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Immune Checkpoint Inhibitors for Cancer and Venous Thromboembolic Events

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Abstract

Background—Immune checkpoint inhibitors (ICI) are widely used cancer treatments. There are limited data the risk for developing venous thromboembolism (VTE) among patients on an ICI.

Methods—This was a retrospective study of 2854 patients who received ICIs at a single academic center. VTE events, defined as a composite of deep vein thrombosis (DVT) or pulmonary embolism (PE), were identified by individual chart review and were blindly adjudicated using standard imaging criteria. A self-controlled risk-interval design was applied with an "at-risk period" defined as the two-year period after, and the "control period", defined as the two-year prior to treatment. The hazard ratio (HR) was calculated using a fixed-effect proportional hazards model.

Results—Of the 2854 patients, 1640 (57.5%) were men; mean age was 64±13 years. The risk for VTE was 7.4% at 6 months and 13.8% at 1 year after starting an ICI. The rate of VTE was >4-fold higher after starting an ICI (HR 4.98, 95% CI 3.65 – 8.59, p<0.001). There was a 5.7-fold higher risk for DVT (HR 5.70, 95% CI 3.79 – 8.59, p<0.001) and 4.75-fold higher risk for PE (HR 4.75, 95% CI 3.20 – 7.10, p<0.001). Comparing patients with and without a VTE event, a history of melanoma and older age predicted a lower risk of VTE, while a higher Khorana risk score, history of hypertension, and history of VTE predicted a higher risk.

Conclusions—The rate of VTE among patients on an ICI is high and increases after starting an ICI.

Keywords

Immune Checkpoint Inhibitors; Venous Thromboembolism; Cardio-oncology; Anticoagulation; Cancer; Vascular Medicine

INTRODUCTION

Immune Checkpoint Inhibitors (ICI) are monoclonal antibodies that target specific negative immunological regulators and, as a result, leverage the immune response to treat malignancy[1]. The use of an ICI was first approved by the Food and Drug Administration for treatment of melanoma in 2011[2]. Since then, the indications for use of ICI have been rapidly increasing and, as of January 2020, ICIs were indicated in treatment of 17 malignancies with over 100 ongoing trials evaluating its efficacy for cancer treatment[3, 4]. Our knowledge of some of the potential adverse effects of ICI therapy, specifically some of the cardiovascular effects is limited[5–10]. There are limited data on the risk for venous thromboembolism (VTE) among patients on an ICI. This knowledge gap is important as malignancy and immune activation and inflammation with ICI are both established risk factors for VTE[11, 12]. In addition, ICIs have been linked to other vascular diseases such as atherosclerosis[13]. A study of 672 patients treated with ICI observed 47 VTE events with cumulative incidence of 12.9% and another single-center study of 228 patients with melanoma treated with an ICI identified VTE events in 16.2% of study subjects[14, 15]. However, uncertainties remain as many studies have not reported a control comparison and other studies evaluating the risk of acute vascular events with ICI use have not shown an increase[16, 17]. Therefore, we aimed to

determine whether the risk for VTE after ICI use, whether this risk is increased after starting an ICI, and the risk factors for VTE after ICI use.

METHODS

Study Design, Setting and Population

This was a single center, retrospective cohort study. The database was built upon a protocol approved by institutional review boards at Partners Healthcare (now Mass General Brigham), detailing electronic medical records access in all patients who have received immune checkpoint inhibitors at Massachusetts General Hospital (Boston, MA, USA) until March 2019. Given the limitations in obtaining comparable contemporary controls (patients with similar cancer who were not treated with ICIs), we performed a self-controlled risk-interval design[18]. The use of an ICI was defined through a pharmacy database. Clinical characteristics and outcome data were extracted from the Research Patient Data Registry (RPDR).

Covariates

Demographics, medical history, medication usage were obtained through RPDR. Anticoagulation history was confirmed through review of electronic medical records. Oncologic data were collected, including date of ICI initiation, the specific type of ICI, cancer diagnosis prior to treatment, prior cardiotoxic cancer treatment, radiation therapy history, corticosteroid use, occurrence of any irAEs. History of cardiovascular events and Khorana score were defined as prior studies[13, 19]. Specifically, history of cardiovascular events is defined by defined as a composite of myocardial infarction, coronary revascularization, and ischemic stroke. Khorana risk score is a composite score involving five variables. Cancer types associated higher risk of VTE are given two points (stomach, pancreas) or one point (lung, lymphoma, gynecologic, bladder, testicular). Pre-treatment platelet counts $\geq 350 \times 10^9$ /L, hemoglobin <10 g/dL, pre-treatment leukocyte count >11 $\times 10^9$ /L and BMI ≥ 35 kg/m^2 each is assigned one point.

Outcome Measures: Clinical Study

The primary study end-point was the occurrence of VTE event, defined as a composite of deep venous thrombosis or pulmonary embolism using standardized radiographic findings (supplemental document 1). The secondary study end-point was each of the individual components of the primary end-point. These events were searched through RPDR, confirmed through review of electronic medical records and were blindly adjudicated by members of the study team.

Statistical Analysis

Descriptive statistics were used to assess the distribution of variables. Categorical demographic variables were described as counts and percentage. Continuous variables were summarized with mean and standard deviation or median and interquartile ranges. We defined period of ICI exposure (risk period) as two years after initiation of ICI treatment and control period as two years prior to ICI initiation (Supplemental Figure 1). A fixed-effect Cox proportional hazards regression model was used to estimate the hazard ratio (HR) for

VTE event during risk period compared to control period[20]. To address competing risk, cause-specific hazard ratios were used[21]. Individuals were right-censored if they did not experience a VTE event by the end of follow-up or were lost to follow-up. Univariate and multivariate Cox regression was used to establish association between baseline risk factors and VTE risk. Risk factors that were statistically significant in the univariate model were included in a multivariate analysis. In addition, effect modifier analyses were performed by stratifying the study subjects based on risk factors; interactions between potential effect modifiers were interrogated. Sensitivity analyses were performed by excluding those who have died or lost to follow-up prior to the end of study. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina). p-values of < 0.05 were considered statistically significant and all testing was two-sided.

RESULTS

Baseline demographics and cardiovascular risk

Of the 2854 patients, 1640 (57.5%) were men; mean age was 64±13 years old with 2479 (91.7%) patients being Caucasian (Table 1). Many had established cardiovascular risk factors including hypertension (n=1356, 49.2%) and diabetes mellitus (n= 433, 15.7%). A prior VTE was noted in 12.5%; 9.6% of all patients, independent of VTE history, were on anticoagulation at the time of ICI initiation. Most patients had a Khorana score of 0 and 1 (36.5%, 35.5%, respectively).

Oncologic History

The most common cancer types were non-small cell lung cancer (n=781, 28.4%) and melanoma (n=778, 28.2%, Table 1). About one fifth of the patients had received radiation therapy (n=572, 20.8%) and 10.4% of the patients had received fluorouracil (n=284). Overall, ICIs were started a median of 652 days (IQR 195–1972) after cancer diagnosis. Checkpoint inhibitor-based immunotherapies that target the programmed death protein 1 (PD1) pathway were the most commonly prescribed (n=2147, 75.2%, Table 1). Corticosteroid therapy was prescribed in 417 (17.8%) patients within 30 days prior to ICI initiation. Across the entire cohort, 1179 (42.9%) patients had irAEs; within these 1179 patients, 734 (62.3%) received corticosteroid therapy for treatment of these immune mediated adverse effects.

Risk of venous thromboembolism after initiation of immune checkpoint inhibitors

The median length of observation for patients post-ICI initiation was 194 days (IQR 65412). The adjusted incidence rate for VTE was higher after starting an ICI. There were 259 events (4.85 per 100 person-years) during the control interval and 244 events (11.75 per 100 person-years) during the at-risk interval. There was a higher incidence rate for both PE and DVT (Table 2). A graph depicting the rate of VTE over time is shown in Figure 1. We observed that rate of VTE minimally increased with cancer progression prior to ICI initiation and was the highest immediately after ICI initiation. From there, it subsequently declined but the risk of VTE never returned to the baseline risk prior to ICI (Figure 1). The absolute risk for VTE was 7.4% at 6 months after starting and ICI and 13.8% at 1 year after an ICI. Analysis with fixed-effect proportional hazards model demonstrated an

over 4-fold increase in risk of VTE post ICI compared to pre-ICI (Hazard Ratio [HR] 4.98, 95% confidence interval [CI] 3.65 – 6.79, p<0.001, Table 3). To additionally control for competing risk, we tested the rates of VTE after exclusion of subjects who died within 6 months, 1 year and 2 years of starting ICI treatment in separate analyses and similarly observed an increase in VTE rates after ICI (Table 3, Supplemental Table 1, 2 and 3). The trends of VTE risks relative to ICI initiation remained largely unchanged as well (Figure 2 and 3). Out of 2854 patients, 892 patients died before the study period ended or a VTE event could have occurred. Among the remaining 1962 patients, 1208 were lost to follow-up (defined by last medication change, last new diagnosis code or last appointment) before the 2-year study period ended and 510 patients were followed up to the end of the study and did not experience either death or a VTE event. As the median length of observation in the post-ICI period was significantly shorter than 730 days, we also performed sensitivity analysis by excluding patients who were dead and lost to follow up by the end of 2-year period and found similar results (Table 3, Figure 4). Given that the control period included in the study was 2 years and some patients could have been cancer free in that period of time, we examined incidence rates of VTE events at different intervals pre- and post-ICI (Supplemental Table 7). The incidence rate of DVT, PE, and VTE were 2.26, 2.88, and 4.67 events per 100 person years at 3 months prior to ICI initiation. In comparison, at 3 months post ICI initiation, the rates of DVT, PE, VTE were 12.41, 9.45 and 19.24 per 100 person years, respectively. At 2 years post ICI initiation, the rates of DVT, PE, VTE were 7.67, 7.08 and 12.48 events per 100 person years, suggesting that increase in VTE post ICI is unlikely to be due to patients being cancer free during control period.

Risk factors for VTE post ICI

Compared to patients who were VTE free in the two-year period post-ICI, those who developed VTE were modestly younger (63±12 vs. 65±13 years) and were more likely to have prior history of VTE (18.4 vs. 12.5%, Table 1). In the regression analysis, a history of hypertension and age less than 65 predicted VTE in both adjust and unadjusted models (Supplemental Table 4, Table 4). History of prior VTE predicted increased VTE risk in the univariate analysis but not in the multivariate analysis. Patients who had VTE had a higher Khorana Risk Score (p=0.0014, Table 1) and a Khorana score 2 predicted a higher risk for VTE post-ICI in both univariate and multivariate models (Table 4, Supplemental Table 4). Patients who had a VTE occur within 2 years of ICI initiation had a higher rate of urothelial cancer (9.4 vs. 6.0%), but a lower rate of melanoma (20.1 vs. 29.0%). Melanoma predicted a lower risk of VTE in both unadjusted and adjusted analyses (Supplemental Table 4, Table 4). To address whether VTE rates with an ICI use differed across cancer types, we examined incidence rates of VTE pre- and post- ICI across cancer groups (Supplemental Table 6, Supplemental Figure 2). There was an increase in rates of VTE among most cancer types post ICI initiation compared to 2 years prior to ICI use. To interrogate whether the degree of VTE risk potentiation is uniform across cancer types, we used a multi-level categorical variable to describe cancer types to address the mutually exclusive nature of this variable. In comparison to patients with lung cancer, those with melanoma had a lower risk of developing VTE with ICI use (HR 0.42, 95% CI 0.30 – 0.61, p<0.001, Supplemental Table 8), while patients in all other cancer groups had similar increase in risk of VTE with ICI use. No statistically significant difference was observed in the risk of VTE among use

of different classes of ICI (Table 1, Supplemental Table 4). There were also no differences in the prior use of potentially cardiotoxic cancer therapy, time from cancer diagnosis to ICI initiation, the occurrence of irAEs, or corticosteroid use. Line-associated DVTs occurred in 14 patients before an ICI (incidence rate 0.39 per 100 person years) and in 13 patients after an ICI (incidence rate 0.62 per 100 person years), an over 3-fold increase in DVTs post ICI initiation (HR 3.25, 95% CI 1.06–9.97, p=0.039). This increase in event rate was comparable to all DVTs within 2 years of starting an ICI (Table 3). A total of 262 patients were on therapeutic anticoagulation at the time of ICI initiation. The median time between start of anticoagulation to the start of ICI was 173 days (IQR 56, 382). Therapeutic anticoagulation at initiation of ICI did not predict VTE risk (Supplemental Table 4, Table 4). Among those who were on therapeutic anticoagulation at the time of ICI, length of time on anticoagulation did not predict risk of VTE with an ICI use (HR 0.96, 95% CI 0.54 – 1.70). However, the increase in VTE risk with ICI use was attenuated by baseline anticoagulation (patients on anticoagulation HR 0.92, 95% CI 0.52 – 1.62; patients not on anticoagulation HR 4.65, 95% CI 3.26 – 6.63, p-value for interaction <0.001, Supplemental Table 5, Supplemental Figure 3).

DISCUSSION

In this study, we characterized the risk for VTE among 2854 patients treated with an ICI. The risk for a VTE at 6 months and 1 year after starting an ICI was high at 7.4% and 13.8%, respectively. In comparison to the period prior to ICI, the risk of developing VTE was more than 4-fold higher after starting an ICI. The higher rate for VTE events was observed for both PE and DVT. A history of hypertension and a higher Khorana risk score predicted a higher risk of VTE, while older age and a history of melanoma were associated with lower risk of VTE. This increase in VTE risk with ICI use was lowered with the use of anticoagulation.

There have been individual case reports describing VTE events in patients with cancer undergoing ICI treatment[22–25]. Beyond case reports, several studies have evaluated the combined outcome of arterial and venous thromboembolic events with ICI use with conflicting results; most of these studies have not performed a control comparison limiting the conclusions. For example, in a report of 122 patients on an ICI, incidence of combined arterial and venous thrombosis events was 8.2% with VTE in 5 (4.1%) patients[26]. In a study evaluating 672 patients treated with an ICI there was a cumulative incidence of 12.9% for VTE[15]. In contrast, two prior studies of patients with non-small cell lung cancer who received ICIs (vs. traditional chemotherapy) identified no difference in acute vascular events (both arterial and venous) after initiation of therapy[16,17]. Further, randomized trials testing the effect of ICIs have not reported a high incidence of VTEs[27–29]. In a meta-analysis of 20,273 patients from 68 retrospective and prospective studies, the authors found the incidence rate of VTE to be similar in both ICI and non-ICI arms[30]. The reason for the difference in findings is not clear. Several negative studies had a relatively smaller sample size and, here, we provide data on a population of almost 3,000 patients. We also compared the rates of VTE with a control period and found that the rate of VTE increased 4-fold after ICI treatment and reported a similar rate to prior studies of VTE on an ICI at 12 months[14, 15]. Additionally, we included all cancer types expanding the external relevance of

the study findings. It is also possible that meta-analysis of clinical trials may underestimate the occurrence of a VTE or may reflect the different population included. Specifically, the meta-analysis reported a 2.7% rate of VTE at a follow-up that varied from a few months up to three years[30]. In comparison, multiple studies, including ours, report a VTE rate that ranges from approximately 13 to 16% at one year[14, 15]. Finally, prior studies that evaluated the efficacy of combination therapy of ICI with anti-angiogenic therapies, which are known to be thrombogenic, did not report VTE as a potential side effect. This finding might be due to the fact that these studies confined adverse effects to those that occurred in at least 10% of the patients[31–34]. Our results suggest use of ICI as a risk factor for VTE and further studies to corroborate such findings should be pursued.

The risk factors for VTE with ICI are also not completely understood. A recent single center retrospective cohort study evaluated 228 patients with melanoma who received ICIs, where the use of combination therapy was high, and identified that VTEs developed in 37 (16.2%) patients over median follow-up of 27.3 months. The study identified combination therapy, a Khorana Score 1, a history of coronary disease, and anticoagulation at time of ICI as risk factors for developing VTE while on an ICI. Our findings are complementary but also significantly additive. We identified that a history of hypertension, a younger age, and a Khorana Risk Score 2 were predictive of the occurrent of VTE after an ICI whereas melanoma was associated with a lower risk.

Immunomodulatory therapy in other cancers has been associated with an increase in VTE. Patients with multiple myeloma (MM) have an increased incidence of VTE due to both the malignancy itself and the therapy. This risk is heightened in those treated with combination therapy[35, 36]. For example, the combination of thalidomide with dexamethasone increased the incidence of VTE from baseline rate of 3 – 4% to 14 – 26%[35]. Additional studies found that prophylactic anticoagulation in patients with MM on immunomodulatory drugs can reduce VTE risk[37]. These findings have resulted in a scoring system and established guidelines for the prophylactic anticoagulation in patients with MM treated with combination therapy including thalidomide/lenalidomide[35, 38, 39]. We identified that while therapeutic anticoagulation did not predict VTE, it mediated the increase in VTE seen with ICI use. Our results suggest use of ICI may be a risk factor for VTE. Further studies to corroborate such findings should be pursued and, if confirmed, the subsequently performance of clinical trials to evaluate the efficacy of prophylactic anticoagulation in patients without contraindication undergoing ICI treatment would be indicated.

Study Limitations:

This was a retrospective self-controlled study. The self-controlled nature of the analysis limits our ability to control for time-dependent factors but is effective in eliminating the effect of time-invariant confounders. Our study lacked the data to differentiate those who received ICI only therapy as compared to those who received combination of chemotherapy with ICI, limiting our ability to interrogate the potential effect of combination therapy on risk of VTE. Furthermore, we did not have another cohort of patients to validate our findings in, limiting the strength of the findings. We interrogated the effect of the cancer progression on VTE risks by eliminating those who died within 6 months and one year of starting ICI;

thus, we could demonstrate a persistently elevated VTE risk associated with ICI initiation. We did not observe any difference in time from cancer diagnosis to ICI initiation between patients who did and did not develop VTE. Both findings suggest but not confirm that the higher VTE risk we observed is not likely solely a function of more advanced cancer but may also be an effect of exposure to an ICI. While the length of observation was limited by the high death and lost to follow up rate during the post-ICI period, we performed sensitivity analysis by eliminating patients who were either dead or lost to follow up by the end of 2-year study period and demonstrated similar findings. Our study may also be prone to ascertainment bias where more VTE events would have been detected if patients received more surveillance scans with active treatment. In total, almost half of the PE diagnoses (43%) were made via staging scans (Supplemental Table 9). However, more PEs were diagnosed incidentally on staging scans in the pre-ICI period as compared to post-ICI period (51% vs 34%). Thus, it is unlikely that increased rates of PEs observed in the risk period is a reflection of increased incidental diagnosis via an increased number of surveillance scans. In understanding the effect of anticoagulation at the time of ICI on the risk VTE with ICI use, the study design was limited by its inability to control for baseline VTE, and thus how anticoagulation associates with VTE. This would need to be addressed using a non-ICI control cohort to compare risks of VTE between the two groups, while adjusting for anticoagulation history and also history of VTE in a multivariate model.

In conclusion, this study demonstrated an increased risk of VTE in cancer patients in the first 2 years after initiating ICI. Younger age, a history of hypertension, and a higher Khorana score predicted higher risk of VTE, whereas patients with melanoma had a lower risk of developing VTE. Anticoagulation at the time of ICI initiation significantly mediated this risk. Our study highlights the need for increased clinical suspicion for VTE in patients with cancer receiving ICIs. Upon confirmation of the findings via additional studies, randomized trials testing the effect of prophylactic anticoagulation with ICI initiation would be reasonable.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Declaration of competing interest

Abbreviation List:

CI	Confidence Interval
DVT	Deep Vein Thrombosis
HR	Hazard Ratio
ICI	Immune Checkpoint Inhibitors
irAE	immune-related Adverse Event
MM	Multiple myeloma
PE	Pulmonary Embolism
RPDR	Research Patient Data Registry
VTE	Venous Thromboembolism

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Highlights

- Rate of venous thromboembolism (VTE) increases after starting an ICI

- Patients with a higher Khorana score are more likely to develop VTE with an ICI

- Compared to lung cancer, patients with melanoma have lower risk of VTE on an ICI

- Anticoagulation can attenuate the increase in risk of VTE with an ICI use.

- Clinical suspicion for VTE in patients receiving ICIs should be increased.

Figure 1:
Incidence rates of venous thromboembolism events (deep vein thrombosis, pulmonary embolism, deep vein thrombosis/pulmonary embolism) before and after initiation of immune checkpoint inhibitors (entire cohort n=2854)

Incidence Rates of Venous Thromboembolism Before and After Initiation of Immune Checkpoint Inhibitors (Excluding those who died in the first 6 months)

Figure 2:
Incidence rates of venous thromboembolism events (deep vein thrombosis, pulmonary embolism, deep vein thrombosis/pulmonary embolism) before and after initiation of immune checkpoint inhibitors- excluding those who died within 6 months of starting ICI (n=2287)

Incidence Rates of Venous Thromboembolism Before and After Initiation of Immune Checkpoint Inhibitors (Excluding those who died in the first year)

Figure 3:
Incidence rates of venous thromboembolism events (deep vein thrombosis, pulmonary embolism, deep vein thrombosis/pulmonary embolism) before and after initiation of immune checkpoint inhibitors- excluding those who died within 1 year of starting ICI (n=2077)
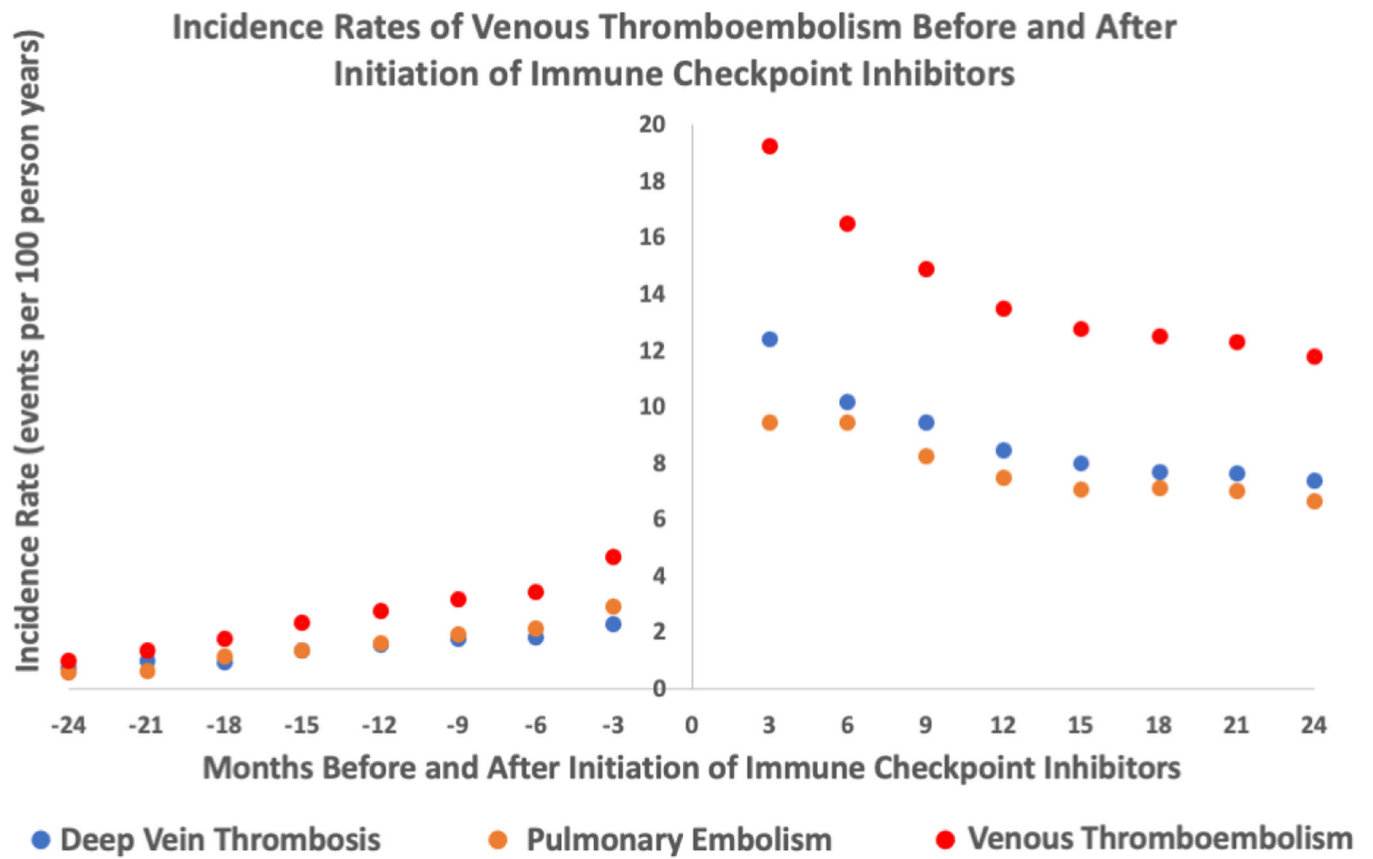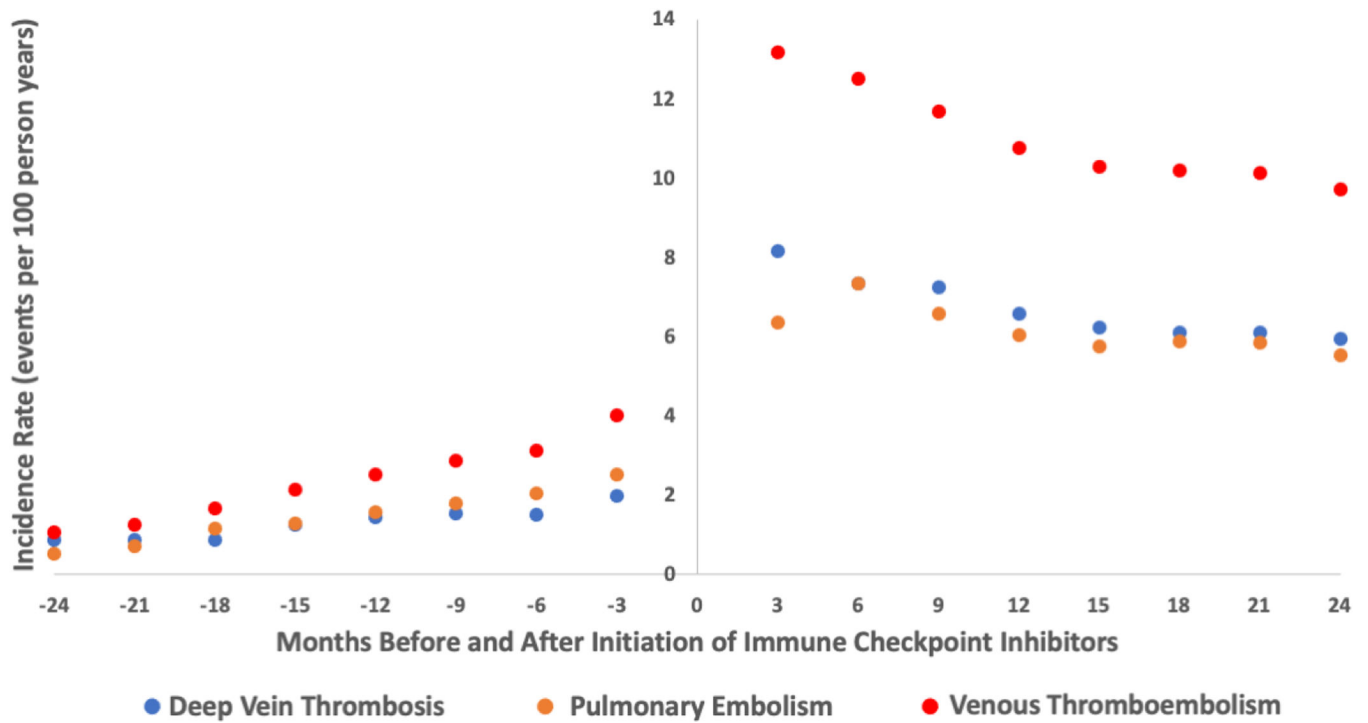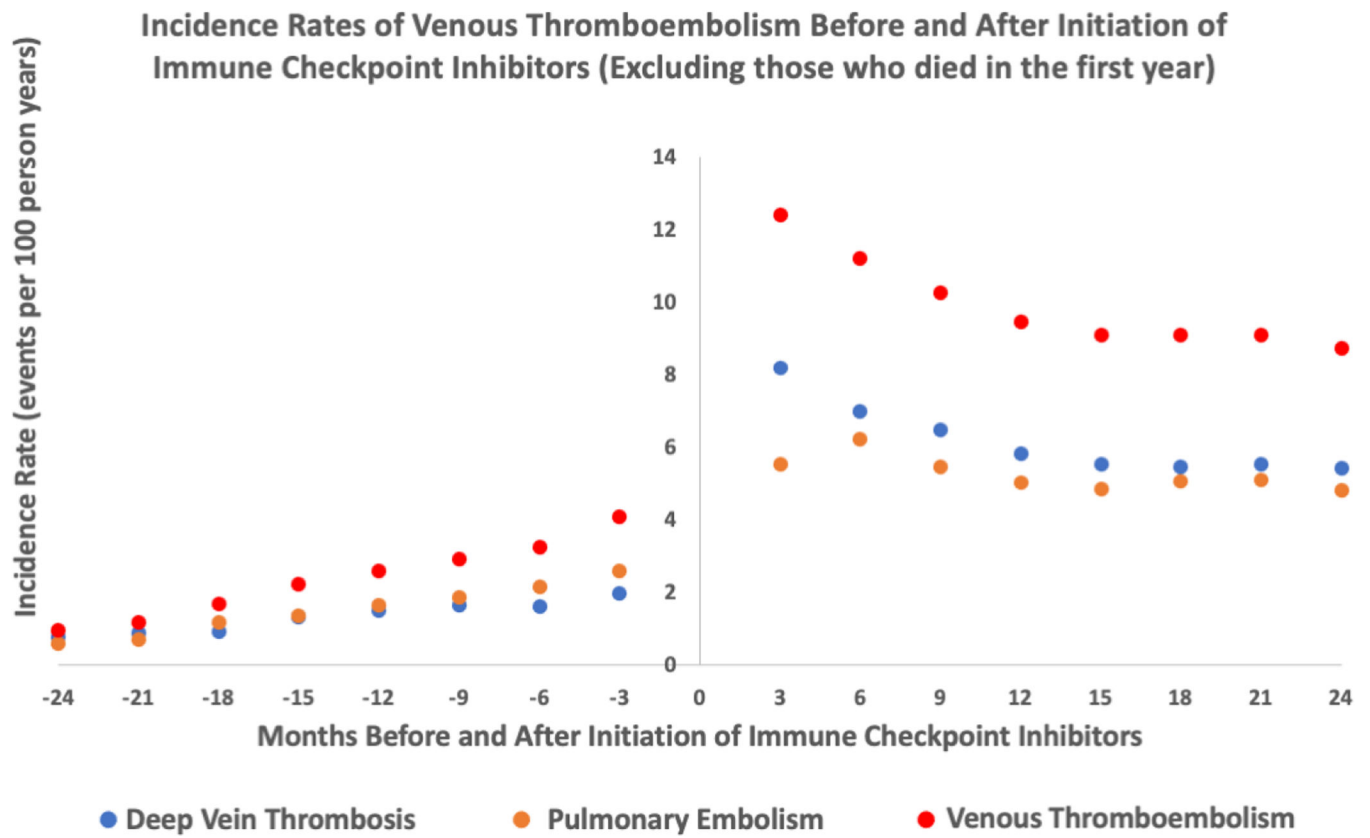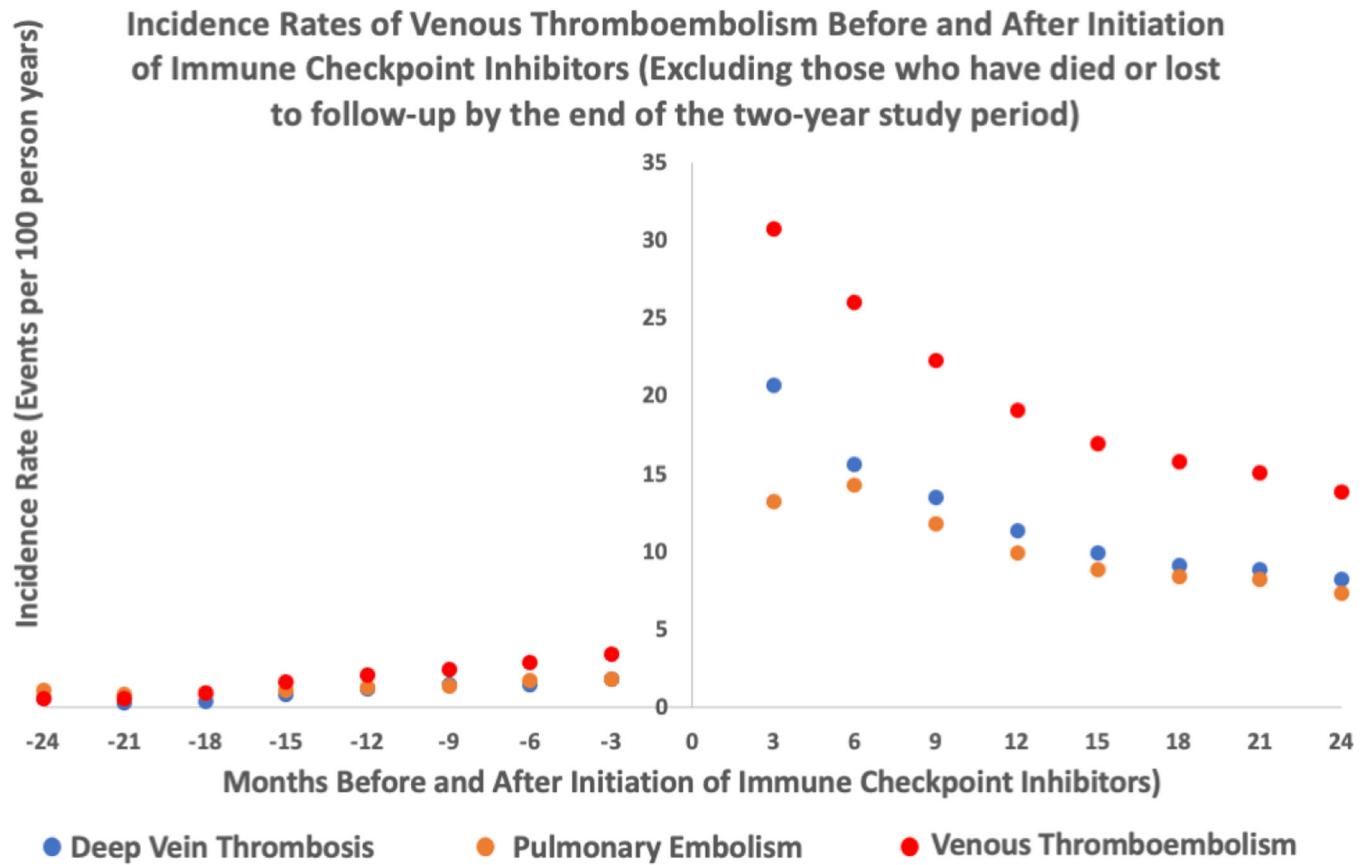
Figure 4:
Incidence rates of venous thromboembolism events (deep vein thrombosis, pulmonary embolism, deep vein thrombosis/pulmonary embolism) before and after initiation of immune checkpoint inhibitors- excluding those who died or were lost to follow up within 2 years of starting ICI (n=754)

Table 1

Baseline Characteristics at the Start of the Immune Checkpoint Inhibitors

	All patients		Patients with VTE events within 2 years from ICI start		Patients with no VTE events within 2 years from ICI start		P value
Demographics							
Number of patients	2854		244		2610		
Male	1640 (57.5%)		130 (53.3%)		1510(57.9%)		0.18
Age (years)	64±13		63±12		65±13		0.047
	Data available (n)	*Number (%)*	*Data available (n)*	*Number (%)*	*Data available (n)*	*Number (%)*	
Race							
White	2704	2479 (91.7%)	241	216 (89.6%)	2463	2263 (91.9%)	0.12
Asian		96 (3.6%)		11 (4.6%)		85 (3.5%)	
Black or African American		57 (2.1%)		10 (4.2%)		47 (1.9%)	
Hispanic		29 (0.9%)		1 (0.4%)		24 (1.0%)	
Other		43 (1.6%)		3 (1.2%)		44 (1.6%)	
Baseline Risk Factors							
Hypertension	2756	1356 (49.2%)	244	118 (48.4%)	2512	1238 (48.9%)	0.78
Diabetes mellitus	2756	433 (15.7%)	244	39 (16.0%)	2512	394 (15.7%)	0.90
Smoking current or prior	2756	429 (15.6%)	244	27 (15.2%)	2512	392 (15.6%)	0.92
Chronic kidney disease	2756	327 (11.9%)	244	23 (9.4%)	2512	304 (12.1%)	0.21
History of myocardial infarction	2854	136 (4.5%)	244	11 (4.5%)	2598	125 (4.8%)	1.00
History of any coronary revascularization	2854	195 (6.9%)	244	7 (2.9%)	2598	188 (7.2%)	0.008
History of ischemic stroke	2854	82 (2.9%)	244	6 (2.5%)	2598	76 (2.9%)	0.84
History of any cardiovascular event	2854	322 (11.3%)	244	20 (8.2%)	2598	302 (11.6%)	0.11
History of venous thromboembolism	2854	358 (12.5%)	244	45 (18.4%)	2610	313 (12.0%)	0.004
Khorana Risk score							
0	2136	779 (36.5%)	195	51 (26.2%)	1941	728 (37.5%)	0.0014
1		759 (35.5%)		78(40.0%)		681 (35.1%)	
2		428 (20.0%)		41(21.0%)		387 (19.9%)	
3		135 (6.3%)		19(9.7%)		116(6.0%)	
4		33 (1.5%)		5(2.6%)		28 (1.4%)	
5		2 (0.09%)		1(0.5%)		1 (0.05%)	
Baseline Cardiovascular Medications							
Angiotensin Converting Enzyme Inhibitor or Angiotensin II Receptor Blocker	2704	612 (22.6%)	239	52 (21.8%)	2465	560 (22.7%)	0.73
Statins	2704	705 (26.1%)	243	89 (36.6%)	2515	772 (30.1%)	0.057

		All patients		Patients with VTE events within 2 years from ICI start		Patients with no VTE events within 2 years from ICI start		P value
Aspirin	2704	578 (21.4%)		239	61 (25.5%)	2465	517 (20.1%)	0.10
Other anti-platelet	2704	66 (2.4%)		239	3 (1.3%)	2486	63 (2.6%)	0.21
Any anticoagulation	2730	262 (9.6%)		244	27 (11.1%)	2486	235 (9.5%)	0.42
Low Molecular Weight Heparin (treatment dosing)	2730	139 (5.1%)		244	21 (8.6%)	2486	116 (4.8%)	0.014
Direct Oral Anticoagulant	2730	60 (2.2%)		244	4 (1.6%)	2486	56 (2.3%)	0.82
Warfarin	2730	96 (3.5%)		244	6 (2.5%)	2486	90 (3.6%)	0.46
Cancer Types								
Non-small cell lung	2754	781 (28.4%)		244	82 (33.6%)	2511	699 (27.8%)	0.056
Melanoma		778 (28.2%)			49 (20.1%)		729 (29.0%)	0.003
Head and neck		334 (12.1%)			27 (11.1%)		307 (12.2%)	0.59
Renal and genitourinary		174 (6.3%)			23 (9.4%)		151 (6.0%)	0.036
Breast		119 (4.3%)			11 (4.5%)		108 (4.3%)	0.88
Gastrointestinal		109 (3.9%)			12 (4.9%)		97 (3.9%)	0.42
Gynecologic		107 (3.9%)			11 (4.5%)		96 (3.8%)	0.60
Non-Hodgkin Lymphoma		76 (2.7%)			6 (2.5%)		70 (2.8%)	0.76
Hepatocellular		58 (2.1%)			4 (1.6%)		54 (2.2%)	0.60
Cholangiocarcinoma		39 (1.4%)			2 (0.8%)		37 (1.5%)	0.41
Pancreatic		37 (1.3%)			5 (2.1%)		32 (1.3%)	0.32
Other		142 (5.2%)			12 (4.9%)		130 (5.2%)	0.86
Prior Cancer Therapies								
Radiation therapy	2756	572 (20.8%)		244	51 (20.9%)	2512	521 (20.7%)	0.93
Anthracyclines	2723	151 (5.5%)		242	15 (6.2%)	2481	136 (5.5%)	0.64
Tyrosine kinase inhibitors	2723	61 (2.2%)		242	7 (2.9%)	2481	54 (2.2%)	0.47
5- Fluorouracil	2723	284 (10.4%)		242	22 (9.1%)	2481	262 (9.6%)	0.58
Platinum-based chemotherapy	2723	1022 (37.5%)		242	94 (38.8%)	2481	928 (37.4%)	0.68
Janus kinase Inhibitors	2723	1 (0.04%)		242	0	2481	1 (0.04%)	1.00
Tumor necrosis factor inhibitors	2723	11 (0.4%)		242	0	2481	11 (0.4%)	0.62
Mitogen-activated protein kinase kinase inhibitor	2723	44 (1.6%)		242	2 (0.84%)	2481	42 (1.7%)	0.43
Anaplastic lymphoma kinase inhibitor	2723	11 (0.4%)		242	1 (0.41%)	2481	10 (0.40%)	1.00
Immune Checkpoint Inhibitor Type								
Single Therapy								
Programmed death-ligand-1	2854	283 (9.9%)		244	30 (12.3%)	2610	253 (9.7%)	0.21
Cytotoxic-T-Lymphocyte associated protein 4	2854	225 (7.9%)		244	14 (5.7%)	2610	211 (8.1%)	0.22
Programmed death-protein 1	2854	2147 (75.2%)		244	180 (73.8%)	2610	1968 (75.4%)	0.58

	All patients		Patients with VTE events within 2 years from ICI start		Patients with no VTE events within 2 years from ICI start		P value
Cytotoxic-T-Lymphocyte associated protein 4 or programmed death protein 1	2854	2(0.1%)	244	0 (0%)	2610	2 (0.08%)	1.00
Combination Therapy							
Cytotoxic-T-Lymphocyte associated protein 4/ Programmed death protein 1	2854	197 (6.9%)	244	20 (8.2%)	2610	176 (6.7%)	0.36
Corticosteroid treatment at start of ICI	2342	417 (17.8%)	208	41 (19.7%)	2134	376 (17.6%)	0.45
Time from cancer diagnosis to ICI initiation – days (IQR)	2745	652 (195–1972)	243	550 (170–1870)	2502	665 (199–1975)	0.15
Immune Related Adverse Events (irAE) with ICI Use							
Gastrointestinal	2748	500 (18.2%)	243	36 (14.8%)	2505	464 (18.5%)	0.15
Skin	2748	429 (15.6%)	243	33 (13.6%)	2505	396 (15.8%)	0.36
Pulmonary	2748	189 (6.9%)	243	26 (10.7%)	2505	163 (6.5%)	0.014
Hepatic	2748	179 (6.5%)	243	14 (5.8%)	2505	165 (6.6%)	0.62
Endocrine	2748	175 (6.4%)	243	21 (8.6%)	2505	154 (6.2%)	0.13
Renal	2748	120 (4.4%)	243	8 (3.3%)	2505	112 (4.5%)	0.39
Neuromuscular	2815	98 (3.8%)	241	8 (3.3%)	2574	90 (3.5%)	0.88
Pancreas	2748	61 (2.2%)	243	2 (0.8%)	2505	59 (2.4%)	0.12
Any of the above adverse events	2748	1179 (42.9%)	243	103 (42.4%)	2505	1076 (43.0%)	0.86
Corticosteroids use for irAE	2748	734 (26.7%)	243	69 (28.4%)	2505	665 (26.6%)	0.53
Baseline Clinical Parameters and Lab Values							
	Data available (n)	*Mean±SD*	*Data available (n)*	*Mean±SD*	*Data available (n)*	*Mean±SD*	
Body mass index - (kg/m²)	2271	27.0±6.4	206	27.0±5.6	2065	27.0±6.5	0.81
Systolic blood pressure (mmHg)	2297	127.6±18.6	207	126.6±17.0	2090	127.7±18.7	0.40
Hemoglobin (g/dL)	2599	11.9±2.0	231	11.7± 1.9	2368	11.9±2.0	0.11
Platelets (thousands/uL)	2598	253.8± 113.0	230	284.1±130.7	2368	251.0±110.8	<0.001
High density lipoprotein (mg/dL)	810	50.0±20.0	74	51.6±20.6	736	49.8±20.0	0.44
Low density lipoprotein (mg/dL)	785	100.0±36.9	73	107.5±38.4	712	99.2±36.6	0.067
Glomerular filtration rate (mL/min/1.73m²)	1035	68.2±23.9	88	67.6±23.2	947	68.3±24.0	0.81
	Data available (n)	*Median (IQR)*	*Data available (n)*	*Median (IQR)*	*Data available (n)*	*Median (IQR)*	
White blood count (thousand/uL)	2701	7.1 (5.5–9.3)	239	7.6(5.7–10.2)	2462	7.1(5.5–9.2)	0.0081

Table 2:

Incidence rate ratios for VTE events within two years pre-and post-immune checkpoint inhibitors (n=2854)

	Pre-Immune Checkpoint Inhibitor		Post-Immune Checkpoint Inhibitor	
	Number of events	Incidence rate (per 100 person-years)	Number of events	Incidence rate (per 100 person-years)
Deep Vein Thrombosis	126	2.30	155	7.37
Pulmonary Embolism	162	2.95	140	6.61
Venous Thromboembolism	259	4.85	244	11.75

Table 3:

Fixed-effect cause-specific proportional hazards regression analysis for VTE events within two years pre-and post-immune checkpoint inhibitors

	Entire Cohort (n=2854)		Patients who are alive at 6 months' post immune checkpoint inhibitors (n=2287)		Patients who are alive at 1 year post immune checkpoint inhibitors (n=2077)		Patients who are alive and have not been lost to follow up at 2 years post immune checkpoint inhibitors (n=754)	
	Hazard ratio (95% confidence Interval)	P value	Hazard ratio (95% confidence Interval)	P value	Hazard ratio (95% confidence Interval)	P value	Hazard ratio (95% confidence Interval)	P value
Deep Vein Thrombosis	5.70 (3.79, 8.59)	<0.001	4.58 (2.99, 7.00)	<0.001	4.04 (2.61, 6.26)	<0.001	5.73 (3.13, 9.92)	<0.001
Pulmonary Embolism	4.75 (3.20, 7.10)	<0.001	3.76 (2.50, 5.66)	<0.001	3.18 (2.08, 4.86)	<0.001	4.47 (2.64, 7.56)	<0.001
Venous Thromboembolism	4.98 (3.65, 6.79)	<0.001	3.98 (2.89, 5.48)	<0.001	3.49 (2.51, 4.86)	<0.001	4.89 (3.26, 7.35)	<0.001

Table 4:

Multivariate Cox regression analysis for association between risk factors and a VTE event post ICI initiation comparing patients who developed VTE while on an ICI (n=259) to those who did not have a VTE event (n=2610)

	Hazard Ratio (95% confidence interval)	P value
Age >65	0.75 (0.58, 0.98)	0.03
History of hypertension	1.37 (1.06, 1.77)	0.015
History of smoking	1.24 (0.89, 1.73)	0.21
VTE prior to ICI	1.42 (0.99, 2.06)	0.06
Melanoma	0.59 (0.41, 0.85)	0.004
Non-small cell lung cancer	1.10 (0.81, 1.51)	0.54
Renal and genitourinary	1.47 (0.92, 2.35)	0.10
Therapeutic anticoagulation at initiation of ICI	1.04 (0.67, 1.63)	0.86
Khorana Risk Score 2	1.54 (1.14, 2.09)	0.005