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RESEARCH

Venous thrombotic events and impact on outcomes in patients treated with first-line single-agent pembrolizumab in PD-L1 ≥ 50% advanced non small cell lung cancer

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Abstract

Background Few data are available on the impact of venous thrombotic events (VTE) in patients with metastatic non-small cell lung cancer (mNSCLC) treated with immunotherapy.

Methods This is a secondary analysis of the ESKEYP study, a national, retrospective, multicenter study that consecutively included all PD-L1 ≥ 50% mNSCLC patients who initiated first-line treatment with pembrolizumab monotherapy. From May 2017 to November 2019, 845 patients were included (from availability of pembrolizumab in this indication in France to the authorization of the combination with chemotherapy). Impact of VTE and patient characteristics were analyzed.

Results Of the 748 patients (88.5%) with available data, the incidence of VTE was 14.8% (111/748). At pembrolizumab initiation, Khorana score was ≥ 2 for 55.0% (61/111) of them. Recurrence of VTE was reported for 4 of the 111 patients and 5 had bleeding complications. Patients with VTE were significantly younger, had more frequently long-term corticosteroids treatment and more often liver metastases. Progression-free survival (PFS) was significantly shorter in patients with VTE compared to patients without VTE: 6.1 (95% CI 4.1–9.0) months vs. 8.3 (6.9–10.3) months (p = 0.03). VTE did not significantly impact overall survival (OS): 15.2 (10.0–24.7) months with VTE and 22.6 (18.4–29.8) months without VTE (p = 0.07). In multivariate analysis for PFS and OS, HRs for VTE were 1.3 (0.99–1.71), p = 0.06 and 1.32 (0.99–1.76), p = 0.05.

Conclusion The incidence of VTE appears to be as high with in first-line immunotherapy as with chemotherapy in patients with mNSCLC, with in patient with VTE, a no significant trend for lower PFS and OS in multivariate analysis. more marked impact on PFS than on OS.

Keywords Non-small cell lung cancer · Immunotherapy · Checkpoint inhibitors · Venous thrombotic events

Abbreviations

CI	Confidence interval
ECOG	Eastern Cooperative Oncology Group
HR	Hazard ratio
ICI	Immune checkpoint inhibitor
IQR	Interquartile range
mNSCLC	Metastatic non-small cell lung cancer
NSCLC	Non-small cell lung cancer
OS	Overall survival
ORR	Overall response rate
PD-1	Programmed cell death-1
PD-L1	Programmed cell death ligand-1
PFS	Progression-free survival
TPS	Tumor proportion score
VTE	Venous thrombotic events

Extended author information available on the last page of the article

Introduction

The hypercoagulable state associated to cancer and its treatment lead to an increased risk of venous thrombotic events (VTE) (Khorana et al. 2008). Thus, the risk of VTE which includes pulmonary embolism and deep venous thrombosis, is increased by a factor of 4.1 in cancer patients and by a factor of 6.5 with chemotherapy treatment (Silverstein et al. 1998; Heit et al. 2000). In non-small cell lung cancer (NSCLC), the 6-month VTE rate ranges from 6 to 13% in patients treated with platinum-based chemotherapy (Kuderer et al. 2018; Mulder et al. 2019). In addition, NSCLC patients

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with VTE are associated with a lower overall survival (OS) (Khorana et al. 2007; Shen et al. 2017).

The advent of immune checkpoint inhibitors (ICIs) has transformed the therapeutic landscape of NSCLC. Monoclonal antibodies that target programmed cell death-1 (PD-1) or programmed cell death ligand-1 (PD-L1) demonstrated efficacy in different settings, including lung cancer (Borghaei et al. 2015; Brahmer et al. 2015; Herbst et al. 2016; Reck et al. 2016; Rittmeyer et al. 2017).The aim of ICI therapy is to block immune checkpoints in order to restore immune system function (Zhou et al. 2021). The immune system, inflammation and the coagulation system are intimately connected. Activation of immune cells by ICI is potentially associated with increased synthesis of pro-inflammatory cytokines, which in turn promote a state of hypercoagulability with a risk of thrombosis (Foley and Conway 2016). A recent systematic review and meta-analysis addressed the issue of treatment-related adverse events of PD-1 and PD-L1 inhibitors in clinical trials, but thrombosis did not emerge as an issue and was not reported as a common adverse event (Wang et al. 2019). However, patients participating in clinical trials are selected according to stringent criteria and are strictly followed thus possibly leading to an underestimation of the thromboembolism risk. In addition, studies evaluating the incidence of VTE in NSCLC treated with ICI remain scarce (Deschenes-Simard et al. 2021; Nichetti et al. 2019). As a consequence, the impact of thrombotic complications associated with these new treatments in NSCLC patients and their risk factors remain poorly known.

The recent ESCKEYP study included patients with PD-L1 $\geq$ 50% metastatic non-small cell lung cancer (mNSCLC) who initiated first-line treatment with pembrolizumab monotherapy. Data were analyzed to evaluate the rate of VTE and its impact on outcomes.

Material and methods

Type of study and patients

The results of the ESCKEYP study (GFPC 05-2018) were recently published (Descourt et al. 2022). This was a national retrospective multicentric trial that included consecutive patients with PD-L1 $\geq$ 50% mNSCLC initiating first-line single-agent pembrolizumab. In this secondary analysis, the rate of VTE and the impact on efficacy outcomes were analyzed.

The main eligibility criteria of the ESCKEYP study were the followings: treatment-naïve adults with histologically or cytologically confirmed mNSCLC, PD-L1 $\geq$ 50%, negative for *EGFR* and *ALK* mutations and with at least one measurable lesion. Patients with brain metastases could be included. Patients were excluded if they had autoimmune disease contraindicating immunotherapy, active infection (hepatitis B, C, HIV) or organ or bone marrow transplant.

According to the first French registration in 2015, a dose of 200 mg of pembrolizumab was administered intravenously every 3 weeks. Pembrolizumab was discontinued for progressive disease or unacceptable toxicity as judged by the investigator.

The study was conducted in accordance with the Declaration of Helsinki and was approved by a national independent Ethics Committee (2019-A02073-54; December 11, 2019). Patients received written and oral information on the study and gave their consent to participate in the study and for the use of their medical data for research purposes.

Data collected

The main data collected for the present analysis were: sociodemographic data, disease history, smoking status, ECOG performance status, NSCLC characteristics (histology, stage, metastatic sites at diagnosis, PD-L1 expression, mutations or rearrangements), administration of corticosteroids (more than 10 mg/day for more than 10 days), previous course of antibiotics (more than 10 days), tumor progression (new sites or existing sites), Khorana score, VTE, biological parameters (albumin, C-reactive protein) and leucocytes and lymphocytes counts. Tumor response was assessed locally (RECIST 1.1 criteria). Patients were assessed from the first administration of Pembrolizumab for the occurrence of VTE and survival. In this non interventional study, imaging tests (doppler ultrasound, computed tomography, or ventilation/perfusion lung scans) were performed following local practice, in case of VTE symptoms or usual lung cancer management (incidental thrombosis could be detected).

Statistical analysis

Categorical variables are expressed as number (percentage) of the population and continuous variables as median (interquartile range [IQR]). Patient characteristics at initiation of first-line pembrolizumab treatment were compared according to the occurrence or non-occurence of VTE during follow-up using chi-square test or Fisher's exact test for discrete variables and Student's t-test for quantitative variables.

The PFS and OS of patients who developed VTE were compared with those who did not, using the Kaplan–Meier method. OS was defined as the time from the date of initiation of pembrolizumab treatment to the date of death from any cause measured at the date of last contact or cutoff date (January 18, 2021). PFS was defined as the time from the date of initiation of pembrolizumab treatment to the date of first disease progression or death from any cause. Survival curves according to the presence of VTE or not were compared using the log-rank test.

Cox proportional hazards models were used to investigate each variable's association with median OS and PFS. Variables achieving statistically significant prognostic association were then entered into a multivariable Cox regression model to determine their independent impact. Univariable and multivariable logistic-regression models were used to estimate odds ratios (OR) and their 95% confidence intervals (CIs) for significant ORR-factor relationships. Associations between categorical variables were assessed with Pearson's chi-square or Fisher's exact test. Statistical significance was defined as $p < 0.05$.

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA).

Results

Patient characteristics and incidence of VTE

Patients with mNSCLC and PD-L1 ≥ 50% treated in first line with pembrolizumab were included consecutively in 33 centers from May 2017 (date of availability of pembrolizumab in this indication in France) to November 22, 2019 (approval of pembrolizumab plus chemotherapy). The median follow-up time of the ESCKEYP study cohort was 25.8 (95% CI 24.8–26.7) months.

VTE was reported for 111 (14.8%) of 748 evaluable patients. At pembrolizumab initiation, Khorana score was ≥ 2 for 55.0% (61/111) of them. Recurrence of VTE was reported for 4 of the 111 patients and 5 had bleeding complications.

The characteristics of patients according to whether or not a VTE was reported are presented in Table 1. VTEs were more frequently reported in patients younger than 70 years (77.5% vs. 64.4%; p = 0.0068), in patients treated with corticosteroids (19.8% vs. 10.1%; p = 0.003) and in patients with liver metastases (23.4% vs. 12.1%; p = 0.0014). No differences were reported for gender, performance status, histology, presence of *KRAS* or *BRAF* mutation, PD-L1 expression or bone or brain metastases.

Efficiency outcomes

The overall response rate (ORR) was 46.8% in patients with VTE and 44.6% in patients without VTE (Table 2).

Median PFS was significantly shorter in patients with VTE (6.1 months; 95% CI 4.1–9.0) than in patients without VTE (8.3 months; 95% CI 6.9–10.3; p = 0.03) (Fig. 1). Median OS was numerically lower in patients with VTE (15.2 months; 95% CI 10.0–24.7) compared to patients without VTE (22.6 months; 95% CI 18.4–29.8), with a trend for worse OS, but statistical significance was not achieved (p = 0.07) (Fig. 2).

Multivariate analysis for survival

There was a trend for VTE to be an independent factor for shorter PFS, but statistical significance was not achieved (Table 3). No other predictive factors of PFS were found.

VTE was a significant independent factor predictive of shorter OS (HR, 1.32; 95 CI 0.99–1.76; p = 0.05). The other independent predictive factors of shorter OS were age ≥ 70 years, no smoking, non-adenocarcinoma, performance status 2–4, antibiotics, bone metastases and *KRAS* status (Table 3).

Discussion

In this retrospective study, we report a VTE rate of 14.8% in mNSCLC patients treated with first-line pembrolizumab after a median follow-up of 25.8 months. This rate appears to be consistent with other recently reported studies for first-line ICI in NSCLC. In the study of Deschênes-Simard et al. in 593 NSCLC patients treated with various ICIs, the cumulative incidence of VTE was 14.8% (95% CI 7.4–22.2) (Deschenes-Simard et al. 2021). In the prospective observational APPOLO study performed in mNSCLC treated with ICIs, VTE was reported in 13.8% of patients (Nichetti et al. 2019). In the study of Icht*et al*, the 6-month VTE incidence was 7.1% with chemotherapy and 4.5% with single-agent ICI (n = 176) (Icht et al. 2021). The retrospective study of Hill et al. included 1587 NSCLC patients who received a first-line treatment: the 6-month cumulative incidence of VTE by treatment type was 5.0% (chemotherapy), 7.6% (ICIs), 9.9% (chemotherapy plus concomitant ICI), 9.4% (chemotherapy and durvalumab maintenance), and 11.1% (targeted therapies); 12-month incidences were 6.5%, 9.0%, 12.8%, 12.2%, and 13.1%, respectively (Hill et al. 2021). Overall, these VTE rates are comparable to those reported for various cancer types treated by ICI therapy: after a median follow-up of 8.5 months and a median of 2 lines of treatments, cumulative incidences of VTE was 12.9%. VTE rates were comparable between tumor types and immune checkpoint inhibitors (Hill et al. 2021).

We observed that patients with VTE were significantly younger, more often with long-term corticosteroid therapy and more often with liver metastases. The observation of younger age (< 65 years) for VTE risk in NSCLC treated with ICI was previously observed in the study of Deschênes-Simard et al.; these authors reported also that tumors with PD-L1 ≥ 1%, a time < 12 months from diagnosis to first-line ICI and active smoking were independent risk factors of VTE (Deschenes-Simard et al. 2021). Nichetti*at al* also reported that current smoking and PD-L1 > 50% were risk factors in mNSCLC patients treated with ICI (Nichetti et al. 2019). In the study of Hill et al., smoking was an independent factor of VTE in NSCLC patients receiving first-line

Table 1 Patient characteristics

	All population (n = 748)	With VTE (n = 111)	Without VTE (n = 637)	P-value
Female gender, n (%)	514 (68.7)	72 (64.9)	442 (69.4)	0.34
Age, years, n (%)	N = 747	N = 111	N = 636	
≥ 70	252 (33.7)	25 (22.5)	227 (35.6)	0.006
< 70	496 (66.3)	86 (77.5)	410 (64.4)	
Smoking status, n (%)	N = 726	N = 110	N = 616	
Current/former smoker	677 (93.3)	102 (92.7)	575 (93.3)	0.81
No smoker	49 (6.7)	8 (7.3)	41 (6.7)	
Weight loss, n (%)	N = 653	N = 96	N = 557	
< 5%	422 (64.6)	58 (60.4)	364 (65.4)	0.35
≥ 5%	231 (35.4)	38 (39.6)	193 (34.6)	
Body mass index, kg/m, n (%)	N = 805	N = 108	N = 697	
< 18	51 (6.3)	5 (4.6)	46 (6.6)	0.72
18–30	692 (86.0)	94 (87.0)	598 (85.6)	
≥ 30	62 (7.7)	9 (8.3)	53 (7.6)	
ECOG performance status, n (%)	N = 695	N = 108	N = 587	
0–1	549 (79.0)	84 (77.8)	465 (79.2)	0.74
2–4	146 (21.0)	24 (22.2)	122 (20.8)	
Corticosteroid treatment, n (%)	N = 746	N = 111	N = 635	
Yes	86 (11.5)	22 (19.8)	64 (10.1)	0.003
Antibiotic treatment,[a] n (%)	N = 730	N = 109	N = 621	
Yes	129 (17.7)	25 (22.9)	104 (16.7)	0.12
Histology, n (%)	N = 744	N = 111	N = 633	
Adenocarcinoma	521 (70.0)	82 (73.9)	439 (69.4)	0.34
Other	223 (30.0)	29 (26.1)	194 (30.6)	
Metastases, n (%)	N = 748	N = 111	N = 637	
Brain	155 (20.7)	24 (21.6)	131 (20.6)	0.80
Bone	260 (34.8)	47 (42.3)	213 (33.4)	0.07
Liver	103 (13.8)	26 (23.4)	77 (12.1)	0.001
PD-L1-positive tumor, n (%)	N = 694	N = 99	N = 595	
TPS > 75%	360 (51.9)	54 (54.5)	306 (51.4)	0.57
Genetics, n (%)	N = 748	N = 111	N = 637	
KRAS	218 (29.1)	37 (33.3)	181 (28.4)	0.29
BRAF	24 (3.2)	6 (5.4)	18 (2.8)	0.15
Biological parameters, n (%)				
Albumin	N = 460	N = 64	N = 396	
≤ 30 g/L	107 (23.3)	22 (34.4)	85 (21.5)	0.02
C-reactive protein	N = 352	N = 57	N = 295	
> 5 mg/L	304 (86.4)	53 (93.0)	251 (85.1)	0.11
White blood cells	N = 678	N = 91	N = 587	
> 10,000/mm^3	288 (42.5)	44 (48.4)	244 (41.6)	0.22
Neutrophil-to-lymphocyte ratio	N = 642	N = 88	N = 554	
≥ 4	388 (60.4)	56 (63.6)	332 (59.9)	0.51

TPS tumor proportion score

[a]Within 3 months before pembrolizumab

systemic therapy (Hill et al. 2021). The fact that current and former smokers were considered as a single class in our study and that the threshold of PD-L1 expression was > 75% may explain why we did not observe differences between the VTE and non-VTE groups for these characteristics. A poorer performance status has been associated with increased thromboembolic risk in metastatic cancer patients (mainly renal cell carcinoma and melanoma) treated with

Table 2 Response rates of patients to first-line single-agent pembrolizumab according to VTE status

	All population (N = 748)	With VTE (n = 111)	Without VTE (n = 637)
Best response, n (%)	N = 712	N = 109	N = 603
Complete response	33 (4.6)	4 (3.7)	29 (4.8)
Partial response	287 (40.3)	47 (43.1)	240 (39.8)
Stable disease	170 (23.9)	19 (17.4)	151 (25.0)
Progressive disease	222 (31.2)	39 (35.8)	183 (30.3)
Overall response rate (ORR), n (%)	320 (44.9)	51 (46.8)	269 (44.6)
No evaluable	36	2	34

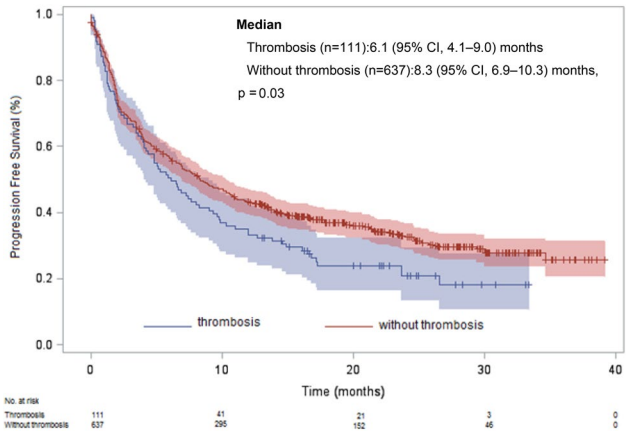

Fig. 1 Median progression free survival from initiation of first-line single-agent pembrolizumab according to the presence or not of VTE

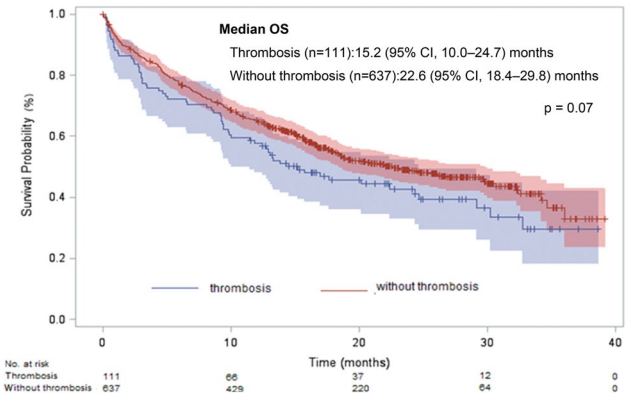

Fig. 2 OS from initiation of first-line single-agent pembrolizumab according to the presence or not of VTE

immunotherapy (Guven et al. 2021). However, this characteristic was not found with an increased rate in NSCLC patients with VTE in the present study and in the study of Moik*et al* (Moik et al. 2021). The Khorana score, which is used to predict VTE and guide thromboprophylaxis in cancer, has been validated in patients treated with chemotherapy. This score does not appear to predict high-risk NSCLC patients treated with ICI, as reported by Ichtet al (Icht et al. 2021).

The impact of VTE on efficacy has been rarely reported in patients treated with ICIs. We did not observe an impact of VTE on ORR in our cohort. Nevertheless, PFS was significantly shorter in patients with VTE than in patients without VTE (6.1 vs. 8.3 months, respectively). Even if some preclinical data suggest that anticoagulation therapy could improve efficacy of ICI, hypercoagulable state and VTE are probably associated with tumor aggressiveness (Choi et al. 2021)**.** An effect of VTE was not observed on PFS and ORR by Deschêne-Simard et al. after treatment of NSCLC by ICI (Deschenes-Simard et al. 2021). In our study, except VTE, no others factors impact the median PFS (Table 3).

Median OS was numerically higher in patients without VTE (22.6 months) compared to patients without VTE (15.2 months), but statistical significance was not achieved. In multivariate analysis for OS, there is a also a trend for worse OS in patients with VTE. The consequences of VTE on survival in NSCLC patients treated with ICI remain unclear. Thus, Moik*et al* reported an association between the occurrence of VTE and increased mortality (Moik et al. 2021). Nichetti*et al* also observed an increased risk of death after diagnosis of a VTE in mNSCLC treated with ICI (Nichetti et al. 2019). In contrast, in the study of Deschênes-Simard et al., there was no correlation between VTE and OS (Deschenes-Simard et al. 2021). It is established that the risk of death is increased after VTE (Sogaard et al. 2014). However, it has to been noticed that the impact of VTE on OS seems to be lower in the last few years, probably because of the early detection of VTE (incidental events), the improvement of supportive care and the better efficiency of new anti-cancer agents (Ording et al. 2021).The relatively short duration of follow-up in these studies could explain why no stronger impact on survival was reported. Apart from the VTE, the other independent predictive factors of shorter OS, age ≥ 70 years, no smoking, non-adenocarcinoma, performance status 2–4, antibiotics, bone metastases and *KRAS* status have also been described in other studies (Amrane et al. 2020; Justeau et al. 2022).

Data from literature suggest a benefit of thromboprophylaxis in patients with lung cancer treated with chemotherapy (Fuentes et al. 2017; Thein et al. 2018). In the study of Nichetti*et al*, NSCLC patients treated with ICIs experienced longer PFS if they had received antiplatelet treatment in univariate analysis; this effect was not confirmed in

Table 3 Multivariate analysis for PFS and OS

Factors	Test vs. reference	PFS			OS		
		HR[a]	CI 95%	p-value	HR[a]	CI 95%	p-value
Sex	Female vs. male	0.90	0.72–1.14	0.39	0.92	0.72–1.17	0.48
Age	≥ 70 vs. < 70 years	1.05	0.84–1.32	0.65	1.30	1.03–1.63	0.03
Smoking	No vs. current/ex–smoker	1.35	0.90–2.00	0.15	1.62	1.10–2.38	0.01
Histology	non adenocarcinoma vs. adenocarcinoma	1.13	0.89–1.45	0.32	1.46	1.14–1.89	0.003
Performance status	2–4 vs. 0–1	1.24	0.96–1.60	0.15	1.76	1.38–2.24	< 0.0001
Corticosteroids	No vs. yes	0.83	0.59–1.16	0.27	0.87	0.61–1.23	0.42
Antibiotics	No vs. yes	0.80	0.69–1.03	0.08	0.72	0.56–0.93	0.01
Brain metastases	Yes vs. no	1.08	0.83–140	0.58	1.19	0.89–1.56	0.24
Bone metastases	Yes vs. no	1.16	0.93–1,44	0.20	1.64	1.32–2.04	< 0.0001
Liver metastases	Yes vs. no	1.29	0.94–1.64	0.13	1.27	0.95–1.68	0.10
PD-L1	> 75% vs. ≤ 75%	0.90	0.72–1.09	0.70	0.91	0.73–1.13	0.38
KRAS	Yes vs. no	1.14	0.88–1.45	0.32	1.30	1.0–1.69	0.05
BRAF	Yes vs. no	0.91	0.50–1.68	0.77	0.71	0.37–1.39	0.31
VTE	Yes vs. no	1.30	0.99–1.71	0.06	1.32	0.99–1.76	0.05

VTE venous thrombotic event

[a]Survival shorter for HR > 1

multivariate analysis (Nichetti et al. 2019). Further prospective randomized trials are needed to establish the benefit of thromboprophylaxis in NSCLC patients treated with ICIs.

The multicentric design and large sample size of consecutively included patients are the main strengths of this study. In addition, patients received first-line single-agent pembrolizumab and therefore the risk of introducing bias related to another treatment was reduced. Finally, all patients meeting the inclusion criteria during the study period were included, limiting the risk of selection bias. Regarding, study limits, we did not evaluate the impact of anticoagulant and antiplatelet treatments on the VTE. Other limitations are the retrospective design and the absence of centralized tumor assessment.

Moreover, this study meets the needs of clinicians to have evaluation of cancer-associated thrombosis (CAT) in real life, whereas it is not usually reported in clinical trials for new anticancer agents. Finally, CAT seems to have particularities according to each type of cancer reinforcing the interest of studies dedicated to a single location.

In conclusion, the incidence of VTE appears to be high with first-line immunotherapy as with chemotherapy in patients with mNSCLC, with a non statistical significant trend for VTE to be an independent factor for shorter PFS and shorter OS.

Author contributions All authors contributed to patient recruitment; Project development: HD, LG, DC, DR, CC and GM; Clinical data collection: JG, RC, SA, CH, BO, BGL, PJ and AK; Data analysis: HD, LG, CC and MG; Manuscript writing: HD, CC, MG; all authors participated to manuscript editing and approved the final version.

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Availability of data and material Datasets analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests Conflicts of interest/Competing interests: L. Greillier reports grants, personal fees and non-financial support from AstraZeneca, Boehringer Ingelheim, Roche, Sanofi Aventis, Bristol-Myers Squibb, Merck Sharp & Dohme, Lilly, Novartis, Pfizer, Takeda, Bayer and Amgen, outside the submitted work. C. Chouaid reports grants, personal fees and non-financial support from AstraZeneca, Boehringer Ingelheim, GSK, Roche, Sanofi Aventis, Bristol-Myers Squibb, Merck Sharp & Dohme, Lilly, Novartis, Pfizer, Takeda, Bayer and Amgen, outside the submitted work. C. Decroisette reports personal fees and non-financial support from AstraZeneca, Boehringer Ingelheim, Roche, Sanofi Aventis, Bristol-Myers Squibb, Merck Sharp & Dohme, Lilly, Novartis, Pfizer, Takeda, and Amgen, outside the submitted work. M. Pérol reports personal fees and non-financial support from Roche, Eli Lilly, Pfizer, Boehringer Ingelheim, Merck Sharp & Dohme, Bristol-Myers Squibb, Novartis, AstraZeneca, Takeda, Gritstone, Sanofi, GlaxoSmithKline, Amgen, Chugai, Illumina, Daïchi-Sankyo and Abbvie outside the submitted work. R. Descourt reports personal fees and non-financial support from AstraZeneca, Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Pfizer, Takeda, and Chugai, outside the submitted work. C. Ricordel, J.B. Auliac, L. Falchero, R. Gervais, R. Veillon, S. Vieillot, F. Guisier, M. Marcq, G. Justeau, L. Bigay-Game, M. Bernardi, P. Fournel, H. Doubre, J. Pinsolle and K. Amrane report no conflict of interest.

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Ethical approval The study was conducted in accordance with the Declaration of Helsinki and was approved by a national independent Ethics Committee (2019-A02073-54; December 11, 2019).

Consent to participate Patients received written and oral information on the study and gave their consent to participate in the study and for the use of their medical data for research purposes.

References

Amrane K, Geier M, Corre R, Léna H, Léveiller G, Gadby F et al (2020) First-line pembrolizumab for non-small cell lung cancer patients with PD-L1 ≥50% in a multicenter real-life cohort: The PEMBREIZH study. Cancer Med. 9:2309–2316. https://doi.org/10.1002/cam4.2806

Borghaei H, Paz-Ares L, Horn L et al (2015) Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 373:1627–1639. https://doi.org/10.1056/NEJMoa1507643

Brahmer J, Reckamp KL, Baas P et al (2015) Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 373:123–135. https://doi.org/10.1056/NEJMoa1504627

Choi JU, Lee NK, Seo H et al (2021) Anticoagulation therapy promotes the tumor immune-microenvironment and potentiates the efficacy of immunotherapy by alleviating hypoxia. J Immunother Cancer. https://doi.org/10.1136/jitc-2021-002332

Deschenes-Simard X, Richard C, Galland L et al (2021) Venous thrombotic events in patients treated with immune checkpoint inhibitors for non-small cell lung cancer: A retrospective multicentric cohort study. Thromb Res 205:29–39. https://doi.org/10.1016/j.thromres.2021.06.018

Descourt R, Greillier L, Perol M et al (2022) First-line single-agent pembrolizumab for PD-L1-positive (tumor proportion score >/= 50%) advanced non-small cell lung cancer in the real world: impact in brain metastasis: a national French multicentric cohort (ESCKEYP GFPC study). Cancer Immunol Immunother. https://doi.org/10.1007/s00262-022-03232-2

Foley JH, Conway EM (2016) Cross talk pathways between coagulation and inflammation. Circ Res 118:1392–1408. https://doi.org/10.1161/CIRCRESAHA.116.306853

Fuentes HE, Oramas DM, Paz LH, Casanegra AI, Mansfield AS, Tafur AJ (2017) Meta-analysis on anticoagulation and prevention of thrombosis and mortality among patients with lung cancer. Thromb Res 154:28–34. https://doi.org/10.1016/j.thromres.2017.03.024

Guven DC, Aksun MS, Sahin TK et al (2021) Poorer baseline performance status is associated with increased thromboembolism risk in metastatic cancer patients treated with immunotherapy. Support Care Cancer 29:5417–5423. https://doi.org/10.1007/s00520-021-06139-3

Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd (2000) Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med 160:809–815. https://doi.org/10.1001/archinte.160.6.809

Herbst RS, Baas P, Kim DW et al (2016) Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 387:1540–1550. https://doi.org/10.1016/S0140-6736(15)01281-7

Hill H, Robinson M, Lu L, Slaughter D, Amin A, Mileham K, Patel JN (2021) Venous thromboembolism incidence and risk factors in non-small cell lung cancer patients receiving first-line systemic therapy. Thromb Res 208:71–78. https://doi.org/10.1016/j.thromres.2021.10.014

Icht O, Darzi N, Shimony S et al (2021) Venous thromboembolism incidence and risk assessment in lung cancer patients treated with immune checkpoint inhibitors. J Thromb Haemost 19:1250–1258. https://doi.org/10.1111/jth.15272

Justeau G, Huchot E, Simonneau Y, Roa M, Le Treut J, Le Garff G et al (2022) Impact of KRAS G12C mutation in patients with advanced non-squamous non-small cell lung cancer treated with first-line pembrolizumab monotherapy. Lung Cancer 174:45–49

Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH (2007) Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost 5:632–634. https://doi.org/10.1111/j.1538-7836.2007.02374.x

Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW (2008) Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 111:4902–4907. https://doi.org/10.1182/blood-2007-10-116327

Kuderer NM, Poniewierski MS, Culakova E et al (2018) Predictors of Venous Thromboembolism and Early Mortality in Lung Cancer: Results from a Global Prospective Study (CANTARISK). Oncologist 23:247–255. https://doi.org/10.1634/theoncologist.2017-0205

Moik F, Chan WE, Wiedemann S et al (2021) Incidence, risk factors, and outcomes of venous and arterial thromboembolism in immune checkpoint inhibitor therapy. Blood 137:1669–1678. https://doi.org/10.1182/blood.2020007878

Mulder FI, Candeloro M, Kamphuisen PW et al (2019) The Khorana score for prediction of venous thromboembolism in cancer patients: a systematic review and meta-analysis. Haematologica 104:1277–1287. https://doi.org/10.3324/haematol.2018.209114

Nichetti F, Ligorio F, Zattarin E et al (2019) Is There an interplay between immune checkpoint inhibitors, thromboprophylactic treatments and thromboembolic events? Mechanisms and impact in non-small cell lung cancer patients. Cancers (Basel). https://doi.org/10.3390/cancers12010067

Ording AG, Skjoth F, Sogaard M, Hojen AA, Overvad TF, Noble S, Goldhaber SZ, Larsen TB (2021) Increasing incidence and declining mortality after cancer-associated venous thromboembolism: a nationwide cohort study. Am J Med. 134:868–876865. https://doi.org/10.1016/j.amjmed.2021.01.031

Reck M, Rodriguez-Abreu D, Robinson AG et al (2016) Pembrolizumab versus Chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 375:1823–1833. https://doi.org/10.1056/NEJMoa1606774

Rittmeyer A, Barlesi F, Waterkamp D et al (2017) Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung

cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 389:255–265. https://doi.org/10.1016/S0140-6736(16)32517-X

Shen Q, Dong X, Tang X, Zhou J (2017) Risk factors and prognosis value of venous thromboembolism in patients with advanced non-small cell lung cancer: a case-control study. J Thorac Dis 9:5068–5074. https://doi.org/10.21037/jtd.2017.11.116

Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd (1998) Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med 158:585–593. https://doi.org/10.1001/archinte.158.6.585

Sogaard KK, Schmidt M, Pedersen L, Horvath-Puho E, Sorensen HT (2014) 30-year mortality after venous thromboembolism: a population-based cohort study. Circulation 130:829–836. https://doi.org/10.1161/CIRCULATIONAHA.114.009107

Thein KZ, Yeung SJ, Oo TH (2018) Primary thromboprophylaxis (PTP) in ambulatory patients with lung cancer receiving chemotherapy: a systematic review and meta-analysis of randomized controlled trials (RCTs). Asia Pac J Clin Oncol 14:210–216. https://doi.org/10.1111/ajco.12770

Wang Y, Zhou S, Yang F et al (2019) Treatment-related adverse events of PD-1 and PD-l1 inhibitors in clinical trials: a systematic review and meta-analysis. JAMA Oncol 5:1008–1019. https://doi.org/10.1001/jamaoncol.2019.0393

Zhou F, Qiao M, Zhou C (2021) The cutting-edge progress of immune-checkpoint blockade in lung cancer. Cell Mol Immunol 18:279–293. https://doi.org/10.1038/s41423-020-00577-5

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