ORIGINAL RESEARCH

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The efficacy of immune checkpoint inhibitors following discontinuation for long-term response or toxicity in advanced or metastatic non-small-cell lung cancers: A retrospective study

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Abstract

Background and Aims: The treatment of metastatic non-small-cell lung cancer (NSCLC) has been revolutionized by the arrival of immune checkpoint inhibitors (ICI). For patients without immune related adverse events (irAEs), it is recommended to continue the treatment as long as it provides clinical benefit or until unacceptable toxicity appears. The aim of our study was to evaluate survival data among patients with advanced or metastatic NSCLC following ICI discontinuation for reasons of long-term response or toxicity (irAEs).

Methods: We included all patients with advanced or metastatic NSCLC treated with nivolumab and pembrolizumab at the Centre Jean Perrin, Clermont-Ferrand, France (January 1, 2016 to May 31, 2019). We focused on two groups in this study population: "Voluntary treatment discontinuation" (medical decision as a result of long-term response and patient decision) and "Treatment discontinuation due to toxicity" (irAEs). The primary endpoint was to evaluate the postdiscontinuation outcomes of these two groups: progression-free survival (PFS) and overall survival (OS), and rechallenge in the "voluntary discontinuation" group.

Results: The final analysis concerned 146 patients, including 10 (7%) in the "discontinuation due to toxicity" group, 11 (8%) in the "voluntary discontinuation" group, 100 (68%) who discontinued treatment as a result of progression and 25 (17%) whose treatment was still on-going. The median PFS in the "discontinuation due to toxicity" group was not reached, and in the "voluntary discontinuation" group ($n = 11$) was 37 months ($p = 0.4$), versus 2 months in the progression group ($p < 0.001$). The median OS in "discontinuation due to toxicity," and in the "voluntary discontinuation" groups was not reached ($p = 0.5$), versus 10 months in the progression group ($p < 0.001$).

Conclusion: Treatment discontinuation following long-term response to ICI treatment showed sustained response and long-term survival after discontinuation. The incidence of irAEs was associated with better long-term survival, even after ICI discontinuation.

KEYWORDS

immune-related adverse events, immunotherapy, long-term response, metastatic non-small-cell lung cancer, nivolumab, pembrolizumab, treatment discontinuation

1 | INTRODUCTION

Worldwide, lung cancer is the leading cause of cancer death among men and the second leading cause of cancer death among women.[1] There were 2 million new cases in 2018 worldwide.[2] Approximately 80% to 85% of lung cancers are non-small-cell lung cancers (NSCLC).[3] The treatment of metastatic NSCLC has been revolutionized by the use of immune checkpoint inhibitors.

Immune checkpoint inhibitors (ICIs), including anti-Programmed Death-1/Programmed Death-Ligand-1 (PD-1/PDL-1) antibodies, aim to restore antitumor immunity.[4] They have been shown to provide long-term response, as demonstrated in several studies,[5–8] even in the case of discontinuation.[9] For the time being, recommendations suggest that treatment should be continued as long as it provides clinical benefit or until toxicity is deemed unacceptable. The discontinuation of ICI treatment following long-term response is currently under discussion. In a phase-1 study on nivolumab,[9] patients received treatment for up to 2 years or until complete response (CR), the appearance of unacceptable toxicity, or progression. Overall survival curves levelled off 3 years after treatment initiation. Other retrospective studies[10–13] have shown that long-term responders can experience longer PFS and OS after treatment discontinuation. In contrast, Spigel,[14] in a prospective, study showed that discontinuation of ICIs after 1 year was more deleterious than continuation of treatment.

ICIs are associated with immune-related adverse events (irAEs).[15] Nevertheless, several studies have proved that irAEs are associated with treatment efficacy and good survival outcomes.[16–30] The association between treatment discontinuation due to toxicity and efficacy is not well known.

The aim of our study was to evaluate survival data under anti-PD-1 antibodies among patients with advanced or metastatic NSCLC after treatment discontinuation following long-term response or toxicity (irAEs).

2 | PATIENTS AND METHODS

This was a retrospective single-center study conducted at the Centre Jean Perrin, the Comprehensive Cancer Centre in Clermont-Ferrand, France. Ethics approval was obtained on September 24, 2020 (CECIC Rhône-Alpes-Auvergne, Grenoble, IRB 5921). From the January 1, 2016 to the May 31, 2019, we included all patients with advanced or metastatic NSCLC treated with monotherapy nivolumab or pembrolizumab and with a minimum of 6 months follow-up. We excluded patients with missing data. All patients were informed of the study in a nonopposition letter. Among these patients, we focused on patients with treatment discontinuation as follows:

- "Voluntary treatment discontinuation" (medical decision following long-term response ≥6 months and the patient's decision).
- "Treatment discontinuation due to toxicity" (irAEs).

The primary objective was to compare survival in the two treatment discontinuation groups (progression-free survival [PFS] and overall survival [OS]). The secondary objectives were to evaluate in the study population (patients with advanced or metastatic NSCLC treated with monotherapy nivolumab or pembrolizumab) factors associated with long-term response to treatment and factors associated with progression after treatment discontinuation (in the two groups described above: "voluntary treatment discontinuation" and "treatment discontinuation due to toxicity"). Long-term response was defined as response of ≥6 months.

The patients' medical records were retrospectively reviewed, and the following information was collected: gender, age, performance status (PS), other cancer history, smoking status, lung cancer histology, PDL1, EGFR, KRAS, ALK, ROS1, BRAF status, the initial and current stages of lung cancer, metastatic sites, brain metastases, treatments received, local brain treatments received, treatment line, neutrophil/lymphocyte ratio (NLR), eosinophils, albumin (at treatment initiation), irAEs, progression, and date of death or last follow-up assessment. Immune-related adverse events were evaluated using the National Cancer Institute's common terminology criteria for adverse events (NCI-CTCAE v4.0), and divided into skin, thyroid, hepatic, colitis, and other toxicities (increased creatinine, anaemia, thrombopenia, myalgia, arthralgia, encephalitis, hypophysitis, pneumonitis, and adrenal insufficiency).

Supplementary data was collected in the two treatment discontinuation groups: response at the first evaluation scan during treatment and at the last evaluation scan (stable disease [SD], partial response [PR], CR, progression) before treatment discontinuation, if there was progression after treatment discontinuation (on known

disease sites or new sites), or if there was a response in case of rechallenge after progression.

3 | STATISTICAL ANALYSES

This study includes data analyses on retrospective data. For the descriptive analysis, all variables of interest are expressed for the overall population and in the three cohorts "voluntary treatment discontinuation," "treatment discontinuation due to toxicity," and "treatment discontinuation due to progression." A comparison between the "voluntary treatment discontinuation" and "treatment discontinuation due to toxicity" groups was performed using Fisher's exact test. For the hypothesis tests, we used two-tailed tests at the conventional level of significance of 0.05. Patients' characteristics between groups were compared using Fisher's exact test and Wilcoxon-Mann–Whitney's test. Progression-free survival (PFS) was defined as the time from start of ICI line to disease progression or death from any cause, patients being censored at the time they were last known to be alive and progression-free. Overall survival (OS) was defined as the time from start of ICI line to death from any cause, patients being censored at the time they were last known to be alive. Survival curves were estimated according to the Kaplan–Meier method and compared using the log-rank test. Median follow-up was calculated using the reverse Kaplan–Meier method, and 95% confidence intervals (CI) for survival using the log approach based on the cumulative hazard function. Univariable and multivariable Cox regression models and maximally selected rank statistics (with conditional Monte-Carlo method for p value adjustment) were used to analyse factors associated with long-term response to treatment. Model selection for the multivariable model was performed using the lasso method Factors

associated with disease progression after treatment discontinuation were investigated in univariate analysis using Fisher's exact test and Wilcoxon-Mann–Whitney test; no multivariable model was appropriate. Statistical analyses were performed with R software, version 4.1.0 (R-Project, GNU GPL, http://cran.r-project.org/).

4 | RESULTS

4.1 | Patient characteristics

We included 150 patients treated with pembrolizumab or nivolumab monotherapy for advanced or metastatic NSCLC, at the Centre Jean Perrin during the inclusion period. Among them, four patients were excluded because their treatment had taken place in another center, so that we did not have access to information on toxicity.

The final analysis was conducted on 146 patients, including 10 (7%) in the "discontinuation due to toxicity" group and 11 (8%) in the "voluntary discontinuation" group, 100 (68%) who discontinued treatment because of progression and 25 (17%) whose treatment was still on-going (Figure 1).

The median age at treatment initiation was 65 years and 58% were men. The majority of patients had a good general status and were smokers: 74% were PS 0 or 1 and 87% were smokers. The most frequent type was adenocarcinoma (72%). Forty-one per cent had cerebral metastases. Forty-two per cent had prolonged response to treatment (≥6 months).

The median treatment duration was 3.3 months. The majority of treatments consisted of a second line of metastatic treatment (due to the period of patient inclusion). Patient characteristics are presented in Tables 1–3.
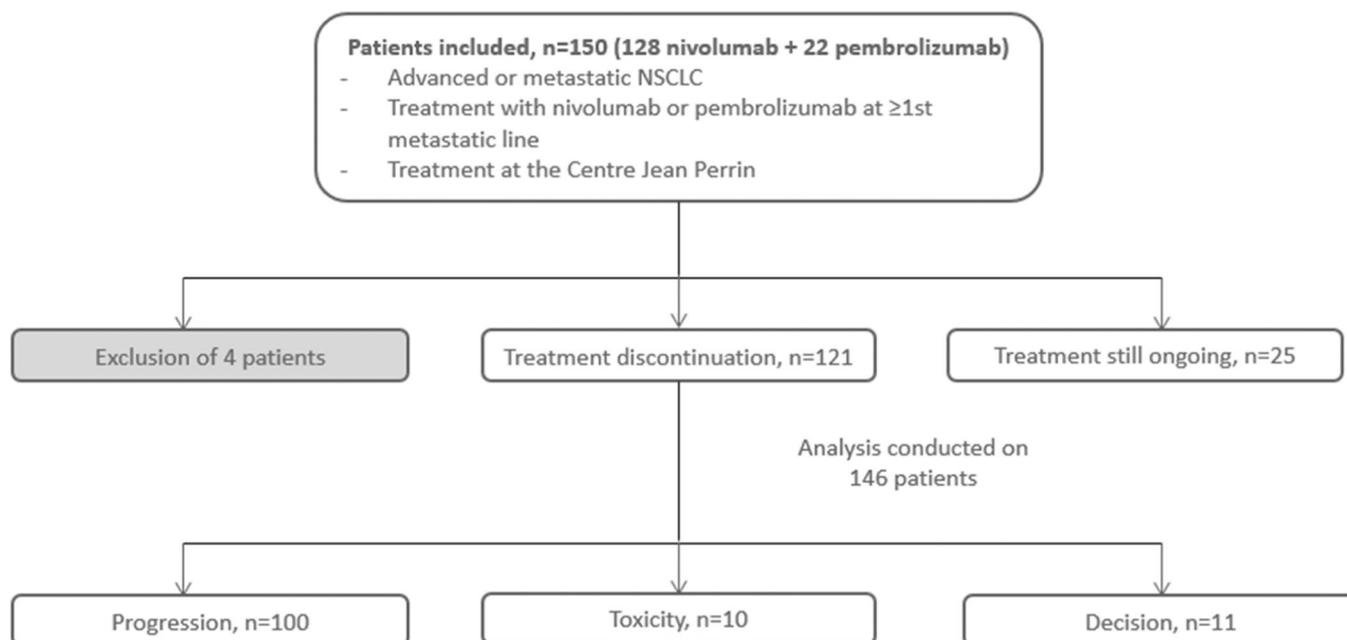
FIGURE 1 Flowchart of participants.

TABLE 1 Patient characteristics: Gender, performance status, smoking status, histology, KRAS mutation, brain metastases, treatment, and long-term response.

Variable	Levels	Total	Toxicity	Decision	Progression
PS	0	30 (24)	3 (30)	4 (36)	13 (16)
	1	62 (50)	6 (60)	5 (46)	41 (51)
	2	26 (21)	1 (10)	2 (18)	20 (25)
	3	5 (4)	0 (0)	0 (0)	5 (6)
	4	1 (1)	0 (0)	0 (0)	1 (1)
Other cancer history	No	101 (70)	8 (80)	8 (73)	69 (70)
	Yes	43 (30)	2 (20)	3 (27)	29 (30)
Other cancer history, curative treatment	No	8 (19)	0 (0)	0 (0)	5 (17)
	Yes	35 (81)	2 (100)	3 (100)	24 (83)
Smoking status	No	18 (13)	2 (20)	3 (27)	11 (12)
	Yes	122 (87)	8 (80)	8 (73)	83 (88)
Histology	ADK	104 (72)	9 (90)	8 (73)	69 (70)
	SCC	31 (21)	1 (10)	2 (18)	24 (24)
	Other	10 (7)	0 (0)	1 (9)	6 (6)
KRAS mutation	No	57 (61)	2 (29)	8 (89)	38 (60)
	Yes	37 (39)	5 (71)	1 (11)	25 (40)
Stage	IIIB LA	3 (2)	0 (0)	0 (0)	1 (1)
	IV Metastatic	143 (98)	10 (100)	11 ((100)	99 (99)
Local treatment of brain metastases before ICI	No	24 (39)	1 (25)	0 (0)	17 (38)
	WBRT	23 (38)	3 (75)	2 (67)	16 (36)
	SRT	9 (15)	0 (0)	1 (33)	7 (16)
	Surgery + WBRT	2 (3)	0 (0)	0 (0)	2 (4)
	Surger y +SRT	3 ((5)	0 (0)	0 (0)	3 (7)
Local treatment of brain metastases during ICI	No	57 (93)	4 (100)	3 (100)	43 (96)
	WBRT	1 (2)	0 (0)	0 (0)	1 (2)
	SRT	3 (5)	0 (0)	0 (0)	1 (2)
Last updated status	Deceased	79 (54)	1 (10)	3 (27)	75 (75)
	Alive	67 (45.9)	9 (90)	8 (73)	25 (25)
Long response	No	85 (58.2)	1 (10)	0 (0)	80 (80)
	Yes	61 (41.8)	9 (90)	11 (100)	20 (20)

Note: Values are presented as: Counts (percentages).

Abbreviations: ADK, adenocarcinoma; SCC, squamous cell carcinoma; SRT, stereotactic radiation therapy; WBRT, whole brain radiation therapy.

Patient characteristics were comparable across the three "toxicity," "decision" and "progression" groups, except for treatment duration ($p = 0.05$), maximum toxicity grade ($p = 0.04$), and KRAS mutation ($p = 0.03$). Treatment duration was obviously longer in the "voluntary treatment discontinuation" group, resulting from long-term response to treatment. The toxicity grade was naturally higher in the "discontinuation due to toxicity" group. There were fewer cases of KRAS mutation in the "voluntary treatment discontinuation" group.

4.2 | Voluntary discontinuation group

This group was composed of 11 patients (8%). All patients received nivolumab for metastatic NSCLC. Ten patients discontinued the treatment on the basis of medical decision after a long-term response, and one patient discontinued after 1.5 months because she did not want to continue with the treatment. For the 10 patients who discontinued following medical decision: one patient discontinued between 6 and 12 months; 1 patient between 12 and 18

TABLE 2 Patient characteristics: Treatment line and toxicities.

Variable	Grade	Total	Toxicity	Decision	Progression
Treatment line	1	24 (16)	1 (10)	0 (0)	15 (15)
	2	108 (74)	9 (90)	9 (82)	73 (73)
	3	9 (6)	0 (0)	1 (9)	8 (8)
	4	2 (1)	0 (0)	1 (9)	1 ((1)
	5	2 (1)	0 (0)	0 (0)	2 (2)
	6	1 (1)	0 (0)	0 (0)	1 (1)
Skin toxicity	0	111 (76)	7 (70)	8 (73)	82 (82)
	1	21 (14)	1 (10)	2 (18)	10 (10)
	2	12 (8)	1 (10)	1 (9)	8 (8)
	3	2 (1)	1 (10)	0 (0)	0 (0)
Thyroid toxicity	0	100 (68)	2 (20)	6 (55)	74 (74)
	1	31 (21)	4 (40)	3 (27)	20 (20)
	2	14 (10)	4 (40)	2 (18)	5 (5)
	3	1 (1)	0 (0)	0 (0)	1 (1)
Hepatic toxicity	0	137 (94)	8 (80)	11 (100)	96 (96)
	1	5 (3)	0 (0)	0 (0)	2 (2)
	2	2 (1)	0 (0)	0 (0)	2 (2)
	3	2 (1)	2 (20)	0 (0)	0 (0)
Colitis toxicity	0	131 (90)	6 (60)	10 (91)	92 (92)
	1	7 (5)	0 (0)	1 (9)	4 (4)
	2	3 (2)	2 (20)	0 (0)	1 (1)
	3	5 (3)	2 (20)	0 (0)	3 (3)
Other toxicities	0	122 (84)	4 (40)	5 (45)	95 (95)
	1	11 (8)	1 (10)	2 (18)	2 (2)
	2	5 (3)	3 (30)	2 (18)	0 (0)
	3	8 (5)	2 (20)	2 (18)	3 (3)
Max toxicity grade	0	68 (47)	0 (0)	1 (9)	57 (57)
	1	37 (25)	0 (0)	4 (36)	23 (23)
	2	24 (16)	3 (30)	4 (36)	14 (14)
	3	17 (12)	7 (70)	2 (18)	6 (6)

Note: Values are presented as: Count (percentage).
Abbreviations: Max grade tox, maximum toxicity grade; Tox, toxicity.

months; 2 patients between 18 and 24 months and 6 patients after ≥24 months. The median treatment duration was 24.3 months. The median follow-up after discontinuation was 9 months.

In the voluntary discontinuation group, at the time of treatment discontinuation, one patient (9%) presented CR, seven patients (64%) PR and three patients (27%) SD. Treatment responses in this group are presented in Table 4.

TABLE 3 Patient characteristics: Treatment duration, biology, and follow-up after treatment discontinuation.

Variable	Cohort	Number of available data	Median (IQR)
Number of ICI cycles	Total	146	7.5 (3.2–21.7)
	Toxicity	10	14.5 (7.7–50.2)
	Decision	11	57 (40–66.5)
	Progression	100	4 (3–9.2)
Treatment duration	Total	146	3 (1–10)
	Toxicity	10	7.5 (3–23.7)
	Decision	11	29 (18.5–32)
	Progression	100	2 (1–4)
Albumin	Total	99	35 (29.4–38.9)
	Toxicity	4	36.2 (34.5–39)
	Decision	9	36.7 (31.2–39)
	Progression	70	33.3 (28.5–38.6)
NLR	Total	120	3.5 (2.1–6.5)
	Toxicity	10	3.9 (2.7–5.3)
	Decision	10	2.5 (1.7–5.5)
	Progression	79	4.5 (2.6–6.9)
Eosinophil count	Total	120	0.11 (0.06–0.25)
	Toxicity	10	0.11 (0.08–0.2)
	Decision	10	0.18 (0.08–0.27)
	Progression	79	0.1 (0.06–0.22)
Follow-up duration after discontinuation	Total	146	3 (1–9)
	Toxicity	10	14 (5.5–21.7)
	Decision	11	8 (6–10)
	Progression	100	3 (1–9)

Abbreviations: IQR, interquartile range; NLR, neutrophil/lymphocyte ratio.

4.3 | Discontinuation due to toxicity

This group was composed of 10 patients (7%): 9 received nivolumab, 1 received pembrolizumab. One patient presented a squamous cell carcinoma and eight presented adenocarcinomas. Five patients presented a KRAS mutation. Five patients had brain metastases: three of them were treated with whole-brain radiation therapy. Two patients discontinued the treatment for skin toxicity, two for hepatitis, three for colitis, two for other toxicities (arthralgia, pneumonitis) and one for various irAEs (thyroid, adrenal insufficiency and colitis). Most of the time, treatment was discontinued because of grade-3 toxicities (seven patients: grade 3; three patients: grade 2). Toxicities in this group are presented in Table 2.

TABLE 4 Treatment responses in the "voluntary discontinuation" group.

Variable	Levels	Count (percentage)
First evaluation scan	PR	7 (64)
	SD	3 (27)
	Progression	1 (9)
Last evaluation scan	CR	1 (9)
	PR	7 (64)
	SD	3 (27)
Progression after discontinuation	No	7 (64)
	Yes	4 (36)
Progression in the same lesions	No	0 (0)
	Yes	4 (100)
Rechallenge	No	2 (50)
	Yes	2 (50)

Abbreviations: CR, complete response; PR, partial response; SD, stable disease.

The median treatment duration was 7.1 months. The median follow-up duration after treatment discontinuation was 11 months. The patients' median age was 65 years. The group was composed of eight females and two males.

4.4 | Progression group

This group was composed of 100 patients (68%): 88 patients received nivolumab and 12 received pembrolizumab. Most of them presented adenocarcinomas (70%), 24% had squamous cell carcinomas. The median treatment duration was 2 months. The median follow-up duration after treatment discontinuation was 3 months. Only 20% were long responders to treatment (Table 5).

4.5 | Response evaluation

In the overall cohort (n = 146), 42% presented a long-term response to treatment: SD, PR, or CR ≥6 months.

In the "discontinuation due to toxicity group," at the first evaluation scan, eight patients presented PR and two presented SD. At the last evaluation scan, one patient presented CR and nine presented PR.

4.5.1 | Progression-free survival

Study population
The median PFS in the study population was 4 months (IQR (1–26), 95% CI (3–9)). The median follow-up was 25 months (95% CI (20–31)).

TABLE 5 Treatment responses in the "progression" group.

Variable	Levels	Count (percentage)
First evaluation scan	PR	7 (64)
	SD	3 (27)
	Progression	1 (9)
Last evaluation scan	CR	1 (9)
	PR	7 (64)
	SD	3 (27)
Progression after discontinuation	No	7 (64)
	Yes	4 (36)
Progression in the same lesions	No	0 (0)
	Yes	4 (100)
Rechallenge	No	2 (50)
	Yes	2 (50)

The progression-free-survival curve for the study population is presented in Figure 2.

The "voluntary discontinuation" and "discontinuation for toxicity" groups
The median PFS in the "voluntary discontinuation" group (n = 11) was 37 months (95% CI lower bound 26). The median PFS was not reached (95% CI lower bound 28) in the "discontinuation for toxicity" group. The median PFS was 2 months (IQR (1–4)) in the progression group.

PFS curves in the "voluntary discontinuation" group showed a levelling off after treatment discontinuation. After a median treatment duration of 24 months, PFS was 37 months, meaning that patients did not present progression for approximately 1 year without treatment.

PFS was improved in the "discontinuation due to toxicity" group compared to the progression group (p < 0.001). It was also improved in the "voluntary discontinuation" group compared to the progression group (p < 0.001). There was no statistical difference between the "voluntary discontinuation" and "discontinuation for toxicity" groups (p = 0.4) (Figure 3).

4.5.2 | Overall survival

Study population
The median OS in the study population was 22 months (IQR (4–42), 95% CI (12–28)) (Figure 4).

"Voluntary discontinuation" and "discontinuation for toxicity" groups
The median OS in the "voluntary discontinuation" or "discontinuation for toxicity" groups was not reached. The median OS in the progression group was 10 months (IQR (3–25), 95% CI (5 to −12)).

The median OS was improved in the "voluntary discontinuation" group compared to the progression group (p < 0.001). It was also
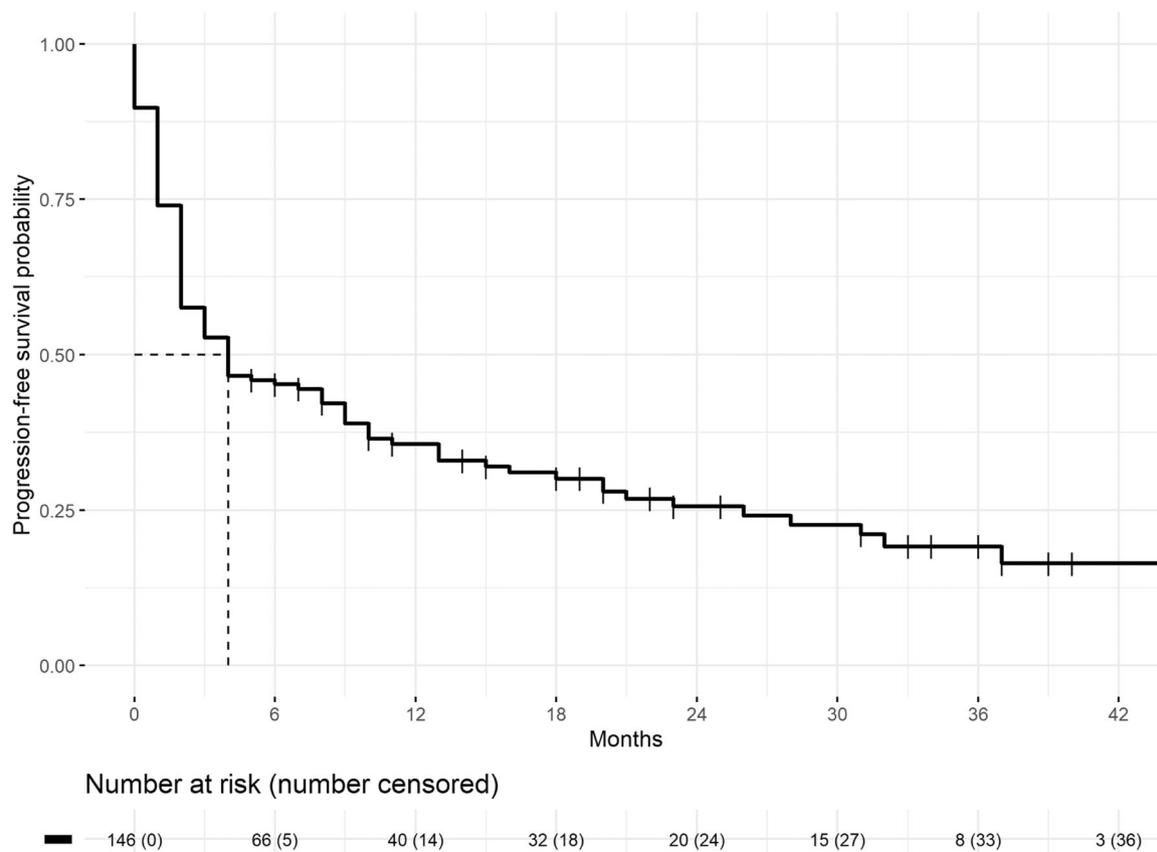
FIGURE 2 Progression-free survival curve for the study population.

statistically improved in the "discontinuation for toxicity" group compared to the progression group (p < 0.001). There was no statistical difference between the "voluntary discontinuation" and "discontinuation for toxicity" groups (p = 0.5) (Figure 5).
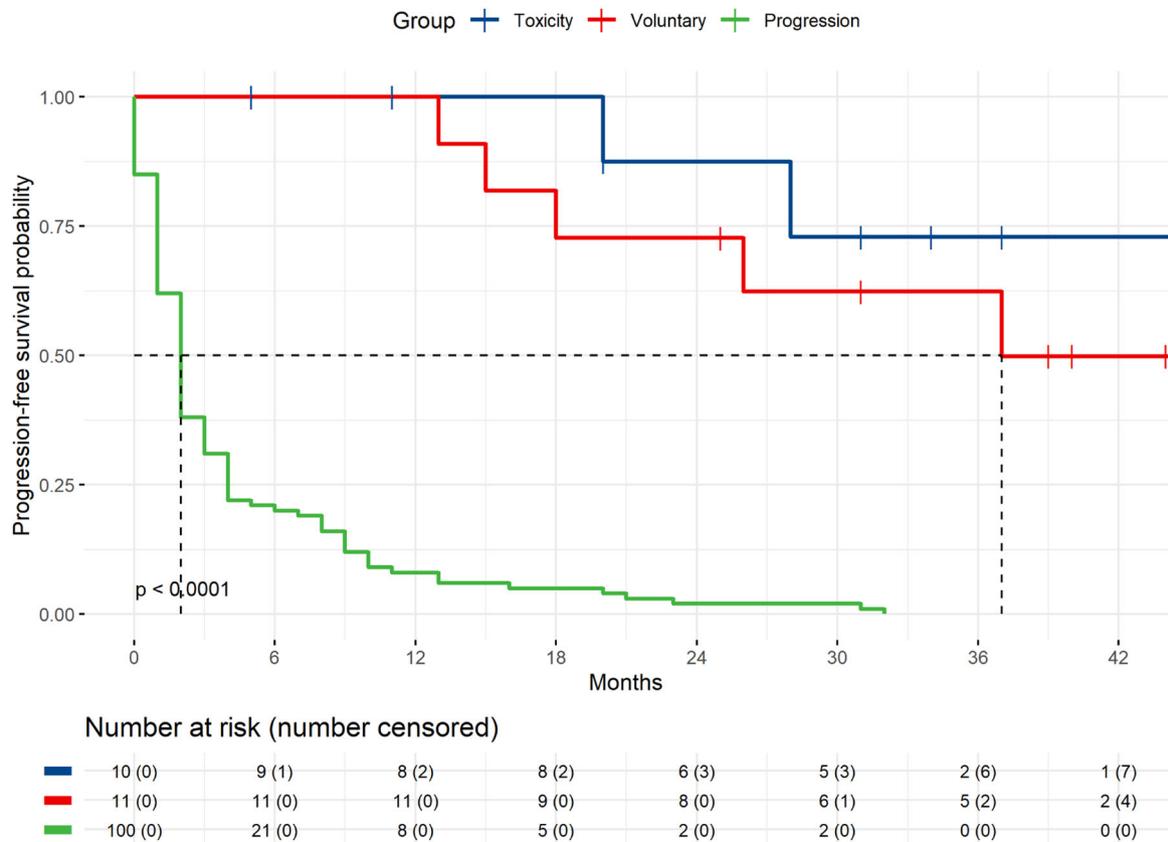
4.5.3 | Rechallenge in the "voluntary discontinuation" group

Four patients from this group presented progression after treatment discontinuation. All patients had an adenocarcinoma with no known mutation, and the progression occurred in the known lesions. One patient (A) discontinued treatment after 1.5 months, and progression occurred 14 months after discontinuation. She was 83-year-old, her performance status (PS) was 2, and the metastatic sites were bone and the pleura. The only evaluation scan during treatment showed SD. The other three patients discontinued treatment following a medical decision in view of their long-term response. The first one (B) stopped after 21.8 months; he was 64-year-old with a PS of 1. Metastatic sites were multiple (the brain, the adrenal glands, the liver, the bones, and the lymph nodes). He received stereotactic radiation therapy on the brain metastases before ICI treatment. The first evaluation scan showed progression. The second patient (C) stopped after 33.7 month; he was 76-year-old with a PS of 0, and the only

metastatic site was pulmonary. The first evaluation scan showed SD. The third patient (D) discontinued treatment after 16.1 months; he was 66-year-old with a PS of 1 and the metastatic sites were pulmonary, the lymph nodes, and the bones. The first evaluation scan showed a PR. For these three patients, the last evaluation scan before treatment discontinuation showed a PR for two patients and SD for one patient (compared to previous scans). We noted slow progression for all of them during ICI treatment on the intermediate scans, but treatment was continued because of the clinical benefit provided by ICIs.

Among these patients, two (B and C) were re-challenged with nivolumab treatment: both continued to experience slow progression during treatment, but ICIs were continued.

Seven patients discontinued treatment and progression did not occur after discontinuation. The median treatment duration was 29.5 months (minimum 8.8 months, maximum 42.2 months). Two patients had brain metastases and received whole brain radiation therapy before ICI treatment. The patient who had discontinued earlier (8.8 months) was 87-year-old, which could explain the decision to discontinue the treatment. The first evaluation scan showed SD. The last evaluation scan before discontinuation showed local progression of the primary pulmonary lesion, so the patient received radiotherapy treatment and progression did not occur after treatment discontinuation. The other six patients presented a PR at the

FIGURE 3 Progression-free survival curves in the "voluntary discontinuation" group, the "discontinuation for toxicity" group and the "progression group."

first evaluation scan. At the last evaluation scan, five patients still presented a PR and one patient presented a CR. None of them (55%) received another treatment after ICI discontinuation.

4.5.4 | Rechallenge in the "discontinuation for toxicity" group

The majority (9 out of 10) of patients in this group presented a long-term response to treatment (≥6 months).

Progression occurred for two patients after treatment discontinuation due to toxicity.

Progression occurred for one patient in the same lesions as those treated before, in the brain, and received stereotactic radiotherapy. One patient exhibited progression with the development of new lesions and received only palliative treatments.

No patient received a rechallenge.

### 4.5.5 | Factors associated with long-term response to treatment

In our cohort, 42% of the patients had a long-term response (≥6 months). Univariate analysis showed an association between long

PFS and the following factors: performance status (PS 0–2 vs. 3–4, $p < 0.001$), maximum toxicity grades 0–1 versus 2–4 ($p < 0.001$), high albumin ($p = 0.001$), and low NLR ($p = 0.03$). These results are presented in Table 6. There was a 6-month difference in PFS between the "PS 0–2" and "PS 3–4" groups. We investigated thresholds better able to distinguish long-term responders using maximally selected rank statistics method: albumin >35; NLR < 4.7 (multiplicity-adjusted $p = 0.002$ and 0.05 respectively).

In multivariate analysis, PS and maximum toxicity grade remained statistically significant (HR = 2, 95% CI (1.4–2.7), $p < 0.001$, and, respectively, HR = 0.5, 95% CI (0.4–0.7), $p < 0.001$).

4.5.6 | Factors associated with disease progression after treatment discontinuation

This analysis was performed in the "voluntary discontinuation" and "discontinuation due to toxicity" groups ($n = 21$, hence a low-powered analysis). In these groups, progression occurred for seven patients (33%) after treatment discontinuation. The only factor associated with this in univariate analysis was the response at the first evaluation scan during ICI treatment ($p = 0.03$). A patient who presented SD at the first evaluation scan rather than a PR had a greater likelihood of experiencing disease progression after
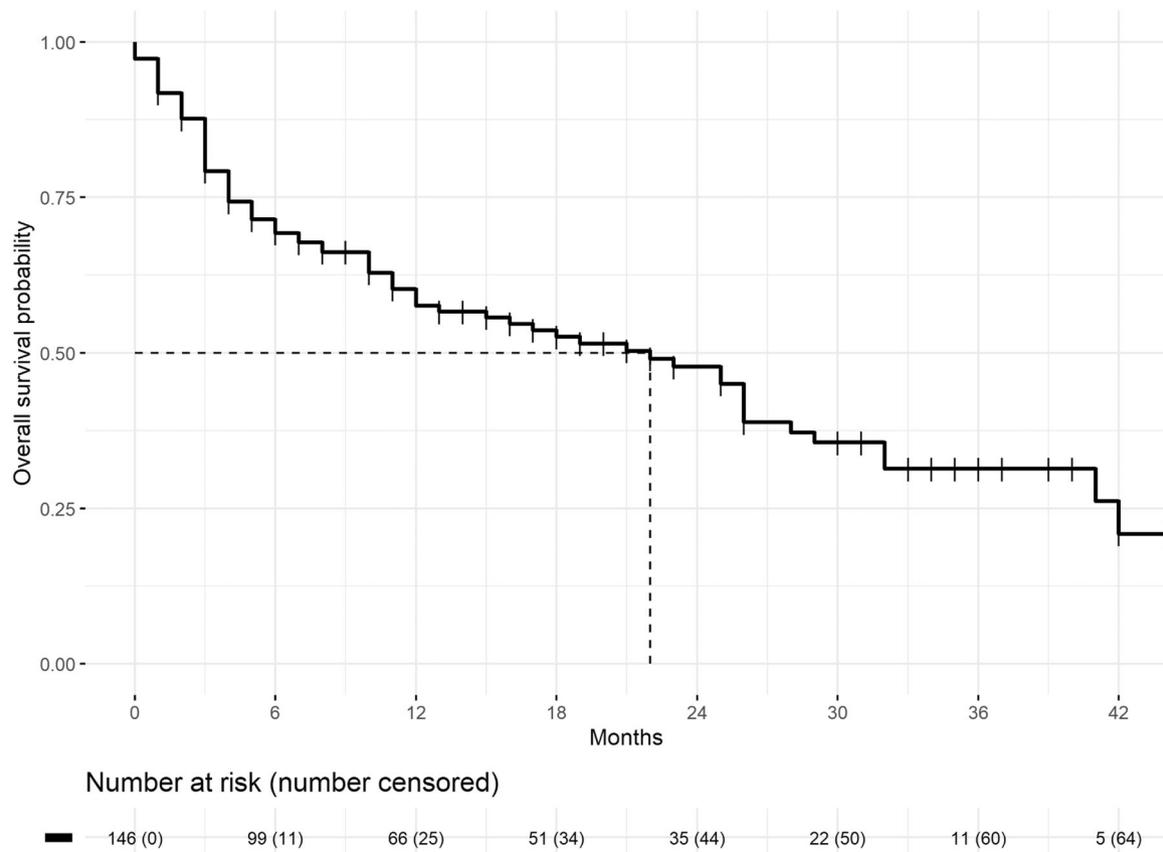
FIGURE 4 Overall survival curve for the study population.

treatment discontinuation. Among the seven patients who experienced disease progression after treatment discontinuation, two (13%) presented a PR and five (71%) presented SD.

5 | DISCUSSION

5.1 | Population

In our study population, 68% of the patients discontinued treatment for progression, 7% for toxicity, and 8% following medical decision; 42% presented long-term response to treatment (SD, PR, or CR ≥ 6 months). These results are in accordance with the literature data: in the phase-1 CA209-003 study,[9] 59% of the patients discontinued treatment for reasons of progression and 42% presented a long-term response.
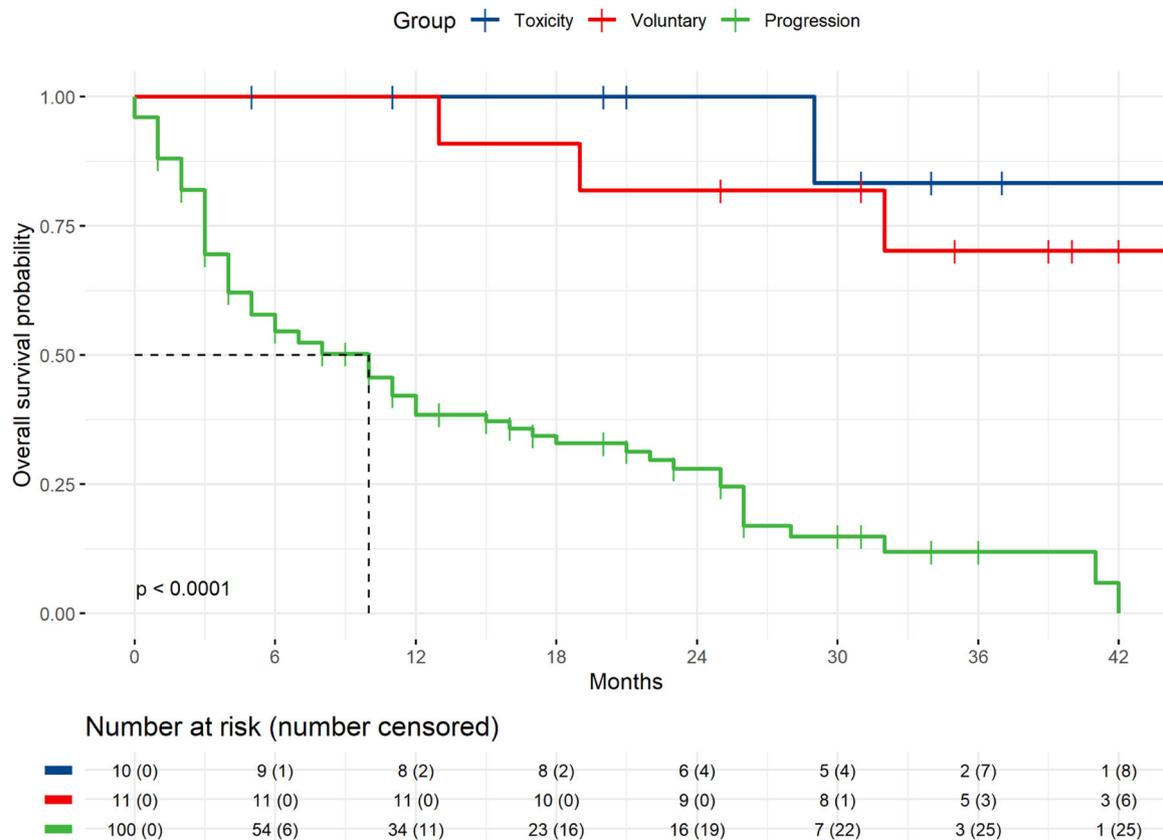
5.2 | Voluntary discontinuation

The median treatment duration before discontinuation was about 2 years. The aim of this real-life study was to evaluate the efficacy of ICI treatments after discontinuation for long-term response (6 months). The power of this study was weak and treatment durations

were nonuniform, but we have shown that, among all the patients receiving the treatment for ≥6 months (n = 10), 70% did not experience progression after treatment discontinuation. We were able to highlight the fact that the three patients who experienced progression after treatment discontinuation all presented slow progression under ICI treatment on the intermediate scans. This should alert to the need to select patients for treatment discontinuation more carefully.

In the Gettinger study,[9] treatment was discontinued in case of progression or CR, or after 2 years. Patients presented long-term response after treatment discontinuation and survival curves showed levelling off after 3 years of treatment. All patients with brain metastases were excluded. This levelling-off was also observed in our study with a median PFS of 37 months [95% CI lower bound: 26] in the "voluntary discontinuation" group. Of the three patients presenting brain metastases, all received local treatment before ICI treatment. Only one patient among them experienced progression after treatment discontinuation, suggesting that the presence of treated brain metastases does not influence progression after discontinuation.

Spigel and colleagues, in a prospective study, showed that a treatment duration of 1 year before voluntary discontinuation was not enough.[14] We tried to evaluate this conclusion by applying a 6-month treatment duration. The long-term responders were thus

FIGURE 5 Overall survival curves in the "voluntary discontinuation" group, the "discontinuation for toxicity" group and the "progression group."

defined in our study by response lasting ≥6 months, but finally, the median treatment duration in the "voluntary discontinuation" group was 2 years. In this group, after a median treatment duration of 24 months, PFS was 37 months, which meant that progression did not occur for these patients for approximately 1 year without treatment. We have shown in our real-life study that there was a sustained response, except for patients who experienced slow progression during ICI treatment.

In another large retrospective, multicenter study, the authors reported on 107 patients with NSCLC controlled by ICIs after 18 months or more.[13] Treatment was discontinued for 50% of these patients, and the median treatment duration in this population was 26 months. Treatment was discontinued in 46% of the cases following the prescribers' choice, and 22% because of toxicity. The median follow-up from treatment discontinuation was 21 months (95% CI 15.0 to −26.1 months). After discontinuation, progression occurred for 33% of the patients. These authors found long PFS and OS rates after treatment discontinuation. At 12 months, the median PFS was 71% (95% CI 56.8–81.5) and the median OS 90% (95% CI 77.7–95.7). At 24 months, the median PFS was 63% (95% CI 46.1–76.2) and the median OS 84% (95% CI 68.7–92.2). This study thus confirms our results. It also highlights the fact that response is better in case of complete or PR at the time of treatment discontinuation, than for patients with SD. Therefore, patients who

can benefit from treatment discontinuation need to be selected more carefully.

Larger prospective studies are required to better address the issue of treatment discontinuation after 2 years and to evaluate predictive factors for progression after discontinuation for a selection of patients who can discontinue treatment. Patients presenting slow progression, and possibly SD[13] in case of sustained clinical benefit, should not stop the treatment.

5.3 | Discontinuation due to toxicity

In our study, the toxicity rate (irAEs) was 53%, 12% were grade ≥3, and treatment was discontinued for toxicity in 7% of the cases. In the first studies on nivolumab and pembrolizumab,[5–7,31] toxicity rates were between 19% and 37%, toxicity for grade ≥3 was between 5% and 16%, and treatment was discontinued for toxicity in 3%–7% of the cases. The global toxicity rate was high in our study compared to the literature, possibly because of the retrospective nature of the analysis.

The main result was a significant improvement in PFS ($p = 0.05$) and OS ($p = 0.057$) compared to the progression group. Median PFS and OS were not reached in this group compared to 2 and 10 months respectively in the progression group. There was no significant

TABLE 6 Factors associated with long-term response to treatment.

Variable	HR	95% CI	p Value (FDR-adjusted)	Number of available data
PS: 0–1 vs. 2–4	2.9	(1.8–4.5)	<0.001	124
Smoking status: No vs. yes	1.1	(0.6–2.1)	0.7	140
Histology adenocarcinoma: No vs. yes	1	(0.6–1.5)	0.9	145
Histology: Squamous cell carcinoma	1.2	(0.7–1.9)	0.6	145
PDL1: Negative vs. positive	0.7	(0.3–1.6)	0.6	49
KRAS	1	(0.6–1.7)	0.9	94
Brain metastases	1.2	(0.8–1.8)	0.4	143
Brain metastases: Local treatment before ICI	0.8	(0.4–1.5)	0.7	61
Brain metastases: Local treatment during ICI	0.3	(0–1.6)	0.3	61
Treatment line: 1 vs 2 vs. ≥3			0.5	146
Maximum toxicity grades: ≤1 vs. ≥2	0.4	(0.2 to −0.6)	<0.001	146
Albumin	0.94	(0.9–0.97)	0.001	99
NLR	1.05	(1–1.1)	0.03	120
Eosinophil count	0.9	(0.2–3)	0.9	120

difference between PFS and OS in this group compared to the "discontinuation on medical decision" group.

Komiya and colleagues showed a significant improvement in PFS ($p = 0.026$) and OS ($p = 0.031$) among patients who discontinued treatment due to toxicity ($n = 18$). This study compared patients who had discontinued treatment for toxicity and patients who had discontinued for other reasons.[32] Tachihara and colleagues reported long-term survival among patients who had stopped treatment due to toxicity ($n = 19$): the median PFS was 10.2 months (95% CI 3.2–17.1 months), but survival was not compared with the rest of the study population, and the toxicities included all types of toxicity other than irAEs (bleeding, etc.).[33]

Ksienski and colleagues showed a decreased OS for patients who had discontinued treatment due to toxicity ($n = 56$): OS at 12 weeks was 8.3 months versus 14.5 months ($p = 0.008$). We can note that the rate of discontinuation due to toxicity was about twice as high as the rates for grade ≥3 toxicity.[34] In our study, 73% of discontinuations due to toxicity were linked to grade ≥3 toxicity. It is likely that the high rate of discontinuation due to grade <3 toxicity in the Ksienski

study could explain the different results. Ksienski, unlike the majority of the literature data,[16–25] found a decreased survival in case of grade >2 irAEs ($p < 0.05$). Naqashalso's recent study showed that patients who had discontinued treatment due to toxicity ($n = 108$) had decreased survival: the median OS was 3.6 versus 17.6 months (HR 2.61, 95% CI [1.61–4.21]; $p < 0.001$).[35] These two studies report results that differ from those in our study. We can note that the rates of treatment discontinuation due to toxicity were very high (20.7% and 20.3%), which could explain the different results and the need to select patients for whom ICIs can be definitively discontinued for reasons of toxicity. Russano and colleagues also studied 24 patients who presented NSCLC and who discontinued treatment following early severe adverse events (after one or two ICI administrations).[36] They did not find any survival benefit in the group that had discontinued treatment for toxicity, compared to other patients who did not experience severe irAEs. This study was different from ours because it selected early irAEs. In our study, the median treatment duration before discontinuation due to toxicity was 7.1 months.

5.4 | Factors associated with long-term response to treatment

Our study has highlighted factors associated with long-term response to treatment: low performance status, high grade toxicity, high albumin, and low NLR. These results are in accordance with the literature data. Patients with a poor general condition (high PS, low albumin) presented poor survival rates.[9] Bagley and colleagues also showed this association for NLR ≤ 5.[37] An eosinophil factor was not found, but this association has been evidenced in melanomas in particular.[38,39]

We did not find PDL1 expression to be a factor associated with long-term response. PDL1 expression is not necessary for a response to anti-PD1 treatments[40] but high expression rates are linked to response.[41,42] In our study, most patients received nivolumab as second line or above. In France, PDL1 expression is not required for nivolumab prescription in this indication and has to be ≥50% for pembrolizumab prescription as a First treatment line, or ≥1% as a second treatment line (a few years ago PDL1 was not systematically tested for). Thus, PDL1 was known for only 49 patients in the cohort; among them, 21 patients were in the pembrolizumab group (≥1%).

5.5 | Factors associated with disease progression after treatment discontinuation

The only factor found was PR compared to SD at the first evaluation scan during ICI treatment ($p = 0.03$). In the literature,[33,43] response to treatment has been associated with better OS. The response at the last evaluation scan before treatment discontinuation was not found to be a factor, suggesting that fast responses to ICI treatment had a better prognosis and a more sustained response to treatment.

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Our study is in accordance with results from Bilger's study, which showed that response (partial and CR) at the time of discontinuation was associated with improved survival.[13]

The main limitations of our study are the retrospective design and the small sample size from only one center. Further research involving a larger multicenter cohort is needed to validate these findings.

6 | CONCLUSION

In our study, patients presenting a long-term response to ICI treatment (median duration of 2 years) presented a sustained response and long-term survival after treatment discontinuation. This analysis suggests that patients for whom treatment is to be discontinued should be carefully selected and patients presenting slow progression during ICI treatment should not discontinue treatment. Patients presenting SD at the first evaluation scan have a greater likelihood of progression after treatment discontinuation than patients with a PR. The results of the first evaluation scan during ICI treatment could be a predictive factor for treatment discontinuation after long-term response.

In our study, no difference in survival (PFS and OS) was found between the two discontinuation groups (voluntary discontinuation and discontinuation due to toxicity).

Our findings suggest that the incidence of irAEs is strongly associated with long-term survival outcomes, even after treatment discontinuation. This study provides an understanding of immunotherapy's role in the management of lung cancer. A prospective validation trial is needed to confirm our findings.

AUTHOR CONTRIBUTIONS

Laure Vacher: Conceptualization; data curation; investigation; methodology; project administration; writing—original draft; writing—review & editing. **Maureen Bernadach**: Conceptualization; investigation; methodology; project administration; writing—review & editing. **Ioana Molnar**: Formal analysis; methodology; writing—review & editing. **Judith Passildas-Jahanmohan**: Conceptualization; data curation; methodology; project administration; writing—review & editing. **Pascale Dubray-Longeras**: Conceptualization; investigation; methodology; project administration; writing—review & editing. All authors have read and approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data/materials that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions. Judith Passildas Jahanmohan had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

The lead author J. Passildas-Jahanmohan affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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