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NIVOLUMAB TREATMENT IN ADVANCED NON-SMALL CELL LUNG CANCER (aNSCLC): OUTCOMES IN A FRENCH NATIONWIDE RETROSPECTIVE COHORT (THE UNIVOC STUDY)

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Introduction

- The introduction of immune checkpoint inhibitors represents a major advance in the treatment of lung cancer, allowing sustained recovery in a significant proportion of patients [1, 2].
- Nivolumab is a monoclonal anti-PD-1 antibody licensed for the treatment of locally advanced or metastatic non-small cell lung cancer (aNSCLC) after prior chemotherapy in adults.
- Two large randomised studies in patients with aNSCLC demonstrated that nivolumab was superior to docetaxel at extending overall survival (OS) in both non-squamous cell (NSq) [3] and squamous cell (Sq) disease [4].
- It is important to confirm that these benefits can be replicated in everyday clinical practice.
- The French national hospital database (PMSI) contains information on all patients treated with nivolumab in France, and thus provides a valuable source of information to examine use and outcomes of nivolumab in everyday clinical practice.
- The objectives of the present study were as follows:
  - To evaluate the characteristics of patients treated with nivolumab for aNSCLC according to histology
  - To estimate treatment time to nivolumab discontinuation in these patients.
  - To estimate OS in these patients.

Methods

Patients and data source

- All patients with aNSCLC initiating nivolumab in a second- or later- line setting identified in the PMSI database [5]. in 2015-2016 were included.
- All enrolled patients were followed until December 2017 with a minimum of 12 months follow-up.
- Patients with aNSCLC were identified from the ICD code (C34*) in the hospitalisation discharge summary.

Data extraction

- For patients starting nivolumab in 2015 or 2016, all inpatient and outpatient hospitalisations between 1st January 2011 and 31st December 2017 were extracted from the database.
- Demographic variables were documented at the time of the first nivolumab administration.
- Cancer duration was defined as the interval between first hospitalisation with lung cancer and first nivolumab administration.
- Comorbidities were identified from the ICD codes in the hospitalisation discharge summary for any hospital stay in the seven-year extraction period.
- Patients with NSq-aNSCLC were identified through the proxy measure of treatment with bevacizumab or pemetrexed, as previously described [7].
- The duration of nivolumab treatment was defined as the interval between the hospital visit at which nivolumab administration ws first documented and discontinuation, defined as no new treatment for at least six weeks after the previous treatment (ie three missed treatments) or death, if the patient died. The date of discontinuation was defined as the last treatment date plus 14 days, or the date of death.
- Patients who died in hospital were identified and OS defined as the interval between the index hospitalisation and the date of death.

Statistical analysis

- Descriptive statistics were used to describe demographic and clinical patient characteristics and treatment patterns.
- Patient characteristics were compared between patients with NSq-aNSCLC and those with Sq-aNSCLC using the χ^2 test for categorical variables or Student's *t*-test for continuous variables.
- Treatment discontinuation rates and OS were determined from Kaplan-Meier actuarial survival curves.

Results

Study population

- 10452 patients with aNSCLC initiating nivolumab were documented in the PMSI database.
- These included 5805 with NSq-aNSCLC (55.5%) and 4647 patients with Sq-aNSCLC (44.5%).
- Patient characteristics at baseline are compared between patients with NSq- and Sq- aNSCLC in **Table 1**.
- Compared to patients with Sq-aNSCLC, those with NSq-aNSCLC were on average younger, less frequently men. They more frequently presented with cerebral metastases but less frequently presented common comorbidities. In patients with NSq-aNSCLC, nivolumab was more frequently initiated in university hospitals or comprehensive cancer clinics (p<0.001 for all comparisons).

Table 1. Patients characteristics

	NSq-aNSCLC (N = 5805)	Sq-aNSCLC (N = 4647)	Overall population (N = 10,452)
Age[1] (mean ± SD; years)	**61.9 ± 9.3**	**66.1 ± 9.5**	63.8 ± 9.6
Gender (men: n, %)	**3 733 (64.3%)**	**3 687 (79.3%)**	7 420 (71.0%)
Type of hospital[1] (n, %)			
General hospital	**2 012 (34.7%)**	**1 855 (39.9%)**	3 867 (37.0%)
University hospital	**1681 (29.0%)**	**1 233 (26.5%)**	2 914 (27.9%)
Comprehensive cancer clinic	**618 (10.6%)**	**402 (8.7%)**	1 020 (9.8%)
Other	**1 494 (25.7%)**	**1 157 (24.9%)**	2 651 (25.4%)
Cancer duration[2] (mean ± SD; mo)	21.6 ± 21.1	17.2 ± 19.9	19.7 ± 20.6
Presence of cerebral metastases (n, %)	**1 332 (22.9%)**	**468 (10.1%)**	1 800 (17.2%)
Previous curative surgery (n, %)	853 (14.7%)	776 (16.7%)	1 629 (15.6 %)
Prior CT duration[3] (mean ± SD; mo)	18.1 ± 18.1	13.9 ± 15.7	16.3 ± 17.2
Comorbidities (n, %)			
Hypertension	**917 (15.8%)**	**1 069 (23.0%)**	1 986 (19.0%)
Diabetes	**388 (6.7%)**	**546 (11.7%)**	934 (8.9%)
Renal failure	**246 (4.2%)**	**233 (5.0%)**	479 (4.6%)
COPD	**508 (8.8%)**	**840 (18.1%)**	1 348 (12.9%)
Pulmonary insufficiency	**61 (1.1%)**	**92 (2.0%)**	153 (1.5%)
Other chronic pulmonary disease	**455 (7.8%)**	**448 (9.6%)**	903 (8.6%)

[1]At which nivolumab treatment was initiated; [2]time since first hospitalisation with lung cancer; [3]at time of first nivolumab treatment.
COPD: chronic obstructive pulmonary disease; CT: chemotherapy; SD: standard deviation.
For variables in **bold** the difference between the Sq and NSq subgroups was statistically significant (p <0.001).

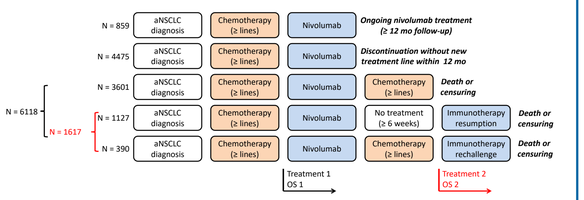
Treatment duration

- The median treatment duration with nivolumab was identical in both NSq-aNSCLC and Sq-aNSCLC (2.8 months (95%CI: 2.8 – 2.8 months.

Treatment sequences

- Overall, 5118 (53%) patients were retreated after the end of the initial nivolumab course (**Figure 1**). 1517 of these (30%) received a second course of immunotherapy (1511 with nivolumab and 6 with pembrolizumab)
- 1127 patients resumed nivolumab without intervening chemotherapy and 390 were rechallenged with nivolumab after chemotherapy (**Figure 1**).
- The median IO treatment duration during retreatment was 4.0 months for resumption and 3.0 months for rechallenge.

Figure 1. Treatment sequences



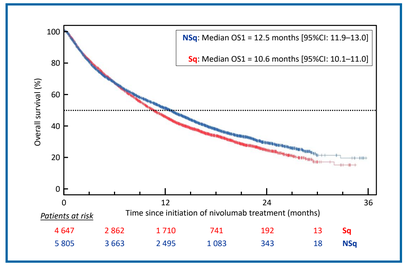
Overall survival during initial nivolumab course (OS1) – all patients enrolled

- Median OS and one and two- year OS rates were slightly higher in patients with NSq-aNSCLC compared to those with Sq-aNSCLC (**Table 2; Figure 2**)

Table 2. Overall survival (OS1) according to histology – all patients enrolled

	NSq-aNSCLC (N = 5,805)	Sq-aNSCLC (N = 4,647)	P-value
12 month OS rate	51%	46%	0.001 (logrank test)
24 month OS rate	29%	25%	
Median OS1 [95% CI] (mo)	12.5 [11.9 – 13.0]	10.6 [10.1 – 11.0]	

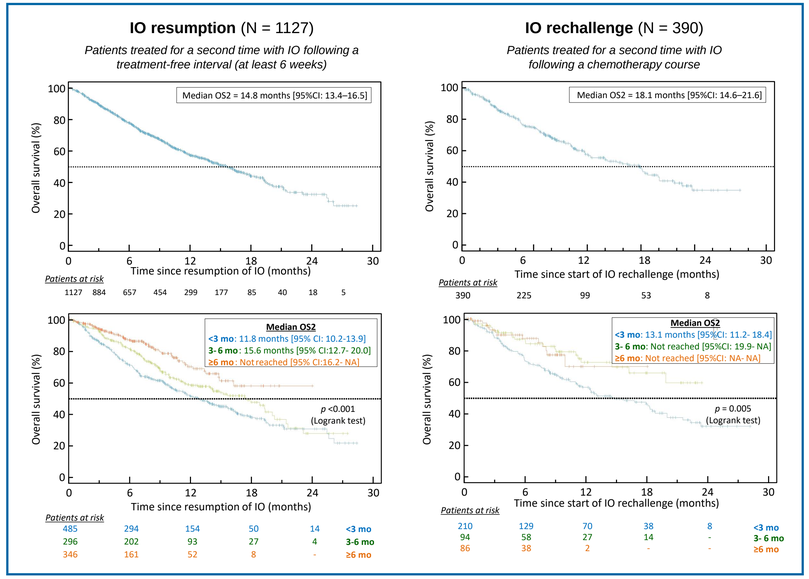
Figure 2. Overall survival (OS1) according to histology



Overall survival during retreatment (OS2)

- Median OS following IO reinitiation (OS2) was 14.8 months in case of resumption and 18.1 months in case of rechallenge (**Figure 3**),
- OS2 was significantly longer in patients with a first nivolumab treatment duration of ≥3 months (**Figure 3**).

Figure 3. Overall survival (OS2) during immunotherapy retreatment



Conclusions

- Over the two-year enrolment period, over ten thousand patients with aNSCLC were treated with nivolumab; a previous study of the PMSI database [7] reported 22,000 incident cases of aNSCLC in 2011, suggesting that nivolumab was offered to a significant proportion of patients in France for whom it is indicated.
- The characteristics of patients receiving nivolumab were very similar to those of all patients with aNSCLC in France [7], suggesting that the treatment was not being limited to a particular segment of the aNSCLC population. Compared to patients included in the pivotal clinical trials [3,4], the patients in this study were older, had been diagnosed with cancer for longer and had a higher incidence of cerebral metastases.
- In spite of these differences, the median treatment duration (2.8 months) was identical to that observed in the pivotal clinical trials and median OS1 durations were very similar (10.6 months versus 9.2 months in Sq-aNSCLC an 12.6 months versus 12.2 months in NSq-aNSCLC) [8].
- A majority of patients (53%; 5118/9593) with aNSCLC who discontinued nivolumab received a subsequent systemic therapy and around 30% (1517/5118) of these patients were retreated with immunotherapy, either as a resumption or as a rechallenge following chemotherapy.
- Median OS during the second course of immunotherapy (OS2) suggests good outcomes (>15 months) and was longer in patients with a first nivolumab treatment duration with nivolumab of ≥3 months.
- Limitations of the approach include notably the absence of reasons for changing treatment and that no data on treatment safety is available.
- These results should be considered exploratory in the absence of a comparison with another effective therapy and awaiting complementary information from other prospective cohort studies dedicated to immunotherapy rechallenge.

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Conflict of interest

- CC reports consultancy fees/from Astra Zeneca, Boehringer Ingelheim, MSD, Pierre Fabre Oncology, Lilly, Roche, Bristol-Myers Squibb, Novartis, Lilly, Pierre Fabre Oncology and Boehringer Ingelheim. MGL reports consultancy fees/research funding from Bristol-Myers Squibb, Astra Zeneca, MSD, Roche and Novartis. CC, FEC and AFG are employed by Bristol-Myers Squibb. RJ and BJ are employees of HEVA.

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