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# Tetracyclines increase the survival of NSCLC patients treated with EGFR TKIs: a retrospective nationwide registry study

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## ABSTRACT

**Background** With the first and second-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), clinical benefit and rash correlate together. EGFR TKI-induced rash can be alleviated with tetracyclines, but it is unknown whether the use of tetracyclines can increase the survival of non-small-cell lung cancer (NSCLC) patients treated with EGFR TKIs.

**Methods** We collected all the patients (n=1271) who had reimbursement for EGFR TKIs (gefitinib, erlotinib and afatinib) in Finland 2011–2016, had purchased TKIs, and had data available at nationwide cancer registry. The survival was analysed from the first EGFR TKI purchase to death or end-of follow-up, and patients were stratified according to TKIs, purchases of antibiotics, their ATC class and timing.

**Results** 802 (63.1%) patients had antibiotic purchases −14 to +200 days from the first EGFR TKI purchase, 447 of these tetracyclines. 322 (25.3%) had had purchased antibiotics −14 to +14 days (prophylaxis) from the first EGFR TKI purchase, 188 of these tetracyclines. Purchase of antibiotics was associated with improved survival (HR 0.80, 95% CI 0.71 to 0.91), which limited to tetracycline purchases only (HR 0.72, 95% CI 0.64 to 0.82). The largest survival benefit was seen with the prophylactic use of tetracyclines (HR 0.74, 95% CI 0.62 to 0.88). The benefit from tetracyclines was limited to erlotinib only (HR 0.68, 95% CI 0.58 to 0.78) which was retained in multivariate analysis. Prophylactic use of tetracyclines was associated with a longer erlotinib treatment duration (HR 0.81, 95% CI 0.61 to 0.96) but not with dose reductions or treatment breaks.

**Conclusions** Tetracyclines improve the survival of NSCLC patients treated with the first and second-generation EGFR TKIs and they should be considered as a prophylaxis when initiating EGFR TKIs with high incidence of rash.

## Key questions

### What is already known about this subject?
► The clinical benefit from epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and EGFR TKI-induced rash correlate together and TKI rash can be alleviated with tetracyclines. It is unknown whether the use of tetracyclines can increase the survival of non-small-cell lung cancer (NSCLC) patients treated with EGFR TKIs.

### What does this study add?
► This is the first study to provide evidence that tetracyclines can improve the survival of EGFR TKI-treated NSCLC patients. The survival benefit was the most prominent with the prophylactic use of the tetracyclines, and with EGFR TKIs related to a high incidence of rash.

### How might this impact on clinical practice?
► Our study provides a strong evidence that prophylactic tetracyclines should be used on patients treated with EGFR TKIs associated with a high incidence of rash since this might not only alleviate treatment side effects but also improve the survival.

## BACKGROUND

Non-small-cell lung cancer (NSCLC) is the leading cause of cancer-related mortality worldwide and about 70% of patients have an advanced disease at diagnosis. The treatment of advanced NSCLC consists mainly of medical therapy with cytotoxic chemotherapy, immune checkpoint inhibitors and/ or targeted agents such as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs). EGFR TKIs were originally approved for the second or later line treatment of NSCLC without molecular selection.[1,2] Later, molecular characterisation has led to the identification of new subgroups such as *EGFR* mutated NSCLCs[3,4] in which EGFR TKIs yield a superior response rate, progression-free survival (PFS) and quality-of-life (QoL) scores when compared to chemotherapy in the first-line setting.[5] Recent studies with mutation specific EGFR TKI osimertinib have shown that this agent can improve PFS compared to the first-generation TKIs in the first line and to chemotherapy in T790M-mutation positive patients in the later line setting.[6,7]

All EGFR TKIs are mainly well tolerated with less than 10% of patients discontinuing the treatment because of adverse events (AEs)

in clinical trials. Rash is the most frequent AE (~50% to 80%) of EGFR TKIs which, however, occurs less frequently among the gefitinib users compared to erlotinib, afatinib or dacomitinib. Another typical AE, diarrhoea, is much more commonly seen with the second generation, irreversible EGFR TKIs afatinib and dacomitinib than the first generation TKIs gefitinib or erlotinib.[8–10] With the T790M-mutation specific EGFR TKI osimertinib, the frequency and severity of both, the rash and diarrhoea, are less frequent compared to older TKIs.[6 7 10]

EGFR is expressed in the basal layer of the epidermis where its'roles include,among others, stimulation of epidermal growth, inhibition of differentiation and acceleration of wound healing. Inhibition of EGFR results in an inflammation of the keratinocytes leading to dermatological manifestations from a simple rash to a severe dermatitis, mainly acneiform rash. The onset of the rash is usually within 2–4 weeks after the initiation of the TKIs, but it can also be earlier or delayed.[11] Many studies have shown that patients who develop skin rash due to EGFR TKIs are more likely to respond to the treatment, and rash has been found to be an independent predictive factor for improved survival.[12 13]

A pre-emptive treatment seems to be more effective than a reactive treatment in limiting the incidence and severity of the skin toxicity of EGFR TKIs. The use of moisturisers and topical steroids, avoiding sun exposure and irritants can be used to reduce skin rash. A meta-analysis of four trials has suggested that antibiotics might reduce the relative risk of severe EGFR rash by 42%–77% and improve QoL.[14 15] However, none of the clinical trials have been able to show that antibiotics/tetracyclines could improve the survival among the EGFR TKI users.

In this study, we investigated the use of antibiotics in NSCLC patients treated with EGFR TKIs. Our aim was to study whether tetracycline antibiotics would increase the survival of these patients. The study was carried out using national registries that enable the collection of data with a significantly larger number of subjects compared to previous prospective clinical trials in the topic.

## METHODS

We collected all the patients who had received entitlement to special reimbursement for EGFR TKIs (gefitinib, erlotinib and afatinib) in the Special Reimbursement Register of Social Insurance Institution (SII) of Finland in 2011–2016 (n=1541). Of this population, final analysis was carried out with patients (n=1271) who had purchases of EGFR TKIs in the prescription database of SII and had data available at the nationwide Finnish Cancer Registry. Drug purchases and dates of deaths in Statistics Finland were collected until 31.12.2017. Survival was analysed from the first EGFR TKI purchase date to death or end-of follow-up, death counted as an event. Patients were stratified according to purchase of the first EGFR TKI (gefitinib, erlotinib or afatinib), purchase of antibiotics and their Anatomical Therapeutic Chemical

(ATC) class, and timing of antibiotic purchases. Timing of antibiotic purchases was analysed from the first EGFR TKI purchase date and grouped as the overall use (−14 to 200 days), prophylaxis (−14 to +14 days) or later use (+15 to 200 days). EGFR TKI dose reduction was characterised as a purchase of TKI with a lower dose compared to the initial purchased dose within 200 days from the first EGFR TKI purchase. EGFR TKI treatment break was characterised as a treatment break of >30 d during the first 200 days defined by the TKI purchases and the quantity of tablets purchased. EGFR TKI treatment length was analysed from the first EGFR TKI purchase to the last purchase plus days on the treatment according to the number of tablets in the last purchase, and treatment discontinuation before the 31st of December 2017 was counted as an event. However, a gap of 10 days between purchases was allowed to account for a continuation of the treatment.

Informed consent was not required due to the register nature of the study.

IBM SPSS Statistics V.24 for Windows was applied for statistical analysis. Comparisons between groups were assessed using $\chi^2$ analysis. Survival was analysed by using the Kaplan-Meier method with the log-rank test. In univariate and multivariate analysis, Cox regression was used. In multivariate analysis, Cox proportional hazard models were used to adjust for sex, initial stage and tumour histology. Confidence level of 95% was considered as statistically significant.

## RESULTS
### Patients
All the patients (n=1514) who had received reimbursement for EGFR TKIs (gefitinib, erlotinib, afatinib) for NSCLC in Finland 2011–2016 were identified from the national reimbursement registry. In Finland, reimbursements for gefitinib and afatinib are based on the presence of activating *EGFR* mutations in the tumours. For erlotinib, reimbursement is based on progression on the first-line therapy or *EGFR* activating mutations and these patients are registered under the same reimbursement number and cannot be separated. Based on personal identity codes, we combined data for the same patients from Prescription database (EGFR TKIs and antibiotics), Finnish Cancer Registry (cancer related data) and Statistics Finland (deaths) 2011–2017. The final analysis was carried out on patients (n=1271) who had the EGFR TKI reimbursement, had purchases of EGFR TKIs and had data available in the Finnish Cancer Registry. The patients had a median exposure time for TKIs of 104 days (SD 241d) and a median follow-up time of 300 days (SD 445d).

### Antibiotic Purchases and Survival
We analysed the cohort by (1) the timing of the antibiotic purchases from the time of the first EGFR TKI purchase and by (2) the ATC class of antibiotic (all), tetracycline or non-tetracycline. For the timing analysis,
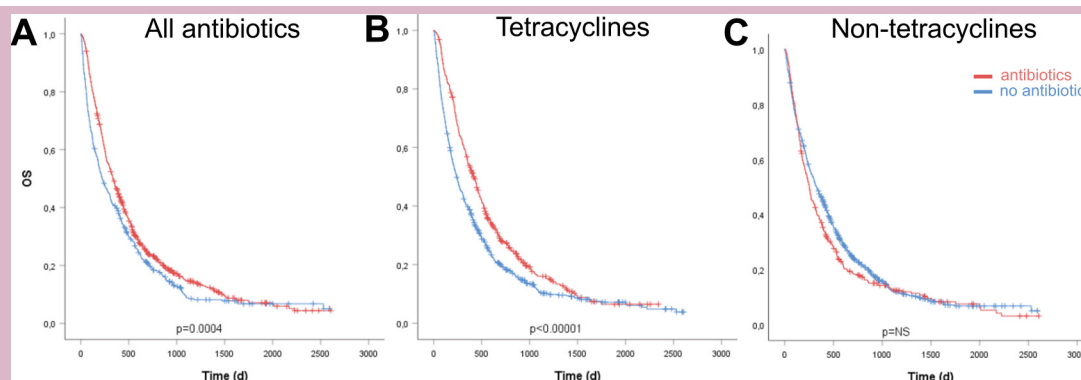
**Figure 1** Kaplan-Meier analysis for survival in the whole cohort according to use of antibiotics. (A) all antibiotics (red) versus no antibiotics (blue); (B) tetracycline antibiotics (red) versus no antibiotics (blue); (C) non-tetracycline antibiotics (red) versus no antibiotics (blue). Crosses indicate censored events. OS, overall survival.

we grouped the antibiotic purchases into three categories: −14 to +200 days from the first EGFR TKI purchase (all), −14 to +14 days (prophylaxis) and +15 to +200 days (late use). In the cohort, 802 (63.1%) of the patients had antibiotic purchases up to 200 days from the first EGFR TKI purchase, 447 (55.7%) of these tetracyclines. A total of 322 (25.3%) had had purchased antibiotics −14 to +14 days (prophylaxis) from the first EGFR TKI, 188 of these tetracyclines (58.3%) (online supplemental table 1).

The purchase of antibiotics was associated with an improved survival compared to no antibiotic purchases in the whole cohort (HR 0.81, 95% CI 0.71 to 0.91). The survival benefit was limited to tetracycline purchases only (HR 0.72, 95% CI 0.64 to 0.82) while the purchase of other ATC class antibiotics was associated with a worsen survival (HR 1.14 95% CI 0.99 to 1.30) (figure 1A–C, table 1). The largest survival benefit was seen with the prophylactic use

of tetracyclines (HR 0.74, 95% CI 0.62 to 0.88) but later (+15 to +200 days) purchases (HR 0.81, 95% CI 0.70 to 0.94) also benefited the patients. The largest survival benefit was seen when the patient had purchased tetracyclines both as a prophylaxis and later (HR 0.55, 95% CI 0.43 to 0.70) (figure 2A–C, table 1).

### Tetracycline antibiotics and different EGFR TKIs
Next, we carried out an analysis on the benefit of tetracyclines to survival according to the first EGFR TKI (gefitinib, erlotinib or afatinib) since EGFR TKIs have a different risk for the development of the the rash. The benefit of tetracyclines was limited to erlotinib only (HR 0.68, 95% CI 0.58 to 0.78) while there was no difference among the gefitinib users. The afatinib users had even a greater benefit (HR 0.35) of tetracyclines but this was non-significant due to the small sample size. For the erlotinib users, a larger survival difference was seen with

**Table 1** Univariate analysis for survival according to the antibiotic use, Anatomical Therapeutic Chemical (ATC) class and the timing of purchases

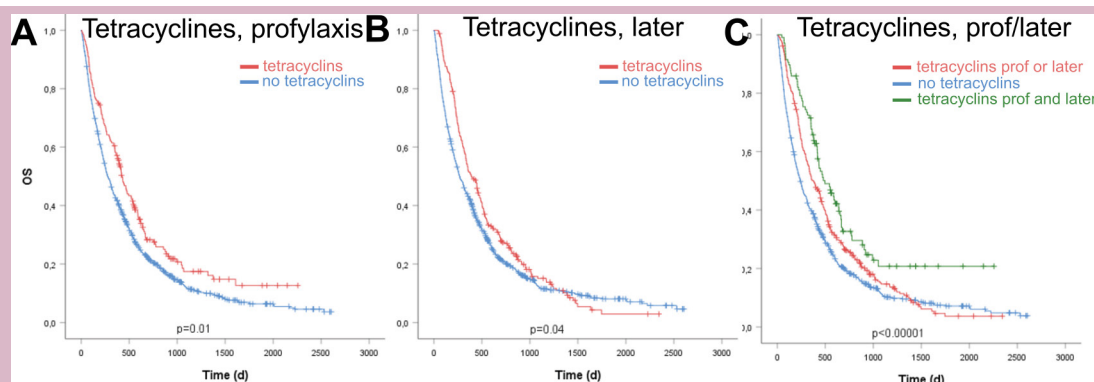| | HR | 95% CI | P value |
|---|---|---|---|
| Antibiotic purchases −14 to +200 d | | | |
| Yes versus no | 0.801 | 0.709 to 0.906 | <0.001 |
| Tetracycline purchases −14 to +200 d | | | |
| Yes versus no | 0.722 | 0.636 to 0.819 | <0.001 |
| Non-tetracycline purchases −14 to +200 d | | | |
| Yes versus No | 1.135 | 0.995 to 1.295 | NS |
| Tetracycline purchases −14 to +14 days | | | |
| Yes versus no | 0.737 | 0.618 to 0.88 | <0.001 |
| Tetracycline purchases +15 to +200 days | | | |
| Yes versus no | 0.806 | 0.695 to 0.935 | 0.004 |
| Tetracycline purchases −14 to +14 days or +15 to 200 days | | | |
| Yes versus no | 0.782 | 0.682 to 0.896 | <0.001 |
| Tetracycline purchases −14 to +14 days and +15 to 200 days | | | |
| Yes versus no | 0.552 | 0.433 to 0.703 | <0.001 |

NS, not significant.

**Figure 2** Kaplan-Meier analysis for survival in the whole cohort according to the timing of tetracycline purchase from the first EGFR TKI purchase. (A) prophylactic (−14 to +14 days) tetracyclines (red) versus no prophylactic tetracyclines (blue); (B) later (+15 to 200 days) tetracyclines (red) versus no tetracyclines (blue); (C) tetracyclines either as prophylaxis or later (red) versus tetracyclines as prophylaxis and later (green) versus no tetracyclines (blue). Crosses indicate censored events. EGFR, epidermal growth factor receptor; OS, overall survival; TKI, tyrosine kinase inhibitor.

the prophylactic use of tetracyclines compared to later use (HR 0.69 vs 0.80) (figure 3, table 2). The benefit of tetracyclines in the erlotinib users was further studied in a multivariate model including sex, initial stage and tumour histology, factors which were significantly associated with survival in the univariate analysis. The results showed that the beneficial effect of tetracyclines was retained in multivariate analysis for the whole population and for the erlotinib users (table 2).

### The effect of the tetracycline prophylaxis to erlotinib breaks, dose reductions and treatment duration

The effect of the prophylactic tetracycline was analysed for treatment breaks and dose reductions among the erlotinib users using Fisher's exact test. Prophylactic use of tetracyclines was not associated with treatment breaks for more than 30 days or with dose reductions during the first 200 days. The erlotinib treatment duration was studied with Kaplan-Meier analysis. The results showed that the use of prophylactic tetracyclines was associated with a longer treatment duration compared to no prophylaxis

(HR 0.81, 95% CI 0.68 to 0.95, p=0.012) with a median treatment duration of 120 vs 90 days (not shown).

### DISCUSSION

EGFR TKIs are standard-of-care approaches in the first-line treatment for advanced *EGFR* mutant lung cancer and these agents are also indicated for unselected NSCLC patients in later settings. With the first or second-generation EGFR TKIs, rash and diarrhoea are the most important side effects,[10][16] which can lead to a decline of QoL, and TKI dose reductions and treatment breaks. The presence of rash has been linked to an improved prognosis on EGFR TKI treated NSCLC patients with unknown or *EGFR* wild-type tumour genotype[12][13] but this is far less studied in the *EGFR* mutant disease.[17–19] Studies have shown that tetracycline antibiotics can decrease the severity of the rash, and these can be used in prophylactic or reactive fashion.[20][21] It is, however, unknown whether the use of tetracyclines could improve the survival of NSCLC patients treated with EGFR TKIs.
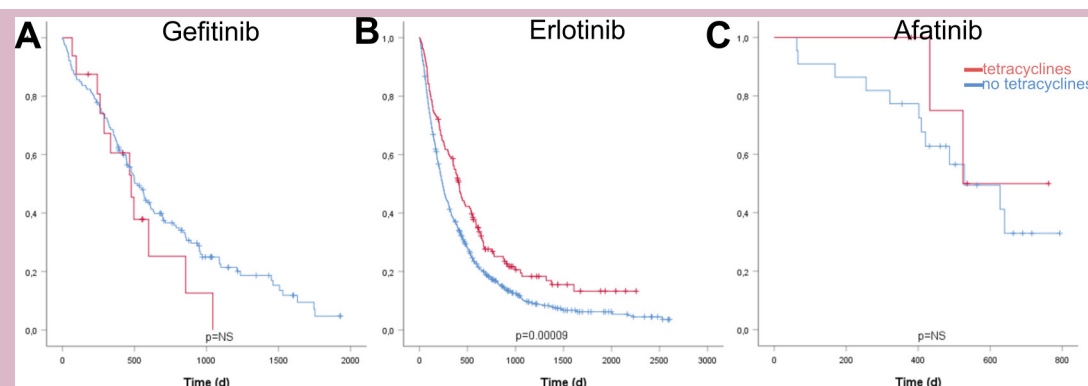


**Figure 3** Kaplan-Meier analysis for survival according to the first EGFR TKI (gefitinib, erlotinib or afatinib) and the use of prophylactic tetracyclines. (A) prophylactic tetracyclines (red) versus no prophylactic tetracyclines (blue) in the gefitinib users; (B) prophylactic tetracyclines (red) versus no prophylactic tetracyclines (blue) in the erlotinib users; (C) prophylactic tetracyclines (red) versus no prophylactic tetracyclines (blue) in the afatinib users. Crosses indicate censored events. EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

**Table 2** Univariate and multivariate analysis for survival according to tetracyclines and EGFR TKI

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P value | HR | 95% CI | P value |
| **Sex** | | | | | | |
| Male versus female | 1.326 | 1.176 to 1.495 | <0.001 | | | |
| **Stage** | | | | | | |
| Localised versus advanced | 0.642 | 0.503 to 0.819 | <0.001 | | | |
| **Histology** | | | | | | |
| Adecarcinoma versus other | 0.800 | 0.706 to 0.906 | <0.001 | | | |
| **Tetracycline purchases −14 to +200 days** | | | | | | |
| Yes versus no | 0.722 | 0.636 to 0.819 | <0.001 | 0.726 | 0.629 to 0.837 | <0.001 |
|   Gefitinib | | | | | | |
| Yes versus no | 0.994 | 0.675 to 1.462 | NS | | | |
|   Erlotinib | | | | | | |
| Yes versus no | 0.683 | 0.597 to 0.784 | <0.001 | 0.701 | 0.602 to 0.816 | <0.001 |
|   Afatinib | | | | | | |
| Yes versus no | 0.345 | 0.108 to 1.104 | NS | | | |
| **Tetracycline purchases −14 to +14 days** | | | | | | |
| Yes versus no | 0.737 | 0.618 to 0.880 | <0.001 | 0.79 | 0.647 to 0.965 | 0.02 |
|   Gefitinib | | | | | | |
| Yes versus no | 1.374 | 0.754 to 2.503 | NS | | | |
|   Erlotinib | | | | | | |
| Yes versus no | 0.689 | 0.572 to 0.830 | <0.001 | 0.755 | 0.614 to 0.929 | 0.008 |
|   Afatinib | | | | | | |
| Yes versus no | 0.561 | 0.125 to 2.518 | NS | | | |
| **Tetracycline purchases +15 to +200 days** | | | | | | |
| Yes versus no | 0.806 | 0.695 to 0.935 | 0.004 | 0.767 | 0.648 to 0.909 | 0.002 |
|   Gefitinib | | | | | | |
| Yes versus no | 0.874 | 0.575 to 1.330 | NS | | | |
|   Erlotinib | | | | | | |
| Yes versus no | 0.796 | 0.679 to 0.932 | 0.005 | 0.761 | 0.635 to 0.912 | 0.003 |
|   Afatinib | | | | | | |
| Yes versus no | 0.369 | 0.082 to 1.670 | NS | | | |

EGFR, epidermal growth factor receptor; NS, not significant; TKIs, tyrosine kinase inhibitors.

In the current study, we provide results of a large, nationwide cohort of patients treated EGFR TKIs for NSCLC indication. In Finland, purchases of all the reimbursed drugs, including drug, tablet strength, the number of tablets purchased and date of the purchase, are registered in the Prescription database of SII. These data enable studying of concurrent purchases of drugs and data can be linked to other available registries such as Finnish Cancer Registry, and Statistics Finland using personal identity codes to study survival, cancer diagnostic and treatment in addition to drug purchases. Our study hypothesis was that tetracycline prophylaxis can improve survival, TKI treatment duration, and decrease the number of EGFR TKI dose reductions and treatment breaks. The major finding of our study was that tetracycline prophylaxis increased the survival and TKI treatment duration of NSCLC patients treated with erlotinib. A similar tendency was also seen with the afatinib users, which, however, was statistically non-significant probably due to the small sample size. Interestingly, the gefitinib users did not bare additional benefit from the use of tetracyclines suggesting that the benefit of tetracyclines comes from the inhibiton of rash . Furthermore, erlotinib and afatinib are dosed with a maximal tolerated dose (MTD) which is associated with a higher frequency and severity of rash compared to less than MTD dosing of gefitinib.[22–24]

Previous moderate sized (n=90–150) prospective clinical trials have investigated the tetracycline prophylaxis of rash in NSCLC patients treated with erlotinib, afatinib

or dacomitinib. The studies have shown that the tetracycline prophylaxis reduces the number and severity of TKI induced rash. However, none of the studies have shown that the use of tetracyclines can improve the survival.[25–27] In the Pan-Canadian study, patients assigned for prophylactic or reactive tetracycline use with erlotinib in the second or later line setting, had a longer median survival compared to controls but this was statistically insignificant.[25] Our study had a significantly larger number of patients (n=1271) compared to these prospective clinical trials, and roughly 15% had received tetracycline prophylaxis. We hypothesized that national registries with large enough patient numbers could enable studying the effect of tetracyclines to survival.

There are some cautions which should be considered when evaluating our results. The retrospective nature of the study poses confounding factors compared to prospective randomised clinical trials. However, all the prospective trials presented so far have had an inadequate number of subjects to fully investigate the effect of tetracycline prophylaxis to survival, and to our knowledge (ClinicalTrials.gov), there are no ongoing trials in the field. Therefore, we feel that our retrospective study with a large number of subjects provides important clinical information. Our study is based on drug purchases only, which can bring another level of uncertainties to the data. In cancer care, however, there is a high level of patient adherence, and it is likely that the purchased drugs are used with a very large percentage. We sought to control the uncertainties of drug purchases by grouping the subjects based on the timing of tetracycline purchases. We feel that the data on prophylactic tetracycline (−14 to +14 days of the first EGFR TKI purchase) provides an estimate with least confounding factors since a severe TKI rash rarely develops prior to 2 weeks from an onset of EGFR TKI use. For the later use of tetracyclines (+15 to 200 days), there are more factors generating bias, for example, patients in need for rash management are generally considered to have a better prognosis,[13] and because several patients die before 200 days and, for that, have less time to be exposed to antibiotics.

Our study results support the use of tetracycline prophylaxis on NSCLC patients treated with a first or second-generation EGFR TKI excluding gefitinib. The use of first and second-generation TKIs is declining due to the introduction of the first-line osimertinib in the management of *EGFR* mutant NSCLC and reduced numbers of genetically unselected patients exposed to EGFR TKIs in the later line settings. Osimertinib is a third-generation T790M-mutation specific EGFR TKI that is associated with a lower insidence of rash than the older EGFR TKIs[10] and, for that, prophylactic rash measures are generally not recommended and probably provide no additional benefit. The registration trial of the first-line osimertinib (FLAURA) showed that osimertinib was superior in PFS and OS compared to gefitinib and erlotinib.[7 28] It should be noted, however, that in the FLAURA trial, prophylactic tetracyclines were not admitted. In the light of our study

results, one could speculate that the outcomes of the erlotinib treated patients might have been improved if prophylactic tetracyclines would have been allowed. Even though the number of patients exposed to older EGFR TKIs is declining, these agents will still be used in a large-scale fashion in countries without the first-line reimbursement for osimertinib, patients with significant osimertinib toxicity and other indications. Therefore, we feel that our results still have a very important clinical significance.

Our study with a large retrospective cohort based on national registries suggest that tetracyclines can improve the survival of NSCLC patients treated with erlotinib. To our knowledge, this is the first study to provide evidence that tetracyclines can alter the survival of EGFR TKI treated NSCLC patients. Our study provides a strong evidence that prophylactic tetracyclines should be used on patients treated with EGFR TKIs associated with a high incidence of rash.

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