Title

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Title

Pharmacokinetics of edoxaban in EGFR-mutated non-small cell lung cancer patients with venous thromboembolism

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**Abbreviations**: VTE; venous thromboembolism, DOACs; Direct oral anticoagulants, EGFR; epidermal growth factor receptor, TKIs; tyrosine kinase inhibitors (TKIs), PK; pharmacokinetics, DVT; Deep vein thromboses, PTE; pulmonary thromboembolism, CYP; cytochrome P450, NSCLC; non-small cell lung cancer, AUC0-∞; area under the concentration-time curve, MRT; mean residence time, AUMC; area under the first moment curve, Ke; elimination rate constant, t1/2; half-life, CL; clearance, Vdss; volume of distribution at steady state, LC; liquid chromatography, MS/MS; tandem mass spectrometry.

Abstract

**Background**: The risk of venous thromboembolism (VTE) is seven times higher in patients with cancer than in those without cancer. Low-molecular-weight heparin is the standard treatment for cancer-associated VTE. Direct oral anticoagulants (DOACs) were non-inferior to low-molecular-weight heparin with respect to the composite outcome of recurrent VTE. Warfarin has a risk of bleeding when used in combination with gefitinib and erlotinib (EGFR-tyrosine kinase inhibitors, or TKIs). It is unclear whether combination treatment of EGFR-TKIs and DOACs pose the same risk. We aimed to identify anticancer drugs and anticoagulants that can be used safely together, as accompanying research to the observational study of the VTE incidence rate in lung cancer patients (Rising-VTE/NEJ037 study). **Methods**: Twelve patients receiving EFGR-TKI monotherapy and VTE treatment were enrolled. Blood samples were collected in time series after the first dose of edoxaban. A further set of samples were collected within 8 to 15 days after dosing EGFR-TKIs. The pharmacokinetics (PK) of edoxaban was analyzed using a non-compartmental model. **Results**: Edoxaban concentration (30 mg once daily) was analyzed in eight patients. The PK analysis showed no considerable differences before and after co-administration of EGFR-TKIs (gefitinib, erlotinib, and afatinib). **Conclusions**: These findings indicate that the PK of edoxaban was not considerably influenced by co-administration with EGFR-TKIs (gefitinib, erlotinib, and afatinib).
Keywords: edoxaban; venous thromboembolism; EGFR-TKIs; direct oral anticoagulants; pharmacokinetics

## 1. **Introduction**

Deep vein thromboses (DVT) can cause fatal pulmonary thromboembolism (PTE). Acute pulmonary arterial dysfunction caused by PTE has a 30% mortality rate [1], but this decreases to 2%–8% with treatment [2], and early diagnosis, appropriate treatment, and prevention are thought to improve prognosis. As most PTEs are caused by DVT, and approximately 50% of proximal DVTs develop into PTE [3], the two diseases are collectively referred to as venous thromboembolism (VTE) [4].

VTE is a common complication of cancer and its therapy. The prognosis for cancer patients with VTE is poor, with a 1-year survival rate of 12% and the mortality rate two-times more than that of cancer patients without VTE [5]. The incidence of VTE in hospitalized patients with cancer is two-times higher than that in patients without cancer [6]. In a population-based case–control study, cancer without chemotherapy was associated with a four-fold increased risk of thrombosis, whereas cancer with chemotherapy increased the risk to six-fold [7]. Prophylactic anticoagulant therapy is recommended for hospitalized cancer patients and patients receiving chemotherapy who have a high risk of developing VTE [5,8,9]. Direct oral anticoagulants (DOACs) have been shown to be effective against cancer-associated thrombosis [10-12]. VTE in patients with cancer has been treated with various blood-thinning agents, including rivaroxaban [10], apixaban [11], and edoxaban [12]. Edoxaban was non-inferior to low-molecular-weight heparin (dalteparin) in avoiding recurrent VTE or major bleeding [12].

The currently published studies on drug-drug interactions associated with DOACs focused on medications (e.g., cytochrome P450 (CYP)3A4 inhibitors and P-glycoprotein competitors) that

share a common metabolic pathway with DOACs [13-15]. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are key drugs for the treatment of EGFR mutation-positive non-small cell lung cancer (NSCLC). Some EGFR-TKIs can potentially affect the metabolism of DOACs via CYP3A4 inhibition, resulting in reduced or enhanced effect of DOACs. For example, *in vitro* studies in human liver microsomes showed that gefitinib has a weak inhibitory potential on CYP3A4 activities [16]. Furthermore, erlotinib treatment induced CYP3A4 activity in patients with NSCLC [17].

Here, we designed an observational study on the pharmacokinetics (PK) of edoxaban with EGFR-TKI in patients with NSCLC.

## 2. Materials and methods

### 2.1 Study population

Patients with untreated EGFR-mutated NSCLC with cancer-associated VTE were recruited. All included patients were aged ≥20 years, with the performance status (Eastern Cooperative Oncology Group) of 0-2, NSCLC at an advanced stage for which radical treatment was not possible, and an expected survival period of 6+ months from the time consent was obtained. Planned treatments included gefitinib, erlotinib, or afatinib monotherapy with edoxaban as an anticoagulant therapy. Patients who had a history of edoxaban allergy, reduced renal function (creatinine clearance less than 30 mL/min), liver disease with abnormal blood coagulation, or interstitial lung disease were excluded. Patients were further excluded if they had already been treated for VTE, had alanine transaminase more than two times the facility standard value or total bilirubin more than 1.5 times the facility standard value, or had active bleeding or uncontrolled hypertension as defined by

systolic blood of more than 170 mmHg or diastolic blood pressure of more than 100 mmHg despite taking an antihypertensive agent. Pregnant or breastfeeding women, patients taking aspirin more than 100 mg/day, patients taking other antiplatelet drugs, patients taking drugs that affect kinetics of edoxaban via P-glycoprotein inhibition, and patients with acute bacterial endocarditis were also excluded.

2.2 Study design and treatments

The Rising-VTE/NEJ037 study is an observational study of the incidence of thromboembolism in patients with lung cancer and includes an evaluation of the efficacy and safety of edoxaban in patients with active cancer and VTE. Among patients enrolled in the Rising-VTE/NEJ037 study, those with indications for both EGFR-TKIs and edoxaban entered this study (Figure 1). The protocols were approved by the local ethics committee (November 30, 2015, jRCTs No. 061180026) and were performed in accordance with the 2013 Declaration of Helsinki. All patients signed informed consent before inclusion.

This clinical trial was a multicenter, collaborative, open-label PK study conducted at 26 participating facilities in Japan. VTE screening was performed by contrast-enhanced computed tomography or lower limb echo. Treatment with edoxaban was recommended if VTE was diagnosed by screening. Patients with VTE at the time of diagnosis were initially treated with unfractionated heparin by continuous intravenous infusion or subcutaneous injection, and then treated with daily oral edoxaban at 30 mg for those weighing less than 60 kg or 60 mg for those weighing more than 60 kg. Edoxaban dose was also reduced to 30 mg when patients were

concomitantly using quinidine sulphate hydrate, verapamil hydrochloride, erythromycin, or cyclosporine; or had creatinine clearance of 30 mL/min or less.

Blood samples were collected into heparin-treated vacuum tubes at 0.5, 1, 2, 4, 8, and 24 h after the first edoxaban administration, and then gently mixed by inversion and placed on ice. All blood samples were centrifuged at 1400 × *g* for 10 min at 4 °C. Plasma was collected and stored at -20 °C. Following this, the patients were treated with EGFR-TKI anticancer therapies of any variety (gefitinib/erlotinib/afatinib). Blood samples were again collected at 0.5, 1, 2, 4, 8, and 24 h within 15 days from day 8 after starting EGFR-TKIs, when EGFR-TKIs are expected to reach a steady state [18-20]. VTE screening was repeated 6 months after the start of oral edoxaban. All adverse events were recorded (Figure 2).

2.3 Pharmacokinetic analysis

Plasma concentrations of edoxaban were determined according to the area under the concentration-time curve (AUC0-∞) and the mean residence time (MRT) as follows:

$$\mathrm{AUC} = \int_0^{\infty} \mathrm{C}\,\mathrm{dt}$$

$$\mathrm{MRT} = \int_0^{\infty} \mathrm{t}\cdot\mathrm{C}\,\mathrm{dt} \Big/ \int_0^{\infty} \mathrm{C}\,\mathrm{dt}$$

where, C dt is the concentration of edoxaban plasma concentration at time t. The MRT and area under the first moment curve (AUMC) were defined as the first moment of the concentration-time curves of edoxaban. These moment parameters were calculated by trapezoidal integration using Numeric Analysis Program for Pharmacokinetics (Napp ver. 2.01, Hisaka et al) [21]. Analysis of nonlinear and non-steady state hepatic extraction was performed with a dispersion model using the

finite difference method. The elimination rate constant (Ke) for edoxaban and first-order kinetics of the concentration-time profile of edoxaban up to infinite time after the administration were calculated based on C∞.

2.4.1 Liquid chromatography-tandem mass spectrometry; Edoxaban

The standard sample for calibration curve using human plasma (1, 2, 5, 25, 50, 250, and 500 ng/mL) and edoxaban sample (2, 25, and 400 ng/mL, n=2 for each concentration) with the actual sample (the amount of plasma used: 50 μL) were pretreated using the solid-phase extraction method. Plasma edoxaban concentration was measured using liquid chromatography-tandem mass spectrometry (LC/MS/MS). All blood concentration measurements of edoxaban were entrusted to SHIN NIPPON BIOMEDICAL LABORATORIES.

2.4.2 Liquid chromatography-tandem mass spectrometry; EGFR-TKI

Plasma concentrations of gefitinib and erlotinib in patients were determined by LC-MS/MS [22,23]. TSQ Quantum™ Access MAX Triple Quadrupole Mass (Thermo Fisher Scientific Inc., USA) was used with electrospray ionization in the positive ion mode at 450 °C and 3000 V. EGFR-TKI concentrations were quantified from ion peak area ratio (ratio of gefitinib or erlotinib and clozapine) of the sample calculated by selected reaction monitoring. The MS/MS conditions for gefitinib, erlotinib, and clozapine were optimized with conditions shown in Table 1. Plasma samples (200 μL) were spiked with 25 μL of clozapine and 1.25 mL of acetonitrile and vortexed vigorously. Samples were then centrifuged at 1850 × *g* for 5 min at 4 °C and 1.2 mL of supernatant was evaporated under a gentle stream of nitrogen at 40 °C. Residues were treated with 250 μL of 50% acetonitrile and dissolved for 10 min and centrifuged at 2050 × *g* for 5 min. Five microliters of the supernatant was injected for the quantitative analysis by LC-MS/MS. Chromatographic analysis

was performed using a high-performance liquid chromatographic system (Accela; Thermo Fisher Scientific Inc, Waltham, Massachusetts). The mobile phase consisted of a combination of phase A (4 mM ammonium formate, pH 3.2), and phase B (90% acetonitrile/10% phase A). Phase B was initiated as 5% of the mobile phase for 1 min, increased to 35% over 0.83 min, further increased linearly to 37% over 4.5 min, increased linearly up to 90% over 4 min, continued at 90% for 2.9 min, then decreased linearly to 0% over 0.1 min, and increased back to 5%. Separations were performed at a flow rate of 150 µL/min at 30 °C on an X bridge C18 HPLC column (3.5 µm, 2.1 mm × 100 mm; Waters, Milford, Massachusetts).

### 2.5 Statistical analysis

The PK set for analysis comprised data from 12 enrolled subjects administered edoxaban. The PK of edoxaban was statistically analysed in 8 cases. The two cases were excluded because the edoxaban dose used was 60 mg and it was not appropriate to compare with the 30 mg group. In the remaining two cases, the PK parameters by moment analysis could not be estimated from the patient's blood concentration-time profile. The plasma trough concentration of EGFR-TKI was analyzed in 10 cases because of two samples were defective. Statistical analyses were performed using GraphPad Prism 7 (GraphPad Software, La Jolla, CA, USA). Qualitative variables are reported as frequency and percentage, and quantitative variables as median or mean and standard deviation. Differences in PK parameters were analyzed using the Wilcoxson signed-rank test. The results with a P value of 0.05 or less were considered statistically significant.

## 3 Results

### 3.1 Patient characteristics

Demographic data of all 12 included patients are shown in Table 2. Edoxaban was administered at 30 mg to 10 patients weighing less than 60 kg. Three types of EGFR-TKIs were used, including gefitinib to 4 patients, erlotinib to 7 patients, and afatinib to 1 patient. No changes to EGFR-TKI treatments were made within the 6-month period. No patients took drugs that affect edoxaban kinetics through P-glycoprotein inhibition between study enrollment and PK blood sampling.

3.2 Pharmacokinetics

Table 3 shows the PK parameters for edoxaban alone and edoxaban combined with EGFR-TKIs. The AUC0-∞, MRT, AUMC, Ke, half-life (t1/2), clearance (CL), and volume of distribution at steady state (Vdss) for edoxaban did not change before and after taking EFGR-TKIs. Similar results were obtained when EGFR-TKI was limited to Erlotinib (Table 3). No significant difference in plasma concentration of edoxaban was observed at any time point (Figure 3A). Similar results were obtained for each EGFR-TKI type (Figure 3B, 3C, 3D). After 24 h, the plasma edoxaban concentration was 0.0439 μg/mL when edoxaban was administered alone. It was 0.0259 μg/mL when edoxaban was co-administered with EGFR-TKIs. Simultaneous administration of edoxaban and EGFR-TKIs did not change the plasma edoxaban concentrations.

Table 4 shows EGFR-TKI plasma trough concentration. Patients taking 250 mg gefitinib ($N = 3$) showed a mean trough level of 323.4 ± 34.7 ng/mL. In patients taking 150 mg erlotinib ($N = 2$), the mean was 1927.1 ± 291.4 ng/mL and in patients taking 100 mg erlotinib ($N = 5$), the mean was 1425 ± 422.2 ng/mL.

### 3.3 Adverse events

Epistaxis was reported in three patients. None required special treatment, and all experienced this event only once. The prothrombin time-international standard ratio (INR) measured 6 months after the introduction of edoxaban showed no hyperprolongation (I N R: 0.99-1.58). No serious adverse event (grade 3 or 4) was reported.

## 4 Discussion

### 4.1 Drug interaction

This is the first study to examine edoxaban PK in combination with EGFR-TKI in patients with cancer. There was no increase in the plasma level of edoxaban even after concomitant EGFR-TKI administration. The plasma concentration measured at 24 h after the administration of 30 mg was 0.0259–0.0439 μg/mL in this study. It is within the effective concentration. Previous plasma concentration data indicate that edoxaban at doses of 15–60 mg, the mean trough blood concentration is 0.016–0.0485 μg/mL [24]. It was within the same blood concentration range as previously reported.

Warfarin dosage was significantly different among patients; individual and varying degrees of tolerance were observed besides interactions with various drugs and foods. There have been reports of PT-INR prolongation when warfarin was used in combination with EGFR-TKIs [25-27]. DOACs are less susceptible to dietary effects than warfarin, and there are only a few reports of drug-drug interactions. However, attention must be paid to CYP3A4 metabolism. Administration of dual inhibitors of P-glycoprotein and CYP3A4 increased edoxaban exposure. This effect was mainly due to P-glycoprotein inhibition, and the influence of CYP3A4 inhibition was not remarkable. [14]

CYP3A4 is involved in the edoxaban metabolic process, but the involvement of CYP3A4 is as low as <10% [28]. Therefore, we aimed to confirm the safety of administration of edoxaban in combination with EGFR-TKIs.

No serious bleeding events were reported, and only one study patient was unable to complete the study due to cancer progression and death. There were no incidents of DVT relapse, and the therapeutic purpose was achieved safely.

4.2 Effects of EGFR-TKIs

A previous study on 87 patients [median body surface area (BSA) of 1.66 $m^2$], the mean trough concentration after the administration of 250 mg gefitinib was 173.9 ng/mL [29]. Patients taking 250 mg gefitinib (N = 3) showed a mean trough level of 323.4 ± 34.7 ng/mL in our study when combined with edoxaban. Another study (N = 26, median BSA 1.79 $m^2$) reported a mean trough concentration of 720 ng/mL after the administration of 150 mg erlotinib [30]. For erlotinib 100 mg, a study in 10 patients (median BSA 1.69 $m^2$) reported the mean trough concentration of 722 ng/mL [30]. Similarly, in our study, when edoxaban was used in combination, the mean trough concentration of erlotinib 150 mg (N = 2) and erlotinib 100 mg (N = 5) was 1927.1 ± 291.4 and 1425 ± 422.2 ng/mL, respectively. The plasma trough concentration of EGFR-TKI in this study did not decrease when combined with edoxaban. Conversely, in our study, the concentration of EGFR-TKIs was higher than that reported previously. The reason may be the low BSA rather than drug interaction. A study in 26 patients (median BSA 1.57 $m^2$) administered 150 mg erlotinib reported a trough concentration of 1380 ng/mL [31]. We examined a group of patients with a lower BSA than that in a previous study [30]. The median BSA of our patients was 1.43 $m^2$, which was also lower

than that of the previous study [31]. Similarly, for gefitinib 250 mg [29] and erlotinib 100 mg [31], the BSA was lower than that of the previous studies, and consequently, the trough level of EGFR-TKI increased.

### 4.3 Study limitations

Our study was limited by the small sample size, with only 10 patients yielding analysable trough concentration data. Therefore, further studies with a sample size are needed to ensure statistical reliability. However, although over 1000 cases have been registered in the main Rising-VTE/NEJ037 study, further accumulation of patients was difficult. In addition, the timing of PK blood sample collection for edoxaban alone was not uniform. For example, there were cases in which PK blood sampling was performed on the day edoxaban was introduced and cases in which PK blood sampling was performed 4 weeks later. However, limiting the days of edoxaban administration delays the initiation of EGFR-TKIs. This was not observed due to the urgency of treating NSCLC.

## 5 Conclusions

Edoxaban PK parameters were not affected by EGFR-TKI used concomitantly. EGFR-TKI can exacerbate the control of coagulation due to interaction with warfarin. Edoxaban possibly enables stable VTE treatment without increasing the risk of bleeding even when used in combination with EGFR-TKI.

## Conflict of interest

The Rising-VTE PK study includes investigator-initiated clinical trials led by Shimane University and funded by Daiichi Sankyo Co., Ltd. TH, KH, AT, MK, AN, JS, MH, NI, NI, MY, KF, TK, and NN have no conflicts of interest to declare. YT reports personal fees from AstraZeneca, Daiichi Sankyo Co., Ltd and Chugai Pharmaceutical Co., Ltd outside the work. TI reports personal fees from Boehringer-Ingelheim, AstraZeneca, and Pfizer outside the work.

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Figure legends

Figure. 1. A flow diagram of the present study. VTE; venous thromboembolism, EGFR; epidermal growth factor receptor, PK; pharmacokinetics.

Figure. 2. Dosing and corresponding blood samples. Blood samples were collected at 0.5, 1, 2, 4, 8, and 24 h (6 time points). Blood collection with EGFR-TKI combination was performed within 8 to 15 days after starting EGFR-TKIs (6 points). The trough measurement was performed immediately before oral administration of EGFR-TKIs.

Figure 3

Figure 3A; Time course of mean plasma edoxaban (30 mg once daily, $N = 8$) concentrations at 0.5, 1, 2, 4, 8, and 24 h after the first edoxaban administration. After 24 h, the plasma edoxaban concentration was 0.0439 μg/mL when edoxaban was administered alone. It was 0.0259 μg/mL when edoxaban was co-administered with EGFR-TKIs. Figure 3B; edoxaban+erlotinib, Figure 3C; edoxaban+gefitinib, Figure 3D; edoxaban+afatinib.

**Table 1. Operating conditions of tandem mass spectrometry**

| | Precursor ion (m/z) | Product ion (m/z) | Collision energy (eV) |
|---|---|---|---|
| Gefitinib | 447.1 | 128 | 35 |
| Elrotinib | 393.9 | 278 | 35 |
| Clozapin | 327.1 | 270 | 35 |

**Table 2. Summary of demographics**

| Demographics | consented subjects<br>Total (*N*=12) | PK measurable cases<br>Edoxaban 30mg (*N*=8) |
|---|---|---|
| Age, median (range), y | 74.5 (59-91) | 81 (63-91) |
| Sex, n (%) | | |
| Female | 9 (75) | 7 (87.5) |
| Male | 3 (25) | 1 (12.5) |
| Height, median (range), cm | 150 (135-183) | 143 (138-154) |
| Weight, median (range), kg | 49.6 (40.2-85) | 49.6 (43.1-59) |
| Body surface, median (range), $m^2$ | 1.42 (1.21-2.07) | 1.40 (1.27-1.54) |
| Creatinine clearance (range), mL/min | 62.22 (30.83-116.62) | 57.22 (30.83-72.51) |
| Edoxaban dose | | |
| 30mg | 10 (83) | 8 (100) |
| 60mg | 2 (17) | – |
| EGFR-TKIs, n (%) | | |
| Gefitinib | 4 (33.3) | 2 (25) |
| Erlotinib | 7 (58.4) | 5 (62.5) |

| | | |
|---|---|---|
| Afatinib | 1 (8.3) | 1 (12.5) |

EGFR-TKIs, Epidermal growth factor receptor–tyrosine kinase inhibitors.

**Table 3. PK parameters of edoxaban after oral administration (30 mg once daily).** Values are presented as mean ± standard deviation.

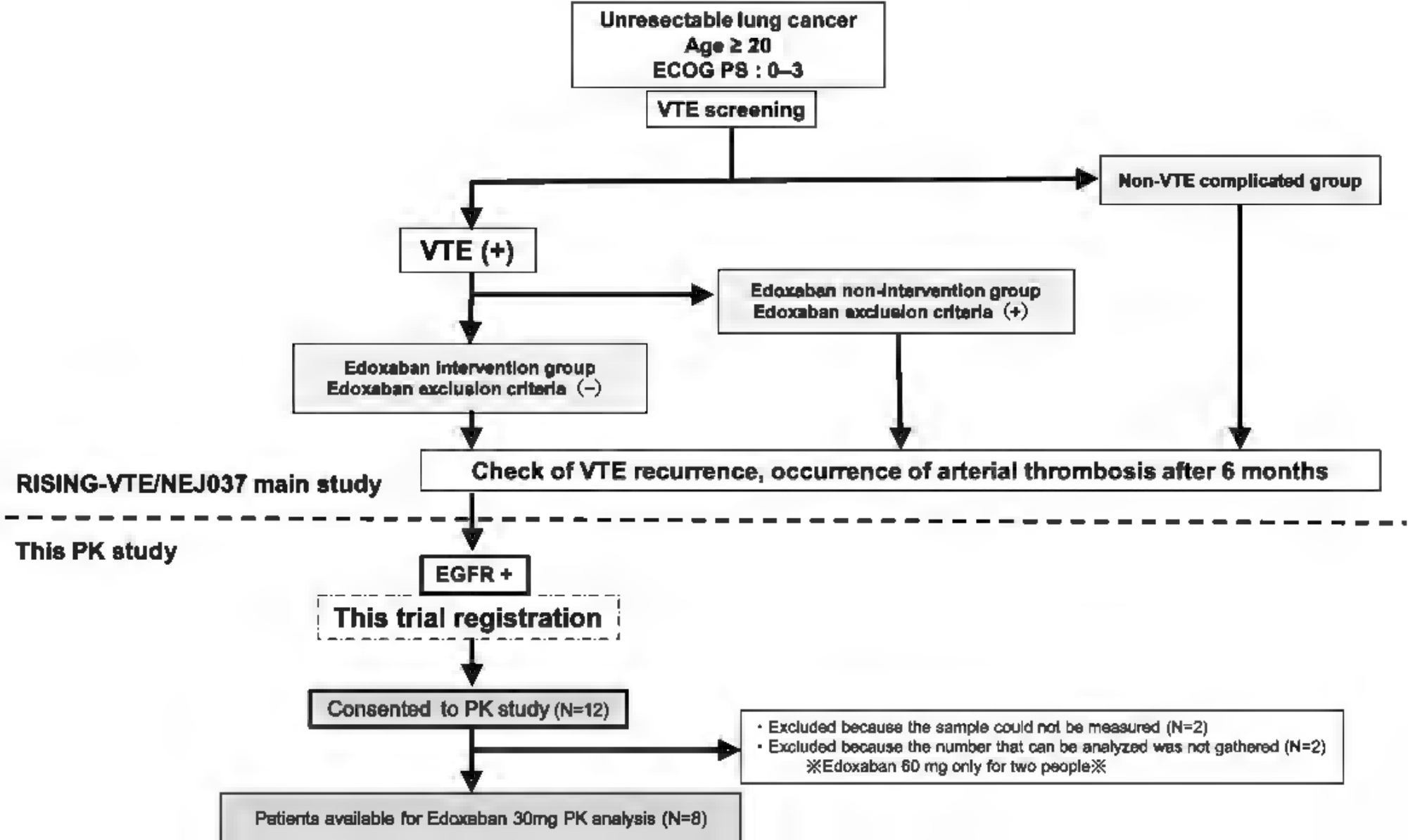
| | All EGFR-TKIs | | | Erlotinib | | |
|---|---|---|---|---|---|---|
| PK parameter | Edoxaban 30mg (N=8) | Edoxaban + EGFR-TKIs (N=8) | *P* | Edoxaban 30mg (N=5) | Edoxaban + Erlotinib (N=5) | *P* |
| AUC0-∞ (lg/mL) | 2.17 ± 0.60 | 2.51 ± 0.79 | 0.38 | 2.52 ± 0.33 | 2.76 ± 0.94 | >0.99 |
| MRT (h) | 10.98 ± 3.99 | 9.97 ± 4.02 | 0.64 | 13.00 ± 3.75 | 11.04 ± 4.72 | 0.43 |
| AUMC (h) | 24.62 ± 11.61 | 27.70 ± 22.77 | 0.94 | 32.05 ± 6.36 | 34.02 ± 27.61 | 0.62 |
| Ke ($h^{-1}$) | 0.11 ± 0.04 | 0.10 ± 0.02 | 0.74 | 0.10 ± 0.05 | 0.09 ± 0.03 | 0.81 |
| T1/2 (h) | 7.39 ± 3.66 | 7.28 ± 2.23 | 0.74 | 8.29 ± 4.56 | 8.00 ± 2.55 | 0.81 |
| CL (L/h) | 15.19 ± 5.75 | 12.72 ± 2.83 | 0.25 | 12.08 ± 1.70 | 11.72 ± 3.25 | >0.99 |
| Vdss (L/kg) | 157.51 ± 56.15 | 117.23 ± 16.57 | 0.25 | 160.86 ± 69.16 | 117.41 ± 12.51 | 0.62 |

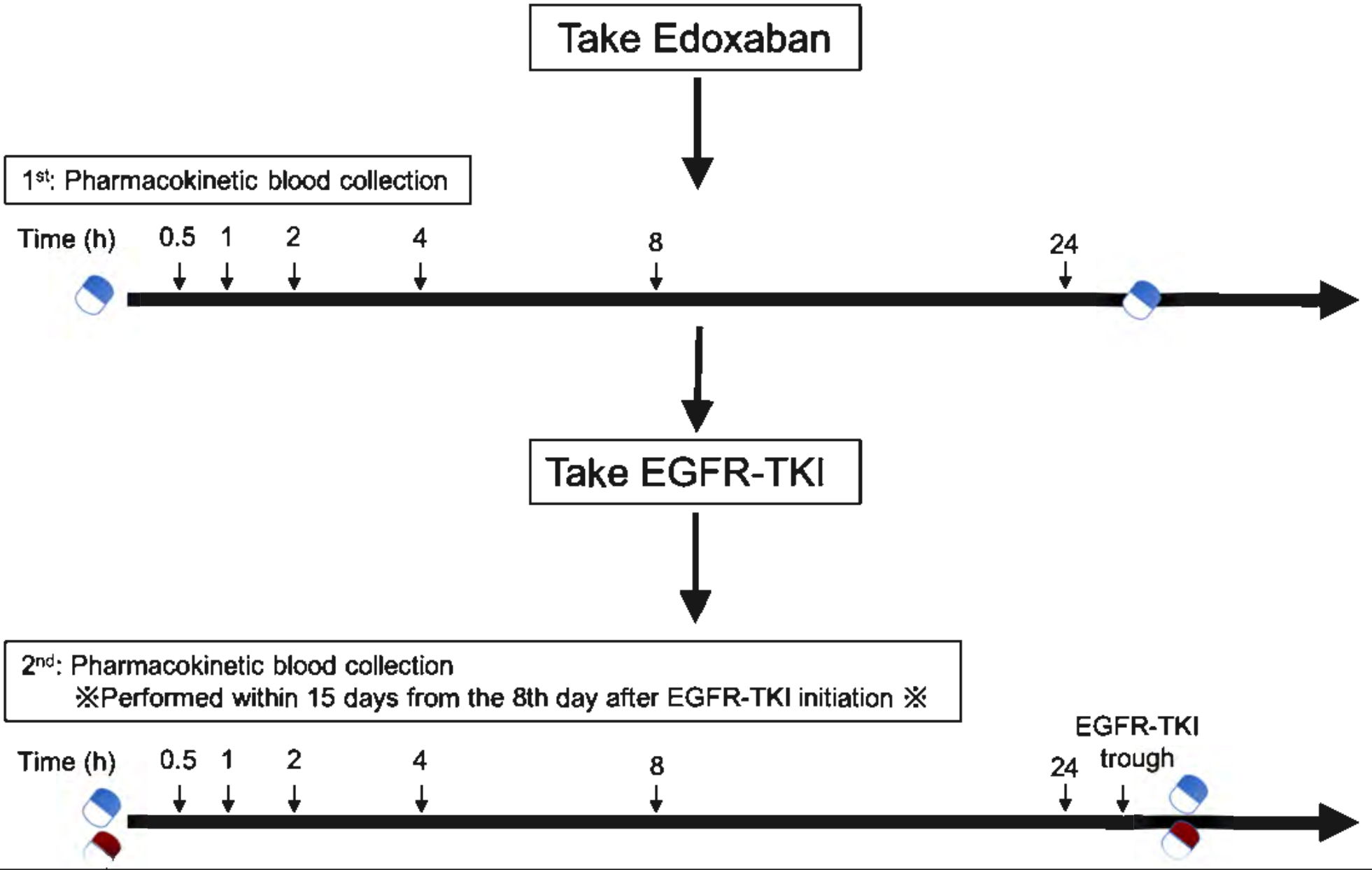
AUC0-∞: area under the curve for the time 0-∞ h, MRT: mean residence time, AUMC: area under the first moment curve, Ke: elimination rate constant, T1/2: half-life, CL: clearance, Vdss: volume of distribution at steady state

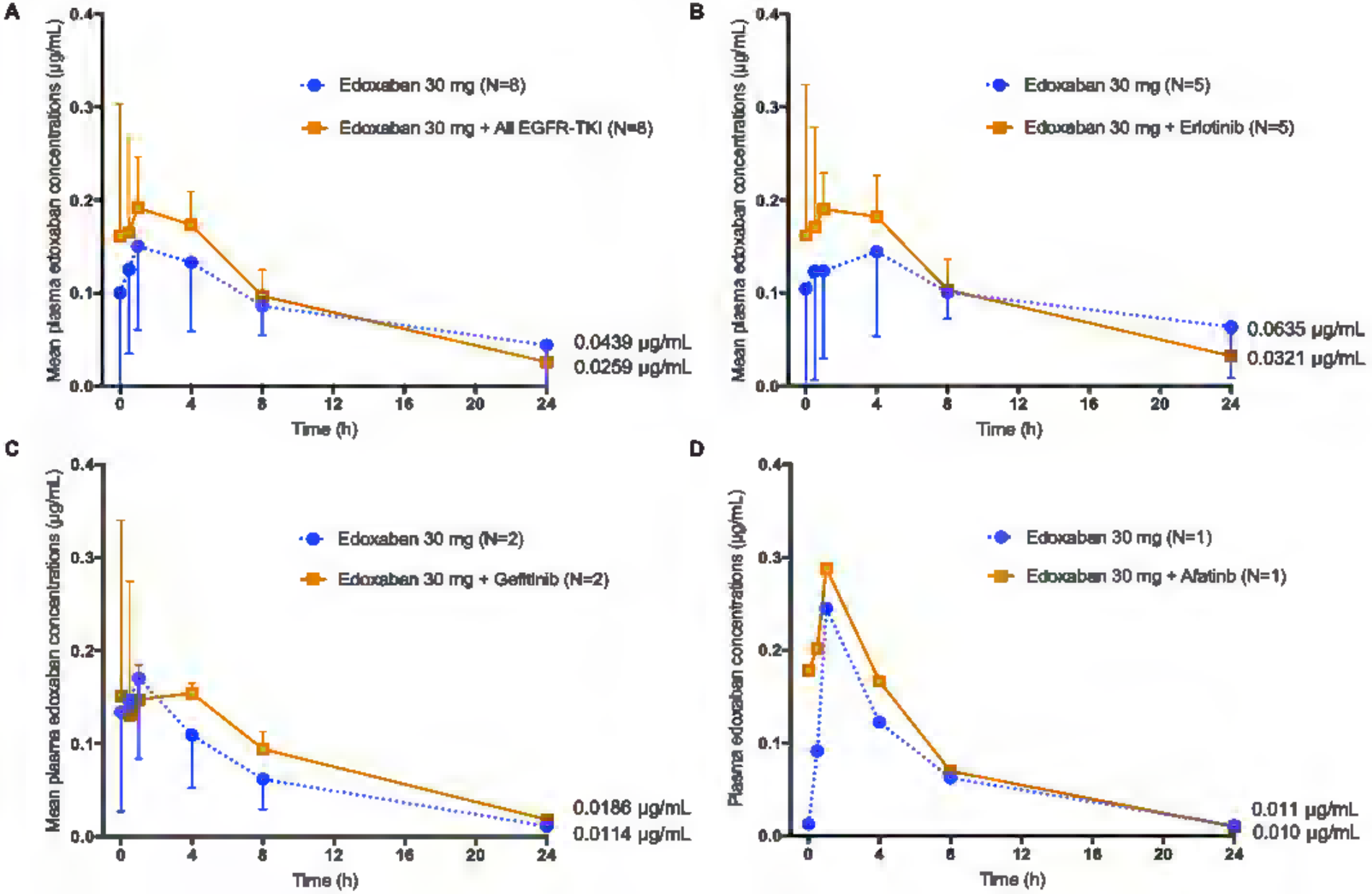
**Table 4. EGFR-TKI plasma trough concentration.**

| | Trough concentration (ng/mL) |
|---|---|
| Gefitinib 250 mg (*N* = 3) | 323.4 ± 34.7 |
| Erlotinib 150 mg (*N* = 2) | 1927.1 ± 291.4 |
| Erlotinib 100 mg (*N* = 5) | 1425 ± 422.2 |

Values are presented as mean ± standard deviation.


Unresectable lung cancer
Age ≥ 20
ECOG PS : 0–3
VTE screening
Non-VTE complicated group
VTE (+)
Edoxaban non-intervention group
Edoxaban exclusion criteria (+)
Edoxaban intervention group
Edoxaban exclusion criteria (–)
Check of VTE recurrence, occurrence of arterial thrombosis after 6 months
RISING-VTE/NEJ037 main study
This PK study
EGFR +
This trial registration
Consented to PK study (N=12)
・Excluded because the sample could not be measured (N=2)
・Excluded because the number that can be analyzed was not gathered (N=2)
※Edoxaban 60 mg only for two people※
Patients available for Edoxaban 30mg PK analysis (N=8)


Take Edoxaban
1st: Pharmacokinetic blood collection
Time (h)
0.5
1
2
4
8
24
Take EGFR-TKI
2nd: Pharmacokinetic blood collection
※Performed within 15 days from the 8th day after EGFR-TKI initiation ※
Time (h)
0.5
1
2
4
8
24
EGFR-TKI trough


A
Mean plasma edoxaban concentrations (µg/mL)
0.4
0.3
0.2
0.1
0.0
Edoxaban 30 mg (N=8)
Edoxaban 30 mg + All EGFR-TKI (N=8)
0.0439 µg/mL
0.0259 µg/mL
0
4
8
12
16
20
24
Time (h)
B
Mean plasma edoxaban concentrations (µg/mL)
Edoxaban 30 mg (N=5)
Edoxaban 30 mg + Erlotinib (N=5)
0.0635 µg/mL
0.0321 µg/mL
Time (h)
C
Mean plasma edoxaban concentrations (µg/mL)
Edoxaban 30 mg (N=2)
Edoxaban 30 mg + Gefitinib (N=2)
0.0186 µg/mL
0.0114 µg/mL
Time (h)
D
Plasma edoxaban concentrations (µg/mL)
Edoxaban 30 mg (N=1)
Edoxaban 30 mg + Afatinb (N=1)
0.011 µg/mL
0.010 µg/mL
Time (h)