Immune Checkpoint Inhibitors-Associated Thrombosis

Subjects: Others

Contributor: Tzu-Fei Wang , Marc Carrier

Tumor cells evade immune destruction by activating immune checkpoint receptor proteins including cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) found on T cells, and programmed death ligand 1 (PD-L1) found on tumor cells. A type of novel anticancer therapy termed “immune checkpoint inhibitors (ICIs)” involves monoclonal antibodies that specifically target these proteins and prevent immune escape from tumor cells. Immune checkpoint inhibitors (ICIs) target programmed cell death (PD) 1 receptor and its ligand PD-L1, and have become an integral part of treatment regimens in many cancers including lung cancer, renal cell carcinoma, melanoma, and more. Cancer is associated with a significantly increased risk of venous thromboembolism compared to non-cancer patients, and the risks increase further with anticancer therapies including ICIs. Cancer-associated thrombosis can lead to hospitalizations, delayed cancer treatment, and mortality.

immune checkpoint inhibitors thrombosis cell death

1. Introduction

Tumor cells evade immune destruction by activating immune checkpoint receptor proteins including cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) found on T cells, and programmed death ligand 1 (PD-L1) found on tumor cells. A type of novel anticancer therapy termed “immune checkpoint inhibitors (ICIs)” involves monoclonal antibodies that specifically target these proteins and prevent immune escape from tumor cells. Since the approval of the first ICI (ipilimumab) in 2011, seven ICIs have been approved in Canada and the United States in approximately 20 different malignancies (**Table 1**), including ipilimumab (anti-CTLA-4), nivolumab, pembrolizumab, cemiplimab (anti-PD-1), and atezolizumab, durvalumab, avelumab (anti-PD-L1). As such, patients eligible for ICI treatment significantly increased from 1.5% in 2011 to 43.6% in 2018 [1]. Sustained responses and significant improvement in survival have been seen with these novel therapies, and they have become the mainstay of therapies in many cancers such as melanoma, lung cancer, renal cell carcinoma (RCC), and more [2].

Table 1. Summary of approved immune checkpoint inhibitors (and their indications).

Immune Checkpoint Inhibitors	Target	Approved Indication
Ipilimumab	CTLA-4	Melanoma NSCLC

Immune Checkpoint Inhibitors	Target	Approved Indication
		RCC Colorectal cancer Malignant pleural mesothelioma
Pembrolizumab	PD-1	Melanoma NSCLC Urothelial carcinoma RCC Bladder cancer Esophageal/esophagogastric junction cancer Colorectal cancer Endometrial cancer Cervical cancer Breast cancer Head and neck squamous cell carcinoma Hodgkin lymphoma Primary mediastinal B cell lymphoma
Nivolumab	PD-1	Melanoma NSCLC RCC Head and neck squamous cell carcinoma Classical Hodgkin lymphoma Hepatocellular carcinoma
Cemiplimab	PD-1	NSCLC Cutaneous squamous cell carcinoma Cutaneous basal cell carcinoma Cervical cancer
Atezolizumab	PD-L1	NSCLC Small cell lung cancer Urothelial carcinoma
Avelumab	PD-L1	Urothelial carcinoma Merkel cell carcinoma
Durvalumab	PD-L1	NSCLC Urothelial carcinoma

Mostly approved for unresected or metastatic cancers, refer to individual monographs for detailed approval indications for each cancer. Abbreviations: NSCLC: non-small cell lung cancer; RCC: renal cell carcinoma.

Although thrombosis was not raised as a major concern in initial randomized controlled trials (RCTs) leading to the approval of ICIs, reports of thromboembolic disease had emerged from post-marketing wide use of these agents. Cancer-associated thrombosis is a known phenomenon, and it is estimated that 20% of cancer patients will develop thrombosis during their cancer journey [3]. It can result in hospitalizations, delayed cancer treatment, significant morbidity, and mortality [4][5]. Patients often experience psychosocial and financial distresses from the diagnosis of thrombosis as well [6][7]. Therefore, the optimal prevention and treatment strategies for cancer-associated thrombosis are crucial in the care of cancer patients.

2. Mechanism of Thrombosis and Immunotherapy

While the exact mechanisms of ICI-associated thrombosis remain unclear, studies have made strides to understand them. Programmed cell death protein 1 is crucial in downregulating pro-atherogenic T cell responses, so PD-1 antibodies can exacerbate atherosclerotic inflammatory vascular lesions [8]. Studies have shown that ICIs are found to be associated with increased T cell activation and endothelial inflammation, leading to thrombosis formation and accelerated atherosclerosis [9][10]. Similar to other immune-related adverse events associated with ICIs such as colitis and pneumonitis, ICIs release the break on immunoregulatory pathways, lead to an increase in inflammation and related cytokines, activate blood and endothelial cells, as well as release of neutrophil extracellular traps (NETs), and eventually result in thrombosis [11].

3. Incidence of Thrombosis in Patients Receiving Immune Checkpoint Inhibitors

Initial RCTs investigating the efficacy of ICIs as anticancer treatment did not report thrombosis as a major adverse event of concern. An initial meta-analysis of these RCTs showed a modest rate of VTE at 2.7% (95% confidence interval [CI] 1.8–4.0) and an arterial thrombosis (ATE) rate of 1.1% (95% CI 0.5–2.1) [12]. Another meta-analysis of RCTs and prospective studies of ICI use in patients with melanoma and non-small cell lung cancer (NSCLC) also reported similar rates (VTE rates: 1.5% in melanoma and 1.9% in NSCLC) [13]. Most recently, an updated meta-analysis showed no significantly increased risk of VTE (odds ratio [OR] 0.99, 95% CI 0.82–1.19) in patients treated with ICIs compared to non-ICI regimens [14]. However, all of these meta-analyses suffered from the possibility of underreporting of thrombosis events in RCTs in the first place. Solinas et al. excluded 40% of the eligible RCTs from analysis as they did not specifically report rates of thrombosis [12]. In addition, in these studies, thrombosis events were reported as adverse events based on the Common Terminology Criteria for Adverse Events (CTCAE) criteria instead of planned outcomes, and adverse events were often only reported if they were over certain percentages. Significant underreporting of thrombosis events had been shown in previous oncology RCTs with focus on efficacy of cancer therapies compared to thromboprophylaxis trials, which requires close attention for data interpretation [15].

Since the approval and wide clinical use of various ICIs, occurrences of venous and/or arterial thromboses are increasingly reported. **Table 2** summarized the results of 27 cohort studies reported to date, with the majority being retrospective cohorts from single centers. Most (80–100%) patients had metastatic cancer, with the most common cancers including NSCLC, melanoma, and RCC. All studies included a variety of different ICIs available in clinical care. The incidence of thrombosis differed widely among studies, due to diverse types of underlying malignancies, concurrent cancer therapies (such as chemotherapy), and variable follow-up durations. In general, the incidence of VTE was 5–8% at 6 months and 10–15% at 12 months (**Table 2**). Overall, the rates reported in these retrospective cohort studies were higher than those reported from RCTs (1–2% in meta-analyses) [12][13], but not considerably higher when considering the 6-month risks of VTE of 9–10% in ambulatory cancer patients with Khorana score of ≥ 2 receiving chemotherapy [16]. However, given the efficacy of ICIs, the exposure of ICIs can be prolonged, and the risks of thrombosis can continue to accumulate. Sheng et al. showed that the thrombosis rate did not plateau until approximately 30 months in patients with metastatic RCC and 36 months in those with metastatic urothelial cancer

[17][18]. Therefore, as patients continue ICIs, the risks of thrombosis can continue to increase. This is worth noting as compared to chemotherapy, for which the highest risk of thrombosis is typically seen within the first 6 months.

Table 2. Summary of incidence rates of venous and arterial thrombosis from retrospective studies of cancer patients receiving immune checkpoint inhibitors (studies missing follow-up durations were not included).

Study	Country	N	Type of Cancer	Stage IV	Follow-up [Median (IQR)]	VTE Incidence % (95% CI)	ATE Incidence % (95% CI)
Hegde et al. 2017 [19] Abstract	USA	76	Lung	N/A	10.8 mo	18.4	2.6
Ibrahimi et al. 2017 [20] Abstract	USA	154	Lung 20.8% Melanoma 20.1% Ovarian 12.3%	92%	7 mo (198 days)	10.4	0
Bar et al. 2019 [21]	Israel	1215	All cancers Melanoma 40.5% Lung 28.7%	N/A	12 mo	AVE (MI, stroke, PE, DVT) 6 mo: 4.9 12 mo: 5.8	
Nichetti et al. 2019 [22]	Italy	217	NSCLC	95.4%	37.8 mo	7.4	6.5
Ando et al. 2020 [23]	Japan	122	Lung, kidney, stomach, urothelial, melanoma	N/A	N/A Time to thrombosis 90 days (range 6–178)	4.1	4.9
Drobni et al. 2020 [24]	USA	2842	All cancers NSCLC 28.8% Melanoma 27.9%	N/A	2 years	N/A	Composite: 5.35/100 person-yrs MI: 2.49 Stroke: 2.08
Deschênes-Simard et al. 2021 [25]	Canada	593	NSCLC	87.2%	12.7 (4.9–22.7) mo	9.9 (7.5–12.3) 76.5 (59.9–97.8) per 1000	1.3

Study	Country	N	Type of Cancer	Stage IV	Follow-up [Median (IQR)]	VTE Incidence % (95% CI)	ATE Incidence % (95% CI)
						person-years	
Gong et al. 2021 [26]	USA	2854	All cancers NSCLC 28.4% Melanoma 28.2%	N/A	194 days (IQR 65–412)	6 mo: 7.4 12 mo: 13.8	N/A
Gutierrez-Sainz et al. 2021 [27]	Spain	229	Lung 48% Melanoma 23.6% RCC 11.8%	96.5%	9.8 mo	7 (4–10)	N/A
Guven et al. 2021 [28]	Turkey	133	RCC 26.3% Melanoma 24.1% NSCLC 18.8%	100%	10.1 (5.8–18.5) mo	11.3	N/A
Haist et al. 2021 [29]	Germany	280	Melanoma	100%	28 mo (95% CI 23.4–32.6)	12.5	4.3
Hill et al. 2021 [30]	USA	435 (a) ICI: 171 (b) ICI+chemo: 157 (c) chemo then durvalumab: 107	NSCLC	47%	N/A	6 mo: (a) 7.6 (4.3–12.2) (b) 9.9 (5.8–15.3) (c) 9.4 (4.8–15.8) 12 mo: (a) 9.0 (5.3–14.0) (b) 12.8 (7.8–19.0) (c) 12.2 (6.8–19.2)	N/A
Icht et al. 2021 [31]	Israel	176	NSCLC	85.8%	6 mo (187 days)	4.5 (2.1–8.3)	N/A

Study	Country	N	Type of Cancer	Stage IV	Follow-up [Median (IQR)]	VTE Incidence % (95% CI)	ATE Incidence % (95% CI)
Kewan et al. 2021 [32]	USA	552	All cancers NSCLC 47.3%	100%	12.1 mo	12.1	1.3
Madison et al. 2021 [33] ^	USA	6127	Lung	N/A	6 mo	6.3	2.6
Moik et al. 2021 [34]	Austria	672	Melanoma 30.4% NSCLC 24.1% RCC 11%	85.8%	8.5 mo	6 mo: 5.0 (3.4–6.9) 12mo: 7.0 (5.1–9.3) Overall: 12.9 (8.2–18.5)	6 mo: 1.0 (0.4–2.0) 12 mo: 1.8 (0.7–3.6) Overall 1.8 (0.7–3.6)
Roopkumar et al. 2021	USA	1686	Lung 49.6% Melanoma 13.2%	90.3%	438 days (range 7–1971)	6 mo: 7.1 12 mo: 10.9 Overall: 24	N/A
Sheng et al. 2021 [17]	USA	351	RCC	100%	12.8 mo	11	2
						Total thromboembolism: 6 mo: 4.4 (2.6–6.9) 12 mo: 9.8 (6.8–13.4)	
Sussman et al. 2021	USA	228	Melanoma	81.1%	27.3 mo	6 mo: 8.0 (4.9–12.0) 12 mo: 12.9 (8.9–17.7)	6 mo: 2.2 (0.8–4.8) 12 mo: 4.5 (2.3–7.8)
Alma et al. 2022 [35]	France	481	Lung	86%	9.8 mo	9.8	N/A
Bjornhart et al. 2022 [36]	Denmark	146 prospective (A) *	NSCLC	87%	16.5 mo	6 mo: 13.0 12 mo: 14.4 Overall: 14	N/A

Study	Country	N	Type of Cancer	Stage IV	Follow-up [Median (IQR)]	VTE Incidence % (95% CI)	ATE Incidence % (95% CI)
		426 retrospective (B)				6 mo: 4.9 12 mo: 5.6 Overall: 6	
Canovas et al. 2022 [37]	Spain	665	Lung	91.2%	14 mo	6.9 All thrombosis: 8.4 (6.23–10.6)	1.5
		291	Melanoma [42][43][44]	82.5%	17 mo	4.8 All thrombosis: 5.8 (3.34–9.18)	1.0
Endo et al. 2022 [38]	Japan	120	Lung	62.5%	within 6 mo	2.5	4.2
Khorana et al. 2023 [39] ^	USA	(a) ICI: 605 (b) ICI+chemo: 602	NSCLC	100%	9.1 mo	6 mo: (a) 8.1 (b) 12.8 12 mo: (a) 13.5 (10.6–16.5)	N/A

Study	N	Type of cancer	Follow-up (mo)	VTE (%), (95% CI)	ATE (%), (95% CI)
Mulder et al. 2021 [43]	370	All cancers	6	4.1 (2.3–6.7)	N/A
			12	7.1 (4.2–11.1)	
Moik et al. 2021 [43] Abstract	3259	All cancers	6	3.9 (3.3–4.7)	1.3 (0.9–1.8)
			12	5.7 (4.9–6.6)	2.2 (1.7–2.8)
			24	7.3 (6.2–8.4)	3.1 (2.4–3.8)
Overvad et al. 2022 [44]	3946	All cancers	6	2.6	1.3
			12	3.8	1.9
2022 [—]					6 mo: 9.1 (6.0–13.0) 12 mo: 13.6 (9.6–18.4)

Abbreviations: ATE—arterial thrombosis; CI—confidence interval; mo—months; VTE—venous thromboembolism.

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Whether ICI combinations or combined ICI and chemotherapy would be associated with an increased risk of VTE (compared to single ICI or chemotherapy alone) is also an area of debate. Sussman et al. showed that ICI combinations were associated with a higher risk of VTE compared to single agent ICI [45]. A recent meta-analysis also showed that compared to mono-ICI, combined ICIs were associated with an increased risk of VTE and myocardial infarction in those with NSCLC [13]. However, another study showed that combined ICIs were not associated with higher risks [46]. Similarly, some studies showed an increased risk of ICI-chemotherapy

^ A prospective cohort employed screening-detected VTE by computed tomography venography and pulmonary angiography. Outcomes identified by ICD codes. Gong: VTE after ICI compared to pre, HR 4.98 (3.65–8.59).
Abbreviations: ATE—arterial thrombosis; AVE—arterial event; CI—confidence interval; DVT—deep vein

thrombosis, ICI and to checkpoint inhibitor [30][41], while others showed similar rates of thrombosis in patients receiving ICI and chemotherapy [21]. Recently, in the analysis of United States database of 2799 patients with stage IV NSCLC, first-line ICI-based regimens were associated with a 26% reduction in the risk of VTE compared to chemotherapy-based regimens, while the risks were comparable between ICI/chemo versus chemotherapy alone [39]. It is worth noting that a fair comparison of the risks of thrombosis associated with combination of chemotherapy and ICIs to ICI alone or chemotherapy alone could be challenging, as the baseline characteristics of these patients commonly differ significantly.

Data on the incidence or arterial thrombosis were even more scant, with rates within 1-2% over a follow-up period of 6 to 17 months (**Table 2**). A recent meta-analysis showed an increased risk of arterial thrombosis (OR 1.58, 95% CI 1.21–2.06) associated with ICI regimens [14]. In a matched cohort study of 2842 patients, Drobni et al. revealed that there was a three-fold increased risk of cardiovascular events after the start of ICIs compared to other anticancer therapies. The risks were similarly increased when they compared before and after ICI use in the same patients [24]. They also found ICI to be associated with a > three-fold higher rate of progression of total aortic plaque volume, which can be attenuated with concomitant use of corticosteroids or statins [24].

4. Prevention and Treatment of Thrombosis in Patients on Immune Checkpoint Inhibitors

Recent RCTs including AVERT and CASSINI trials demonstrated the efficacy and safety of prophylactic doses of apixaban and rivaroxaban, respectively, in the prevention of cancer-associated thrombosis in ambulatory cancer patients with intermediate-high risk patients (Khorana score ≥ 2) [47][48]. Major international guidelines have since suggested consideration of primary VTE prophylaxis in this population [49][50]. However, whether this practice can also apply to patients receiving ICIs remains unclear, as Khorana score, derived from a chemotherapy-treated population, had been shown to be suboptimal in risk stratification for patients on ICIs [17][22][28][30][31][32][34][35][36]. Patients with Khorana score of ≥ 2 on chemotherapy are associated with a 6-month risk of VTE of 9–10% [16], and whether the ICI-treated population with a 6-month VTE risk of 5–8% can derive sufficient benefit to warrant primary thromboprophylaxis in all patients receiving ICIs remains investigational. Further identification of high-risk patient population may be needed.

References

1. Haslam, A.; Prasad, V. Estimation of the Percentage of US Patients With Cancer Who Are Eligible for and Respond to Checkpoint Inhibitor Immunotherapy Drugs. JAMA Netw. Open. 2019, 2, e192535.
2. Himmel, M.E.; Saibil, S.D.; Saltman, A.P. Immune checkpoint inhibitors in cancer immunotherapy. CMAJ 2020, 192, E651.

3. Lyman, G.H.; Eckert, L.; Wang, Y.; Wang, H.; Cohen, A. Venous thromboembolism risk in patients with cancer receiving chemotherapy: A real-world analysis. Oncologists 2013, 18, 1321–1329.
4. Khorana, A.A.; Francis, C.W.; Culakova, E.; Kuderer, N.M.; Lyman, G.H. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J. Thromb. Haemost. 2007, 5, 632–634.
5. Lloyd, A.J.; Dewilde, S.; Noble, S.; Reimer, E.; Lee, A.Y.Y. What Impact Does Venous Thromboembolism and Bleeding Have on Cancer Patients' Quality of Life? Value Health 2018, 21, 449–455.
6. Noble, S.; Nelson, A.; Scott, J.; Berger, A.; Schmidt, K.; Swarnkar, P.; Lee, A. Patient Experience of Living With Cancer-Associated Thrombosis in Canada (PELICANADA). Res. Pract. Thromb. Haemost. 2020, 4, 154–160.
7. Font, C.; Nelson, A.; Garcia-Fernandez, T.; Prout, H.; Gee, P.; Noble, S. Patients' Experience of Living with Cancer-associated thrombosis in Spain (PELICANOS). Support Care Cancer 2018, 26, 3233–3239.
8. Jackson, S.P.; Darbousset, R.; Schoenwaelder, S.M. Thromboinflammation: Challenges of therapeutically targeting coagulation and other host defense mechanisms. Blood 2019, 133, 906–918.
9. Kunimasa, K.; Nishino, K.; Kimura, M.; Inoue, T.; Tamiya, M.; Kumagai, T.; Imamura, F. Pembrolizumab-induced acute thrombosis: A case report. Medicine 2018, 97, e10772.
10. Cochain, C.; Chaudhari, S.M.; Koch, M.; Wiendl, H.; Eckstein, H.H.; Zernecke, A. Programmed cell death-1 deficiency exacerbates T cell activation and atherogenesis despite expansion of regulatory T cells in atherosclerosis-prone mice. PLoS ONE 2014, 9, e93280.
11. McCrae, K.R.; Swaidani, S.; Diaz-Montero, C.M.; Khorana, A.A. Old is new again: Emergence of thromboembolic complications in cancer patients on immunotherapy. Thromb. Res. 2022, 213, S51–S57.
12. Solinas, C.; Saba, L.; Sganzerla, P.; Petrelli, F. Venous and arterial thromboembolic events with immune checkpoint inhibitors: A systematic review. Thromb. Res. 2020, 196, 444–453.
13. Giustozzi, M.; Becattini, C.; Roila, F.; Agnelli, G.; Mandala, M. Vascular events with immune checkpoint inhibitors in melanoma or non-small cell lung cancer: A systematic review and meta-analysis. Cancer Treat Rev. 2021, 100, 102280.
14. Ma, Z.; Sun, X.; Zhang, Y.; Li, H.; Sun, D.; An, Z.; Zhang, Y. Risk of Thromboembolic Events in Cancer Patients Treated with Immune Checkpoint Inhibitors: A Meta-analysis of Randomized Controlled Trials. Thromb. Haemost. 2022, 122, 1757–1766.

15. Chiasakul, T.; Patell, R.; Maraveyas, A.; Carrier, M.; Zwicker, J.I. Discordant reporting of VTE in pancreatic cancer: A systematic review and meta-analysis of thromboprophylaxis versus chemotherapeutic trials. J. Thromb. Haemost. 2021, 19, 489–501.
16. Ay, C.; Dunkler, D.; Marosi, C.; Chiriac, A.-L.; Vormittag, R.; Simanek, R.; Quehenberger, P.; Zielinski, C.; Pabinger, I. Prediction of venous thromboembolism in cancer patients. Blood 2010, 116, 5377–5382.
17. Sheng, I.Y.; Gupta, S.; Reddy, C.A.; Angelini, D.; Funchain, P.; Sussman, T.A.; Sleiman, J.; Ornstein, M.C.; McCrae, K.; Khorana, A.A. Thromboembolism in Patients with Metastatic Renal Cell Carcinoma Treated with Immunotherapy. Target Oncol. 2021, 16, 813–821.
18. Sheng, I.Y.; Gupta, S.; Reddy, C.A.; Angelini, D.; Funchain, P.; Sussman, T.A.; Sleiman, J.; Ornstein, M.C.; McCrae, K.; Khorana, A.A. Thromboembolism in Patients with Metastatic Urothelial Cancer Treated with Immune Checkpoint Inhibitors. Target Oncol. 2022, 17, 563–569.
19. Hegde, A.M.; Stroud, C.R.; Cherry, C.R.; Yogarajah, M.; Cherukuri, S.D.; Walker, P.R. Incidence and impact of thromboembolic events in lung cancer patients treated with nivolumab. J. Clin. Oncol. 2017, 35 (Suppl. 15), e20624.
20. Ibrahimi, S.; Machiorlatti, M.; Vesely, S.K.; Malla, M.; Modhia, F.; Jones, S.A.; Cherry, M.A. Incidence of Vascular Thromboembolic Events in Patients Receiving Immunotherapy: A Single Institution Experience. Blood 2017, 130, 4864.
21. Bar, J.; Markel, G.; Gottfried, T.; Percik, R.; Leibowitz-Amit, R.; Berger, R.; Golan, T.; Daher, S.; Taliansky, A.; Dudnik, E.; et al. Acute vascular events as a possibly related adverse event of immunotherapy: A single-institute retrospective study. Eur. J. Cancer 2019, 120, 122–131.
22. Nichetti, F.; Ligorio, F.; Zattarin, E.; Signorelli, D.; Prelaj, A.; Proto, C.; Galli, G.; Marra, A.; Apollonio, G.; Porcu, L.; et al. Is There an Interplay between Immune Checkpoint Inhibitors, Thromboprophylactic Treatments and Thromboembolic Events? Mechanisms and Impact in Non-Small Cell Lung Cancer Patients. Cancers 2019, 12, 67.
23. Ando, Y.; Hayashi, T.; Sugimoto, R.; Nishibe, S.; Ito, K.; Kawada, K.; Ikeda, Y.; Yamada, S.; Imaizumi, K. Risk factors for cancer-associated thrombosis in patients undergoing treatment with immune checkpoint inhibitors. Investig. New Drugs 2020, 38, 1200–1206.
24. Drobni, Z.D.; Alvi, R.M.; Taron, J.; Zafar, A.; Murphy, S.P.; Rambarat, P.K.; Mosarla, R.C.; Lee, C.; Zlotoff, D.A.; Raghu, V.K.; et al. Association Between Immune Checkpoint Inhibitors With Cardiovascular Events and Atherosclerotic Plaque. Circulation 2020, 142, 2299–2311.
25. Deschênes-Simard, X.; Richard, C.; Galland, L.; Blais, F.; Desilets, A.; Malo, J.; Cvetkovic, L.; Belkaid, W.; Elkrief, A.; Gagné, A.; et al. Venous thrombotic events in patients treated with immune checkpoint inhibitors for non-small cell lung cancer: A retrospective multicentric cohort study. Thromb. Res. 2021, 205, 29–39.

26. Gong, J.; Drobni, Z.D.; Alvi, R.M.; Murphy, S.P.; Sullivan, R.J.; Hartmann, S.E.; Gilman, H.K.; Lee, H.; Zubiri, L.; Raghu, V.K.; et al. Immune checkpoint inhibitors for cancer and venous thromboembolic events. Eur. J. Cancer 2021, 158, 99–110.
27. Gutierrez-Sainz, L.; Martinez-Marin, V.; Viñal, D.; Martinez-Perez, D.; Pedregosa, J.; Garcia-Cuesta, J.A.; Feliu, J. Incidence of venous thromboembolic events in cancer patients receiving immunotherapy: A single-institution experience. Clin. Transl. Oncol. Off. Publ. Fed. Span. Oncol. Soc. Natl. Cancer Inst. Mex. 2021, 23, 1245–1252.
28. Guven, D.C.; Aksun, M.S.; Sahin, T.K.; Aktepe, O.H.; Yildirim, H.C.; Taban, H.; Ceylan, F.; Kertmen, N.; Arik, Z.; Dizdar, O.; et al. Poorer baseline performance status is associated with increased thromboembolism risk in metastatic cancer patients treated with immunotherapy. Support. Care Cancer Off. J. Multinatl. Assoc. Support. Care Cancer 2021, 29, 5417–5423.
29. Haist, M.; Stege, H.; Pemler, S.; Heinz, J.; Fleischer, M.I.; Graf, C.; Ruf, W.; Loquai, C.; Grabbe, S. Anticoagulation with Factor Xa Inhibitors Is Associated with Improved Overall Response and Progression-Free Survival in Patients with Metastatic Malignant Melanoma Receiving Immune Checkpoint Inhibitors-A Retrospective, Real-World Cohort Study. Cancers 2021, 13, 5103.
30. Hill, H.; Robinson, M.; Lu, L.; Slaughter, D.; Amin, A.; Mileham, K.; Patel, J.N. Venous thromboembolism incidence and risk factors in non-small cell lung cancer patients receiving first-line systemic therapy. Thromb. Res. 2021, 208, 71–78.
31. Icht, O.; Darzi, N.; Shimony, S.; Jacobi, O.; Reinhorn, D.; Landman, Y.; Leader, A. Venous thromboembolism incidence and risk assessment in lung cancer patients treated with immune checkpoint inhibitors. J. Thromb. Haemost. 2021, 19, 1250–1258.
32. Kewan, T.; Ko, T.; Flores, M.; Sallam, Y.; Haddad, A.; Daw, H. Prognostic impact and risk factors of cancer-associated thrombosis events in stage-IV cancer patients treated with immune checkpoint inhibitors. Eur. J. Haematol. 2021, 106, 682–688.
33. Madison, C.J.; Melson, R.A.; Conlin, M.J.; Gundle, K.R.; Thompson, R.F.; Calverley, D.C. Thromboembolic risk in patients with lung cancer receiving systemic therapy. Br. J. Haematol. 2021, 194, 179–190.
34. Moik, F.; Chan, W.-S.E.; Wiedemann, S.; Hoeller, C.; Tuchmann, F.; Aretin, M.-B.; Fuereder, T.; Zöchbauer-Müller, S.; Preusser, M.; Pabinger, I.; et al. Incidence, risk factors, and outcomes of venous and arterial thromboembolism in immune checkpoint inhibitor therapy. Blood 2021, 137, 1669–1678.
35. Alma, S.; Eloi, D.; Léa, V.; Julie, C.; Valérie, M.; Pierre, G.; Hilgers, W.; Philippe, G.; Christine, Z.; Philippe, D. Incidence of venous thromboembolism and discriminating capacity of Khorana score in lung cancer patients treated with immune checkpoint inhibitors. J. Thromb. Thrombolysis 2022, 54, 287–294.

36. Bjørnhart, B.; Kristiansen, C.; Asmussen, J.; Hansen, K.H.; Wedervang, K.; Jørgensen, T.L.; Herrstedt, J.; Schytte, T. Clinical impact of venous thromboembolism in non-small cell lung cancer patients receiving immunotherapy. Thromb. Res. 2023, 221, 164–172.
37. Cánovas, M.S.; Garay, D.F.; Moran, L.O.; Pérez, J.R.; Rubio, C.M.G.; de Mena, M.L.; Portero, B.O.; Castro, J.B.; Lage, Y.; Lavin, D.C.; et al. Immune checkpoint inhibitors-associated thrombosis in patients with lung cancer and melanoma: A study of the Spanish society of medical oncology (SEOM) thrombosis and cancer group. Clin. Transl. Oncol. 2022, 24, 2010–2020.
38. Endo, S.; Honda, T.; Kawahara, T.; Sakakibara, R.; Mitsumura, T.; Okamoto, T.; Miyazaki, Y. Profile of metastatic lung cancer patients susceptible to development of thromboembolism during immunotherapy. Cancer Treat. Res. Commun. 2022, 31, 100547.
39. Khorana, A.; Palaia, J.; Rosenblatt, L.; Pisupati, R.; Huang, N.; Nguyen, C.; Barron, J.; Gallagher, K.; Bond, T.C. Venous thromboembolism incidence and risk factors associated with immune checkpoint inhibitors among patients with advanced non-small cell lung cancer. J. Immunother. Cancer 2023, 11, e006072.
40. May, S.B.; La, J.; Milner, E.; Riaz, N.; Amos, C.; Garcia, D.A.; Carrier, M.; Zakai, N.; Do, N.V.; Brophy, M.; et al. Venous Thromboembolism Risk in Cancer Patients Receiving First-Line Immune Checkpoint Inhibitor Vs. Chemotherapy. Blood 2022, 140, 7968–7970.
41. Sanfilippo, K.M.; Luo, S.; Lyman, G.H.; Calverley, D.C.; Kuderer, N. Identification of Risk Factors for and Development of a Predictive Model for Immunotherapy-Associated Venous Thromboembolism (VTE) in Patients with Non-Small Cell Lung Cancer. Blood 2022, 140, 2803–2804.
42. Mulder, F.I.; Horváth-Puhó, E.; van Es, N.; van Laarhoven, H.W.M.; Pedersen, L.; Moik, F.; Ay, C.; Büller, H.R.; Sørensen, H.T. Venous thromboembolism in cancer patients: A population-based cohort study. Blood 2021, 137, 1959–1969.
43. Moik, F.; Ay, C.; Horváth-Puhó, E.; Pabinger, I.; Mulder, F.I.; van Es, N.; Sørensen, H.T. Risk of Venous and Arterial Thromboembolic Events in Patients Receiving Targeted Anti-cancer Therapy–A Nationwide Cohort Study. Available online: https://abstracts.isth.org/abstract/risk-of-venous-and-arterial-thromboembolic-events-in-patients-receiving-targeted-anti-cancer-therapy-a-nationwide-cohort-study/ (accessed on 2 February 2023).
44. Overvad, T.F.; Skjøth, F.; Piazza, G.; Noble, S.; Ording, A.G.; Larsen, T.B.; Nielsen, P.B. The Khorana score and venous and arterial thrombosis in patients with cancer treated with immune checkpoint inhibitors: A Danish cohort study. J. Thromb. Haemost. JTH 2022, 20, 2921–2929.
45. Sussman, T.A.; Li, H.; Hobbs, B.; Funchain, P.; McCrae, K.R.; Khorana, A.A. Incidence of thromboembolism in patients with melanoma on immune checkpoint inhibitor therapy and its adverse association with survival. J. Immunother. Cancer 2021, 9, e001719.

46. Roopkumar, J.; Swaidani, S.; Kim, A.S.; Thapa, B.; Gervaso, L.; Hobbs, B.P.; Wei, W.; Alban, T.J.; Funchain, P.; Kundu, S.; et al. Increased Incidence of Venous Thromboembolism with Cancer Immunotherapy. Medicine 2021, 2, 423–434.
47. Carrier, M.; Abou-Nassar, K.; Mallick, R.; Tagalakis, V.; Shivakumar, S.; Schattner, A.; Kuruvilla, P.; Hill, D.; Spadafora, S.; Marquis, K.; et al. Apixaban to Prevent Venous Thromboembolism in Patients with Cancer. N. Engl. J. Med. 2019, 380, 711–719.
48. Khorana, A.A.; Soff, G.A.; Kakkar, A.K.; Vadhan-Raj, S.; Riess, H.; Wun, T.; Streiff, M.B.; Garcia, D.A.; Liebman, H.A.; Belani, C.P.; et al. Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer. N. Engl. J. Med. 2019, 380, 720–728.
49. Key, N.S.; Khorana, A.A.; Kuderer, N.M.; Bohlke, K.; Lee, A.Y.; Arcelus, J.I.; Wong, S.L.; Balaban, E.P.; Flowers, C.R.; Francis, C.W.; et al. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update. J. Clin. Oncol. 2020, 38, 496–520.
50. Lyman, G.H.; Carrier, M.; Ay, C.; Di Nisio, M.; Hicks, L.K.; Khorana, A.A.; Leavitt, A.D.; Lee, A.Y.Y.; Macbeth, F.; Morgan, R.L.; et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: Prevention and treatment in patients with cancer. Blood Adv. 2021, 5, 927–974.