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Title: Prognostic impact of concomitant pH-regulating drugs in patients with non-small cell lung cancer receiving epidermal growth factor receptor tyrosine kinase inhibitors: The Tokushukai REAl-world Data project 01-S1

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Abstract

Purpose

This study aimed to examine the prognostic impact of concomitant pH-regulating drug use in patients with epidermal growth factor receptor (*EGFR)*-mutation-positive non-small-cell lung cancer (NSCLC) receiving EGFR- tyrosine kinase inhibitors (TKIs).

Methods

We conducted a nationwide retrospective cohort study and reviewed clinical data of consecutive patients with NSCLC treated with first-line EGFR-TKIs in 46 hospitals between April 2010 and March 2020. Cox regression analyses were conducted to examine the differences in overall survival (OS) between patients treated with and without concomitant pH-regulating drugs, including potassium-competitive acid blockers (P-CABs), proton pump inhibitors (PPIs), and H_2-receptor antagonists (H_2RAs).

Results

A total of 758 patients were included in the final dataset, of which 307 (40%) were administered concomitant pH-regulating drugs while receiving frontline EGFR-TKIs. After adjusting for basic patient characteristics, patients administered gefitinib, erlotinib, afatinib, and osimertinib with concomitant pH-regulating drugs had lower OS values than those without concomitant pH-regulating drugs, with hazard ratios of 1.74 (with a 95%

confidence interval of 1.34–2.27), 1.33 (0.80–2.22), 1.73 (0.89–3.36), and 5.04 (1.38–18.44), respectively. The 2-year OS rates of patients receiving gefitinib with or without concomitant pH-regulating drugs were 65.4 and 77.5%, those for erlotinib were 55.8 and 66.6%, and those for afatinib were 63.2 and 76.9%, respectively. The 1-year OS rates of patients receiving osimertinib with or without concomitant pH-regulating drugs were 88.1% and 96.9%, respectively.

Conclusion

In addition to first-generation EGFR-TKIs, second and third-generation EGFR-TKIs can also result in OS deterioration in patients with *EGFR* mutation-positive NSCLC when used concurrently with pH-regulating drugs.

Keywords: non-small cell lung cancer; epidermal growth factor receptor tyrosine kinase inhibitor; osimertinib; pH-regulating drugs; proton pump inhibitors; drug interaction

1. Introduction

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are used as the standard treatment for *EGFR*-mutation-positive non-small cell lung cancer (NSCLC) [1], and can prolong both progression-free survival (PFS) and overall survival (OS) compared to those by conventional chemotherapies. Afatinib, a second-generation EGFR-TKI, has been shown to prolong PFS more than chemotherapy in several randomized phase III trials [2-4]. It has also been shown to improve PFS, time to treatment failure (TTF), and overall response rates more than that of gefitinib in a randomized phase IIb trial [5, 6]. Osimertinib, a third-generation EGFR-TKI, reported better survival outcomes compared to that of gefitinib and erlotinib in the FLAURA trial and is now considered the first-line treatment for patients with lung cancer with *EGFR* mutations [7, 8].

The pharmacokinetic variability of EGFR-TKIs differs from that of parenteral anticancer agents. Most orally administered drugs are soluble in the stomach to ensure adequate absorption, and the solubility is pH-dependent for some drugs. PH-regulating drugs, however, increase gastric pH levels and impair the abilities of some oral drugs to reach sufficient therapeutic concentrations systemically. The absorption of gefitinib and erlotinib decreases with increasing gastric pH. Thus, concomitant pH-regulating drugs use, proton pump inhibitors (PPIs), and histamine H_2 receptor antagonists (H_2RAs) have

been associated with poor prognoses [9-13]. Gastric pH changes due to concomitant pH-regulating drug use do not interfere with afatinib and osimertinib absorption [14-16]; however, a decrease in OS was nevertheless reported in one study evaluating the combination of afatinib and PPIs [17]. Additionally, whether the combination of osimertinib and pH-regulating drugs actually contributes to OS variability remains to be fully elucidated. Therefore, as part of the Tokushukai REAl-world Data (TREAD) project 01, we aimed to investigate the prognostic impacts of concomitant pH-regulating drug use in patients with *EGFR* mutation-positive NSCLC, who received first-line EGFR-TKI therapy [18].

2. Materials and Methods

2.1.Study populations

This nationwide retrospective cohort study was conducted as part of the TREAD project, described separately elsewhere [19]. This study was approved by the Institutional Review Board of Tokushukai Medical Group (TGE01427-024), and the requirement for informed consent was waived owing to the retrospective nature of the study.

We evaluated patients with advanced/recurrent NSCLC who received EGFR-TKIs as a first-line palliative therapy at the Tokushukai Medical Group hospitals. These included

46 hospitals with 14,829 beds, using a shared medical record system (e-Karte and Newtons2; Software Service Inc., Osaka, Japan) and a common chemotherapy protocol system (srvApmDrop; Software Service Inc., Osaka, Japan) between 1 April 2010 and 31 March 2020. Patients with active double-cancers, without complete treatment histories, or with unknown or wild-type *EGFR* mutations were excluded (Figure 1).

2.2.Data collection

Explanatory variables at the time of first-line EGFR-TKI initiation (sex, age, Eastern Cooperative Oncology Group performance status [ECOG-PS], body mass index [BMI], smoking status, disease status, histology, and *EGFR* mutation status), details of NSCLC treatments (EGFR-TKIs, other systemic agents, surgery, and radiotherapy), and prognoses (final date of survival confirmation, date of death, and cause of death) were extracted from the medical record system, chemotherapy protocol system, and National Cancer Registry Data in Japan [20]. Data on concomitant medications during EGFR-TKI administration was collected from the medical record. This information included details about the timing of pH-regulating drugs administration, such as potassium-competitive acid blockers (P-CABs), PPIs, and H_2RAs, to ascertain whether they were initiated before or after the first-line TKI treatment initiation. Treatment patterns were defined based on

148 claimed prescriptions after sequential systemic therapy with first-line EGFR-TKIs.

149

150 ***2.3.Statistical analysis***

151 Basic statistics analysis was conducted to summarize the distributions of variables
152 associated with patient-/tumour-related factors, other prognostic factors, and the primary
153 and secondary endpoints. Survival analysis of OS was performed using Cox regression.
154 The start and end dates of this study were 1 April 2010 and 31 March 2020, respectively,
155 and the time variable was the duration from EGFR-TKI therapy initiation to death from
156 any cause. Finally, the censored cases included patients who were alive at the study end
157 date or who dropped out of the study for any reason. A stratified Cox proportional model
158 was used to construct Kaplan–Meier survival curves adjusted by various prognostic
159 factors of interest, and its significance was obtained using a likelihood ratio test. Cox
160 regression analysis was first performed using all the prognostic factors (sex, age, BMI,
161 smoking status, histology, disease status, *EGFR* mutation status, first-line EGFR-TKI,
162 and study period, with or without concomitant pH-regulating drug usage). Subsequently,
163 a model selection was performed using backward elimination based on the Akaike
164 information criterion (AIC) to obtain an optimal model consisting of useful prognostic
165 factors [21]. In this study, when none of the P-CABs, PPIs, or H_2RAs were administrated,

it was defined as “without concomitant pH-regulating drugs,” and when any one of the three was administrated as “with concomitant pH-regulating drugs.” All analyses were performed using R software, version 4.0.5. All statistical analyses were two-sided, and probability values of < 0.05 were considered statistically significant.

3. Results

3.1.Patient characteristics

A total of 1,117 patients with *EGFR* mutation-positive advanced NSCLC were included in our study. Figure 1 shows that after excluding 359 ineligible patients, 758 were included in the final analysis, of which 307 (40%) had EGFR TKIs and pH-regulating drugs (P-CABs, 14 patients; PPI, 226 patients; and H_2RA, 107 patients) combination. At the end of the study period, 375 patients had died, and 496 patients had discontinued the first-line EGFR-TKIs. Table 1 summarises the baseline demographic and clinical characteristics of the first-line EGFR-TKIs. Table 2 shows the administration timing of each pH-regulating drug, which means whether the pH-regulating drug was administrated before or after the first-line TKI treatment. Most of the patients were receiving pH-regulating drugs before TKI administration.

3.2. Cox regression analysis

Cox regression analyses evaluating prognostic factors for OS showed that sex, age, BMI, disease status, *EGRF* mutation status, first-line EGFR-TKI, and administration with/without concomitant pH-regulating drugs significantly affected OS. After adjusting age, sex, BMI, disease status, and *EGFR* mutation status, the hazard ratios for patients receiving concomitant pH-regulating drugs while taking gefitinib, erlotinib, afatinib, and osimertinib, compared to those not taking pH-regulating drugs were 1.74 (with a 95% confidence interval of 1.34–2.27), 1.33 (0.80–2.22), 1.73 (0.89–3.36), and 5.04 (1.38–18.44), respectively (Table 3). The 2-year OS rates of patients receiving gefitinib with or without concomitant pH-regulating drugs were 65.4% and 77.5%, those for erlotinib were 55.8 and 66.6%, and those for afatinib were 63.2% and 76.9%, respectively. The 1-year OS rates of patients receiving osimertinib with or without concomitant pH-regulating drugs were 88.1% and 96.9%, respectively.

3.3. Kaplan–Meier survival curves

The Kaplan–Meier survival curves for gefitinib, erlotinib, afatinib, and osimertinib "without concomitant pH-regulating drugs" and "with concomitant pH-regulating drugs" are shown in Figure 2. Figure 2 (a) and (b) show crude Kaplan–Meier survival curves and those adjusted for age, sex, BMI, disease status, and *EGFR* mutation status, respectively. In all four EGFR-TKIs, patients who received concurrent pH-regulating drugs had a

poorer OS compared to those who did not.

The Kaplan–Meier survival curves of the groups taking pH-regulating drugs prior to or after EGFR-TKI treatment are shown in Figure 3. Although differences were not statistically significant (p=0.35), there was a trend towards a reduced OS in patients receiving pH-regulating drugs prior to EGFR-TKI treatment. The crude Kaplan-Meier survival curves for each pH-regulating drug "without pH-regulating drug concomitant use" and "with pH-regulating drug concomitant use" are shown in Figure S1.

4. Discussion

The results of the current TREAD study showed patients on concomitant pH-regulating drugs use with EGFR-TKIs had lower OS, and the effect was statistically significant for gefitinib and osimertinib. Previous retrospective and cohort studies have reported the impact of pH-regulating drugs on cancer therapies treated with first-generation EGFR-TKIs. Although a few studies failed to elucidate the effect of pH-regulating drugs on the efficacy of TKIs [22, 23], many studies showed shorter PFS and/or OS by concomitant use of pH-regulating drugs [9-13, 24, 25] and the effect was statistically significant in some studies similar to our study [9-13]. Despite repeated warnings from pharmaceutical companies and regulatory authorities regarding the concurrent administration of first-generation EGFR TKIs and pH-regulating medications, our real-world study revealed a

prevalence of simultaneous usage of EGFR TKIs and pH-regulating medications as high as 40%. Although the absorption of first-generation EGFR TKIs decreases with the concomitant use of pH-regulating drugs, second-generation afatinib shows relatively high dissolution rates in the physiological pH range (1–7.5) [15]. Absorption of afatinib is unlikely to decrease by pH changes caused by concomitant pH-regulating drug use. Ho et al. demonstrated that in patients with *EGFR*-mutant NSCLC treated with afatinib in the first-line therapy, the concomitant administration of PPIs increased patient mortality. They speculated that the accelerated metabolism of afatinib and changes in the gut microbiota were responsible for the shortened OS [17]. Likewise, the current study confirmed a shorter OS in afatinib-treated patients with *EGFR*-mutant NSCLC, who also received concomitant PPIs. Although several systematic reviews and meta-analyses have shown that concomitant pH-regulating drug use during EGFR-TKI administration is associated with an increased risk of death in patients with NSCLC, this has not been reported for osimertinib [13, 14, 17]. To the best of our knowledge, this is the first study showing that concomitant administration of pH-regulating drugs shortened the survival of patients with *EGFR*-mutation-positive NSCLC treated with osimertinib. Moreover, this scenario was consistent for P-CAB, PPI, and H_2RA, regardless of pH-regulating drug agents (Figure S1).

In a clinical pharmacological study involving healthy volunteers, the combination of osimertinib with omeprazole did not show any clinically relevant effects on the area under the blood concentration-time curve or maximum plasma concentration of osimertinib, suggesting that an increase in gastric pH does not affect osimertinib absorption [16]. Several other factors may explain the decreased OS rates in patients using afatinib or osimertinib alongside pH-regulating drugs. First, interactions between metabolites of pH-regulating drugs and cysteine (CYS) of EGFR-TKs may lead to decreased activity of afatinib and osimertinib. The H^+/K^+ ATPase proton pump is composed of two subunits (α and β), with the α subunit containing a total of 28 cysteine residues. Disulfide covalent bonds with the CYS 813 residues of the ATPase enzymes of the H^+/K^+ ATPase proton pump cause irreversible inhibition of the pump [26, 27]. The PPIs pharmacophore is 2-pyridylmethylsulfinylbenzimidazole. The five PPI products currently on the market in Japan (omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole) all contain this basic structural backbone. The sulfinyl moiety and its metabolites, sulfenamide and sulfenic acid, irreversibly inhibit the H^+/K^+ ATPase proton pump by forming disulfide bonds with the cysteine residue [28]. Gefitinib, a 4-anilinoquinazoline inhibitor, is structurally similar to erlotinib. It exerts its inhibitory effects by forming hydrogen bonds between the nitrogen atom at the first position of the quinazoline ring

256 and the amide group of methionine (MET) 793 in the ATP binding pocket [29, 30]. On
257 the other hand, both afatinib and osimertinib exert their inhibitory effects by binding to
258 the CYS 797 residue of the ATP-binding site of mutant EGFR-TK via covalent bond
259 formation [31-33]. It is possible that sulfenamide/sulfenic acid, a metabolite of PPI, forms
260 disulfide binds to CYS 797 at the ATP binding site of EGFR-TK, thus inhibiting the
261 binding of afatinib and osimertinib, thereby reducing their tumor-suppressive effects.
262 H_2RA is a histamine receptor ligand containing thiourea. Sulfenic acid, the first oxidation
263 product of thiourea, inhibits protein function by forming disulfide complexes with
264 cysteine [34, 35]. Therefore, H_2RA and P-CAB, like PPI, may also bind to cysteine by
265 producing the metabolite sulfenic acid (Figure S2, S3).
266 Second, drug-drug interactions between osimertinib and the final metabolites of pH-
267 regulating drugs might lead to a reduction in the activity of osimertinib. PPIs are absorbed
268 from the small intestine, reach gastric wall cells from the blood, accumulate in their
269 secretory glands, become activated by acids, and exert their effects by forming disulfide
270 bonds with the thiol group of the cysteine residue of the H^+/K^+ ATPase. Additionally, the
271 final metabolites of omeprazole contain thiyl radicals [36, 37]. These compounds react
272 with the α,β-carbonyl group of osimertinib during the metabolic process [38], which may
273 reduce its activity. In other words, drug interactions between the metabolites of

274 osimertinib and omeprazole may exist, and the pharmacokinetics of their metabolism may
275 be a factor behind the decrease in OS rates observed under this treatment combination.
276 Since both H_2RA and P-CAB have sulfonyl groups, their metabolites or reduced thiol
277 groups may react with osimertinib (Figure S2, S4).

278 Finally, infection-related complications arising from the long-term oral administration
279 of pH-regulating drugs may have a negative impact on OS, regardless of pharmacokinetic
280 factors. There is a concern that prolonged administration of pH-regulating drugs may lead
281 to infectious complications. The results of a prospective, randomized, double-blind study
282 of adverse events associated with 3 years of PPIs vs. placebo treatment reported
283 significant differences in terms of intestinal infections (as adverse events) [39, 40]. The
284 risks of developing recurrent *Clostridioides difficile* infections and increases in
285 *Enterococcaceae* and *Streptococcaceae* gut bacteria have been reported to be associated
286 with the administration of PPIs and P-CABs [41, 42]. Recent meta-analyses have shown
287 that intestinal infections caused by *Salmonella* and *Campylobacter*, which cannot survive
288 in strongly acidic conditions, increase with PPI administration [43, 44]. Some physicians
289 have expressed concerns that the prolonged administration of pH-regulating drugs may
290 lead to intestinal infections, which can decrease the ability of the stomach and the lower
291 esophagus to kill bacteria, in turn increasing the risk of aspiration pneumonia [45]. In this

292 study, there was a trend for shortened OS of patients taking pH-regulating drugs prior to
293 EGFR-TKI treatment (Figure 3). It is assumed that the longer the period of administration
294 of pH-regulating drugs, the greater the negative effects on EGFR-TKI treatment.

295 The present study has some limitations. Because this was a retrospective study, first, it
296 did not assess actual medication adherence; thus, biases may have been introduced.
297 Second, information on performance status was missing in many patients, and PFS could
298 not evaluated. Third, it did not consider patients who received over-the-counter
299 medications or who had them prescribed in other hospitals or pharmacies, supporting the
300 likelihood of underestimating the proportion of patients using pH-regulating drugs.
301 Fourth, although we have confirmed whether pH-regulating drugs were prescribed prior
302 to EGFR-TKIs, we have not investigated the duration of this treatment, which raises
303 concerns about the possibility of immortal time bias. Finally, the number of events was
304 insufficient to assess the OS rates of patients treated with afatinib and osimertinib between
305 2014 and 2020. Therefore, further long-term follow-up studies are needed to assess the
306 OS with osimertinib treatment more accurately. Despite these limitations, the strength of
307 this study lies in its inclusion of a large population, clearly demonstrating that the
308 concurrent use of pH-regulating drugs negatively impacts OS in patients with *EGFR*-
309 mutation-positive NSCLC. The impacts were observed not only with gefitinib and

erlotinib, which are known to be affected by reduced absorption due to gastric acid inhibition, but also with afatinib and osimertinib, for which interactions with pH-regulating drugs are not well-established. Further investigation of the interaction mechanisms between EGFR-TKIs and pH-regulating drugs is required.

5. Conclusion

Our real-world study demonstrated that the concurrent use of pH-regulating drugs significantly and adversely affected OS in patients with advanced/recurrent NSCLC receiving all-generation EGFR-TKIs as a first-line palliative therapy. Thus, physicians should be cautious in concurrently prescribing EGFR-TKIs and pH-regulating drugs.

Statements and Declaration

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Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors declare no actual or potential conflict of interest. Some authors have received research funding, honoraria, or scholarship donations from various pharmaceutical companies and other organizations outside of the submitted work, none of which construe actual or potential conflicts of interest. KU has received speaker and consultant honorarium from Chugai, Astra Zeneca, Boehringer-Ingelheim Japan, Bristol Myers Squibb, Nipponkayaku. YI received speaker bureau fees/honoraria from Bayer, Bristol-Myers Squibb, Daiichi-Sankyo, Pfizer, and Ono Pharm outside of the submitted work. RS has received speaker and consultant honorarium from Daiichi-Sankyo, Ono Parm, Taiho Parm, Chugai. TF has received speaker and consultant honorarium from Astra Zeneca, Boehringer-Ingelheim Japan, Chugai Pharmaceutical Co Ltd. HM has received speakers' bureau fees/honoraria from Daiichi-Sankyo and Ono Pharm; research funding from Astellas-Amgen Biopharma, Bayer, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Incite, Novartis, Ono Pharm, Pfizer, and Rakuten Medical; and

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Declaration of Generative AI and AI-assisted technologies in the writing process

None declared.

References

[1] Hayashi H, Nadal E, Gray JE, Ardizzoni A, Caria N, Puri T, Grohe C (2022) Overall treatment strategy for patients with metastatic NSCLC with activating *EGFR* mutations. Clin Lung Cancer 23:e69–e82. https://doi.org/10.1016/j.cllc.2021.10.009

[2] Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, Geater SL, Orlov S, Tsai CM, Boyer M, Su WC, Bennouna J, Kato T, Gorbunova V, Lee KH, Shah R, Massey D, Zazulina V, Shahidi M, Schuler M (2013) Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with *EGFR* mutations. J Clin Oncol 31:3327–3334. https://doi.org/10.1200/JCO.2012.44.2806

[3] Wu YL, Zhou C, Hu CP, Feng J, Lu S, Huang Y, Li W, Hou M, Shi JH, Lee KY, Xu CR, Massey D, Kim M, Shi Y, Geater SL (2014) Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring *EGFR* mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol 15:213–222. https://doi.org/10.1016/S1470-2045(13)70604-1

[4] Yang JC, Sequist LV, Geater SL, Tsai CM, Mok TS, Schuler M, Yamamoto N, Yu CJ, Ou SH, Zhou C, Massey D, Zazulina V, Wu YL (2015) Clinical activity of afatinib in

patients with advanced non-small-cell lung cancer harbouring uncommon *EGFR* mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. Lancet Oncol 16:830–838. https://doi.org/10.1016/S1470-2045(15)00026-1

[5] Park K, Tan EH, O'Byrne K, Zhang L, Boyer M, Mok T, Hirsh V, Yang JC, Lee KH, Lu S, Shi Y, Kim SW, Laskin J, Kim DW, Arvis CD, Kölbeck K, Laurie SA, Tsai CM, Shahidi M, Kim M, Massey D, Zazulina V, Paz-Ares L (2016) Afatinib versus gefitinib as first-line treatment of patients with *EGFR* mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Lancet Oncol 17:577–589. https://doi.org/10.1016/S1470-2045(16)30033-X

[6] Paz-Ares L, Tan EH, O'Byrne K, Zhang L, Hirsh V, Boyer M, Yang JC, Mok T, Lee KH, Lu S, Shi Y, Lee DH, Laskin J, Kim DW, Laurie SA, Kölbeck K, Fan J, Dodd N, Märten A, Park K (2017) Afatinib versus gefitinib in patients with *EGFR* mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial. Ann Oncol 28:270–277. https://doi.org/10.1093/annonc/mdw611

[7] Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, Zhou C, Reungwetwattana T, Cheng Y, Chewaskulyong B, Shah R, Cobo M, Lee KH, Cheema P, Tiseo M, John T, Lin MC, Imamura F, Kurata T, Todd A, Hodge R, Saggese M, Rukazenkov Y, Soria JC, FLAURA Investigators (2020) Overall survival with

389 osimertinib in untreated, *EGFR*-mutated advanced NSCLC. N Engl J Med 382:41–
390 50. https://doi.org/10.1056/NEJMoa1913662
391 [8] Cho BC, Chewaskulyong B, Lee KH, Dechaphunkul A, Sriuranpong V, Imamura F,
392 Nogami N, Kurata T, Okamoto I, Zhou C, Cheng Y, Cho EK, Voon PJ, Lee JS, Mann
393 H, Saggese M, Reungwetwattana T, Ramalingam SS, Ohe Y (2019) Osimertinib
394 versus standard of care EGFR TKI as first-line treatment in patients with *EGFR*m
395 advanced NSCLC: FLAURA Asian subset. J Thorac Oncol 14:99–106.
396 https://doi.org/10.1016/j.jtho.2018.09.004
397 [9] Chu MP, Ghosh S, Chambers CR, Basappa N, Butts CA, Chu Q, Fenton D, Joy AA,
398 Sangha R, Smylie M, Sawyer MB (2015) Gastric Acid suppression is associated with
399 decreased erlotinib efficacy in non-small-cell lung cancer. Clin Lung Cancer 16:33–
400 39. https://doi.org/10.1016/j.cllc.2014.07.005
401 [10] Lam LH, Capparelli EV, Kurzrock R (2016) Association of concurrent acid-
402 suppression therapy with survival outcomes and adverse event incidence in oncology
403 patients receiving erlotinib. Cancer Chemother Pharmacol 78:427–432.
404 https://doi.org/10.1007/s00280-016-3087-6
405 [11] Chen YM, Lai CH, Chang HC, Chao TY, Tseng CC, Fang WF, Wang CC, Chung YH,
406 Wang YH, Su MC, Liu SF, Huang KT, Chen HC, Chang YC, Lin MC (2016) PH-

regulating drug use and de novo brain metastases in patients with epidermal growth factor receptor-mutant non-small cell lung cancer who were treated using first-line first-generation epidermal growth factor receptor tyrosine kinase inhibitors. PLOS ONE 11:e0149722. https://doi.org/10.1371/journal.pone.0149722

[12] Fang YH, Yang YH, Hsieh MJ, Hung MS, Lin YC (2019) Concurrent proton-pump inhibitors increase risk of death for lung cancer patients receiving 1st-line gefitinib treatment - a nationwide population-based study. Cancer Manag Res 11:8539–8546. https://doi.org/10.2147/CMAR.S222278

[13] Lee CH, Shen MC, Tsai MJ, Chang JS, Huang YB, Yang YH, Hsieh KP (2022) Proton pump inhibitors reduce the survival of advanced lung cancer patients with therapy of gefitinib or erlotinib. Sci Rep 12:7002. https://doi.org/10.1038/s41598-022-10938-x

[14] Xu ZY, Li JL (2019) Comparative review of drug–drug interactions with epidermal growth factor receptor tyrosine kinase inhibitors for the treatment of non-small-cell lung cancer. Onco Targets Ther 12:5467–5484. https://doi.org/10.2147/OTT.S194870

[15] Nakao K, Kobuchi S, Marutani S, Iwazaki A, Tamiya A, Isa S, Okishio K, Kanazu M, Tamiya M, Hirashima T, Imai K, Sakaeda T, Atagi S (2019) Population pharmacokinetics of afatinib and exposure-safety relationships in Japanese patients

425 with EGFR mutation-positive non-small cell lung cancer. Sci Rep 9:18202.
426 https://doi.org/10.1038/s41598-019-54804-9
427 [16] Vishwanathan K, Dickinson PA, Bui K, Cassier PA, Greystoke A, Lisbon E, Moreno
428 V, So K, Thomas K, Weilert D, Yap TA, Plummer R (2018) The effect of food or
429 omeprazole on the pharmacokinetics of osimertinib in patients with non-small-cell
430 lung cancer and in healthy volunteers. J Clin Pharmacol 58:474–484.
431 https://doi.org/10.1002/jcph.1035
432 [17] Ho MC, Chung YS, Lin YC, Hung MS, Fang YH (2022) Combination use of first-
433 line afatinib and proton-pump inhibitors reduces overall survival among patients with
434 EGFFR mutant lung cancer. Onco Targets Ther 15:1573–1582.
435 https://doi.org/10.2147/OTT.S387165
436 [18] Uryu K, Imamura Y, Shimoyama R, Mase T, Fujimura Y, Hayashi M, Ohtaki M,
437 Otani K, Hibino M, Horiuchi S, Fukui T, Fukai R, Chihara Y, Iwase A, Yamada N,
438 Tamura Y, Harada H, Shinozaki N, Tsuya A, Fukuoka M, Minami H (2023) Stepwise
439 prolongation of overall survival from first to third generation EGFR-TKIs for EGFR
440 mutation-positive non-small-cell lung cancer: the Tokushukai REAl-world Data
441 project (TREAD 01). Jpn J Clin Oncol. https://doi.org/10.1093/jjco/hyad162
442 [19] Shimoyama R, Imamura Y, Uryu K, Mase T, Fujimura Y, Hayashi M, Ohtaki M,

443 Ohtani K, Shinozaki N, Minami H (2022) Real-world outcomes of systemic therapy
444 in Japanese patients with cancer (Tokushukai REAl-World Data project: TREAD):
445 study protocol for a nationwide cohort study. Healthcare (Basel, Switzerland) 10:2146.
446 https://doi.org/10.3390/healthcare10112146
447 [20] National Cancer Registry (Ministry of Health, Labour and Welfare), tabulated by
448 Cancer Information Service, National Cancer Center, Japan.
449 https://ganjoho.jp/reg_stat/statistics/data/dl/en.html. Accessed Febr 28, 2023
450 [21] Akaike H (1973) Information theory and an extension of the maximum likelihood
451 principle. Institute of Statistical Mathematics, p 199–213
452 [22] Saito Y, Takekuma Y, Kobayashi M, Shinagawa N, Shimizu Y, Kinoshita I, Dosaka-
453 Akita H, Iseki K, Sugawara M (2021) Impact of histamine type-2 receptor antagonists
454 on the anticancer efficacy of gefitinib in patients with non-small cell lung cancer. Eur
455 J Clin Pharmacol 77:381–388. https://doi.org/10.1007/s00228-020-03013-9
456 [23] Su VY, Yang KY, Huang TY, Hsu CC, Chen YM, Yen JC, Chou YC, Chang YL, He
457 CH (2020) The efficacy of first-line tyrosine kinase inhibitors combined with co-
458 medications in Asian patients with EGFR mutation non-small cell lung cancer. Sci
459 Rep 10:14965. https://doi.org/10.1038/s41598-020-71583-w
460 [24] Zenke Y, Yoh K, Matsumoto S, Umemura S, Niho S, Ohmatsu H, Goto K, Ohe Y

(2016) Clinical impact of gastric acid-suppressing medication use on the efficacy of erlotinib and gefitinib in patients with advanced non-small-cell lung cancer harboring *EGFR* mutations. Clin Lung Cancer 17:412–418. https://doi.org/10.1016/j.cllc.2016.01.006

[25] Li J, Nickens D, Wilner K, Tan W (2021) Evaluation of the effect of proton pump inhibitors on the efficacy of dacomitinib and gefitinib in patients with advanced non-small cell lung cancer and *EGFR*-activating mutations. Oncol Ther 9:525–539. https://doi.org/10.1007/s40487-021-00156-2

[26] Sachs G, Shin JM, Vagin O, Lambrecht N, Yakubov I, Munson K (2007) The gastric H,K ATPase as a drug target: past, present, and future. J Clin Gastroenterol 41 Supplement 2:S226–S242. https://doi.org/10.1097/MCG.0b013e31803233b7

[27] Asano S （2011） Molecular basis of gastric acid secretion in parietal cells. Membrane 36:278–285. https://doi.org/10.5360/membrane.36.278

[28] Roche VF (2006) The chemically elegant proton pump inhibitors. Am J Pharm Educ 70:101. https://doi.org/10.5688/aj7005101

[29] Yun CH, Boggon TJ, Li Y, Woo MS, Greulich H, Meyerson M, Eck MJ (2007) Structures of lung cancer-derived EGFR mutants and inhibitor complexes: mechanism of activation and insights into differential inhibitor sensitivity. Cancer

Cell 11:217–227. https://doi.org/10.1016/j.ccr.2006.12.017

[30] Stamos J, Sliwkowski MX, Eigenbrot C (2002) Structure of the epidermal growth factor receptor kinase domain alone and in complex with a 4-anilinoquinazoline inhibitor. J Biol Chem 277:46265–46272. https://doi.org/10.1074/jbc.M207135200

[31] Shi K, Wang G, Pei J, Zhang J, Wang J, Ouyang L, Wang Y, Li W (2022) Emerging strategies to overcome resistance to third-generation EGFR inhibitors. J Hematol Oncol 15:94. https://doi.org/10.1186/s13045-022-01311-6

[32] Ward RA, Anderton MJ, Ashton S, Bethel PA, Box M, Butterworth S, Colclough N, Chorley CG, Chuaqui C, Cross DA, Dakin LA, Debreczeni JÉ, Eberlein C, Finlay MR, Hill GB, Grist M, Klinowska TC, Lane C, Martin S, Orme JP, Smith P, Wang F, Waring MJ (2013) Structure- and reactivity-based development of covalent inhibitors of the activating and gatekeeper mutant forms of the epidermal growth factor receptor (EGFR). J Med Chem 56:7025–7048. https://doi.org/10.1021/jm400822z

[33] Cross DA, Ashton SE, Ghiorghiu S, Eberlein C, Nebhan CA, Spitzler PJ, Orme JP, Finlay MR, Ward RA, Mellor MJ, Hughes G, Rahi A, Jacobs VN, Red Brewer M, Ichihara E, Sun J, Jin H, Ballard P, Al-Kadhimi K, Rowlinson R, Klinowska T, Richmond GH, Cantarini M, Kim DW, Ranson MR, Pao W (2014) AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors

497 in lung cancer. Cancer Discov 4:1046–1061. https://doi.org/10.1158/2159-8290.CD-
498 14-0337
499 [34] Durant GJ, Emmett JC, Ganellin CR, Miles PD, Parsons ME, Prain HD, White GR
500 (1977) Cyanoguanidine-thiourea equivalence in the development of the histamine
501 H2-Receptor Antagonist, cimetidine. J Med Chem 20:901–906.
502 https://doi.org/10.1021/jm00217a007
503 [35] van Vugt-Lussenburg BMA, Capinha L, Reinen J, Rooseboom M, Kranendonk M,
504 Onderwater RCA, Jennings P (2022) 'Commandeuring' xenobiotic metabolism:
505 advances in understanding xenobiotic metabolism. Chem Res Toxicol 35:1184–1201.
506 https://doi.org/10.1021/acs.chemrestox.2c00067
507 [36] Figala V, Klemm K, Kohl B, Krüger U, Rainer G, Schaefer H, Senn-Bilfinger J,
508 Sturm E (1986) Acid activation of (H^+-K^+)-ATPase inhibiting 2-(2-pyridylmethyl-
509 sulphinyl) benzimidazoles: isolation and characterisation of the thiophilic "active
510 principle" and its reactions. J Chem Soc Chem Commun (2):125–127.
511 http://doi.org/10.1039/C39860000125
512 [37] Yamakawa T (1993) H^+/K^+-ATPase inhibitors. J Synth Org Chem Jpn 51:89–96.
513 https://doi.org/10.5059/yukigoseikyokaishi.51.86
514 [38] Dénès F, Pichowicz M, Povie G, Renaud P (2014) Thiyl radicals in organic synthesis.

515 Chem Rev 114:2587–2693. https://doi.org/10.1021/cr400441m

516 [39] Shin JM, Kim N (2013) Pharmacokinetics and pharmacodynamics of the proton
517 pump inhibitors. J Neurogastroenterol Motil 19:25–35.
518 https://doi.org/10.5056/jnm.2013.19.1.25

519 [40] Moayyedi P, Eikelboom JW, Bosch J, Connolly SJ, Dyal L, Shestakovska O, Leong
520 D, Anand SS, Störk S, Branch KRH, Bhatt DL, Verhamme PB, O'Donnell M,
521 Maggioni AP, Lonn EM, Piegas LS, Ertl G, Keltai M, Bruns NC, Muehlhofer E,
522 Dagenais GR, Kim JH, Hori M, Steg PG, Hart RG, Diaz R, Alings M, Widimsky P,
523 Avezum A, Probstfield J, Zhu J, Liang Y, Lopez-Jaramillo P, Kakkar AK,
524 Parkhomenko AN, Ryden L, Pogosova N, Dans AL, Lanas F, Commerford PJ, Torp-
525 Pedersen C, Guzik TJ, Vinereanu D, Tonkin AM, Lewis BS, Felix C, Yusoff K,
526 Metsarinne KP, Fox KAA, Yusuf S (2019) Safety of proton pump inhibitors based on
527 a large, multi-year, randomised trial of patients receiving Rivaroxaban or aspirin,
528 gastroenterology 157:682–691.e2–691.e2.
529 https://doi.org/10.1053/j.gastro.2019.05.056

530 [41] Watanabe K, Shimodaira Y, Takahashi S, Fukuda S, Koizumi S, Matsuhashi T, Iijima
531 K (2021) Potent acid suppression with vonoprazan vs proton pump inhibitors does
532 not have higher association with Clostridioides difficile infection. Am J Gastroenterol

116:1632–1637. https://doi.org/10.14309/ajg.0000000000001309

[42] Freedberg DE, Toussaint NC, Chen SP, Ratner AJ, Whittier S, Wang TC, Wang HH, Abrams JA (2015) Proton pump inhibitors alter specific taxa in the human gastrointestinal microbiome: A crossover trial. Gastroenterology 149:883–5.e9. https://doi.org/10.1053/j.gastro.2015.06.043

[43] Hafiz RA, Wong C, Paynter S, David M, Peeters G (2018) The risk of community-acquired enteric infection in proton pump inhibitor therapy: systematic review and meta-analysis. Ann Pharmacother 52:613–622. https://doi.org/10.1177/1060028018760569

[44] Bavishi C, Dupont HL (2011) Systematic review: the use of proton pump inhibitors and increased susceptibility to enteric infection. Aliment Pharmacol Ther 34:1269–1281. https://doi.org/10.1111/j.1365-2036.2011.04874.x

[45] Xun X, Yin Q, Fu Y, He X, Dong Z (2022) Proton pump inhibitors and the risk of community-acquired pneumonia: an updated meta-analysis. Ann Pharmacother 56:524–532. https://doi.org/10.1177/10600280211039240

551 **Tables**

552 Table 1. Patient's characteristics according to first-line EGFR-TKIs

Characteristics	Category	Total N=758 (%)	PH-regulating drug treatment (+) N=307 (40.5)	PH-regulating drug treatment (-) N=451 (59.5)
Sex	Women	444 (58.6)	182 (59.3)	262 (58.1)
	Men	314 (41.4)	125 (40.7)	189 (41.9)
Age (years)	< 80	562 (74.1)	223 (72.6)	342 (75.8)
	≥ 80	196 (25.9)	84 (27.4)	109 (24.2)
ECOG-PS	0	75 (9.9)	17 (5.5)	58 (12.9)
	1	211 (27.8)	87 (28.3)	124 (27.5)
	≥2	55 (7.3)	34 (11.1)	21 (4.7)
	NA	417 (55.0)	169 (55.1)	248 (55.0)
Body mass index	< 25	659 (86.9)	264 (86.0)	390 (86.5)
	≥ 25	73 (9.6)	29 (9.4)	41 (9.1)
	NA	26 (3.4)	16 (3.9)	20 (4.4)
Smoking status	Current or former	161 (21.2)	225 (73.3)	325 (72.1)
	Never	550 (72.6)	69 (22.5)	92 (20.4)
	NA	47 (6.2)	13 (4.2)	34 (7.5)
Histology	Adenocarcinoma	701(92.5)	278 (90.6)	423 (93.8)
	Others	57(7.5)	29 (9.4)	28 (6.2)
Disease status	Advanced/inoperable	83 (11.9)	32 (10.4)	51 (11.3)
	Metastatic	522 (68.9)	227 (73.9)	295 (65.4)
	Recurrent	153 (20.2)	48 (15.6)	105 (23.3)
EGFR mutational status	Del 19	314 (41.4)	133 (43.3)	181 (40.1)
	L858R	315 (41.6)	115 (37.5)	200 (44.3)
	T790M	42 (5.5)	17 (5.5)	25 (5.5)
	Other uncommon mutations*	59 (7.8)	35 (11.4)	24 (5.3)
	Positive (detail unknown)**	28 (3.7)	7 (2.3)	21 (4.7)

	Gefitinib	411 (54.2)	162 (52.8)	249 (55.2)
First-line EGFR-TKI	Erlotinib	107 (14.1)	54 (17.6)	53(11.8)
	Afatinib	104 (13.7)	40 (13.0)	64 (14.2)
	Osimertinib	136 (17.9)	51 (16.6)	85 (18.8)

553 ECOG-PS, Eastern Cooperative Oncology Group performance status Scale; EGFR,

554 epidermal growth factor receptor; NA, not available; TKI, tyrosine kinase inhibitor

555 *Exon 18 G719X (n=33), exon 19 K739-I744 duplication (n=1), exon 20 insertion (n=4),
556 exon 20 S768I (n=4), exon 21 L861Q (n=17)
557 **During the early 2010s, information was only available indicating the presence or
558 absence of mutations.

559

560

561 Table 2. Administration timing for each pH-regulating drug

Timing of taking pH-regulating drugs*	H_2RAs (n=107)	PPIs (n=226)	P-CABs (n=14)
Prior to the start of TKI treatment	82 (76.6)	153 (67.7)	13 (92.9)
After the start of TKI treatment	25 (23.4)	73 (32.3)	1 (7.1)

562 *There were 40 cases in which pH-regulating drugs were changed during the study period.

563 H_2RAs, H_2-receptor antagonists; PPIs, proton pump inhibitors; P-CABs, potassium-

564 competitive acid blockers; TKI, tyrosine kinase inhibitor

565 Table 3. Hazard ratios of the pH-regulating drug administration vs. non-pH-regulating drug groups for each EGFR-TKI

EGFR-TKI	PH-regulating drug treatment	Univariate analysis		Multivariate analysis (adjusted for background factors)	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Gefitinib	-	1.000	–	1.000	–
	+	1.885 (1.462–2.429)	0.000	1.742 (1.338–2.268)	0.000
Erlotinib	-	1.000	–	1.000	–
	+	1.328 (0.833–2.116)	0.233	1.329 (0.797–2.216)	0.275
Afatinib	-	1.000	–	1.000	–
	+	1.952 (1.021–3.733)	0.043	1.729 (0.891–3.356)	0.101
Osimertinib	-	1.000	–	1.000	–
	+	4.569 (1.404–14.870)	0.012	5.040 (1.378–18.436)	0.015

566 CI, confidence interval; HR, hazard ratio; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor

567

568

569

570 **Figure captions**

571 Figure 1 Consort diagram

572 EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor

573

574 Figure 2 Kaplan–Meier survival curves for “without concomitant pH-regulating drugs”
575 and “with concomitant pH-regulating drugs” by (A) Gefitinib, (B) Erlotinib, (C) Afatinib,
576 and (D) Osimertinib. Crude Kaplan–Meier survival curves are shown in (a), and adjusted
577 Kaplan–Meier survival curves for sex, age, body mass index, disease status, and EGFR
578 mutation status are shown in (b)

579 BMI, body mass index; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase
580 inhibitor

581

582 Figure 3 Kaplan–Meier survival curves according to the time of pH-regulating drug
583 administration. Red curves indicate patients who were taking pH-regulating drugs before
584 receiving EGFR TKIs, and blue curves indicate patients who were taking pH-regulating
585 drugs after receiving EGFR TKIs. Crude Kaplan–Meier survival curves are shown in (a),
586 and adjusted Kaplan–Meier survival curves for sex, age, BMI, disease status, and *EGFR*
587 mutation status are shown in (b)

588 BMI, body mass index; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase

589 inhibitor

590

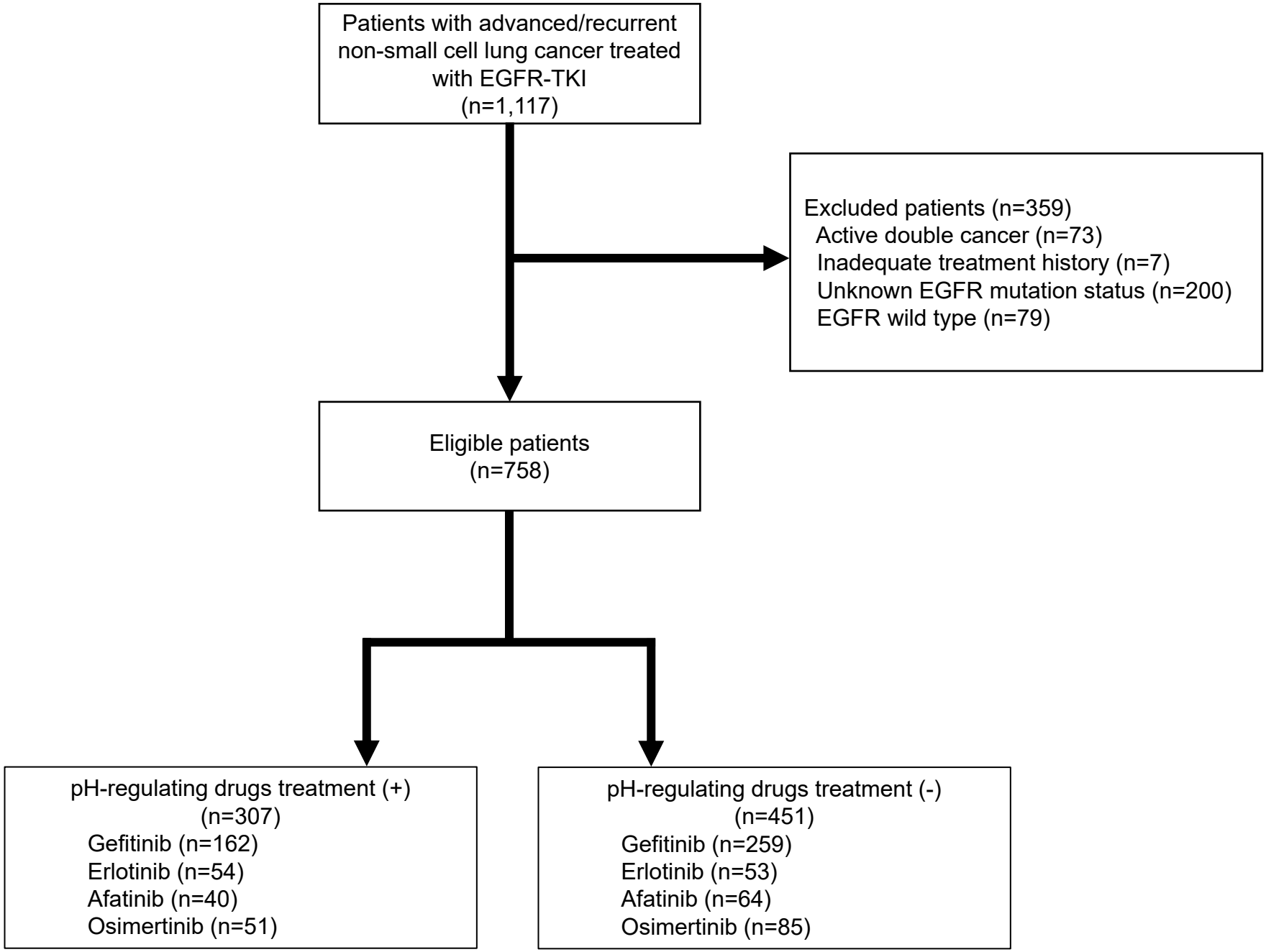


Figure 1. Consort diagram

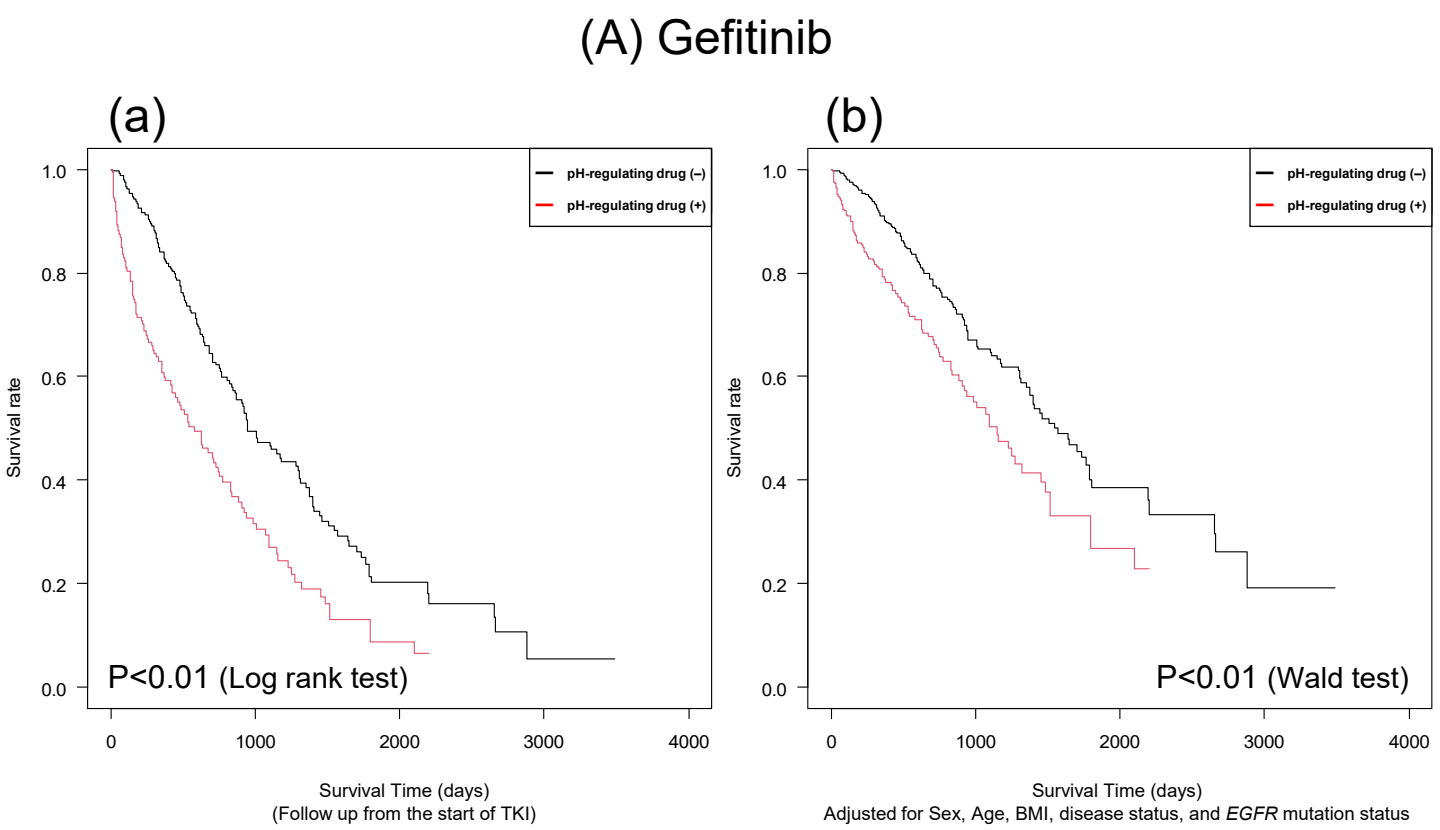
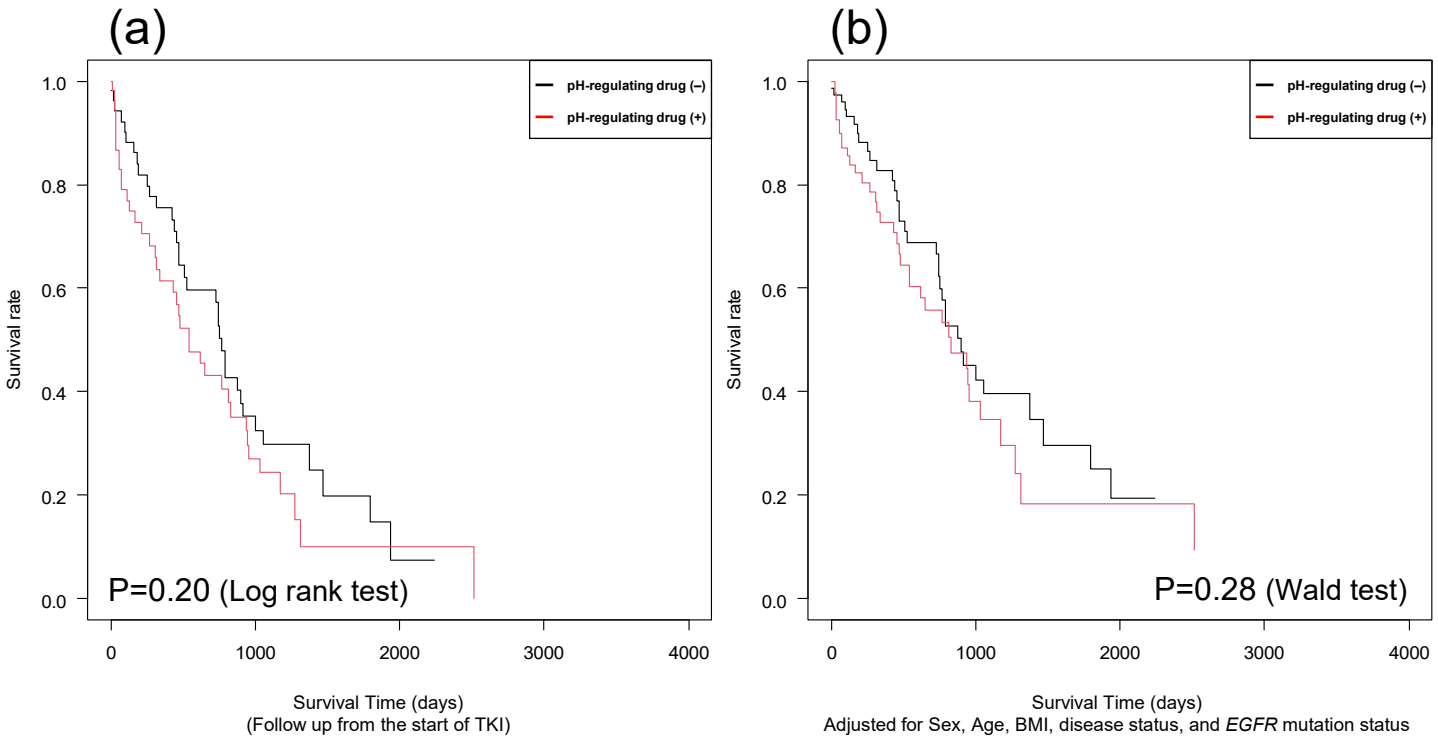
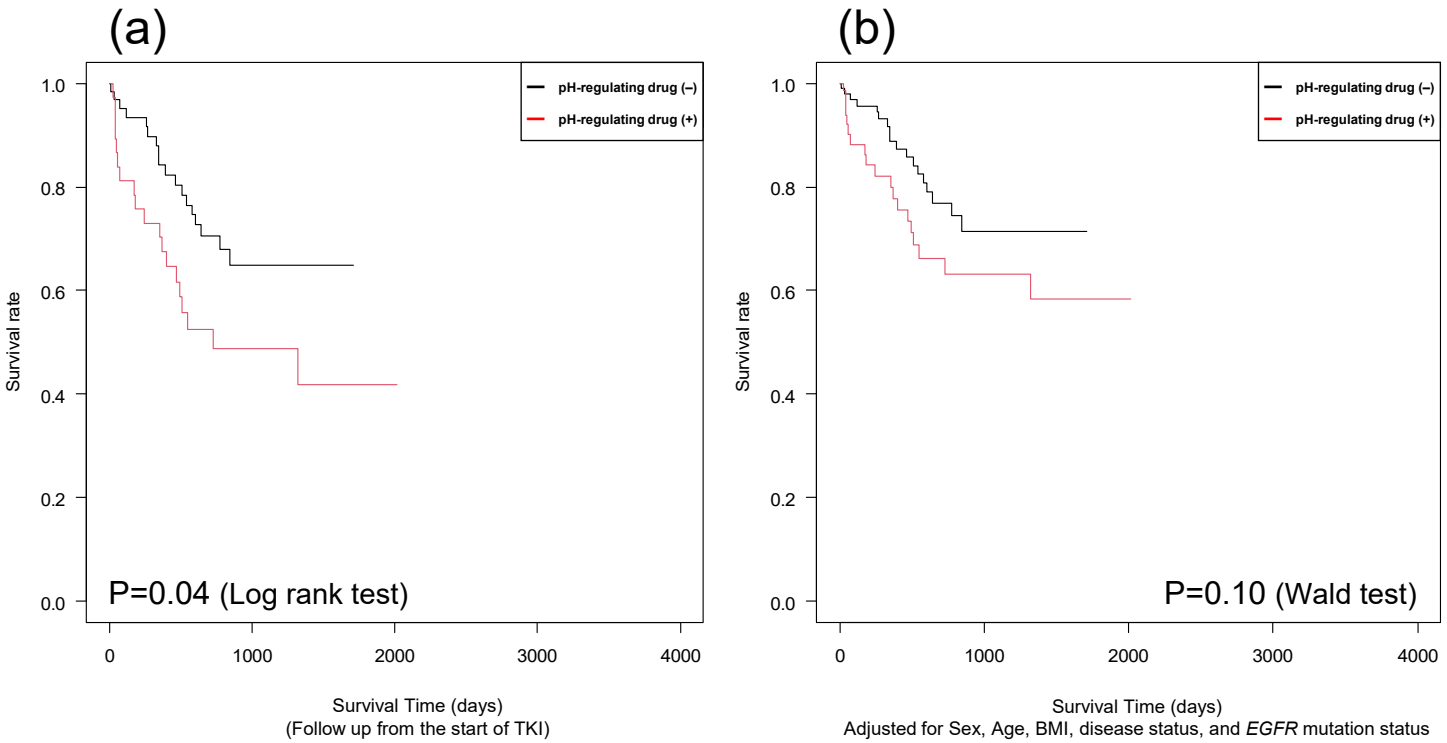


Figure 2. Kaplan–Meier survival curves for “without concomitant pH-regulating drugs” and “with concomitant pH-regulating drugs” by (A) Gefitinib, (B) Erlotinib, (C) Afatinib, and (D) Osimertinib. Crude Kaplan–Meier survival curves are shown in (a) and adjusted Kaplan–Meier survival curves for sex, age, body mass index, disease status, and *EGFR* mutation status are shown in (b).

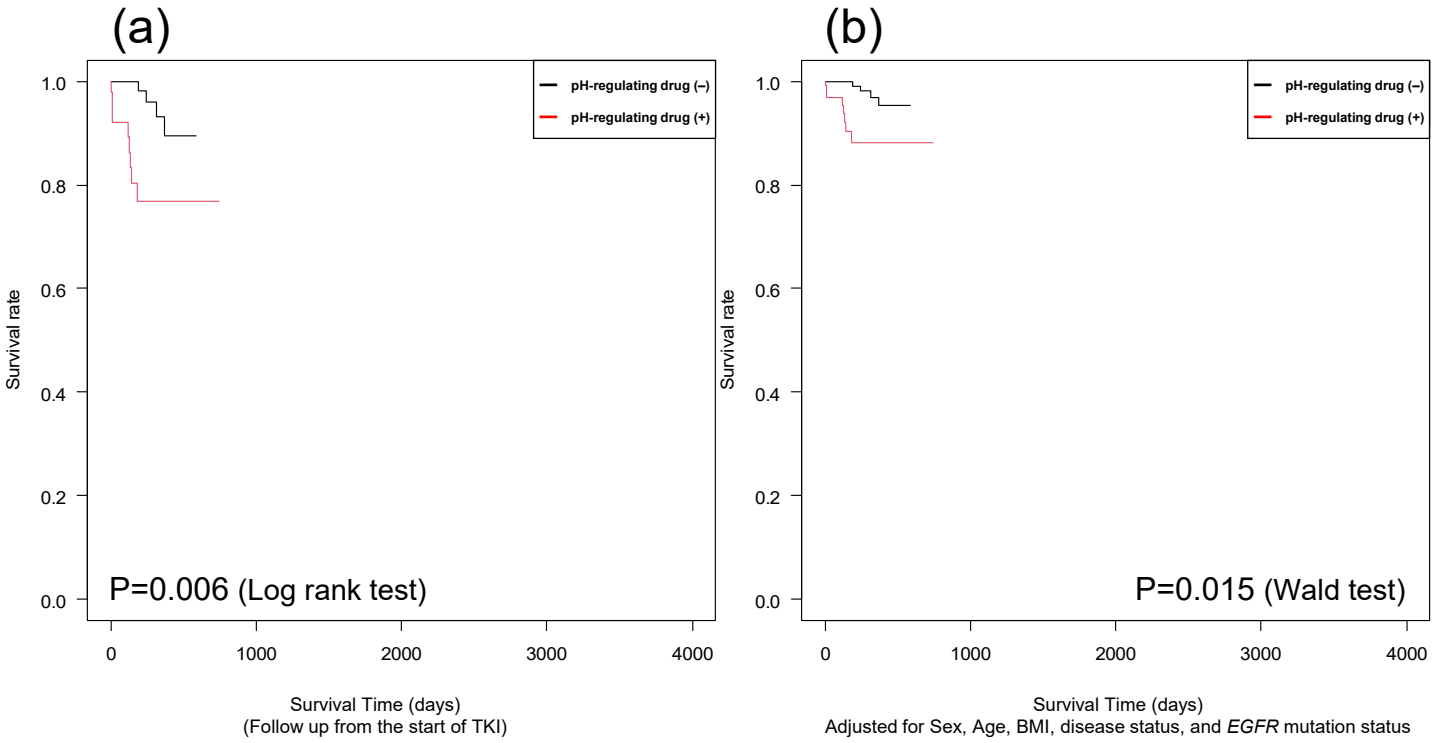
(B) Erlotinib


(a)
pH-regulating drug (–)
pH-regulating drug (+)
Survival rate
1.0
0.8
0.6
0.4
0.2
0.0
P=0.20 (Log rank test)
0
1000
2000
3000
4000
Survival Time (days)
(Follow up from the start of TKI)
(b)
pH-regulating drug (–)
pH-regulating drug (+)
Survival rate
1.0
0.8
0.6
0.4
0.2
0.0
P=0.28 (Wald test)
0
1000
2000
3000
4000
Survival Time (days)
Adjusted for Sex, Age, BMI, disease status, and *EGFR* mutation status

(C) Afatinib


(a)
pH-regulating drug (–)
pH-regulating drug (+)
Survival rate
1.0
0.8
0.6
0.4
0.2
0.0
P=0.04 (Log rank test)
0
1000
2000
3000
4000
Survival Time (days)
(Follow up from the start of TKI)
(b)
pH-regulating drug (–)
pH-regulating drug (+)
Survival rate
1.0
0.8
0.6
0.4
0.2
0.0
P=0.10 (Wald test)
0
1000
2000
3000
4000
Survival Time (days)
Adjusted for Sex, Age, BMI, disease status, and EGFR mutation status

(D) Osimertinib



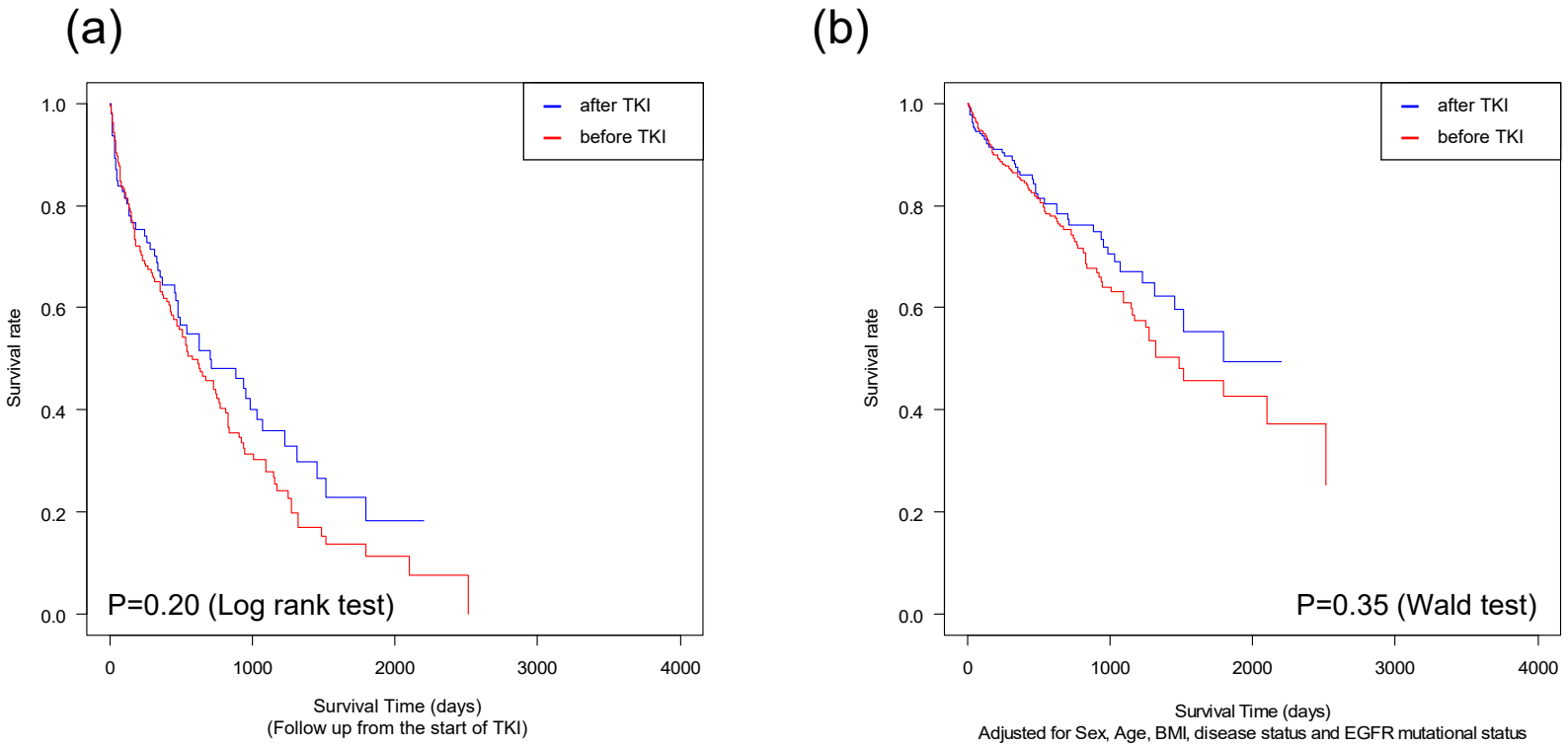


Figure 3. Kaplan–Meier survival curves according to the time of pH-regulating drug administration. Red curves indicate patients who were taking pH-regulating drugs before receiving EGFR TKIs, and blue curves indicate patients who were taking pH-regulating drugs after receiving EGFR TKIs. Crude Kaplan–Meier survival curves are shown in (a), and adjusted Kaplan–Meier survival curves for sex, age, body mass index, disease status, and *EGFR* mutation status are shown in (b).