Factor XI inhibitors in cancer-associated venous thromboembolism: what's next?

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ABSTRACT

Venous thromboembolism (VTE) is an important cause of morbidity and mortality in individuals with active cancer. Most cancer-associated VTE occurs in the ambulatory setting in individuals receiving systemic therapy. Multiple anticoagulants are currently available for the treatment of cancer-associated VTE; a major drawback is the risk of bleeding. No drugs are currently approved for primary prevention of VTE in cancer in the outpatient setting. Adherence/compliance issues, drug-drug interactions, and concerns about renal and hepatic metabolism are other ongoing concerns with these agents. Thus, there are major unmet needs in the quest to optimize the treatment and prevention of VTE in cancer. Factor XI (FXI) has only a small impact in hemostasis but contributes significantly to thrombosis. It is therefore a potential therapeutic target with less concern for enhancing bleeding. Several early-phase studies suggest that FXI inhibitors have reduced risk of bleeding at therapeutic doses in prevention of venous and arterial events in selected non-cancer settings, including atrial fibrillation and postoperative thromboprophylaxis after orthopedic surgery. Multiple studies are now addressing the utility of this new class of drugs in cancer-associated VTE including completed, ongoing and planned trials of primary prevention and treatment. This narrative review addresses the role of FXI in thrombosis, the rationale for FXI inhibitors in primary and secondary prevention settings in malignancy and provides an overview of preliminary results and future directions.

Key words: factor XI; cancer-associated thrombosis; venous thromboembolism

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Introduction

Individuals with active cancer are at high risk for venous thromboembolism (VTE) which includes deep venous thrombosis (DVT) and pulmonary embolism (PE), as well as a lower but still elevated risk of arterial thromboembolism (ATE) including myocardial infarction, stroke and peripheral arterial embolism. The risk of VTE is driven by several factors associated with malignancy, including the type of cancer (with particularly high rates in pancreatic cancer, primary brain tumors and lymphomas), stage of disease, treatment (including chemotherapy and immunotherapy) and can be predicted by a variety of biomarkers including components of the complete blood count and validated risk assessment tools.[1] VTE is highly consequential for individuals with cancer since it can lead to hospitalization or urgent care visits, interrupt or delay systemic therapy, complicate post-surgical recovery and – perhaps most importantly – is associated with increased risk of both short-term and long-term mortality. Primary and secondary prevention of VTE in malignancy is therefore an important component of overall cancer care.

Anticoagulant agents have historically been used for treatment or secondary prevention of VTE in the setting of malignancy. Initial studies of anticoagulants focused on drug development in the non-cancer setting and results were then extrapolated to the cancer setting. However, it soon became apparent that individuals with cancer had higher rates of both recurrent VTE and, paradoxically, bleeding, and newer trials began to focus specifically on the population of people with cancer. A landmark first step occurred with the completion of the first large randomized clinical trial (RCT) specifically in cancer, CLOT, which established low-molecular-weight heparins

(LMWHs) monotherapy for 6 months as the standard of care of treatment of cancer-associated VTE.[2] Other studies established the benefit of direct oral anticoagulants (DOACs) in primary and secondary prevention of both VTE and, to some extent, ATE in this population. Currently available agents include vitamin K antagonists, heparin and LMWHs such as enoxaparin, dalteparin and tinzaparin, and DOACs including edoxaban, rivaroxaban and apixaban. Although significant advances have been made in the treatment and prevention of VTE in malignancy, bleeding remains a concern in the setting of both primary and secondary prevention. An emerging class of agents, factor XI (FXI) inhibitors, hope to address this major practice gap. Since FXI only has a minor role in hemostasis but is important for thrombus expansion, the hope is that making FXI a therapeutic target will maintain antithrombotic efficacy but reduce the potential for bleeding.[3] This is borne out by clinical experiences in individuals with FXI deficiency who have lower incidence of VTE and ischemic stroke but do not have the kind of major bleeding observed in individuals with hemophilia A or B.[4-9] Many candidates that inhibit FXI *via* different mechanisms are in various stages of drug development, with several studies focusing primarily on the cancer population.

This narrative review focuses primarily on cancer-associated VTE, summarizing the current landscape of primary and secondary prevention in individuals with cancer, addressing major knowledge gaps and providing an overview of ongoing studies, preliminary results and future directions for FXI inhibitors in malignancy.

Treatment and secondary prevention of cancer-associated VTE: current landscape and gaps

The treatment of cancer-associated VTE had historically followed the paradigm of treatment of non-cancer-associated VTE, with initial parenteral anticoagulation with either LMWH, unfractionated heparin or fondaparinux followed by a vitamin K antagonist such as warfarin. However, with a growing proportion of cancer survivors afflicted with VTE, it became apparent that VTE in malignancy had a different natural history with higher rates of recurrent VTE as well as higher rates of bleeding.[10] The landmark CLOT trial was the first to focus exclusively on treatment of cancer-associated VTE and established that six months of monotherapy with the LMWH dalteparin was superior to the then-standard of LMWH transitioning to warfarin.[2] This was partly later confirmed by the subsequent CATCH trial using a different LMWH, tinzaparin.[11] A large meta-analysis of eleven RCTs with 2,777 participants comparing LMWH with VKAs also confirmed the superiority of LMWH in reducing the risk of recurrent VTE (7.5% *vs* 12.9%, risk ratio [RR] 0.58, 95% confidence interval [CI] 0.45-0.75) with similar rates of bleeding (4.7% *vs* 4.8%, RR 0.99, 95% CI 0.67-1.45).[12] Through the 2000s and early 2010s, LMWH thus became the standard of care treatment of cancer-associated VTE.

This paradigm was shifted with the introduction of DOACs in the 2010s. Initially, these agents were studied in the non-cancer population (albeit including some patients with cancer) but subsequent RCTs focused on individuals with active cancer. Since 2018, five RCTs have directly compared DOACs with dalteparin for the treatment of acute cancer-associated VTE. These included Hokusai VTE Cancer with edoxaban, SELECT-D with rivaroxaban and CARAVAGGIO with apixaban.[13-15] These trials suggested improved efficacy with DOACs although concern was raised about gastrointestinal bleeding risk in the edoxaban and rivaroxaban trials. In a recent meta-analysis of ten RCTs with 4,713 participants, DOACs were associated with a significant reduction in the risk of VTE (incidence risk ratio, IRR 0.66, 95% CI 0.56 to 0.79) with no differences in total bleeding (IRR = 1.10, 95% CI 0.80;1.50) or mortality (IRR 1.00, 95% CI, 0.89-1.12).[16] DOACs have therefore become the new standard of care for treatment of cancer-associated VTE, although guidelines advise caution in the setting of gastrointestinal and genitourinary malignancies because of the risk of bleeding observed in some RCTs.[17,18]

The optimal duration of anticoagulation beyond the initial 3-6 months remains an important issue in cancer-associated VTE, particularly in patients with persistent active malignancy or ongoing systemic therapy. In the phase 3 API-CAT trial, extending anticoagulation with reduced-dose apixaban (2.5 mg twice daily) for 12 months after completion of at least 6 months of prior anticoagulation was noninferior to continued full-dose apixaban for recurrent VTE and was associated with a lower incidence of clinically relevant bleeding.[19,20] Additional randomized data also support longer-duration anticoagulation in selected cancer-associated PE populations; in the ONCO PE trial (low-risk PE), 18 months of rivaroxaban was associated with a lower incidence of recurrent VTE compared with 6 months, without a statistically significant increase in major bleeding.[21,22]

However, there remain several unmet needs and knowledge gaps in this setting. Bleeding remains a major concern in the use of DOACs and LMWHs in the setting of malignancy, where bleeding rates are high with or without the use of anticoagulation.[23] There are concerns about patient adherence and compliance with oral agents used once or twice daily or subcutaneous agents used similarly for prolonged periods of time in individuals with an already-heavy burden of illness from cancer.[24] Drug-drug interactions with anti-cancer therapies are a concern for some DOACs.[25,26] Finally, renal or hepatic dysfunction – not uncommon in malignancy – can lead to drug accumulation and increase risk of bleeding. Newer, safer agents that address these unmet needs are therefore needed. FXI inhibitors aim to meet these needs.

Primary prevention of cancer-associated VTE: current landscape and gaps

Primary thromboprophylaxis is a highly effective approach that is now standard-of-care in several high-risk settings for VTE such as after major abdominopelvic or orthopedic surgery or during inpatient hospitalization. Given the high incidence and prevalence of VTE in cancer as well as its deleterious consequences, it makes sense to consider primary thromboprophylaxis in this setting as well. However, initial RCTs of prophylaxis did not sufficiently take into account the wide variation in risk for VTE between subgroups of the cancer population and therefore did not result in a clinically meaningful absolute risk reduction of VTE.[27,28] More recent RCTs have utilized risk-stratification tools to identify high-risk patients for prophylaxis, primarily using the first validated risk score in this setting, the Khorana score (KS).[29,30] In a meta-analysis of 4,500 participants enrolled

in six RCTs, LMWHs or DOACs were successfully able to reduce VTE risk meaningfully in intermediate- to high-risk patients (RR, 0.51; 95% CI, 0.34-0.67).[31] Current guidelines therefore recommend consideration of thromboprophylaxis in individuals at higher risk for VTE (KS ≥2).[17,18,32]

However, there are several challenges to implementation of thromboprophylaxis in current outpatient oncology settings. The risk of bleeding seen in treatment and secondary prevention remains a concern in the primary prevention setting as well, despite lower dosing in prophylaxis.[29] Adherence and compliance issues are also a concern in a population heavily burdened by the major comorbid condition of malignancy. Despite the recommendations of current guidelines, there is no anticoagulant agent that currently has regulatory approval for primary prophylaxis anywhere in the world. This can limit access or coverage of these drugs in the US and many other countries. FXI inhibitors hold great promise in this setting since they have the potential to overcome some of these challenges, particularly the risk of bleeding. In addition, for some FXI inhibitors, lower-frequency parenteral dosing can aid compliance and adherence issues and adds to the possibility of greater utilization.

Why target FXI?

FXI, a serine protease, can be activated to FXIa and plays an important role in the amplification of thrombin generation, which can drive thrombus expansion. FXI is important for the intrinsic coagulation pathway (contact activation) which in recent studies has been shown to be important in malignancy.[33] However, FXI only plays a small role in normal hemostasis.[3,34] This "hemostasis-sparing" effect of FXI – also termed as the "uncoupling of hemostasis and thrombosis" - has led to interest in this molecule as a therapeutic target, with the potential to minimize bleeding risk. Support for this hypothesis comes from epidemiologic studies demonstrating reduced risk of cardiovascular events in FXI-deficient patients. For instance, in a large United Kingdom Biobank study, genetic disposition to lower FXI levels was associated with reduced risk of venous thrombosis and ischemic stroke, but not major bleeding.[35] Indeed, spontaneous major bleeds are rare in individuals with inherited FXI deficiency.[36]

A large variety of FXI inhibitors are therefore currently being investigated in a variety of settings (Table 1). Unlike prior generations of antithrombotics which were either only parenteral (e.g., LMWHs) or only oral (e.g., DOACs), FXI inhibitors have very diverse pharmacology. They include: antisense oligonucleotides (ASOs) which bind to mRNA targets in the liver, inhibiting the synthesis of FXI; monoclonal antibodies such as gruticibart or abelacimab which are given parenterally and have a rapid onset of action but durable effect (in weeks) and small molecules such as asundexian and milvexian that are similar to DOACs in terms of oral bioavailability and short duration of activity requiring daily administration. Other classes of FXI inhibitors such as natural peptides, aptamers and small interfering RNAs are less advanced in clinical development.

Table 1. Select list of FXI inhibitors: characteristics and mechanisms of action.

Category	Drug	Mode of administration	Onset of activity	Duration of activity	Current status
Small molecules	Asundexian[42,45]	Oral (once daily)	Rapid (peak: 1-4 h)	Short (half-life: ~15-18 h)	Mixed/active phase 3: • Stroke: *Positive* top-line results from Ph 3 OCEANIC-STROKE (Nov 2025). • AFib: Ph 3 OCEANIC-AF stopped early due to inferior efficacy (Nov 2023).
	Milvexian[60-62]	Oral (twice daily)	Rapid (peak: 2-4 h)	Short (half-life: ~11-18 h)	Active phase 3: • Stroke: LIBREXIA-STROKE recruiting. • ACS: LIBREXIA-ACS active. • AFib: LIBREXIA-AF active.
	SHR2285[63]	Oral	Rapid	Short	Active phase 2: • Early clinical development; phase 1/2 data published.
Monoclonal antibodies	Abelacimab[40,53,54,64]	IV (loading) Subcutaneous (maintenance)	Rapid (intravenous) Delayed (subcutaneous)	Long (half-life: ~20-30 days; dosed monthly)	Active phase 3: • CAT: MAGNOLIA & ASTER trials recruitment held • AFib: AZALEA-TIMI 71 stopped early for *superior* safety *vs* rivaroxaban; LILAC ongoing.
	Osocimab[39]	IV	Rapid	Long (half-life: ~30-44 days)	Completed phase 2 (FOXTROT, CONVERT)
Antisense oligonucleotides	Fesomersen[65,66]	Subcutaneous	Slow (weeks to steady state)	Long (dosed monthly)	Currently no active phase 3.
Small interfering RNA	SRSD107[67]	Subcutaneous	Slow	Long (12 weeks)	Active phase 2 trial post total knee arthroplasty (NCT07140523)

FXI trials in non-cancer settings

The clinical development of FXI inhibitors has to some extent followed traditional antithrombotic drug development paradigms, with Phase II and Phase III studies now evaluating these agents across a range of non-cancer medical and surgical settings.[37] Although a full overview of these trials is beyond the scope of this article, this section provides a summary of select ongoing studies.

Post orthopedic surgery VTE prophylaxis

Orthopedic surgery, especially total knee arthroplasty (TKA), has served as a key model for evaluating FXI inhibitors due to the high baseline risk of postoperative VTE. The antisense oligonucleotide IONIS-FXIRx (formerly FXI-ASO) significantly reduced VTE compared with enoxaparin while maintaining a favorable bleeding profile in a Phase II TKA trial.[38] Similarly, the monoclonal antibody osocimab demonstrated non-inferiority and, at some doses, superiority *vs* enoxaparin for thromboprophylaxis after knee arthroplasty.[39] Across these studies, FXI inhibitors consistently show preserved hemostasis despite robust FXI suppression, supporting the biological rationale for targeting this pathway. Larger studies are ongoing.

Atrial fibrillation

FXI inhibitors have also been investigated for stroke prevention in atrial fibrillation (AF), where bleeding concerns with current anticoagulants remain significant. In the AZALEA-TIMI 71 trial, abelacimab demonstrated a significantly lower incidence of bleeding compared with rivaroxaban in patients with AF who were at moderate-to-high risk of stroke.[40] Of 1,287 patients who underwent randomization to abelacimab or rivaroxaban, the incidence of major or clinically relevant nonmajor bleeding was 3.2 events per 100 person-years for the 150 mg dose compared with 8.4 for rivaroxaban (HR for 150-mg abelacimab vs. rivaroxaban, 0.38 [95% CI, 0.24 to 0.60]; HR for 90-mg abelacimab *vs* rivaroxaban, 0.31 [95% CI, 0.19 to 0.51]; $p<0.001$ for both). The study was not designed to definitively test efficacy against stroke or systemic embolism. Overall, the rates of these events were low but numerically more frequent in the two abelacimab groups than in the rivaroxaban group (1.21 *per* 100 person-years with 150-mg abelacimab and 1.36 *per* 100 person-years with 90-mg abelacimab *vs* 0.83 per 100 person-years with rivaroxaban [HR for 150-mg abelacimab *vs* rivaroxaban, 1.47 [95% CI, 0.56 to 3.85]; hazard ratio for 90-mg abelacimab *vs* rivaroxaban, 1.65 [95% CI, 0.64 to 4.25]). In the PACIFIC-AF trial, the oral FXIa inhibitor, asundexian, resulted in significantly lower bleeding compared with apixaban, confirming its safety advantage.[41] However, the large Phase III OCEANIC-AF trial was terminated early because asundexian demonstrated inferior efficacy in preventing stroke or systemic embolism compared with apixaban.[42, 43] These findings suggest that while FXI inhibition provides a meaningful reduction in bleeding risk, it may not deliver sufficient antithrombotic potency as monotherapy in high-risk cardioembolic disease. Results from additional trials are awaited.

Secondary prevention after ischemic stroke

The AXIOMATIC-SSP trial evaluated multiple doses of the oral FXIa inhibitor milvexian in addition to dual antiplatelet therapy. Although several dosing regimens showed numerical reductions in recurrent ischemic stroke and covert infarction, the study did not demonstrate a statistically significant dose-response relationship for the primary composite efficacy endpoint.[44] These findings indicate potential biological activity but highlight the need for larger, adequately powered Phase III trials to determine whether FXIa inhibition provides meaningful clinical benefit in secondary stroke prevention. Although peer-reviewed published data were not available at the time of this writing, the OCEANIC-STROKE trial evaluating asundexian 50 mg daily for secondary prevention after non-cardioembolic ischemic stroke appears to have met both its primary efficacy and safety endpoints, with no increase in major bleeding compared with antiplatelet therapy alone.[45] Full results are awaited, but these findings could significantly impact therapeutic options in this setting.

Acute coronary syndromes

In acute coronary syndromes (ACS), residual thrombotic risk persists despite optimal antiplatelet therapy. FXI inhibitors have been explored as adjunctive therapy to reduce this risk without exacerbating bleeding. PACIFIC-AMI evaluated asundexian added to dual antiplatelet therapy after myocardial infarction and found no significant reduction in the composite of cardiovascular death, MI, stroke, or stent thrombosis.[46] Although bleeding outcomes were favorable, the neutral efficacy results indicate that platelet-driven arterial thrombosis may not be sufficiently modulated by FXI pathway inhibition alone. The Phase III Librexia-ACS trial was recently discontinued following a scheduled interim analysis that judged the trial unlikely to meet its primary efficacy endpoint, despite no new safety issues emerging.[47]

End-stage renal disease

Hemodialysis induces substantial contact pathway activation due to continuous blood–membrane interaction, making FXI inhibition a mechanistically strong strategy in this setting. In a Phase II study, the antisense oligonucleotide IONIS-FXIRx produced dose-dependent reductions in FXI activity of approximately 56-71% and was associated with fewer dialysis-circuit thrombosis events compared with placebo, without an increase in major bleeding.[48] These results highlight the hemodialysis setting as a promising indication for FXI pathway inhibition, given both the high thrombotic burden, the high risk of bleeding and the limitations of current anticoagulation options.

Clinical implications

Across non-cancer indications, FXI inhibitors consistently show a more favorable bleeding profile compared with conventional anticoagulants. Efficacy appears most consistent in clinical settings where intrinsic or contact pathway activation predominates, such as orthopedic surgery and hemodialysis.

Although efficacy has been less convincing in cardioembolic or strongly platelet-driven arterial conditions such as atrial fibrillation and acute coronary syndromes, the positive Phase III findings from OCEANIC-STROKE demonstrate that FXI inhibition can provide meaningful benefit in select settings when combined with antiplatelet therapy. Results from ongoing studies will help determine whether FXI inhibitors become standard therapy or remain reserved for patients with elevated bleeding risk in selected indications.

FXI inhibitor trials in cancer

Historically, drug development of new anticoagulant drugs has followed a standard paradigm of establishing safety and efficacy in post-orthopedic procedure settings, prevention of stroke in atrial fibrillation and in treatment of mostly non-cancer-associated acute VTE. Once regulatory approval is obtained for these initial indications, either industry-sponsored or investigator-initiated studies are conducted in the cancer population. In recent years, however, there has been a growing awareness of the large population of individuals with cancer at risk for both VTE and ATE. As a result, FXI inhibitor drug development appears to be departing from the traditional paradigm to evaluate safety and efficacy specifically in cancer settings at earlier stages of drug development. This section and Table 2 provide an overview of recently completed, ongoing and planned clinical studies of FXI inhibitors in the cancer setting.

Gruticibart

Gruticibart (previously known as xisomab 3G3 or AB023) is a recombinant humanized antibody that targets the apple 2 domain of FXI, preventing FXIIa-mediated contact activation of FXI (but allows FXI activation via other pathways). An open-label, non-randomized interventional study evaluated the safety and benefit of gruticibart in individuals with cancer undergoing central line placement.[49] Patients were excluded if at risk for bleeding (including acute leukemia and brain tumors or CNS metastases). In the intervention trial, 11 patients were enrolled and given a single dose of gruticibart (2 mg/kg) through the venous catheter within 24 h of placement. Surveillance ultrasound to detect catheter thrombosis was conducted on day 14, alongside pharmacokinetic and pharmacodynamic studies. The drug prolonged APTT compared to baseline and overall incidence of screen-detected catheter-associated thrombosis was 12.5%. In contrast, a concurrently enrolled control arm of similar patients had an incidence of 40% in 11 patients, although participants were not randomized between the two arms. No significant bleeding or other concerns were identified. The results of these small non-randomized studies are promising, but larger prospective randomized studies are needed to confirm and extend these findings.

Abelacimab

Abelacimab is a fully human monoclonal antibody with dual mechanisms of action: it binds to the catalytic domain of FXI, locking it in an inactive state and ii) it inhibits activated FXI (FXIa). Intravenous administration results in near-complete suppression of FXI within hours, and this can be maintained for up to 30 days. Proof of clinical activity was first shown in an early-phase trial evaluating postoperative VTE after total knee arthroplasty, where a single dose at the highest level (150 mg) reduced VTE incidence by 80% compared to enoxaparin, with no concomitant increase in bleeding.[50] The clinical activity of this agent in a more chronic setting was also established in a large trial in individuals with atrial fibrillation at moderate-to-high risk for stroke, as discussed earlier (AZALEA-TIMI 71, NCT04755283).[40]

Two complementary randomized trials are currently evaluating the benefit of abelacimab in the treatment of cancer-associated VTE: ASTER (NCT05171049) and MAGNOLIA (NCT05171075). The rationale for two separate studies is the current practice pattern of two competing standards of care for treatment of VTE in this setting: DOACs for most patients, and LMWHs for patients at high risk of bleeding (specifically those with gastrointestinal and genitourinary cancers).[17,18] ASTER compares abelacimab with apixaban for treatment of acute VTE when a DOAC is indicated whereas MAGNOLIA compares abelacimab with dalteparin also in the treatment of acute VTE for patients with GI or GU cancers with preserved primary who are at risk for bleeding and for whom a LMWH monotherapy treatment is indicated.[51,52] ASTER planned on enrolling 1,655 patients and MAGNOLIA planned on enrolling 1,020 patients from over 200 sites in 20 countries worldwide. In both studies abelacimab was given at the dose of 150 mg IV on day 1 and subcutaneously once-monthly thereafter for up to 6 months. For both studies, the primary efficacy outcome was time to first VTE recurrence (defined as new proximal DVT or PE or unexpected death for which PE cannot be excluded). Secondary outcomes included time to first major or clinically relevant nonmajor bleeding and net clinical benefit which was defined as survival without recurrent VTE and without bleeding events.

At the time of publication of this review, these studies were listed on clinicaltrials.gov as active but not recruiting.[53,54] No publicly available data provides additional details or outcomes of patients recruited thus far in this large, randomized trial but certainly the premature suspension of these studies is discouraging.

REGN9933^{A2} and REGN7508^{Cat}

REGN9933^{A2} and REGN7508^{Cat} are fully human monoclonal antibodies that bind to distinct FXI domains. REGN9933^{A2} binds to the apple 2 domain, blocking FXI activation by FXIIa. REGN7508^{Cat} binds to the catalytic domain and blocks FXIa activity as well as FXI activation by FXIIa and thrombin. Both agents were recently evaluated for safety and efficacy in preventing postoperative VTE in comparison with enoxaparin and apixaban in two randomized phase II trials, ROXI-VTE-I and ROXI-VTE-II.[55] REGN7508^{Cat} was found to be superior to enoxaparin for VTE prevention; REGN9933^{A2} was not found to be superior to enoxaparin.

In addition to studies in atrial fibrillation and post total knee arthroplasty, these compounds are being studied in the ambulatory setting as well. ROXI-CATH (NCT06299111) is an ongoing trial that is evaluating safety and efficacy of these agents in preventing VTE in adults with a peripherally inserted central catheter (PICC). Although not exclusively targeting cancer patients, this study is likely to include a large proportion of individuals with cancer. The study includes patients for whom PICC is clinically indicated for at least 14 days but excludes those requiring anticoagulation or antiplatelet therapy or who are expected to receive cancer-directed therapy or other treatments known to cause severe thrombocytopenia. This study is currently actively recruiting.

Specifically targeting the cancer population are two separate prevention and treatment randomized controlled trials. ROXI-CAT I is a primary prevention trial in high-risk individuals with cancer treated with REGN7508^{Cat} for 6 months, compared to placebo (since no current anticoagulant has approval for primary prevention).[56] ROXI-CAT II is a treatment (secondary prevention) trial in individuals with cancer and acute VTE treated with the same agent for 6 months in comparison to apixaban. Results of these planned trials will be enormously influential in determining the fate of FXI inhibitors in the prevention and treatment of cancer-associated VTE.

Table 2. Select completed, ongoing and planned clinical trials of FXI inhibitors in active cancer.

Study	Study design	Study arm	Control arm	Select inclusion criteria	Select exclusion criteria	Primary end point	Secondary end point	Results (if available)	Current status
Prevention of catheter-associated thrombosis									
Pfeffer *et al.*[49] NCT04465780	Phase 2, single center, open label, non-randomized	Gruticibart *via* catheter within 24 h of catheter placement	Concurrent, non-interventional companion control group	Known solid tumors, platelet count ≥100,000	Acute leukemia, contraindication to anticoagulation	Incidence of catheter associated thrombosis up to day 30, with screening ultrasonography	Incidence of major or CRNM bleed up to day 60	12.5% screen-detected catheter-associated thrombus	Published
ROXI-CATH[68] NCT06299111	Phase 2 randomized, double-blind, placebo	REGN9933, REGN 7508	Placebo single dose	PICC indicated for at least 2 weeks. (ECOG) Performance status ≤2	Known thromboembolic disease or thrombophilia Therapeutic anticoagulation & antiplatelet therapy	Incidence of confirmed VTE Incidence of TEAEs up to day 100 Severity of TEAEs up to day 100	Incidence of major or CRNM bleed	N/A	Completed
Primary prevention of cancer-associated VTE									
SHR-2004[58] NCT06220123	Phase 2, randomized active control	SHR-2004 subcutaneously 180mg D1, 120mg D15.	Enoxaparin 40mg subcutaneously + rivaroxaban 10mg till D28	Stage III/IV/ recurrent ovarian cancer, candidate for surgery	Brain metastasis. History of VTE. On atrial fibrillation medication with anticoagulation	Incidence of VTE up to day 28. Major or CRNM bleed	Incidence of each component of VTE till day 85.	VTE: 12.6% for study drug *vs* 20.2% for control arm Major bleed: 2.2% for study drug *vs* 1.9% for control arm	Completed (181)
ROXI-CAT I[56]	Randomized controlled	REGN7508	Placebo	N/A	N/A	N/A	N/A	N/A	Anticipated start 2026
Treatment of acute VTE in cancer									
ASTER[53] NCT05171049	Phase 3, multicenter, randomized open label	Abelacimab, 150 mg intravenously then monthly subcutaneously x 6 months	Apixaban in usual dose	Adults ≥18 yrs. Confirmed malignancy. Confirmed acute VTE	Thrombectomy/ caval filter. >120 h of pre-treatment with OACs. Unstable PE. Platelets <50,000/mm^3	Time to first event of VTE recurrence within 6 months	Time to first event of MB or CRNM bleed. Survival without VTE recurrence, or major or CRNM bleeding.	N/A	Recruitment on hold
MAGNOLIA[54] NCT05171075	Phase 3, multicenter, randomized, open label	Abelacimab, 150 mg intravenously then monthly subcutaneously x 6 months	Dalteparin in usual dose	Confirmed gastrointestinal or genitourinary cancers with concern for bleeding risk with oral agents. Confirmed acute VTE.	Thrombectomy/ caval filter. >120 hrs. of pre-treatment with oral anticoagulants Unstable PE. Platelets <50,000/mm^3	Time to first event of VTE recurrence consisting of new proximal DVT, new PE or fatal PE within 6 months	Time to first event of MB or CRNM bleed. Survival without VTE recurrence, or MB or CRNM bleed.	N/A	Recruitment on hold
ROXI-CAT II	Randomized, controlled	REGN7508	N/A	N/A	N/A	N/A	N/A	N/A	Anticipated start in 2026

SHR-2004

SHR-2004 is a humanized monoclonal antibody that selectively binds to the protease domain of FXI and FXIa with high affinity. A first-in-human study established tolerability of this drug and demonstration of decrease in FXI activity and prolongation of APTT after intravenous and subcutaneous administration in a dose- and time-dependent manner.[57] This molecule has been studied in a randomized phase II clinical trial to evaluate its safety and efficacy in preventing postoperative VTE in patients undergoing ovarian cancer surgery in comparison to enoxaparin/rivaroxaban (NCT06220123). Patients were included if they had stage III-IV or recurrent ovarian cancer. Patients were excluded for prior history of VTE, increased risk of bleeding or cardiac comorbidities. The primary efficacy endpoint was the incidence of VTE, including assessments with surveillance ultrasonography up to day 28. Primary safety endpoints included ISTH-defined major and CRNM bleeding.[57,58] In preliminary data presented in early 2025, the investigators reported results from 181 patients in the modified intention-to-treat population. VTE occurred in 12.6% of patients in the SHR-2004 group *vs* 20.2% in the enoxaparin/rivaroxaban group, confirming noninferiority (p=0.01).[59] Although the study drug was associated with lower rates of VTE compared to standard of care, major and non-major bleeding events were not significantly different (2.2% for SHR-2004 *vs* 1.9% for enoxaparin/rivaroxaban, respectively). These results are encouraging, providing the first proof-of-concept that FXI inhibitors can be effective as thromboprophylaxis in the setting of a malignancy known to be high-risk for VTE. Larger, prospective studies that are better powered to evaluate safety differences, and that can confirm and extend these findings are eagerly awaited.

Unresolved questions and future directions

There is no question that FXI inhibitors have the potential to address several unmet needs related to the public health problem of cancer-associated VTE; the high incidence of VTE coupled with the high incidence of bleeding makes this an ideal setting in which to evaluate these hemostasis-sparing agents. At the same time, conflicting results from clinical trials as well as the premature suspension of some ongoing studies such as ASTER and MAGNOLIA has led to uncertainty in the field and a reconsideration of ongoing studies.

The mixed results from clinical trials have broadly led to two areas of concern. Firstly, is the failure of an individual FXI inhibitor a reflection of the drug itself, or of the entire class? For instance, assuming the premature discontinuation of the abelacimab trials is related to efficacy: is inhibition of FXI activity by abelacimab inadequate or is the frequency of administration insufficient?

Mechanistically, it is plausible that the contribution of FXI to thrombus propagation varies across cancer settings, and that FXI inhibition could be less effective in contexts where thrombin generation is driven predominantly by non–contact-pathway mechanisms. In malignancy, systemic inflammation and tumor-derived extracellular vesicles can promote coagulation and contact system/intrinsic pathway activation has been demonstrated in selected cancers.[33,34] These parallel prothrombotic drivers may provide alternative routes for thrombin generation and propagation even when FXI/FXIa activity is suppressed, particularly in highly inflammatory tumors or during systemic therapy. In addition, redundancy within coagulation amplification loops may diminish the relative contribution of FXI to thrombus propagation in some scenarios.

From a pharmacologic perspective, "inadequate inhibition" may reflect not only frequency of administration but also mechanism of action and PK/PD exposure. Agents that primarily block FXI activation may differ biologically from those that directly inhibit FXIa catalytic activity, particularly if thrombin-mediated FXI activation remains operative. For long-acting parenteral agents, trough levels and interpatient variability may influence protection across the dosing interval; for oral agents, adherence, drug–drug interactions, and organ dysfunction may lead to subtherapeutic exposure. Future studies incorporating pharmacodynamic biomarkers such as FXI activity or calibrated thrombin generation may help determine whether dose intensity or tailored dosing strategies improve efficacy without compromising safety.

Or, conversely, will FXI inhibition fail even with greater inhibition or more frequent duration given the complicated pathophysiology of cancer-associated VTE? This is a question particularly unique to FXI inhibitors given the wide heterogeneity of drug mechanisms, modes of administration, time of onset and duration of activity (Table 1). Biomarkers of contact activation are typically not measured in these studies to provide additional information. The development process for prior classes of antithrombotics such as LMWHs and DOACs did not have to address such issues given the relative homogeneity of individual drugs within these classes. Secondly, should FXI inhibitors be tested in all settings or are they particularly suitable for certain settings only? A case could be made that the hemostasis-sparing effect of FXI inhibitors is especially needed in primary prevention of VTE where bleeding concerns have considerably affected utilization of available antithrombotics. These and related questions need to be considered and answered thoughtfully as the drug development of FXI inhibitors evolves over the next decade, if we are to be able to employ this exciting new class of agents in our ongoing quest to reduce the public health burden of cancer-associated VTE.

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