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.

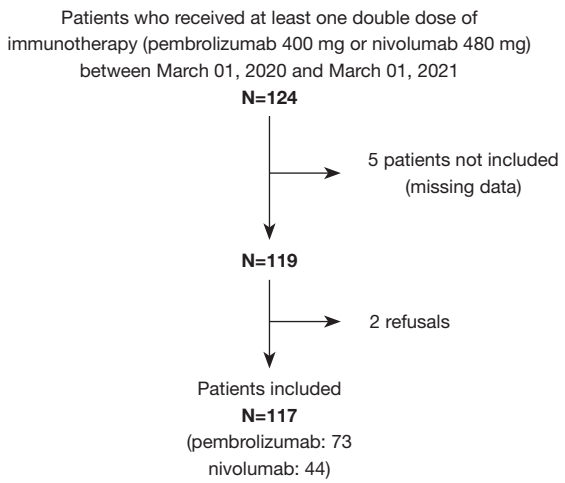

Figure S1 Flow chart of IDEE (Immunothérapie Double dose Etendue: Experience bretonne) Study.

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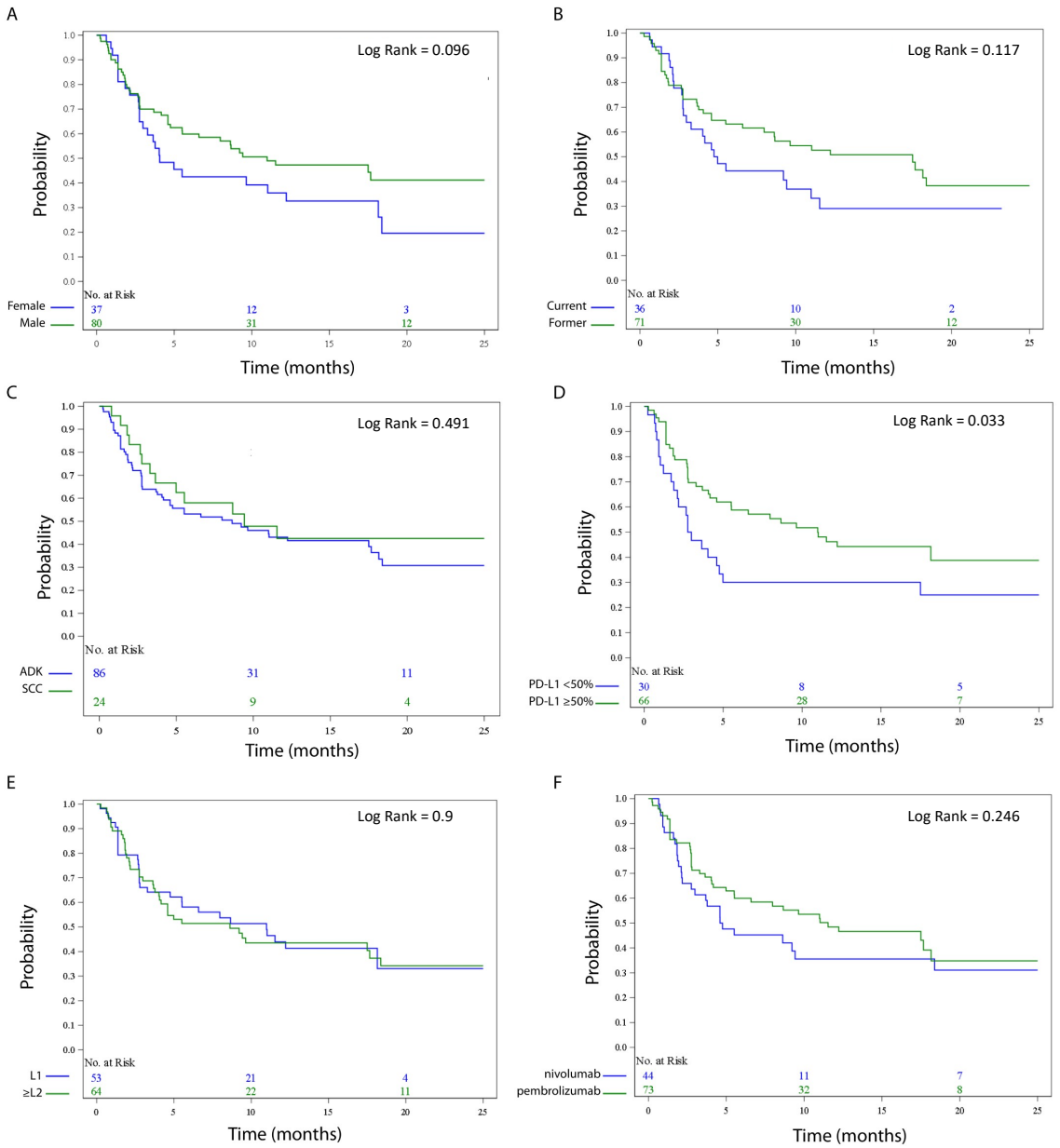

Figure S2 Time to double-dose treatment failure according to subgroup analysis. (A) TDDF according gender; (B) TDDF according smoking history; (C) TDDF according pathology subtype (ADK: adenocarcinoma; SCC: squamous cell carcinoma); (D) TDDF according PD-L1 tumor propensity score; (E) TDDF according 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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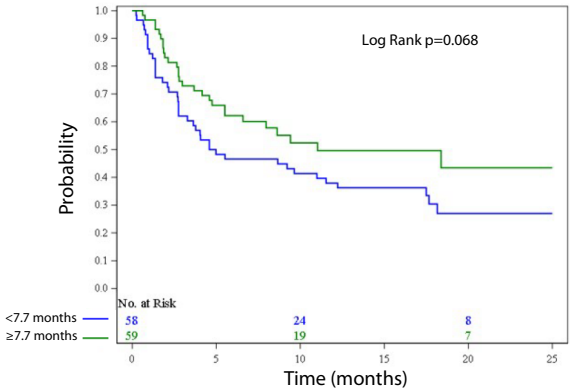

Figure S3 Time to double-dose treatment failure according to median prior exposition to immunotherapy.

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