Impact of pembrolizumab treatment duration on overall survival and prognostic factors in advanced non-small cell lung cancer: a nationwide retrospective cohort study

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Summary

Background The efficacy of front-line pembrolizumab has been established in studies that limit treatment duration to 2 years, but decision to stop pembrolizumab after 2 years is often at physician's discretion. ATHENA is a retrospective cohort study using a comprehensive administrative database aimed firstly at exploring the optimal duration of pembrolizumab and secondly real-life prognosis factors in patients with advanced non-small cell lung cancer (NSCLC).

Methods Using the French National Health Insurance database (SNDS), we identified patients with incident lung cancer in France from 2015 to 2022. Treatments and patients' characteristics were extracted or inferred from hospital, outpatient care, pharmacy delivery reports. The duration's hazard ratio (HR) was estimated with Cox model weighted by inverse of propensity score to account for confounding. Prognostics factors in first line population were identified with Cox model selected by a LASSO procedure.

Findings 391,106 patients with lung cancer were identified, of whom 43,359 received up-front pembrolizumab for an advanced disease. There were 67% (29,040/43,359) of male and the median age at diagnosis was 65 years old. After a median follow-up time of 25.9 months (min–max, [0–97.6]), the median overall survival (OS) after pembrolizumab initiation in first line was 15.7 [CI 95, 15.3–16.0] months. In multivariable analysis, several covariables were independently associated with worse OS, including male sex with chemo-immunotherapy, age, hospital category, high deprivation index, inpatient hospitalization for first pembrolizumab, and history of diabetes, diuretic, beta blocker, painkiller prescription. At landmark time of 29 months after pembrolizumab initiation, continuation beyond 2 years was not associated with better OS than a fixed 2-year treatment, HR = 0.97 [0.75–1.26] p = 0.95.

Interpretation This study supports the notion that stopping pembrolizumab after 2 years could be safe for patients with advanced NSCLC. However, because observational studies are prone to confounding and selection bias, causality cannot be affirmed.

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Keywords: Pembrolizumab; NSCLC; Cohort; Real-life data; IPTW

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Research in context

Evidence before this study

Evidence from clinical trials is necessary for drug approval, but real-world data provide useful information that can differ from clinical trials. We searched PubMed from the inception of the database until May 2024 using the search terms ("immunotherapy" or "immune checkpoint inhibitor" or "pembrolizumab") and "prognostic factor" and "real-world" and ("advanced lung cancer" OR "advanced non-small cell lung cancer"). Few studies had sample sizes of several hundred or thousand patients and most of them were retrospective monocentric studies with limited sample sizes that identified lower survival rates in real-world settings than in clinical trials. Factors such as PD-L1, high number of metastatic sites, smoking status, performance status, mutational status, squamous histology and steroid use were reported. Effect of sex was conflicting and not always reported.

The decision to continue or stop pembrolizumab after two years remains unclear for many clinicians. We searched PubMed from the inception of the database until May 2024 using the search terms ("immunotherapy" or "immune checkpoint inhibitor" or "pembrolizumab") and "duration" and ("advanced lung cancer" and "advanced non-small cell lung cancer"). One American retrospective study suggested that stopping pembrolizumab after 2 years was safe.

Added value of this study

This study offers a nearly comprehensive analysis of the French population, representing the largest real-world dataset on pembrolizumab treatment, comprising 43,359 lung cancer patients.

For the first time, a history of diabetes, beta blocker usage, and prior prescription of painkillers are associated with a higher risk of death in this population.

Additionally, for the first time, the volume of patients treated with pembrolizumab at a center was associated with survival, with treatment in low-volume centers being associated with a higher risk of death.

It confirms the safety of a fixed 2-year duration of pembrolizumab treatment.

Implications of all the available evidence

Public health policies should take into account the volume of patients treated at each center.

De-escalation trials for long responders to pembrolizumab should be encouraged.

Introduction

Lung cancer is the leading cause of cancer-related deaths in the United States (US) and European countries,[1] with a growing incidence due to the smoking epidemic, especially among women.[2] In France, it was estimated to be responsible for 33,000 deaths in 2018. Immune checkpoint blockers (ICB), such as pembrolizumab, nivolumab, atezolizumab, or durvalumab, were developed in the 2010s and have revolutionized the treatment and prognosis of advanced non-small cell lung cancer (NSCLC).[3] Thanks to these immunotherapies, targeted therapies, and a decrease in incidence, NSCLC mortality in the US has dropped by 9% over approximately fifteen years.[4] The first checkpoint blocker approved by the European Medicines Agency (EMA) for untreated patients with advanced NSCLC is pembrolizumab. Pembrolizumab is indicated for patients with advanced NSCLC and high PD-L1 expression (≥50%) since January 2017[5] and for patients with advanced NSCLC in combination with chemotherapy since February 2019.[6] In France, pembrolizumab is the only ICB reimbursed in untreated advanced NSCLC. Patients with high PD-L1 untreated advanced NSCLC can receive pembrolizumab alone or with chemotherapy, whereas patients with PD-L1<50% must receive pembrolizumab plus chemotherapy. The outcomes from clinical trials have been validated with 5 years of follow-up. In KEYNOTE-024, the median survival for pembrolizumab alone in high PD-L1 NSCLC was 26 months, with a 5-year survival rate of 31.9%.[7] In KEYNOTE-189, the median survival for pembrolizumab plus chemotherapy in nonsquamous NSCLC was 22 months, with a 5-year survival rate of 19.4%,[8] and in KEYNOTE-407, the median survival for pembrolizumab plus chemotherapy in squamous NSCLC was 17 months, with a 5-year survival rate of 18.4%.[9] However, clinical trials do not always represent the reality of everyday practice, with frequent underrepresentation of elderly patients, patients with altered general status, and severe comorbidities,[10] leading to inferior survival in real-world settings.[11] For example, the median age in KEYNOTE-024 was 64.5 years old, whereas the median age at diagnosis is nearly 70 years old and increasing. A recent study showed that trial-ineligible metastatic NSCLC patients treated with pembrolizumab monotherapy had significantly worse outcomes than trial-eligible patients.[12] Another difference between clinical trials and everyday practice is treatment duration. In KEYNOTE-189, the maximal duration of pembrolizumab was 2 years (35 cycles), whereas the EMA authorized continuation of pembrolizumab after this date. In clinical practice, physicians may be reluctant to stop an active therapy for patients with metastatic disease. Among patients who completed the full 35 cycles and stopped pembrolizumab, 18.6% died within 3 years after the last cycle,[7] but it is unknown whether these recurrences would have occurred regardless of pembrolizumab intake. On the other hand, continuing pembrolizumab indefinitely potentially induces adverse events and

certainly induces financial toxicity.[13] Recently, Sun et al. performed a retrospective analysis on 706 NSCLC patients treated with frontline immunotherapy that did not find a difference in overall survival (OS) between stopping or continuing at 2 years.[14]

The French National Health Data System (SNDS) is a database that includes anonymous data of reimbursed claims from insurance plans linked to hospital discharge summaries, the national death registry, and covers 98.8% of the French population from birth (or immigration) to death (or emigration).[15] Its exploitation allows for the addressing of various research problems, especially in pharmacoepidemiology.[16–18] Using the SNDS, we created the largest real-world data cohort ever published on NSCLC patients treated with pembrolizumab, with two objectives: describe the real-world survival outcomes and prognostic factors of these patients and to assess the effect of continuing pembrolizumab after 2 years of treatment.

Methods

Data sources

The SNDS includes demographic and medical data on most outpatient services reimbursed by the National Health Insurance since 2006, encompassing prescribed drugs, patient eligibility for full reimbursement of health care expenses related to specific costly or long-term diseases (LTD), and physician visits. It also comprises diagnoses related to hospital admissions and procedures performed during hospitalization. Data collection for reimbursement is nearly comprehensive and automatic, facilitated by an insurance card with an electronic chip owned by all adults legally residing in France. This card is presented when a patient picks up a drug at a pharmacy or is admitted to the hospital. Prescription fills are coded according to the Anatomical Therapeutic Chemical (ATC) classification, diagnoses are registered according to the International Classification of Diseases, 10th Revision (ICD-10), and main medical and surgical procedures are coded according to the Common Classification of Medical Procedures (CCAM). As it is a reimbursement database, clinical information such as the content of pathology reports or tumor stage is not available, but it can sometimes be extrapolated from patterns of care reimbursed to patients.

Study population

The ATHENA cohort was developed from the French National Health Data System (SNDS) and included all patients with an incident diagnosis of lung cancer in France from January 1st, 2015, to December 31, 2022. Inclusion criteria were any hospitalization or any expenses for a long-term condition identified by ICD-10 lung cancer codes (C33, C34, D02.1, and D02.2) and being older than 18 years old. Exclusion criteria were at least one onset of a hospitalization with a lung cancer code during the 5 previous years preceding the study period and same-sex twins or changes in insurance plans (because their identifiers are not always unique and therefore a source of errors). Patients with another cancer diagnosis, identified the previous year prior to the date index, were also excluded to avoid misclassification bias (lung metastasis of another cancer coded as lung cancer). The index date was defined as the first occurrence of a lung cancer code.

Outcomes and covariates

Demographic data included age (as a categorical variable), sex and deprivation index.[19] Comorbidities included severe myocardial infarction, severe heart failure, severe cerebrovascular disease, severe peripheral artery disease, chronic respiratory disease, diabetes, severe kidney failure, severe hepatopathy, other cancer, renin-angiotensin-aldosterone system inhibitors (RASI) prescription, antiplatelet agent prescription, diuretic prescription, beta-blocker prescription, non-steroidal anti-inflammatory (NSAI) prescription, antipsychotic prescription, antidepressant prescription, lipid-lowering drug prescription, thyroid hormone substitute prescription, painkiller prescription, opiate substitution therapy prescription. These variables were measured up to 12 months before diagnosis and the 6 months before immunotherapy stop (between 16 and 22 months after pembrolizumab start, Supplementary Figure S1). Pembrolizumab and pemetrexed are reimbursed as onerous drugs, so all their infusions are available in SNDS. Chemo-immunotherapy vs immunotherapy alone and first-line immunotherapy are not subject to specific reimbursement, so they were inferred from algorithms. Other related treatment variables were the duration of the first hospitalization (outpatient vs inpatient hospitalization), radiation therapy during the first 4 months of treatment, antiepileptic prescription during fill the first 4 months of treatment, exposure to antibiotics, steroids, or proton-pump inhibitors (PPI) at immunotherapy start (1 month before to 1 month after), and the type of hospital for the first pembrolizumab infusion. ECOG and PD-L1 tumor status were not available, but patients with altered performance status tends to receive treatment in inpatient clinics and low PDL1 patients receive pembrolizumab plus chemotherapy. Thus, first pembrolizumab in inpatient clinics and chemo-immunotherapy were used as imperfect proxy for those variables. Centers were ranked by the average volume of new patients treated with pembrolizumab per year. High-volume centers were defined as the top 10% by volume, and low-volume centers as the bottom 60%. This corresponded to treating, on average, at least 32 new patients per year with pembrolizumab for high-volume centers, 11 to 31 new patients per year for intermediate-volume centers, and 10 or fewer new patients per year for low-volume centers. Detailed definitions are available in Supplementary Table S1.

Statistical analysis

Categorical variables were described by proportions, and numerical variables by median (med) and interquartile range (IQR). Median follow-up was estimated using the inverse Kaplan–Meier method. Time-to-event endpoints were estimated using the Kaplan–Meier method. Unless specified otherwise, overall survival was defined as the time between pembrolizumab start and death from any cause. Patients without events were censored at last care reimbursement date. The cut-off date for the analysis was June 30, 2023.

Duration analysis

The population of interest was the patients with at least 22 months of pembrolizumab (Supplementary Figure S1). We defined stopping pembrolizumab as having the last infusion date between 22 and 26 months after treatment start (2 years with a 2-month margin). If patients had two infusion dates over 6 months apart, we considered that they stopped pembrolizumab at the earliest of the two infusion dates. If patients had a chemotherapy session within 2 months after the last pembrolizumab infusion, we considered it as a stop motivated by progression, and they were excluded. This 2-month gap was considered given that the normal gap between two pembrolizumab infusions is 3–6 weeks, and a new systemic treatment is usually initiated a few weeks after progression discovery. To account for potential confounding, we used a propensity score analysis. We first estimate the propensity score for each patient, or the probability of pembrolizumab continuation, with a multivariable logistic regression on chemo-immunotherapy, sex, age at diagnosis, year of diagnosis, type of center, deprivation index, first pembrolizumab in inpatient hospitalization, antibiotics at first pembrolizumab, PPI at first pembrolizumab, steroids at first pembrolizumab, radiotherapy at baseline, radiotherapy at stop, antiepileptic at baseline, antiepileptic at stop, chronic respiratory disease at stop, diabetes at stop, antiplatelet drug at stop, anticoagulant at stop, diuretic at stop, beta blocker at stop, lipid lowering drug at stop, non-steroidal anti-inflammatory at stop, painkiller at stop, antipsychotic at stop, antidepressant at stop and thyroid hormone replacement drug at stop. These covariables were chosen because they were either potential confounders of the relationship between pembrolizumab continuation and survival or risk factors for death according to clinical knowledge. These propensity scores were then used to compute stabilized weights for each patient (with additional truncation of the 1% most extreme weights). Finally, a Cox proportional hazards model, weighted with these stabilized weights was used to estimate the hazard ratio of pembrolizumab continuation vs pembrolizumab discontinuation.[20] A robust variance sandwich estimator was used to compute 95% confidence intervals. Finally, to prevent immortal time bias, given the hypothesis that patients may have stopped pembrolizumab because they were dying, we applied a 3-month landmark, meaning only patients alive at 29 months were analyzed. Proportional hazards assumption was verified with Schoenfeld residuals. Positivity assumption was verified with weight's plotting (Suplemmentary Figure S2) and conditional exchangeability assumption after propensity score weighting was verified with absolute standardized mean differences (ASMD) depicted in a love plot (Supplementary Figure S3). A characteristic with an ASMD between treatment arms lower than 0.1 was deemed well balanced, as proposed elsewhere.[21] We performed several sensitivity analyses: we changed the timepoint of landmark: 1, 3, 6 months; for patients who continued pembrolizumab after 2 years, we performed a descriptive exploratory analysis between those receiving infusion every three weeks (mean interval between infusion $\leq$ 31.5 days) and those receiving infusion every six weeks (mean interval between infusion >31.5 days); for patients who were still alive at 29 months, we performed an exploratory analysis of the causes of death. Data were not available after 2021. We accounted for competing risk and estimated cumulative incidence functions of death by lung cancer vs death by other cause.

Prognostic analysis

The population of interest was all patients treated by pembrolizumab, alone or with chemotherapy in advanced first line. All database covariable described in patient's characteristics were included in a LASSO regression model to predict death probability. A 10-fold cross-validation was used to identify the shrinkage penalty producing the lowest test mean squared error. Selected covariates were then included in a multivariable Cox proportional hazards model. To evaluate the quantity of potential confounding, we tested the survival impact of artificial tears prescription as a negative control. To avoid potential immortal-time bias caused by our definition, survival curves of chemo-immunotherapy vs immunotherapy are presented with a 2-month landmark.

All statistical tests were 2-tailed, with a type I error of 5%. To account test multiplicity, all p-value tested were corrected with Benjamini-Hochberg method.[22] Statistical analyses were performed with SAS (version 9.4) and RStudio (version 4.1.2).

Role of funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Regulatory approval and ethical aspects

Gustave Roussy Cancer Center is certified to have a permanent regulatory access to SNDS, so this study did not require specific authorization form the French data

protection authority. The SNDS is a strictly anonymous database, so informed consent was not needed. This study has been declared prior to data extraction on the Health Data Hub online platform (No. F20230713113749). It followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Results

First-line population

Between 2015 and 2022, 546,251 insurance recipients with a lung cancer code were identified. We excluded 8647 recipients because they were same-sex twins or changed insurance plans, 146,223 prevalent lung cancer cases and 275 patients under 18 years old. This left 391,106 patients with incident lung cancer, of whom 50,083 received treatment with pembrolizumab. After excluding patients receiving later-line pembrolizumab and those diagnosed with another concomitant cancer, 43,359 patients received pembrolizumab as first-line treatment. Among them, 23,668 died within the first 2 years, 3282 stopped pembrolizumab early (before 2 years of treatments, 13,195 were right-censored, meaning they were alive but had less than 2 years of follow-up and finally, 3214 patients were available for analysis of treatment duration beyond 2 years (Fig. 1). In the first line population, the median age at diagnosis was 65 years old [IQR: 58–71], with 67.0% being men and 61.3% receiving chemo-immunotherapy and the most common prescribed co-medications were painkillers (74.9%), steroids at pembrolizumab initiation (55.6%), PPI at pembrolizumab initiation (45.2%), lipid lowering drugs (35.3%), renin angiotensin system inhibitors prescriptions (34.5%) and non-steroidal non-inflammatory drugs (32.5%) (Table 1).

Overall survival and prognostic factors in first-line population

After a median follow-up time of 25.9 months [25.6–26.2], the median OS of all pembrolizumab patients was 15.3 [15.1–15.6] months. The median OS of pembrolizumab in first line was 15.7 [15.3–16.0] months, compared to 13.7 [13.0–14.1] months for later lines (Supplementary Figure S4). In the first line pembrolizumab population, overall survival rates were as follows: 56.7% [55.8–56.7] at 1 year, 39.7% [39.2–40.3] at 2 years, 30.9% [30.4–31.5] at 3 years, 25.9% [25.2–26.5] at 4 years and 22.3% [21.6–23.1] at 5 years (Supplementary Table S2). After applying a 2-month landmark, the median OS for pembrolizumab alone was 22.4 [21.5–23.1] months, compared to 19.9 [19.5–20.5] months for pembrolizumab plus chemotherapy (Fig. 2A). The median OS for first line pembrolizumab was 18.9 [18.2–19.6] months in women vs 14.5 [14.1–14.8] months in men (Fig. 2B). After applying

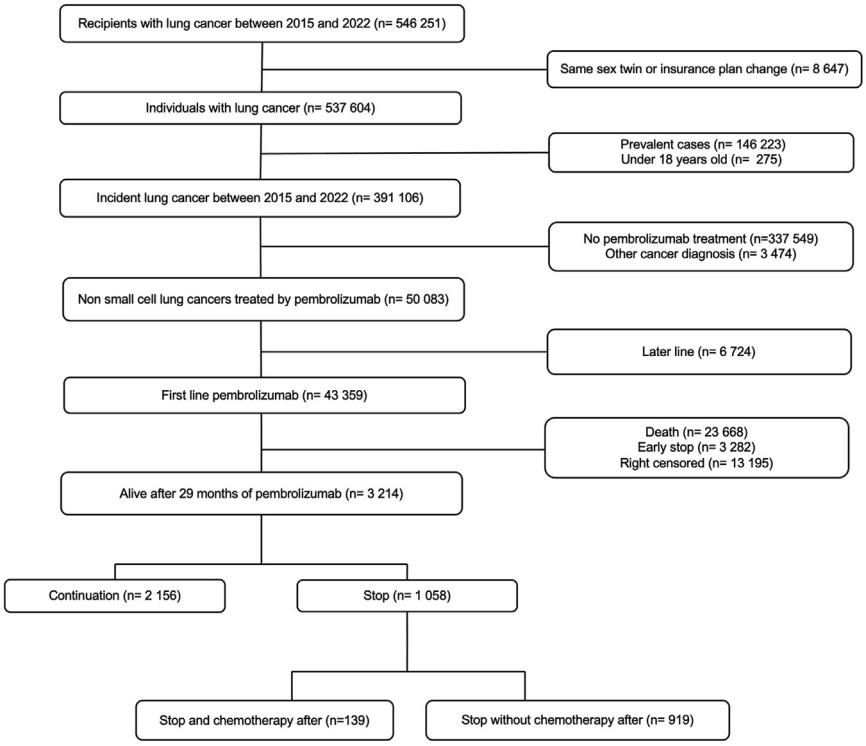

Fig. 1: **Flow chart**.

	Continuation (n = 2156)	Stop (n = 919)	Alive at 29 months (n = 3075)	First line pembrolizumab (n = 43,359)
Male sex (n, %)	1403 (65.1%)	563 (61.2%)	1966 (63.9%)	29,040 (67.0%)
Year of diagnosis (n, %)				
2015–16	75 (3.5%)	30 (3.3%)	105 (3.4%)	937 (2.2%)
2017–18	679 (31.5%)	230 (25.0%)	909 (29.6%)	6039 (13.9%)
2019–20	1388 (64.4%)	647 (70.4%)	2035 (66.2%)	15,346 (35.4%)
2021–22	14 (0.6%)	12 (1.3%)	26 (0.8%)	21,037 (48.5%)
Age at diagnosis (med, IQR)	63 [56–69]	63 [55–69]	63 [56–69]	65 [58–71]
Age category (n, %)				
[18–50)	205 (9.5%)	83 (9.0%)	288 (9.4%)	3001 (6.9%)
[50–60)	605 (28.1%)	254 (27.6%)	859 (27.9%)	9586 (22.1%)
[60–70)	839 (38.9%)	357 (38.8%)	1196 (38.9%)	17,011 (39.2%)
[70–80)	387 (17.9%)	178 (19.4%)	565 (18.4%)	10,935 (25.2%)
[80–91]	120 (5.6%)	47 (5.1%)	167 (5.4%)	2826 (6.5%)
Type of hospital (n, %)				
High volume	851 (39.5%)	533 (58.0%)	1384 (45.0%)	18,708 (43.1%)
Intermediate volume	989 (45.9%)	284 (30.9%)	1273 (41.4%)	18,130 (41.8%)
Low volume	316 (14.6%)	102 (11.1%)	418 (13.6%)	6521 (15.1%)
Deprivation index (n,%)				
First quantile	310 (14.4%)	146 (15.9%)	456 (14.8%)	6362 (14.7%)
Second quantile	401 (18.6%)	178 (19.4%)	579 (18.8%)	7718 (17.8%)
Third quantile	402 (18.6%)	162 (17.6%)	564 (18.3%)	7872 (18.1%)
Fourth quantile	419 (19.4%)	167 (18.2%)	586 (19.1%)	8302 (19.1%)
Fifth quantile	403 (18.7%)	169 (18.4%)	572 (18.6%)	7926 (18.3%)
(NA)	221 (10.2%)	97 (10.5%)	318 (10.3%)	5179 (11.9%)
First pembrolizumab in inpatient hospitalization (n, %)	503 (23.3%)	198 (21.5%)	701 (22.8%)	12,346 (28.5%) 5NA
Chemo-immunotherapy (n, %)	879 (40.8%)	365 (39.7%)	1244 (40.4%)	26,599 (61.3%)
With pemetrexed (n, %)	697 (32.3%)	294 (32.0%)	991 (32.2%)	20,197 (46.6%)
Radiation therapy at baseline (n, %)	316 (14.6%)	137 (14.9%)	453 (14.7%)	6888 (15.9%)
Antiepileptic at baseline (n, %)	195 (9.0%)	75 (8.2%)	270 (8.8%)	3064 (7.1%)
Antibiotics at baseline (n, %)	550 (25.5%)	256 (27.8%)	806 (26.2%)	11,262 (26.0%)
Proton pump inhibitors at baseline (n, %)	925 (42.9%)	389 (42.3%)	1314 (42.7%)	19,591 (45.2%)
Steroid at baseline (n, %)	1017 (47.2%)	434 (47.2%)	1451 (47.2%)	24,097 (55.6%)
Severe myocardial infarction at diagnosis (n, %)	13 (0.6%)	4 (0.4%)	17 (0.5%)	331 (0.8%)
Severe heart failure at diagnosis (n, %)	6 (0.3%)	9 (1.0%)	15 (0.5%)	315 (0.7%)
Severe cerebrovascular disease at diagnosis (n, %)	20 (0.9%)	16 (1.7%)	36 (1.2%)	532 (1.2%)
Severe occlusive arteriopathy of the lower limbs at diagnosis (n, %)	14 (0.6%)	4 (0.4%)	18 (0.6%)	529 (1.2%)
Diabetes at diagnosis (n, %)	234 (10.8%)	89 (9.7%)	323 (10.5%)	5465 (12.6%)
Severe kidney disease at diagnosis (n, %)	7 (0.3%)	2 (0.2%)	9 (0.3%)	103 (0.2%)
Severe liver disease at diagnosis (n, %)	1 (0.05%)	0 (0%)	1 (0.03%)	16 (0.04%)
Renin Angiotensin System Inhibitor at diagnosis (n, %)	680 (31.5%)	268 (29.2%)	948 (30.8%)	14,951 (34.5%)
Antiplatelet at diagnosis (n, %)	600 (27.8%)	271 (29.5%)	871 (28.3%)	12,790 (29.5%)
Anticoagulant at diagnosis (n, %)	245 (11.4%)	107 (11.6%)	352 (11.4%)	6110 (14.1%)
Diuretic at diagnosis (n, %)	197 (9.1%)	81 (8.8%)	278 (9.0%)	4735 (10.9%)
Beta blocker at diagnosis (n, %)	374 (17.3%)	172 (18.7%)	546 (17.7%)	9185 (21.2%)
Lipid lowering drug at diagnosis (n, %)	718 (33.3%)	278 (30.2%)	996 (32.4%)	15,301 (35.3%)
Non-steroidal anti-inflammatory at diagnosis (n, %)	759 (35.2%)	303 (33.0%)	1062 (34.5%)	14,098 (32.5%)
Antipsychotic at diagnosis (n, %)	68 (3.1%)	34 (3.7%)	102 (3.3%)	1329 (3.1%)
Antidepressant at diagnosis (n, %)	327 (15.2%)	140 (15.2%)	467 (15.2%)	6614 (15.2%)
Thyroid hormone replacement drug at diagnosis (n, %)	148 (6.9%)	61 (6.6%)	209 (6.8%)	2961 (6.8%)
Painkiller at diagnosis (n, %)	1594 (73.9%)	658 (71.6%)	2252 (73.2%)	32,485 (74.9%)
Opiate substitute drug at diagnosis (n, %)	22 (1.0%)	8 (0.9%)	30 (1.0%)	339 (0.8%)
Artificial tears at diagnosis (n, %)	71 (3.3%)	28 (3.0%)	99 (3.2%)	1603 (3.7%)
Radiotherapy at stop (n, %)	95 (4.4%)	28 (3.0%)	123 (4.0%)	
Antiepileptic at stop (n, %)	180 (8.3%)	78 (8.5%)	258 (8.4%)	

(Table 1 continues on next page)

	Continuation (n = 2156)	Stop (n = 919)	Alive at 29 months (n = 3075)	First line pembrolizumab (n = 43,359)
(Continued from previous page)				
Severe myocardial infarction at stop (n, %)	2 (0.09%)	4 (0.4%)	6 (0.2%)	
Severe heart failure at stop (n, %)	3 (0.1%)	1 (0.1%)	4 (0.1%)	
Severe cerebrovascular disease at stop (n, %)	8 (0.4%)	2 (0.2%)	10 (0.3%)	
Severe occlusive arteriopathy of the lower limbs at stop (n, %)	15 (0.7%)	7 (0.7%)	22 (0.7%)	
Diabetes at stop (n, %)	253 (11.7%)	100 (10.9%)	353 (11.5%)	
Severe kidney disease at stop (n, %)	7 (0.3%)	5 (0.5%)	12 (0.4%)	
Severe liver disease at stop (n, %)	1 (0.04%)	0 (0%)	1 (0.03%)	
Renin Angiotensin System Inhibitor at stop (n, %)	595 (27.5%)	217 (23.6%)	812 (26.4%)	
Antiplatelet at stop (n, %)	596 (27.6%)	251 (27.3%)	847 (27.5%)	
Anticoagulant at stop (n, %)	482 (22.3%)	187 (20.3%)	669 (21.8%)	
Diuretic at stop (n, %)	241 (11.2%)	94 (10.2%)	335 (10.9%)	
Beta blocker at stop (n, %)	402 (18.6%)	196 (21.3%)	598 (19.4%)	
Lipid lowering drug at stop (n, %)	575 (26.7%)	226 (24.6%)	801 (26.0%)	
Non-steroidal anti-inflammatory at stop (n, %)	209 (9.7%)	84 (9.1%)	293 (9.5%)	
Antipsychotic at stop (n, %)	64 (3.0%)	33 (3.6%)	97 (3.1%)	
Antidepressant at stop (n, %)	327 (15.2%)	171 (18.6%)	498 (16.2%)	
Thyroid hormone replacement drug at stop (n, %)	482 (22.3%)	197 (21.4%)	679 (22.1%)	
Painkiller at stop (n, %)	1344 (62.3%)	580 (63.1%)	1924 (62.6%)	
Opiate substitute drug at stop (n, %)	17 (0.8%)	7 (0.8%)	24 (0.8%)	

Table 1: **Patient's characteristics.**

a 2-month landmark, median OS for pembrolizumab alone was 25.1 [23.6–27.0] months in women vs 21.3 [20.3–22.2] months in men, whereas the median OS for chemo-pembrolizumab was 24.2 [22.9–25.3] months in women vs 18.3 [17.8–18.8] months in men (Fig. 2C). The median OS of pembrolizumab in first line in high-volume centers was 16.8 [16.3–17.4] months, compared to 15.0 [14.6–15.4] months in intermediate volume centers and 14.4 [13.9–15.2] months in low-volume centers (Fig. 2D). The median OS for patients younger than 50 years in first line pembrolizumab population was 18.4 [16.5–20.0] months, compared to 18.3 [17.5–19.5] months in [50–60) years old patients, 16.1 [15.4–16.6] months in [60–70) years old patients, 14.1 [13.7–14.6] months in [70–80) years old patients, 11.7 [10.9–12.4] months in older than 80 years old patients (Supplementary Figure S5).

Several factors independently associated with worsened survival were identified in multivariable analysis (Fig. 3): age over 60 years old, HR = 1.16 [1.09–1.23] p < 0.001; age over 70 years old, HR = 1.26 [1.18–1.35] p < 0.001; age over 80 years old, HR = 1.42 [1.31–1.53] p < 0.001; being diagnosed in 2021–22, HR = 1.12 [1.03–1.22] p = 0.04, being treated in an intermediate volume center, HR = 1.12 [1.08–1.15] p < 0.001; being treated in a low volume center, HR = 1.18 [1.13–1.23] p < 0.001; being in the fourth quantile of deprivation index, HR = 1.09 [1.04–1.13] p = 0.001; being in the fifth quantile of deprivation index, HR = 1.10 [1.05–1.15] p = 0.001; needing hospitalization for first pembrolizumab, HR = 1.73 [1.68–1.79] p < 0.001; a history of diabetes, HR = 1.12 [1.08–1.13] p < 0.001; a history of diuretic prescription, HR = 1.08 [1.03–1.13] p = 0.004; a history of beta blocker prescription, HR = 1.09 [1.05–1.12] p < 0.001; and a history of painkiller prescription, HR = 1.07 [1.03–1.11] p < 0.001. Our negative control, an history of artificial tears prescription, was not associated with survival, HR = 0.99 [0.93–1.07] p = 0.98. There was a significative interaction between sex and chemo-immunotherapy. Hazard ratio for male sex vs female sex in pembrolizumab alone was HR = 1.06 [1.01–1.11] p = 0.05; but hazard ration for male sex vs female sex in pembrolizumab plus chemotherapy group was HR = 1.27 [1.23–1.31] p < 0.001.

Impact of duration

Characteristics of patients who stopped or continued pembrolizumab after 2 years are detailed in Table 1. Before propensity score weighting, their characteristics were well balanced, except for year of diagnosis and patient's volume of center (Supplementary Figure S2). Median duration of pemetrexed was 7.6 months in patients who stopped and 7.6 months in patients who continued. Median number of cycles of pemetrexed was 11.0 in patients who stopped and 10.0 in patients who continued. Patients who continued pembrolizumab after 2 years had a median treatment time of pembrolizumab of 33.2 months. Among the patients alive at the 29-months landmark time, the median follow-up was 41.7 months [41.3–42.4]. In a separated analysis, we studied factors independently associated with the

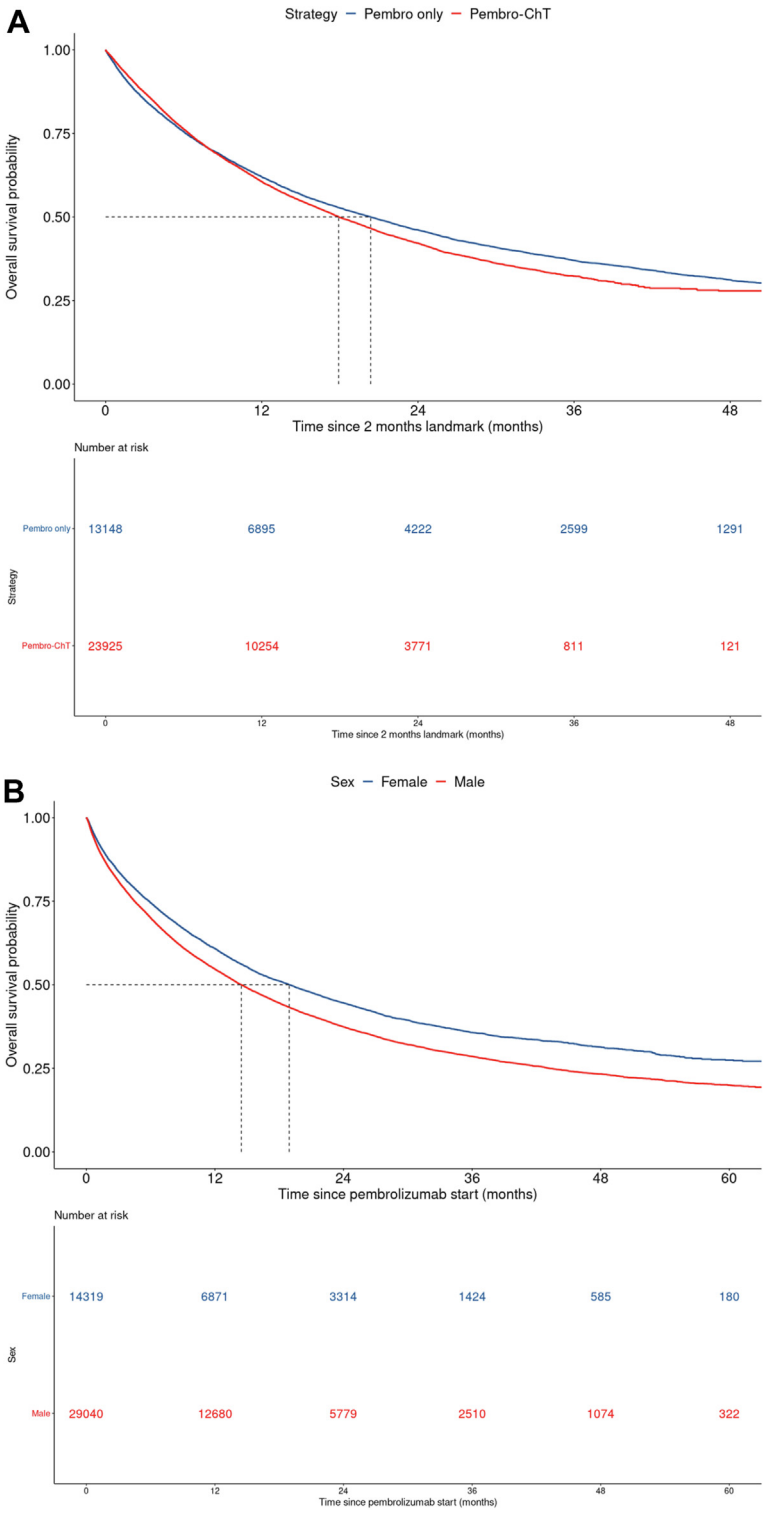

Fig. 2: **A. Overall survival of pembrolizumab by pembrolizumab alone or with chemotherapy. B: Overall survival of pembrolizumab by sex. C: Overall survival of pembrolizumab by sex and chemo-immunotherapy. D: Overall survival of first line pembrolizumab by center category**. A 2-month landmark is performed to avoid immortal time bias for Figure A and C.

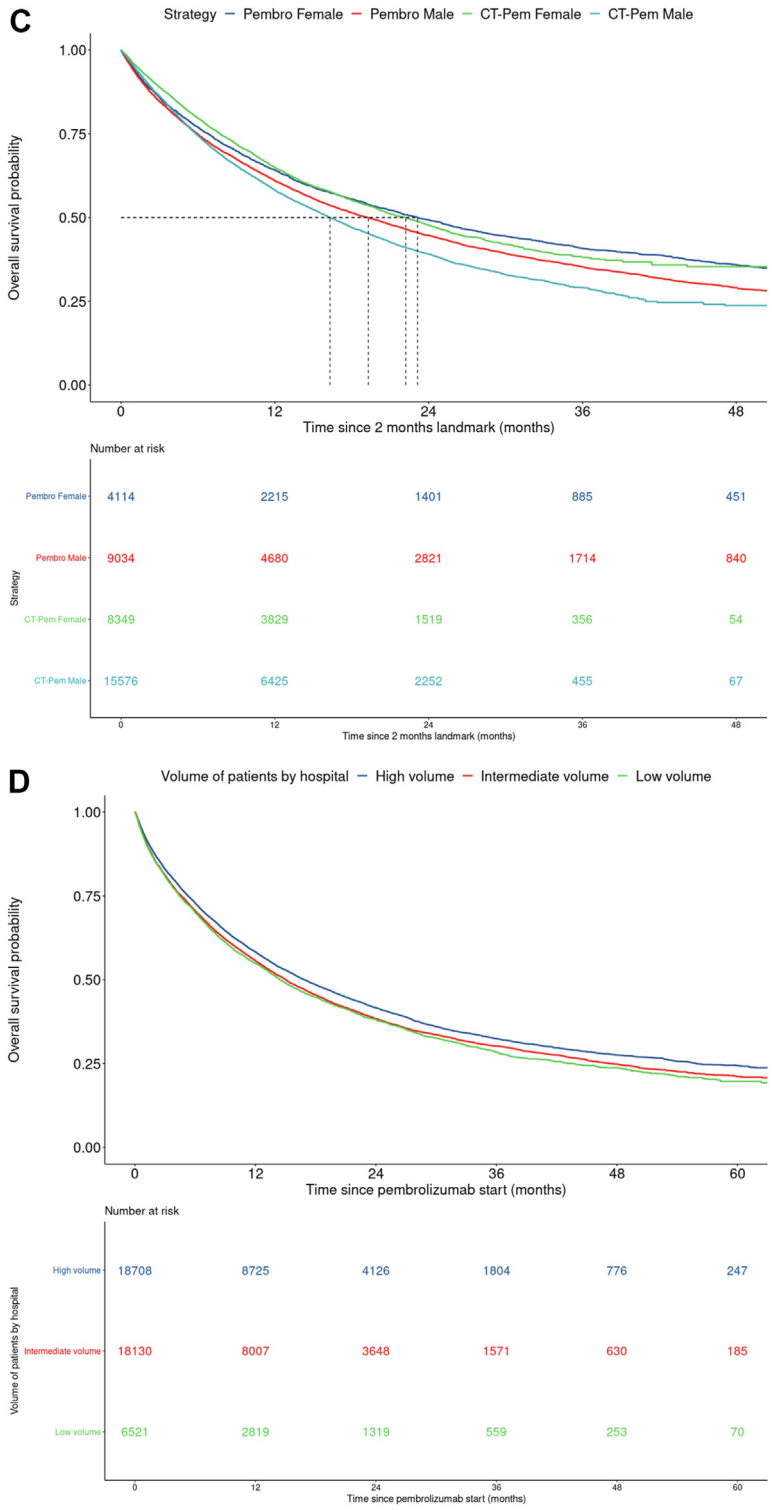

Fig. 2: Continued.

Variable	Number (n=38176)	Adjusted Hazard Ratio (95% CI)	Corrected p-value
Male sex in pembrolizumab only	10266	1.06 [1.01-1.11]	0.05
Male sex in chemo-immunotherapy	15364	1.27 [1.23-1.31]	<0.001 *
Age at diagnosis [50-60) vs [18-50)	8261	1.03 [0.96-1.10]	0.59
Age at diagnosis [60-70) vs [18-50)	14899	1.16 [1.09-1.23]	<0.001 *
Age at diagnosis [70-80) vs [18-50)	9930	1.26 [1.18-1.35]	<0.001 *
Age at diagnosis [80-97) vs [18-50)	2642	1.42 [1.31-1.53]	<0.001 *
Diagnosis in 2017-18 (vs 2015-16)	5461	0.98 [0.90-1.07]	0.79
Diagnosis in 2019-20 (vs 2015-16)	13541	1.08 [0.99-1.18]	0.16
Diagnosis in 2021-22 (vs 2015-16)	18272	1.12 [1.03-1.22]	0.04 *
Intermediate volume center (vs High volume)	16127	1.12 [1.08-1.15]	<0.001 *
Low volume center (vs High volume)	5685	1.18 [1.13-1.23]	<0.001 *
Second quantile of deprivation index vs first	7717	1.04 [0.99-1.09]	0.17
Third quantile of deprivation index vs first	7872	1.05 [1.00-1.10]	0.11
Fourth quantile of deprivation index vs first	8301	1.09 [1.04-1.13]	0.001 *
Fifth quantile of deprivation index vs first	7927	1.10 [1.05-1.15]	0.001 *
First pembrolizumab in full hospitalization	10682	1.73 [1.68-1.79]	<0.001 *
Severe myocardial infarction at diagnosis	289	1.09 [0.94-1.26]	0.45
Severe cerebrovascular disease at diagnosis	462	1.02 [0.91-1.14]	0.87
Chronic respiratory disease at diagnosis	10877	0.98 [0.95-1.01]	0.45
Severe kidney disease at diagnosis	93	1.17 [0.90-1.51]	0.45
Diabetes at diagnosis	5122	1.12 [1.08-1.17]	<0.001 *
Anticoagulant at diagnosis	5589	1.03 [0.99-1.07]	0.24
Renin-angiotensin system inhibitor at diagnosis	13882	1.01 [0.98-1.04]	0.62
Diuretic at diagnosis	4394	1.08 [1.03-1.13]	0.004 *
Beta blocker at diagnosis	8539	1.09 [1.05-1.12]	<0.001 *
Non-steroidal anti-inflammatory at diagnosis	12758	1.03 [0.99-1.06]	0.20
Thyroid hormone replacement drug at diagnosis	2733	0.96 [0.91-1.01]	0.27
Painkiller at diagnosis	29279	1.07 [1.03-1.11]	<0.001 *
Artificial tears at diagnosis	1482	0.99 [0.93-1.07]	0.98

***Fig. 3:* Forest plot of prognosis factors in first line pembrolizumab population**. Adjusted Hazard Ratio were estimated with a multivariable proportional hazard Cox model adjusted on: sex, age at diagnosis, type of center, deprivation index, first pembrolizumab in inpatient hospitalization, severe myocardial infarction at diagnosis, severe cerebrovascular disease at diagnosis, severe kidney disease at diagnosis, chronic respiratory disease at diagnosis, severe kidney disease at diagnosis, diabetes at diagnosis, renin-angiotensin systeme inhibitor at diagnosis, anticoagulant at diagnosis, diuretic at diagnosis, beta blocker at diagnosis, non-steroidal anti-inflammatory at diagnosis, thyroid hormone replacement at diagnosis, painkiller at diagnosis, artificial tears at diagnosis, chemoimmunotherapy, antibiotics at first pembrolizumab, PPI at first pembrolizumab, steroid at first pembrolizumab, radiotherapy at baseline.

probability of continuing pembrolizumab after 2 years in multivariable logistic regression. The only factor independently associated with pembrolizumab continuation was being treated in an intermediate or low-volume center, OR = 2.33 [1.94–2.82] p < 0.001 or OR = 2.14 [1.64–2.82] p < 0.001 respectively (Supplementary Figure S6). Receiving chemo-immunotherapy and receiving radiotherapy before cessation were associated with a higher probability of continuing pembrolizumab, but these associations were not significant after correction for test multiplicity. A history beta blocker prescription at stop was independently associated with the probability of stopping pembrolizumab after 2 years, OR = 0.73 [0.58–0.92] p = 0.03. Between 29 and 60 months, 250 and 90 patients who were respectively in the continuation and discontinuation groups died. The survival rates among the patients still alive at 29 months, were 95.0% [94.0–96.0] at 4-years, 85.6% [83.7–87.6] at 5-years and 77.0 [74.2–80.0] at 6-years in the continuation group and 96.1% [94.7–97.5] at 4-years, 87.3% [84.4–90.3] at 5-years and 77.2% [72.2–82.6] at 6-years in the stop group. After weighting on the propensity score, continuation beyond 2 years was not associated with better OS, HR = 0.97 [0.75–1.26] p = 0.95 (Fig. 4). Our results were consistent in landmark sensitivity analyses at 27-months, 29-months and 32-months (data not shown). Survival curves and survival rates depending on 3- or 6-weeks interval are available in Supplementary Figure S7 and Supplementary Table S3. This analysis was exploratory, and no test was performed, but it seems that a 6-week interval did not harm patient. Cumulative incidence functions of causes of death are available in Supplementary Figure S8 and number of deaths by cause is available in Supplementary Table S4. This analysis was also exploratory, and no test was performed, but it seems that patients who stopped at 2 years had more deaths from lung cancer but less deaths from other causes.

Discussion

In this retrospective cohort study using a comprehensive medico-administrative database, pembrolizumab demonstrated a median OS of 15.7 months and a 5-year survival of 22.3%, which is consistent with previously published data.[10,23] We identified the need for first pembrolizumab in full hospitalization as an unfavorable prognostic factor. Several reasons could lead to hospitalization, including the use of cisplatin rather than carboplatin, but our first hypothesis is that patients with poor general status tend to be hospitalized. This is

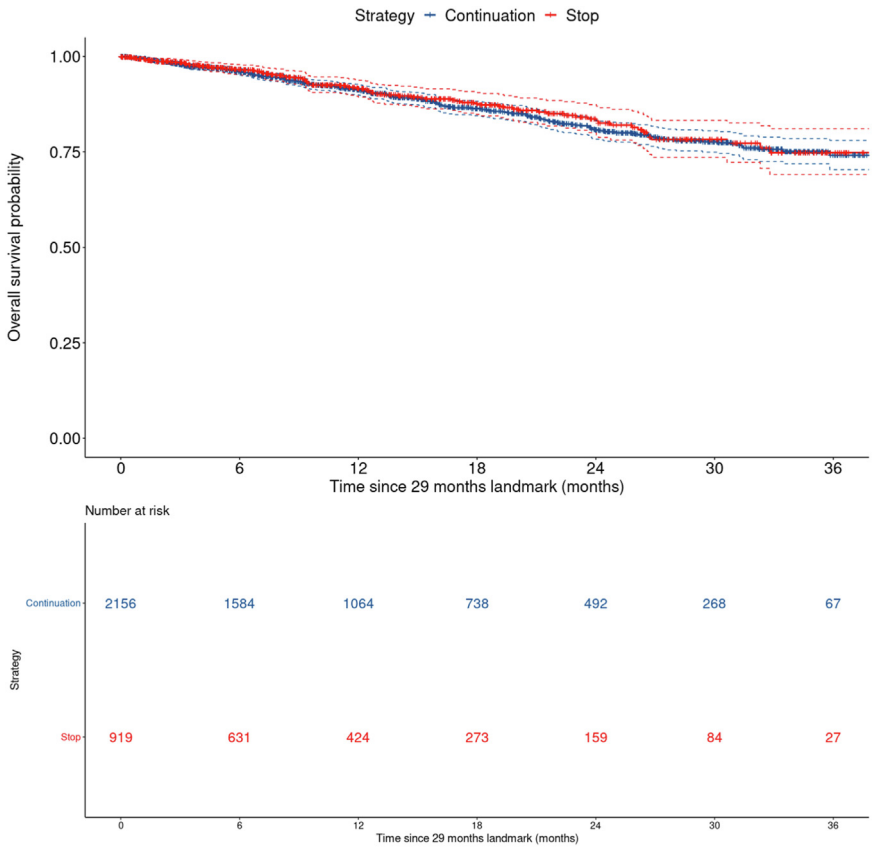

Fig. 4: **Overall survival of pembrolizumab in first line after 2 years**. A 29-month landmark is performed to avoid immortal time bias. Patients who stopped but had a chemotherapy session within 2 months after last pembrolizumab infusion are excluded (stop motivated by progression).

consistent with a recent meta-analysis that identified a Performance status (PS) of 0–1 as associated with better survival in real-world data than poorer PS.[24] A history of painkiller prescription was associated with worsened OS, which could indicate a more symptomatic disease with a higher tumoral burden.[25] A beta blocker pre-treatment has been identified as a prognostic factor in a small monocentric study[26] and could reflect the pejorative impact of cardiac comorbidities such as high blood pressure, heart failure, or myocardial infarction. A history of diuretic, associated with worse OS, is also linked with higher cardiac comorbidities. We also showed that diabetes was independently associated with worsened OS, although this factor is little reported in the literature.[27,28] This higher risk of death is likely explained by cardiovascular complications (hearth attack, stroke, nephropathy), but could also partially result of diabetes-induced immunosuppression.[29] Indeed, diabetes impacts immune response at different levels: impairment of cytokine production, decrease in the recruitment of leukocytes, including CD8+ T cells, lower expression of toll-like receptors (TLR), neutrophils, macrophages, and natural killer dysfunctions, and hyperglycemia was also associated with lower activation of the complement. Thus, it is plausible that immune checkpoint inhibitor activity is decreased within this environment. For the first time, we highlighted that centers treating a high volume of patients with pembrolizumab had higher survival than lower volume centers, a relationship already described with thoracic surgery and more generally most cancer surgeries.[30] This is consistent with publications that showed that establishing networks of reference centers is associated with better OS in sarcomas.[31] This relationship wasn't known for systemic treatments and various factors could explain this survival difference: patients treated in low volume centers may have lesser access to healthcare and have more comorbidities. However, we adjusted for several comorbidities and index of deprivation of the living town. Despite the certain existence of socio-regional inequalities in France, healthcare access is universal, and cancer-associated care is fully reimbursed. It is likely that high volume centers provide easier access to trained oncologists with a multidisciplinary board with expert radiologists, pathologists, or surgeons that should improve the better selection of treatment indication, better management of the treatment of adverse event,

and better access to staging exams such as PET-scan or molecular profile. Our analysis on pembrolizumab duration, which found that the volume of the center was the main factor influencing the decision to stop pembrolizumab at 2 years, shows that practices and expertise vary by center volume. A recruitment bias is still possible and cannot be measure in our data. A meta-analysis of 23 clinical trials on immunotherapy for advanced solid-organ cancers found an overall survival benefit for both females and males, with no statistically significant difference between the sexes, consistent even in the advanced NSCLC subgroup.[32] Our study shows that female sex is independently associated with a better survival outcome than male sex. There is conflicting evidence in literature about the sex effect. A pejorative effect of male sex was also observed in another large real-world data study in advanced NSCLC.[33] But in a meta-analysis of 8 randomized controlled trial in advanced NSCLC, male sex was associated with a better progression-free survival.[34] Generally, males tend to have lower life expectancies than women, mainly due to lifestyle habits[35] and our population, cardiovascular drug prescriptions were more frequent in men than women, indicating more frequent comorbidities. This could lead to more frequent exclusion form clinical trials and could explain the discrepancies between real-world and clinical trial data. Women in our study had also more pemetrexed prescriptions, indicating that men had more squamous tumor, which have a worse prognosis.[36] Moreover, histology is suggested to play a role in how sex modulates immunotherapy efficacy.[37] In this nationwide cohort, male sex was associated with even worse prognosis in chemotherapy plus pembrolizumab subgroup. A previous meta-analysis suggested that women with advanced lung cancer might benefit more from the addition of chemotherapy to immunotherapy compared with men.[38] In the KEYNOTE-189 trial,[6] women performed better than men in the subgroup analysis. Estrogens play a role in immune pathway and especially in the PD-1 one[39] and favors immunosuppressive T regulator. Chemotherapy addition in women could synergize and have in higher impact in immune environment than in men. Male sex is identified as a bad prognosis factor in patients treated with chemotherapy alone[40] and men may have more toxicities issues. Median survival in patients with chemo-immunotherapy was lower than median survival in patients with pembrolizumab alone, but all patients with pembrolizumab alone have a high PD-L1 tumor, so it is not possible to compare these two outcomes. The association of being diagnosed in 2021–2022 and worse OS is explained by the facts that early pembrolizumab authorizations were only for PD-L1 high tumors and that with increasing availability of prescription in later years, the selection of patient is less stringent.

We did not find any association between OS and pembrolizumab continuation after 2 years. This suggests the absence of benefit to continue pembrolizumab. Our results on pembrolizumab duration are consistent with those previously published.[14] The American study provided more details on tumor and patients' characteristics (histology, PD-L1, and PS), despite the latter two needing imputation for missing data. However, our study has a larger sample size, measures covariates at diagnosis and at pembrolizumab stop, includes a larger number of covariates, and utilizes a more elaborate statistical method to prevent confounding bias. The estimated cost of pembrolizumab of France is around 80 000 euros per Quality-Adjusted Life Year,[41] thus stopping infusion for patient who will not benefit from it could reduce the financial burden on the healthcare system.

With around 50,000 NSLCL patients treated by pembrolizumab, our study is by far the largest real-world cohort on the subject. We gathered all the infusions in this setting at a nationwide scale. Thus, the external validity is optimal. For example, we included patients treated in small centers, with old age (25% of patients were older than 71 years old), and 18.1% of included patients died during the first 3 months of treatment. All those patients wouldn't likely have been included in clinical trials. Another strength for the duration analysis is the adjustment with covariates at diagnosis but especially before pembrolizumab stop, which should provide a better handling of confounding. We also used a propensity score method to limit confounding bias.

Our study has several limitations. First, a retrospective study on administrative data can be prone to selection and confounding bias. The difference observed could be explained by unmeasured confounding factors. However, we used causal inference methods such as propensity scores to limit confounding. Several important prognosis factors are absent from the database, so we were not able to include them, but we tried to approximate them. Expression level of tumor PD-L1 was not available, but in France pembrolizumab alone in the first line is only authorized for NSCLC patients with a high expression of PD-L1 (≥50%), thus by adjusting for pembrolizumab alone vs pembrolizumab plus chemotherapy, we adjust partially on tumor PD-L1 status. Performance status was not available, but we approximated it with the length of the first hospitalization (patients with poor general state tend to be the inpatient clinic rather than in the outpatient clinic). Those two missing variables are important confounders and interpretation of our results should be careful. Status disease (progression or response) was not available, but we were able to adjust on variables which indicate disease activity (prescription of painkiller and radiation therapy before pembrolizumab discontinuation). We did

not know if patients had brain metastasis, but we adjusted for radiation therapy, steroid, and antiepileptic prescription fills that could all potentially be the consequence of brain metastases. Histology classification was not possible, but pembrolizumab doesn't have authorization in France for small cell lung cancer neither for early NSCLC, and pemetrexed is authorized only for non-squamous NSCLC. Thus, all our patients should have an advanced NSCLC, and those receiving pemetrexed should have a non-squamous histology. Finally, some misclassification bias is possible with our algorithms, for example for chemo-immunotherapy identification, but it should be nondifferential and little impactful in relation to the total number of patients.

Conclusion

This retrospective nationwide cohort study on first-line pembrolizumab in NSCLC found that age, male sex, needing first pembrolizumab in the inpatient clinic, not being treated in high volume centers, and histories of diabetes, painkiller, betablocker, and diuretic prescription fills were independently associated with worsened OS. Male sex was especially associated with worse survival in the chemo-immunotherapy population. Pembrolizumab discontinuation at 2 years was not associated with a higher risk of death. Because claim databases can be vulnerable to selection and confounding bias, these results are statistical associations but not causal. De-escalation strategy trials are more necessary than ever to optimize the management of patients treated with immunotherapy. Particular attention should be paid to patients at high risk of death, such as diabetic patients, to better understand how to improve their treatment. Finally, it seems important that all patients should have access to sufficient expertise to guarantee the quality of their care.

Contributors

AdRo, StFo and BeBe contributed to the study design and conceptualisation of the study. AdRo, JuBo, AlLo, StMi and StFo designed the statistical analysis plan. AdRo conducts the data curation. AdRo conducted the formal analysis. All authors contributed to the writing of the manuscript.

Data sharing statement

Individual participant data is not available. Raw database can be available after being granted access by the French Health Dara Hub platform.

Declaration of interests

AdRo, JuBo, AlLo, AnBo, NoSiTi and StFo declare no conflict of interest related to this research. StMi was *scientific committee study member*: Roche and *data and safety monitoring member of clinical trials:* Sensorion, Biophytis, Servier, IQVIA, Yuhan, Kedrion. DaPl received *personal fees from* AstraZeneca, Abbvie, Bristol Myers Squibb, Daiichi-Sankyo, Merck, Novartis, Janssen, Pfizer, Roche, and Sanofi-Aventis. FaBa received *institutional fees from* AbbVie, ACEA, Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer-Ingelheim, Eisai, Eli Lilly Oncology, F. Hoffmann–La Roche Ltd, Genentech, Ipsen, Ignyta, Innate Pharma, Loxo, Novartis, Medimmune, Merck, MSD, Pierre Fabre, Pfizer, Sanofi-Aventis and Takeda. JoRe was *adviser* for Bayer, BMS, Boehringer Ingelheim, GenMab, Janssen, MSD and Takeda, received *speaker fees from* Janssen and Pfizer, *Honoraria* from MSD and *Travel fees* from AstraZeneca, BMS, OSE Immunotherapeutics and Roche. PeLa received *fees* from Janssen, AstraZeneca, Sanofi, Amgen, Astellas, and Ipsen, *Travel accommodation* from Ipsen, Janssen, Astellas, Pfizer, Sanofi, Daichi and had *consultant/advisory role for* Astellas, AZ, Sanofi, BMS and *Grants* from Servier. MiAl received *personal fees from* Sandoz and Viatris and *Grants from* Amgen, AstraZeneca, and Sandoz. MaFr received *fees* from Janssen, MSD and Sandoz and *Grants* from Ipsen. AnLe received *academic research* grants from Roche, AstraZeneca, Beigene, ParmaMar. CeLePe received *honoraria:* Prime Oncology, Medscape (Inst), had a *Consulting or Advisory Role for:* AstraZeneca (Inst), Roche (Inst), Bristol Myers Squibb and perceived *Travel, Accommodations, Expenses from:* Janssen Oncology. AnGa perceived *Travel, accommodation, congress registration expenses from* Boehringer Ingelheim, Novartis, Pfizer, Roche, Sanofi, had a *Consultant/Expert role for* Novartis and received *Research Grants from* Astrazeneca, BMS, Boehringer Ingelheim, Janssen Cilag, Merck, Novartis, Pfizer, Roche, Sanofi. BeBe received *Grants from* AbbVie, Amgen, AstraZeneca, Chugai Pharmaceutical, Daiichi-Sankyo, Ellipse, EISAI, Genmab, Genzyme Corporation, Hedera Dx, Inivata, IPSEN, Janssen, MSD, Pharmamar, Roche-Genentech, Sanofi, Socar Research, Tahio Oncology, and Turning Point Therapeutics.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2024.100970.

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