

# Exploratory retrospective study of risk factors for thromboembolism treated with multi-kinase inhibitor pazopanib or lenvatinib

Kenta Nio, MD, PhD<sup>a,b</sup>, Kenji Tsuchihashi, MD, PhD<sup>b</sup>, Keisuke Taguchi, MD<sup>b</sup>, Tomoyasu Yoshihiro, MD<sup>c</sup>, Kyoko Yamaguchi, MD, PhD<sup>c</sup>, Mamoru Ito, MD, PhD<sup>b</sup>, Shohei Moriyama, MD<sup>b</sup>, Mitsuhiro Fukata, MD, PhD<sup>b</sup>, Toshifumi Fujiwara, MD, PhD<sup>d</sup>, Nokitaka Setsu, MD, PhD<sup>d</sup>, Makoto Endo, MD, PhD<sup>d</sup>, Yoshihiro Matsumoto, MD, PhD<sup>d</sup>, Yasuharu Nakashima, MD, PhD<sup>d</sup>, Takahiro Wakasaki, MD, PhD<sup>e</sup>, Ryuji Yasumatsu, MD, PhD<sup>e</sup>, Hiroshi Ariyama, MD, PhD<sup>c</sup>, Hitoshi Kusaba, MD, PhD<sup>b</sup>, Junji Kishimoto, MA<sup>f</sup>, Koichi Akashi, MD, PhD<sup>c</sup>, Eishi Baba, MD, PhD<sup>g,\*</sup>

## Abstract

Tyrosine kinase inhibitors (TKI) work against various types of cancer by inhibiting angiogenic signaling. Little is understood about the incidence, characteristics, and risk factors associated with thromboembolism induced by TKI in routine clinical practice. We retrospectively analyzed data derived from 29 patients with thyroid cancer or soft tissue sarcoma (STS) treated with lenvatinib (n = 10) and pazopanib (n = 19). Eight (arterial n = 4; venous n = 4) thromboembolic events developed in 6 (20%) patients. Thromboembolisms occurred during a mean of 149 (range, 42–847) days from starting TKI. The primary disease progressed in all patients with thromboembolism. The overall survival durations of patients with and without improved thromboembolism were 572 [95% confidence interval (CI), 225–918] and 176 (95% CI, 84–394) days, respectively, which did not significantly differ ( $P = 0.33$ ). Patients with and without improved thromboembolism survived after onset for 122 (95% CI, 71–173) versus 27 (95% CI, 21–42) days ( $P = 0.049$ ), which significantly differed. Univariate analysis and variate selection for multivariate analysis selected a history of thromboembolism as the most powerful risk factor for new thromboembolism. In summary, the frequency of thromboembolism in clinical practice was higher than that in previous clinical trials. Furthermore, a history of thromboembolism was a risk factor for the development of new thromboembolism in patients treated with TKI. Thromboembolism developed particularly as the primary disease progressed. Our findings require validation in a large-scale study.

**Keywords:** Multiple kinase inhibitor, Thromboembolism, Pazopanib, Lenvatinib

Tyrosine kinase inhibitors (TKI) are included in standard regimens to treat various types of cancer. Targets of TKI often include angiogenic signaling molecules such as vascular endothelial growth factor (VEGFR). Although inhibiting angiogenic

signaling can suppress tumor progression, side effects such as thromboembolism are clinically important<sup>[1]</sup>.

Previous studies of thromboembolism in patients treated with TKI mainly comprise meta-analyses of clinical trials. One study of 24,855 patients in 48 clinical trials associated VEGFR-TKI with increased risk of all-grade arterial thromboembolisms [ATE; relative risk (RR), 3.09; 95% confidence interval (CI), 1.41–6.76;  $P = 0.033$ ]<sup>[2]</sup>. Another study of 9711 patients in 19 clinical trials found that VEGFR-TKI increased the risk of ATE (odds ratio, 2.26; 95% CI, 1.38–3.68;  $P = 0.001$ ]<sup>[3]</sup>. On the other hand, the study of 7441 patients from 17 trials did not find the TKI increased risk of venous thromboembolism (VTE) (RR, 1.10; 95% CI, 0.73–1.66;  $P = 0.64$ ]<sup>[4]</sup>. Another study of 2372 from 14 trials also did not find the association of TKI with increased risk of VTE (RR, 0.912; 95% CI, 0.617–1.348;  $P = 0.643$ ]<sup>[5]</sup>. However, the incidence and characteristics of thromboembolism in routine clinical practice where patient populations have heterogenous backgrounds remain unknown. Furthermore, risk factors for thromboembolism among patients treated with TKI have not been described.

The target and its inhibitory potency of various TKI differ, leading to distinct clinical effectiveness and side effects. Lenvatinib inhibits VEGFR2 strongly, which is the main receptor kinase in the VEGFR family for angiogenesis<sup>[6]</sup>. The randomized phase III SELECT trial found the efficacy of lenvatinib compared with placebo in patients with advanced thyroid cancer that was refractory to iodine-131<sup>[7]</sup>. Pazopanib is a TKI that is used to treat STS and renal cell carcinoma

<sup>a</sup>Department of Medical Oncology, Sasebo Kyosai Hospital, Nagasaki, <sup>b</sup>Department of Hematology, Oncology and Cardiovascular Medicine, Kyushu University Hospital, Departments of <sup>c</sup>Medicine and Biosystemic Science, <sup>d</sup>Orthopaedic Surgery, <sup>e</sup>Otorhinolaryngology, Graduate School of Medical Sciences, Kyushu University, <sup>f</sup>Center for Clinical and Translational Research, Kyushu University Hospital and <sup>g</sup>Department of Oncology and Social Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

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\*Corresponding author. Address: Department of Oncology and Social Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan. Tel: +81-92-642-6921; fax: +81-92-642-6922. E-mail address: e-baba@intmed1.med.kyushu-u.ac.jp (E. Baba).

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in Japan. The randomized phase III PALETTE trial showed the efficacy of pazopanib compared with a placebo in patients with progressive angiogenesis inhibitor-naïve STS despite previous standard chemotherapy<sup>[8]</sup>. The SELECT trial found a 5.4% incidence of both arterial and VTE in patient with treated with lenvatinib, which was higher than those associated with other TKI. The incidences of ATE and VTE in the PALETTE trial of pazopanib were 0.8% and 2.9%, respectively. Another study of the risk of ATE induced by various TKI showed that the RR of ATE was higher with pazopanib than with sorafenib and axitinib<sup>[2]</sup>. These findings suggested that lenvatinib and pazopanib are associated with an increased risk of thromboembolism. Therefore, we aimed to investigate the incidence and characteristics of thromboembolism in patients treated with lenvatinib or pazopanib in routine clinical practice. We also analyzed the risk factors associated with thromboembolism.

## Methods

### Patients

We analyzed data derived from 29 patients [median age, 60 (range, 20–83) y; male, 18 (62%)] with thyroid cancer (n=10) and STS (n=19) who were initially treated with TKI at our institution between January 2013 and January 2018. The cutoff for data was March 2019. Clinical information was retrospectively collected from electronic medical records. The inclusion criteria comprised histologically confirmed metastatic or recurrent thyroid cancer or STS, under treatment with lenvatinib 24 mg/d for thyroid cancer or pazopanib 800 mg/d for STS, and organ function sufficient to tolerate chemotherapy. This study was approved by the Ethics Committee at Kyushu University Hospital.

### Diagnosis and treatment of VTE or ATE

Both ATE and VTE were recorded as thromboembolic events. Any thromboembolic event that occurred between starting a TKI and continuing until 1 year after the final dose was included in the analysis. Both ATE and VTE were diagnosed using contrast-enhanced computed tomography, magnetic resonance imaging, or vascular ultrasonography. A history of thromboembolism was defined as any thromboembolic event that occurred before starting TKI or controlled by anticoagulant treatment. Both ATE and VTE were treated essentially according to the clinical practice guidelines issued by the Japan Stroke Society and the Japanese Circulation Society, respectively<sup>[9,10]</sup>. The therapeutic agents were selected based on the status of each patient. Arterial thromboembolism was treated using antiplatelet agents, heparin or warfarin and VTE was treated with direct oral anticoagulants or low-molecular-weight heparin. An intravenous filter was placed for patients at high risk of pulmonary embolism. Treatment for ATE and VTE was continued until serious side effects emerged or the medications became ineffective.

### Statistics

Correlations between clinical characteristics and the development of thromboembolism were analyzed by logistic regression analysis. The odds ratios of paired values were calculated for body mass index and history of thromboembolism using 2 by 2 frequency tables after weighing 0.5. Variates selection within variates in univariate analysis for multivariate analysis was performed by forward selection using the minimum Bayesian information

criterion model. The survival of patients with and without thromboembolic resolution was estimated using the Kaplan-Meier method, and differences among them were compared by log-rank tests. Hazard ratios were estimated using median survival time assuming exponential distribution. All data were statistically analyzed using JMP software (SAS Institute Inc., Tokyo, Japan).

## Results

### Patients

Ten and 19 patients were, respectively, treated with lenvatinib and pazopanib (Table 1), and followed up for an average of 485 days. The patients treated with lenvatinib or pazopanib were aged a median of 71 and 37 years, respectively, and 4 (40%) and 14 (74%) patients, respectively, were male. Three (10%) of all had a history of thromboembolism. One patient (3%) was under medication for thromboembolism. Lenvatinib was administered as first-line chemotherapy, whereas 4 (21%), 12 (63%) and 3 (16%) patients received pazopanib as first-line, second-line, and later than second-line chemotherapy, respectively. Rates of responses to lenvatinib and pazopanib were 20% and 5%, and those of disease control were 80% and 58%, respectively.

### Univariate and multivariate analyses for risk of thromboembolism

Among age, sex, performance status (PS), body mass index, history of thromboembolism, number of previous treatment lines,

**Table 1**

#### Patient's characteristics.

Characteristic	Lenvatinib, n (%)	Pazopanib, n (%)	Total, n (%)
Number of patients	10	19	29
Median age (range) (y)	71 (57–78)	37 (20–83)	60 (20–83)
Sex			
Male	4 (40)	14 (74)	18 (62)
Female	6 (60)	5 (26)	11 (38)
ECOG PS			
0	1 (10)	5 (26)	6 (21)
1	3 (30)	11 (58)	14 (48)
2	4 (40)	3 (16)	7 (24)
3	2 (20)	0 (0)	2 (7)
History of thrombosis			
Yes	1 (10)	2 (11)	3 (10)
No	9 (90)	17 (89)	26 (90)
Histology			
Thyroid cancer	10		10 (34)
Soft tissue sarcoma	—	19	19 (66)
Metastatic site more than 3	2 (20)	2 (11)	4 (14)
Treatment line			
1	10 (100)	4 (21)	14 (48)
2	0	12 (63)	12 (41)
More than 3	0	3 (16)	3 (10)
Best response			
CR	0	0	0
PR	2 (20)	1 (5)	3 (10)
SD	6 (60)	10 (53)	16 (55)
PD	2 (20)	7 (37)	9 (31)
NE	0	1 (5)	1 (3)

CR indicates complete response; ECOG, Eastern Cooperative Oncology Group; NE, not evaluated; PD, progressive disease; PR, partial response; PS, performance status; SD, stable disease.

**Table 2**  
**Observed thromboembolism.**

No.	Events	TKI	Primary Disease
1	DVT	Lenvatinib	Thyroid cancer
2	Brain infarction	Lenvatinib	Thyroid cancer
3	DVT	Lenvatinib	Thyroid cancer
4	Portal thrombosis	Pazopanib	Hepatic angiosarcoma
5	Splenic infarction, brain infarction	Pazopanib	Unclassified pleomorphic sarcoma
6	Brain infarction, pulmonary embolism	Pazopanib	Alveolar soft part sarcoma

DVT indicates deep venous thrombosis.

primary disease, number of organs with metastasis, hemoglobin, platelets, creatinine, lactate dehydrogenase, albumin, and C-reactive protein, univariate analysis significantly associated only a history of thromboembolism with the development of thromboembolism during TKI therapy ( $P=0.0023$ ; Table 2). Variates selection within variates in a univariate analysis by forward selection identified only a history of thromboembolism.

### Thromboembolic events

Six (20%) patients comprising 3 each treated with lenvatinib and pazopanib experienced a total of 8 thromboembolic events (Tables 3, 4) that included brain infarcts ( $n=3$ ), deep venous thrombosis ( $n=2$ ), and splenic infarction, pulmonary embolism and portal thrombosis ( $n=1$  each). Splenic and brain infarcts, as well as pulmonary embolism, occurred in patient no. 6 (Table 4). One patient with a medical history of portal thrombosis relapsed (patient no. 4), 1 with arterial thromboembolism treated using clopidogrel sulfate developed splenic and brain infarcts and 1 with lower limb paralysis developed deep venous thrombosis. Thromboembolisms developed in 5 patients during treatment and 1 had a thrombotic event after completing treatment. The PS of the 6 patients with thromboembolism before treatment was categorized as 1 ( $n=5$ ) and 3 ( $n=1$ ) due to lower-limb paralysis. The PS of patients already with thromboembolism at the onset of events were 1 ( $n=2$ ), 2 ( $n=1$ ), 3 ( $n=2$ ), and 4 ( $n=1$ ). The PS of 4

(67%) patients deteriorated on the onset of events compared with the start of treatment. The median elapsed time between the start of treatment and the occurrence of thromboembolic events was 149 (range, 42–847) days.

### Survival of patients after thromboembolism

The overall survival of patients with and without improved thromboembolism was 572 (95% CI, 225–918) versus 176 (95% CI, 84–394) days ( $P=0.33$ ). No death was associated with thromboembolism, as the primary disease was the cause of death in all of the patients (Table 4). Therapy for thromboembolism was effective for 2 of 6 patients. The overall survival of the 2 patients after thromboembolism onset was 122 (95% CI, 71–173) days which was significantly longer than 27 (95% CI, 21–42) days for the 4 patients who were refractory to therapy for thromboembolism ( $P=0.049$ ; hazard ratios = 0.21).

### Discussion

Meta-analyses indicate that TKI is associated with the increased risk of ATE<sup>[2,3]</sup>. However, the data is little reported in clinical practice. Further, the risk factor for the development of thromboembolism in patients treated with TKI is not known. To our knowledge, the present study firstly found that a history of thromboembolism is a strong risk factor for the development of thromboembolism in patients treated with lenvatinib or pazopanib in clinical practice.

The phase III SELECT trial of lenvatinib for patients with advanced thyroid cancer reported an incidence of 5.4% for both ATE and VTE<sup>[7]</sup>. The phase III PALETTE trial of pazopanib for patients with advanced STS found 0.8% and 2.9% incidences of ATE and VTE, respectively<sup>[8]</sup>. Six (20.7%) of our patients experienced thromboembolism. Concretely, 33% and 15% of our patients treated by lenvatinib and pazopanib developed thromboembolism. These frequencies were higher than those found in the phase III trials. To explain this, we examined whether the population of the present study meets the eligibility criteria of the SELECT and PALETTE trials. We firstly found that at least 60% ( $n=6$ ) of our patients with thyroid cancer was

**Table 3**  
**Univariate analysis and variate selection of clinical characteristics associated with development of thromboembolism.**

	Univariate Analysis			Selected Model		
	OR	95% CI	P	OR	95% CI	P
Age (< 65 vs. ≥ 65 y)	0.78	0.12–5.16	0.79	—	—	—
Sex (female vs. male)	1.88	0.29–12.36	0.5	—	—	—
PS (≥ 2 vs. 0-1)	0.38	0.0037–3.79	0.37	—	—	—
BMI (≥ 25 vs. <25)	0.45	0.0020–9.92	0.58	—	—	—
History of thromboembolism (yes vs. no)	47	1.98–1117.65	0.0023	47	1.98–1117.65	0.0023
No. previous chemotherapy (≥ 1 vs. 0)	0.92	0.14–5.89	0.92	—	—	—
Primary disease (thyroid ca. vs. sarcoma)	2.29	0.35–15.32	0.38	—	—	—
No. metastatic organs (≥ 3 vs. <3)	1.33	0.059–13.33	0.82	—	—	—
Hb	0.79	0.50–1.17	0.25	—	—	—
Plts	1	0.90–1.07	0.99	—	—	—
Cre	1.8	0.029–104	0.77	—	—	—
LDH	1	0.99–1.01	0.91	—	—	—
Alb	0.93	0.24–3.9	0.92	—	—	—
CRP	0.89	0.61–1.29	0.48	—	—	—

Alb indicates albumin; BMI, body mass index; CI, confidence interval; Cre, creatinine; CRP, C-reactive protein; Hb, hemoglobin; LDH, lactate dehydrogenase; OR, odds ratio; Plts, platelets; PS, performance status.

**Table 4**

**Characteristics and clinical course of patients who developed thromboembolism.**

Events	TKI/Primary	Age/Sex	History of TE	PS Before Treatment	Best Response	Response at PS at the Onset of		Period From Initiation of TKI (d)	Treatment for TE	Response to Anticoagulant Therapy	Therapy for		Overall Survival (d)	Cause of Death
						TE	TE				Primary Disease	After TE		
DVT	Lenvatinib/ thyroid ca.	59/F	No	1	SD	PD	3	76	Apixaban, IVC filter	No	Yes	30	106	Primary disease
Brain infarction	Lenvatinib/ thyroid ca	64/M	No	1	PD	PD	2	52	Heparin, warfarin	Yes	Yes	173	225	Primary disease
DVT	Lenvatinib/ thyroid ca	76/M	Brain infarction	3	SD	PD	4	847	Edoxaban	Yes	No	71	918	Primary disease
Portal thrombosis	Pazopanib/ STS	60/F	Portal thrombosis	1	PD	PD	1	373	Low molecule Heparin	No	No	21	394	Primary disease
Splenic infarction, brain infarction	Pazopanib/ STS	83/M	Arterial thrombosis	1	PD	PD	1	42	Clopidogrel sulfate	No	No	42	84	Primary disease
Brain infarction, pulmonary embolism	Pazopanib/ STS	24/M	No	1	SD	PD	3	221	Heparin	No	No	24	245	Primary disease

DVT indicates deep venous thrombosis; IVC, inferior vena cava; PD, progressive disease; PS, performance status; SD, stable disease; STS, soft tissue sarcoma; TE, thromboembolism; Thyroid ca, thyroid cancer; TKI, tyrosine kinase inhibitor.

ineligible for the SELECT trial. We included patients with anaplastic (n = 2) and squamous cell thyroid cancer (n = 1). Three of our patients did not undergo 131-I therapy previously. Within these differences, anaplastic and squamous cell thyroid cancer is more aggressive and poorer prognosis than differentiated thyroid cancer<sup>[11]</sup>. Second, we found at least 26% (n = 5) of our patients with STS would have been ineligible for the PALETTE trial. Three patients were PS ≥ 2 and 2 patients developed brain metastasis, which were excluded in PALETTE trial. Thus, total 38% of our patients did not meet the eligible criteria of either of the SELECT or the PALETTE trials. Moreover, 73% of our patients had PS ≤ 1 when they started TKI therapy, whereas > 90% and 100% of patients in the SELECT and PALETTE trials, respectively, had PS ≤ 1. Furthermore, in STS patients, the ratio of patients with histology other than leiomyosarcoma and synovial sarcoma was 89% in the present study, compared with 56.7% of patients in the PALETTE trial, which found that pazopanib was more effective against these 2 histologic types than any other types. The RR and disease control rate of pazopanib in our study were 5% and 58%, respectively, compared with 6% and 73%, respectively, in the PALETTE trial. In summary, the present study comprises the patients with a different background from previous clinical trials and included more patients with the histology of poor prognosis in thyroid cancer patients, with the histology less responsive to lenvatinib in STS patients and with poor PS. These differences might explain the higher incidence of thromboembolism in the present study.

The risk factors for the development of thromboembolism during TKI therapy remain unknown. Our univariate and multivariate analyses identified a history of thromboembolism as the strongest risk factor for new thromboembolism in patients treated with TKI. Three of 6 patients with thromboembolism had a history of thromboembolism. One patient treated with lenvatinib experienced a brain infarction 30 years ago but did not relapse without medication. This patient had deep venous thrombosis. Another patient treated with pazopanib had a history of portal thrombosis. That patient was initially diagnosed with idiopathic portal hypertension, and portal thrombosis was noted before he received a liver transplant. Thereafter, portal thrombosis did not develop. The third patient who was treated with pazopanib had arterial thrombosis controlled with clopidogrel sulfate. The exclusion criteria associated with risk for thromboembolism in the SELECT trial of lenvatinib comprised significant cardiovascular or gastrointestinal dysfunction. The exclusion criteria of the PALETTE trial of pazopanib, comprised cerebrovascular accidents, and transient ischemic attack, deep vein thrombosis or pulmonary embolism within the 6 months preceding the trial. History of thrombosis in our patients was not among the exclusion criteria of the SELECT and PALETTE trials. History of ATE has shown to be the risk factor for new ATE in patients treated with anti-VEGF-A antibody, bevacizumab, by multivariate analyses<sup>[12]</sup>. Our result suggests that a history of thromboembolism is associated with the increased risk of new thromboembolism in patients treated with TKI.

The median period from the start of treatment to the development of thromboembolism of 149 (range, 42–847) days suggests that the emergence of thromboembolism is not an early event. Our patients developed thromboembolism as the primary disease progressed. This finding indicates that thromboembolism

does not occur at the start of TKI treatment, but rather when the primary disease progresses. Furthermore, the PS in four of six patients with thromboembolism deteriorated. Given that the initial PS was not a risk factor for thromboembolism by multivariate analysis, careful monitoring of thromboembolic development is important, especially when the primary disease progresses and PS deteriorates. Thromboembolism developed at the site most affected by the primary malignant disease in 2 of 6 patients: portal thrombosis in a patient with hepatic angiosarcoma and venous thrombosis in veins compressed by the primary disease in the other patients. These suggest that the site of the primary disease is related to the location where thrombosis arises. We found higher d-dimer values in 4 of 6 patients after thromboembolism occurred compared with before starting TKI therapy. Elevated d-dimer values can predict arterial and venous thromboembolism<sup>[13]</sup>. Monitoring d-dimer values might help to detect asymptomatic thromboembolism.

The median survival of patients with and without thromboembolism that was resolved by treatment was 122 versus 27 days, which significantly differed. Although the present study included a small patient cohort and a large-scale study is required to validate our findings, some reasons are considered for the differences in survival. First, 50% and 25% of our patients with and without resolved thromboembolism, respectively, underwent later line therapies. This could account for the better survival rate for the patients with resolved thromboembolism. Second, the primary disease was the cause of death among all our patients, suggesting that patients with unresolved thromboembolism developed thromboembolism when their primary disease progressed more than those with solved thromboembolism. As reflecting the differences of disease status, the average LDH values, which mirrors tumor burden<sup>[14]</sup>, of the patients with and without improved thromboembolism were 223 and 593 IU/L, respectively, although the difference did not reach significance due to the low number of patients ( $P=0.16$ ). Further investigation is needed to identify factors that affect survival in patients with thromboembolism.

One of several potential limitations in the present study is not to analyze ATE and VTE separately due to the low number of patients. Mechanistically, ATE is mainly due to atherosclerotic lesions with activated platelets, whereas VTE comprises fibrin-rich thrombosis<sup>[15]</sup>. Previous reports indicate that bevacizumab, anti-VEGF-A antibody, is associated with the incidence of both ATE and VTE through dysregulation of vascular homeostasis maintained by endothelial cells, leukocytes, platelets, and various substances such as nitric oxide and prostaglandins<sup>[16]</sup>. On the other hand, the previous meta-analysis showed TKI increased the risk of ATE, not VTE. In the present study, both ATE and VTE were observed. Precise analysis distinguishing ATE and VTE based on the data of a large scale of patients are expected. Further, not only VEGFR but also FGFR signaling also plays an important role in vascular homeostasis<sup>[17]</sup>. The targets of lenvatinib and pazopanib also include FGFR signaling. Targets of each TKIs and their inhibitory potency can impact on the frequency and kinds of thromboembolism associated with TKIs. Our study also has other limitations. One is the small patient cohort. Accordingly, selected model is affected by randomness and not confirmative. The statistical power to determine differences in survival after thromboembolism developed was low and should be investigated and validated in a larger study. Second, 2 histologic malignant types, namely STS and thyroid cancer were analyzed together, although univariate and

multivariate analyses did not identify differences between them. Third, confounding bias was not eliminated in this study because of the nature of the retrospective study in a single institution.

In summary, the findings of this retrospective analysis suggest that the incidence of thromboembolism is higher in daily clinical practice than in clinical trials. Thromboembolic events tended to occur when the primary disease progressed. A history of thromboembolism is an independent risk factor for new thromboembolism in patients treated with TKI. Our findings require validation in a large-scale study.

## Ethical approval

This study has been approved by the ethical review board of Kyusyu University Hospital. Reference number 2019-355.

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None.

## Authors' contribution

K.N. and K.T. have contributed to study design, data acquisition, analysis and writing the manuscript. H.K. contributed to study design and supervise the study. M.F., H.A., and K.A. contributed to develop the study design. J.K. contributed statistical analysis of this study. T.F., N.S., M.E., Y.M., and Y.N. collected the data of orthopedic patients and advised on this study design. T.W. and R.Y. collected the data of otorhinolaryngological patients and advised on the study. K.T., T.Y., K.Y., M.I., and S.M. contributed to data collection. E.B. is a corresponding author and contributed to supervise the study and the writing of the final manuscript. All authors approved the manuscript to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Conflict of interest disclosures

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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## Guarantor

Eishi Baba

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