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A phase II trial of nivolumab and denosumab association as second-line treatment for stage IV non-small–cell lung cancer (NSCLC) with bone metastases: DENIVOS study (GFPC 06-2017)

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BACKGROUND

- Bone metastases are frequent in patients with NSCLC and often associated with a worse prognosis. Denosumab blocks RANK-Ligand binding to its receptor and inhibits osteoclastogenesis. In case of bone metastasis (BM), denosumab is used to prevent and delay Skeletal Related Events (SRE). Retrospective studies suggested a synergistic interaction between denosumab and immune-checkpoint inhibitors.
- The main objective of DENIVOS trial was to evaluate the efficacy of a **second-line treatment combining nivolumab and denosumab**, **after first-line platinum-based chemotherapy, in stage IV, Performans status 0/1 NSCLC patients, with bone metastases and without EGFR or Braf V600E mutations or ALK/ROS-1 translocation.**

OBJECTIVES

- DENIVOS study (GFPC 06-2017) was a **national, phase II multicenter, single-arm trial , including stage IV NSCLC with bone metastases.**
- **Primary endpoint was objective response rate (ORR) in patients with PD-L1 <1% and ≥ 1%.**
- **Secondary endpoints** were to evaluate:

✓ for the entire population, and according to the the the PD-L1–expression level, the disease-control rate (DCR), the ORR, the OS and progression-free survival (PFS);
✓ according to the histological type (adenocarcinoma vs. squamous cell), the DCR, the ORR, the OS and PFS
✓ the time to the first SRE (defined by vertebral collapse, spinal cord compression, pathologic fracture, hypercalcemia, external radiotherapy, surgery)
✓ the toxicities of the association of Denosumab with Nivolumab.

- Responses were locally assessed according to RECIST v1.1; OS and PFS were assessed by Kaplan-Meier method.

RESULTS

- Between November 8, 2018 and December 31, 2021, **82 patients were included.**
- At the cutoff date of **March 31, 2022**, **median follow-up was 24.4 month**s (95CI%, 20.4 to 26.2), median number of infusions were five (IQR, 3-10) for nivolumab and three (IQR, 2-6) for denosumab.

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Table 1
Patient demographic and baseline disease characteristics (N=82)

Characteristic	% (n) OR median [IQR]
Age (years)	67 years (61-73)
Gender, males	79.3% (65)
ECOG Performans status	
PS 0	20.7% (17)
PS 1	79.3% (65)
Smoking status	
Active	28.0% (23)
Former	65.9% (54)
Never smoker	6.1% (5)
History of Corticosteroids before inclusion	17.1% (14)
Histology, % (n)	
Adenocarcinoma	76.8% (63)
Squamous cell carcinoma	15.9% (13)
Others	7.3% (6)
Median number of bone metastasis (BM) sites at inclusion	3 (IQR, 2-4)
Median time interval between diagnosis of BM and inclusion (months)	5 months (2-8)
PDL1	
<1%	47.6% (39)
≥1%	52.4% (43)
≥50%	6.5% (5)
Oncogenic mutations (other than EGFR/ALK/ROS/Braf) status known in 69 patients	
Mutation, yes	47.8% (33)
One mutation	34.8% (24)
Several muations	13.0% (9)
In case of mutation, Kras mutated	87.9% (29)
Metastasis sites	
Brain	25.6% (21)
Lung	32.9% (27)
Liver	26.8% (22)
Adrenal gland	26,8% (22)
Others	30.5% (25)
Number of SRE before inclusion	**N =14**
Vertebral collapse	27.3% (3)
Pathologic fracture	18.2% (2)
Hypercalcemia	9.10% (1)
External radiotherapy	54.5% (6)
Surgery	18.2% (2)
Spinal cord compression	0

Efficacy outcomes

ORR was 10.3% (95CI%, 4.1 to 23.6) among PDL-1 negative patients, and 20.9% (95CI%, 11.5 to 35.2) among PD-L1 ≥ 1%.
ORR was 15.9% (95CI%, 9.5-25.3) in overall population, and disease control rate was 42.7% (95CI%, 32.5-53).

Median progression-free survival was **1.7 months** (IQR, 1.5-5.3) and Median overall survival was **8.3 months** (95CI%, 5.3-12.9) for the entire population without difference between negative and positive PD-L1 (figure 1 and 2).

Safety

- Overall, there was 79 Grade 3+ adverse events, occurring in 20.4% of patients.
- No treatment-related death was reported.
- Among these, 14 (17.7%) were treatment related adverse events (TrAE): 5 gastrointestinal, 3 hepatobiliary disorder, 5 muskulosqueletal disorders, 1 skin and subcutaneous disorder.

Table 2
Efficacy of Nivolumab+Denosumab

CR, %	0
PR, %	15.9% (95%CI, 9.5%-25.3%)
SD, %	26.8% (95%CI, 18.4%-37.3%)
PD, %	57.3% (95%CI, 46.5%-67.4%)

SRE occured in ten patients (12%) after a median of 2.1 months (IQR, 1.2-3.3) :

- 2 Vertebral collapse
- 1 Pathologic fracture
- 0 Hypercalcemia
- 6 External radiotherapy
- 0 Surgery
- 1 Spinal cord compression

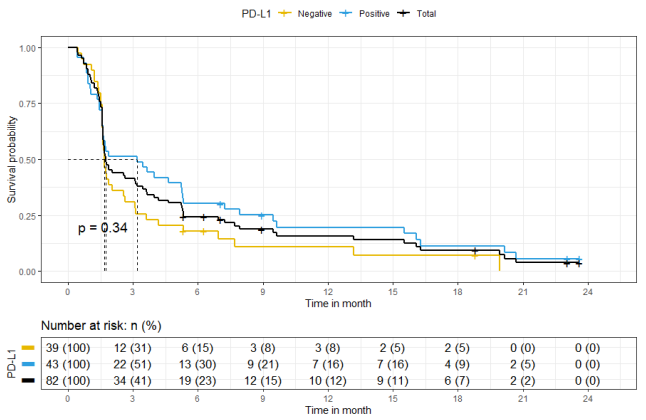

Figure 1. Progression free survival

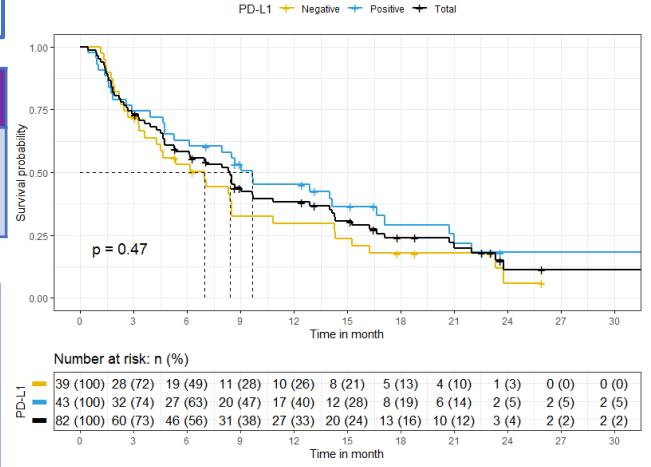

Figure 2. Overall survival

CONCLUSION

The nivolumab and denosumab association is an effective treatment option in the second-line setting of NSCLC with bone metastases. ORR observed is in line with pivotal phase III studies. No unexpected toxicity was observed.