Pursuit or discontinuation of anti-PD1 after 2 years of treatment in long-term responder patients with non-small cell lung cancer

Camille Ardin, Sarah Humez, Vincent Leroy, Alexandre Ampere, Soraya Bordier, Fabienne Escande, Amélie Turlotte, Luc Stoven, David Nunes, Alexis Cortot and Clément Gauvain

Abstract

Background: The optimal duration of immune checkpoint inhibitor (ICI) treatment for patients with advanced non-small cell lung cancer (NSCLC) remains to be determined. Treatment durations in cornerstone phase 3 clinical trials vary between a fixed 2-year duration and pursuit until disease progression. Clinical practices may thus differ according to the attending physician.

Objectives: Here we provide real-world data about treatment decisions at 2 years, with subsequent clinical outcomes.

Design and Methods: This multicentric observational study included patients with advanced NSCLC whose disease was controlled after 2 years of pembrolizumab or nivolumab. The primary outcome was the decision to discontinue ICI treatment or not, along with factors motivating this decision. Secondary outcomes included progression-free survival (PFS) (according to treatment continuation or not) and adverse events.

Results: A total of 91 patients were included, of which 60 (66%) had been pre-treated. The programmed death-ligand 1 expression level was ≥50% in 43 patients (47%). In 61 patients (67%), ICI was continued after 2 years of treatment. This decision was significantly associated with the care center ($p < 0.001$) but neither with the tumor response at 2 years, as evaluated by CT scan or PET scan, nor with clinical status, immune-related adverse events, or previous locally treated oligo-progressive disease under ICI. Two years after the 2-year decision, PFS was 68.5%, [95% confidence interval (CI) (53.3–88.0)] in the 'ICI discontinuation' group and 64.1% [95% CI (51.9–79.2)] in the 'ICI pursuit' group; hazard ratio for relapse was 1.14 [95% CI (0.54–2.30), $p = 0.77$]. The overall survival rate at 24 months after discontinuation was 89.2% [95% CI (78.4–100)] for the 'discontinuation' group and 93.1% [95% CI (85.8–100)] for the 'pursuit' group. Given insufficient power, overall survival could not be compared.

Conclusion: The decision to continue ICI or not after 2 years of treatment depends mainly on the care center and does not seem to impact survival. Larger, randomized data sets are required to confirm this result.

Keywords: ICI treatment duration, long-term responders, nivolumab, non-small cell lung cancer, pembrolizumab

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide, with nearly 1.8 million deaths in 2020.[1] Treatment of advanced non-small cell lung cancer (NSCLC) in the absence of any targetable molecular alteration mainly relies on immunotherapy, with or without chemotherapy.[2] Immune checkpoint inhibitors (ICIs) such as nivolumab,

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pembrolizumab, and atezolizumab have significantly improved patients' prognosis[3–5] and have led to the emergence of a population with long-lasting responses referred to as 'long-term responders'. These are usually defined as patients with a continued response after 2 years of treatment, although there is no consensus on this definition.[6,7]

Optimal treatment duration in long-term responders has not yet been determined. In cornerstone phase 3 clinical trials, treatment duration has varied from a fixed 2 years[8,9] to pursuit until disease progression or loss of clinical benefit.[10,11] Five-year overall survival in these studies seems to be similar, although the populations studied might not be identical.[3–5,12,13]

Interestingly, in metastatic melanoma it is proposed to consider discontinuing ICI before 2 years or at 2 years according to the patient's metabolic tumor burden, as assessed by Positron emission tomography – computorized tomography (PET-CT).[14] To date, there are no guidelines addressing ICI treatment duration in NSCLC nor for minimal assessment before potential discontinuation. In the absence of official guidelines, treatment duration remains at the clinicians' discretion and entails a risk of late adverse events and of burdening the healthcare system financially.[15]

Thus, the main objective of our study was to assess clinicians' practices regarding treatment duration in long-term-responders (discontinuation or pursuit until progressive disease) and the factors associated with this decision. We also aimed to assess the impact of ICI discontinuation on further oncological evolution and adverse events. Lastly, we examined the predictive value of the PET-scan for relapse.

Methods

Patients
This multicentric observational study examined data from seven hospitals in France, covering a period from May 2017 to June 2021. Patients with stage IIIB/C or IV NSCLC administered single-agent ICI treatment were screened by means of pharmaceutical registers, to limit memory bias. Patients were included if they had received ICI for at least 2 years and had controlled disease after 2 years of ICI treatment. No selection was performed regarding treatment line, clinical status, or tumor programmed death-ligand 1 (PD-L1)

expression rate. Exclusion criteria were as follows: treatment discontinuation for any reason within 2 years of ICI treatment start; evidence of general progression before the date corresponding to 2 years of treatment; oligoprogressive disease, even treated by surgery or radiotherapy, if it occurred during the 6-month period preceding the 2-year cut-off. On the other hand, provided the disease was controlled at the time of the 2-year evaluation, patients with oligoprogressive disease treated by focal intervention within the first 18 months of ICI treatment could be included. The 6-month period before the 2-year threshold was arbitrarily determined: as our first point of interest was the decision of the clinician to continue or discontinue ICI treatment at 2 years of treatment, 6-month hindsight after focal progression seemed an acceptable and clinically meaningful delay before interrupting treatment.

Data collected
Clinical characteristics at diagnosis, such as age, gender, smoking history, histology, mutational status, and tumor PD-L1 expression rates were recorded. Mutational status was assessed with DNA-based Ampliseq Next Generation Sequencing multiplex panels (22–36 genes) or using Pyrosequencing, SNaPshot, and fragment analyses to detect KRAS, EGFR, HER2, BRAF, and MET mutations. The tumor PD-L1 expression rate was assessed by immunohistochemistry with the 22C3 antibody and was defined as the percentage of tumor cells with membrane PD-L1 staining.

At the beginning of the ICI sequence, we collected the patient's general condition [using the World Health Organization Performance Status scale (WHO PS)], prior treatments, number of metastatic sites, the existence of cerebral metastasis, and whether or not corticosteroid therapy was administered. During the ICI course, the occurrence of any immune-related toxicity (assessed using the common terminology criteria for adverse events (CTCAE) v5.0.) or focal progression and subsequent treatment were recorded. Two years after the initiation of ICI treatment, we reported the decision to continue or discontinue ICI and its motivation: according to medical letters, the reasons for the decision were classified into three categories: 'patient's choice' or 'medical choice' when explicitly recorded, 'local practices' when explicitly recorded or when no other motives were found. The specific case of programed discontinuation after 2 years of treatment (with a tolerance of minus

3 months to plus 6 months), without any notion of disease progression, toxicity, or specific motives, was classified in the category 'local practices'. From the clinicians' notes, results (if available) of morphological and/or metabolic assessments (performed or not by PET scan or bone scan according to local practice) at the 2 years of treatment assessment (more or less 3 months) were reported. After the 2-year treatment cut-off, any ICI treatment discontinuations and their motivations, relapses and their treatment modalities, and new immune-related adverse events (irAEs) were collected. Here we define progression-free survival (PFS) as the period between the 2-year ICI treatment cut-off and progressive disease or death, whichever occurred first. Tumor burden evolution was described according to the RECIST v1.1 criteria. The metabolic response was considered complete if no significant FDG uptake remained detectable. It was considered partial in the case of decreased Fluoro deoxy glucose (FDG) uptake compared to baseline, as assessed by a nuclear radiologist. Given the heterogeneity of center practices regarding criteria for response assessment, we did not retain a specific threshold.

Study endpoints

The primary endpoint was the decision to continue or interrupt treatment after 2 years, along with the factors associated with this decision. Secondary endpoints included assessment and comparisons of PFS according to the treatment group in the overall population and in the population having no history of oligoprogressive disease and according to the metabolic tumor burden assessment through PET-CT at 2 years, along with data collection regarding late-occurring irAEs.

Statistical analysis

Continuous variables are presented as means ± standard deviation in the case of a normal distribution or as medians [interquartile range, IQR] in the other cases. Categorical variables are expressed as percentages of patients. Univariate analysis was performed using the Chi^2 test to identify factors associated with the decision to stop ICI treatment. The following variables were tested: WHO PS, irAE occurrence, focal progression occurrence, morphological response, metabolic response, and care center.

PFS curves were estimated using the Kaplan-Meier method and compared by means of the log-rank test. A multivariate Cox proportional hazard regression model was applied to estimate hazard ratios (HRs) with 95% confidence intervals (95% CIs), with adjustment on PD-L1, histological subtype, 2-year WHO PS, existence of cerebral metastasis number of prior line of treatment, number of metastatic sites was performed. A p value < 0.05 was considered statistically significant. Sensitivity analysis excluding oligoprogressive patients was performed to assess their impact on PFS.

In order to control multiplicity and alpha inflation, the relationship with metabolic tumor burden was assessed graphically by means of swimmer plots. All statistical analyses were performed using R version 4.6.0 (R Foundation for Statistical computing).

Results

Clinical and tumor characteristics prior to ICI

A total of 509 patients received at least one injection of NIVOLUMAB and 247 patients received at least one injection of PEMBROLIZUMAB from September 2015 to June 2019, for a total of 756 patients. Among them, 91 (12%) patients completed 2 years of ICI treatment [53 patients (10%) under Nivolumab, and 38 patients (15%) under Pembrolizumab], from May 2017 to June 2021 and were included in the analysis. Their characteristics at the beginning of the ICI treatment line are summarized in Table 1.

A total of 68 patients were male (75%), age was 62.7 ± 9.5 years, and 89 patients (98%) were current or former smokers. A total of 24 patients had WHO PS ⩾ 2. A total of 60 patients (66%) had received at least one prior treatment, 53 patients (58%) received nivolumab and the remaining received pembrolizumab.

The most frequent histology was adenocarcinoma (71%) and 78 patients (86%) had metastatic disease. The PD-L1 expression rate was above 50% in 43 patients (47%); data were missing for 28 patients (31%).

Clinical characteristics of the study population after 2 years of treatment

Clinical characteristics and information regarding disease evolution and toxicity over the first 2 years of treatment are reported in Table 2.

Table 1. Baseline characteristics (*N* = 91).

Demographic and clinical characteristics		Tumor characteristics	
Medical center, *n* (%)		Histology, *n* (%)	
University hospital	35 (38.5)	Adenocarcinoma	65 (71)
Community hospitals	56 (61.5)	Squamous cell carcinoma	20 (22)
Sex, *n* (%)		Other carcinoma	5 (7)
Male	68 (74.7)		
Age, mean (±standard deviation)	62.7 (±9.5)	Number of metastatic sites, *n* (%)	
Smoking status, *n* (%)		0	13 (14)
Current or former	89 (97.8)	1	36 (40)
Missing data	2 (2.2)	2	19 (21)
Median pack-year of smoking [IQR]	40 [30; 50]	≥3	23 (25)
BMI (kg/m²), *n* (%)		Brain metastasis, *n* (%)	26 (29)
<18	14 (15.4)	of which already treated before ICI treatment	17 (19)
18–25	43 (47.3)	PD-L1 expression level, *n* (%)	
25–30	22 (24.2)	PD-L1 < 1%	11 (12.1)
>30	12 (13.2)	PD-L1 1–49%	9 (9.9)
WHO performance status, *n* (%)		PD-L1 ≥ 50%	43 (47.2)
0	13 (14.3)	Missing data	28 (30.8)
1	54 (59.3)	Molecular status, *n* (%)	
≥2	24 (26.4)	WT or not available	47 (51.6)
Number of prior treatment line, *n* (%)		TP53	25 (27.5)
0	31 (34.1)	KRAS	23 (25.2)
1	47 (51.6)	including G12C	7 (7.7)
≥2	13 (14.3)	BRAF	5 (5.5)
ICI treatment, *n* (%)		including V600E	1 (1.1)
Nivolumab	53 (58.2)	MET	2 (2.2)
Pembrolizumab	38 (41.8)	Other mutations	7 (7.7)

BMI, body mass index; ICI, immune checkpoint inhibitor; IQR, interquartile range; PD-L1, programmed death-ligand 1; WHO, World Health Organization; WT, wild type.

After 2 years of treatment, seven patients (8%) had WHO PS ≥ 2. An objective morphological response was observed in 73 patients (80%) and an objective metabolic response was reported in

55 patients (60%). Seven patients (8%) experienced focal progression within the first 18 months, treated by focal intervention.

More precisely, the number of patients considered with a complete morphological response was 4 (13%) in the 'interruption' and 2 (3%) in the 'pursuit' group. Similarly, the number of patients considered to have achieved a complete metabolic response was 16 (53%) in the 'interruption' group *versus* 16 patients (26%) in the 'pursuit' group.

Moreover PET-CT was more frequently performed in the 'interruption' group, with only 4 patients (13%) with no assessment, *versus* 28 patients (46%) in the 'pursuit' group.

irAEs occurred in 70 patients (77%); adverse event occurrence rate during the first 2 years of treatment was similar between the two groups. A total of 125 adverse events were noted; 98% (123/125) were grade 1 or 2. The most common irAEs (occurring in 10% of patients or more) were thyroid disorder (24 patients, 26%), pruritus (23 patients, 25%), rash (21 patients, 23%), digestive tract disorders (12 patients, 13%), rheumatological disorders (11 patients, 12%), and fatigue (9 patients, 9%). The two grade $\geqslant 3$ irAEs were severe diarrhea. In one case, severe diarrhea occurred at 35 cycles of pembrolizumab and led to subsequent interruption of ICI. In the other case, severe diarrhea led to introducing corticosteroid therapy and pembrolizumab was continued until 2 years of treatment.

Decision to continue or interrupt ICI treatment and decision-motivating factors
A total of 61 patients (67%) continued to receive ICI beyond 2 years of treatment. There was a high discrepancy according to the care center. In the university hospital, 8 out of 35 patients (23%) continued ICI, whereas 53 out of 56 patients (95%) continued ICI in community centers. The reasons for the decision to continue or stop ICI were patient choice for 16 patients out of 91 (18%), medical rationale for 3 out of 91 patients (3%), and local practices for 72 out of 91 patients (79%).

The decision to interrupt ICI or not was unrelated to the type of ICI administered (nivolumab or pembrolizumab). Care center was the only variable significantly associated with treatment continuation or not ($p < 0.001$) (Table 3).

No significant association was found between the decision to interrupt ICI treatment and performance status, irAE occurrence, or prior local progression occurrence or metabolic or morphological assessment.

Among the 61 patients who continued ICI beyond 2 years, 34 (56%) discontinued ICI later on, among which 15 (25%) discontinued within 8 months of the 2-year cut-off. Median duration of treatment after the 2-year cut-off was 15 months (IQR [8–20]), with an extreme value at 42 months. Nine interruptions (26%) were motivated by the occurrence of toxicities, 8 (24%) by progression, 3 (9%) by medical rationale (SARS-Cov2 infection, stroke with heavy consequences, cognitive disorders), and 3 (9%) by patient choice. Lastly, 11 interruptions (32%) were based on no motive other than physician discretion.

Ulterior evolution according to the 2-year decision
Median follow-up (observation time in event-free patients) was 26.7 months (IQR [19.2–35.7]) after the 2-year treatment cut-off.

A total of 11 patients (12%) died during follow-up, 6 (7%) in the 'interruption' group, and 5 (5%) in the 'pursuit' group. Overall survival (OS) rates at 12 and 24 months after discontinuation were respectively 96.7% (95% CI, 90.5–100%) and 89.2% (95% CI, 78.4–100%) for the 'discontinuation' group and 100% and 93.1% (95% CI, 85.8–100%) for the 'pursuit' group. OS could not be compared for lack of events.

A total of 30 patients (33%) experienced at least one relapse: 9 (10%) in the 'interruption' group and 21 (23%) in the 'pursuit' group. Median PFS was not reached in either the 'interruption' or the 'pursuit' group. PFS rates at 12 and 24 months were respectively 79.7% (95% CI, 66.5–95.6%) and 68.5% (95% CI, 53.3–88.0%) for the 'interruption' group, and 81.5% (95% CI, 72.3–92%) and 64.1% (95% CI, 51.9–79.2%) for the 'pursuit' group. There was no significant difference between the two groups [HR, 1.14 (95% CI, 0.54–2.30), $p = 0.77$] (Figure 1). This result persisted in the multivariate analysis: HR for relapse was 1.42 (95% CI, 0.50–3.99, $p = 0.51$) after adjustment on PD-L1 [HR, 1.00 (95% CI, 0.99–1.02)], histological subtype [for epidermoid subtype HR, 0.49 (95% CI, 0.13–1.89), for indifferenciate subtype HR, 1.61 (95%

Table 2. Outcomes at the end of 2 years of ICI treatment, in overall population, and in the two subgroups, according to the 2-years decision of pursuit or interrupt the ICI treatment.

Characteristics	Overall population	'Pursuit' group (N = 61)	'Interruption' group (N = 30)
Relative dose intensity (number of injections received on theorical number of injections), median [IQR]			
Nivolumab	90 [81–96%]	85 [74–94]	97 [94–100]
Pembrolizumab	97 [88–100%]	98 [88–100]	98 [91–102]
WHO performance status, n (%)			
0	32 (35.2)	18 (29.5)	14 (46.7)
1	52 (57.1)	38 (62.3)	14 (46.7)
2	7 (7.7)	5 (8.2)	2 (6.7)
Morphological assessment (RECIST v1.1), n (%)			
Complete response	6 (6.6)	2 (3.3)	4 (13.3)
Partial response	67 (73.6)	43 (70.5)	24 (80)
Stability	9 (9.9)	7 (11.5)	2 (6.7)
Missing data	9 (9.9)	9 (14.7)	0
Metabolic assessment, n (%)			
Complete response	32 (35.2)	16 (26.2)	16 (53.3)
Partial response	23 (25.3)	14 (22.9)	9 (30)
Stability	4 (4.4)	3 (4.9)	1 (3.3)
Missing data	32 (35.2)	28 (46)	4 (13.3)
Oligoprogressive disease before the 2 years cutoff	7 (7.7)	6 (9.3)	1 (3.3)
(focal treatment), n (%)			
Patients with at least 1 adverse event (any grade) during the first 2 years, n (%)	70 (77)	47 (77)	23 (76.6)
Number of immune-related adverse events, n	125	87	38
Grade 1	92	64	28
Grade 2	31	21	10
Grade ⩾3	2	2	

ICI, immune checkpoint inhibitors; IQR, interquartile range; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization; WT, wild type.

CI, 0.15–17.63)], 2-year WHO PS [HR, 1.20 (95% CI, 0.49–2.91)], existence of cerebral metastasis [HR, 0.88 (95% CI, 0.22–3.49)], the number of prior line of treatment [HR, 0.92 (95% CI 0.41–2.04)], the number of metastatic sites [HR, 1.17 (95% CI, 0.77–1.78)].

A sensitivity analysis was performed after exclusion of oligoprogressive patients, without any significant impact on the result: HR, 1.22 (95% CI, 0.57–2.60%, p=0.62).

In most cases, the first progressive event involved a single tumor site (23 patients, 25%); two

patients (2%) had bifocal progression and five (6%) had multiple-site progression. Among the 25 patients with focal or bifocal progression, 21 (84%) received local treatment, including stereotaxic ablative radiation therapy for 19 patients, surgery followed by radiation therapy for 2 patients, chemo-radiotherapy for 2 patients, and chemotherapy alone for 1 patient. One other patient died before any new therapeutic project could be initiated. Among the five patients with systemic progression, chemo-immunotherapy was administered to two patients, chemotherapy alone to one patient, and ICI rechallenge to one patient.

Beyond 2 years, a total of 22 irAEs were reported (Table 4).

A total of 14 patients (23%) in the 'pursuit' group experienced at least one irAE and 1 (3%) in the 'interruption' group experienced two irAEs. The most common irAE of any grade was rash (5 cases out of 61 patients, 8%), followed by rheumatological (7%), hematological (7%), and digestive tract disorders (5%). Most of these irAEs were grade 1 or 2. We noted two cases with a grade 3 irAE in the 'pursuit' group: one case of severe colitis and one with diffuse arthritis, requiring immunosuppressive treatment for more than 2 years.

Table 3. Chi^2 test results, testing relation between potential explanatory variables and the decision to interrupt ICI treatment.

Explanatory variable	*p* Value
Care center	0.001
WHO performance status at 2 years	0.27
Immune-related adverse event occurrence	0.9
Focal progression before 2 years cut-off	0.66
Morphological assessment (RECIST)	0.21
Metabolic assessment	0.53

ICI, immune checkpoint inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization.

Metabolic assessment at 2 years

Figure 2 displays the relationship between metabolic response at 2 years and PFS in the two different groups. Among the patients with a complete metabolic response at 2 years, the PFS rates at 24 months were 74% [95% CI (55–99.6%)] in
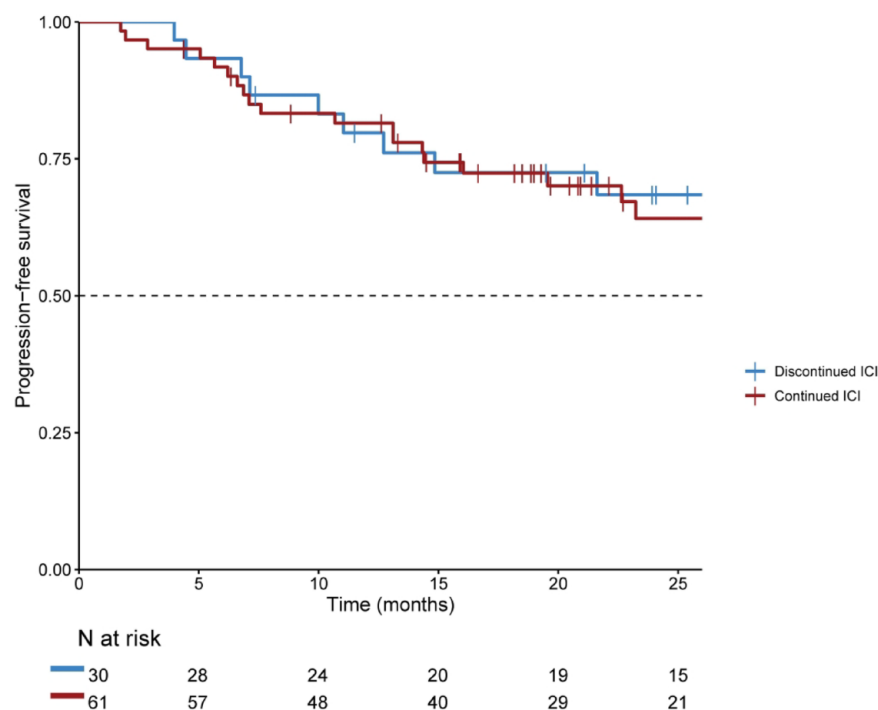

Figure 1. Kaplan-Meier estimated curves for PFS, from the 2-year decision, according to pursuit or discontinuation of the ICI therapy. Dashes indicate censored data.
ICI, immune checkpoint inhibitor; PFS, progression-free survival.

Table 4. Number of immune-related adverse events occurred beyond the 2-year cut-off.

Adverse event, n (%)	'Pursuit' group (N = 61)						'Interruption' group (N = 30)					
	Grade 1 (%)		Grade 2 (%)		Grade 3–4 (%)		Grade 1 (%)		Grade 2 (%)		Grade 3–4(%)	
Thyroid disorder	1	(1.6)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Hypophysitis	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Pruritus	1	1.6	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Rash	2	(3.3)	3	(4.9)	0	(0)	0	(0)	0	(0)	0	(0)
Hepatitis	1	(1.6)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Digestive tract disorders	1	(1.6)	1	(1.6)	1	(1.6)	0	(0)	0	(0)	0	(0)
Rheumatological disorder	2	(3.3)	1	(1.6)	1	(1.6)	0	(0)	0	(0)	0	(0)
Hematological disorder	3	(4.9)	1	(1.6)	0	(0)	0	(0)	0	(0)	0	(0)
Pneumonitis	0	(0)	0	(0)	0	(0)	1	(3.3)	0	(0)	0	(0)
Fatigue	1	(1.6)	0	(0)	0	(0)	1	(3.3)	0	(0)	0	(0)
Total events	12	(19.5)	6	(9.7)	2	(3.2)	2	(6.6)	0	(0)	0	(0)

the 'discontinuation' group and 74.5% [95% CI (55.7–99.6%)] in the 'pursuit' group. In the patients with no complete metabolic response at 2 years, the PFS rates at 24 months were 70% [95% CI (45.7–100%)] in the 'discontinuation' group and 52.3% [95% CI (33–82.8%)] in the 'pursuit' group. Although no statistical comparison was performed because of the risk of inflating the alpha risk, response durations did not appear longer in patients with complete metabolic response.

Discussion

To our knowledge, our study is the first to report clinicians' attitudes regarding treatment continuation after 2 years in long-term responders, along with outcomes according to whether treatment was pursued.

The proportion of 'long-term responders' patients, usually defined as patients responding during at least 2 years to treatment, in our study is broadly 12%; 10% of patients exposed to nivolumab completed 2 years of treatment, which is near to the rate reported in the pooled analysis of Checkmate 017 and 057 (13.4%)[3]; 15% of patients exposed to pembrolizumab completed 2 years of treatment compared to the 20% of long-term responders in KEYNOTE

042 (PFS in patients with PD-L1 > 1%, in first line of treatment).[9] Proportion of long-term responders patients in our study is lower than those reported in the main clinical trials; wider real-life exposure to immunotherapy, in a less selected population than in clinical trials, could explain this result.[16]

The clinical characteristics of the patients included in this study were similar to those of patients with newly diagnosed NSCLC except for the smoking status, since 98% of the patients had a history of smoking.[17,18] This is in agreement with data highlighting the link between smoking history and a better response to ICI therapy[19–21] and with the absence of approval in France for ICI for first-line treatment of EGFR-mutated and ALK-rearranged NSCLC. Of note, 26% of long-term responders had a poor PS at the beginning of the ICI therapy, which confirms that these patients can derive a prolonged benefit from ICI.[22,23]

Regarding the molecular characteristics of the tumors, only half of the patients in this study had PD-L1 ≥ 50%. Interestingly, 11 (about 12%) of these long-term responders had PD-L1 ≤ 1%. This contrasts with the results of a recent Korean real-life retrospective study of patients with advanced NSCLC treated with an ICI for 2 years
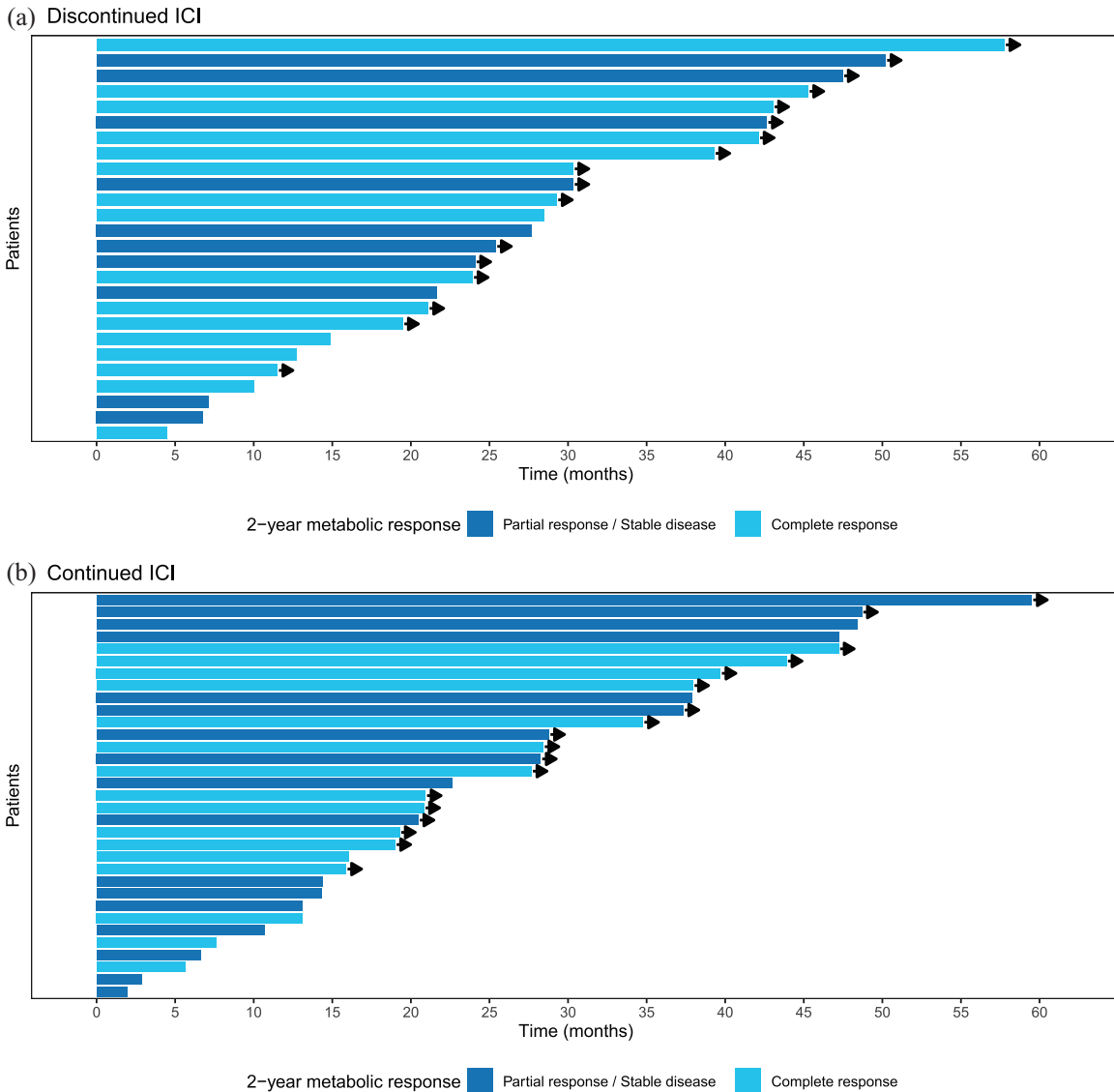
(a) Discontinued ICI

(b) Continued ICI

Figure 2. Swimmer plot representing the duration of response, according to metabolic assessment after 2 years of ICI treatment, in the 'interruption' group (a) and the 'pursuit' group (b).
ICI, immune checkpoint inhibitor.

before cessation[24]: the investigators reported 98% of patients with PD-L1 ⩾ 50% and no patient with PD-L1 ⩽ 1%. It is known that PD-L1 expression is heterogeneous in tumors,[25] and this may explain our result. Nevertheless, it's worth noting that PD-L1 was developed to predict overall response and not long-term responses.[26] Our result supports the view that tools better than the tumor PD-L1 expression rate alone are needed to predict the response to ICI therapy. This is an active field of research.[27]

After 2 years of treatment, the main characteristics which seemed different between the two populations were the proportion of patients considered with a complete morphological response: four patients (13%) in the 'interruption' group *versus* two patients (3%) in the 'pursuit' group, and the proportion of patients considered to have achieved a complete metabolic response: 16 patients (53%) in the 'interruption' group *versus* 16 patients (26%) in the 'pursuit' group. This suggests that morphological and metabolic 2-year assessment that could influence the decision to interrupt ICI treatment. However, in our study, we found that neither metabolic response nor morphological response at 2 years of treatment were associated with the decision of

ICI treatment interruption. The only significant factor was the center of care, reflecting the impact of the local practices.

Our study has found no significant difference in terms of PFS according to whether ICI was continued or not beyond 2 years. This may be due to insufficient power in our study: indeed, multivariate analysis is underpowered due to low number of events; so, we cannot exclude a true difference of small amplitude. The result might also have been impacted by the proportion of patients (25%) in the 'pursuit' group having interrupted ICI treatment within 8 months of the 2-year cutoff. On the other hand, a prolonged response to ICI treatment even in the absence of further injections might be due to the long half-life of ICI in the blood combined with the presence of PD-1 receptor on T-cells[28,29] or to the phenomenon of immune memory.[30,31] This view is supported by the observation of patients maintaining prolonged responses despite having stopped immunotherapy, particularly in the event of toxicities.[32,33] Yet such patients might constitute a special case that cannot be extrapolated to patients having received ICI without any major toxicities leading to ICI interruption. In this latter population, the Checkmate 153 trial including patients with previously treated advanced or metastatic NSCLC compared a fixed 1-year period of nivolumab treatment with continuation until progressive disease[34]: this study showed decreased OS in the 1-year fixed-duration group [HR for death: 0.62 (95% CI, 0.42–0.92) in favor of continued nivolumab]. Thus, carrying out treatment for a fixed 1-year period appears less favorable than continuing treatment until loss of clinical benefit. One should note, however, that 1 year is less than the 2-year threshold which usually defines long-term responders.[7] Moreover, a Korean real-life retrospective study including patients with advanced NSCLC having received ICI treatment for 2 years before cessation[24] reported a 1-year PFS rate of 81.1% and an estimated OS rate of 96.4%. These results are similar to ours for the 'discontinuation' group [1-year PFS: 79.7% (95% CI (66.5–95.6%)); estimated OS rate: 96.7% (95% CI (90.5–100%))]. In KEYNOTE 010, furthermore, similar PFS rates were observed in patients having completed 35 injections of pembrolizumab.[35] Thus, 2 years of treatment could be a duration sufficient for refining the selection of patients eligible for ICI discontinuation. Yet in the case of NSCLC, there are no criteria for selecting patients eligible for discontinuing

ICI, in contrast to the PET-CT-scan-based recommendations applicable to advanced melanoma, as previously mentioned.[13]

In our study there was no obvious relationship between the metabolic response after 2 years of treatment and PFS, except for a trend toward decreased PFS in the 'continuation' group in case of no complete metabolic response. This result, however, should be interpreted with caution, as no centralized review of PET-CT scans was performed, and potential discrepancies in the conclusions of exams are likely to induce a measurement bias. Interestingly, the use of PET-CT is more frequent in the 'interruption' group, with only 4 patients (13%) with no assessment, *versus* 28 patients (46%) in the pursuit group. This could suggest that results of PET-CT impact the decision to stop the treatment, by analogy with current melanoma recommendations where discontinuation of immunotherapy should be conditional on a complete metabolic response.[13] However, there are currently no guidelines addressing the use of PET-CT in the monitoring of advanced NSCLC in France, but this exam is not routinely recommended in Europe, due to its high sensitivity and relatively low specificity[36] though it is performed by some centers in France according to availability and local practices.

The present results, however, do not support the use of PET-CT to select patients as recommended in advanced melanoma.[13]

The occurrence of irAEs of 'any grade' beyond 2 years of treatment was not rare in our study. Yet comparing rates between groups is subject to performance bias, as patients in the 'pursuit' group were likely to be examined with more caution and also more frequently (every 2–6 weeks, according to the molecule and to possible adaptation of the rhythm of administration) than patients in the 'interruption' group (every 3–6 months). Nevertheless, such adverse events appeared to occur less frequently when ICI was stopped at 2 years: both in our study and in the princeps trials of pembrolizumab,[5,8,37,38] the rate of immuno-induced adverse events beyond 2 years was in the range of 2–4% for any grade. This contrasts with data from the CheckMate 017 and 057 trials, in which nivolumab was continued until clinical benefit was lost, showing toxicity beyond 2 years in up to 31% of patients, including 6% grade 3–5 adverse events.[3,39]

Lastly, the option of stopping treatment raises the question of rechallenge. In our cohort, only one patient was rechallenged with ICI and died 3 months later. The question of ICI rechallenge remains open: objective response rates range from 11 to 46%, depending on the cause having led to discontinuation of ICI therapy (toxicity, discontinuation due to a clinical decision such as a defined period or cycle of ICI treatment, ICI rechallenge after an intercurrent line of another systemic therapy).[40]

Our study has several limitations. The main one is data collection based on medical records, responsible for inaccuracies and missing data, particularly concerning toxicity evaluation and the co-treatments administered. Collecting from medical letters the reason for the decision to stop or continue treatment could lead to misinterpretations in the few cases where the decision was not clearly explained. Secondly, the limited size of our population (91 patients) limited the power of the statistical analyses and the number of statistical tests performed without control of the overall alpha risk, although limited, exposes to the possibility of false positives. Yet the multicentric nature of our work has allowed us to study a wide range of current practices in real life and to highlight the heterogeneity of management in the absence of guidelines, resulting in clinical and financial costs. The recall bias inherent in retrospective data was controlled by conducting systematic research on patients through prescription software. Lastly, this study is the first description, in the same real-life population, of oncological evolution according to the pursuit or interruption of immunotherapy after 2 years.

In conclusion, treatment duration in long-term responders to ICI relies mainly on local practices and does not seem to impact PFS beyond 2 years. Larger prospective non-inferiority trials are required to confirm this latter point and to promote practice homogeneity across centers.

Declarations

Ethics approval and consent to participate
This study was carried out in accordance with the ethics rules applicable in France and falls within the scope of Reference Methodology (RM) 004, governing studies involving the re-use of existing data. Collected data were anonymized. A statement relating to the computerized processing of data was filed with the Data Protection Delegate of the Lille University Hospital Centre (N°940). Included patients were informed that their data might be used retrospectively for research purposes if they did not object. Given the study's retrospective nature, no signed consent was required.

Consent for publication
Not applicable.

Author contributions
Camille Ardin: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Writing – original draft; Writing – review & editing.

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