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ABSTRACT

Objectives: Nivolumab is now a reference treatment for patients with advanced non-small cell lung cancer (NSCLC) after failure of prior platinum-based chemotherapy. Little data are available on treatment approaches following discontinuation of nivolumab and on the interest of a second course of immunotherapy after nivolumab discontinuation. The aims of this study were to describe treatment pathways following nivolumab discontinuation and to describe survival following retreatment with immunotherapy.

Materials and methods: The analysis includes all patients with NSCLC recorded in a national hospital database, starting nivolumab in 2015-2016. Nivolumab treatment was considered discontinued if ≥3 infusions were missed. Patients starting a second course of PD-1 inhibitor following nivolumab discontinuation were analysed according to the duration of their initial nivolumab treatment course.

Results: 10,452 patients were included (71 % men; mean age: 63.8 ± 9.6 years; squamous histology: 44 %). Median nivolumab treatment duration was 2.8 months [IQR :1.4–6.9]. Median OS was 11.5 months [95 %CI: 11.1–11.9]; 5118 (53.4 %) patients received post nivolumab therapy lines: 1517 (29.6 %) of these received a second course of PD-1 inhibitor, either after a treatment-free interval (resumption: n = 1127) or after intervening chemotherapy (rechallenge: n = 390). Median OS after nivolumab discontinuation was 15.0 months [13.9–16.7] in the resumption group and 18.4 months [14.8–21.9] in the rechallenge group. Median OS was significantly longer in patients with an initial nivolumab treatment duration ≥3 months.

Conclusion: In this real-world setting, outcome after retreatment with a PD-1 inhibitor following a first course of nivolumab was significantly better in patients with a longer duration of initial nivolumab treatment.

1. Introduction

The introduction of immune checkpoint inhibitors (ICI) over the last decade has represented a major advance in the treatment of many types of cancer, allowing sustained recovery and, potentially, disease remission in a significant proportion of patients [1,2]. Nivolumab is a fully human monoclonal antibody directed against the programmed cell death protein 1 (PD-1), first licensed for the treatment of metastatic melanoma in 2015, and subsequently for a number of other types of cancer. In lung cancer, it is licensed for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. Two large randomised studies in patients with advanced non-squamous (NSq) NSCLC (CheckMate057 [3]) and squamous (Sq) NSCLC (CheckMate017 [4]) comparing nivolumab to docetaxel have demonstrated its efficacy at extending overall survival (OS) [5,6], and the interest of nivolumab in treating NSCLC has been confirmed in many subsequent studies in routine clinical practice [7–18].

Treatment with a PD-1 inhibitor has also been shown to be effective

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as first-line treatment of advanced NSCLC [19] and this is now becoming the standard of care in this context. This raises the question of what is the most appropriate option for second line treatment following PD-1 treatment in first line. With standard chemotherapy, the dogma has been to change to a different agent in second line, since disease progression is assimilated to the development of drug resistance. However, this dogma has recently been challenged [20]. In the case of immunotherapy, the mechanism of action, involving resetting the immune memory, and the possibility of predicting clinical response from biomarkers [21,22], the notion of a second course of immunotherapy is an attractive one.

Retreatment with PD-1 inhibitor, as a subsequent therapy, has been reported in limited numbers of patients in randomised clinical trials of nivolumab or pembrolizumab in NSCLC [19,23,24] and there are a limited number of reports of rechallenge with immunotherapy, which have generally involved small numbers of patients [25–31]. Regarding the relative benefit of rechallenge compared to the initial treatment course, the available data are encouraging [27,28] even though no definitive conclusions can be drawn given the limited experience and the heterogeneity in the definitions of retreatment and in the protocols used. Importantly, in patients restarting PD-1 inhibitor after discontinuation due to the occurrence of an adverse event, safety seems acceptable [29,30].

In general, these studies have been neither large enough nor long enough to answer crucial new clinical questions such as the utility of retreatment of patients following nivolumab discontinuation and, in particular, the utility of rechallenge with PD-1 inhibitors. The present report uses data extracted from the French national healthcare database (SNDS) to describe these patients and their treatment over time. The specific objectives of this study (the UNIVOC study) were to describe OS in a large population of unselected patients with advanced NSCLC treated with nivolumab in France, to describe post-nivolumab treatment patterns and to evaluate the consequences of subsequent retreatment with a PD-1 inhibitor after initial nivolumab discontinuation.

2. Methods

This was a retrospective observational cohort study using data from the French National Hospital discharge database (PMSI; *Programme de Médicalisation des Systèmes d'Information*).

2.1. Data source

The PMSI database covers all stays in medical, surgical or obstetric facilities in all public and private hospitals in France. Individual patients are assigned a unique anonymous identifier which is retained until death, which enables them to be tracked across multiple hospitalisations throughout their life. The information in the database covers more than 95 % of all hospitalisations in France. The reasons for hospitalisation are documented in the patient discharge summary using one or more diagnostic codes based on the International Classification of Diseases, 10th revision (ICD-10) classification.

Data available in the PMSI database includes all medical procedures or acts undertaken during inpatient stays or outpatient visits, identified by a specific costing code. The destination of the patient upon discharge (*eg* long-stay care facility or nursing home) is documented, including whether the patient dies in hospital. Sociodemographic data is limited to age at admission and gender. Medication is not documented, except in the case of certain expensive or innovative medications, including nivolumab and pembrolizumab, which are eligible for separate funding and are only available in hospital. Delivery of such treatments is documented in an associated database (FICHCOMP).

2.2. Patient selection

The study population included all patients hospitalised with lung cancer in the PMSI database through an ICD-10 code for lung cancer (C34*) as PD, RD or SAD from 1 st January 2015 to 31 st December 2016 and receiving nivolumab at least once during this period.

2.3. Data extraction

The date of the first treatment with nivolumab was taken as the index date. All hospital stays following the index date until 31st December 2017 were extracted. At the index hospitalisation, the age and gender was identified for each patient. Cancer history was documented from all hospital stays by the study population between 1st January 2011 and the index date. The time since diagnosis of NSCLC was defined as the interval between the diagnosis of NSCLC and the index date. Duration of chemotherapy was defined as the interval between the first chemotherapy administration in the advanced setting and the index date. Previous curative surgery was identified by the codes for these procedures in the discharge summaries for any of the previous hospitalisations. In this database, individual chemotherapies are not itemised and only drugs eligible for extra-DRG funding are notified, namely bevacizumab, pemetrexed, nivolumab and pembrolizumab.

The histological type of NSCLC (Sq or NSq) was identified through the proxy measure of a previous specific treatment for NSq-NSCLC, namely bevacizumab or pemetrexed. Comorbidities were identified from the discharge summaries of all hospitalisations between 1st January 2011 and 31st December 2017. The analysis was limited to a set of six comorbidities of specific interest, namely hypertension, diabetes, renal failure, chronic obstructive pulmonary disease (COPD), pulmonary insufficiency and other chronic pulmonary disease. The presence of cerebral metastases at the index hospitalisation or any previous hospitalisation was documented as previously described [32].

The treatment duration of nivolumab was defined as the interval between the index date and discontinuation, defined as no new treatment for at least six weeks after the previous treatment (*ie* three missed administrations) or death. Since the nivolumab regimen was fortnightly, the date of discontinuation was defined as the last administration date plus 14 days, or the date of death.

Patients who discontinued nivolumab were identified and classified into one of three groups: (i) death or no further anticancer treatment identified, (ii) systemic post-nivolumab treatment limited to systemic chemotherapy only and (iii) systemic post-nivolumab treatment with a PD-1 inhibitor (retreatment). Retreatment was in turn classified as either 'immunotherapy resumption' or 'immunotherapy rechallenge'. Resumption was defined as a new treatment cycle of immunotherapy after at least three skipped infusions of nivolumab (no chemotherapy in between the two courses of treatment with a PD-1 inhibitor). Rechallenge was defined as a new treatment cycle of immunotherapy following standard chemotherapy.

Deaths during hospital stays, which account for around 80 % of NSCLC deaths [33] were identified. Nonetheless, the cause of death is not documented.

2.4. Statistical analysis

Data presentation is principally descriptive. Patient characteristics were compared between Sq-NSCLC and NSq-NSCLC using the χ^2 test for categorical variables or Student's *t*-test for continuous variables. Multivariate analysis of the association between the choice of therapy after the initial nivolumab course (standard chemotherapy only or IO retreatment) and patient characteristics available from the PMSI database was performed using a logistic regression model. Variables associated with choice of treatment with a p value < 0.10 in univariate analysis were entered into a multivariate analysis, in which a p value < 0.05 was considered statistically significant. Time to treatment discontinuation (TTD) and OS rates were determined from Kaplan-Meier actuarial survival curves. Two types of OS were estimated,

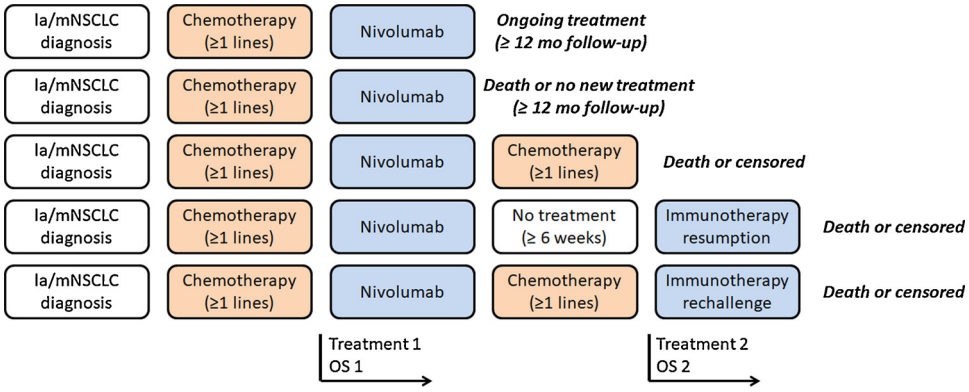

Fig. 1. Treatment sequences and overall survival determination.
la/mNSCLC: locally advanced or metastatic non-small-cell lung cancer; OS: overall survival.

namely OS from the index date (first administration of nivolumab; OS1) and OS from the start of retreatment with a PD-1 inhibitor (OS2) for patients who received a second course of PD-1 inhibitor. For the latter, OS2 were described as a function of the duration of initial nivolumab treatment with intervals of < 3 months, 3–6 months and ≥6 months. Differences in survival curves were estimated with the log rank statistic (Fig. 1). A Cox proportional hazard model was performed to identify variables independently associated with survival. Statistical analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC, USA).

2.5. Ethics

The study was conducted in accordance with International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP) and applicable regulatory requirements. Since this was a retrospective study of an anonymised database and had no influence on patient care, ethics committee approval was not required. The study was performed according to the MR006 guideline of the French data protection agency (*Commission Nationale de l'Informatique et des Libertés*; CNIL) with respect to the confidentiality of individual patient data.

3. Results

3.1. Study sample

A total of 10,452 patients hospitalised with lung cancer and receiving at least one administration of nivolumab during the study period were identified. These included 5805 patients with NSq-NSCLC (55.5 %) and 4647 with Sq-NSCLC (44.5 %). The characteristics of these patients are presented in Table 1. The mean age was 63.8 years, being significantly lower in NSq-NSCLC than in SqNSCLC. Cerebral metastases were present in 17.2 % of patients, more frequently in NSq-NSCLC. Comorbidities were commonly reported, most frequently hypertension (19.0 %) and chronic obstructive pulmonary disease (COPD; 12.9 %).

3.2. Initial nivolumab course

During the initial treatment course with nivolumab, the median treatment duration was 2.8 months in both Sq-NSCLC and NSq-NSCLC. Median OS1 was 11.5 (95 %CI: 11.1–11.9 months), being 10.6 [95 %CI: 10.1–11.0] months in Sq-NSCLC compared to 12.5; 95 %CI [11.9–13.0] months in NSq-NSCLC (Fig. 2).

3.3. Treatment sequences after nivolumab

Following discontinuation of nivolumab, 5118 (53.4 %) patients received at least one other systemic therapy. The majority (3601; 70.4 %) received only systemic chemotherapy; whilst the remaining 1517 patients received a further course of nivolumab or pembrolizumab (Fig. 3). Eighteen of these patients (0.04 %) received pembrolizumab (six as resumption and twelve as rechallenge) and the remainder nivolumab. This was started after a treatment gap without any intervening chemotherapy in 1127 patients (74.3 %; resumption group) or following an intervening chemotherapy course in 390 patients (25.7 %; rechallenge group). The characteristics of these patients receiving a second course of PD-1 inhibitor are presented in Supplemental Table 1.

In 1 127 patients in the resumption group, the median interval between discontinuation of the initial course of nivolumab and resumption of a PD-1 inhibitor was 9 weeks and the median duration of the second course of PD-1 inhibitor was 4.0 months. Median survival after the start of the second course of PD-1 inhibitor (OS2) was 14.8 [95 % CI: 13.4–16.5] months (Fig. 4).

In the 390 patients in the rechallenge group, the second course of PD-1 inhibitor was started after a median interval of 11 weeks after the end of the first course of nivolumab treatment. The median duration of the second course of PD-1 inhibitor was 3.0 months. Median survival following the start of this second course (OS2) was 18.1 months [95 % CI: 14.6–21.6] (Fig. 4).

For all patients starting a second course of PD-1 inhibitor, OS2 was significantly longer ($p < 0.001$; logrank test) in the patients who had been treated the longest during the initial nivolumab course (Fig. 4).

Using a Cox analysis of the OS2 data the only variable identified was duration of the initial nivolumab treatment. In the IO resumption group, compared to patients initially treated for < 3 months, the hazard ratio was 0.56 [95 % CI: 0.46–0.70; p < 0.0001] in patients initially retreated for 3–6 months and 0.19 [95 % CI: 0.14 – 0.25; p < 0.0001] in those initially treated for ≥6 months. The thresholds of 3 and 6 months correspond approximately to the median and upper quartile of the range of initial treatment duration, respectively (Table 1). In the IO rechallenge group, the corresponding hazard ratios were 0.35 [95 % CI: 0.22 – 0.56; p < 0.0001] (3–6 months) and 0.19 [95 % CI: 0.10 – 0.33; p < 0.0001] (≥6 months).

3.4. Factors associated with choice of post-nivolumab treatment sequences

In multivariate regression analysis (Table 2), the only variables associated with the choice of IO retreatment over standard chemotherapy alone were a longer duration of the initial nivolumab treatment (OR = 1.17 [95 % CI: 1.01–1.36] and OR = 1.48 [95 % CI: 1.28–1.71], respectively for patients treated 3–6 months and 6 months or more compared to less than 3 months) and the presence of certain comorbidities (hypertension and COPD).

Table 1
Patients characteristics.

Baseline characteristics[1]	NSq-NSCLC (N = 5805)	Sq-NSCLC (N = 4647)	Overall population (N = 10,452)
Age (mean ± SE; years)	61.9 ± 9.3*	66.1 ± 9.5	63.8 ± 9.6
Gender (men: n, %)	3733 (64.3 %)*	3687 (79.3 %)	7420 (71.0 %)
Time since diagnosis[2] (mean ± SD; mo)	21.6 ± 21.1	17.2 ± 19.9	19.7 ± 20.6
Presence of cerebral metastases	1,332 (22.9 %)*	468 (10.1 %)	1800 (17.2 %)
Previous curative surgery	853 (14.7 %)	776 (16.7 %)	1 629 (15.6 %)
Time since first chemotherapy[3] (mean ± SD; mo)	18.1 ± 18.1	13.9 ± 15.7	16.3 ± 17.2
Comorbidities	*		
Hypertension	**917 (15.8%)**	**1069 (23.0 %)**	1986 (19.0 %)
Diabetes	**388 (6.7%)**	**546 (11.7 %)**	934 (8.9 %)
Renal failure	**246 (4.2%)**	**233 (5.0 %)**	479 (4.6 %)
Chronic obstructive pulmonary disease	**508 (8.8%)**	**840 (18.1 %)**	1348 (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 %)
Time to treatment discontinuation[4]			
Median [IQR] (months)	2.8 [1.4–6.9]	2.8 [1.4–6.2]	2.8 [1.4–6.6]
Patients in treatment at 12 months (%; [95 % CI])	14.6 % [13.7–15.5]	12.2 % [11.3–13.1]	13.5 % [12.9–14.2]
Overall survival; OS1 (months)			
Median [95 % CI]	12.5 [11.9–13.0]	10.6 [10.1–11.0]	11.5 [11.1–11.9]

[1] At which nivolumab treatment was initiated.
[2] Time since first hospitalisation with lung cancer.
[3] At time of first nivolumab treatment.
[4] Of initial nivolumab treatment. IQR: interquartile range; NSq: non-squamous cell; Sq: squamous cell; 95 % CI: 95 % confidence intervals.
* For variables in **bold** the difference between the NSq and Sq subgroups was statistically significant ($p < 0.001$).

4. Discussion

This analysis of a nationwide medico-administrative database describes data from over ten thousand patients with advanced NSCLC treated with nivolumab following prior chemotherapy over the two years following its availability in France. This is one of the largest cohort of patients treated with nivolumab to be reported to date. A previous study of the PMSI database reported 22,000 incident cases of metastatic lung cancer in 2011 [34]. Assuming that NSCLC accounts for around 80 % of these cases [35] and that around 50 % of patients never receive a second-line treatment [36] this would suggest that nivolumab was offered to a significant part of the patients in France for whom it was indicated.

We have previously described the characteristics of all patients with NSCLC in the PMSI database hospitalised with lung cancer for the first time in 2011 [34], using an identical selection procedure as in the present study. Compared to this reference population, patients prescribed nivolumab were somewhat younger and less frequently presented comorbidities. However, the observed differences are relatively modest and could be explained by second-line attrition bias favourable to healthier patients. In addition, compared to the clinical trial data from the CheckMate017 and CheckMate057 studies, [3–5], the mean initial nivolumab treatment duration was identical (NSq and Sq histology combined), and median OS was very similar in both Sq-NSCLC and NSq-NSCLC.

Given the large number of patients enrolled, it was possible to explore subsequent treatment pathways in patients who discontinued nivolumab. Around half of them received a further systemic therapy,

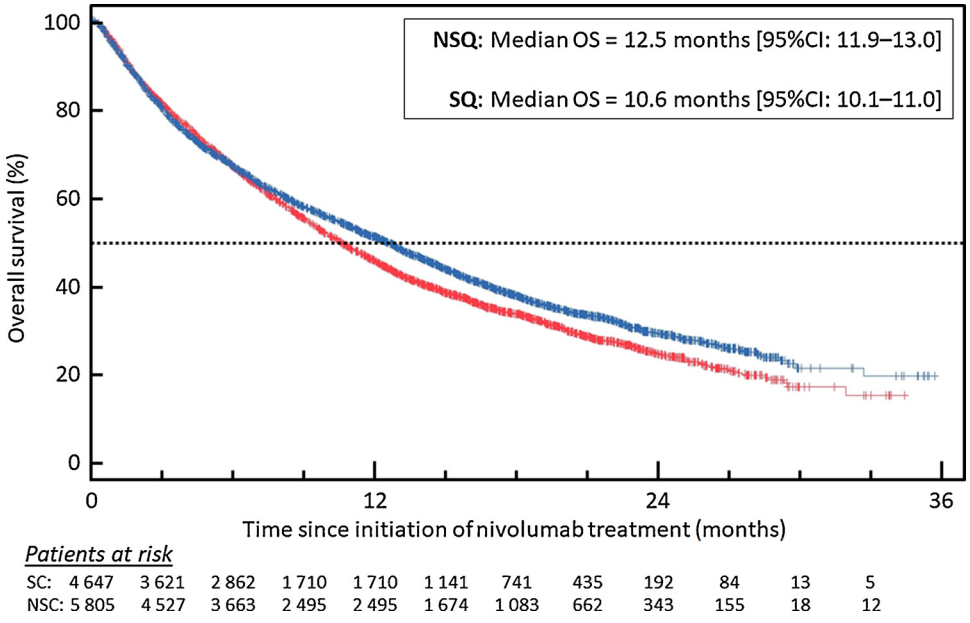

Fig. 2. Overall survival (OS1) according to histology.
Data are presented as Kaplan-Meier survival curves. Blue curves: non-squamous cell non-small cell lung cancer (NSQ); red curve: squamous cell non-small cell lung cancer (SQ). OS: overall survival.

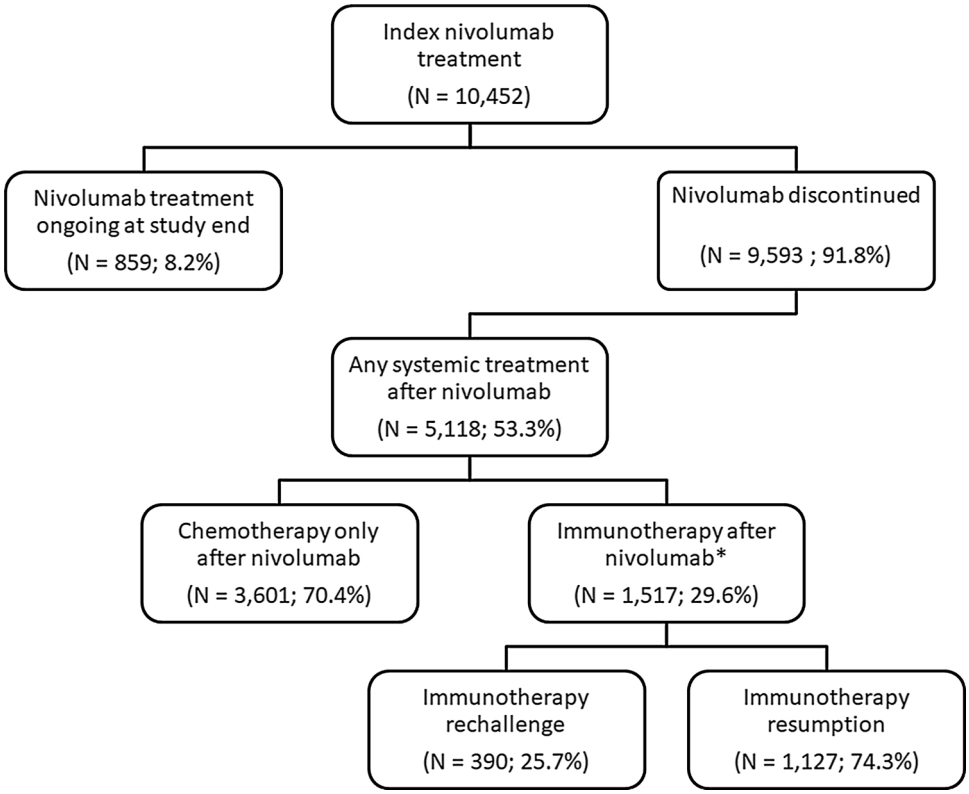

Fig. 3. Patient treatment trajectories.
Percentages are calculated in each case with respect to the previous line.*Eighteen patients were prescribed pembrolizumab as immunotherapy after nivolumab (six as resumption and twelve as rechallenge), the remaining 1499 were prescribed a second course of nivolumab.

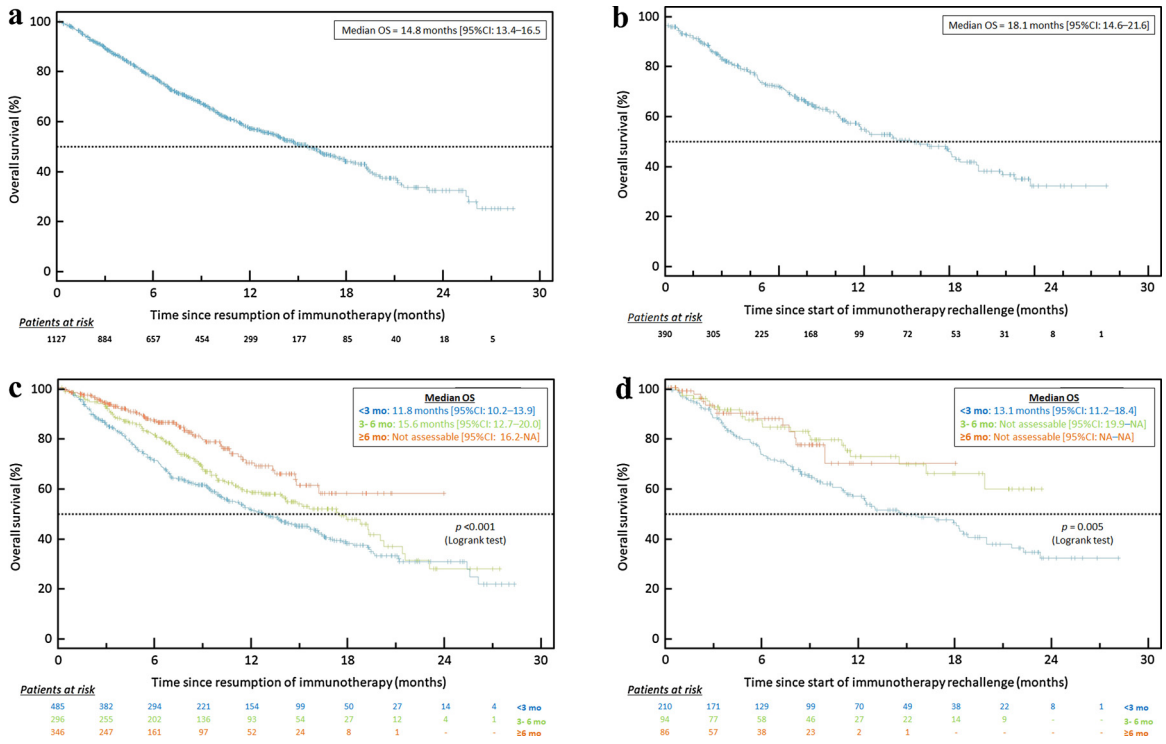

Fig. 4. Overall survival (OS2) during retreatment with a PD-1 inhibitor.
Data are presented as Kaplan-Meier survival curves. A: PD-1 inhibitor resumption; B: PD-1 inhibitor rechallenge. C – D: as above, as a function of the initial nivolumab treatment duration. CI: confidence intervals; NA: not assessable; OS: overall survival.

Table 2
Univariate and multivariate logistic regression analysis of factors of receiving a second PD-1 inhibitor.

Patients' characteristics	All patients with 2nd PD-1 inhibitor course (N = 1517)	All patients with post-nivolumab chemotherapy only (N = 3601)	Univariate analysis		Multivariate analysis	
			OR (95 % CI)	P value	OR (95 % CI)	P value
Age (mean ± SD; years)	63.5 ± 9.7	63.4 ± 9.4	1.00 (0.99–1.01)	0.634	–	–
Gender (men: n, %)	1057 (69.7 %)	2526 (70.2 %)	1.02 (0.90–1.17)	0.737	–	–
Histology (non-squamous; n, %)	810 (53.4 %)	2047 (56.9 %)	**1.15 (1.02–1.30)**	**0.023**	**NS**	**NS**
Cancer duration						
Less than 1 year	689 (45.4 %)	1729 (48.0 %)	Reference		–	–
1 to 5 years	741 (48.9 %)	1678 (46.6 %)	1.11 (0.98–1.25)	0.103	–	–
5 years and more	87 (5.7 %)	194 (5.4 %)	1.13 (0.86–1.47)	0.388	–	–
Cerebral metastases	254 (16.7 %)	562 (15.6 %)	1.09 (0.93–1.28)	0.310	–	–
Duration of initial nivolumab course						
< 3 months	695 (45.8 %)	1888 (52.4 %)	**Reference**		**Reference**	
3 – 6 months	390 (25.7 %)	912 (25.3 %)	**1.16 (1.00–1.35)**	**0.046**	**1.17 (1.01–1.36)**	**0.035**
≥6 months	432 (28.5 %)	801 (22.2 %)	**1.47 (1.27–1.70)**	**< 0.001**	**1.48 (1.28–1.71)**	**< 0.001**
Comorbidities (yes vs. no)						
Hypertension	297 (19.6 %)	592 (16.4 %)	**1.24 (1.06–1.44)**	**0.007**	**1.21 (1.03–1.42)**	**0.019**
Diabetes	138 (9.1 %)	289 (8 %)	1.15 (0.93–1.42)	0.206	–	–
Renal failure	68 (4.5 %)	147 (4.1 %)	1.10 (0.82–1.48)	0.515	–	–
COPD	222 (14.6 %)	425 (11.8 %)	**1.28 (1.08–1.53)**	**0.005**	**1.24 (1.03–1.48)**	**0.021**
Pulmonary insufficiency	24 (1.6 %)	42 (1.2 %)	1.36 (0.82–2.26)	0.230	–	–
Other chronic pulmonary disease	147 (9.7 %)	274 (7.6 %)	**1.30 (1.06–1.61)**	**0.014**	NS	NS

which involved a second course of PD-1 inhibitor (principally nivolumab again) in around one third of cases, either as a resumption (without an intervening course of systemic chemotherapy) or as a re-challenge (after an intervening course of systemic chemotherapy. This is a relatively high proportion of patients moving onto a third-line therapy, compared with patients with NSCLC receiving only conventional chemotherapy as the first two treatment lines, of whom over seventy percent are not prescribed a third-line therapy [36]. Multivariate results showed that one of the main criteria associated with the choice of retreating patients with a PD1-inhibitor is the duration of the initial nivolumab treatment, in particular if this first course has exceeded six months. Duration of initial treatment may be a proxy for a favourable initial treatment response, whereas early discontinuation for whatever reason may indicate treatment failure. The only other variable identified in the multivariate analysis was the presence of certain comorbidities. The explanation for this association is unclear, but it is possible that physicians may prefer to treat more fragile patients with an immunotherapy rather than giving standard chemotherapy, whose safety profile is less favorable. There are probably other criteria explaining physicians' choices for receiving a second course of PD1-inhibitor, which were not captured in our study as they are not documented in the PMSI database. For example, an objective response or a specific immune-related toxicity during the first treatment may influence the decision to retreat, and the same is true of biomarkers such as high expression of PD-L1.

The patients who received a second course of PD-1 inhibitor after a drug holiday following nivolumab discontinuation (resumption group) or after an intervening course of standard chemotherapy (rechallenge group) had a median OS2 during the second course of over twelve months, which compares favourably with OS1 during the initial nivolumab treatment, and also with OS after standard chemotherapy in third-line treatment of advances NSCLC [37]. These findings are consistent with those of earlier small studies suggesting that retreatment with PD-1 inhibitors may be beneficial [27,28]. We observed that OS2 was longer in patients who had been treated with nivolumab for longer in the initial treatment course, which may be perhaps related to a progressive consolidation of an immune memory during the first treatment course.

The findings can also be compared with a recently published cohort of 144 patients who were managed by ICI retreatment with a PD-1 inhibitor or a PDL-1 inhibitor after discontinuation of the first ICI course [38]. In this study, median OS during retreatment was 1.5 years, which is comparable to the median OS2 of 18.1 months for re-challenged patients in the present study. It was also observed that median OS was longer in patients discontinuing their first ICI course due to toxicity than in patients discontinuing due to disease progression, and was also longer in patients who had not received standard chemotherapy than in those who had. Identification of which patients most benefit from retreatment with ICIs and, importantly, which patients do not, will be a major question to address in future prospective studies. Biomarkers may be useful here, as they have been proposed to be for predicting response and resistance to ICIs in the initial treatment course [21,22].

The limitations of this study are principally inherent to the structure and content of the PMSI database. Firstly, no information is available on the outcomes of any tests, including biomarkers such as PD-L1 expression status. The only effectiveness measure that can be extracted is OS. Even this may not be captured perfectly, since only in-hospital deaths are recorded and patients who die at home or in nursing homes, for example, will not be identified as having died but would have been censored at the last observation. Nonetheless, it has been reported that around 80 % of patients who die from lung cancer in France die in hospital [33]. Secondly, no information was available on progression and on the reasons for stopping or restarting immunotherapy or moving to systemic chemotherapy. For the same reason, information is not available on objective response rate or progression-free survival. For example, patients receiving a second course of PD-1 inhibitor as a resumption could represent two different clinical situations, either resumption after a long discontinuation (≥6 weeks) for the management of a toxicity or resumption after a drug holiday due to prolonged response. Indeed, the median duration of the initial nivolumab treatment reported in this group was relatively long (3.8 months) and one third of patients had been treated initially for at least 6 months. For patients receiving PD-1 inhibitor as a rechallenge, the intercalated chemotherapy between the two courses of PD-1 inhibitor would indicate progression during initial nivolumab treatment. Thirdly, individual chemotherapy regimens could not be identified, with the exception of bevacizumab or pemetrexed. Oral treatments not administered in hospital such as EGFR inhibitors and ALK inhibitors could not be identified at all. However the study also has major strengths, in particular the large number of patients enrolled, and the exhaustive nature of the PMSI database which ensures that all patients treated with nivolumab

in France are captured.

In conclusion, this large study indicates that that the effectiveness of treatment with a PD-1 inhibitor is maintained during retreatment and that this may be a valid therapeutic option for routine clinical practice in selected patients. The possibility is of particular significance as immunotherapy comes to be used as first-treatment of advanced NCSLC and even in the adjuvant setting. Further studies are merited in order to identify which patients are likely to benefit most from retreatment with a PD-1 inhibitor.

Declaration of Competing Interest

MGL reports consultancy fees/research funding from Bristol-Myers Squibb, Astra Zeneca, MSD, Roche and Novartis. FEC, CC, and AFG are employed by Bristol- Myers Squibb. BJ and RJ are employees of HEVA.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. JBA was supported by grants from Fondation pour la Recherche Médicale (FRM).

Credit author statement

FEC and AFG initiated the study. Together with MGL, RC, JBA and CChouaid, they formed the UNIVOC study Steering Committee, which oversaw study design, data collection and analysis, and preparation of the manuscript. BJ was responsible for the operational conduct of the study, RJ performed the statistical analysis and CCalvet, JRP and VG advised on the implementation and interpretation of the study.

Data availability

The source database (PMSI) contains personal health data containing potentially identifying and sensitive patient information. According to French law (Decree N° 2016-1871 dated 28th December 2016, concerning the processing of personal data in the SNDS), PMSI data are available exclusively from the database holder, the CNAMTS (*Caisse nationale de l'assurance maladie des travailleurs salariés*), to institutions who meet the criteria for access to confidential data, following procurement of consent from the National Health Data Institute (INDS) and the French data protection authority (CNIL). Publication of individual patient data is not permitted. The INDS, which is responsible for access to health data in France, is a one-stop-shop window for access to the SNDS database (including the PMSI database). The contact address for the INDS is *Institut National des Données de Santé* (INDS), 19 rue Arthur Croquette, 94220 Charenton-le-Pont, Telephone: +33 1 45 18 43 90; Email: contact@indsante.fr; Website: https://www.indsante.fr/fr.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.12.017.

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