



# Apixaban in Japanese patients with cancer-associated venous thromboembolism: a multi-center phase II trial

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**Title:** Apixaban in Japanese patients with cancer-associated venous thromboembolism:  
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28    **Abstract**

29    **Background.** Recent pivotal phase III trials involving direct oral anticoagulant (DOAC)  
30    versus low molecular weight heparin have demonstrated the utility of DOACs in  
31    Western patients with cancer-associated venous thromboembolism (VTE). However,  
32    these trials did not include Japanese patients. This phase II trial evaluated the safety and  
33    efficacy of apixaban in Japanese patients with cancer-associated VTE  
34    (UMIN000028447).

35    **Method and Results.** Apixaban was initiated at 10 mg twice daily for 7 days, followed  
36    by 5 mg twice daily for 23 weeks. Primary endpoint was the incidence of major or  
37    clinically relevant non-major (CRNM) bleeding events during the treatment period. The  
38    study was terminated due to safety concerns after enrolling 27 patients. Median age was  
39    71 years; median body weight was 51.3 kg; and major primary tumor site was the  
40    gastrointestinal tract (26%) and lung (19%). On median follow-up of 5.4 months, major  
41    and CRNM bleeding occurred in five and two patients, respectively; hence, major plus  
42    CRNM bleeding occurred in 26% (95% confidence interval, 11-46%). No recurrent  
43    VTE or VTE-related death occurred. Estimated overall survival at 6 months was 68%.

44    **Conclusion.** This study **demonstrated** the excessive bleeding risk of apixaban at the  
45    standard dose in Japanese patients with cancer-associated VTE.

46

47    **Key words:** cancer-associated venous thromboembolism; apixaban; phase II trial;

48    Japanese

## **Introduction**

Thromboembolism is a life-threatening condition which is reported to be the second-leading cause of death in cancer patients after cancer itself [1]. Venous thromboembolism (VTE) is the most common type of thromboembolism occurring in cancer patients, and its incidence has increased markedly in recent years, probably owing to a combination of aggressive anticancer drug therapy, aging of cancer patients, and enhanced VTE detection. Although anticoagulant treatment is the recommended standard of care for acute VTE, this treatment is complicated by both a high risk of recurrent VTE and bleeding events in cancer patients [2]. Hence, optimal treatment strategies for this patient category have been investigated. Low molecular weight heparins (LMWHs) over 6 months are the standard anticoagulants for cancer-associated VTE in numerous guidelines [3-5] and a review from the 9<sup>th</sup> congress of the Asian-Pacific Society on Thrombosis and Hemostasis [6], because of their superior efficacy and similar safety profile to vitamin K antagonists (VKAs), represented by warfarin [7-10].

In recent years, direct oral anticoagulants (DOACs) that directly inhibit either factor IIa (e.g. dabigatran) or factor Xa (e.g. edoxaban, rivaroxaban, and apixaban) have shown clinical benefits in various clinical settings, including prevention of stroke in

atrial fibrillation [11-14] and treatment of acute VTE [15-20]. Moreover, the latest results of international phase III trials comparing DOACs with LMWH in patients with cancer-associated VTE provide novel evidence for the utility of DOACs as an alternative to LMWH [21-24]. Because LMWHs are not approved for acute VTE in Japan, Japanese physicians tend to prescribe DOACs for cancer-associated VTE as the first choice instead of VKAs [25], despite limited prospective evidence; specifically, few Asian cancer patients were included among the head-to-head comparison in phase III trials of DOACs and VKAs [15-20], and very few Asian and no Japanese cancer patients were enrolled in studies comparing DOACs and LMWHs [21-24].

Here, we report the results of a phase II trial of apixaban in Japanese patients with cancer-associated venous thromboembolism (J-CAV) that evaluated the safety and efficacy of apixaban in Japanese patients with cancer-associated VTE.

## **Methods**

### *Study Design*

J-CAV was an open-label, non-randomized, multicenter phase II study conducted at three centers in Japan. A single-arm design was selected because 1) LMWH was not approved for acute VTE in Japan, 2) phase III trials demonstrated the clinical advantage

of DOACs compared to VKAs [7-10], and 3) an indirect comparison of DOACs for the treatment of acute VTE revealed that apixaban had the lowest incidence rates of recurrent VTE and major bleeding among DOACs [26]. Study duration, endpoints, and key eligibility criteria were based on pivotal phase III trials using apixaban (Table S1, [20, 23, 24, 27]), and the study protocol was approved by the institutional review board of each participating center. The trial was performed in accordance with the Declaration of Helsinki and registered at the UMIN Clinical Trials Registry as UMIN000028447. All patients provided written informed consent before study entry. An independent data and safety monitoring committee oversaw the emerging data to protect the participants and the integrity of this study.

#### *Patient Population*

The inclusion criteria were patients with active cancer presenting with newly diagnosed symptomatic or incidental deep vein thrombosis (DVT), or symptomatic or incidental pulmonary embolism (PE), or both, as confirmed by diagnostic imaging. For DVT, only cases with  $\geq 5$  mm thrombi detected by venous ultrasound with B-mode compression were eligible [28]. Further, for isolated distal DVT, only cases of proximal extension after serial imaging were eligible. PE was diagnosed by spiral computed

103 tomography scan, perfusion-ventilation lung scan, or catheter-guided pulmonary  
104 angiogram [17]. Active cancer was defined by any of the following: a) cancer diagnosis  
105 within the previous 6 months, b) recurrent regionally advanced or metastatic cancer, c)  
106 cancer for which treatment had been administered within the previous 6 months, or d)  
107 hematological malignancy that was not in complete remission [29]. In addition, patients  
108 had to be aged  $\geq 20$  years.

109 Exclusion criteria included thrombectomy; use of fibrinolytic agents or anticoagulant  
110 therapy prior to trial enrollment for more than 7 days; another indication for long-term  
111 anticoagulation therapy, thienopyridine therapy, or treatment with aspirin  $> 165$  mg  
112 daily; use of a factor Xa inhibitor within the previous 3 months; clinically significant  
113 liver disease, active bleeding, or a high risk of bleeding; Eastern Cooperative Oncology  
114 Group performance status of 3 to 4; and life expectancy of less than 6 months.

115 Additional exclusion criteria were platelet count  $< 50,000/\mu\text{l}$ , creatinine clearance  $< 30$   
116 ml/min using the Cockcroft-Gault formula, aspartate aminotransferase or alanine  
117 aminotransferase  $\geq 3$  times the upper limit of normal, and prothrombin time-  
118 international normalized ratio (PT-INR)  $> 1.6$ . The cutoff values for exclusion criteria  
119 in the present study were set in accordance with those in the ADAM-VTE trial (Table  
120 S1, [23]).

121

122 *Treatment Intervention*

123 Apixaban treatment was according to the standard dosage and administration; it was  
124 initiated at 10 mg twice daily for 7 days, followed by 5 mg twice daily for 23 weeks.

125 There were no dose modifications in this study, including dose reductions. An extended  
126 observation period was planned for 24 weeks. Continuing apixaban after the 24-week  
127 intervention period was allowed at the discretion of physicians.

128

129 *Study Endpoints*

130 Primary endpoint was the incidence rate of the adjudicated composite of the  
131 International Society on Thrombosis and Haemostasis (ISTH)-defined major and  
132 clinically relevant non-major (CRNM) bleeding events during the 24-week intervention  
133 period (Table S2, [30]). Key secondary endpoints included the incidence rate of the  
134 adjudicated composite of recurrent VTE and VTE-related death during the 24-week  
135 intervention period (Table S2, [17]), residual vein thrombosis, and overall survival.  
136 Lower extremity venous ultrasound with B-mode compression was used to assess DVT  
137 subjects and enhanced computed tomography was used to assess thrombotic burden in  
138 PE subjects. Imaging obtained at weeks 4 (optional), 24 and 48 was compared with

imaging at the baseline. VTE detected during imaging tests performed for reasons other than VTE suspicion, such as evaluation of cancer treatment response, was also counted. For DVT, residual vein thrombosis was defined as thrombus occupying > 40% of the vein diameter [31]. Thrombotic burden was also classified as improved, worsened, or no change [27]. In addition, post thrombotic syndrome was recorded.

All clinical endpoints (bleeding events, recurrent VTE, or death) as well as laboratory tests were monitored at least every 4 weeks throughout the study. Bleeding events were defined using ISTH criteria (Table S2, [30]). The severity of major bleeding at clinical presentation was adjudicated into four categories (Table S2, [32]). Bleeding risk was analyzed with pre-specified items (age  $\geq$  80 years old, body weight  $\leq$  60 kg, and serum creatinine  $\geq$  1.5 mg/dl) according to the dose adjustment criteria for apixaban in the prevention of stroke in atrial fibrillation [14]. In addition, the length of hospital stay was recorded.

### *Statistical Considerations*

For the primary endpoint - the incidence rate of the adjudicated composite of ISTH-defined major/CRNM bleeding - the null hypothesis ( $\leq$  13%; incidence rate of the apixaban group in the AMPLIFY trial [20]) and alternative hypothesis ( $\geq$  28%;

incidence rate of the unfractionated heparin plus warfarin group in the AMPLIFY-J trial [27]) were tested with a one-sided significance level of 2.5% and power of 80%. Given an anticipated dropout rate of 10%, the target number of patients was calculated to be 62.

All analyses were performed using SPSS for Windows, version 23.0 (IBM, Armonk, NY). Binominal confidence intervals (CIs) for bleeding events or recurrent VTE were estimated by the exact method. For time-to-event analyses, Kaplan-Meier estimates and 95% CIs were calculated. All statistical analyses were two-sided, and probability values of  $<0.05$  were considered statistically significant.

## **Results**

Registration for this study was suspended due to safety concerns after 27 patients were enrolled from February 2018 to June 2019. After an unplanned interim analysis and consultation with the data and safety monitoring committee, the study was terminated on August 19, 2019, with a median follow-up period of 5.4 (range, 0.4-10.7) months.

### *Patient Characteristics*

Patient characteristics are summarized in Table 1. The major primary tumor sites were gastrointestinal tract, followed by lung and breast, and the most common histological diagnosis was adenocarcinoma. Most solid cancer patients had metastatic disease (18 of 25; 72%) and were receiving anticancer treatment at the registration, of whom a majority (16 of 18; 89%) were receiving cytotoxic agents.

#### *Bleeding Events*

Major and CRNM bleeding occurred in five (19%) and two patients (7%), respectively; hence, the primary endpoint of major/CRNM bleeding occurred in 26% (95% CI, 11-46). A summary of these seven bleeding events is provided in Table 2. Among five major bleedings, one episode was category 3 (intracranial bleeding), three were category 2 (two upper gastrointestinal bleedings and one postoperative bleeding), and one was category 1 (intraocular bleeding). Estimated cumulative incidence rate of major/CRNM bleeding and major bleeding at 6 months was 31% and 25%, respectively (Figure 1). In addition, two minor bleedings were observed (two hemoptysis).

With regard to bleeding risk, incidence rates of major/CRNM bleeding seemed higher in patients who had low body weight (5 of 16; 31%) than in patients without (2 of 11;

18%). No severe laboratory abnormalities which conflicted with the inclusion criteria (e.g. hepatic events) occurred throughout the study period.

#### *Recurrent VTE*

No recurrent VTE or VTE-related death occurred in these 27 patients (95% CI, 0-13%).

#### *Residual Vein Thrombosis and Thrombotic Burden Assessment*

Seventeen of 27 patients (63%) received a diagnosis of DVT via compression ultrasound, and 3 other patients (11%) were diagnosed as DVT plus PE according to ultrasound imaging and spiral computed tomography at the time of diagnosis. Among the seven patients who underwent ultrasound imaging in week 4, thrombosis completely disappeared in three patients (43%), and three patients (43%) showed improvement with residual vein thrombosis defined as thrombus occupying > 40% of the vein diameter [30]. Thrombosis remained unchanged in one patient (14%), and no increase was observed. Among the 17 patients who underwent ultrasound imaging at any time during the 24-week intervention, four patients (24%) achieved complete disappearance, four (24%) reported improvement without residual vein thrombosis, and seven (41%)

210 demonstrated improvement with residual vein thrombosis. Two patients (12%) showed  
211 no change, and no patient showed worsening. No post thrombotic syndrome was  
212 observed throughout the study period.

213

#### 214 *Survival*

215 During the study period, 17 episodes of cancer progression and seven deaths (26%)  
216 occurred. All deaths were due to cancer progression, except one patient who died of  
217 pneumonia. No fatal bleeding was observed. Estimated overall survival at 6 months was  
218 68% (Figure 2).

219

#### 220 *Length of Hospital Stay and Treatment Compliance*

221 Thirteen patients (48%) were hospitalized at the time of registration. The median  
222 length of hospital stay was 11 (range, 3-42) days. Study treatment was discontinued due  
223 to completion of the 24-week intervention (n = 12; 44%), bleeding events (n = 7; 26%),  
224 disease progression (n = 3; 11%), study termination (n = 3; 11%), and patient refusal (n  
225 = 2; 7%). No patient had a dose reduction of apixaban during the treatment period, but  
226 eight patients (30%) had treatment interruption, with a median period of 14 (range, 2-  
227 59) days, due to poor patient compliance (n = 4; 15%) or planned surgery (n = 4; 15%).

228 Three of 12 patients continued the use of apixaban (5 mg) after the 24-week  
229 intervention period.

230

## 231 **Discussion**

232 This phase II trial failed to demonstrate the safety of apixaban for Japanese patients  
233 with cancer-associated VTE, despite being prescribed at the approved standard dose.  
234 The primary endpoint of major/CRNM bleeding occurred in 26%, and the incidence of  
235 major bleeding was 19%, although no recurrent VTE or VTE-related death was  
236 observed. The incidence of major bleeding events in this trial was unexpectedly high. In  
237 contrast, a Taiwanese database study demonstrated that DOACs used in cancer patients  
238 with VTE caused similar rates of major bleeding compared with LMWH [34].  
239 However, that was a retrospective study, and the most patients received rivaroxaban, not  
240 apixaban. Although the incidence of major bleeding (7.4% [34]) seemed lower than that  
241 in our study (18.5%) and a Japanese retrospective study (17.8%, [35]), it was still higher  
242 than those in the pivotal trials (0-6.9%, [20-24, 27, 33]). In line with our present study,  
243 the incidence of major bleeding in a Japanese post-marketing surveillance study (9.2%  
244 [36]) seemed higher than those of the international randomized studies (0-3.8%, [23,  
245 24]). The eligibility criteria and dosing of the present and previous phase III trials were

similar (Table S1, [20, 23, 24, 27]). Several possible explanations for the high incidence of bleeding in **our present** patients should be considered.

First, the low body weight in this study (median, 51.3 kg) might have resulted in an increase in bleeding events. Actually, body weight  $\leq 60$  kg is one of the dose adjustment criteria for apixaban in the prevention of stroke in atrial fibrillation [14] and for edoxaban in the treatment of VTE [17]. However, such dose reduction of apixaban is not recommended for VTE. Accordingly, the same dose of apixaban was used regardless of body weight in the current study, and five of seven patients who had major/CRNM bleeding had body weight  $\leq 60$  kg. (Table 2). In a phase I study of apixaban in healthy subjects [37], compared with the reference body weight group (65-85 kg), the low body weight group ( $\leq 50$  kg) had an approximately 27% higher maximum observed plasma concentration ( $C_{\max}$ ) and 20% higher area under the concentration-time curve (AUC). The authors from the pharmaceutical companies concluded that this change was unlikely to require dose adjustment for apixaban based on body weight alone, but that caution was warranted in the presence of additional factors which could increase apixaban exposure.

Ethnic factors may enhance bleeding as well. Meta-analyses in the VKAs era [38, 39] showed that Japanese patients have a higher bleeding risk than Western patients with

264 anticoagulant treatment, although the mechanisms for this have not been fully  
265 elucidated. In a simulation based on a population pharmacokinetics model of apixaban  
266 [40], compared with the typical non-Asian VTE subjects, the typical Japanese VTE  
267 subjects had an approximately 42% and 50% higher  $C_{\max}$  and AUC, respectively. In this  
268 context, a regulatory review report from the Pharmaceuticals and Medical Devices  
269 Agency [41] did not affirm the appropriateness of the recommended dosage and  
270 administration of apixaban for Japanese VTE subjects. In addition to low body weight,  
271 Japanese ethnicity increases apixaban exposure. Pharmacokinetics/pharmacodynamic  
272 studies showed that anti-factor Xa activity consistently exhibited a close linear  
273 relationship with apixaban plasma concentration [37, 40, 42], and apixaban exposure  
274 was correlated with bleeding events [42]. On the other hand, a subgroup analysis of  
275 HOKUSAI VTE study [43] demonstrated that East Asian patients had similar rates of  
276 major/CRNM bleeding in non-East Asian patients, partially because low body weight  
277 was set as one of the dose adjustment criteria for edoxaban [17]. Of course, there are  
278 several differences between studies and DOAC agents [44], however, these  
279 considerations and our data suggest that apixaban at the standard dose is an overdose for  
280 Japanese patients with cancer-associated VTE.

A second possible explanation is information bias. Clinical trials that stop early are at risk of overestimating treatment effects, especially in small studies [45]. Due to its early termination, our trial included only 27 patients, and it was possible that bleeding events were concentrated in the early study period.

Lastly, a degree of selection bias was also likely present. The patients in this study might have had a higher bleeding risk than those in the previous studies [21-24, 34-36]: for example, most solid cancer patients had metastatic disease (18 of 25; 72%) and were receiving anticancer treatment at registration (18 of 27; 77%). In addition, three of seven patients who were suffering from major/CRNM bleeding had luminal gastrointestinal cancers with an intact primary and/or active gastrointestinal mucosal abnormality (Table 2). These were documented as novel bleeding risk factors based on the results of recent phase III trials which compared DOACs with LMWH [21, 22]. Although these trials excluded Japanese patients, our data suggested that these risk factors are also applicable in Japanese patients.

Regarding efficacy, the absence of recurrent VTE or VTE-related death in this study and improvement in thrombotic burden in 88% of patients were comparable with the results of previous studies [27, 46]. Concerning convenience and compliance, the median length of stay in hospitals of 11 days and permanent study drug discontinuation

299 rate of 7% at the patient's discretion were also comparable with the results of previous  
300 studies [27, 44, 47]. Overall, problems with this study were restricted to overdose  
301 leading to bleeding in Japanese patients with cancer-associated VTE, albeit that the  
302 study was terminated early and had a small number of subjects (n = 27).

303 Allowing for these limitations as well as the nature of the non-randomized trial  
304 design, this study is the first prospective interventional trial focusing on DOACs for  
305 Japanese cancer-associated VTE, and clearly demonstrates the high bleeding risk of  
306 apixaban even with the standard dose and administration method. Further studies to  
307 refine the dosage of apixaban are necessary.

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311

312    **Compliance with ethical standards**

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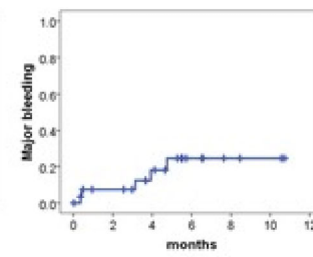
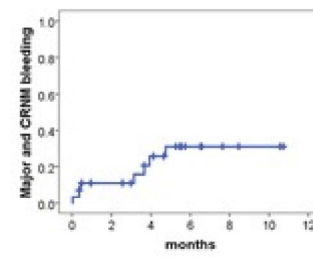
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499    **Legends for Figures**

500    **Figure 1.** (A) Kaplan-Meier plot of cumulative incidence rate of major and clinically  
501    relevant non-major bleeding ( $n = 27$ ). (B) Kaplan-Meier plot of cumulative incidence  
502    rate of major bleeding ( $n = 27$ ).

503

504    **Figure 2.** Kaplan-Meier plot for overall survival ( $n = 27$ ).



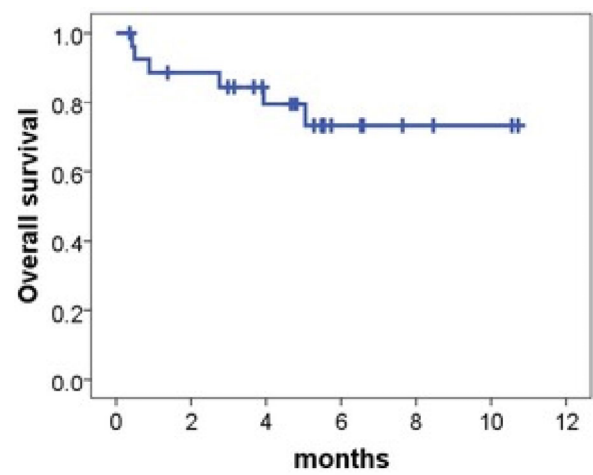


Table 1. Patient characteristics (n = 27)

| Baseline characteristics                                                                        | n = 27           |
|-------------------------------------------------------------------------------------------------|------------------|
| Median age (range, years)                                                                       | 71 (38-82)       |
| Female                                                                                          | 14 (52%)         |
| Eastern Cooperative Oncology Group Performance Status (0/1/2)                                   | 9/13/5           |
| Median body weight (range, kg)                                                                  | 51.3 (40.0-90.7) |
| Median hemoglobin (range, g/dl)                                                                 | 11.4 (7.8-16.2)  |
| Median platelets (range, K/ $\mu$ l)                                                            | 206 (50-501)     |
| Median prothrombin time-international normalized ratio (range)                                  | 1.00 (0.84-1.34) |
| Median D-dimer (range, $\mu$ g/dl)                                                              | 3.4 (0.8-19.4)   |
| Median serum creatinine (range, mg/dl)                                                          | 0.71 (0.32-1.25) |
| Primary site (gastrointestinal/lung/breast/genitourinary/pancreas/hematologic malignancy/other) | 7/5/4/4/3/2/2    |
| Histology (adenocarcinoma/squamous cell carcinoma/hematologic malignancy/other)                 | 15/7/2/3         |
| Diagnostic procedure (compression ultrasound/spiral computed tomography/both)                   | 17/7/3           |
| Deep venous thrombosis/pulmonary embolism/both,                                                 | 19/2/6           |
| Symptomatic                                                                                     | 15 (56%)         |
| Recurrent, regionally advanced or metastatic solid cancer                                       | 20/25 (80%)      |
| Unfractionated heparin prior to registration                                                    | 2 (7%)           |
| Prior surgery ( $\leq$ 6 months)                                                                | 7 (26%)          |
| On-going or prior radiotherapy ( $\leq$ 6 months)                                               | 12 (44%)         |

On-going or prior systemic therapy ( $\leq 6$  months)

21 (78%)

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Table 2. Summary of major and clinically relevant non-major (CRNM) bleeding events (n = 7)

|                           | Case 1                                         | Case 2                                         | Case 3                                         | Case 4                                         | Case 5                          | Case 6                             | Case 7                 |
|---------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|---------------------------------|------------------------------------|------------------------|
| Age, sex                  | 56F                                            | 66M                                            | 51F                                            | 53F                                            | 72F                             | 75F                                | 60M                    |
| ECOG-PS                   | 1                                              | 1                                              | 1                                              | 0                                              | 1                               | 1                                  | 1                      |
| BW (kg)                   | 57.7                                           | 60.0                                           | 69.0                                           | 51.3                                           | 50.9                            | 46.8                               | 75.0                   |
| Hemoglobin (g/dl)         | 12.4                                           | 10.5                                           | 12.3                                           | 10.4                                           | 7.8                             | 13.2                               | 8.2                    |
| Platelet (K/μl)           | 238                                            | 235                                            | 206                                            | 365                                            | 515                             | 139                                | 50                     |
| PT-INR                    | 0.84                                           | 1.00                                           | 0.97                                           | 1.09                                           | 1.34                            | 0.89                               | 1.09                   |
| Serum creatinine (mg/dl)  | 0.52                                           | 0.52                                           | 1.02                                           | 0.49                                           | 1.07                            | 0.55                               | 0.60                   |
| CG-Ccr (ml/min)           | 110.0                                          | 118.6                                          | 71.1                                           | 107.5                                          | 38.2                            | 65.3                               | 138.9                  |
| Primary disease           | Intraocular lymphoma                           | Pancreas adenocarcinoma                        | Malignant peritoneal mesothelioma              | Breast adenocarcinoma                          | Clear cell renal cell carcinoma | Esophageal squamous cell carcinoma | Small cell lung cancer |
| Stage                     | I                                              | IV                                             | IV                                             | I                                              | (Recurrent)                     | IV                                 | IV                     |
| On-going treatment        | Cytotoxic agent without angiogenesis inhibitor | Cytotoxic agent without angiogenesis inhibitor | Cytotoxic agent without angiogenesis inhibitor | Cytotoxic agent without angiogenesis inhibitor | Immune check point inhibitors   | None                               | None                   |
| Overall survival (months) | 10.9+                                          | 6.6                                            | 8.8+                                           | 7.1+                                           | 0.9                             | 3.7+                               | 1.2                    |
| Bleeding characteristics  |                                                |                                                |                                                |                                                |                                 |                                    |                        |

|                        |                        |                     |                                                |               |                      |                                              |                        |
|------------------------|------------------------|---------------------|------------------------------------------------|---------------|----------------------|----------------------------------------------|------------------------|
| Site                   | Vitreous               | Gastric             | Brain                                          | Breast        | Duodenum             | Airway                                       | Airway                 |
| Timing (months)        | 0.4                    | 3.9                 | 4.8                                            | 2.7           | 0.4                  | 3.7                                          | 0.0                    |
| Severity<br>(category) | Major (1)              | Major (2)           | Major (3)                                      | Major (2)     | Major (2)            | CRNM                                         | CRNM                   |
| Cause                  | Intravitreal injection | Invasion to stomach | Reversible cerebral vasoconstriction syndrome* | Major surgery | Invasion to duodenum | Intact primary disease (invasion to trachea) | Intact primary disease |
| Classical risks**      | None                   | None                | None                                           | None          | None                 | None                                         | None                   |

\* The only vascular risk factor was dyslipidemia. Prior continuous administration of cytotoxic agents with cisplatin plus pemetrexed followed by gemcitabine over 4 years may be a cause of reversible cerebral vasoconstriction syndrome.

\*\*Intracranial or intraocular bleeding  $\leq$  6 months, gastro-intestinal bleeding and/or endoscopically verified ulcer disease  $\leq$  6 months, head trauma or other major trauma  $\leq$  1 month, major surgery and/or neurosurgery  $\leq$  2 weeks, ischemic stroke  $\leq$  2 weeks, gross hematuria, intracranial neoplasm, prior angiogenesis inhibitor  $\leq$  6 weeks

ECOG-PS, Eastern Cooperative Oncology Group Performance Status; BW, body weight; CG-Ccr, Cockcroft-Gault Creatinine clearance; PT-INR, prothrombin time-international normalized ratio

Table S1. Comparison with pivotal phase III trials: study design.

|                          | <b>AMPLIFY [20]<br/>(NCT00643201)</b>                                    | <b>AMPLIFY-J [27]<br/>(NCT01780987)</b>                            | <b>ADAM VTE [23]<br/>(NCT02585713)</b>                 | <b>CARAVVAGIO [24]<br/>(NCT03045406)</b>           | <b>Current study<br/>(UMIN000028447)</b>                           |
|--------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------|--------------------------------------------------------|----------------------------------------------------|--------------------------------------------------------------------|
| No. of patients          | 5614 (no Japanese)                                                       | 80 (all Japanese)                                                  | 287 (no Japanese)                                      | 1168 (no Japanese)                                 | 27 (all Japanese)                                                  |
| Study treatment          | Apixaban vs UFH/warfarin                                                 | Apixaban vs UFH/warfarin                                           | Apixaban vs dalteparin                                 | Apixaban vs dalteparin                             | Apixaban (single arm)                                              |
| Study duration           | 24 weeks                                                                 | 24 weeks                                                           | 180 days                                               | 6 months                                           | 24 weeks                                                           |
| Primary endpoint         | Recurrent VTE/VTE-related death                                          | Major/CRNM bleeding                                                | Major bleeding                                         | Recurrent VTE                                      | Major/CRNM bleeding                                                |
| Key secondary endpoints  | Recurrent VTE/VTE-related death or major bleeding<br>Major/CRNM bleeding | Recurrent VTE/VTE-related death<br>Thrombotic burden deterioration | Recurrent VTE/VTE-related death<br>Major/CRNM bleeding | Recurrent VTE or major bleeding<br>Quality of life | Recurrent VTE/VTE-related death<br>Thrombotic burden deterioration |
| Key eligibility criteria |                                                                          |                                                                    |                                                        |                                                    |                                                                    |
| Age                      | ≥ 18 years old                                                           | ≥ 20 years old                                                     | ≥ 18 years old                                         | Age ≥ 18 years old                                 | Age ≥ 20 years old                                                 |
| VTE                      | Symptomatic proximal DVT or PE                                           | Proximal DVT or PE                                                 | VTE or splanchnic/cerebral vein thrombosis             | Proximal DVT or PE                                 | VTE                                                                |
| Active cancer            | (no limitation)                                                          | (no limitation)                                                    | Yes                                                    | Yes (including cancer diagnosed within 2 years)    | Yes                                                                |
| Life expectancy          | ≥ 6 months                                                               | ≥ 6 months                                                         | ≥ 60 days                                              | ≥ 6 months                                         | ≥ 6 months                                                         |
| ECOG-PS                  | (no limitation)                                                          | (no limitation)                                                    | 0-2                                                    | 0-2                                                | 0-2                                                                |

|                                                                      |                               |                               |                                                       |                 |                                                                                  |
|----------------------------------------------------------------------|-------------------------------|-------------------------------|-------------------------------------------------------|-----------------|----------------------------------------------------------------------------------|
| Concomitant thienopyridine                                           | Ineligible                    | Ineligible                    | Ineligible                                            | Ineligible      | Ineligible                                                                       |
| Concomitant dual antiplatelet therapy                                | Ineligible                    | Ineligible                    | (no limitation)                                       | (no limitation) | (no limitation)                                                                  |
| Concomitant use of aspirin < 165 mg/day                              | (no limitation)               | (no limitation)               | (no limitation)                                       | (no limitation) | (no limitation)                                                                  |
| Concomitant use of cytochrome P-450 3A4/P-glycoprotein               | (no limitation)               | (no limitation)               | Ineligible (strong inhibitor of cytochrome P-450 3A4) | Ineligible      | Ineligible (HIV protease inhibitor, Azole antifungals, or Macrolide antibiotics) |
| Use of a Factor Xa inhibitor                                         | (no limitation)               | (no limitation)               | Ineligible ( $\leq 3$ months)                         | (no limitation) | Ineligible ( $\leq 3$ months)                                                    |
| Active bleeding/high risk of bleeding/bleeding tendency              | Ineligible                    | Ineligible                    | Ineligible                                            | Ineligible      | Ineligible                                                                       |
| Uncontrolled hypertension                                            | Ineligible                    | Ineligible                    | (no limitation)                                       | Ineligible      | (no limitation)                                                                  |
| Clinically significant liver disease                                 | Ineligible                    | Ineligible                    | Ineligible                                            | Ineligible      | Ineligible                                                                       |
| Intracranial/intraocular bleeding                                    | Ineligible ( $\leq 6$ months) | Ineligible ( $\leq 6$ months) | Ineligible ( $\leq 6$ months)                         | (no limitation) | (no limitation)                                                                  |
| Gastrointestinal bleeding and/or endoscopically proven ulcer disease | Ineligible ( $\leq 6$ months) | Ineligible ( $\leq 6$ months) | Ineligible ( $\leq 6$ months)                         | (no limitation) | (no limitation)                                                                  |
| Head trauma/other major trauma                                       | Ineligible ( $\leq 2$ months) | Ineligible ( $\leq 1$ month)  | Ineligible ( $\leq 1$ month)                          | (no limitation) | (no limitation)                                                                  |
| Major surgery                                                        | Ineligible ( $\leq 2$ months) | Ineligible ( $\leq 1$ month)  | Ineligible ( $\leq 1$ week)                           | (no limitation) | (no limitation)                                                                  |

|                       |                             |                              |                              |                            |                            |
|-----------------------|-----------------------------|------------------------------|------------------------------|----------------------------|----------------------------|
| Ischemic stroke       | Ineligible ( $\leq 1$ week) | Ineligible ( $\leq 2$ weeks) | (no limitation)              | (no limitation)            | (no limitation)            |
| Neurosurgery          | Ineligible ( $\leq 1$ week) | Ineligible ( $\leq 2$ weeks) | Ineligible ( $\leq 2$ weeks) | (no limitation)            | (no limitation)            |
| Planned major surgery | Ineligible                  | Ineligible                   | (no limitation)              | (no limitation)            | (no limitation)            |
| Intracranial neoplasm | Ineligible                  | Ineligible                   | (no limitation)              | (no limitation)            | (no limitation)            |
| Platelet count        | $\geq 100,000 /\mu\text{l}$ | $\geq 100,000 /\mu\text{l}$  | $\geq 50,000 /\mu\text{l}$   | $\geq 75,000 /\mu\text{l}$ | $\geq 50,000 /\mu\text{l}$ |
| Hemoglobin            | $\geq 9$ g/dl               | $\geq 9$ g/dl                | (no limitation)              | $\geq 8$ g/dl              | (no limitation)            |
| CG-Ccr                | $\geq 25$ ml/min            | $\geq 25$ ml/min             | $\geq 30$ ml/min             | $\geq 30$ ml/min           | $\geq 30$ ml/min           |
| AST/ALT               | $< 3$ times the ULN         | $< 2$ times the ULN          | $< 3$ times the ULN          | $< 3$ times the ULN        | $< 3$ times the ULN        |
| Total bilirubin       | $< 1.5$ times the ULN       | $< 1.5$ times the ULN        | (no limitation)              | $< 2$ times the ULN        | (no limitation)            |
| PT-INR                | (no limitation)             | (no limitation)              | $< 1.6$                      | (no limitation)            | $< 1.6$                    |

UFH, unfractionated heparin; VTE, venous thromboembolism; CRNM, clinically relevant non-major; DVT, deep vein thrombosis; PE, pulmonary embolism;

ECOG-PS, Eastern Cooperative Oncology Group Performance Status; HIV, human immunodeficiency virus; CG-Ccr, Cockcroft-Gault Creatinine clearance; AST,

aspartate aminotransferase; ALT, alanine aminotransferase; PT-INR, prothrombin time-international normalized ratio; ULN, upper limit of normal

Table S2. Definition of major endpoints.

| Major endpoint                                 | Definition                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Major bleeding<br>[30, 32]                     | <ul style="list-style-type: none"> <li>■ Acute clinically overt bleeding accompanied by one or more of the following: <ul style="list-style-type: none"> <li>• A decrease in hemoglobin of 2 g/dl or more</li> <li>• A transfusion of 2 or more units of packed red blood cells</li> <li>• Bleeding that occurs in at least one of the following critical sites: <ul style="list-style-type: none"> <li>➤ intracranial</li> <li>➤ intraspinal</li> <li>➤ intraocular (within the corpus of the eye; thus, a conjunctival bleed is not an intraocular bleed)</li> <li>➤ pericardial</li> <li>➤ intraarticular</li> <li>➤ intramuscular with compartment syndrome</li> <li>➤ retroperitoneal</li> </ul> </li> <li>• Bleeding that is fatal</li> </ul> </li> <li>■ The severity of major bleeding at clinical presentation was adjudicated by an independent clinical events committee [3] according to the following prespecified categories: <ul style="list-style-type: none"> <li>• category 1 included bleeding events that were not considered to be a clinical emergency</li> <li>• category 2 included bleeding events that could not be classified in any of the other categories because they led to some treatment but were not considered to be a clinical emergency</li> <li>• category 3 included bleeding events that were considered to be a clinical emergency, such as bleeding with hemodynamic instability or intracranial bleeding with neurologic symptoms</li> <li>• category 4 included bleeding events that led to death before or almost immediately after the patient entered the hospital</li> </ul> </li> </ul> |
| Clinically relevant non-major bleeding<br>[30] | <ul style="list-style-type: none"> <li>■ Acute clinically overt bleeding that consists of: <ul style="list-style-type: none"> <li>• Any bleeding compromising hemodynamics</li> <li>• Any bleeding leading to hospitalization</li> <li>• Subcutaneous hematoma larger than 25 cm<sup>2</sup>, or 100 cm<sup>2</sup> if there was a traumatic cause</li> <li>• Intramuscular hematoma documented by ultrasonography, epistaxis that lasted for more than 5 minutes, was repetitive (i.e., two or</li> </ul> </li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

more

- Episodes of bleeding more extensive than spots on a handkerchief within 24 hours), or led to an intervention (e.g., packing or electrocoagulation)
- Gingival bleeding occurring spontaneously (i.e., unrelated to eating or tooth brushing) or lasting for more than 5 minutes
- Hematuria that was macroscopic and was spontaneous or lasted for more than 24 hours after instrumentation (e.g., catheter placement or surgery) of the urogenital tract
- Macroscopic gastrointestinal hemorrhage, including at least one episode of rectal
- Blood loss, if more than a few spots on toilet paper
- Hemoptysis, if more than a few speckles in the sputum and not occurring within the context of pulmonary embolism
- Any other bleeding type considered to have clinical consequences for a patient such as medical intervention, the need for unscheduled contact (visit or telephone call) with a physician, or temporary cessation of a study drug; or associated with pain or impairment of activities of daily life

Minor bleeding  
[30]

- All acute clinically overt bleeding events not meeting the criteria for either major bleeding or clinically relevant nonmajor bleeding were classified as minor bleeding.

Recurrent  
pulmonary  
embolism (PE)  
[17]

- Symptoms of PE with one of the following findings:
  - A new intraluminal filling defect in (sub)segmental or more proximal branches on spiral computed tomography (CT) of the chest.
  - A new intraluminal filling defect, or an extension of an existing defect, or a new sudden cutoff of vessels more than 2.5 mm in diameter on the pulmonary angiogram.
  - A new perfusion defect of at least 75% of a segment with a local normal ventilation result (high probability) on ventilation/perfusion lung scintigraphy (VQ scan).
  - Inconclusive spiral CT, pulmonary angiography, or VQ scan evidence of a new or recurrent PE with demonstration of a new or recurrent DVT in the lower extremities by compression ultrasound (CUS) or venography

Recurrent deep  
vein thrombosis  
(DVT) [17]

- Symptoms of DVT with one of the following findings:
  - For a NEW DVT:
    - abnormal CUS, including grey-scale or color-coded Doppler
    - an intraluminal filling defect on venography
  - For a RECURRENT DVT:

- abnormal CUS where compression had been normal or, if noncompressible during screening, a substantial increase (4 mm or more) in diameter of the thrombus during full compression
- an extension of an intraluminal filling defect, or a new intraluminal filling defect, or an extension of nonvisualization of veins in the presence of a sudden cutoff on venography

Death [17]

- For all patients who died during the study, the cause of death was adjudicated to one of the following categories:
    - Venous thromboembolism (VTE)-related death
      - PE (based on objective diagnostic testing, autopsy)
      - Unexplained death (and VTE cannot be ruled out)
      - Sudden death (and VTE cannot be ruled out)
    - Cardiovascular-related death
    - Cancer
    - Bleeding
    - Infectious disease
    - Other known cause (to be specified)
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