Targeted anti-cancer agents and risk of venous thromboembolism

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Received: June 18, 2024.
Accepted: September 11, 2024.

https://doi.org/10.3324/haematol.2023.284778

Abstract

The incidence of one-year venous thromboembolism (VTE) after cancer diagnosis is reported to be increasing for several types of cancer. The introduction of targeted anti-cancer therapies and immunotherapy into the therapeutic armamentarium of medical oncologists contributed to the significantly improved response rates and survival times of cancer patients. In recent years, a potential prothrombotic effect of several targeted anti-cancer agents and immunotherapy drugs has been suggested; however, the methodological limitations of clinical trials evaluating the possible role of these classes of drugs on the VTE risk often make the interpretation of their results difficult. It is still not clear whether the increased risk of VTE is more closely correlated to the expression of specific oncogenic profiles than to the administration of specific therapies against these mutations. Furthermore, the increased survival rates observed with these agents could influence the prevalence of VTE events in cancer patients by the competing risk mortality on the risk of VTE. To date, the available data have suggested that the risk of VTE varies among different categories of targeted therapy, being most reported for anti-vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR), monoclonal antibodies and immune checkpoint inhibitors, and less reported for tyrosine kinase inhibitors (TKI). The risk of VTE seems to significantly increase when targeted therapy is administered in combination with traditional anti-cancer agents. Considering the uncertainties in estimating the rate of thrombotic complications associated with targeted therapy, the need for antithrombotic prophylaxis in cancer patients receiving targeted therapies still needs to be specifically assessed. In this review, we examine available evidence of the literature and the methodological limitations of clinical trials, and we discuss the potential future perspectives.

Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis and pulmonary embolism (PE), is a common complication among patients with cancer and is a significant cause of death in this population.[1] Coinciding with improved cancer outcomes, the overall 1-year incidence of VTE after cancer diagnosis has risen from 1% to over 3% in recent decades.[2]

Several factors may influence the VTE risk in cancer patients. Cancer is a well-known risk factor for thromboembolic events, increasing the risk of developing VTE approximately 9-fold in comparison to the general population, with heterogeneous risks according to cancer types and stages.[2] Other established risk factors include patients' characteristics (demographic characteristics, comorbidities) and treatment-related factors such as certain types of chemotherapy, surgery, radiotherapy, and central venous catheters.[3,4]

In the past two decades, various targeted anti-cancer agents have been developed, leading to a paradigm shift in anti-neoplastic treatment towards more personalized cancer treatment. In clinical oncology, these agents have dramatically revolutionized patient care, resulting in significant improvements in treatment responses and overall survival of patients. Increased survival due to the therapies is, over time, likely to be associated with an increase in events as patients will have longer exposure to other cancer-related prothrombotic factors. Targeted therapies are a heterogeneous group of drugs, administrable either orally

or intravenously, that comprise, among others, monoclonal antibodies, small molecule inhibitors including tyrosine kinase inhibitors (TKI), anti-hormonal agents, and immune regulatory molecules. Available literature suggests, often with modest evidence, a potential prothrombotic effect for certain classes of targeted therapy. In addition, recent data have highlighted significant rates of thrombotic complications in patients treated with immune checkpoint inhibitors (ICI).[5]

This review comprehensively summarizes the current evidence on risk profiles and potential mechanisms of thrombosis in cancer patients treated with targeted therapies, highlighting the limitations of existing data and exploring possible future perspectives.

Search strategy and article selection

We performed a systematic review of the medical literature to identify studies on the prothrombotic effect of targeted cancer therapy. A literature search of the PubMed electronic database (through the Medline) was carried out without time limits. Only studies published in English were considered.

Anti-angiogenic therapies

Angiogenesis is predominantly driven by vascular endothelial growth factor (VEGF) and its receptors, VEGFR1 and VEGFR2.[6] Targeted VEGF/R therapies, such as monoclonal antibodies (bevacizumab, ramucirumab, aflibercept) and TKI (sorafenib, sunitinib) inhibit the VEGF/R pathway, reducing tumor angiogenesis. Both monoclonal antibodies and TKI modulate angiogenesis through different mechanisms but share the common outcome of affecting vascular function and integrity.[7] The first drug proved to have anti-neoplastic properties by selectively inhibiting VEGF function was bevacizumab, a humanized monoclonal immunoglobulin G targeting soluble VEGF-A. While bevacizumab is recognized to be associated with an increased risk of arterial thromboembolic events, its role in the development of VTE is still a matter of debate. Meta-analyses have yielded controversial results regarding the risk of VTE associated with bevacizumab therapy compared to chemotherapy alone. While some studies did not demonstrate a statistically significant increase in VTE, the largest meta-analysis by Totzeck *et al.*, which reviewed 22 trials involving 20,050 participants, observed a significantly higher VTE risk with bevacizumab (pooled Relative Risk [RR]: 1.29; 95% Confidence Interval [CI]: 1.12-1.47).[8] In a meta-analysis by Nalluri *et al.* (15 randomized controlled trials [RCT], N=7,956 patients with various cancers), the risk of VTE was 11.9% with bevacizumab compared to 6.3% in the control arms.[9] However, 2 earlier meta-analyses did not demonstrate any significant increase in VTE risk for bevacizumab therapy.[10,11] In addition, a recent analysis by Saerens *et al.*, examining 9 trials with 5,121 ovarian cancer patients, revealed that bevacizumab treatment increased the VTE risk (RR: 1.32; 95% CI: 1.02-1.79) compared to no bevacizumab treatment.[12] One meta-analysis showed that bevacizumab did not significantly affect the risk of deep vein thrombosis (Odds Ratio [OR]: 2.16; 95% CI: 0.19, 25.16) or pulmonary embolism (OR: 5.12; 95% CI: 0.89, 29.61) in newly diagnosed adult glioblastoma multiforme patients.[13] In contrast, the recombinant fusion protein aflibercept, targeting and inhibiting VEGF-A, seems to have no association with the risk of VTE. Aflibercept is currently approved in combination with chemotherapy in patients with pretreated metastatic colorectal cancer (mCRC). In a meta-analysis of 5 RCT (3,262 patients), Kanukula *et al.* reported that aflibercept was not associated with an increased risk of all-grade VTE compared with placebo or non-aflibercept therapy (7.2% *vs.* 7.3% [RR: 1.00; 95% CI: 0.67-1.51).[14] Targeted anti-cancer therapies that directly act on VEGF-R1/2 exhibit varying prothrombotic risk profiles. Ramucirumab, a human monoclonal antibody targeting VEGF-R2, is used in the treatment of advanced or mCRC, gastric, and lung cancers. Notably, a meta-analysis of 6 RCT found no association between ramucirumab and an increased risk of VTE (RR: 0.7; 95% CI: 0.5-1.1).[15] In addition, various receptors of TKI that target VEGFR1/2, such as sunitinib, sorafenib, pazopanib, cabozantinib, regorafenib, and axitinib, have been developed and introduced into clinical practice. In addition to their anti-angiogenic effects, many of these agents also function as multi-kinase inhibitors, targeting not only VEGFR, but also PDGFR, KIT, RET, and other kinases to various extents. In a large meta-analysis of 14 RCT (N=4,430 patients with various cancers) comparing VTE risk between VEGFR-TKI and controls arms, no differences were observed (RR: 0.91; 95% CI: 0.62-1.35).[16] Interestingly, the risk of VTE in vandetanib trials seemed to be lower than in control arm patients (RR: 0.57; 95% CI: 0.31-1.05).[16] An overview of published studies reporting the risk of VTE in patients treated with anti-angiogenic therapies is shown in Table 1.

Epidermal growth factor receptor-targeted therapies

Different monoclonal antibodies and TKI targeting epidermal growth factor receptors (EGFR) have been developed and are broadly used in clinical practice. Pooled data from RCT indicate a potential modest increase in thromboembolic risk for established EGFR-targeted agents.[17] In a meta-analysis of 17 RCT including 12,870 patients (mostly metastatic lung and colorectal cancer), severe VTE (i.e., grade ≥3) was observed at a higher rate in cetuximab and panitumumab arms compared to the respective control arm patients (RR: 1.46; 95% CI: 1.26-1.69), with a weighted mean incidence of 7.8% in the EGFR-targeted therapy arms.[18] Another meta-analysis including 7,611 patients from 13 RCT compared VTE and arterial thrombotic events (ATE) in patients treated with cetuximab, panitumumab, gefitinib, and erlotinib to respective control arm patients, reporting an RR with EGFR-targeted therapy of 1.32 (95% CI: 1.07-1.63) for VTE

Table 1. Relative risks for venous thromboembolism with antiangiogenic therapy in various cancer types.

Author, year	Anti-angiogenic therapy	Cancer type	N of patients	VTE RR (95% CI)
Scappaticci *et al.*, 2007[10]	Bevacizumab	Lung, colorectal, breast	1,745	0.89 (0.66-1.20)
Nalluri *et al.*, 2008[9]	Bevacizumab	Lung, colorectal, breast, renal, pancreatic	7,956	1.33 (1.13-1.56)
Hurwitz *et al.*, 2011[11]	Bevacizumab	Lung, colorectal, breast, renal, pancreatic	6,055	0.91 (0.77-1.06)
Cortes *et al.*, 2012[85]	Bevacizumab	Breast	3,784	1.02 (0.70-1.61)
Qi *et al.*, 2012[16]	Vandetanib, pazopanib, sorafenib, sunitinib	Lung, colorectal, pancreatic, hepatic, breast, sarcoma	4,430	0.91 (0.62-1.35)
Zhou *et al.*, 2013[25]	Bevacizumab	Ovarian	3,621	1.32 (0.99-1.75)
Li *et al.*, 2015[13]	Bevacizumab	Glioblastoma multiforme	1,645	5.12 (0.89-26.61)*
Totzeck *et al.*, 2017[8]	Bevacizumab	Lung, colorectal, breast, renal, ovarian, gastric	20,500	1.29 (1.13-1.48)
Wang *et al.*, 2018[91]	Bevacizumab, sorafenib, nintedanib, pazopanib, aflibercept	Ovarian	8,721	1.08 (0.79-1.48)
Arnold *et al.*, 2018[15]	Ramucirumab	Lung, colorectal, breast, gastric, hepatic	4,996	0.71 (0.5-1.1)
Kanukula *et al.*, 2019[14]	Aflibercept	Metastatic colorectal cancer	3,262	1.00 (0.67-1.51)
Saerens *et al.*, 2021[12]	Bevacizumab	Ovarian	6,119	1.32 (1.02-1.79)

*Pulmonary embolism. 95% CI: 95% Confidence Interval; N: number; RR: relative risk; VTE: venous thromboembolism.

and of 1.34 (95% CI: 0.94-1.90) for ATE.[19] The risk of VTE was increased with EGFR-targeted monoclonal antibodies (RR 1.34; 95% CI: 1.07-1.68) as opposed to EGFR-targeted TKI (RR: 1.16; 95% CI: 0.61-2.18).[19] Similarly, a recent systematic review indicates a low risk of VTE associated with the currently widely used EGFR-targeted TKI, osimertinib.[20]

Recently, novel agents targeting EGFR have been investigated in patients with lung cancer, including amivantamab and lazertinib. Despite promising efficacy data, concerns have been raised regarding the VTE risk associated with these novel EGFR-targeted treatments.[21,22] In detail, in a phase III clinical trial including patients with advanced pre-treated non-small cell lung cancer (NSCLC), VTE was observed in 22% of patients treated with amivantamab-lazertinib chemotherapy, 10% with amivantamab chemotherapy and 5% in patients treated with chemotherapy only.[23] Similarly, in a large-scale RCT including patients with advanced NSCLC in the first-line setting (N=1,074), 37% of patients treated with amivantamab + lazertinib developed VTE compared to 9% in the osimertinib control arm.[24] Furthermore, in a pivotal RCT including patients with untreated advanced NSCLC (N=307), pulmonary embolism and deep vein thrombosis were reported in 7.9% and 6.6% of patients in the amivantamab chemotherapy arm, compared to 4.5% and 1.9% in the chemotherapy arm, respectively.[25]

In patients with lung cancer, EGFR-targeted therapy is primarily used based on EGFR mutational status, and, therefore, underlying cancer characteristics might in part explain differences in VTE risk according to EGFR-targeted therapies. However, reported VTE rates in patients with lung cancer were particularly high with genetic alterations in *ALK* and *ROS-1*, whereas a similar VTE risk was observed in EGFR-mutant as opposed to wild-type tumors in a retrospective cohort study (6-month cumulative incidence: 8.8% *vs*. 9.2%), arguing against the underlying cancer biology as a driver of VTE risk with EGFR-targeted therapies.[26,27] To the best of our knowledge, any potential underlying mechanisms of thromboembolic risk that could be associated with EGFR-targeted therapies have still not been clarified.

Breakpoint cluster region-Abelson proto-oncogene tyrosine kinase inhibitors

Breakpoint cluster region-Abelson proto-oncogene tyrosine kinase inhibitors (BCR-ABL TKI) have dramatically improved survival in patients with Philadelphia chromosome-positive leukemias. In 2001, imatinib was the first BCR-ABL TKI approved for the treatment of patients with chronic myeloid leukemia (CML).[27] Newer BCR-ABL TKI provide superior survival outcomes in comparison to imatinib. VTE have not been described as a significant adverse effect of BCR-ABL TKI. Venous occlusive events are reported in 0.27% of imatinib-treated patients and 0.72% of patients treated with new-generation TKI.[28]

A large population-based retrospective cohort study evaluating the 5-year ratio of cardiovascular events in 3,722 patients with CML under treatment with imatinib (N=1,906), dasatinib (N=1,269), and nilotinib (N=547) showed no difference in the VTE rate in the second-generation TKI (dasatinib or nilotinib) compared to the imatinib group (Hazard Ratio [HR] 1.25; 95% CI: 0.73-2.16 for dasatinib, HR: 1.04; 95% CI: 0.73-2.16 for nilotinib).[29] These results were confirmed after a propensity score matching analysis.[29]

In another retrospective cohort study that evaluated the incidence of both arterial and venous vascular adverse events (VAE) of CML patients treated with TKI (imatinib, nilotinib, and dasatinib), a higher incidence of VAE was reported in patients treated with second-generation TKI, particularly nilotinib, compared with patients treated with imatinib (HR: 3.13; 95% CI: 1.30-7.51). An increased risk of VAE, compared with imatinib, had also been described for dasatinib, but the difference was not statistically significant (HR: 1.71; 95% CI: 0.71-4.26).[30] Finally, in a phase II study including patients with CML treated with ponatinib, a VTE rate of 5% was reported.[31]

Bruton tyrosine kinase inhibitors

No literature data concerning the VTE risk in patients treated with Bruton TKI are currently available. Ibrutinib is associated with an increased risk of atrial fibrillation. The concurrent use of anticoagulation with ibrutinib has been associated with an increased risk of major and non-major clinically relevant bleeding in cancer patients.[32]

Anaplastic lymphoma kinase -/ ROS proto-oncogene 1 receptor tyrosine kinase inhibitor

Anaplastic lymphoma kinase (*ALK*) rearrangements are detected in approximately 5% of patients with NSCLC, especially among younger patients and non-smokers. Patients with *c-ros oncogene 1* (*ROS1*) rearrangements account for a further 1-2% of NSCLC patients. Recently, several publications have reported a 3-5-fold elevated risk of VTE events in patients with NSCLC carrying these oncogenic mutations with an overall 5-year VTE rate of up to 15.7%.[33-47] In addition, in patients with *ROS-1*-rearranged NSCLC, a rate of VTE recurrences of up to 30-35% was reported.[34]

The most prescribed targeted treatments with ALK- or ROS1-targeted therapy are represented by crizotinib, alectinib, and brigantinib. Crizotinib is a selective TKI for *ALK*, *MET*, and *ROS1* rearrangements first approved in patients with metastatic NSCLC. In a large cohort study, Roopkumar *et al*. reported that approximately 50% of the documented VTE events occurred before the start of treatment with ALK-targeted TKI.[35]

A recent report showed a numerically higher proportion of thromboembolic events (TE events) in patients with *ROS1*-, *ALK*- or EGFR-positive NSCLC who were receiving treatment with TKI or TKI plus chemotherapy compared to untreated patients or treated with chemotherapy only at the time of the thrombotic event (56% *vs*. 44%).[36] Similar results were reported in another study conducted in patients with NSCLC who received first-line treatment, with chemotherapy, ICI (pembrolizumab, nivolumab, atezolizumab, avelumab, and durvalumab) and/or oral targeted therapies (erlotinib, gefitinib, afatinib, osimertinib, crizotinib, alectinib, ceritinib). A cumulative incidence of VTE at six and 12 months associated with targeted therapy of 11.1% and 13.1%, respectively, was observed in these patients, and these rates were higher in patients who received targeted therapies compared with chemotherapy alone. Of note, there was no difference in the rates reported between those receiving EGFR or ALK inhibitors. The combination of CHT and ICI was also predictive of VTE in multivariate analysis.[37]

In a systematic review and meta-analysis including 5,767 patients with NSCLC, the overall incidence of TE during TKI treatment averaged 23% (95% CI: 17-28%). Assessing the incidence of VTE in the different molecular subtypes of NSCLC, 21.6% of patients carrying the *ALK* mutation and 44% of those carrying the *ROS1* mutation developed a VTE event. Up to 90% of patients had received TKI therapy as a first-line treatment.[38]

This observation has been confirmed by Lin *et al*., who reported an inferior progression-free survival after TKI therapy in patients who experienced TE in comparison to patients without TE, both in the ALK$^+$ cohort (5.6 *vs*. 12.9 months, $P<0.0001$) and in the ROS1$^+$ cohort (9.6 *vs*. 17.6 months, $P=0.0481$).[39]

Finally, a Cochrane meta-analysis that evaluated the safety of ALK-TKI administered as monotherapy for the treatment of advanced *ALK*-arranged NSCLC documented no differences in the rate of overall adverse events, including thrombotic events, for ALK-TKI *versus* chemotherapy alone (RR: 1.01; 95% CI: 1.00-1.03). In addition, no difference in terms of the rate of adverse events was documented between next-generation ALK-TKI (RR: 1.00; 95% CI: 0.98-1.01) compared with first-generation ALK-TKI (crizotinib).[40]

Synoptically, the high risk of VTE associated with *ALK* and *ROS1* translocation prior to initiation of TKI therapy suggests cancer-intrinsic factors as drivers of hypercoagulability. This concept is supported by a higher tissue factor expression in *ALK*-fusion-positive cancers.

B-Raf and MAPK/ERK kinase inhibitors

No evidence concerning an increased rate of VTE in patients treated with B-Raf (BRAF) or mitogen-activated protein kinase (MEK) inhibitors in monotherapy compared to chemotherapy or placebo has been reported.[48,49] Recently, a systematic review and metanalysis of 5 RCT described a 4-fold increased risk of PE in melanoma patients treated with combination therapy of BRAF and MEK inhibitors in comparison to patients treated with BRAF inhibitor monotherapy (RR: 4.36; 95% CI: 1.23-15.44). The risk of PE was higher for patients with a mean follow-up time longer than 15 months (RR: 7.70; 95% CI: 1.40-42.12).[50]

These findings were also confirmed in a study using a large pharmacovigilance database, where BRAF/MEK combination therapy was associated with cardiovascular events compared with BRAF monotherapy (OR: 1.8; 95% CI: 1.12-2.89).[51]

Hormonal therapies

The concept of anti-hormonal therapies represents an early example of 'personalized' cancer therapies. An increased risk of VTE for the non-steroidal selective estrogenic re-

ceptor modulator tamoxifen was observed early during clinical evaluations. In an early meta-analysis including 7 RCT, pooled VTE risk estimates were 2.8% for tamoxifen and 0.8% for control arm patients in premenopausal women, and 8.0% with tamoxifen + chemotherapy, 2.3% with tamoxifen and 0.4% with observation only.[52] Confirmatory data are available from a large database analysis of patients with early-stage breast cancer undergoing adjuvant tamoxifen therapy. Here, the risk of VTE was increased 3.5-fold during the first two years, whereas no significant differences in risk were observed thereafter during the complete 5-year treatment period.[53] Another large-scale database analysis including 13,202 patients reported an annual risk for VTE of 2% during tamoxifen therapy, which was especially pronounced during the early phase of treatment.[54] In contrast to tamoxifen, consistent data for aromatase inhibitors suggest no increase in thromboembolic risk in treated patients.[54,55] In recent years, inhibitors of cyclin-dependent kinases 4/6 (CDK4/6i) are increasingly used in addition to hormonal therapy in hormone-receptor-positive breast cancer both in the metastatic and adjuvant treatment settings. Consistent data from post-hoc analyses of clinical trials and observational studies suggest an increased VTE risk with CDK4/6i.[18] In a meta-analysis of 8 RCT including 4,557 patients with metastatic breast cancer, the RR for VTE was 2.62 (95% CI: 1.21-5.65) with CDK4/6i compared to control arm patients.[56] Furthermore, confirmatory data were recently published from an analysis based on an adverse event reporting system (FAERS) reporting an increase in the number of reports of VTE as an adverse event in CDKi-treated patients.[57] Synoptically, considerable data are available concerning thromboembolic risk associated with CDK4/6i treatment, suggesting an increased risk of both VTE and ATE, especially for palbociclib and abemaciclib, whereas lower rates were observed for ribociclib.[58] Currently, there are no dedicated studies regarding the potential mechanisms of CDK4/6i-associated thromboembolic risk, yet cancer-specific mutations in *CDKN2B*, an inhibitor of CDK4/6, have been linked to an increased risk of cancer-associated thrombosis.

Immune checkpoint inhibitors

Immune checkpoint inhibitors (ICI) represent a class of monoclonal antibodies directed at intercellular signaling molecules involved in regulating physiologic immune responses.[59] These involve, among others, the programmed death 1 (PD-1) and corresponding ligand (PD-L1) axis, with PD-L1 being over-expressed in many cancers, leading to impaired T-cell mediated antitumor immunity. By inhibiting PD-1/PD-L1, the physiologic anti-cancer immune response is reinvigorated. Furthermore, cytotoxic T-lymphocyte-associated-protein 4 (CTLA4) is a key regulator in the interaction between antigen-presenting cells and T cells. By targeting CTLA4, the systemic threshold of anticancer immunity is strongly affected. Thereby, inhibitors of PD-1/PD-L1 and CTLA4 have revolutionized cancer therapy and led to unprecedented improvements in efficacy and patient survival, often even despite advanced cancer stages.[59]

Immune checkpoint inhibitors lead to a strong and sustained inflammatory response in patients, characterized by a variety of immune-mediated inflammatory adverse events, with stronger individual immune responses linked to improved efficacy and patient outcomes.[60,61] In a meta-analysis of 48 RCT comparing different cardiovascular adverse events between ICI and control arms, the risk of VTE was similar between treatment groups.[62] However, the reported risk of thromboembolism was low, as another early meta-analysis of published trials reported pooled risk estimates for VTE of 2.7% and ATE of 1.1% in ICI-treated patients.[63] These data need to be interpreted with great caution, as severe under-reporting of thromboembolic adverse events in cancer trials has been reported in the past, hampering the possibile generalization of these post-hoc analyses.[64]

Upon implementation of ICI in routine clinical practice, numerous observational studies have since reported a substantial risk of VTE and ATE in patients treated with ICI.[65,66] Reported cumulative risk estimates in published cohorts of ICI-treated patients range from 9-24% for VTE and 2-5% for ATE.[66-74] Importantly, similar risks of VTE/ATE were reported irrespective of underlying cancer types.

Discrepant results were reported from comparative observational studies, evaluating differences in risk of thromboembolic events between ICI-treated patients and different control cohorts. In a single-center case-control study, matching 2,842 individuals treated with ICI to control patients, a 3-fold increase in composite cardiovascular events was found, with similar increases in risk of myocardial infarction, ischemic stroke, and coronary revascularization.[75] Furthermore, a 5-fold increased risk of cardiovascular events was reported in the two years after ICI initiation compared to the timeframe of within two years prior to therapy.[75] Similar observations were reported for VTE, with a 2-fold increase in VTE risk during ICI therapy compared to the pre-treatment period.[76] In addition, in a Danish population-based analysis, immunotherapy within four months after cancer diagnosis was associated with an independent 4-fold increase in VTE risk.[2] Moreover, an analysis of data from the US Food and Drug Administration (FDA)-FAERS suggests an increased reporting of both VTE and ATE in ICI-treated patients.[77] Khorana *et al.* recently reported similarly high rates of VTE in patients with advanced NSCLC undergoing chemotherapy (18.0/100 patient-years) and ICI therapy (13.5/100 patient-years), with the highest risk observed in patients undergoing combined chemo-ICI therapy (22.4/100 patient-years).[72] Finally, in a propensity-score weighted comparative analysis including 1,823 patients with advanced cancers, a similar risk of VTE was observed in patients undergoing first-line systemic therapy with ICI as compared to chemotherapy (6-month cumulative risk: 8.5% *vs.* 8.4%, propensity-score weight-

ed HR: 1.06; 95% CI: 0.88-1.26).[71] An overview of published cohort studies reporting the risk of VTE in patients treated with ICI is shown in Table 2.

Previously, a close interconnection between inflammatory pathways and hemostatic activation had been established.[78,79] Furthermore, autoimmune diseases with a similar clinical phenotype as ICI-induced immune-related adverse events increase the risk of VTE.[80] Therefore, conceptually, thromboembolic events might be affected by the systemic inflammatory stimulus propagated by ICI. This hypothesis is supported by recently published experimental data.[81,82]

Synoptically, observational data indicate a clinically relevant risk of VTE and ATE associated with ICI therapy; yet currently, there are conflicting data regarding the potential underlying causality. Mechanistically, ICI might contribute to an increased thrombotic risk mediated by enhanced immunothrombosis and atherosclerosis. Therefore, due to the often sustained therapy responses observed with ICI, and the increased use of ICI in curative treatment intent, dedicated studies evaluating risk profiles of cardiovascular events in treated patients are of high importance.

Discussion

Targeted therapies have revolutionized cancer care by allowing for treatments to be tailored to individual patient's cancer characteristics and introducing new approaches to disease management. However, despite the prolonged survival rates associated with targeted therapies, cancer-associated thrombotic events remain an important issue in treated patients and might be influenced by the treatment itself.

At present four questions arise for VTE and targeted therapy.

1. Can we argue that targeted anti-cancer therapy is associated with an increased risk of VTE and hypothesize a specific 'class effect'?
2. Does the VTE risk during targeted therapy reflect the direct effect of these agents or rather the underlying risk based on molecular alterations and oncogenic mutations in the tumor that are targeted by the therapy?
3. Could increased survival be associated with both lower incidence rates but more VTE events over time, as seen in common tumors like lung, breast, and prostate cancers?
4. Should we consider antithrombotic prophylaxis in patients treated with targeted anti-cancer therapies?

To answer the first question, we must consider the fact that risk of VTE varies among the different categories of targeted therapy, being most reported during therapies with VEGF- and EGFR-monoclonal antibodies, immunomodulatory drugs, and non-steroidal antiestrogenic receptor modulators.[8-16,18-26,52-58,59-82] There seem to be much less data regarding the risk of VTE associated with TKI available, although an increased incidence of thrombotic events has been reported in the literature for selected second-generation TKI.[30,31] Moreover, the risk of VTE appears to increase when targeted therapy is combined with chemotherapy.[5,10,21-23,25,71]

A possible explanation for variability in VTE risk could be related to the fact that the mechanism of interference with different metabolic and inflammatory pathways varies among different drugs. Furthermore, differences in the patient cohorts receiving treatment might influence the associated thrombotic risk profiles. Moreover, the interpretation of clinical trial results is challenging due to methodological limitations in the studies, such as the retrospective nature of the studies themselves, partly regarding small sample size, the inadequate diagnostic accuracy in diagnosing and reporting VTE, and the variability of the definition of the primary endpoint (with the inclusion often of a miscellany of both arterial and venous thromboembolic events). In addition, differences in follow-up times due to the increased survival with targeted agents, resulting in longer periods at risk in comparison to those in the control groups, may suggest higher rates of thromboembolic events when the follow-up time is not appropriately accounted for in the analysis.

It should be noted, however, that the different meta-analyses evaluating the increase in risk of VTE with targeted therapy compared with chemotherapy alone have generated controversial, and not totally convincing, results. One possible explanation for this variability may be sought in the large discrepancy in reporting of thromboembolic events between clinical trials and actual practice, suggesting a high probability of underestimation or underdiagnosis within clinical trials.

Given all these considerations, we believe that the concept of a 'class effect' on the risk of VTE by target therapy is difficult to sustain, but we do suggest that an assessment to estimate the risk of each individual cancer patient treated with these drugs should be made.

Regarding the second question, it is currently unclear whether the reported thromboembolic risk is more influenced by a direct prothrombotic effect of the different agents of targeted therapy or is rather an expression of the characteristics of treated patients (i.e., advanced stage of cancer disease) or the expression of specific oncogenic mutations. Indeed, several publications have reported a 3-5-fold elevated risk of VTE events in patients with NSCLC carrying *ALK* and *ROS-1* oncogenic mutations, with a VTE rate of up to 15.7% at five years.

Thirdly, increased survival due to the targeted therapies will lead to longer periods of exposure to other cancer-related risk factors for VTE. Over time, this will be associated with an increase in VTE events, as patients will have longer exposure to other cancer-related prothrombotic factors. The associated increased person-time at risk would result in more events, and would increase the prevalence of VTE events but decrease the incidence rates. The increased opportunity to develop VTE, because of improved survival, is the antithesis to the competing risk of mortality (that tends to overestimate incidence rates) and hence this also would lead to reduced incidence rates.

Fourthly, in the absence of consistent data from the litera-

Table 2. Reported rates of venous thromboembolism in published observational cohorts in patients with cancer treated with immune checkpoint inhibitors.*

Author, year	Design	N of patients	Cancer type	Median FU mth	VTE %	Selected reported risk factors
Nichetti *et al.*, 2019[90]	Single center prospective cohort study	217	NSCLC	37.8	7.4	-
May *et al.*, 2022 (Abstract)[92]	Healthcare-based cohort study (VA)	1,660	Various, first-line, stage III-IV	10.9	6 mth: 6.1 CI	-
Moik *et al.*, 2021 (Abstract)[93]	Population-based cohort study	3,259	Various	-	12 mth: 5.7 CI 24 mth: 7.3 CI	-
Gong *et al.*, 2021[76]	Single-center cohort study	2,854	Various (28% NSCLC, 28% melanoma)	6.5	11.75/100 PY 6 mth: 7.4 CI 12 mth: 13.8 CI	Khorana score, hypertension, prior VTE
Roopkumar *et al.*, 2021[68]	Single-center cohort study	1,686	Different cancer types (13% melanoma, 50% NSCLC)	14.4	24 6 mth: 7.1 CI 12 mth: 10.9 CI	Younger age, metastasis, inflammatory biomarkers
Hill *et al.*, 2021[37]	Single-center cohort study	1,587 (ICI: N=171; CTX+ICI: N=157; CTX+durva: N=107)	NSCLC, first-line	-	12 mth: ICI: 8.1 CI ICI+CTX: 11.7 CI CTX-durva: 12.8 CI	-
Moik *et al.*, 2021[66]	Single-center cohort study	672	Various (30% melanoma, 24% NSCLC)	8.5	12.9 6 mth: 5.0 12 mth: 7.0	Prior VTE, Stage IV, Khorana score: negative
Gutierrez-Sainz *et al.*, 2021[89]	Single-center cohort study	229	Various (48% NSCLC, melanoma 24%)	9.8	7	Female sex, melanoma
Sussman *et al.*, 2021[70]	Single-center cohort study	228	Melanoma	27.3	6 mth: 8.0 CI 12 mth: 12.9 CI N=37 events	ICI combination, Khorana score: ≥1
Deschênes-Simard *et al.*, 2021[73]	Single-center cohort study	593	NSCLC	12.7	9.9	Younger age, higher PDL1, smoking
Sheng *et al.*, 2021[88]	Single-center cohort study	351	Metastatic RCC	12.8	11	Khorana score: negative
Kewan *et al.*, 2021[67]	Multicenter cohort study	552	Stage IV, different cancers (47% NSCLC, 32% GU, 17% melanoma)	12.1	10.5	AC at baseline Khorana score: negative
Sanfilippo *et al.*, 2022 (Abstract)[94]	Healthcare-based cohort study (VA)	1,457	Various	-	6 mth: 5.3 CI	ICI-CTX combination, prior VTE
Cánovas *et al.*, 2022[86]	Multicenter cohort study	956	Lung (N=665), melanoma (N=291)	14	Lung: 6.9 Melanoma: 4.8	-
Sheng *et al.*, 2022[69]	Single-center cohort study	279	Urothelial cancer	5.6	13	-
Khorana *et al.*, 2023[72]	Single-center cohort study	2,299 (ICI: N=605; CTX: N=1,092; ICI+CTX: N=602)	Advanced NSCLC, first-line	9.1	ICI: 13.4 17.8/100 PY ICI+CTX: 18.1 22.4/100 PY	-
Li *et al.*, 2023[77]	Healthcare database analysis	1,823	Different cancers, first-line (stages III, IV)	-	8.5	-
Doubre *et al.*, 2023[74]	Post hoc analysis of multicenter retrospective cohort study	748	Advanced NSCLC, PDL1 ≥50%, pembrolizumab monotherapy	25.8	14.8	-
Cánovas *et al.*, 2023[87]	Multicenter cohort study	407	RCC (N=210), bladder (N=197)	13	RCC: 4.3 Bladder: 8.6	-

*Selected cohorts based on cohort size of number (N) >200 patients, sorted by sample size. AC: adriamycin (doxorubicin) and cyclophosphamide; CI: cumulative incidence; CTX: chemotherapy; durva: durvalumab; FU: follow-up; GU: genitourinary cancers; ICI: immune checkpoint inhibitor; mth: months; NSCLC: non-small cell lung cancer; PDL1: programmed death-ligand; PY: person-years; RCC: renal cell carcinoma; VA: Veterans Affair; VTE: venous thromboembolism.

ture on the estimated risk of VTE associated with targeted anti-cancer therapies, we cannot give any suggestions as to the appropriateness of thromboprophylaxis in patients receiving targeted therapy. Although international guidelines recommend that cancer patients, when they are initiating new systemic anti-cancer treatments, should receive a risk-stratified thromboprophylaxis based on risk assessment models, most risk scores (e.g., Khorana score) do not include the evaluation of anti-cancer treatment. The PROTECHT score, a risk assessment model that added chemotherapy to the variables of the Khorana score, has not been sufficiently validated.[83] Finally, the potential benefits of thromboprophylaxis would need to be carefully weighed against increased bleeding risk. For example, the use of bevacizumab was associated with an increased risk of bleeding explained by the inhibition of VEGF.

A post-hoc analysis of the Caravaggio study showed no increased risk of bleeding or thromboembolic recurrence in patients randomized to VTE anticoagulant treatment with apixaban compared with dalteparin in the subgroup of patients treated with TKI.[84] However, this analysis was performed on a relatively small cohort of patients, and hence there was significant uncertainty. Studies evaluating the efficacy and safety of antithrombotic prophylaxis in cancer patients treated with targeted therapy will be needed before antithrombotic prophylaxis can be recommended in this category of patients.

Conclusion

In conclusion, targeted anti-cancer therapies have become a main treatment strategy, leading to prolonged survival in cancer patients. An increased risk of VTE associated with several novel targeted therapies was reported, yet risk seems to be highly heterogeneous, and, for the moment, no definite conclusions regarding causality can be drawn. Further studies evaluating the incidence of thromboembolic events associated with targeted anti-cancer therapies, and the possible efficacy and safety of specific antithrombotic prophylaxis strategies, are needed.

Disclosures

FM has received travel/congress support from Novartis, and honoraria for lectures from Servier and Bristol-Myers Squibb. AC receives consulting and research fees from AbbVie, AstraZeneca, Bayer, Bristol-Myers Squibb, Daiichi-Sankyo, Janssen, Johnson & Johnson, Leo Pharma, Medtronic, Pfizer, Sanofi, and Viatris. MV and MG have no conflicts of interest to disclose.

Contributions

All Authors contributed equally to writing and editing this manuscript. All authors approved the final manuscript for publication.

References

1. Timp JF, Braekkan SK, Versteeg HH, et al. Epidemiology of cancer-associated venous thrombosis. Blood. 2013;122(10):1712-1723.
2. Mulder FI, Horváth-Puhó E, van Es N, et al. Venous thromboembolism in cancer patients: a population-based cohort study. Blood. 2021;137(14):1959-1969.
3. Kröger K, Weiland D, Ose C, et al. Risk factors for venous thromboembolic events in cancer patients. Ann Oncol. 2006;17(2):297-303.
4. Königsbrügge O, Pabinger I, Ay C. Risk factors for venous thromboembolism in cancer: novel findings from the Vienna Cancer and Thrombosis Study (CATS). Thromb Res. 2014;133(Suppl 2):S39-S43.
5. Li A, May SB, La J, et al. Venous thromboembolism risk in cancer patients receiving first-line immune checkpoint inhibitor versus chemotherapy. Am J Hematol. 2023;98(8):1214-1222.
6. Rajabi M, Mousa SA. The role of angiogenesis in cancer treatment. Biomedicines. 2017;5(2):34.
7. Neufeld G, Cohen T, Gengrinovitch S, et al. Vascular endothelial growth factor (VEGF) and its receptors. FASEB J. 1999;13(1):9-22.
8. Totzeck M, Mincu RI, Rassaf T. Cardiovascular adverse events in patients with cancer treated with bevacizumab: a meta-analysis of more than 20,000 patients. J Am Heart Assoc. 2017;6(8):e006278.
9. Nalluri SR, Chu D, Keresztes R, et al. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. JAMA. 2008;300(19):2277-2285.
10. Scappaticci FA, Skillings JR, Holden SN, et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. J Natl Cancer Inst. 2007;99(16):1232-1239.
11. Hurwitz HI, Saltz LB, Van Cutsem E, et al. Venous thromboembolic events with chemotherapy plus bevacizumab: a pooled analysis of patients in randomized phase II and III studies. J Clin Oncol. 2011;29(13):1757-1764.
12. Saerens M, De Jaeghere EA, Kanervo H, et al. Risk of thromboembolic events in ovarian cancer: does bevacizumab tilt the scale? A systematic review and meta-analysis. Cancers (Basel). 2021;13(18):4603.
13. Li X, Huang R, Xu Z. Risk of adverse vascular events in newly diagnosed glioblastoma multiforme patients treated with bevacizumab: a systematic review and meta-analysis. Sci Rep. 2015;5:14698.
14. Kanukula R, Ganta S, Sirumalla Y, et al. Risk of venous thromboembolic events in patients with cancer treated with aflibercept: a systematic review and meta-analysis of randomized controlled trials. Am J Ther. 2019;26(4):e549-e552.
15. Arnold D, Fuchs CS, Tabernero J, et al. Meta-analysis of individual patient safety data from six randomized, placebo-controlled trials with the antiangiogenic VEGFR2-binding monoclonal antibody ramucirumab. Ann Oncol. 2017;28(12):2932-2942.
16. Qi WX, Min DL, Shen Z, et al. Risk of venous thromboembolic events associated with VEGFR-TKIs: a systematic review and

meta-analysis. Int J Cancer. 2013;132(12):2967-2974.
17. Moik F, Ay C. Venous and arterial thromboembolism in patients with cancer treated with targeted anti-cancer therapies. Thromb Res. 2022;213(Suppl 1):S58-S65.
18. Miroddi M, Sterrantino C, Simmonds M, et al. Systematic review and meta-analysis of the risk of severe and life-threatening thromboembolism in cancer patients receiving anti-EGFR monoclonal antibodies (cetuximab or panitumumab). Int J Cancer. 2016;139(10):2370-2380.
19. Petrelli F, Cabiddu M, Borgonovo K, et al. Risk of venous and arterial thromboembolic events associated with anti-EGFR agents: a meta-analysis of randomized clinical trials. Ann Oncol. 2012;23(7):1672-1679.
20. Petrelli F, Cabiddu M, Borgonovo K, et al. Osimertinib-related venous thromboembolism in non-small lung cancer. Thromb Res. 2022;210:63-66.
21. Moik F, Riedl JM, Ay C. VTE with amivantamab plus chemotherapy in NSCLC. N Engl J Med. 2024;390(6):578-579.
22. Moik F, Riedl JM, Ay C. Correspondence to: amivantamab plus chemotherapy with and without lazertinib in EGFR-mutant advanced NSCLC after disease progression on osimertinib: primary results from the phase III MARIPOSA-2 study. Ann Oncol. 2024;35(3):327.
23. Passaro A, Wang J, Wang Y, et al; MARIPOSA-2 Investigators. Amivantamab plus chemotherapy with and without lazertinib in EGFR-mutant advanced NSCLC after disease progression on osimertinib: primary results from the phase III MARIPOSA-2 study. Ann Oncol. 2024;35(1):77-90.
24. Cho BC, Felip E, Spira AI, et al. Amivantamab plus lazertinib vs osimertinib as first-line treatment in patients with EGFR-mutated, advanced non-small cell lung cancer (NSCLC): primary results from MARIPOSA, a phase III, global, randomized, controlled trial. Ann Oncol. 2023;34(Suppl 2):S1306.
25. Zhou C, Tang KJ, Cho BC, et al. Amivantamab plus chemotherapy in NSCLC with EGFR exon 20 insertions. N Engl J Med. 2023;389(22):2039-2051.
26. Qian X, Fu M, Zheng J, et al. Driver genes associated with the incidence of venous thromboembolism in patients with non-small-cell lung cancer: a systematic review and meta-analysis. Front Oncol. 2021;11:680191.
27. Savage DG, Antman KH. Imatinib mesylate-a new oral targeted therapy. N Engl J Med. 2002;346(9):683-693.
28. Haguet H, Douxfils J, Mullier F, et al. Risk of arterial and venous occlusive events in chronic myeloid leukemia patients treated with new generation BCR-ABL tyrosine kinase inhibitors: a systematic review and meta-analysis. Expert Opin Drug Saf. 2017;16(1):5-12.
29. Nunes RAB, Neves PDMM, da Costa LMA, et al. Five-year cardiovascular outcomes in patients with chronic myeloid leukemia treated with imatinib, dasatinib, or nilotinib: a cohort study using data from a large multinational collaborative network. Front Cardiovasc Med. 2023;10:888366.
30. Chen MT, Huang ST, Lin CW, et al. Tyrosine kinase inhibitors and vascular adverse events in patients with chronic myeloid leukemia: a population-based, propensity score-matched cohort study. Oncologist. 2021;26(11):974-982.
31. Jain P, Kantarjian H, Jabbour E, et al. Ponatinib as first-line treatment for patients with chronic myeloid leukaemia in chronic phase: a phase 2 study. Lancet Haematol. 2015;2(9):e376-e383.
32. Wang TF, Baumann Kreuziger L, Leader A, et al. Characteristics and outcomes of patients on concurrent direct oral anticoagulants and targeted anticancer therapies-TacDOAC registry: communication from the ISTH SSC Subcommittee on Hemostasis and Malignancy. J Thromb Haemost. 2021;19(8):2068-2081.
33. Dou F, Li H, Zhu M, et al. Association between oncogenic status and risk of venous thromboembolism in patients with non-small cell lung cancer. Respir Res. 2018;19(1):88.
34. Chiari R, Ricciuti B, Landi L, et al. ROS1-rearranged non-small-cell lung cancer is associated with a high rate of venous thromboembolism: analysis from a phase II, prospective, multicenter, two-arms trial (METROS). Clin Lung Cancer. 2020;21(1):15-20.
35. Roopkumar J, Poudel SK, Gervaso L, et al. Risk of thromboembolism in patients with ALK- and EGFR-mutant lung cancer: a cohort study. J Thromb Haemost. 2021;19(3):822-829.
36. Wang HY, Wu SG, Lin YT, et al. Risk of thromboembolism in non-small-cell lung cancers patients with different oncogenic drivers, including ROS1, ALK, and EGFR mutations. ESMO Open. 2022;7(6):100742.
37. Hill H, Robinson M, Lu L, et al. Venous thromboembolism incidence and risk factors in non-small cell lung cancer patients receiving first-line systemic therapy. Thromb Res. 2021;208:71.
38. Liu Y, Wang W, Wu F, et al. High discrepancy in thrombotic events in non-small cell lung cancer patients with different genomic alterations. Transl Lung Cancer Res. 2021;10(3):1512-1524.
39. Lin M, Lu Y, Yu Q, et al. Common genetic driver mutation in NSCLC and their association with thromboembolic events: a retrospective study. Lung Cancer. 2022;172:29-34.
40. Cameron LB, Hitchen N, Chandran E, et al. Targeted therapy for advanced anaplastic lymphoma kinase (ALK)-rearranged non-small cell lung cancer. Cochrane Database Syst Rev. 2022;1(1):CD013453.
41. Verso M, Chiari R, Mosca S, et al. Incidence of Ct scan-detected pulmonary embolism in patients with oncogene-addicted, advanced lung adenocarcinoma. Thromb Res. 2015;136(5):924-927.
42. Davidsson E, Murgia N, Ortiz-Villalón C, et al. Mutational status predicts the risk of thromboembolic events in lung adenocarcinoma. Multidiscip Respir Med. 2017;12:16.
43. Zer A, Moskovitz M, Hwang DM, et al. ALK-rearranged non-small-cell lung cancer is associated with a high rate of venous thromboembolism. Clin Lung Cancer. 2017;18(2):156-161.
44. Zugazagoitia J, Biosca M, Oliveira J, et al. Incidence, predictors and prognostic significance of thromboembolic disease in patients with advanced ALK-rearranged non-small cell lung cancer. Eur Respir J. 2018;51(5):1702431.
45. Ng TL, Smith DE, Mushtaq R, et al. ROS1 gene rearrangements are associated with an elevated risk of peridiagnosis thromboembolic events. J Thorac Oncol. 2019;14(4):596-605.
46. Dou F, Zhang Y, Yi J, et al. Association of ALK rearrangement and risk of venous thromboembolism in patients with non-small cell lung cancer: a prospective cohort study. Thromb Res. 2020;186:36-41.
47. Icht O, Leader A, Batat E, et al. Arterial and venous thromboembolism in ALK-rearrangement-positive non-small cell lung cancer: a population-based cohort study. Oncologist. 2023;28(6):e391-e396.
48. Chapman PB, Robert C, Larkin J, et al. Vemurafenib in patients with BRAFV600 mutation-positive metastatic melanoma: final overall survival results of the randomized BRIM-3 study. Ann Oncol. 2017;28(10):2581-2587.

49. Maio M, Lewis K, Demidov L, et al; BRIM8 Investigators. Adjuvant vemurafenib in resected, BRAFV600 mutation-positive melanoma (BRIM8): a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. Lancet Oncol. 2018;19(4):510-520.
50. Mincu RI, Mahabadi AA, Michel L, et al. Cardiovascular adverse events associated with BRAF and MEK inhibitors: a systematic review and meta-analysis. JAMA Netw Open. 2019;2(8):e198890.
51. Guha A, Jain P, Fradley MG, et al. Cardiovascular adverse events associated with BRAF versus BRAF/MEK inhibitor: cross-sectional and longitudinal analysis using two large national registries. Cancer Med. 2021;10(12):3862-3872.
52. Saphner T, Tormey DC, Gray R. Venous and arterial thrombosis in patients who received adjuvant therapy for breast cancer. J Clin Oncol. 1991;9(2):286-294.
53. Hernandez RK, Sorensen HT, Pedersen L, et al. Tamoxifen treatment and risk of deep venous thrombosis and pulmonary embolism: a Danish population-based cohort study. Cancer. 2009;115(19):4442-4449.
54. Walker AJ, West J, Card TR, et al. When are breast cancer patients at highest risk of venous thromboembolism? A cohort study using English health care data. Blood. 2016;127(7):849-857.
55. Xu X, Chlebowski RT, Shi J, et al. Aromatase inhibitor and tamoxifen use and the risk of venous thromboembolism in breast cancer survivors. Breast Cancer Res Treat. 2019;174(3):785-794.
56. Thein KZ, Htut TW, Ball S, et al. Venous thromboembolism risk in patients with hormone receptor-positive HER2-negative metastatic breast cancer treated with combined CDK 4/6 inhibitors plus endocrine therapy versus endocrine therapy alone: a systematic review and meta-analysis of randomized controlled trials. Breast Cancer Res Treat. 2020;183(2):479-487.
57. West MT, Smith CE, Kaempf A, et al. CDK 4/6 inhibitors are associated with a high incidence of thrombotic events in women with breast cancer in real-world practice. Eur J Haematol. 2021;106(5):634-642.
58. Gervaso L, Montero AJ, Jia X, et al. Venous thromboembolism in breast cancer patients receiving cyclin-dependent kinase inhibitors. J Thromb Haemost. 2020;18(1):162-168.
59. Robert C. A decade of immune-checkpoint inhibitors in cancer therapy. Nat Commun. 2020;11(1):3801.
60. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2018;378(2):158-168.
61. Barth DA, Moik F, Steinlechner S, et al. Early kinetics of C reactive protein for cancer-agnostic prediction of therapy response and mortality in patients treated with immune checkpoint inhibitors: a multicenter cohort study. J Immunother Cancer. 2023;11:12.
62. Dolladille C, Akroun J, Morice P-M, et al. Cardiovascular immunotoxicities associated with immune checkpoint inhibitors: a safety meta-analysis. Eur Heart J. 2021;42(48):4964-4977.
63. Solinas C, Saba L, Sganzerla P, et al. Venous and arterial thromboembolic events with immune checkpoint inhibitors: a systematic review. Thromb Res. 2020;196:444-453.
64. Chiasakul T, Patell R, Maraveyas A, et al. Discordant reporting of VTE in pancreatic cancer: a systematic review and meta-analysis of thromboprophylaxis versus chemotherapeutic trials. J Thromb Haemost. 2021;19(2):489-501.
65. Moik F, Riedl JM, Englisch C, et al. Update on thrombosis risk in patients with cancer: focus on novel anticancer immunotherapies. Hamostaseologie. 2024;44(1):40-48.
66. Moik F, Chan W-SE, Wiedemann S, et al. Incidence, risk factors, and outcomes of venous and arterial thromboembolism in immune checkpoint inhibitor therapy. Blood. 2021;137(12):1669-1678.
67. Kewan T, Ko T, Flores M, et al. 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(5):682-688.
68. Roopkumar J, Swaidani S, Kim AS, et al. Increased incidence of venous thromboembolism with cancer immunotherapy. Med. 2021;2(4):423-434.
69. Sheng IY, Gupta S, Reddy CA, et al. Thromboembolism in patients with metastatic urothelial cancer treated with immune checkpoint inhibitors. Target Oncol. 2022;17(5):563-569.
70. Sussman TA, Li H, Hobbs B, et al. Incidence of thromboembolism in patients with melanoma on immune checkpoint inhibitor therapy and its adverse association with survival. J Immunother Cancer. 2021;9(1): e001719.
71. Li A, May SB, La J, et al. Venous thromboembolism risk in cancer patients receiving first-line immune checkpoint inhibitor versus chemotherapy. Am J Hematol. 2023;98(8):1214-1222.
72. Khorana AA, Palaia J, Rosenblatt L, et al. 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(1).
73. Deschênes-Simard X, Richard C, Galland L, 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.
74. Doubre H, Greillier L, Justeau G, et al. 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. J Cancer Res Clin Oncol. 2023;149(16):15095-15102.
75. Drobni ZD, Alvi RM, Taron J, et al. Association between immune checkpoint inhibitors with cardiovascular events and atherosclerotic plaque. Circulation. 2020;142(24):2299-2311.
76. Gong J, Drobni ZD, Alvi RM, et al. Immune checkpoint inhibitors for cancer and venous thromboembolic events. Eur J Cancer. 2021;158:99-110.
77. Li H, Sun X, Sun D, et al. Thromboembolic events associated with immune checkpoint inhibitors: a real-world study of data from the food and drug administration adverse event reporting system (FAERS) database. Int Immunopharmacol. 2021;98:107818.
78. Stark K, Massberg S. Interplay between inflammation and thrombosis in cardiovascular pathology. Nat Rev Cardiol. 2021;18(9):666-682.
79. Esmon CT. Inflammation and thrombosis. J Thromb Haemost. 2003;1(7):1343-1348.
80. Zöller B, Li X, Sundquist J, et al. Autoimmune diseases and venous thromboembolism: a review of the literature. Am J Cardiovasc Dis. 2012;2(3):171-183.
81. McCrae KR, Swaidani S, Diaz-Montero CM, et al. Old is new again: emergence of thromboembolic complications in cancer patients on immunotherapy. Thromb Res. 2022;213(Suppl 1):S51-S57.
82. Alghamdi EA, Aljohani H, Alghamdi W, et al. Immune checkpoint inhibitors and potential risk of thromboembolic events: analysis of the WHO global database of individual case safety reports.

Saudi Pharm J. 2022;30(8):1193-1199.
83. Verso M, Agnelli G, Barni S, et al. A modified Khorana risk assessment score for venous thromboembolism in cancer patients receiving chemotherapy: the Protecht score. Intern Emerg Med. 2012;7(3):291-292.
84. Verso M, Munoz A, Agnelli G. Bleeding risk with concomitant administration of VEGF-TKIs and anticoagulant agents. Semin Oncol. 2023;50(3-5):67-70.
85. Cortes J, Calvo V, Ramírez-Merino N, et al. Adverse events risk associated with bevacizumab addition to breast cancer chemotherapy: a meta-analysis. Ann Oncol. 2012;23(5):1130-1137.
86. Cánovas MS, Garay DF, Moran LO, 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(10):2010-2020.
87. Cánovas MS, Garay DF, Adoamnei E, et al. Immune checkpoint inhibitor-associated thrombosis in patients with bladder and kidney cancer: a study of the Spanish Society of Medical Oncology (SEOM) thrombosis and cancer group. Clin Transl Oncol. 2023;25(10):3021-3031.
88. Sheng J, Li H, Yu X, et al. Efficacy of PD-1/PD-L1 inhibitors in patients with non-small cell lung cancer and brain metastases: a real-world retrospective study in China. Thorac Cancer. 2021;12(22):3019-3031.
89. Gutierrez-Sainz L, Martinez-Marin V, Viñal D, et al. Incidence of venous thromboembolic events in cancer patients receiving immunotherapy: a single-institution experience. Clin Transl Oncol. 2021;23(6):1245-1252.
90. Nichetti F, Ligorio F, Zattarin E, 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 (Basel). 2019;12(1):67.
91. Wang H, Xu T, Zheng L, et al. Angiogenesis inhibitors for the treatment of ovarian cancer: an updated systematic review and meta-analysis of randomized controlled trials. Int J Gynecol Cancer. 201;28(5):903-914.
92. May SB, La J, Milner E, et al. Venous thromboembolism risk in cancer patients receiving first-line immune checkpoint inhibitor vs. chemotherapy. Blood. 2022;140:7968.
93. Moik F, Ay C, Horváth-Puhó E, et al. Risk of venous and arterial thromboembolic events in patients receiving targeted anti-cancer therapy – a nationwide cohort study, research and practice in thrombosis and haemostasis. https://onlinelibrary.wiley.com/doi/epdf/10.1002/rth2.12591 Accessed September 30, 2024.
94. Sanfilippo KM, Luo S, Lyman GH, et al. 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.