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Association of concurrent acid-suppression therapy with survival outcomes and adverse event incidence in oncology patients receiving erlotinib

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Abstract

Purpose—Acid-suppression therapy is known to decrease the systemic exposure of erlotinib. The erlotinib prescribing information also recommends staggering dosing with a histamine-2 receptor antagonist (H_2RA) and avoiding concurrent use of a proton-pump inhibitor (PPI). This retrospective analysis evaluated the frequency of concurrent acid-suppression therapy in oncology patients receiving erlotinib and its association with outcomes.

Methods—All patients prescribed erlotinib within UC San Diego Health System between February 26, 2011 and February 28, 2014 were assessed for eligibility, and for survival outcomes and adverse events.

Results—Of the 76 patients in the analysis, 24 were prescribed both a PPI and an H_2RA with erlotinib therapy (31.6%). The two patient groups, with (n=24) and without PPI/H_2RA (n=52), were similar in clinical characteristics and erlotinib dose. One patient received an H_2RA therapy alone and was excluded from the analysis; no one received PPI therapy alone. Patients receiving erlotinib alone had a longer median progression-free survival (PFS) compared to patients with concurrent PPI/H_2RA therapy (11.0 months vs. 5.3 months; P=0.029). Overall survival (OS) and incidence of rash and/or diarrhea did not correlate with use of acid-suppression therapy.

Conclusion—Nearly one-third of subjects received acid-suppression therapy. Patients treated with erlotinib and PPI/H_2RA therapy had shorter PFS, but similar OS and adverse event profile compared to those who did not receive acid-suppression.

Keywords

oncology; erlotinib; proton-pump inhibitor; histamine-2 receptor antagonist; survival

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INTRODUCTION

The average oncology patient is often on multiple therapeutic agents for comorbid conditions as diverse as depression, heart disease, pain, etc. in addition to their anti-cancer treatment regimen. A prior study showed that physicians routinely prescribe a median of eight medications to treat comorbid conditions in cancer patients [1]. There is thus the potential for drug-drug interactions that may alter the safety or efficacy of therapy. Acid-suppression therapy is common in the oncology patient population and up to one-third of cancer patients received acid-suppression treatment in the United States between 1999 to 2011 [2]. However, the increase in gastric pH with acid suppression has the potential to decrease absorption of other medications, which may have pH-dependent solubility. The prescribing information for several oral kinase inhibitors, including, but not limited to, bosutinib [3], dasatinib [4], and palbociclib [5] state that concurrent use with acid-suppression therapy can result in reduced drug concentrations.

Erlotinib is an oral epidermal growth factor receptor tyrosine kinase inhibitor (TKI). In the United States, it is approved for the treatment of non-small cell lung cancer (NSCLC) and pancreatic cancer [6]. The current erlotinib prescribing information recommends avoidance of proton pump inhibitors (PPIs) if possible. When treatment with a histamine-2 receptor antagonist (H_2RA) is required, erlotinib must be taken 10 hours after H_2RA dosing and at least two hours before the next dose of the H_2RA [6]. These recommendations were based on a study done in healthy volunteers [7] and there is conflicting evidence on efficacy and safety outcomes in the cancer patient population [8,9]. Thus, the true effect of acid-suppression on survival and safety outcomes in oncology patients taking erlotinib is incompletely elucidated. Although erlotinib should not be taken with PPIs and administration should be staggered with H_2RA administration, it may not be possible to adhere to dosing and administration recommendations in all clinical scenarios. If acid-suppression is administered and lowers erlotinib exposure, it is conceivable that both benefits and adverse events are attenuated. This study aimed to determine the frequency of acid-suppression therapy use with erlotinib and measure its potential association with progression-free survival (PFS), overall survival (OS), and incidence of adverse events in patients receiving erlotinib as standard of care.

MATERIALS AND METHODS

The current study evaluated a subset of patients on the UC San Diego PREDICT study (Profile Related Evidence Determining Individualized Cancer Therapy Study) [10] conducted in accordance with the UC San Diego Health System Institutional Review Board guidelines. Patients on the PREDICT protocol were screened through pharmacy records to identify those who had been prescribed erlotinib through the UC San Diego Health System between February 26, 2011 and February 28, 2014. Patients who received erlotinib as part of combination chemotherapy, never started erlotinib therapy, or had a duration of erlotinib therapy ≤14 days were excluded from the study. Data was extracted from the UC San Diego Health System electronic health records (Epic Systems Corp, Verona, Wisconsin) primarily through chart review of oncology physician notes written as part of standard of care and medication prescription information, but also from hospital records and telephone

encounters. Data included erlotinib prescription dates and doses, PFS, OS, PPI and H_2RA prescriptions, age, sex, weight, date of cancer diagnosis, cancer type, and adverse events (rash and diarrhea of any grade). PFS was calculated as the difference in months from the start date of erlotinib therapy to the date of physician-assessed progression or death. OS was calculated as the difference in months from the start date of erlotinib therapy to the date of death. At the time of analysis, patients without progression (for PFS) or still alive (for OS) were censored as of that date.

Concurrent acid-suppression therapy was defined as the prescription of a PPI or H_2RA while on erlotinib therapy. Patients who were prescribed acid-suppression therapy within the date range of erlotinib therapy or within 90 days of the initiation or discontinuation of erlotinib therapy were included in the concurrent acid-suppression group. Average daily erlotinib dose was calculated using the average prescribed daily dose ordered through the electronic medication order system and did not take into account skipped doses or drug holidays not recorded in the electronic health record.

The difference in adverse events between patients with and without concurrent acidsuppression therapy was assessed using Fisher's exact test. Median PFS and OS were analyzed using the Kaplan-Meier method. The Cox proportional hazards log-rank statistic was used to compare PFS and OS between patients with and without concurrent PPI therapy using the *survfit* and *coxph* functions in the 'survival' package [11] in RStudio version 0.98.1103 and R version 3.2.0 [12]. All statistical analyses were completed using R/RStudio.

RESULTS

Study population

Ninety-four patients were identified through the preliminary screen as having been prescribed erlotinib between February 26, 2011 and February 28, 2011 (Figure 1). Of these patients, 17 were excluded because they either received erlotinib as part of combination therapy or never initiated erlotinib therapy despite having a prescription record in the electronic health record. Fifty-two patients (68.4%) received erlotinib therapy in the absence of H_2RA and PPI administration and 24 (31.6%) patients received erlotinib with both PPI and H_2RA prescriptions during the course of therapy. There was insufficient sample size to evaluate the effects of H_2RA therapy alone (n=1) or PPI therapy alone (n=0); thus these categories were excluded from the analysis. Medication prescriptions and physician notes did not provide sufficient detail to determine if therapy with PPI and H_2RA was sequential or concurrent and the degree of overlap. There was also insufficient detail to determine if H_2RA dosing was staggered with erlotinib dosing as recommended in the erlotinib prescribing information such that erlotinib was taken 10 hours after H_2RA dosing and at least 2 hours before the next dose of the H_2RA [6].

Both groups of patients (those with and without PPI/ H_2RA) were predominately composed of individuals with lung cancer (approximately 90%) and received the same median daily erlotinib dose (150 mg). Baseline demographics, including gender, weight, age, and disease characteristics, including cancer type, metastatic sites, and prior lines of therapy, were balanced between patients with and without concurrent acid-suppression therapy (Table 1).

Outcomes

Patients receiving erlotinib in the absence of acid-suppression had a longer median PFS than those receiving concurrent acid-suppression therapy (11.0 vs. 5.3 months, P=0.029) (Table 2, Figure 2A). Median OS was longer in patients receiving erlotinib alone compared to those with concurrent acid-suppression therapy (28.5 vs. 24.7 months, P=0.38), but this was statistically insignificant (Table 2, Figure 2B).

Safety outcomes

Adverse events were not significantly different in the presence or absence of PPI and H_2RA (Table 3). Rash occurred in 69.8% of patients on erlotinib alone as compared to 83.3% of patients taking concurrent acid suppression therapy (P=0.21). Diarrhea occurred in 54.7% of patients on erlotinib alone as compared to 45.8% of patients taking concurrent acid suppression therapy (P=0.52). Rash and diarrhea occurred in the same patients for 43.4% of patients on erlotinib alone and 45.8% of patients taking concurrent acid suppression (P=0.84). For the study population, adverse events (rash, diarrhea, and concurrent rash/diarrhea) did not show significant differences with sex, cancer type (lung vs. non-lung origin), or age (greater than or less than the median of 66 years) (Table 3).

DISCUSSION

Erlotinib is a small molecule tyrosine kinase inhibitor targeting epidermal growth factor receptor (EGFR). It is FDA approved for treatment of NSCLC and pancreatic cancer [6]. In NSCLC, erlotinib is recommended as first-line therapy in patients with advanced, recurrent, or metastatic non-squamous disease who have known active sensitizing EGFR mutations regardless of performance status [13]. In pancreatic cancer, erlotinib is recommended in combination with gemcitabine as an option for patients with locally advanced or metastatic disease and good performance status [14].

While the FDA-approved prescribing information for erlotinib indicates that concurrent acid-suppression results in decreased bioavailability and subsequent systemic exposure, it is known that acid-suppression therapy, in the form of either a PPI or H_2RA, is used in up to one-third of cancer patients [2]. In a healthy volunteer study, concurrent administration of erlotinib with the PPI omeprazole decreased erlotinib exposure by 46% and maximum concentration by 61%. When erlotinib was administered 2 hours following a 300 mg dose of the H_2RA ranitidine, the erlotinib exposure was reduced by 33% and maximum concentration by 54%. When erlotinib was administered with ranitidine 150 mg twice daily (at least 10 hours after the previous ranitidine evening dose and 2 hours before the ranitidine morning dose), the erlotinib exposure and maximum concentration decreased by 15% and 17%, respectively [6,7]. Despite the prescribing information recommendation, concurrent PPI/H_2RA with erlotinib was administered to approximately one-third of our patients. The aqueous solubility of erlotinib is pH-dependent, with increased solubility at pH levels below 5 and maximal solubility occurring at a pH level of approximately 2 [7]. There is typically a higher degree of reduced bioavailability and systemic exposure with PPIs compared to H_2RAs for oral kinase inhibitors, consistent with the greater efficacy of PPIs [3–6,15]. The prescribing information recommendations were based on a study done in healthy volunteers

[7] and the true effect of acid-suppression on survival and safety outcomes in oncology patients taking erlotinib is not clear.

The current study examined 76 oncology patients at UC San Diego receiving erlotinib therapy. The median PFS was 6 months less for patients using concurrent acid-suppression therapy as compared to those taking erlotinib alone and this difference was statistically significant. The OS was shorter in these patients as well, but the difference was not statistically significant. No change in rates of adverse events was observed. The majority of patients in the study has lung cancer (94.3% in the erlotinib alone group and 83.3% in the erlotinib with acid-suppression group). The 11.0 month PFS rate seen with erlotinib alone is consistent with that described in prior studies of patients with lung cancer receiving erlotinib as first-line therapy [16]. The incidence rates of rash and diarrhea were similar to those reported in the erlotinib prescribing information [6]. While it is possible that the difference in PFS was due to diminished erlotinib concentrations with concurrent acid-suppression therapy, any differences in drug exposure between these groups were not associated with alterations in primary drug toxicities of rash or diarrhea. It is conceivable that the small numbers of patients precluded finding statistically significant results for some of these parameters.

Prior retrospective studies have had discrepant results when evaluating the effect of concurrent acid-suppression therapy (PPI or H_2RA) on PFS, OS, and adverse event incidence (rash, diarrhea, and/or infection) in a NSCLC population [8,9]. Hilton et al utilized data from the phase III BR.21 study in 485 patients with NSCLC on erlotinib as second- or third-line therapy [9,16]. This study found no significant differences in PFS or OS with acid-suppression therapy (either PPI or H_2RA therapy). Patients on concurrent acid-suppression therapy had a similar frequency of rash, but higher frequency of diarrhea compared to patients receiving erlotinib alone. In contrast, the retrospective study described by Chu et al found a difference in PFS and OS with acid suppression therapy (either PPI or H_2RA) for 507 NSCLC patients on erlotinib therapy. There was a greater incidence of rash for the patients without acid-suppression therapy, but diarrhea was not significantly different. This study utilized patient records from a single centralized institution in Canada and the central database was used to document prescription medications in Alberta, Canada and represented patients primarily treated with erlotinib as second-line therapy [8]. Both studies considered PPI or H_2RA therapy as acid-suppression therapy and neither distinguished between H_2RA and PPI therapy in evaluating outcomes. In contrast, in our study, all patients received both PPI and H_2RA therapy in the course of erlotinib therapy.

The current study had several limitations. Given the retrospective study design and dependence on pharmacy records, medication adherence, intensity and duration of each type of acid-suppression therapy could not be determined. It is also unclear if patients attempted to stagger erlotinib with acid reduction therapy as recommended in the prescribing information. Drug levels were not available to determine relationships between the decrease of systemic erlotinib exposure with acid-suppression therapy and therapeutic outcomes. Furthermore, the degree of toxicity (grade 3 and 4 versus less toxicity) could not be determined given the limited information available in clinic notes.

In conclusion, the current study demonstrates frequent use of acid-suppression therapy (PPI and H_2RA) in combination with erlotinib and provides evidence of a potential association of this combination with reduction in PFS. These data suggest that the reduction in erlotinib plasma concentrations expected with acid-suppression therapy may have important clinical relevance. This study supports the recommendation that the concurrent use of PPI therapy with erlotinib should be avoided.

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Conflict of Interest

Lisa H. Lam is a postdoctoral fellow with funding supported by Pfizer Global Research and Development and the Skaggs School of Pharmacy and Pharmaceutical Sciences at the University of California, San Diego. Edmund V. Capparelli has consultant funds from Gilead Sciences, Alexion Pharmaceuticals, The Medicines Company, and Cempra. Razelle Kurzrock has research funding from Guardant, Sequenom, Foundation Medicine, Merck Serono, Pfizer, and Genentech, consultant funds from Sequenom, Actuate Therapeutics and X-Biotech, and an ownership interest in CureMatch Inc. and Novena Inc.

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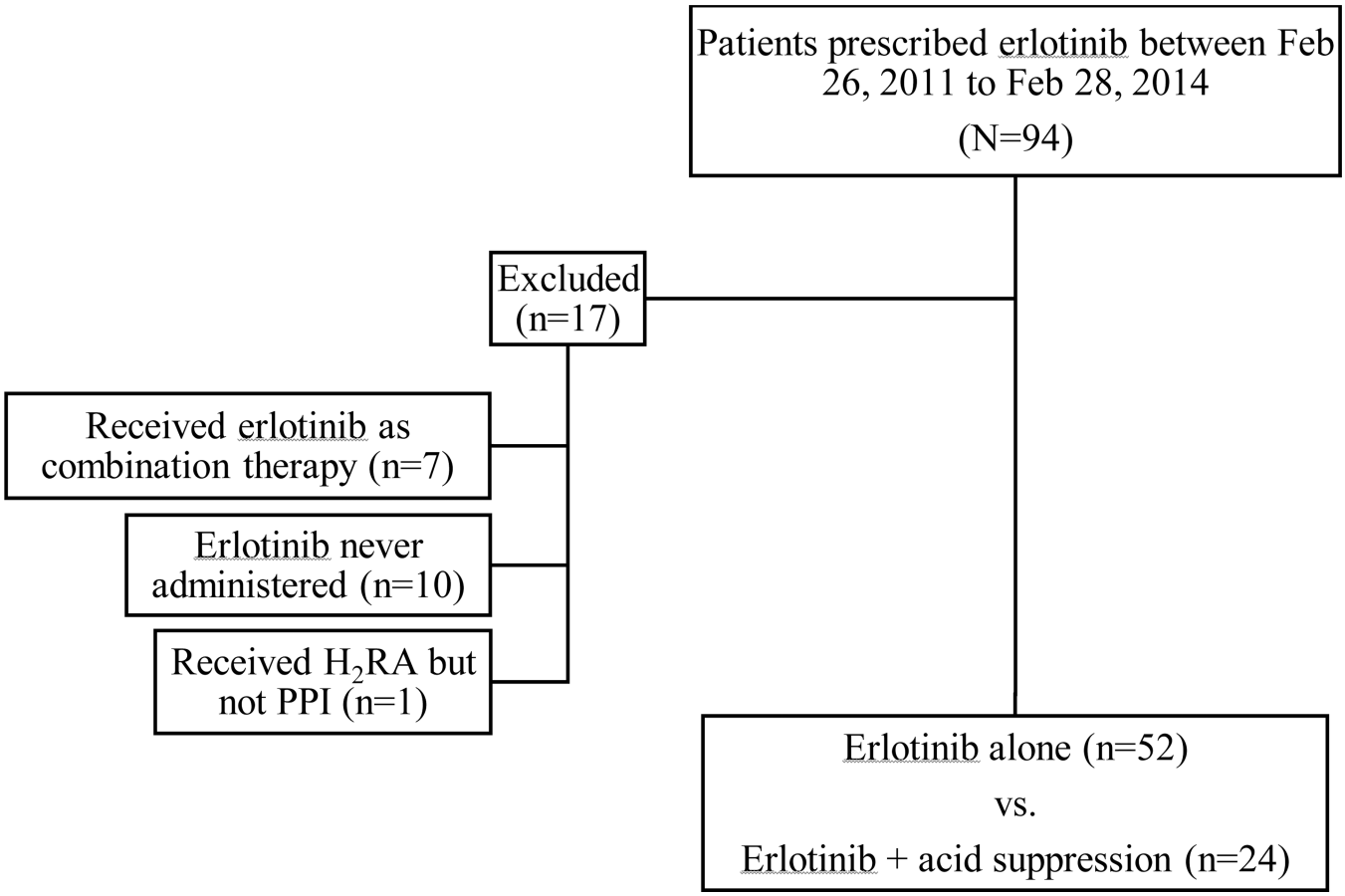

Figure 1.

Consort Diagram. Patients taking erlotinib therapy between February 26, 2011 and February 28, 2014 were identified through pharmacy records. Patients who received erlotinib less than 14 days or as part of combination therapy were excluded from the analysis.

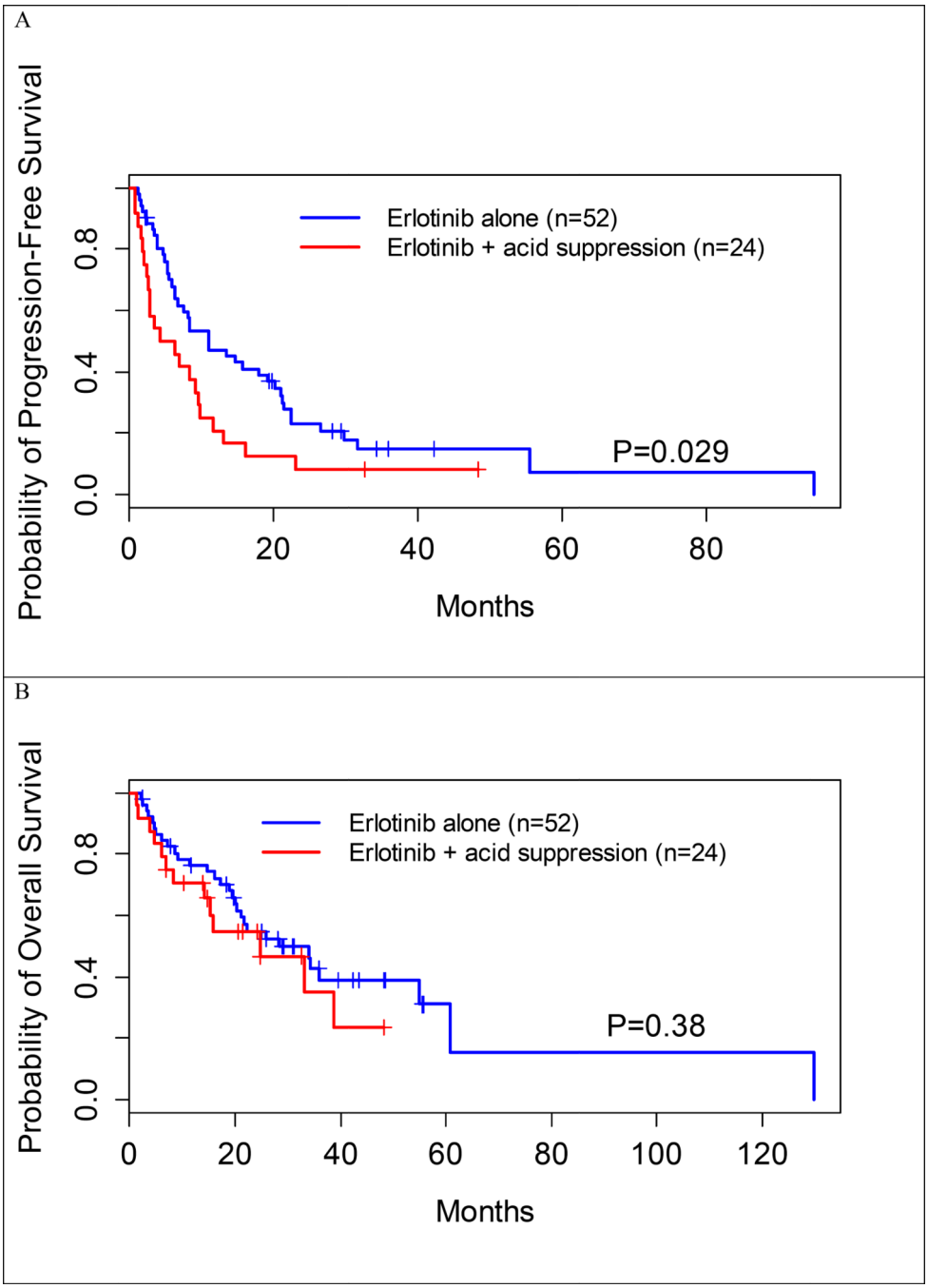

Figure 2.

Kaplan-Meier curves. A. Progression-free survival is significantly improved for patients taking erlotinib in the absence of acid suppression therapy with H_2RA and PPI therapy (11.0 vs. 5.3 months, P=0.029). B. No significant differences in overall survival were seen with the use of concurrent acid-suppression therapy (28.5 vs. 24.7 months, P=0.38).

Table 1

Baseline patient and disease characteristics

	Erlotinib alone	Erlotinib + Acid Suppression (PPI/H_2RA)	P*
Total	52	24	
Male sex, № (%)	31 (59.6)	12 (50.0)	0.46
Weight (kg), median(range)†	66 (35–102)	66 (40–106)	0.72
Age (years) , median (range)‡	67 (46–90)	66 (33–84)	0.085
Prescribed daily erlotinib dose (mg), mean; median (range)§	140; 150 (50–150)	141; 150 (87–150)	0.82
Cancer type, № (%)			
Lung	50 (94.3)	20 (83.3)	0.27
Head & neck	2 (3.8)	2 (8.3)	
Other	1 (1.9)	2 (8.3)	
Metastatic sites, № (%)			
Brain	17 (32.7)	7 (29.2)	1.0
Other	29 (55.7)	15 (62.5)	0.62
Lines of chemotherapy before erlotinib, № (%)			0.64
0	22 (42.3%)	8 (33.3%)	
1	19 (36.5%)	8 (33.3%)	
2	6 (11.5%)	3 (12.5%)	
3	4 (7.7%)	3 (12.5%)	
≥4	1 (1.9%)	2 (8.3%)	
EGFR mutation status			0.71
Activating mutation	30 (57.7%)	13 (54.2%)	
Wild-type	11 (21.2%)	5 (20.8%)	
Unknown status	10 (19.2%)	7 (29.2%)	

Abbreviation: EGFR: epidermal growth factor receptor.

*Fisher's exact test used for testing significance of binary variables and Welch's two sample t-test for continuous variables.

†Weight values were not available for 18 patients.

‡Age at first erlotinib dose.

§Prescribed daily dose does not take into account skipped doses or drug holidays not recorded in the electronic medication order entry system.

Table 2

Comparison of progression-free survival (PFS) and overall survival (OS) between patients with and without acid-suppression therapy (PPI/H_2RA)

		n	Progression-free survival (months)*	P†	Overall survival (months)*	P†
Concurrent acid-suppression therapy	Erlotinib alone	52	11.0 [6.8, 21.0]	0.029	28.5 [20.4, not reached]	0.38
	Erlotinib + acid-suppression	24	5.3 [2.8, 9.7]		24.7 [14.3, not reached]	

Abbreviations: H_2RA=histamine-2 receptor antagonist; PPI=proton pump inhibitor.

*Median [95% confidence interval]

†Log-rank test.

Table 3

Incidence of adverse events in patients on erlotinib with and without concurrent acid suppression (PPI/H_2RA)

		n	Rash n (%)	p†	Diarrhea n (%)	p†	Rash & diarrhea n (%)	p†
Concurrent PPI	Erlotinib alone	52	37 (71.5%)	0.21	29 (55.7%)	0.52	23 (44.2%)	0.84
	Erlotinib + acid-suppression	24	20 (83.3%)		11 (45.8%)		11 (45.8%)	
Sex	Male	33	28 (84.8%)	0.052	17 (51.5%)	0.98	16 (48.5%)	0.43
	Female	43	28 (65.1%)		22 (51.2%)		17 (39.5%)	
Cancer type	Lung	69	51 (73.9%)	0.89	35 (50.7%)	0.30	29 (42.0%)	0.99
	Not lung	7	5 (71.4%)		5 (71.4%)		4 (57.1%)	
Age *	Age > 66 years	40	27 (67.5%)	0.20	23 (57.5%)	0.26	17 (42.5%)	0.86
	Age ≤ 66 years	36	29 (80.6%)		16 (44.4%)		16 (44.4%)	

Abbreviations: PPI: proton pump inhibitor; H_2RA: histamine-2 receptor antagonist.

*Median age is 66 years old

†Calculated using Fisher's exact test