Original Article

Safety and efficacy of immunotherapy using a double-dose regimen in advanced non-small cell lung cancer (NSCLC): results of IDEE study

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Background: Pembrolizumab 400 mg every six weeks (Q6W) and nivolumab 480 mg every four weeks (Q4W) are used since 2020 and the coronavirus disease 2019 (COVID-19) pandemic. This recommendation relied on pharmacokinetic and pharmacodynamic models. The objective of the IDEE (Immunothérapie Double dose Etendue: Experience bretonne) study is to determine the safety and efficacy of this treatment regimen in real life conditions.

Methods: We conducted an observational, retrospective, multicentric study including 117 patients with advanced non-small cell lung cancer (NSCLC) who received pembrolizumab Q6W or nivolumab Q4W between March 2020 and March 2021.

Results: The median age was 67 years, 68% were men with predominantly lung adenocarcinoma. The median time to double-dose regimen failure (TDDF) was 9.2 months. The survival rate at 12 months was 79%. TDDF was not influenced by sex, line of treatment, pathologic subtypes or anti-programmed cell death protein 1 (PD-1) antibody. There was no correlation between TDDF and duration of prior exposition to immunotherapy before switching. Sixty-eight patients experienced double-dose treatment failure, 28% because of toxicity including five definitive discontinuations. Five grade ≥3 immune-adverse events were reported included two cases of pneumonitis, all responding to corticosteroid therapy.

Conclusions: Our multicentric cohort supports the feasibility of pembrolizumab Q6W and nivolumab Q4W for patients with advanced NSCLC. There is no warning signal regarding safety neither efficacy in our real-life data.

Keywords: Non-small cell lung cancer (NSCLC); immune checkpoint inhibitor (ICI); extended interval dosing

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Introduction

Nivolumab and pembrolizumab are anti-programmed cell death protein 1 (PD-1) antibodies, approved for the treatment of advanced non-small cell lung cancer (NSCLC). Pembrolizumab as a monotherapy can be used for first-line treatment in patients with a tumour proportion score (TPS) for programmed death-ligand 1 (PD-L1) of 50% or greater (1) or in association with chemotherapy regardless of PD-L1 status (2). Nivolumab and pembrolizumab are also validated in second-line treatment for patients with TPS PD-L1 ≥1% (3) or regardless of TPS PD-L1 (4). Early phase development trials provided data on pharmacokinetic (PK) properties of immune-checkpoint inhibitors typical for therapeutic antibodies: a small volume of distribution, a long half-life, a low clearance minimally affected by renal or hepatic failure. They were initially approved with doses based on body weight (2 mg/kg Q3W for pembrolizumab and 3 mg/kg Q2W for nivolumab) (4,5). Fixed-flat dosing was validated by modeling studies using PK and exposure responses. A recent study (6) using pooled safety data from phases III clinical trials demonstrated the consistency of overall exposure and similar safety profile between nivolumab 480 mg Q4W compared with 240 mg Q2W and 3 mg/kg Q2W. A similar approach draws the same conclusions for pembrolizumab 400 mg Q6W (7).

The coronavirus pandemic in 2019 speeded up the need for definition of optimal dosing and administration frequency of immune checkpoint inhibitors (ICIs). Considering the vulnerability of patients with lung cancer to coronavirus disease (8), guidelines widely recommended the use of extended intervals to reduce the number of hospital visits for patients with cancer. The French Pneumology Society at that time recommended hanging treatment in patients with stable disease for over a year and switching to extended interval immunotherapy in those with stable disease for less than a year. Following this consensus, the new dosage regimen of pembrolizumab 400 mg Q6W and nivolumab 480 mg Q4W has emerged. In a retrospective study of treatment regimen management at Institute Curie, Basse *et al.* (9) reported that 92% of modifications treatment strategies were in accordance with the published guidelines from March to April 2020. From patient's point of view, those new regimens are likely to bring more convenience and flexibility as Travert *et al.* demonstrated in their retrospective study focusing on quality of life (10).

Few real life clinical data evaluating the safety and feasibility of switching ICIs to double-dose (DD) regimens are available. There is some heterogeneity in the results. The retrospective study with 45 patients of Higashiyama *et al.* (11) raises concern about the safety of pembrolizumab dose doubling with a high percentage of grade 3–4 immune-related adverse events (irAES) up to 38% of patients. In a recent monocentric cohort of Hijmering-Kappelle (12) including 117 patients in the extended interval (EI) dosing cohort, these new schedules appear as a safe and effective strategy without increased relevant toxicity leading to treatment interruption.

The objective of the multicentric IDEE (Immunothérapie Double dose Etendue: Experience bretonne) study is to describe the safety and efficacy of this treatment regimen in real life conditions, using retrospective data from multiple centers in Brittany, France. We present this study in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-141/rc).

Highlight box

Key findings

- In our retrospective study which included 117 patients with advanced non-small cell lung cancer treated with either pembrolizumab every six weeks (Q6W) or nivolumab Q4W, the median time to double-dose regimen failure (TDDF) was 9.2 months. The side effects observed with the double-dose (DD) regimen were consistent with the expected side effects of immune checkpoint inhibitors. Only five grade ≥3 side effects were observed.

What is known and what is new?

- Since the onset of the coronavirus disease crisis, there has been a global adoption of extended DD checkpoint inhibitor regimens. The initial phases of immunotherapy validation provided pharmacokinetic and pharmacodynamic data supporting the equivalence of exposure and safety profiles between these extended regimens and the conventional ones. Over the past three years, retrospective data have emerged, some raising concerns about the safety of doubling the pembrolizumab dose.
- Our investigation aimed to assess the real-life safety and efficacy of these DD regimens across five care centers in Brittany, France.

What is the implication, and what should change now?

- Our reassuring data suggest that these DD regimens can be utilized regardless of the line of treatment, pathological subtype, or the specific immune checkpoint inhibitor prescribed. However, there is limited data on initiating treatment with a DD from the outset: this approach should be taken with caution. Instances of permanent discontinuation of immunotherapy due to toxicity from the DD regimen were rare, allowing clinicians the flexibility to revert to a standard regimen if needed.

Methods

Study design and participants

We conducted an observational, retrospective, multicentric study in 5 hospitals in France (Saint-Malo, Morlaix, Vannes, Rennes and Saint-Brieuc).

All patients with advanced stage III/IV NSCLC [based on 8th edition of IASCL Tumor Node Metastasis (TNM)] received at least one dose of pembrolizumab 400 mg, either as monotherapy or along with chemotherapy, or nivolumab 480 mg from March 01, 2020 to March 01, 2021 were included. The follow-up was carried out until March 2022. Clinical data were collected retrospectively from medical records, from the 1st dose of immunotherapy until March 2022 for each patient. irAEs and clinical endpoints were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 one the basis of biological data, CT scans (RECIST v1.1) and available medical reports with clinical descriptions.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the ethics committee of Rennes University Hospital (CHU Pontchaillou) on March 04, 2022 (No. 22.41) and informed consent was taken from all the patients.

Outcomes

The primary outcome was time to DD regimen failure (TDDF). Failure was defined by discontinuation of DD related to toxicity, progression, death or patient/clinician choice. The number of planned cycles of immunotherapy vary from 2 to 4 years and was based on physician decision. TDDF is defined as the time from the start of the extended regimen to the time of one of the composite endpoint achievements. Patients who completed all planned cycles of immunotherapy were censored at the analysis cutoff date.

Statistical analysis

Time to DD failure was estimated using Kaplan Meier method. Comparison of survival curves across sex, PD-L1 rate (< or ≥50%), pathological subtype, smoking status, line of treatment (1st or 2nd and more), molecule (pembrolizumab or nivolumab), median time of prior exposition to immunotherapy were based on the log-rank test. The survival rate at 12 and 18 months indicate the percentage of patients still alive 12 and 18 months after switching for a DD.

The secondary outcomes, including reasons of failure and safety profiles, were evaluated using the χ^2 test or Fisher's exact test in appropriate conditions. Correlation between the number of months of prior exposure to immunotherapy before switching to DD and the time to failure were assessed using the Pearson test (or Spearman test if necessary). These analyses evaluated at 2-sided significance level of 0.05.

Results

Patient characteristics

Among 117 patients included, 73 patients received at least one dose of pembrolizumab 400 mg and 44 patients at least one dose of nivolumab 480 mg between March 01, 2020 and March 01, 2021 (Figure S1). The baseline characteristics are summarized in *Table 1*. The median age was 67 years, 68% were men. There was a majority of adenocarcinoma (73.5%) and stage IV diseases (82.9%). The proportion of patients on first-line treatment or second line and beyond was comparable, respectively 45.3% and 54.7%. The median time of prior exposure to immunotherapy before switching to a DD was 7.7 months.

Assessment of efficacy

With a median follow-up of 23.3 months, the median TDDF was 9.2 months (*Figure 1*). This TDDF was not influenced by sex (P=0.096), smoking status (P=0.12), pathological subtype (P=0.49), line of treatment (P=0.9) or anti-PD-1 antibody (P=0.25). We found a statistical difference of TDDF according to PD-L1 status with a longer median among patients with PD-L1 TPS ≥50% *vs.* PD-L1 TPS <50% (log rank P=0.033) (Figure S2). The survival rate at 12 and 18 months was 79% and 72% respectively.

Sixty-eight patients experienced DD failure: 28% because of toxicity, 51% because of disease progression. Other reasons were death for four patients (including two patients due to SARS-CoV-2 infection, the other two because of comorbidities). One patient changed his referring hospital. Nine patients stopped the DD schedule by choice of the referring physician. The distribution of causes of DD failure according to the DD duration is shown in *Figure 2*. There was no statistical correlation between TDDF and median time of prior exposition to immunotherapy before switching (P=0.068) (Figure S3).

Table 1 Demographic characteristics (N=117)

Characteristics	Value
Age at diagnostic (years)	
Mean ± SD	67.6±11.0
Median (Q1, Q3)	67.5 (61.3, 74.9)
Min, max	41.4, 93.9
Sex, n (%)	
Female	37 (31.6)
Male	80 (68.4)
Tumour histology, n (%)	
Adenocarcinoma	86 (73.5)
Squamous cell carcinoma	24 (20.5)
Other	7 (6.0)
PD-L1 tumour proportion score, n (%)	
<50%	30 (31.3)
≥50%	66 (68.8)
Missing	21
Stage TNM 8th edition, n (%)	
III	20 (17.1)
IIIA	1
IIIB	13
IIIC	6
IV	97 (82.9)
Treatment line, n (%)	
1	53 (45.3)
2+	64 (54.7)
Anti-PD-1 antibody, n (%)	
Nivolumab	44 (37.6)
Pembrolizumab	73 (62.4)
Smoking status, n (%)	
Current	36 (31.0)
Never	9 (7.8)
Former	71 (61.2)
Missing	1
Months of prior exposure to immunotherapy before switching	
Mean ± SD	7.7±9.8
Median (Q1, Q3)	7.7 (4.5, 15.9)
Min, max	0.0, 49.1
Location of metastasis, n (%)	
Pleural	20 (17.1)
Bone	23 (19.7)
Liver	13 (11.1)
Pericardium	6 (5.1)
Brain	29 (24.8)
Adrenal glands	24 (20.5)
Lung	30 (25.6)
Kidney	1 (0.9)
Digestive tract	1 (0.9)
Lymph nodes	7 (6.0)

PD-L1, programmed death-ligand 1; TNM, Tumor Node Metastasis; PD-1, programmed cell death protein 1; SD, standard deviation.

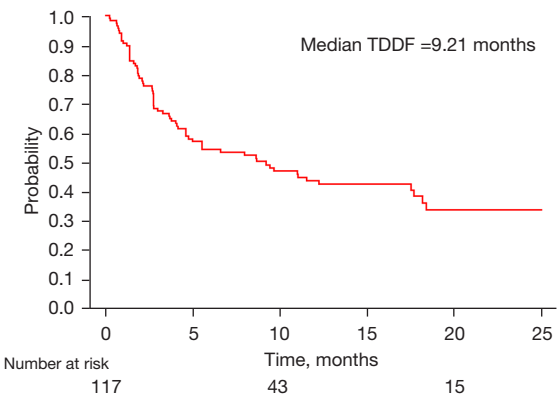

Figure 1 Kaplan-Meier analysis of TTDF. TDDF, time to double-dose treatment failure.

We observed a statistically significant association between the cause of failure and the PD-L1 status (P=0.011) (Table S1). Using Bonferroni adjustment, there were no difference of distribution of PD-L1 status between progression and toxicity even if there was a trend to observe more toxicity-induced failure among the patients with PD-L1 TPS ≥50% (P=0.08).

Assessment of safety

The adverse events (AEs) recorded were similar both during

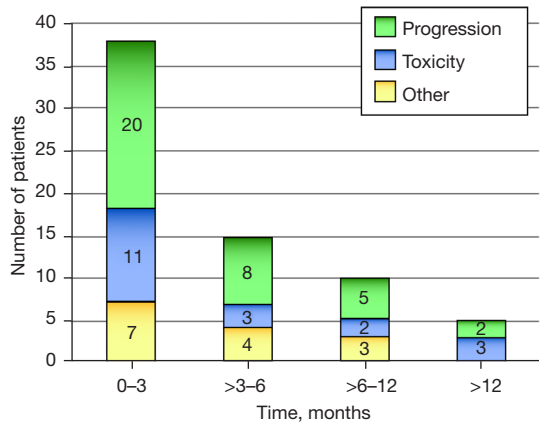

Figure 2 Cause of double-dose failure by time under double-dose (months).

the standard dose (SD) regimen and the DD regimen (Table S2). The most frequent were cutaneous (39% in SD *vs.* 29% in DD), dysthyroidism (24% in SD *vs.* 12% in DD), musculoskeletal (16% in SD *vs.* 11% in DD) and gastrointestinal (12.5% in SD *vs.* 9.4% in DD). In our cohort, 32 patients had no AEs under SD before switching. After switching to the DD, 2/3 of them (20/32) remained without any toxicity. Fourty-nine patients over the 117 patients under DD had no irAEs.

Five cases of grade 3 or more irAEs were reported under extended interval regimen. There was one case of anemia. Two cases of pneumonitis (one grade 4 and one grade 3) appeared under DD respectively 4 and 18 months after switching. Two patients had a grade 3 gastro-intestinal AE under DD with diarrheas and were treated with steroids. They both already had grade 1 gastro-intestinal AE before switching. One of them returned to the SD without recurrence. Considering pneumonitis with DD regimen, there was one case of acute respiratory failure 4 months after switching. The patient was treated with steroid with favorable issue. There was one grade 3 pneumonitis and one case of organizing pneumonia both 18 months after switching. Among the 19 patients who underwent toxicity-induced failure, only five definitively stopped immunotherapy. The remaining 14 patients returned to the standard regimen.

We found a significant statistical association between the existence of toxicity (all grades) during the DD regimen and the immunotherapy used (nivolumab or pembrolizumab) (P=0.03), smoking status (P=0.02) but not according to PD-L1 TPS (P=0.12), gender (P=0.84), year of birth (P=0.98) or histology (P=0.20) (Table S3).

Discussion

In this retrospective multicentric cohort study, we report real life data from patients with advanced NSLC receiving ICIs with SD and DD regimens.

The first key result is that patient experienced a long TDDF. In our cohort, the median TDDF was high (9.2 months) and overall survival rate at 12 and 18 months was 79% and 72% respectively. The distribution of the different causes of DD failure does not seem to differ over time. The favourable TDDF with DD regimen observed in our cohort might be explained by an over-representation of tumors with PD-L1 status ≥50% (68.8% of patients). This is supported by subgroup analyses showing a significant longer TDDF among patients with higher PD-L1 TPS. Interestingly, there is no statistical difference in median TDDF between patients in line 1st and 2nd line and more. Our results suggest that those regimens can be used regardless of the line of treatment, pathological subtype or immune checkpoint antibody prescribed.

Our results are in line with real life data available which mostly find reassuring data. In Jones *et al.* study (13), there was no overall survival difference demonstrated with pembrolizumab dosing Q3W compared to Q6W, using a multivariate analysis that included age, sex and Performans Status. Using time to treatment discontinuation (TTD) as primary outcome, Strohbehn *et al.* (14) found no difference between standard and extended interval dosing in the NSCLC cohort. In their work, median TTD was 112 days for standard interval and 170 days for extended interval [hazard ratio (HR), 1.00; 95% confidence interval (CI): 1.00–1.00; P=0.15]. Of note, this time to treatment-discontinuation is shorter than our TDDF, but the two population are very different: their study included only males, all treated with pembrolizumab, with a higher median age. To our knowledge, there is only one randomized international open trial evaluating nivolumab 480 mg Q4W *vs.* 240 mg Q2W in 163 patients (15). The authors found no difference in progression-free survival rate between the two arms and safety profile was similar. The final results are waiting but the interim analysis seems to support our findings.

We found a statistically significant association between the cause of failure and PD-L1 status (P=0.0114), with a trend but not significant toxicity induced failure among patients with PD-L1 ≥50% (P=0.08). However, there

was no statistical association between toxicity under DD regimen (all grades) and PD-L1 status. For comparison, in Checkmate 057 (4), the frequencies of treatment-related AEs were similar between patients with ≥1% PD-L1 and <1% PD-L1 expression. Interestingly, in the Higashiyama cohort (11) which have a high rate of irAEs, ≥75% of the patients had a PD-L1 status ≥50%.

There was no statistical correlation between time to DD failure and time of prior exposition to immunotherapy before switching. Similarly, Veron *et al.* (16) did not found a statistical association between the occurrence of a grade 3 or more toxicity and prior exposition of ICI in a multivariate analysis. This raises the question for physicians: what is the best timing for switching from a simple dose to a DD regimen? In our study, the median time under immunotherapy before switching was 7.7 months. The spread range from 0 to 39.1 months highlights the heterogeneity of practice. Only six patients started upfront with DD regimen, four of them stopped very quickly because of progression disease. In the Hijmering-Kappelle study (12), it was necessary to have at least two cycles of SD without clinically relevant toxicity before escalating. In the Higashiyama study (11), the median number of cycle of pembrolizumab Q3W before switching was 6 and median time from switching to the manifestation of new irAEs was 63 days. A recent pan-cancer study (17) evaluating safety of extended interval dosing ICIs in several tumor pointed out that some irAEs after switching to a DD regimen represented de novo toxicity. About 43% of any grade and 30.4% of grade 3 and 4 irAEs in their extended interval cohort occurred after only one DD administration. To our knowledge, this pan-cancer study is the largest cohort of NSCLC treated upfront with DD (39 patients). Considering the low level of real life safety evidence, data from this review and from our cohort support a close monitoring of immune-related toxicities during the first DD cycles and especially with patients starting upfront with DD.

Concerning tolerance of DD, the iRAEs occurring during the extended regimen are expected and well-known AEs of immunotherapy. As a reference, in KEYNOTE 024 (18), treatment related AEs occurred in 76.6% of patients, including 31.2% of grade 3–5. In Checkmate 057 (19), 45 patients (10.8%) had grade 3–4 treatment-related AEs. In our cohort, 58% of patients experienced irAEs under DD. There were only five cases of grade 3 or more AEs, all responding to corticosteroid therapy. Rowe *et al.* (20) found consistent data: 3 grade ≥3 irAES over 63 patients under pembrolizumab Q6W. One recent retrospective study (16) in two French hospitals found a higher percentage of grade ≥3 irAEs (13%) among 95 patients with NSCLC. This difference can be explained because populations were different, including patients treated with durvalumab after radio-chemotherapy which may enhanced pulmonary toxicity and a slightly lower proportion of patients treated with nivolumab (25% *vs.* 38% in our cohort). Sixteen percent (19/117) of patients of our cohort underwent toxicity-induced extended regimen failure with 26% of them (i.e., 5/117) who had to definitely stop immunotherapy. Hijmering-Kappelle *et al.* (12) found a higher proportion (26%; 31/117) of treatment adjustments due to AEs, but the same proportion of immunotherapy discontinuation. The recent retrospective study of Dubé-Pelletier *et al.* (21) comparing pembrolizumab Q6W to Q3W found differences between the two groups with regard to immune-mediated AEs requiring to hold and to discontinue immunotherapy (more interruption but less definitive stop in the Q6W group). This might be explained because the two cohorts were not simultaneous (Q6W group was the most contemporary with recruitment from March, 2020 to December, 2021) with a possible experience-effect across years.

We found a statistical association between the presence of toxicity under DD and the antibody used (pembrolizumab versus nivolumab). Coherently, Hijmering-Kappelle (12) observed more AEs in the pembrolizumab extended cohort compared to SD. However, it did not result in an increased number of grade ≥3 events or events leading to treatment interruption or discontinuation. The different type of antibody (humanized for pembrolizumab and human for nivolumab) may carry a different immunogenicity profile which is to be studied. This difference cannot be explained by PK properties which are very similar between the two antibodies.

Three cases of immune-induced pneumonitis were observed in our cohort. This is less than the safety data of the monocentric Higashiyama cohort (11) who found 24.4% of pneumonitis with grade 2 or more in 9 patients. The discrepancies between their study and our cohort have been discussed previously (22). It might be explained because we conducted a multicentric recruitment evaluating both nivolumab and pembrolizumab unlike Higashiyama *et al*. Besides, ethnicity might have play a role in the difference observed, considering Asian origin frequently associated with an increase incidence of lung interstitial disease (23). Our reassuring data concerning pneumonitis are also highlighted in the Dubé-Pelletier *et al.* cohort

(21), with less pneumonitis with the Q6W regimen: 6 (8%) patients in the Q6W group *vs.* 9 (11%) patients in the Q3W group.

If we have a look at the extrathoracic indications of ICIs, the KEYNOTE-555 (24) trial in melanoma finding a benefit-risk profile for pembrolizumab 400 mg Q6W regimen consistent with that of 200 mg or 2 mg/kg Q3W regimens are in line with the literature in NSCLC.

Our study has some limitations notably due to its retrospective nature. irAES were collected based on medical files reported by the physicians during standard care, that might underestimate lower grade toxicities. However, this did not result in an increased rate of grade 3 or more toxicities, and it is therefore acceptable for the real-life application. In our cohort, seven patients underwent initial chemo-immunotherapy. Four experienced AEs during immunotherapy (SD or DD). None discontinued treatment due to toxicity. All adverse effects were attributed to immunotherapy by the attending physician based on timing (after 4 cycles of chemotherapy) and type of AE (cytolysis, arthralgias, and pruritus). Concerning efficacy, these seven patients received their first DD of immunotherapy during maintenance. Three discontinued the DD due to progression at 4, 10, and 1 month post-switch, respectively. Overall, the inclusion of patients initially treated with chemo-immunotherapy before the DD switch in our cohort is highly unlikely to affect our results. There was also a potential selection bias for patients receiving DD because it was started at the discretion of the referring physician. There is a high proportion of PD-L1 TPS ≥50% in our population, but it is in line with French regulatory authorization in this population. Finally, Performance Status data are missing whereas we know it as an impact on safety and efficacy of ICIs.

Despite these limitations, our study had some strengths. The primary outcome of TDDF has been chosen because it's a pragmatic end point for real-world evidence studies which as the potential to accurately capture safety and efficacy (25). The multicentric design minimize the bias linked to the heterogeneities of practice from one center to another. With a very few exclusion criteria, we built a representative cohort of patients treated in the real life setting with a long follow-up (median of 23 months).

Conclusions

Our multicentric cohort supports the feasibility of pembrolizumab Q6W and nivolumab Q4W for patients with advanced NSCLC. Our results are consistent with most of the real-life studies available, including reassuring safety data. Those new extended interval dosing strategies might improve flexibility for patients and their physicians. Further randomized control trials are needed to firmly establish the equivalence of those new schedules.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-141/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-141/dss

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-141/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-141/coif). H.L. receives honoraria, participation on Advisory Board and support for meeting travel from Roche, MSD, Bristol Myers Squibb, Astrazeneca, Sanofi. G.D.C. reports participation on a Data Safety Monitoring Board or Advisory Board for MSD, BMS, Roche, Astrazeneca, Takeda and Sanofi and support for attending meetings by Pfizer. C.R. reports consulting fees from Astrazeneca, MSD, Takeda and BMS. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the ethics committee of Rennes University Hospital (CHU Pontchaillou) on March 04, 2022 (No. 22.41) and informed consent was taken from all the patients.

Open Access Statement: This is an Open Access article

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Supplementary

Table S1 Causes of double-dose failure according to PD-L1 status, anti-PD-1 antibody

Variable	Other*	Progression	Toxicity	P
Cause of failure according to PD-L1 status, n (%)	13	30	15	0.0114 (F)
<50%	2 (15.4%)	17 (56.7%)	3 (20.0%)	
≥50%	11 (84.6%)	13 (43.3%)	12 (80.0%)	
Cause of failure according to anti-PD-1 antibody, n (%)	14	35	19	0.2060 (K)
Nivolumab	4 (28.6%)	18 (51.4%)	6 (31.6%)	
Pembrolizumab	10 (71.4%)	17 (48.6%)	13 (68.4%)	

Qualitative results are expressed as: numbers (%) for each modality and the following tests were used: Chi2 (K) or Fisher (F) tests. *, other: patient/clinician choice, death unrelated to toxicity, change of referral centre. PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein 1.

Table S2 Overall immune-related adverse events (irAE)

Variable	Standard dose (n=111)		Double-dose (n=117)*	
	Grade 1–2	Grade ≥3	Grade 1–2	Grade ≥3
Skin	44 (39.3%)	0 (0.0%)	34 (29.1%)	0 (0.0%)
Thyroid	27 (24.1%)	0 (0.0%)	14 (12.0%)	0 (0.0%)
Musculoskeletal	18 (16.1%)	0 (0.0%)	13 (11.1%)	0 (0.0%)
Gastrointestinal	14 (12.5%)	1 (0.9%)	11 (9.4%)	2 (1.7%)
Hepatitis	3 (2.7%)	1 (0.9%)	3 (2.6%)	0 (0.0%)
Renal dysfunction	3 (2.7%)	0 (0.0%)	2 (1.7%)	0 (0.0%)
Pneumonitis	1 (0.9%)	1 (0.9%)	1 (0.9%)	2 (1.7%)
Adrenal dysfunction	2 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Anemia	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)
Hypophysitis	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Neuropathy	1 (0.9%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Pericarditis	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

*, n=111 for simple dose; n=117 double-dose (6 patients started from the outset with double-dose).

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Table S3 Toxicity under extended-interval regimen according to different variables

Variable	No toxicity	Toxicity (any grades)	P
PD-L1	40 (9)	56 (12)	0.1180 (K)
<50%	16 (40.0%)	14 (25.0%)	
≥50%	24 (60.0%)	42 (75.0%)	
Anti-PD-1 antibody	49 (0)	68 (0)	0.0311 (K)
Nivolumab	24 (49.0%)	20 (29.4%)	
Pembrolizumab	25 (51.0%)	48 (70.6%)	
Smoking status	43 (6)	64 (4)	0.0209 (K)
Current	20 (46.5%)	16 (25.0%)	
Former	23 (53.5%)	48 (75.0%)	
Year of birth*	49 (0)	68 (0)	0.98 (K)
<1952	23 (47.0%)	32 (47.0%)	
≥1952	26 (53.0%)	36 (53.0%)	
Gender	49 (0)	68 (0)	0.84 (K)
Female	15 (31.0%)	22 (32.0%)	
Male	34 (69.0%)	46 (63.0%)	
Histology	49 (0)	68 (0)	0.20 (K)
Adenocarcinoma	39 (79.0%)	47 (69.0%)	
Other**	10 (21.0%)	21 (31.0%)	

Qualitative results are expressed as: total number (missing numbers), numbers (%) for each modality and the following tests were used: Chi^2 (K) or Fisher (F) tests. *, median year of birth in the cohort: 1952; **, squamous cell carcinoma; undifferentiated carcinoma. PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein 1.

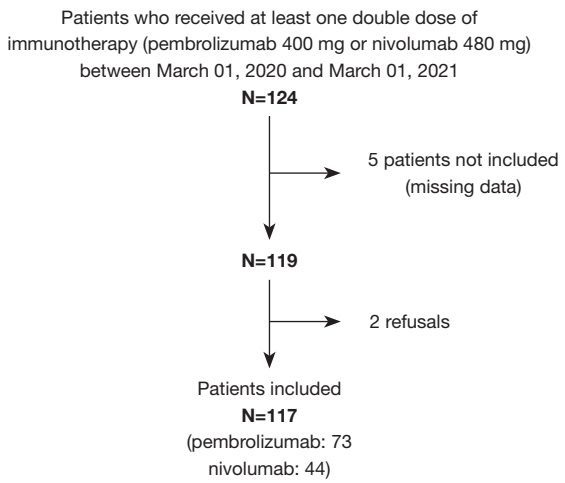

Figure S1 Flow chart of IDEE (Immunothérapie Double dose Etendue: Experience bretonne) Study.

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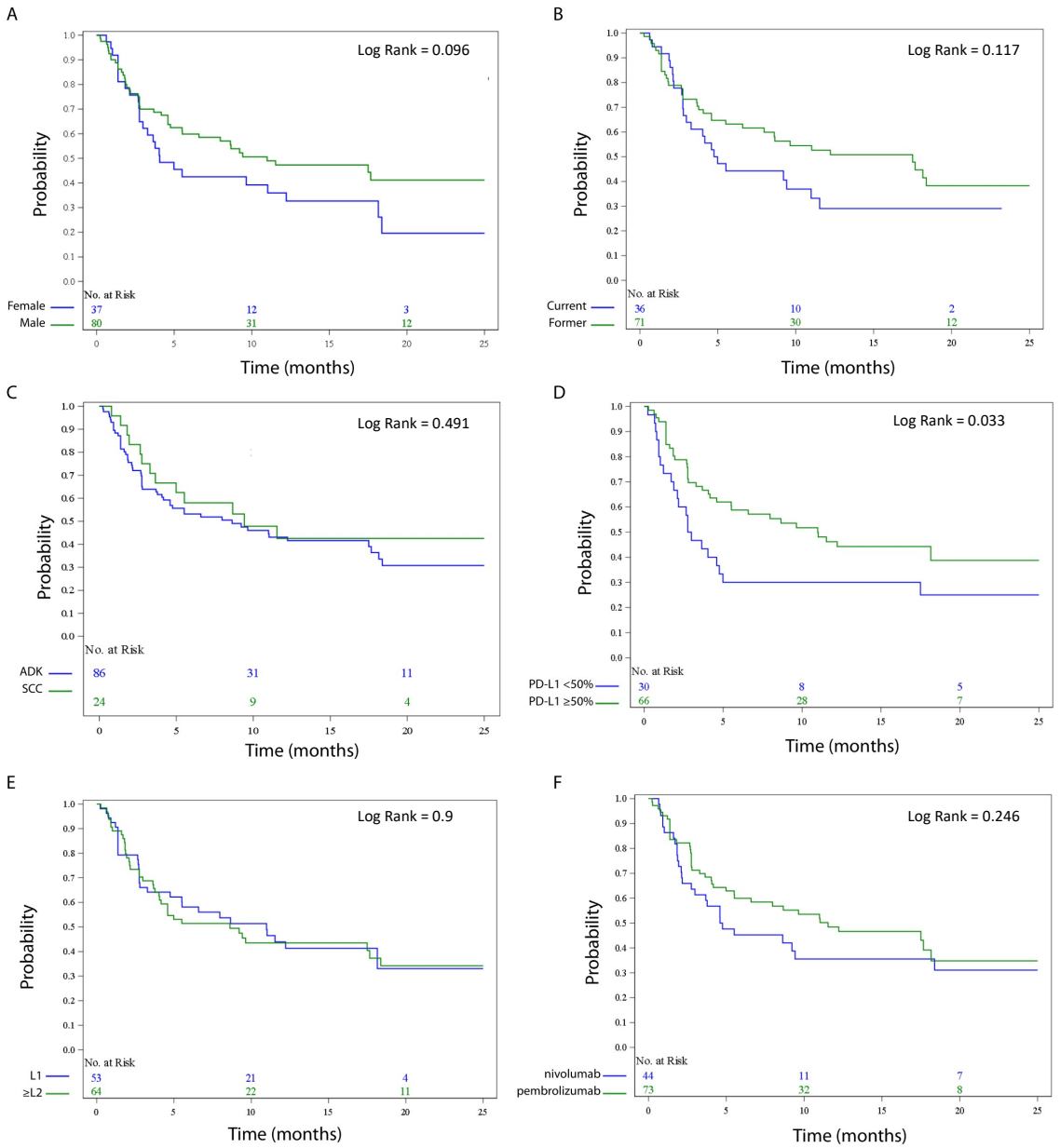

Figure S2 Time to double-dose treatment failure according to subgroup analysis. (A) TDDF according gender; (B) TDDF according smoking history; (C) TDDF according pathology subtype (ADK: adenocarcinoma; SCC: squamous cell carcinoma); (D) TDDF according PD-L1 tumor propensity score; (E) TDDF according line of treatment (L1: first line; ≥L2: 2 lines or more); (F) TDDF according anti-PD-1 antibody. TDDF, time to double-dose treatment failure; PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein 1.

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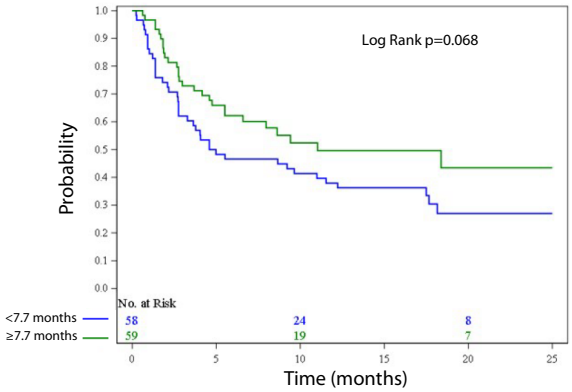

Figure S3 Time to double-dose treatment failure according to median prior exposition to immunotherapy.

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