# Randomised controlled trial of first-line tyrosine-kinase inhibitor (TKI) versus intercalated TKI with chemotherapy for EGFR-mutated nonsmall cell lung cancer

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# Randomised controlled trial of first-line tyrosine-kinase inhibitor (TKI) *versus* intercalated TKI with chemotherapy for *EGFR*-mutated nonsmall cell lung cancer

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Shareable abstract (@ERSpublications)
**Intercalated erlotinib with cisplatin-pemetrexed prolongs PFS compared to erlotinib alone (13.7 *versus* 10.3 months; HR 0.24, 95% CI 0.07–0.83). However, the combination treatment is not favourable due to higher toxicity rates.** https://bit.ly/3AIl5bq

**Cite this article as:** Gijtenbeek RGP, van der Noort V, Aerts JGJV, *et al*. Randomised controlled trial of first-line tyrosine-kinase inhibitor (TKI) *versus* intercalated TKI with chemotherapy for *EGFR*-mutated nonsmall cell lung cancer. *ERJ Open Res* 2022; 8: 00239-2022 [DOI: 10.1183/23120541.00239-2022].



Received: 16 May 2022
Accepted: 5 July 2022
First published: 17 Oct 2022

## Abstract

*Introduction* Previous studies have shown interference between epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors and chemotherapy in the cell cycle, thus reducing efficacy. In this randomised controlled trial we investigated whether intercalated erlotinib with chemotherapy was superior compared to erlotinib alone in untreated advanced EGFR-mutated nonsmall cell lung cancer (NSCLC).

*Materials and methods* Treatment-naïve patients with an activating *EGFR* mutation, ECOG performance score of 0–3 and adequate organ function were randomly assigned 1:1 to either four cycles of cisplatin-pemetrexed with intercalated erlotinib (day 2–16 out of 21 days per cycle) followed by pemetrexed and erlotinib maintenance (CPE) or erlotinib monotherapy. The primary end-point was progression-free survival (PFS). Secondary end-points were overall survival, objective response rate (ORR) and toxicity.

*Results* Between April 2014 and September 2016, 22 patients were randomised equally into both arms; the study was stopped due to slow accrual. Median follow-up was 64 months. Median PFS was 8.8 months (95% CI 4.2–18.8) for CPE and 10.3 months (95% CI 7.1–15.5; hazard ratio (HR) 0.78, 95% CI 0.32–1.91) for erlotinib monotherapy; when compensating for number of days receiving erlotinib, PFS of the CPE arm was superior (HR 0.32, 95% CI 0.10–1.01; p=0.02). ORR was 64% for CPE *versus* 55% for erlotinib monotherapy. Median overall survival was 30.9 months (95% CI 18.5–61.9 months) for CPE compared to 17.2 months (95% CI 11.5–45.5 months) for erlotinib monotherapy (HR 0.66, 95% CI 0.27–1.65 months). Patients treated with CPE had higher rates of treatment-related fatigue, anorexia, weight loss and renal toxicity.

*Conclusion* Intercalating erlotinib with cisplatin-pemetrexed provides a longer PFS compared to erlotinib alone in *EGFR*-mutated NSCLC at the expense of more toxicity.

## Introduction

Since 2004, efforts to combine epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) and chemotherapy in patients with advanced nonsmall cell lung cancer (NSCLC) have been explored, starting with unselected NSCLC patients. Four randomised phase III studies failed to improve outcome of combinations *versus* chemotherapy alone [1–4]. However, it was more important to study the role of adding chemotherapy to the treatment with an EGFR TKI in *EGFR*-mutated NSCLC patients. Cheng and co-workers [5, 6] showed improved progression-free survival (PFS) in the combined arm in a randomised phase II study enrolling Asian *EGFR*-mutated advanced NSCLC patients treated with gefitinib plus pemetrexed *versus* gefitinib alone. However, gefitinib/pemetrexed patients had more toxicity compared to gefitinib alone. In 2020, Noronha *et al*. [7] and Hosomi *et al*. [8] reported in phase III studies superior PFS and overall survival for concurrent gefitinib and carboplatin plus pemetrexed *versus* gefitinib alone as first-line treatment. This suggests that the combination of chemotherapy and TKI treatment overcomes early EGFR resistance mechanisms that emerge when using EGFR TKI alone. Of note, in these studies, only 15% and 22% of all patients received subsequent treatment with osimertinib, respectively.

Although concurrent use of TKI and chemotherapy is shown to be superior in PFS and overall survival, one of the concerns is the interference between EGFR TKI and chemotherapy in *EGFR*-mutated advanced NSCLC, which came from pre-clinical data where G1 cell cycle arrest due to EGFR TKI reduces the cell cycle dependent phase of chemotherapy [9]. However, when administered sequentially with respect to biological availability and half-life, the treatment effects of pemetrexed and erlotinib are synergic [10]. Therefore, to enhance the treatment effect by avoiding such interfering effects, we designed a randomised phase III trial to demonstrate the superiority of first-line treatment with cisplatin+pemetrexed with intercalated erlotinib (CPE) for days 2–16 in a 3-week cycle compared to continuous erlotinib monotherapy in patients with advanced *EGFR*-mutated NSCLC, in terms of PFS, overall survival, objective response rate (ORR) and toxicity.

## Material and methods

### *Study design*

The NVALT-17 trial is a multicentre randomised controlled trial in patients with *EGFR*-mutated advanced NSCLC, who have been randomised in equally to either CPE or erlotinib monotherapy. Patients were enrolled from eight study centres in the Netherlands, and treatment was assigned by participating centre by means of a minimisation technique stratifying for ECOG performance status (0–1 *versus* 2–3) and activating *EGFR* mutation. Clinical data were entered into a web-based electronic data capture system, hosted at the NVALT data centre using the ALEA system. The study was approved by the central medical ethical committee of the University Medical Centre Groningen (nr. 2013/457); all patients gave informed consent before registration.

### *Eligibility criteria*

Treatment-naïve patients with histologically or cytologically confirmed NSCLC having a documented activating *EGFR* mutation in exon 18, 19 or 21; aged >18 years; a performance status of 0–3; and adequate bone marrow, hepatic and renal function were enrolled. Estimated life expectancy should be >12 weeks.

Patients who were poor medical risks because of nonmalignant disease or those with active uncontrolled infection were ineligible, as were patients with symptomatic brain metastases unless local therapy was completed, and systemic corticosteroids had been discontinued ⩾2 weeks before enrolment. Concomitant treatment with any other experimental drug or potent CYP3A4 inhibitor was not allowed. Patients with concurrent or previous malignancy were excluded, except for cervical carcinoma *in situ*, treated basal cell carcinoma, superficial bladder tumours or any cancer curatively treated >2 years prior to study entry. Patients known to be positive for HIV or chronic hepatitis B/C were not eligible.

### *Study procedures*

Baseline evaluations were history including comorbidity, physical examination, blood counts, liver and renal function test and blood chemistry, electrocardiography, computed tomography (CT) of the chest and abdomen, positron emission tomography or bone scan. Subsequent CT scan evaluations were performed every 6 weeks. Tumour response was assessed according to Response Evaluation Criteria in Solid Tumors 1.1 criteria.

### *Treatment protocol*

Patients were randomised to four cycles of cisplatin 75 $mg \cdot m^{-2}$ and pemetrexed 500 $mg \cdot m^{-2}$ plus intercalated (day 2–16) erlotinib 150 mg every 3 weeks followed by maintenance pemetrexed plus erlotinib

(CPE) or daily erlotinib 150 mg (E) alone until disease progression. For comparability, both arms received folic acid 0.5 mg daily and vitamin B12 1000 µg intramuscular once every 6–9 weeks until disease progression.

All adverse events were evaluated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) (version 4.0). At the start of each cycle, absolute neutrophil count had to be $\geqslant 1.5\times10^{9}$ cells·L$^{-1}$ and platelets $\geqslant 100\times10^{9}$ cells·L$^{-1}$. If applicable, chemotherapy dose was adjusted based on platelet ($<50\times10^{9}$ cells·L$^{-1}$) and neutrophil nadir counts ($<0.5\times10^{9}$ cells·L$^{-1}$) from the preceding cycle of therapy and maintained for subsequent cycles. In case of neurosensory toxicity grade $\geqslant 2$ or creatinine clearance $\leqslant 60$ mL·min$^{-1}$, cisplatin dose was reduced. In the event of grade 3 diarrhoea, the study therapy was not administered until resolved. For other nonhaematological effects CTCAE grade $\geqslant 3$ (except alopecia, mucositis), the drug was held until resolution to less than or equal to the baseline value before proceeding. Treatment restarted at a 25% dose reduction if deemed appropriate by the treating physician.

Dose reduction for erlotinib (100 or 50 mg daily) took place whenever toxicity was noted during the study. Within 2 weeks following a dose reduction, erlotinib-related toxicity must have improved by at least one CTCAE grade and be CTCAE grade $\leqslant 2$, otherwise further dose reduction by one level was required.

Study treatment was discontinued if a cycle was delayed for >2 weeks; erlotinib therapy was not restarted unless chemotherapy was postponed definitely. Replacement of cisplatin by carboplatin in case of oto-, neuro- or renal toxicity was allowed.

### Outcomes

The primary end-point was PFS, defined as the time of random assignment to disease recurrence or death, whatever came first. Secondary end-points included overall survival, 6-month and 1-year overall survival rate, ORR, toxicity, symptoms and general health status. Overall survival was measured from the date of randomisation to the date of death. Duration of tumour response was measured from the date of the first objective status assessment of a complete or partial response to the date of progression of disease or death from any cause. All time to event end-points were analysed using the Kaplan–Meier method. Toxicity was recorded according to CTCAE (version 4.0).

### Statistical analysis

The primary objective was to compare PFS between the CPE and erlotinib monotherapy study arms. Cox proportional hazard regression was used to compare PFS between arms both univariately followed by adjustment for the duration of erlotinib treatment. Descriptive statistics were used for patient characteristics. For toxicities occurring in >10% of patients, Fisher's exact test was used to compare the two arms.

**TABLE 1** Baseline patient characteristics

| | CPE | Erlotinib monotherapy | All |
|---|---|---|---|
| **Patients** | 11 | 11 | 22 |
| **Age, years** | 60 (58–64) | 67 (62–68) | 64 (59–68) |
| **Males** | 5 (45) | 5 (45) | 10 (45) |
| **Performance score** | | | |
| 0 | 8 (73) | 7 (64) | 15 (68) |
| 1 | 3 (27) | 4 (36) | 7 (32) |
| **Smoking** | | | |
| Never-smoker | 6 (55) | 2 (18) | 8 (36) |
| Former smoker | 5 (45) | 5 (45) | 10 (45) |
| Current smoker | 0 (0) | 4 (36) | 4 (18) |
| Pack-years | 14 (9–15) | 14 (6–19) | 14 (7–18) |
| **Stage IV** | 11 (100) | 11 (100) | 22 (100) |
| **Nonsquamous** | 11 (100) | 11 (100) | 22 (100) |
| **Type of *EGFR* mutation** | | | |
| Exon 19 deletion | 7 (64) | 7 (64) | 14 (64) |
| L858R | 2 (18) | 3 (27) | 5 (23) |
| Other | 2 (18) | 1 (9) | 3 (13) |

Data are presented as n, median (interquartile range) or n (%). CPE: cisplatin-pemetrexed-erlotinib; EGFR: epidermal growth factor receptor.

**TABLE 2** Outcome measures by treatment arm

| | CPE | Erlotinib monotherapy | HR (95% CI) |
|---|---|---|---|
| **Patients randomised** | 11 | 11 | |
| **PFS months, median (95% CI)** | 8.8 (4.2–18.8) | 10.3 (7.1–15.5) | 0.78 (0.32–1.91)[#] |
| **Overall survival, median (95% CI)** | 30.9 (18.5–61.9) | 17.2 (11.5–45.5) | 0.66 (0.27–1.65) |
| **1-year overall survival, % (95% CI)** | 81.8 (48.2–97.7) | 72.7 (39.0–94.0) | |
| **ORR, % (95% CI)** | 64 (31–89) | 55 (23–83) | |
| Complete response | 1 (9) | 1 (9) | |
| Partial response | 6 (54) | 5 (46) | |
| Stable disease | 4 (36) | 5 (46) | |
| **Duration of response in months, median (95% CI)** | 10.8 (7.3–31.2) | 8.0 (5.5–8.7) | 0.43 (0.12–1.47) |

Data are presented as n or n (%), unless otherwise stated. CPE: cisplatin-pemetrexed-erlotinib; HR: hazard ratio; PFS: progression-free survival; ORR: overall response rate. [#]: after compensating for numbers of days receiving erlotinib HR 0.32, 95% CI 0.10–1.01; p=0.05.

A sample size of 75 subjects per arm was calculated, as an increase in median PFS from 10 to 17 months was estimated, which required a total of 150 eligible patients, with an inclusion rate of 50 patients per year. It was estimated that after 1 year of follow-up, 112 events would be observed, providing 80% power to detect the specified increase in PFS at the 95% confidence level.

## Results

### *Basic characteristics*

150 patients had been scheduled to be enrolled during a 5-year period starting April 2014. However, the trial was terminated prematurely in 2017 due to slow enrolment. During this period, only 22 patients were enrolled in the study, with 11 patients assigned to each arm. The last patient was included on 12 September, 2016. Median follow-up time was 64 months; the most recent follow-up took place in August 2021.

Basic characteristics at baseline were well balanced between the groups. Median age was 64 years (interquartile range (IQR) 59–68 years); 55% were female. All patients had advanced disease and adenocarcinoma histology. 64% of patients had an exon 19 deletion and 23% had an exon 21 L858R mutation (table 1). In the CPE arm, median treatment length was 291 days (range 21–1031 days), compared to 324 days (range 57–932 days) in the erlotinib monotherapy arm. The median number of days of receiving erlotinib was 219 (range 14–994) in the CPE arm compared to 324 (range 53–918) in the erlotinib monotherapy arm. At time of disease progression, five patients from each arm underwent a re-biopsy. In the CPE arm, one patient acquired a T790M mutation, compared to two patients in the erlotinib monotherapy arm.

### *Tumour response and survival*

ORR and duration of tumour response were not different between both arms: in the CPE arm the ORR was 64% (seven out of 11); time to best response was 49 days (IQR 44–90 days), with a median duration of response of 10.8 months. In the erlotinib monotherapy arm, 55% (six out of 11) of patients responded to therapy, with a median response duration of 8 months. The median time to best response was 68 days (IQR 47–148 days). The main end-points are summarised in table 2.

PFS in patients treated with CPE was 8.8 months (95% CI 4.2–18.8 months) compared to 10.3 months (95% CI 7.1–15.5 months) in those treated with erlotinib monotherapy (unstratified hazard ratio (HR) 0.78, 95% CI 0.32–1.91; p=0.58) (figure 1a). With compensation for the number of days receiving erlotinib, the PFS advantage of the CPE over the erlotinib monotherapy arm became more pronounced (HR 0.32, 95% CI 0.10–1.01; p=0.05).

Median overall survival for CPE and erlotinib monotherapy was 30.9 months (95% CI 18.5–61.9 months) *versus* 17.2 months (95% CI 11.5–45.5 months; HR 0.66, 95% CI 0.27–1.65; p=0.38), with a 1-year survival rate of 82% (95% CI 48–98%) for CPE *versus* 73% (95% CI 39–94%) for erlotinib monotherapy (figure 1b).

### *Safety outcomes*

Treatment-related adverse events occurred more often in the CPE group (58 *versus* 37 events), with a numerically higher frequency of patients reporting treatment-related fatigue (45% *versus* 18%; p=0.36), weight loss (18% *versus* 0%; p=0.48) and renal toxicity (27% *versus* 0%; p=0.21), while anorexia was significantly

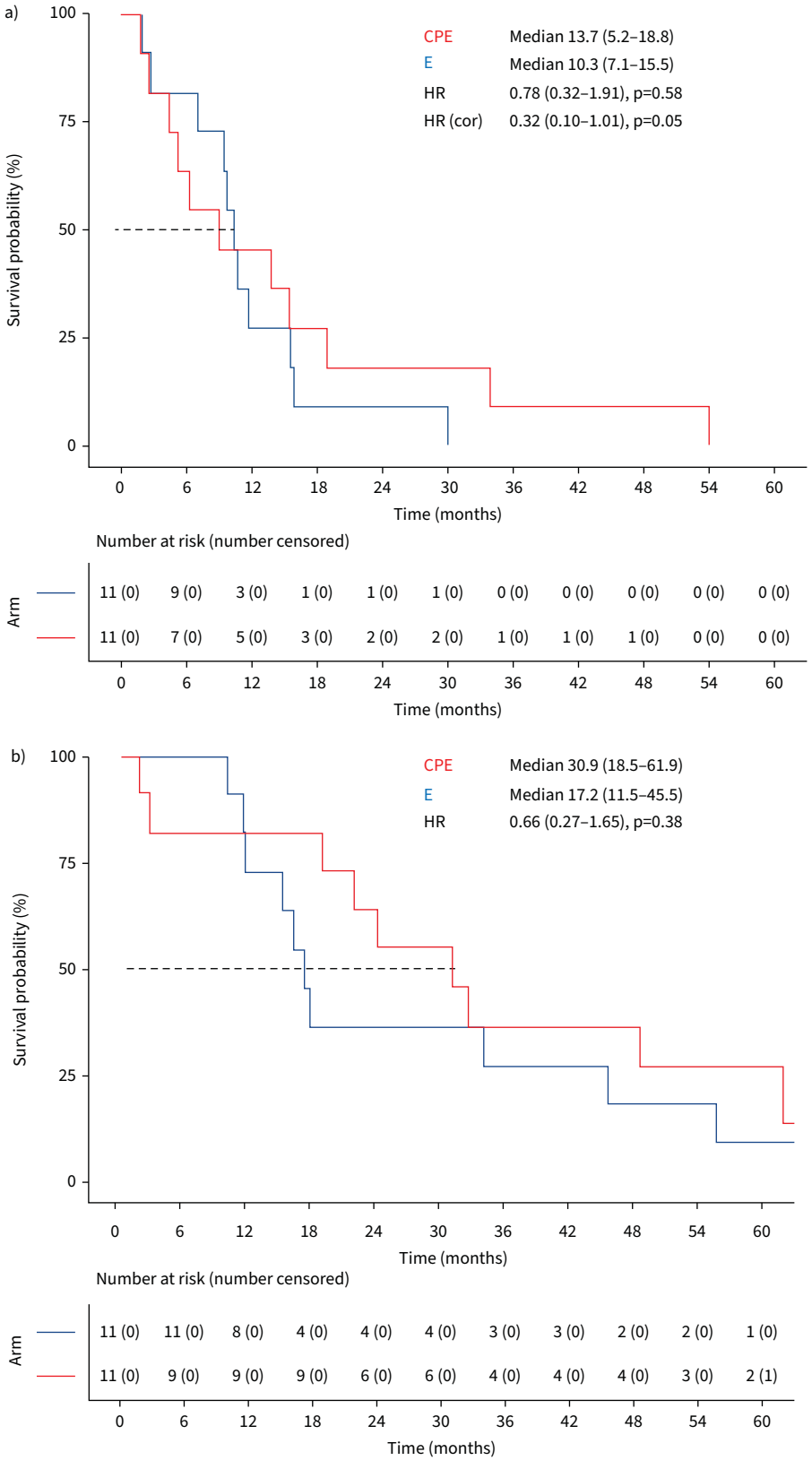


**FIGURE 1** a) Progression-free survival and b) overall survival in months by treatment arm. Data are presented with 95% CI. CPE: cisplatin-pemetrexed-erlotinib; E: erlotinib; HR: hazard ratio; cor: corrected.

**TABLE 3** Number of treatment-related adverse events with incidence ⩾10% or grade ⩾3

| | All grades | | | Grade ⩾3[#] | |
|---|---|---|---|---|---|
| | CPE | E monotherapy | p-value | CPE | E |
| Abdominal pain | 1 | 1 | | 0 | 0 |
| Alopecia | 2 | 0 | 0.48 | 0 | 0 |
| Anaemia | 1 | 0 | | 0 | 0 |
| Anorexia | 6 | 0 | 0.01 | 1 | 0 |
| Diarrhoea | 3 | 1 | 0.59 | 1 | 0 |
| Dry eyes | 0 | 1 | | 0 | 0 |
| Dry skin | 5 | 4 | 1.00 | 0 | 0 |
| Fatigue | 5 | 2 | 0.36 | 1 | 0 |
| Hypocalcaemia | 1 | 0 | | 1 | 0 |
| Hypomagnesaemia | 1 | 0 | | 1 | 0 |
| Mucositis | 1 | 0 | | 1 | 0 |
| Nail infection | 1 | 6 | 0.06 | 0 | 0 |
| Nausea | 2 | 1 | | 1 | 0 |
| Neutropenia | 1 | 0 | | 1 | 0 |
| Pruritus | 1 | 1 | | 0 | 1 |
| Rash | 6 | 8 | 0.66 | 1 | 0 |
| Renal toxicity | 3 | 0 | 0.21 | 2 | 0 |
| Weight loss | 2 | 0 | 0.48 | 0 | 0 |

CPE: cisplatin-pemetrexed-erlotinib; E: erlotinib. [#]: due to limited sample size, no statistical analysis was performed for events grade ⩾3.

increased in the combination arm (55% *versus* 0%; p=0.01 (supplementary material). In addition, the number of reported grade 3 and 4 treatment-related adverse events was higher in the CPE arm (11 *versus* 1). There was one grade 5 adverse event in a patient treated with CPE (epileptic seizures, not treatment-related). An overview of treatment-related adverse events occurring in ⩾10% of patients or grade ⩾3 is shown in table 3.

Of the patients treated with CPE, six (55%) completed all four cycles of cisplatin therapy; one additional patient was switched to carboplatin and completed four cycles with combination chemotherapy. Therapy delays (six times in four patients) and dose reductions of cisplatin or pemetrexed (three patients) were more common in this group. Treatment interruptions for intercalated erlotinib occurred in three patients and dose reductions occurred five times in three patients. However, in the erlotinib monotherapy arm no patient discontinued therapy because of toxicity; there were four treatment interruptions in three patients and dose reduction occurred twice in one patient.

## Discussion

In this study comparing alternating erlotinib with chemotherapy to exclude interfering effects between both treatments *versus* erlotinib alone, we found that PFS and overall survival were numerically better for patients treated with the combination therapy. When stratifying for type of *EGFR* mutation and days receiving erlotinib, PFS was clearly prolonged. The main objection for patients to participate in this study was the availability of TKI monotherapy as a less intensive and toxic treatment regimen.

The improvement in PFS of almost 4 months was observed in only 22 patients and despite the fact that only 55% of the patients tolerated treatment well enough to complete the four cycles of chemotherapy as intended. Combined administration of chemotherapy and EGFR TKI seems promising and the treatment effects are better compared to TKI monotherapy. In two other phase III studies comparing concurrent chemotherapy and EGFR TKI regimens to EGFR TKI monotherapy, significant improvements in PFS of 8 and 9 months (pooled HR 0.50, 95% CI 0.43–0.58) were observed, while HR in our study was 0.62 (95% CI 0.25–1.57) [7, 8]. HR was even lower when correcting for days of erlotinib use, indicating a clinical effect of the combination treatment or intercalation of erlotinib with chemotherapy.

Theoretically, intercalated use of EGFR TKI next to chemotherapy might be more effective in the initial treatment phase in comparison with concurrent use. Pre-clinical studies showed that TKI arrest tumour cells in a cell cycle phase that protects them from cell cycle specific cytotoxic agents such as pemetrexed, reducing the activity of the chemotherapy [10]. Wu *et al*. [11] showed that combined use of pemetrexed and gefitinib had antagonistic effects in gefitinib-sensitive NSCLC cells, while synergistically inhibiting

the growth of gefitinib-resistant NSCLC cells. Li *et al*. [10] showed a synergistic effect when pemetrexed was administered ⩾8 h before erlotinib. This effect may be an indication that the interaction between EGFR TKI and chemotherapy is a clinical meaningful issue that may enlarge the already positive survival outcome of randomised concurrent studies. This NVALT-17 study tried to overcome this interfering mechanism by its intercalated design, with administration of erlotinib starting the day after chemotherapy was completed until day 16, to ensure that erlotinib plasma levels were decreased by approximately four half-lives to prevent interaction between erlotinib and pemetrexed [10, 12].

Patients with *EGFR*-mutated NSCLC will develop disease progression due to acquired TKI resistance. The most common mechanism of acquired resistance to first- and second-generation TKIs is the acquisition of a secondary EGFR mutation, T790M [13]. It is not known if the combination of first-generation TKI with chemotherapy will lead to different resistance mechanisms. Previous trials did not report resistance mechanisms and the number of patients in this study with known acquisition of T790M is too small to draw any conclusion. Osimertinib and newer TKI will induce different resistant mechanisms, both EGFR-dependent and -independent [14].

We reported a higher rate of treatment-related toxicity among patients treated with CPE compared to erlotinib monotherapy. CPE showed not only the typical skin, fatigue and gastrointestinal toxicity, but also seems to result in a higher rate of patients with renal toxicity (three patients, of whom two had grade 3 toxicity) compared with previous trials assessing chemotherapy combined with EGFR TKI. Hosomi *et al*. [8] reported that 25.3% of all patients treated with chemotherapy+TKI experienced creatinine elevation, all grade 1–2. Noronha *et al*. [7] reported 32 (19.5%) patients with renal dysfunction grade ⩽3, of whom 10 had grade 3 dysfunction. The higher rate of renal toxicity in our trial could be due to the use of cisplatin, as in both referenced studies carboplatin was administered. The perceived treatment toxicity compared with TKI monotherapy was one of the major reasons for limited enrolment. As monotherapy TKI was already the most appropriate first-line therapy, we assume that many patients choose this proven effective and less-toxic treatment, reflecting that individual patient goals extend beyond maximal life expectancy and that for some patients the impact of treatment on other goals such as quality of life may be as important as extension of life itself [15, 16].

To our knowledge, this is the first phase III trial reporting on intercalated use of TKI next to chemotherapy in selected EGFR patients and our results do support further exploration of combination treatment of EGFR TKI with other anticancer therapies. However, until a direct head-to-head comparison in a combined chemotherapy approach exists, it remains unclear which treatment regimen, concurrent or intercalated use with which TKI, is most beneficial. Whereas the different-generation TKI may have different effects in subgroups, the switch to upfront treatment with the third-generation EGFR TKI osimertinib will raise the question whether previous results can be improved with osimertinib combination therapies [17]. A phase II trial evaluating combined osimertinib with carboplatin and pemetrexed showed no overall survival or PFS advantage in progressive pre-treated patients with a T790M mutation compared to osimertinib alone [18]. Phase III trials on first-line osimertinib with or without bevacizumab (ClinicalTrials.gov identifier NCT04181060) and osimertinib with or without chemotherapy (FLAURA2/ClinicalTrials.gov identifier NCT04035486) are ongoing [19–21]. Future results will show whether early elimination of resistance clones is more effective with intercalation *versus* the concurrent approach.

## Conclusion

Although the results should be interpreted with caution, since the trial was ended prematurely and as a consequence was underpowered, the addition of chemotherapy to EGFR TKI treatment in an intercalated regimen led to a longer PFS, not statistically different compared to concurrent regimens. Therefore, this study supports the hypothesis that CPE has a longer PFS than erlotinib monotherapy, but the combination of intercalated erlotinib with cisplatin and pemetrexed is not favourable over erlotinib alone, due to toxicity. The results encourage further research combining chemotherapy with upcoming next-generation EGFR treatments.

This article has been revised according to the correction published in *ERJ Open Res* 2023; 10: 50239-2022 [https://doi.org/10.1183/23120541.50239-2022].

Provenance: Submitted article, peer reviewed.

This study is registered at https://eudract.ema.europa.eu/ with identifier number 2013-004303-39. After publication of this article, the study protocol, statistical analysis and data will be available upon request.

Conflict of interest: R.G.P. Gijtenbeek has received support for the present manuscript from Roche, Lilly and Amgen. V. van der Noort has received support for the present manuscript from Roche, Lilly and Amgen. J.G.J.V. Aerts has received support for the present manuscript from Roche, Lilly and Amgen; consulting fees from MSD, BMS, Boehringer Ingelheim, Amphera, Eli-Lilly, Takeda, Bayer, Roche, Astra Zeneca and BIOCAD, outside the submitted work; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events received from MSD, BMS, Boehringer Ingelheim, Amphera, Eli-Lilly, Takeda, Bayer, Roche, Astra Zeneca and BIOCAD, outside the submitted work; and patents planned, issued or pending for an allogenic tumour cell lysate, Amphera, combination immunotherapy in cancer, and a biomarker for immunotherapy, unrelated to this submission. J.A. Staal-van den Brekel has received support for the present manuscript from Roche, Lilly and Amgen. E.F. Smit has received support for the present manuscript from Roche, Lilly and Amgen; grants or contracts from Boehringer Ingelheim, Bayer, Roche/Genentech, AstraZeneca and Bristol-Myers Squibb, outside the submitted work; and consulting fees from Lilly, AstraZeneca, Boehringer Ingelheim, Roche/Genentech, Bristol-Myers Squibb, Merck KGaA, MSD Oncology, Takeda, Bayer, Novartis, Daiichi Sankyo and Seattle Genetics, outside the submitted work. F.H. Krouwels has received support for the present manuscript from Roche, Lilly and Amgen. F.A. Wilschut has received support for the present manuscript from Roche, Lilly and Amgen. T.J.N. Hiltermann has received support for the present manuscript from Roche, Lilly and Amgen; grants or contracts received from Roche, BMS and AstraZeneca, outside the submitted work; consulting fees received from Roche, BMS, AstraZeneca and MSD, outside the submitted work; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events received from BMS, outside the submitted work. W. Timens has received support for the present manuscript from Roche, Lilly and Amgen; and consulting fees received from Merck Sharp Dohme and Bristol-Myers-Squibb, outside the submitted work; and is a board member of the Dutch Society of Pathology and a member of the Council for Research and Innovation of the Federation of Medical Specialists. E. Schuuring has received support for the present manuscript from Roche, Lilly and Amgen; grants or contracts from Abbott, Biocartis, Astrazeneca, Invitae/Archer, Bayer, Bio-Rad, Roche, Agena Bioscience, CC Diagnostics and Boehringer Ingelheim, outside the submitted work; consulting fees from MSD/Merck, AstraZeneca, Roche, Novartis, Bayer, BMS, Lilly, Amgen, Illumina, Agena Bioscience, CC Diagnostics, Janssen Cilag (Johnson&Johnson) and Astellas Pharma, outside the submitted work; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Bio-Rad, Seracare, Roche, Biocartis, Lilly, Agena Bioscience and Illumina, outside the submitted work; and support for attending meetings and/or travel from BioRad and Biocartis, outside the submitted work; and is an unpaid board member of the Dutch Society of Pathology, the European Society of Pathology and the European Liquid Biopsy Society. J.D.J. Janssen has received support for the present manuscript from Roche, Lilly and Amgen. M. Goosens has received support for the present manuscript from Roche, Lilly and Amgen. P.M. van den Berg has received support for the present manuscript from Roche, Lilly and Amgen. A.J. de Langen reports grants from BMS, MSD, Boehringer and AstraZeneca, and nonfinancial support from Merck Serono and Roche, outside the submitted work. J.A. Stigt has received support for the present manuscript from Roche, Lilly and Amgen. B.E.E.M. van den Borne has received support for the present manuscript from Roche, Lilly and Amgen. H.J.M. Groen has received support for the present manuscript from Roche, Lilly and Amgen; grants or contracts from Roche and Boehringer Ingelheim, outside the submitted work; and consulting fees from Lilly, Novartis, Roche/Genentech and AstraZeneca, outside the submitted work. W.H. van Geffen has received support for the present manuscript from Roche, Lilly and Amgen; has unpaid roles for ERS and NVALT, outside the submitted work; and there have been trials run by his department funded by Roche and Amgen. A.J. van der Wekken has received support for the present manuscript from Roche, Lilly and Amgen; grants or contracts from AstraZeneca, Pfizer, Boehringer Ingelheim, Takeda and Roche, outside the submitted work; consulting fees from AstraZeneca, Novartis, Boehringer Ingelheim, Roche, Janssen, Pfizer, Lilly, Takeda and Merck, outside the submitted work; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Pfizer, outside the submitted work; and support for attending meetings and/or travel received from Lilly, outside the submitted work; and has a leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid, for CPCT, outside the submitted work.

Support statement: This study was partly financed by Roche, Lilly and Amgen. The NVALT Data Centre and Schmidt Consultancy provided central and peripheral data management. Funding information for this article has been deposited with the Crossref Funder Registry.

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