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Early View

Original research article

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Please cite this article as: Gijtenbeek RGP, van der Noort V, Aerts JGJV, *et al*. RCT of first-line TKI *versus* intercalated TKI with chemotherapy for EGFR mutated NSCLC. *ERJ Open Res* 2022; in press (https://doi.org/10.1183/23120541.00239-2022).

RCT of first-line TKI versus intercalated TKI with chemotherapy for EGFR mutated NSCLC

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Trial registration: EudraCT 2013-004303-39

This study was partly financed by Roche, Lilly, and Amgen. The NVALT Data Center and Schmidt Consultancy provided central and peripheral data management.

Take home message:

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 favorable due to higher toxicity rates.

Abstract

Introduction

Previous studies have shown interference between EGFR TKI and chemotherapy in the cell cycle, thus reducing efficacy. In this RCT we investigated whether intercalated erlotinib with chemotherapy was superior compared to erlotinib alone in untreated advanced EGFR mutated 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 (E). The primary endpoint was progression free survival (PFS). Secondary endpoints were overall survival (OS), objective response rate (ORR) and toxicity.

Results

Between April 2014 to September 2016 twenty-two patients were randomized equally into both arms, the study was stopped due to slow accrual. Median follow up was 64 months. Median PFS was 13.7 months (95%CI 5.2-18.8) for CPE and 10.3 months (95%CI 7.1-15.5, HR 0.62 (95%CI 0.25-1.57)) for E, when compensating for number of days receiving erlotinib, PFS of CPE arm was superior (HR 0.24 (95% CI 0.07-0.83; p=0.02)). ORR was 64% for CPE versus 55% for E. Median OS was 31.7 months (95%CI 21.8-61.9) for CPE compared to 17.2 months (95%CI 11.5-45.5) for E (HR 0.58 (95%CI 0.22-1.41)). 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.

Keywords:

Non-small cell lung cancer ; epidermal growth factor receptor, tyrosine kinase inhibitor, chemotherapy

1. Introduction

Since 2004, efforts to combine epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) and chemotherapy in patients with advanced NSCLC have been explored, starting with unselected NSCLC patients. Four randomized 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 et al. showed an improved progression free survival (PFS) in the combined arm in a randomized 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 [5, 6]. In 2020 Noronha et al. and Hosomi et al. reported in a phase III studies superior PFS and overall survival (OS) for concurrent gefitinib and carboplatin plus pemetrexed versus gefitinib alone as first-line treatment [7, 8]. 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 superior in PFS and OS, one of the concerns is the interference between EGFR TKI and chemotherapy in EGFR mutated advanced NSCLC that came from preclinical data where G1 cell cycle arrest due to EGFR TKI reduces cell cycle phase dependent 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]. Therefor, to enhance the treatment effect by avoiding such interfering effect, we designed a randomized phase III trial to demonstrate the superiority of first line treatment with cisplatin + pemetrexed with intercalated erlotinib (CPE) for day 2-16 in a 3-week cycle compared to continuous erlotinib monotherapy (E) in patients with advanced EGFR-mutated NSCLC, in terms of PFS, OS, objective response rate (ORR) and toxicity.

2. Material and methods

2.1. Study design

The NVALT 17 trial is a multicenter randomized controlled trial in patients with EGFR mutated advanced NSCLC, who have been randomized in equally to either CPE or E. Patients were enrolled from eight study centers in the Netherlands and treatment was assigned by participating center by means of a minimization technique stratifying for ECOG performance status (PS) (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 Center using the ALEA system. The study was approved by the Central Medical Ethical Committee of the University

Medical Center Groningen (nr. 2013/457), all patients gave informed consent before registration.

2.2. Eligibility Criteria

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

Patients who were at poor medical risks because of non-malignant disease or those with active uncontrolled infection were ineligible, as well as patients with symptomatic brain metastases unless local therapy was completed, and systemic corticosteroids had been discontinued at least two weeks before enrollment. 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 tumors 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.

2.3. Study procedures

Baseline evaluations were history including comorbidity, physical examination, blood counts, liver and renal function test and blood chemistry, electrocardiogram, computed tomography (CT) of the chest and abdomen, positron emission tomography (PET) or bone scan. Subsequent CT scan evaluations were performed every 6 weeks. Tumor response was assessed according to RECIST1.1 criteria.

2.4. Treatment protocol

Patients were randomized to four cycles of cisplatin 75mg/m^2 and pemetrexed 500mg/m^2 plus intercalated (day 2-16) erlotinib 150mg every 3 weeks followed by maintenance pemetrexed plus erlotinib (CPE) or to daily erlotinib 150mg (E) alone until disease progression. For comparability, both arms received folic acid 0,5mg daily and vitamin B12 1000µg intramuscular once every 6 - 9 weeks until disease progression.

All adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria version 4.0. At the start of each cycle, absolute neutrophil count had to be ≥1.5 x10^9/L and platelets ≥100 x 10^9/L. If applicable, chemotherapy dose was adjusted based on platelet (<50 x 10^9/L) and neutrophil nadir counts (<0.5 x 10^9/L) from the preceding cycle of therapy and maintained for subsequent cycles. In case of neurosensory toxicity ≥ grade 2 or creatinine clearance ≤60 ml/min, cisplatin dose was reduced. In the event of grade 3 diarrhea, the study therapy was not administered until resolved. For other non-hematologic effects ≥ CTC grade 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 (100mg or 50mg 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 CTC grade and be CTC Grade ≤2, otherwise further dose reduction by one level was required.

Study treatment was discontinued if a cycle was delayed for more than 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.

2.5. Outcomes

The primary endpoint was PFS defined as the time of random assignment to disease recurrence or death, whatever came first. Secondary endpoints included OS, 6-month and 1-year OS rate, ORR, toxicity, symptoms, and general health status. OS was measured from the date of randomization to the date of death. Duration of tumor response (DoR) 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 endpoints were analyzed using the Kaplan-Meier method. Toxicity was recorded according to Common Terminology Criteria for Adverse Events (CTCAE, version 4.0).

2.6. Statistical Analysis

The primary objective was to compare PFS between the CPE and E study arm. 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 more than 10% of patients, Fisher's exact test was used to compare the two arms.

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 one year of follow-up 112 events would be observed, providing 80% power to detect the specified increase in PFS at the 95% confidence level.

3. Results

3.1. Basic characteristics

A total of 150 patients had been scheduled to be enrolled during a five-year period starting April 2014. However, the trial was terminated prematurely in 2017 due to slow enrollment. During this period, only 22 patients were enrolled in the study, with 11 patients assigned to each arm. The last patient was included on September 12th, 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), females 55%. All patients had advanced disease and adenocarcinoma histology. 64% of patients had an exon 19 deletion and 23% an exon 21 L858R mutation (Table 1). In the CPE arm, median treatment length was 291 days (range 21 – 1031), compared to 324 days (range 57 – 932) in the E 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 E 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 E arm.

3.2. Tumor response and survival

ORR and DoR were not different between both arms; in the CPE-arm the ORR was 64% (7/11), time to best response was 49 days (IQR 44 – 90) with a median duration of response of 10.8 months. In the E arm, 55% of patients (6/11) responded to therapy with a median response duration of 8 months. The median time to best response was 68 days (IQR 47 - 148). The main endpoints are summarized in table 2.

PFS in patients treated with CPE was 13.7 months (95% CI 5.2 – 18.8) compared to 10.3 months (95% CI 7.1 – 15.5) in those treated with E (unstratified hazard ratio (HR) 0.62 (95% CI 0.25 – 1.57; p = 0.31)) (Figure 1A). With compensation for the number of days receiving erlotinib the PFS advantage of the CPE over the E arm became significant (HR 0.24 (95% CI 0.07 – 0.83; p = 0.02)).

Median OS for CPE and E was 31.7 months (95% CI 21.8 – 61.9) versus 17.2 months (95% CI 11.5 – 45.5, HR 0.55, (95% CI 0.22 − 1.41; p = 0.21)), respectively, with a 1-year survival rate of 100% (95% CI 72 − 100) for CPE versus 73% (95% CI 39 − 94) for E (Figure 1B).

3.3. 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 vs. 18%; p = 0.36), weight loss (18 vs. 0%; p = 0.48) and renal toxicity (27 vs. 0%; p = 0.21), while anorexia was significantly increased in the combination arm (55 vs 0%, p =

0.01, Appendix A). The number of reported grades 3 and 4 treatment related adverse events was also 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 at least 10% of patients or were grade ≥3 is shown in table 3.

Of the patients treated with CPE, six patients (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. Also, treatment interruptions for intercalated erlotinib occurred in three patients and dose reductions occurred five times in three patients. However, in the E arm no patient discontinued therapy because of toxicity, there were four treatment interruptions in three patients and dose reduction twice in one patient.

4. **Discussion**

In this study comparing alternating erlotinib with chemotherapy to exclude interfering effects between both treatments versus erlotinib alone, we found that PFS and OS was 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.

This 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 a significant improvement in PFS of 8 and respectively 9 months (pooled HR 0.50 (95% CI 0.43 - 0.58)) was observed, while the 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. Preclinical studies showed that TKI arrest tumor cells in a cell cycle phase that protect them from the cell cycle–specific cytotoxic agents as pemetrexed, reducing the activity of the chemotherapy [10]. Wu et al. 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 [11]. Next, Li et al. showed synergistic effect when pemetrexed was administered at least 8 hours before erlotinib [10]. 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 randomized 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 approximately four halve-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. Also, osimertinib and newer TKI will induce different resistant mechanism, both EGFR dependent or independent [14].

We reported a higher rate of treatment related toxicity among patients treated with CPE compared to E. 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 (3 patients, of whom 2 had grade 3) compared with previous trials assessing chemotherapy combined with EGFR TKI. Hosomi et al. reported that 25.3% of all patients treated with chemotherapy + TKI experienced a creatinine elevation, all grade 1-2 [8]. Noronha et al. reported 32 patients (19.5%) with renal dysfunction grade ≤3, of which 10 had grade 3 [7]. The higher rate of renal toxicity in our trial can 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 enrollment. As monotherapy TKI was already regular upfront therapy, we assume that many patients choose for 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 anti-cancer 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 generations 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 OS or PFS advantage in progressive pretreated 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) or osimertinib with or without chemotherapy (FLAURA2 / ClinicalTrials.gov Identifier: NCT04035486) are ongoing [19–21]. Future will learn whether early elimination of resistance clones is more effective with intercalating versus the concurrent approach.

5. 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 statistical different compared to concurrent regimens. This study supports therefore the hypothesis that CPE has a longer PFS than E monotherapy, but the combination of intercalated erlotinib with cisplatin and pemetrexed is not favorable over erlotinib alone due to toxicity. The results encourage further research combining chemotherapy with upcoming next generation EGFR treatments.

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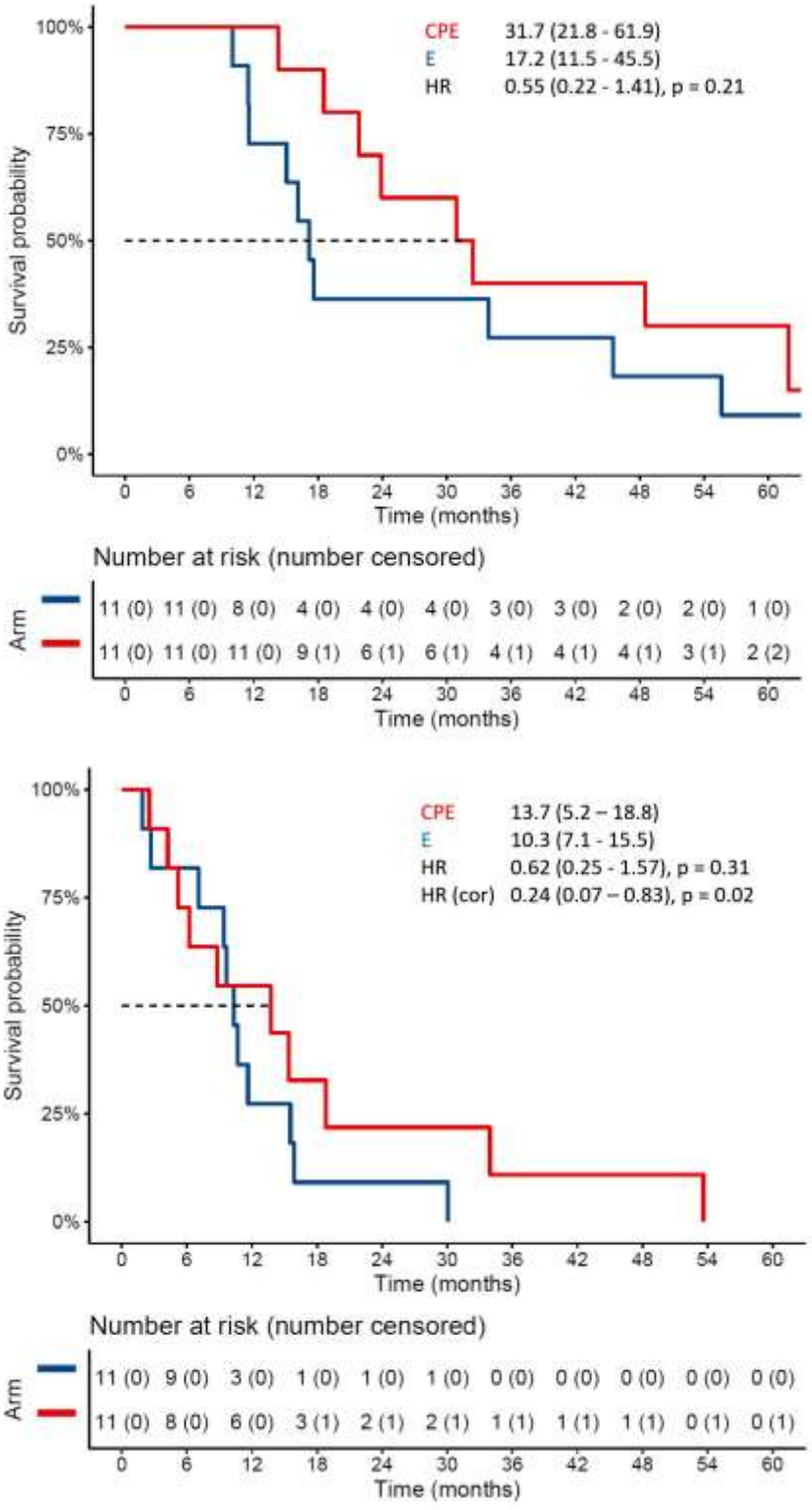

Figure 1 – A) Progression free survival and B) overall survival in months by treatment arm

Table 1 – Baseline patient characteristics

	CPE	E	All
Number of patients	11	11	22
Age (median (IQR))	60 (58 - 64)	67 (62 - 68)	64 (59-68)
Male gender (n (%))	5 (45)	5 (45)	10 (45)
Performance score			
0 (n (%))	8 (73)	7 (64)	15 (68)
1 (n (%))	3 (27)	4 (36)	7 (32)
Smoking			
Never smoker (n (%))	6 (55)	2 (18)	8 (36)
Former smoker (n (%))	5 (45)	5 (45)	10 (45)
Current smoker (n (%))	0 (0)	4 (36)	4 (18)
Pack years (median (IQR))	15 (9 - 15)	14 (6 - 19)	
Stage IV (n (%))	11 (100)	11 (100)	22 (100)
Non-squamous (n (%))	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)
Others	2 (18)	1 (9)	3 (13)

E: erlotinib, CPE: cisplatin-pemetrexed-erlotinib, IQR: interquartile range

Table 2 – Outcome measures by treatment arm

	CPE		**E**		
		95% CI		95% CI	HR (95% CI)
Randomized (n)	11		11		
PFS (median)	13.7	5.2 – 18.8	10.3	7.1 - 15.5	0.62 (0.25 - 1.57)*
OS (median)	31.7	21.8 - 61.9	17.2	11.5 - 45.5	0.55 (0.22 - 1.41)
1-year OS (%)	100	72 - 100	73	39 - 94	
ORR (%)	64	31 - 89	55	23 - 83	
CR (n (%))	1 (9)		1 (9)		
PR (n (%))	6 (54)		5 (46)		
SD (n (%))	4 (36)		5 (46)		
Duration of response (median)	10.8	7.3 – 31.2	8.0	5.5 - 8.7	0.43 (0.12 - 1.47)

* after compensating for numbers of days receiving erlotinib HR 0.24 (95% CI 0.07 – 0.83; p = 0.02).

E: erlotinib, CPE: cisplatin-pemetrexed-erlotinib, CI: confidence interval, HR: hazard ratio, PFS: progression free survival, OS: overall survival, ORR: overall response rate, CR: complete response, PR: partial response, SD: stable disease, NR: not reached

Table 3 – Number of treatment related adverse events with incidence ≥10% or grade ≥3

	All grades			≥ grade 3 *	
	CPE	**E**	**p-value**	**CPE**	**E**
Abdominal pain	1	1		0	0
Alopecia	2	0	0.48	0	0
Anemia	1	0		0	0
Anorexia	6	0	0.01	1	0
Diarrhea	3	1	0.59	1	0
Dry skin	5	4	1.00	0	0
Dry eyes	0	1		0	0
Fatigue	5	2	0.36	1	0
Hypocalcemia	1	0		1	0
Hypomagnesemia	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

E: erlotinib, CPE: cisplatin-pemetrexed-erlotinib

* Due to limited sample size, no statistical analysis was performed for events ≥ grade 3.

Appendix A

Adverse events that were deemed possibly, probably or certainly related to treatment.

	All grades			Grades 3-4			Grade 5		
	Erlo 11	CPE 11	All 22	Erlo 11	CPE 11	All 22	Erlo 11	CPE 11	All 22
Alopecia	0	2	2	0	0	0	0	0	0
Anemia	0	1	1	0	0	0	0	0	0
Anorexia	0	6	6	0	1	1	0	0	0
Diarrhea	1	3	4	0	1	1	0	0	0
Dry mucous	0	1	1	0	0	0	0	0	0
Dry skin	4	5	9	0	0	0	0	0	0
Eye disorders: blepharitis	1	1	2	0	0	0	0	0	0
Eye disorders: blurred vision	0	1	1	0	0	0	0	0	0
Eye disorders: burning eyes	0	1	1	0	0	0	0	0	0
Eye disorders: dry eyes	1	0	1	0	0	0	0	0	0
Eye disorders: teary eyes	0	1	1	0	0	0	0	0	0
Fatigue	2	5	7	0	1	1	0	0	0
Fissures	1	0	1	0	0	0	0	0	0
Folliculitis	0	1	1	0	0	0	0	0	0
Hemorrhage: nos	1	0	1	0	0	0	0	0	0
Hypocalcemia	0	1	1	0	1	1	0	0	0
Hypomagnesemia	0	1	1	0	1	1	0	0	0
Infection: eye	1	0	1	0	0	0	0	0	0
Infection: eyelids	1	0	1	0	0	0	0	0	0
Infection: nail infection	1	0	1	0	0	0	0	0	0
Infection: nails	6	1	7	0	0	0	0	0	0
Malaise	0	1	1	0	0	0	0	0	0
Menopausal/Stopped mentruating	0	1	1	0	0	0	0	0	0
Mouth ulcers	0	1	1	0	0	0	0	0	0
Mucositis: nose	0	1	1	0	1	1	0	0	0
Mucositis: oral	0	1	1	0	0	0	0	0	0
Nausa	1	2	3	0	1	1	0	0	0
Neutrophil count decreased	0	1	1	0	1	1	0	0	0
Pain: abdominal	1	1	2	0	0	0	0	0	0
Pain: nails	1	0	1	0	0	0	0	0	0
Pain: skin	1	0	1	0	0	0	0	0	0
Peripheral sensoral neuropathy	0	2	2	0	0	0	0	0	0
Pimpels	1	0	1	0	0	0	0	0	0
Pimpels and redness under eyelids	0	1	1	0	0	0	0	0	0
Pruritis	1	1	2	1	0	1	0	0	0
Rash	1	1	2	0	0	0	0	0	0
Rash acneiform	8	6	14	0	1	1	0	0	0
Renal disorders: real	0	3	3	0	2	2	0	0	0

insufficiency									
Skin disorders: gorges	1	0	1	0	0	0	0	0	0
Skin peels	0	1	1	0	0	0	0	0	0
Thickened skin	1	0	1	0	0	0	0	0	0
WBC decreased	0	1	1	0	0	0	0	0	0
Weight loss	0	2	2	0	0	0	0	0	0