another drug affecting bone structure and mineralization
	- Formulation: solution for injection. Each vial contains 120 mg of Denosumab in 1.7 mL of solution (70 mg/mL);
	- Planned indications in the SmPC:
	  o Prevention of bone complications (pathological fractures, bone irradiation, medullary compression or bone surgery) in adults with solid tumors and bone metastases,
	  o Treatment of adults and skeletally mature adolescents with giant-cell bone tumors, non-resectable or for which surgical resection is liable to cause severe morbidity;
	- Indication foreseen in this trial: prevention of bone complications (pathological fractures, bone irradiation, medullary compression or bone surgery) in adults with NSCLC and bone metastases;
	- Posology set forth in the SmPC and in the trial: the recommended dose is 120 mg every 4 weeks;
	- Administration route set forth in the SmPC and in the trail: SC injection;
	- Batch number: In this protocol, the drugs are used within their marketing authorization indications. Following the article L1121-16-1 of the of the French CSP, the research is not for commercial purpose and the drugs are used within their marketing authorization indications, thus the supply of the drugs is supported by the French social security.

Duration of treatment	Denosumab could be continued beyond the tumor progression, as long as it is tolerated by the patient.

Associated treatment, dose, mode of administration, batch number	**Nivolumab OPDIVO®**
	- Therapeutic class: antineoplastic monoclonal antibody;
	- Formulation: solution diluted for infusion;
	- Indications set forth in the SmPC:
	  o Treatment of adults with advanced melanoma (non-resectable or metastatic),
	  o Treatment of adults with locally advanced NSCLC or

	metastatic after previous chemotherapy, o Monotherapy for adults with advanced renal cell carcinoma after prior treatment, o Treatment of adults with relapsed/refractory classical Hodgkin lymphoma after autologous stem-cell transplantation and brentuximab vedotin; - Indication foreseen in this trial: treatment of adults with locally advanced NSCLC or metastatic after previous chemotherapy; - Posology set forth in the SmPC: the recommended dose of Nivolumab is 240 mg, IV infusion over 30 minutes, every 2 weeks; - Posology to given in this trial: the same as that set forth in the SmPC (240 mg, IV infusion over 30 minutes, every 2 weeks); - Administration route set forth in the SmPC: IV infusion; - Administration route foreseen in this trial: the same as that set forth in the SmPC (IV infusion over 30 minutes, every 2 weeks); - Batch number: In this protocol, the drugs are used within their marketing authorization indications. Following the article L1121-16-1 of the of the French CSP, the research is not for commercial purpose and the drugs are used within their marketing authorization indications, thus the supply of the drugs is supported by the French social security.
Statistical methods	**Efficacy:** Quantitative variables were expressed as mean (standard deviation), median (quartiles and range). Qualitative variables were expressed as numbers (%). Missing values were indicated, as necessary. The main analysis concerned the ORR at 24 months according to the PD-L1 expression rate (threshold set at 1%): number, percentage and 95% CI, calculated with the exact method. Because 78 subjects must be assessable, a threshold of 13 successes were needed to undertake a phase III trial. That threshold guarantees that the lower limit of the ORR 95% CI didn't include the ineffective threshold of the Denosumab–Nivolumab combination, set at 10%. Concerning the secondary analyses of efficacy: - The 24-month ORR for the entire population, then according to histological type (adenocarcinoma vs squamous-cell): number, percentage and 95% CI, calculated with the exact method. - The time to an SRE was estimated with the Kaplan–Meier method over 24 months of follow-up by subgroups according to the history of anti-resorptive treatment. - The DCR (complete and partial responses + stabilized disease) was expressed as number, percentage and 95% CI, calculated with the exact method, for the entire population, then by subgroups according to the PDL-1–expression rate, and histological type (adenocarcinoma vs squamous-cell). - OS over 24 months was described using the Kaplan–Meier method. Log-rank tests were used to analyze subgroups according to PDL-1–expression rate, then histological type (adenocarcinoma vs squamous-cell). Survival medians, in the overall population and according to PD-L1–expression rate, then histological type (adenocarcinoma vs squamous-cell) were calculated. - PFS over 24 months was described with the Kaplan–Meier method. Log-rank tests were used to analyze subgroups according to PD-L1–

	expression rate, then histological type (adenocarcinoma vs squamous-cell). Medians PFS, in the overall population and according to PD-L1– expression rate, then histological type (adenocarcinoma vs squamous-cell) will be calculated. **Analyses of safety criteria:** AEs were described according to the different hierarchical levels of the MedDRA/NCI-CTC classification. AEs arising between written consent and the first administration of the Denosumab–Nivolumab combination were recorded. Treatment terminations for toxicity were noted. The results of the safety analysis were presented according to the recommendations of the CONSORT Harms and the guideline ICH E3.

Summary – Conclusions

General Considerations :

The overall population corresponds to the typical demographics of non-small cell lung cancer in terms of age and gender: the median age was 67 years old (61-73), 66 years old in non-squamous patients compare to 70 years old in squamous patients. Men were the most numerous in the study (79.3%). They constituted 80% (N = 55) of the non-squamous group and 77% of the squamous group (N = 10). There was a large majority of smokers or ex-smokers (84%) and a predominance of adenocarcinoma (69/82, 84%). There were no significant imbalances observed between non-squamous and squamous characteristics. Plus, at inclusion 17% of the patients had corticosteroids at less than 10mg of prednisolone per day according to the protocol (14/82, 17%). The diagnosis was mainly histological (78/82, 95%). Biopsy was performed on lung tissue in 77% of cases. There were few cases of brain metastases (BM) for a second-line setting (21/82, 25%). Additionally, BM were more frequent in positive PD-L1 (15/43, 35%) than in negative PD-L1 (6/39, 15%). However, the proportion of high expressers (PD-L1 ≥ 50%) was low in this cohort: 4/69 (6%) for non-squamous and 1/13 (8%) for squamous. Negative PD-L1 cases represent about half of the cohort**, which is significant point** as we know that PD-L1 **is typically an enrichment factor for response under immunotherapy.**

Efficacy results:

DENIVOS trial included NSCLC patients with bone metastases treated by the association Nivolumab-Denosumab in second-line setting.

The results for primary endpoints (proportion of patients who have a partial or complete response to immunotherapy (Overall Response Rate (ORR) by PD-L1 status) are as follows:

The median follow-up duration was 8.5 months (95% CI [5.0-11.5]). Patients received an average of four Nivolumab injections (min-max: 1-50) and two Denosumab injections (min-max: 1-25).

The ORR in the overall population is 12.0% (95% CI, 6.3 to 22.0%): 8.0% (95CI%, 2.0% to 22.0%) among negative PD-L1 patients, and 16.0% (95CI%, 7.3% to 31.0%) among PD-L1 ≥ 1%, without statistical difference.

The results for secondary endpoint, same analyses were carried out, according to histological type (squamous vs. non-squamous). ORR was 10.0% (95CI%, 4.5% to 20.0%) among non-squamous patients, and 23.0% (95CI%, 6.2% to 54.0%) among squamous patients, without statistical difference.

The study also revealed that the incidence of skeletal-related events (SRE) was particularly low (12%), with a median event occurring 2.08 months after inclusion.

Survival trends indicate that PD-L1-positive patients may fare better than PD-L1 negative ones, though statistical significance was not consistently achieved. This is in line with immunotherapy efficacy data.

Safety results:

The association Denosumab-Nivolumab was well tolerated with less than 15% of Grade 1-2 adverse events (asthenia, pruritic, gastrointestinal disorders), and 17% of patients (8 patients) with Grade 3-4 toxicities due to Nivolumab. Among these toxicities of special interest: one patient developed an immune related colitis and

one patient developed an interstitial pneumonia. One patient experienced a Grade 4 toxicity due to Denosumab (hypocalcemia). No osteonecrosis of the jaw was seen. One SUSAR (Grade 3 Proctitis) was identified and declared as such to health authorities.

Conclusion:

DENIVOS included NSCLC with bone metastases in second-line setting treated with the association Nivolumab-Denosumab. Demographics characteristics were in line with NSCLC usual characteristics.

However, there was a majority of non-squamous histology and half of the population was PD-L1 negative (48%), which is higher than in the literature. There was very few PD-L1 high expression (≥ 50%), but we know that PD-L1 expression is a factor of good response with immunotherapy. Some patients already had SREs at inclusion. In this frail population, the combination of Nivolumab plus Denosumab demonstrate an ORR, PFS, and OS results seems to be slightly inferior to the pivotal Nivolumab studies in second-line setting and beyond (Checkmate 017 and 057), where details about bone metastases were although not known. Bone metastases are a poor prognostic factor. The DENIVOS population was more vulnerable than in the pivotal studies, which could be one explanation. Nevertheless, these results show that the combination Denosumab-Nivolumab achieve significant response according to the literature. Survival trends indicate that PD-L1 positive patients may fare better than PD-L1-negative ones, though statistical significance was not consistently achieved. This is in line with immunotherapy efficacy data: we know now that PD-L1 expression is a good response factor even if some PD-L1 negative patients can response as well. However, caution must be taken due to the low number of patients in this trial.

The interesting point of the trial is the low incidence of SREs (12%) in this population compared to the literature in second-line setting, could suggesting a protective effect of the Nivolumab-Denosumab combination on bone events, which warrants further investigation. The association Denosumab-Nivolumab was well tolerated.

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