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# Real-World Use and Immunotherapy Rechallenge Outcomes with Nivolumab in Advanced Non-small Cell Lung Cancer in France: Interim Results of the LIST Study

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## ABSTRACT

**Introduction:** Nivolumab is approved in France as monotherapy for the treatment of advanced (locally advanced or metastatic) non-small cell lung cancer (aNSCLC) after prior chemotherapy. The Lung Initiative on Sequence Therapy (LIST) study is evaluating the real-world effectiveness, safety and immunotherapy-rechallenge outcomes with nivolumab in previously treated French patients with aNSCLC.

**Methods:** This longitudinal, prospective, observational study enrolled patients with aNSCLC who received  $\geq 1$  prior line of treatment that included chemotherapy. Three patient cohorts, based on

prior treatment, were assessed: immunotherapy-naïve (cohort 1; prior chemotherapy, no prior immunotherapy), and immunotherapy-experienced, including patients who discontinued prior immunotherapy for reasons other than immunotherapy-related toxicity (cohort 2) and those who discontinued because of immunotherapy-related toxicity (cohort 3). The primary endpoint was time to treatment discontinuation (TTD). Results after at least 12 months of follow-up are reported.

**Results:** At data cut-off (September 2024), 522 patients were enrolled. In cohort 1 ( $N=280$ ), cohort 2 ( $N=197$ ) and cohort 3 ( $N=45$ ), the 12-month TTD rate was 17.7% (95% CI 13.4, 22.5), 14.4% (95% CI 9.8, 19.8) and 16.7% (95% CI 7.3, 29.2), respectively. The main reason for nivolumab discontinuation was disease progression. Younger patients, those with better performance status (PS), longer prior immunotherapy duration and prolonged benefit with prior immunotherapy had numerically higher discontinuation-free rates. Median PFS was 3.2, 2.7 and 3.9 months (95% CI

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2.7–4.1, 2.2–3.4, 2.2–7.4), and median overall survival (OS) was 12.3, 9.5 and 10.4 months (95% CI 8.6–13.7, 7.2–11.3, 7.6–20.1) in cohorts 1, 2 and 3, respectively. Any-grade treatment-related adverse events were reported in 36.1%, 25.0% and 37.0% of patients in the respective cohorts.

**Conclusions:** The 1-year results of LIST show consistent effectiveness and safety of nivolumab in immunotherapy-experienced patients, especially in specific subgroups. Nivolumab safety in patients with prior immunotherapy-related toxicity appeared to be consistent with its expected safety profile.

**Trial Registration:** ClinicalTrials.gov identifier NCT04500535.

## PLAIN LANGUAGE SUMMARY

Immunotherapy is now the standard of care for patients with non-small cell lung cancer; however, it is unclear whether re-treatment (rechallenge) with immunotherapy after previously stopping it is beneficial. The Lung Initiative on Sequence Therapy (LIST) study is examining the effectiveness and safety of immunotherapy rechallenge with nivolumab in previously treated patients with advanced non-small cell lung cancer in real-life practice in France. Results after following three groups of patients for at least 12 months are reported. The three groups were patients who had never received immunotherapy (group 1), patients who had previously received immunotherapy but had discontinued it for reasons other than immunotherapy-related toxicity (group 2) and patients who had previously received immunotherapy and had discontinued it because of immunotherapy-related toxicity (cohort 3). Among 522 included patients (group 1, 280 patients; group 2, 197 patients; group 3, 45 patients), 17.7% of patients in group 1, 14.4% in group 2 and 16.7% in group 3 were still receiving nivolumab at 12 months. Patients who were younger, had better performance status, had received prior immunotherapy for longer and with a longer response to prior immunotherapy appeared to be less likely to discontinue nivolumab. Nivolumab was well tolerated even in patients who had previously discontinued immunotherapy because of immunotherapy-related

toxicity (treatment-related adverse events: group 1, 36.1% of patients; group 2, 25.0%; group 3, 37.0%).

**Keywords:** Immune checkpoint inhibitors; Immunotherapy; Nivolumab; Non-small cell lung cancer; Real-world study

### Key Summary Points

#### *Why carry out this study?*

Immunotherapy is approved for the first-line treatment of advanced non-small cell lung cancer (NSCLC) and is increasingly being used in this setting.

Data are needed to evaluate the effect of prior immunotherapy use on the real-world effectiveness and safety of immunotherapy rechallenge, particularly in patients who discontinued prior immunotherapy because of treatment-related toxicity.

The aim of the ongoing Lung Initiative on Sequence Therapy (LIST) study is to evaluate the real-world effectiveness and tolerability of nivolumab in French patients with advanced NSCLC who received  $\geq 1$  prior line of chemotherapy  $\pm$  immunotherapy.

#### *What was learned from the study?*

Interim 1-year results of the LIST study demonstrated consistent time to treatment discontinuation (TTD), and reasons for discontinuation, with nivolumab monotherapy in immunotherapy-naïve patients, and in immunotherapy-experienced patients (including those who discontinued prior immunotherapy for reasons other than immunotherapy-related toxicity and those who discontinued because of immunotherapy-related toxicity [12-month TTD rate, 17.7%, 14.4% and 16.7%, respectively]).

Rechallenge with nivolumab appears to be a viable option, even in patients who previously experienced immunotherapy-related toxicity, with no excessive overall toxicity observed in these patients.

## INTRODUCTION

The anti-programmed cell death 1 (PD-1) agent nivolumab was approved in Europe in 2015 as monotherapy for the treatment of advanced (locally advanced or metastatic) non-small cell lung cancer (NSCLC) after prior chemotherapy [1]. This approval was based on the randomised controlled CheckMate 017 and 057 trials, in which nivolumab significantly improved clinical response rates and survival outcomes compared with docetaxel [2, 3]. Moreover, long-term CheckMate 017 and 057 data demonstrated that the survival benefit of nivolumab over docetaxel was maintained over 5 years of follow-up [4].

Real-world data are important to further corroborate the effectiveness and safety of approved drugs in various patient populations. Final results of the prospective, non-interventional EVIDENS study (NCT03382496) reflect the effectiveness and safety of nivolumab in French patients with pretreated NSCLC reported in pivotal phase III, randomised clinical trials [5–7]. Almost all patients included in this study were pre-treated with chemotherapy (99.7%), which was mostly platinum based (98.8%) [6, 7]. However, with the approval of immunotherapy for the first-line treatment of advanced NSCLC and its increasing use in this setting [8, 9], it is important to evaluate the effect of prior immunotherapy use on the subsequent effectiveness and safety of nivolumab during real-life treatment of advanced NSCLC. This is particularly important for identifying patients who may benefit from immunotherapy rechallenge after discontinuing prior immunotherapy.

The aim of the ongoing Lung Initiative on Sequence Therapy (LIST) study is to evaluate real-world use of nivolumab (patient/treatment characteristics, effectiveness, safety and rechallenge outcomes) in French patients with advanced NSCLC who received  $\geq 1$  prior line of chemotherapy, alone or in combination with immunotherapy. Here, we present the results with a minimum follow-up period of 1 year for all included patients.

## METHODS

### Study Design

LIST is a longitudinal, observational study, conducted at 99 sites in France and involving 128 physicians and their patients. Patients were enrolled at the time of nivolumab initiation; thus, both retrospective (i.e. patient characteristics and prior treatments) and prospective data (i.e. longitudinal follow-up of nivolumab effectiveness and safety outcomes, and subsequent therapies) are collected. Study objectives are to describe the characteristics of patients treated with nivolumab in real-life settings and how it is administered, to evaluate the overall effectiveness and safety of nivolumab in advanced NSCLC, and to evaluate differences in treatment response according to previous immunotherapies.

The study was conducted in accordance with International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP) and applicable regulatory requirements. All required approvals from ethics committees, independent review committees, regulatory authorities and/or other local governance bodies were obtained prior to study initiation (N° EudraCT/ID RCB number 2020-A00769-30). All patients provided oral informed consent and were permitted to withdraw from the study at any stage.

### Patients

Participating physicians (i.e. pulmonologists, oncologists) from eligible hospitals identified and recruited all consecutive eligible patients, ensuring a representative sample of the target population. Eligible hospitals were those which treated  $\geq 40$  patients who had lung cancer with chemotherapy during 2018. Each physician recruited up to 30 patients over a 30-month accrual period.

Eligible patients were adults ( $\geq 18$  years) with pathologically confirmed advanced NSCLC who initiated nivolumab. The decision to initiate nivolumab was made independently by the treating physician within 1 month prior to study

enrolment. Patients had received  $\geq 1$  prior chemotherapy-based treatment and were stratified into three cohorts based on prior immunotherapy exposure: cohort 1 were immunotherapy-naïve; cohort 2 were immunotherapy-experienced patients who discontinued for reasons other than immunotherapy-related toxicity (e.g. disease progression, treatment protocol completion, patient decision, etc.); and cohort 3 were immunotherapy-experienced patients who discontinued because of immunotherapy-related toxicity. Patients already receiving nivolumab as part of an interventional study for lung cancer treatment at the time of recruitment were excluded. Other exclusion criteria included having received a previous immunotherapy treatment within the 12 weeks preceding the first nivolumab infusion in the context of this study, a diagnosis of another primary cancer within the 5 years preceding the study, or pregnancy.

### Endpoints and Outcomes

The primary endpoint was time to treatment discontinuation (TTD), defined as the time from nivolumab initiation until the earliest treatment discontinuation for any reason, including progressive disease (PD), treatment toxicity, patient preference or death. Secondary endpoints included characteristics of patients initiating nivolumab, progression-free survival (PFS; i.e. the time from nivolumab initiation until the earliest of PD or death), overall survival (OS; i.e. the time from nivolumab initiation until death), clinical response rate, time to next therapy (TTNT; i.e. the time from nivolumab discontinuation until initiation of subsequent systemic therapy), safety and quality of life (QoL).

Retrospective data collected at the time of nivolumab initiation (i.e. patient demographics and clinical characteristics, disease history, prior treatments) and prospective data collected at each follow-up visit (nivolumab effectiveness, clinical assessments and management, patient health status and QoL, adverse drug reactions, subsequent treatments) were entered into electronic case report forms (eCRFs) by each study site. Patients were regularly followed for up to 36 months from the time of nivolumab

initiation according to real-life scheduled visits until consent withdrawal, death, loss of follow-up or the end of the study (whichever came first). No interventions, extra procedures or extra visits were conducted. Data were entered into the eCRF according to prespecified time points (i.e. day 0, week 4, 8, 12, 26 and 38, then year 1, 1.5, 2, 2.5 and 3) using data from the visit nearest to the time point.

Clinical response was assessed by the investigator according to Response Evaluation Criteria for Solid Tumors (RECIST) [10] if available. Best overall response (BOR) was defined as the highest level of response among available tumour assessments during follow-up. Disease control rate (DCR) was defined as the proportion of patients with complete response (CR), partial response (PR) or stable disease (SD).

The incidence and severity of all-cause adverse events (AEs) and treatment-related AEs (TRAEs) were recorded by the treating physician at each visit and coded according to the Medical Dictionary for Regulatory Activities, version 19.1 or higher.

Patient QoL status was evaluated using the summary and subscale scores of the validated European Quality of Life 5 Dimensions–3 Level (EQ-5D-3L) questionnaire at baseline and at each study visit throughout follow-up.

### Statistical Analyses

The sample size calculation was focused on the level of precision when estimating the primary endpoint of TTD, using historical PFS data [2, 3]. This was an approximate calculation due to a lack of prior estimates of TTD with immunotherapy in advanced NSCLC. A total enrolment of 698 patients was planned: for cohorts 1 and 2, enrolment of 273 patients would ensure final inclusion of 246 patients, and for cohort 3, enrolment of 152 patients would ensure final inclusion of 137 patients. Sample size calculations assumed  $\pm 5\%$  (for cohorts 1 and 2) or  $\pm 8\%$  (for cohort 3) precision and a 12-month TTD rate of 20% (for cohorts 1 and 2) or 35% (for cohort 3), with 10% unevaluable patients (for cohorts 1 and 2).

All effectiveness outcomes and QoL were assessed in the analysable population (i.e. patients

enrolled and treated with nivolumab with no deviation on inclusion or exclusion criteria) and all safety outcomes were assessed in the safety population (i.e. patients who received at least one administration of nivolumab regardless of the duration of treatment). TTD analysis was also performed in pre-specified patient subgroups according to age (<65, 65–75 or >75 years), Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0–1 or  $\geq$ 2), duration of last prior immunotherapy (<3, 3–12 or >12 months), having received nivolumab ( $\pm$  chemotherapy) as the only prior immunotherapy, number of prior systemic treatment lines (1, 2 or  $\geq$ 3), reason for last immunotherapy discontinuation (PD or prolonged benefit), and interval from last immunotherapy dose to study nivolumab initiation (<6, 6–12, 12–24 or  $\geq$ 24 months). Although no formal definition or minimum treatment duration for prolonged benefit was provided to investigators, a duration of 2 years was generally regarded as such in France at the time. Response rates were calculated over the total number of patients in each cohort, including patients for whom BOR was not reported.

Analysis of study outcomes was purely descriptive; no formal statistical tests were conducted and no *p* values were calculated. Categorical variables were assessed using the number and proportions of patients and continuous variables were assessed using medians and ranges (minimum, maximum values). Time-to-event outcomes (i.e. TTD, OS, PFS and TTNT) were estimated using the Kaplan–Meier method and reported using descriptive statistics (e.g. medians, 1-year rates) with 95% confidence intervals (CI) and survival curves. Patients were censored at death, last record or assessment if lost to follow-up, or date of enrolment into a clinical trial if known. All statistical analyses were conducted using SAS version 9.4 or higher (SAS Institute, Cary, NC, USA) and R.

## RESULTS

### Patients

At the data cut-off (16 September 2024), 522 patients were enrolled and included in the analysable population (see Fig. S1 in the electronic

supplementary material). Among these, 280 were immunotherapy naïve (cohort 1) and 242 had received prior immunotherapy, which they had discontinued for reasons other than immunotherapy-related toxicity ( $n = 197$ ; cohort 2) or because of immunotherapy-related toxicity ( $n = 45$ ; cohort 3). Included patients were first diagnosed with NSCLC between 2009 and 2022, with patients most commonly diagnosed in 2019 or later (67.7%).

Patient demographic data and disease characteristics are reported in Table 1. The patient population had a median age of 70 years in cohort 1 and 66 years in cohorts 2 and 3. The majority of patients were male (68.6%, 62.9% and 77.8% in cohorts 1, 2 and 3, respectively), had stage IV disease (87.8%, 90.9% and 82.2% in cohorts 1, 2 and 3, respectively) and a good PS (ECOG 0–1 in 73.9%, 75.6% and 68.9% of cohorts 1, 2 and 3, respectively). Former/current smokers represented 89.6% of cohort 1, 88.3% of cohort 2 and 95.6% of cohort 3. At diagnosis, fewer patients had non-squamous histology in cohort 1 (60%) than in cohorts 2 and 3 (76.1% and 75.6%, respectively). Programmed death ligand 1 (PD-L1) expression varied between cohorts, with the majority (60.1%) of patients in cohort 1 having a PD-L1 expression <1%, while 28.9% and 30.9% of patients in cohort 2 and 44.4% and 22.2% of patients in cohort 3 had PD-L1 expression of 1–49% and  $\geq$ 50%, respectively. Among the tumour biomarkers tested, proportions of patients with molecular alterations were consistent with published real-world data [11–13]. *KRAS* mutation was the most represented (~33–40% of patients across the various cohorts), whereas other mutations were rarer: *HER2* (12/194 [6.2%]), *BRAF* (13/248 [5.2%]), *EGFR* (11/306 [3.6%]), *ROS1* (8/277 [2.9%]), *MET* (5/198 [2.5%]) or *ALK* (6/331 [1.8%]).

### Treatment History

All patients had received prior chemotherapy, either for non-advanced disease, advanced disease or both. The majority of patients in cohort 1 (82.5%) had received one line of prior systemic therapy, while patients in cohorts 2 and

**Table 1** Patient baseline demographics and clinical characteristics

	Cohort 1 (N=280)	Cohort 2 (N=197)	Cohort 3 (N=45)
Characteristics at diagnosis			
Male, <i>n</i> (%)	192 (68.6)	124 (62.9)	35 (77.8)
Median age (range), years	70 (38–90)	66 (40–88)	66 (46–89)
Smoking status, <i>n</i> (%)			
Never	29 (10.4)	23 (11.7)	2 (4.4)
Former	182 (65.0)	130 (66.0)	30 (66.7)
Current	69 (24.6)	44 (22.3)	13 (28.9)
Tumour histology, <i>n</i> (%)			
Squamous	102 (36.4)	44 (22.3)	11 (24.4)
Non-squamous	168 (60.0)	150 (76.1)	34 (75.6)
Mixed	8 (2.9)	3 (1.5)	0
Unknown	2 (0.7)	0	0
Characteristics at nivolumab initiation			
ECOG performance status, <i>n</i> (%)			
0	46 (16.4)	39 (19.8)	7 (15.6)
1	161 (57.5)	110 (55.8)	24 (53.3)
≥ 2	73 (26.1)	48 (24.4)	14 (31.1)
Tumour stage, <i>n</i> (%)			
IIIA	4 (1.4)	4 (2.0)	1 (2.2)
IIIB	17 (6.1)	7 (3.6)	5 (11.1)
IIIC	7 (2.5)	5 (2.5)	1 (2.2)
IV	245 (87.8)	179 (90.9)	37 (82.2)
Unknown/missing	7 (2.5)	2 (1.0)	1 (2.2)
Metastasis location, <sup>a</sup> <i>n</i> (%)			
Liver	47 (19.3)	29 (16.3)	7 (18.9)
Bone	78 (32.1)	54 (30.3)	9 (24.3)
Brain	61 (25.1)	38 (21.3)	9 (24.3)
PD-L1 expression, <sup>b</sup> <i>n</i> (%)			
< 1%	134 (60.1)	61 (40.1)	12 (33.3)
1–49%	71 (31.8)	44 (28.9)	16 (44.4)
≥ 50%	18 (8.1)	47 (30.9)	8 (22.2)

Table 1 continued

	Cohort 1 (N=280)	Cohort 2 (N=197)	Cohort 3 (N=45)
Prior treatment lines for advanced disease, <sup>b</sup> n (%)	n = 268	n = 197	n = 45
1	221 (82.5)	9 (4.6)	9 (20.0)
2	38 (14.2)	69 (35.0)	20 (44.4)
≥ 3	9 (3.3)	119 (60.4)	16 (35.6)

ECOG Eastern Cooperative Oncology Group, PD-L1 programmed cell death ligand 1

<sup>a</sup>Data are presented only for metastasis of interest; patients could have ≥ 1 metastasis location. Percentages calculated from the patients with available information on metastasis location

<sup>b</sup>Proportion of evaluable patients

3 were more heavily pretreated with 95.4% and 80% of patients, respectively, having received at least two prior systemic therapies. In patients who had received prior chemotherapy for advanced disease (95.7%, 99.5% and 97.8% in cohorts 1, 2 and 3, respectively), the most common regimen was platinum-based doublets with carboplatin (77.5%, 80.7% and 82.2%, respectively; Table 2). In cohorts 2 and 3, patients had received prior pembrolizumab (54.8% and 48.9%, respectively), mainly as first-line therapy, and prior nivolumab (26.4% and 35.6%, respectively), mostly in second-line or later. Prior targeted therapy for advanced disease had been received by 3.2% of patients in cohort 1, 14.2% in cohort 2 and 6.7% in cohort 3. Overall, few patients had received antiangiogenic therapy (n=90 [17.2%]); those that did, mostly received bevacizumab (n=84 [93.3%]).

## Effectiveness

### TTD and TTNT

After a median follow-up of 33.6 months (cohort 1), 22.8 months (cohort 2) and 24.1 months (cohort 3), median TTD was 3.8, 2.9 and 3.4 months in cohorts 1, 2 and 3, respectively (Fig. 1). The 12-month event-free rate for TTD was 17.7%, 14.4% and 16.7% in cohorts 1, 2 and 3, respectively, with these patients still receiving nivolumab. At data cut-off, among patients with permanent nivolumab

discontinuation (cohort 1, 93.6%; cohort 2, 90.4%; cohort 3, 84.4%), the main reasons for nivolumab discontinuation, as reported by investigators, were disease progression or death, followed by management of toxicities. The proportion of patients who discontinued nivolumab because of disease progression or death was numerically lower in cohort 3 (64.5%) than in cohorts 1 and 2 (75.3% and 79.7%, respectively), and the proportion who discontinued treatment because of toxicity was numerically lower in cohort 2 (4.1%) than in cohorts 1 and 3 (7.1% and 8.9%, respectively). A percentage of patients (1.4%, 0.5% and 2.2% in cohorts 1, 2 and 3, respectively) discontinued nivolumab as a result of having completed their treatment (see Table S1 in the electronic supplementary material).

In the subgroup analysis of TTD, numerically higher 12-month event-free rates for TTD were generally observed in younger patients (<65 vs ≥65 years), especially in cohorts 2 and 3, and in patients with better PS (ECOG 0–1 vs ≥2), longer duration of prior immunotherapy (>12 vs <3 or 3–12 months), especially in cohort 2, and fewer lines of prior systemic therapy (1 vs 2 vs ≥3; Table 3) in cohorts 1 and 2. In patients who had previously received nivolumab (± chemotherapy) as their only prior immunotherapy, the 12-month TTD rate with nivolumab rechallenge was almost 20%. In cohort 2, the 12-month TTD rate with nivolumab was numerically lower in patients who had discontinued prior immunotherapy because of PD than in those with

**Table 2** Prior anticancer therapies (analysable population)

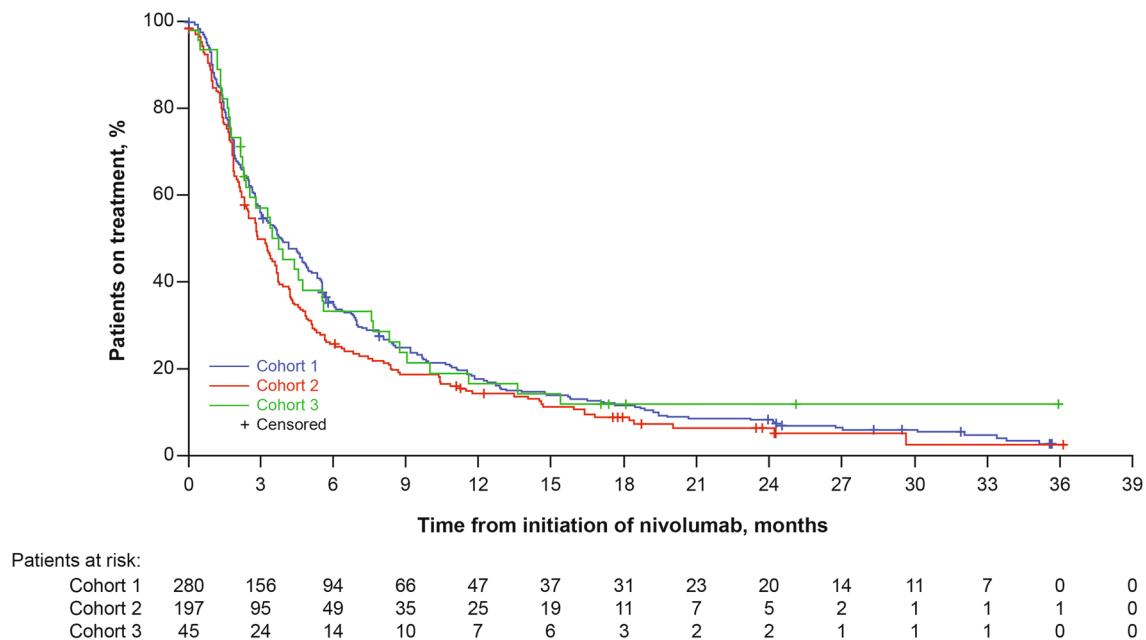
	Cohort 1 (N= 280)	Cohort 2 (N= 197)	Cohort 3 (N= 45)
Prior therapy, <sup>a</sup> n (%)			
Chemotherapy	280 (100.0)	197 (100.0)	45 (100.0)
Immunotherapy	–	197 (100.0)	45 (100.0)
Prior therapy for non-advanced disease, n (%)	39 (13.9)	20 (10.2)	5 (11.1)
Curative excisional therapy	26 (66.7)	17 (85.0)	4 (80.0)
Radiotherapy	16 (41.0)	4 (20.0)	2 (40.0)
Systemic therapy	21 (53.8)	9 (45.0)	3 (60.0)
Prior therapy for advanced disease, (%) <sup>b</sup>			
Excisional surgery	43 (15.4)	26 (13.3)	4 (9.1)
Radiotherapy	135 (48.6)	119 (60.4)	29 (65.9)
Systemic therapy <sup>c</sup>	268 (95.7)	197 (100.0)	45 (100.0)
Chemotherapy of interest	268 (95.7)	196 (99.5)	44 (97.8)
Carboplatin	217 (77.5)	159 (80.7)	37 (82.2)
Pemetrexed	100 (35.7)	145 (73.6)	28 (62.2)
Paclitaxel	142 (50.7)	135 (68.5)	25 (55.6)
Cisplatin	60 (21.4)	56 (28.4)	11 (24.4)
Gemcitabine	12 (4.3%)	55 (27.9%)	8 (17.8%)
Vinorelbine	30 (10.7%)	42 (21.3%)	7 (15.6%)
Docetaxel	8 (2.9%)	33 (16.8%)	4 (8.9%)
Immunotherapy of interest	–	195 (99.0)	44 (97.8)
Pembrolizumab	–	108 (54.8)	22 (48.9)
Nivolumab	–	52 (26.4)	16 (35.6)
Atezolizumab	–	25 (12.7)	1 (2.2)
Durvalumab	–	14 (7.1)	6 (13.3)
Targeted therapy	9 (3.2)	28 (14.2)	3 (6.7)
Antiangiogenic therapy	19 (6.8)	63 (32.0)	8 (17.8)

Multiple therapies per patient were possible

<sup>a</sup>In the non-advanced or advanced settings

<sup>b</sup>Some patients did not have information on the type of prior therapy for advanced disease. In cohort 1, the proportions of patients receiving excisional surgery, radiotherapy or systemic therapy were calculated from 279, 278 and 268 evaluable patients, respectively; in cohort 2, the percentage of patients receiving excisional surgery was calculated from a total of 196 evaluable patients; in cohort 3, the percentages of patients receiving excisional surgery or radiotherapy were calculated from a total of 44 evaluable patients

<sup>c</sup>Some patients received chemotherapy for non-advanced disease but not for advanced disease



**Fig. 1** Kaplan–Meier curve of estimated time to discontinuation

prolonged benefit to prior immunotherapy (12.9% and 27.8%, respectively). Patients in cohort 2 with  $\geq 6$  months between their last prior immunotherapy dose and nivolumab initiation had a numerically higher TTD rate than those with a shorter interval ( $< 6$  months). No trend was observed between PD-L1 expression levels and 12-month TTD event-free rates, regardless of whether patients were immunotherapy naïve or experienced.

In patients who discontinued nivolumab during the study, a new treatment was subsequently started in 43.2% of patients in cohort 1, 41.6% in cohort 2 and 28.9% in cohort 3. Median TTNT was markedly longer in cohort 3 (436 days) than in cohorts 1 and 2 (99 and 71 days, respectively).

**Survival Outcomes and Clinical Response**

Based on Kaplan–Meier estimates at data cut-off, the median PFS was 3.2 months (95% CI 2.7, 4.1) in cohort 1, 2.7 months (95% CI 2.2, 3.4) in cohort 2 and 3.9 months (95% CI 2.2, 7.4) in cohort 3. The 12-month PFS rate was 17.1%, 10.5% and 16.3% in the respective cohorts. The median OS was slightly longer in cohort 1 (12.3 months; 95% CI 8.6, 13.7) than

in cohort 2 (9.5 months; 95% CI 7.2, 11.3) or cohort 3 (10.4 months; 95% CI 7.6, 20.1). The corresponding 12-month OS rates were 52.1%, 40.1% and 46.7%.

In cohorts 1, 2 and 3, the 12-month BOR was CR in 1.1%, 0.5% and 4.4% of patients, respectively; PR in 10.7%, 7.1% and 8.9%, respectively; SD in 34.3%, 31.5% and 31.1%, respectively; and PD in 41.8%, 41.1% and 33.3%, respectively. BOR was not reported in 12.1%, 19.8% and 22.2% of patients in the respective cohorts. The DCR rate was 46.1% (95% CI 40.1, 52.1) in cohort 1, 39.1% (95% CI 32.2, 46.3) in cohort 2 and 44.4% (95% CI 29.6, 60.0) in cohort 3.

**Safety**

All-cause AEs were reported in 74.3%, 62.0% and 73.9% of patients in cohorts 1, 2 and 3, respectively, with a generally similar incidence of grade 3–4 all-cause AEs observed across cohorts (Table 4). While the incidence of any-grade TRAEs was similar in cohorts 1 and 3 (36.1% and 37.0%, respectively), it was lower in cohort 2 (25.0%). Patients in cohort 3 had

**Table 3** Subgroup analysis of time to treatment discontinuation

	Cohort 1		Cohort 2		Cohort 3	
	<i>n</i> <sup>a</sup> / <i>N</i>	12-month TTD, % (95% CI)	<i>n</i> <sup>a</sup> / <i>N</i>	12-month TTD, % (95% CI)	<i>n</i> <sup>a</sup> / <i>N</i>	12-month TTD, % (95% CI)
Overall	262/280	17.7 (13.4, 22.5)	178/197	14.4 (9.8, 19.8)	38/45	16.7 (7.3, 29.2)
Age						
< 65 years	81/86	18.4 (11.0, 27.4)	73/84	21.1 (13.0, 30.6)	13/18	24.1 (7.5, 45.7)
65–75 years	97/108	18.8 (12.0, 26.8)	75/82	9.4 (4.2, 17.2)	15/16	6.9 (0.4, 26.8)
> 75 years	84/86	15.8 (9.0, 24.4)	30/31	9.7 (2.5, 22.9)	10/11 <sup>b</sup>	18.2 (2.9, 44.2) <sup>b</sup>
ECOG PS						
0–1	193/207	19.6 (14.4, 25.4)	134/149	14.9 (9.6, 21.2)	25/31	20.3 (8.3, 36.0)
≥ 2	69/73	12.3 (6.1, 21.0)	44/48	12.8 (5.2, 23.9)	13/14 <sup>b</sup>	8.2 (0.5, 30.5) <sup>b</sup>
Metastatic sites of interest						
Brain	57/61	22.6 (13.0, 33.7)	36/38	8.1 (2.1, 19.6)	–	–
Liver	44/47	7.3 (2.0, 17.6)	26/29	17.2 (6.3, 32.7)	–	–
Bone	71/78	18.3 (10.4, 27.8)	50/54	11.5 (4.7, 21.8)	–	–
PD-L1 expression						
< 1%	125/134	16.9 (11.0, 23.9)	57/61	16.4 (8.4, 26.7)	8/12 <sup>b</sup>	29.2 (7.2, 56.1) <sup>b</sup>
1–49%	67/71	23.4 (14.3, 33.9)	40/44	6.0 (1.1, 17.2)	16/16	12.5 (2.1, 32.8)
≥ 50%	18/18	11.1 (1.9, 29.8)	41/47	16.8 (7.7, 28.8)	–	–
Duration of last prior IO						
< 3 months	–	–	27/28	7.4 (1.3, 21.1)	16/18	22.2 (6.9, 42.9) <sup>b</sup>
3–12 months	–	–	89/98	13.5 (7.4, 21.3)	12/14 <sup>b</sup>	8.3 (0.5, 30.9) <sup>b</sup>
> 12 months	–	–	60/69	18.9 (10.6, 29.0)	9/12 <sup>b</sup>	18.3 (2.9, 44.4) <sup>b</sup>
Nivolumab (± CT) as only prior IO	–	–	43/49	19.6 (9.7, 32.1)	9/13 <sup>b</sup>	18.5 (2.9, 44.6) <sup>b</sup>
Number of prior systemic treatment lines						
1	208/221	18.6 (13.7, 24.0)	–	–	–	–
2	34/38	11.2 (3.6, 23.6)	59/69	19.4 (10.8, 29.8)	16/20	16.4 (4.1, 35.9)
≥ 3	–	–	110/119	12.0 (6.9, 18.6)	14/16	20.5 (5.0, 43.1)
Reason for last IO discontinuation						
Disease progression	–	–	154/169	12.9 (8.3, 18.6)	–	–
Prolonged benefit	–	–	12/16	27.8 (8.8, 51.0)	–	–

Table 3 continued

	Cohort 1		Cohort 2		Cohort 3	
	<i>n</i> <sup>a</sup> / <i>N</i>	12-month TTD, % (95% CI)	<i>n</i> <sup>a</sup> / <i>N</i>	12-month TTD, % (95% CI)	<i>n</i> <sup>a</sup> / <i>N</i>	12-month TTD, % (95% CI)
Interval from last IO dose to nivolumab						
< 6 months	–	–	21/24	5.1 (0.4, 20.6)	–	–
6–12 months	–	–	71/77	17.0 (9.6, 26.3)	14/16	12.5 (2.1, 32.8)
12–24 months	–	–	69/77	14.2 (7.4, 23.2)	15/16	12.5 (2.1, 32.8)
≥ 24 months	–	–	17/19	15.8 (3.9, 34.9)	–	–

CI confidence interval, CT chemotherapy, ECOG PS Eastern Cooperative Oncology Group performance status, IO immunotherapy, TTD time to treatment discontinuation, PD-L1 programmed cell death ligand 1

<sup>a</sup>At data cut-off (16 September 2024)

<sup>b</sup>Low sample size (i.e. less than 15 patients). Note: data for subgroups with 10 patients or fewer are not presented

a higher incidence of grade 3–4 TRAEs (13.0%) than those in cohorts 1 and 2 (7.9% and 3.0%, respectively). The number of TRAEs leading to death (as reported by investigators) was low: two patients in cohort 1 died as a result of colon perforation/sepsis and pulmonary oedema/pulmonary embolism, respectively, and one patient in cohort 3 died as a result of deterioration in general condition and a digestive disorder.

### Quality of Life

EQ-5D-3L subscale scores for mobility, self-care, activity, pain/discomfort and anxiety/depression at baseline and 12 months were generally maintained during nivolumab treatment in all cohorts (see Fig. S2 in the electronic supplementary material). In cohorts 2 and 3, the proportion of patients with ‘extreme problems’ based on EQ-5D-3L scores decreased from baseline to 12 months.

## DISCUSSION

In this interim analysis, the 12-month real-world effectiveness and safety of nivolumab monotherapy in immunotherapy-naïve patients (cohort 1)

was similar to that reported in the CheckMate 017 and 057 studies [2, 3]. At 12 months, the PFS, OS and DCR in cohort 1 (17.1%, 52.1% and 46.1%, respectively) were similar to those observed in CheckMate 017 (21%, 42% and 48.9%, respectively) and CheckMate 057 (19%, 51% and 56.3%, respectively) [2, 3]. Although a 12-month TTD benefit was primarily observed in immunotherapy-naïve patients who were younger ( $\leq 75$  years) or had better ECOG performance scores (0–1), favourable results were also noted in patients who were older ( $> 75$  years) or had worse performance scores ( $\geq 2$ ). This may suggest that nivolumab could be a suitable treatment option in second-line or later for patients who may not be able to benefit from immunotherapy in first line.

Consistent effectiveness results were also observed in patients who received nivolumab after previous discontinuation of immunotherapy (cohorts 2 and 3). Notably, in cohort 3, which comprised immunotherapy-experienced and generally more heavily pretreated patients, the 12-month TTD rate was similar to that of cohort 1. In cohort 2, the 12-month TTD rate with nivolumab was lower in patients who had discontinued prior immunotherapy because of PD (12.9%) than in those with prolonged benefit to prior immunotherapy (27.8%). Similar results were observed in a previously reported 6-month

**Table 4** Safety summary (safety population)

<i>n</i> (%)	Cohort 1 ( <i>N</i> =280)	Cohort 2 ( <i>N</i> =200)	Cohort 3 ( <i>N</i> =46)
All-cause AEs			
Any	208 (74.3)	124 (62.0)	34 (73.9)
Grade 3–4	120 (42.9)	82 (41.0)	20 (43.5)
Leading to death	64 (22.9)	45 (22.5)	12 (26.1)
TRAEs			
Any	101 (36.1)	50 (25.0)	17 (37.0)
Grade 3–4	22 (7.9)	6 (3.0)	6 (13.0)
Leading to death	2 (0.7)	0	1 (2.2)

Data exclude cases of progressive disease reported as AEs

*AEs* adverse events, *TRAEs* treatment-related adverse events

interim analysis of the LIST study [14] and in a retrospective study evaluating anti-programmed death receptor 1 (PD-1)/PD-L1 rechallenge in patients with advanced NSCLC [15]. Numerically higher 12-month TTD rates in patients in cohorts 2 and 3 who were younger (<65 vs 65–75 or >75 years) or had better PS (ECOG 0–1 vs ≥2) suggest that age and PS may be factors associated with the effectiveness of immunotherapy rechallenge; however, it is important to note that no statistical test was conducted and therefore caution should be exercised when interpreting these results. In all three cohorts, response rates were calculated over the total number of patients in each cohort, including a considerable number of patients for whom BOR data were unavailable, which might explain the lower-than-expected response rates compared with the literature [2, 3].

Nivolumab had acceptable tolerability across all three cohorts, with rates of TRAEs consistent with those reported in previous real-world studies with nivolumab [5, 16]. In cohort 3, despite previous treatment discontinuation due to immunotherapy-related toxicity, the rate of any-grade TRAEs was similar to that of cohort 1 (37.0% and 36.1%, respectively), albeit with a numerically higher rate of grade 3–4 TRAEs (13.0% and 7.9%, respectively). These results could indicate that immunotherapy rechallenge with nivolumab might be safe in this group of

patients, and warrants further investigation. However, the lack of excessive toxicity may be due to under-reporting of AEs in the real-world setting. A lower-than-expected rate of treatment-related deaths in the current study (≤2.2%) may also be due to under-reporting in real-life conditions. QoL appeared to be maintained during nivolumab treatment, with some improvements observed in immunotherapy-experienced patients (cohorts 2 and 3).

Our study used a purely descriptive approach, and caution should be used when interpreting results, especially in subgroups with limited sample sizes. Final recruitment in the LIST study did not meet the initially planned inclusions in cohorts 2 and 3. This finding suggests that immunotherapy rechallenge for the treatment of NSCLC is less common than anticipated in France and may reflect physicians' hesitation regarding this approach, especially for patients who discontinued their prior immunotherapy because of related toxicity. Nevertheless, the findings of the subgroup analysis of TTD suggest a numerically greater benefit with immunotherapy rechallenge in patients who had prolonged benefit and good response to prior immunotherapy compared with those with PD on prior immunotherapy. Also, published literature suggest that immune-related toxicity is less common at resumption of immunotherapy than during initial immunotherapy [17]. In

addition, the severity, time to onset and duration of immune-related AEs during initial immunotherapy were not associated with a higher risk of immune-related toxicity at resumption [17].

The findings of our study are also consistent with those of previous retrospective studies of rechallenge with immune checkpoint inhibitors, which indicate that immunotherapy rechallenge may yield a clinical benefit in patients with NSCLC. This benefit was particularly observed in patients who demonstrated a prior benefit and who discontinued their initial treatment for reasons other than disease progression. Although response rates appeared to be lower than those of initial immunotherapy, outcomes remained clinically relevant for certain patient groups, highlighting the need for further research to identify optimal selection criteria [18–21]. Similarly, in our study, better rechallenge results were observed in patients who were younger, had better PS scores, and longer administration of prior immunotherapy (in cohort 2). These results are generally concordant with other studies, which have reported positive predictive effects on survival outcomes for PS and longer duration of prior immunotherapy [19, 21]. Moreover, immunotherapy rechallenge with nivolumab seemed favourable even in later lines of treatment (third line or later), suggesting that nivolumab monotherapy might have consistent effectiveness across lines of treatment.

Particular strengths of this real-world study include its prospective design and the diversity of the study population, which ensures generalisability of the results. Furthermore, the LIST study addresses major data gaps, such as immunotherapy rechallenge with nivolumab monotherapy in the second-line or later setting, at a time when most available data rely mainly on retrospective studies. However, several study limitations also need to be considered. Caution should be exercised in interpreting the findings because of the small population size of cohort 3, which is especially notable in the subgroup analyses. Other potential limitations include the observational study design (versus a randomised, controlled design that would limit selection, performance, detection and reporting bias). Furthermore, as no statistical tests were conducted, the results of subgroup analyses are

purely suggestive, and no formal conclusions can be drawn regarding factors affecting rechallenge results. Although this study may suggest subgroups of patients who could benefit from immunotherapy rechallenge, additional research is required to define predictive criteria for rechallenge outcomes. Randomised controlled trials would help define the optimal population and timing for rechallenge, to establish re-treatment protocols and patient selection algorithms.

## CONCLUSION

Interim LIST study findings suggest that the efficacy and safety of nivolumab observed in the CheckMate 017 and 057 clinical trials in immunotherapy-naïve patients with advanced NSCLC translate to real-life clinical practice. Moreover, nivolumab monotherapy showed favourable results across all three cohorts, indicating consistent real-world effectiveness in immunotherapy-experienced patients, and across lines of treatment. Rechallenge with nivolumab appeared to be a viable option in patients who previously experienced immunotherapy-related toxicity, with no excessive overall toxicity observed in these patients. Subgroup analyses may suggest which patients could benefit from immunotherapy rechallenge with nivolumab, warranting further investigation to best assist clinicians in identifying these patients.

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**Data Availability.** The data presented in this study are available upon reasonable request, in accordance with Bristol Myers Squibb's data sharing policy.

### **Declarations**

**Conflict of Interest.** Benoît Godbert has received consulting and congress fees from AstraZeneca, Bristol Myers Squibb, Merck Sharp & Dohme, Regeneron, Roche, and Sanofi. Elisa Gobbin has received speaker's bureau honoraria from Bristol Myers Squibb, Janssen, Merck Sharp & Dohme, Regeneron, and Sanofi; and is the spouse of an AstraZeneca employee. Chantal Decroisette has participated in advisory boards for Amgen, AstraZeneca, Bristol Myers Squibb, Johnson and Johnson, Merck Sharp & Dohme, Pfizer, Regeneron, Roche, and Takeda. Hervé Lena has participated in advisory boards for Amgen, Bristol Myers Squibb, Merck Sharp & Dohme, Pfizer, Regeneron, and Roche; and has received symposia/lecture fees from AstraZeneca, Bristol Myers Squibb, Merck Sharp & Dohme, Pfizer, Roche, and Takeda. Yaacoub Khalife, Florence Brellier and Anne Fleuriet are employees and hold stock or stock options in Bristol Myers

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**Ethical Approval.** The study was conducted in accordance with International Society for

Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP) and applicable regulatory requirements. All required approvals from ethics committees, independent review committees, regulatory authorities and/or other local governance bodies were obtained prior to study initiation (N° EudraCT/ID RCB number 2020-A00769-30). All patients provided oral informed consent and were permitted to withdraw from the study at any stage.

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