Cancer Chemother Pharmacol (2014) 73:451–457
DOI 10.1007/s00280-013-2370-z

ORIGINAL ARTICLE

# A phase II trial of erlotinib as maintenance treatment after concurrent chemoradiotherapy in stage III non-small-cell lung cancer (NSCLC): a Galician Lung Cancer Group (GGCP) study

**J. Casal Rubio · J. L. Fírvida-Pérez · M. Lázaro-Quintela · F. J. Barón-Duarte · G. Alonso-Jáudenes · L. Santomé · F. J. Afonso-Afonso · M. Amenedo · G. Huidobro · B. Campos-Balea · M. D. López-Vázquez · S. Vázquez**

Received: 3 October 2013 / Accepted: 11 December 2013 / Published online: 19 December 2013


**Abstract**
*Purpose* This single arm, phase II study aims to evaluate the role of epidermal growth factor receptor–tyrosine-kinase inhibitor erlotinib as maintenance therapy following concurrent chemoradiotherapy (cCRT) in unresectable locally advanced non-small-cell lung cancer (NSCLC).
*Methods* Patients with unresectable stage IIIA o dry IIIB NSCLC with no evidence of tumor progression after receiving a standard cCRT regimen with curative intent were included. Oral erlotinib 150 mg/day was administered within 4–6 weeks after the end of the cCRT for a maximum of 6 months if no disease progression or intolerable toxicity occurred. Primary end point was the progression-free rate (PFR) at 6 months. Secondary end points included time to progression (TTP) and overall survival (OS).
*Results* Sixty-six patients were enrolled and received maintenance treatment with erlotinib [average: 4.5 months (95 % CI 4.0–5.0)]. PFR at 6 months was 63.5 % (41/66). With a median follow-up of 22.7 months (95 % CI 13.5–37.1), the median TTP was 9.9 months (95 % CI 6.2–12.1), and the median OS was 24.0 months (95 % CI 17.3–48.6). Most common adverse events (AEs) related to erlotinib were rash (78.8 %; 16.7 % grade 3), diarrhea (28.8 %; 1.5 % grade 3), fatigue (15.2 %; 1.5 % grade 3), anorexia (7.6 %; 1.5 % grade 3) and vomiting (4.6 %; none grade 3). Five patients (7.6 %) were withdrawn due to AEs.

This study is conducted on behalf of the Galician Lung Cancer Group (GGCP).

ClinicalTrials.gov Identifier: NCT00466284.

J. Casal Rubio · M. Lázaro-Quintela · G. Huidobro
Medical Oncology Department, Complexo Hospitalario Universitario de Vigo (CHUVI), Vigo, Spain

J. Casal Rubio (✉)
Medical Oncology Service, Complexo Hospitalario Universitario de Vigo, Avda. Camelias, 106—Hospital Nicolás Peña, 36211 Vigo, Spain
e-mail: joaquin.casal.rubio@sergas.es

J. L. Fírvida-Pérez
Medical Oncology Department, Complexo Hospitalario de Ourense (CHOU), Ourense, Spain

F. J. Barón-Duarte
Medical Oncology Department, Complexo Hospitalario Universitario de Santiago (CHUS), Santiago de Compostela, Spain

G. Alonso-Jáudenes
Medical Oncology Department, Complexo Hospitalario Universitario A Coruña (CHUAC), A Coruña, Spain

L. Santomé
Medical Oncology Department, Hospital Povisa, Vigo, Spain

F. J. Afonso-Afonso
Medical Oncology Department, Complexo Hospitalario Arquitecto Marcide-Novoa Santos, Ferrol, Spain

M. Amenedo
Centro Regional Oncológico de Galicia, A Coruña, Spain

B. Campos-Balea · S. Vázquez
Medical Oncology Department, Hospital Universitario Lucus Augusti (HULA), Lugo, Spain

M. D. López-Vázquez
Radiation Oncology Department, Complexo Hospitalario de Ourense (CHOU), Ourense, Spain

*Conclusions* Erlotinib as maintenance therapy is an active treatment after cCRT in unselected patients with stage III NSCLC, reaching a 6-month PFR of 63.5 % and a median OS of 24 months. The safety profile of maintenance erlotinib was as expected and manageable.

**Keywords** Non-small-cell lung cancer · Erlotinib · Maintenance chemotherapy · Stage III disease

## Introduction

Lung cancer is the most frequent cause of cancer-related deaths in men (951,000 cases) and the second one in women (427,400 cases) worldwide, and its incidence and mortality are gradually increasing [1]. Non-small-cell lung cancer (NSCLC) accounts for nearly 85 % of all cases of lung cancer, with over 30 % of NSCLC patients being diagnosed at a locally advanced stage (stage III), which may render them inoperable [2]. In the 7th edition of TNM classification, the stage III tumors (locally advanced) were reviewed comprising a heterogeneous group of tumors from T1 to T4 and from N0 to N3 [3] though the overall treatment guidelines are not affected [4].

Locally advanced NSCLC that is not amenable to surgical resection is treated with combined modality therapy involving systemic chemotherapy plus radiotherapy (RT), which is associated with improvement in overall survival (OS) compared with RT alone [5]. Moreover, concurrent chemoradiotherapy (cCRT) has demonstrated a greater survival benefit, albeit with a higher toxicity, when compared with a sequential approach [6–8]. Particularly, platinum-based cCRT is the standard treatment for patients with unresectable stage III NSCLC, with an expected median OS of 17 months and 5-year survival rates of ≤15 % [6, 8–11], but is associated with high rates of recurrence and offers a room for improvement.

New potential therapeutic strategies, including targeting epidermal growth factor receptor (EGFR) and other signal transduction or angiogenesis pathways, have being added into current standard treatment to delay cancer progression and improve survival for advanced/metastatic stage NSCLC [12]. Particularly, erlotinib (Tarceva®; Hoffmann-La Roche Inc), an oral EGFR tyrosine-kinase inhibitor (TKI), has demonstrated to prolong survival as maintenance therapy in patients with stage wet IIIB/IV NSCLC after it has been successfully controlled by the appropriate first-line combination therapy in two randomized phase III studies (SATURN and IFCT-GFPC0502 studies) [13, 14]. In fact, based on the SATURN study [13], erlotinib has been approved as maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. Nevertheless, when our study was initiated, the experience for locally advanced (stage III) NSCLC was limited, and although being awaited with interest, the results from the phase III studies in advanced/metastatic stages were not available.

In addition, erlotinib has demonstrated to have radiosensitizing effects in NSCLC cells [15, 16], which improves local tumor control after RT combined with the EGFR–TKI [17]. As the irradiation effects are usually maintained for some time, the administration of maintenance erlotinib as single agent immediately after the completion of cCRT in locally advanced NSCLC patients would maintain the clinical benefit obtained without adversely affecting patient's quality of life as a result of its oral administration and manageable toxicity.

Based on these evidences, the Galician Lung Cancer Group (GGCP) conducted this open-label, non-randomized, single arm, multicenter, phase II study which was aimed to assess the efficacy and safety of erlotinib as maintenance therapy in stage III NSCLC patients achieving disease control after radical treatment with a cCRT combined modality therapy with the intention to reduce recurrence and improve OS rates.

## Patients and methods

### Patient eligibility

Patients with histologically confirmed unresectable stage IIIA–IIIB (without malignant pleural effusion) NSCLC not selected by activating EGFR mutation, who had completed a standard cCRT regimen with curative intention within 4–6 weeks and with no evidence of tumor progression, were enrolled at selected centers belonging to Spanish GGCP group. Other eligibility criteria included patients aged ≥18 years old, with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2 and adequate bone marrow, hepatic and renal functions. Previous exposure to anti-EGFR agents or concomitant treatment with another antineoplasic agent was not allowed. Patients were excluded if they had uncontrolled serious concomitant disease and clinically significant ophthalmologic or gastrointestinal abnormalities (e.g., malabsorption syndrome).

The study was performed after approval by an Independent Ethics Committee of each site and in accordance with the Declaration of Helsinki, good clinical practices and local ethical and legal requirements. Signed informed consent was obtained from all patients before study entry.

### Treatment plan and dose modifications

Eligible patients received treatment with oral erlotinib 150 mg/day within 4–6 weeks after the end of the cCRT

and for a maximum of 6 months if no disease progression or unacceptable toxicity occurred before.

In case of adverse events (AEs) not controlled with the suitable support treatment, dose reductions (in decrements of 50 mg up to a final dose of 50 mg) and interruptions (for ≤2 weeks) were permitted, at the investigator's discretion. Once a patient's dose was reduced, it was not subsequently increased.

Criteria for protocol discontinuation included withdrawal of informed consent, progressive disease, limiting toxicity, the investigator considers that the patient is not obtaining any benefit from the treatment or need of other antineoplasic agents not specified in the protocol.

### Efficacy and safety assessments

A complete medical history and physical examination including PS, laboratory analysis, pulmonary function tests and ECG and radiography of the thorax were required prior to initiating study treatment. Baseline computed tomography scans of the chest and abdomen were required at least 4 weeks before study entry. Medical history and physical examination including PS, vital signs assessments and routine laboratory analysis were repeated every month until end-of-study visit, which occurred 30 days after the end of study treatment.

Radiological assessments of tumor response by computed tomography scan were performed every 2 months until the end-of-study visit. The same tumor assessment technique was used throughout the study. Responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.0) [18]. After completion of study treatment, patients with no disease progression, i.e., with either stable disease (SD), complete response (CR) or partial response (PR), were followed every 3 months until disease progression and/or death (whichever occurred first).

Adverse events were classified by National Cancer Institute Common Toxicity Criteria for AEs (NCI-CTCAE) version 3.0. Patients were evaluated for AEs during erlotinib therapy and until 30 days after the last study drug dose. AEs considered related to study medication were followed until resolution or death.

### Statistical analysis

The primary objective was to determine the progression-free rate (PFR) at 6 months, i.e. percentage of patients without disease progression (CR + PR + SD) at 6 months of starting treatment with erlotinib. Assuming a minimum PFR of 30 %, we proposed an achievement of a 45 % PFR with erlotinib at 6 months, at a level of significance of 95 % (alpha error = 0.05) and a statistical power of 80 % ($\beta$ error = 0.20). An optimal two-stage design as described by Simon was used [19], requiring the enrollment of 46 patients in the first stage and an additional number of patients in the second stage to achieve the minimum foreseen 66 evaluable patients.

Secondary end points included time to progression (TTP) and OS, overall response rate (ORR) and safety. TTP was measured from date of first erlotinib dose until disease progression or death due to progression. OS was measured from date of first erlotinib dose until death from any cause. We used the Kaplan–Meier method to estimate TTP and OS. All efficacy analyses were performed on an intention-to-treat (ITT) basis. A stratified analysis was done to select prognostic factors (age, tumor histology, ECOG PS and smoking status) related to time to event (TTP and OS), and log-rank was used for testing differences. A Cox proportional hazard models were used to analyze the prognostic effect of the resulting significant factors on TTP. The statistical software package used was SAS® version 9.2.

## Results

### Patients and eligibility

From April 2006 to September 2009, 66 patients were enrolled into the study at 9 sites in Spain (Fig. 1). The date of data cutoff was February 20, 2012. Baseline characteristics are summarized in Table 1; 72.7 % of tumors were stage IIIA (1 T3N1 + 16 T1-3N2) and IIIB (34 T4N0 + 10 T1–3 N3 + 5 T4 N3), respectively. All patients had received cCRT as part of initial radical treatment, which commonly consisted in a platinum/taxane combination (86.4 %) plus thoracic RT. Most patients (51 out of 66 patients) received

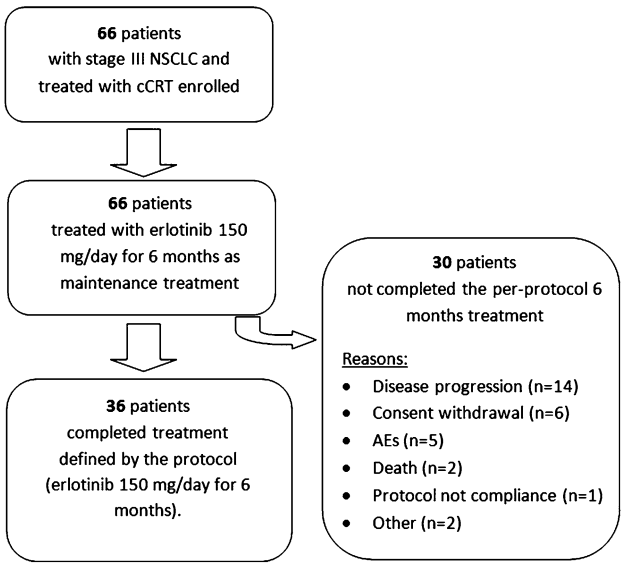


**Fig. 1** Study flowchart

**Table 1** Patient demographics ($N = 66$)

| Characteristics | Patients ($N = 66$) |
|---|---|
| Gender, *n* (%) | |
| Men | 60 (90.9) |
| Race, *n* (%) | |
| Caucasian | 66 (100.0) |
| Age (years) | |
| Median (range) | 61.5 (41.0–79.0) |
| Performance Status (ECOG)[1], *n* (%) | |
| 0 | 21 (31.8) |
| 1 | 40 (60.6) |
| 2 | 1 (1.5) |
| Smoking status[2], *n* (%) | |
| Current smoker | 14 (21.2) |
| Past smoker | 45 (68.2) |
| Never smoker | 2 (3.0) |
| Disease stage, *n* (%) | |
| IIIA | 18 (27.3) |
| IIIB | 48 (72.7) |
| Histology, *n* (%) | |
| Adenocarcinoma | 15 (22.7) |
| Squamous cell carcinoma | 42 (63.6) |
| Large cell carcinoma | 7 (10.6) |
| Other | 1 (1.5) |
| Unknown | 1 (1.5) |
| Prior cCRT, *n* (%) | |
| Platinum + taxane | 56 (84.8) |
| Platinum + gemcitabine | 4 (6.1) |
| Platinum + other QT | 5 (7.6) |
| Gemcitabine–taxane | 1 (1.5) |
| Best response to previous chemotherapy, *n* (%) | |
| CR | 5 (7.6) |
| PR | 53 (80.3) |
| SD | 8 (12.1) |

*cCRT* concurrent chemoradiotherapy; *ECOG* Eastern Cooperative group; *CR* complete response; *PR* partial response; *SD* stable disease

[1] Missing data in four patients

[2] Missing data in five patients

induction CT prior to cCRT, being cisplatin + docetaxel the most frequent CT regimen used. Median prior thoracic RT dose received was 61.2 Gy [interquartile range (IQR) 41.1–66.6 Gy]. At the starting of the study, most patients (80.3 %) had achieved a PR as best response to initial radical treatment.

## Treatment exposure

All 66 patients received maintenance treatment with erlotinib. Average duration of erlotinib treatment was 4.5 months (95 % CI 4.0–5.0). Thirty-six patients (54.6 %) completed maintenance erlotinib per-protocol, with 12 patients receiving the erlotinib dose with modifications and/or delays. Causes for erlotinib temporary discontinuation or dose reduction were AEs in 10 patients and dosing errors in 2 patients.

Reasons for not completing the per-protocol 6 months of maintenance erlotinib were as follows: disease progression ($n = 14$), patient's consent withdrawal ($n = 6$), AEs ($n = 5$), death ($n = 2$), protocol violation ($n = 1$) and other causes ($n = 2$).

At disease progression, 41 patients (out of 53 patients) received additional CT ($n = 35$) or RT ($n = 6$). Pemetrexed ($n = 23$), gemcitabine ($n = 13$), vinorelbine ($n = 15$) or docetaxel ($n = 9$) were the CT drugs most commonly used.

## Treatment responses

All 66 patients were included in the intent to treat analysis. At 6 months after starting erlotinib treatment, there were 63.5 % of patients (41/66) without disease progression (PFR at 6 months).

In the 66 patients, CR was observed in seven (10.6 %) patients and PR in 12 (18.2 %) patients. Thus, an ORR of 28.8 % was achieved. A total of 34 patients (51.5 %) had SD as their best response, while disease progression was observed in 11 (16.7 %) patients. Two patients were not evaluable for response due to nonexistence of response assessment ($n = 1$) or protocol violation ($n = 1$).

## TTP and OS

With a median follow-up time of 22.7 months (95 % CI 13.5–37.1), the median TTP was 9.9 months (95 % CI

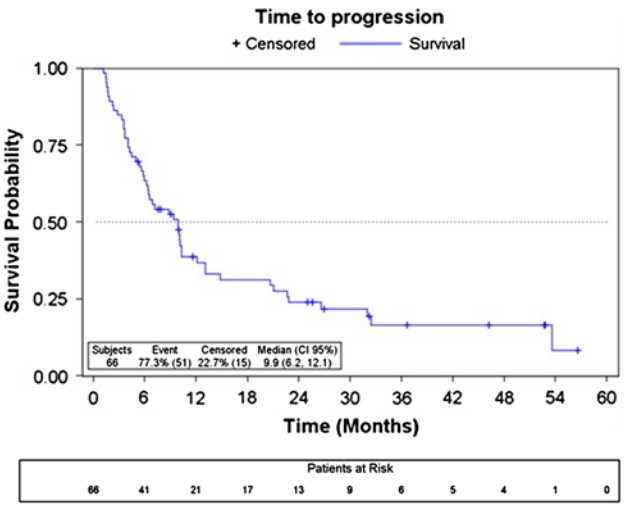


**Fig. 2** Time to progression

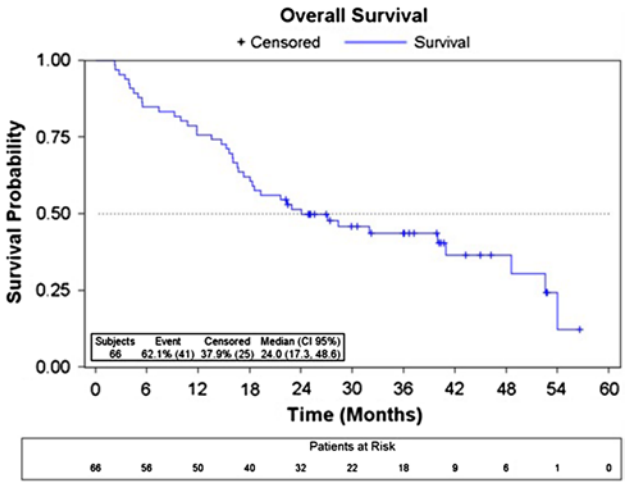


**Fig. 3** Overall survival

6.2–12.1 months; Fig. 2). The median OS was 24.0 months (95 % CI 17.3–48.6 months; Fig. 3) for the ITT population. The prognostic factors analyzed were age, tumor histology, ECOG PS and smoking status (Table 2). To be current smoker (vs. past smoker) was identified as a risk factor for disease progression using the Cox regression analysis [$p = 0.0199$, HR 0.422, IC (0.204; 0.873)].

## Toxicity

All 66 patients received at least one dose of study treatment and were included in the safety analysis. A total of 212 AEs were reported during the study, 118 of which were considered related to study medication. At least one AE was reported in 66 patients. A summary of the most common treatment-related AEs per patient is shown in Table 3.

**Table 3** Most common (>5 %) treatment-related AEs and grade 3/4 treatment-related AEs per patient according to NCI-CTC grade ($n = 66$)

| NCI-CTCAE toxicity, *n* (%) | Overall ($n = 66$) | | | | |
|---|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Total |
| Rash* | 23 (34.9) | 18 (27.3) | 11 (16.7) | – | 52 (78.8) |
| Diarrhea | 17 (25.8) | 1 (1.5) | 1 (1.5) | – | 19 (28.8) |
| Fatigue | 6 (9.1) | 3 (4.6) | 1 (1.5) | – | 10 (15.2) |
| Anorexia | 2 (3.1) | 2 (3.1) | 1 (1.5) | – | 5 (7.6) |
| Vomiting | 1 (1.5) | 2 (3.1) | – | – | 3 (4.6) |
| Upper respiratory infection | – | – | 1 (1.5) | – | 1 (1.5) |
| Bronchial obstruction | – | – | 1 (1.5) | – | 1 (1.5) |

*NCI-CTCAE* National Cancer institute Common Toxicity Criteria

* Verbatim terms included under rash: rash acneiform; dermatitis; skin eruption; facial exanthema; folliculitis; skin toxicity

Grade 3 treatment-related AEs were reported in 14 (21.2 %) patients. The most frequently observed grade 3 treatment-related AE by patient was rash (16.7 %). No treatment-related grade 4 AEs was reported. Erlotinib-related serious AEs were seen in 3 patients.

Five (7.6 %) patients discontinued treatment due to AEs. The main reasons for the discontinuation were dyspnea ($n = 2$); rash ($n = 1$); vomiting, anorexia and diarrhea ($n = 1$); and asthenia and anorexia ($n = 1$) which were considered treatment-related in two patients (vomiting, anorexia and diarrhea in one patient; and rash in one patient).

Two patients died during the study treatment due to disease progression. None died within the first 60 days of the study. No treatment-related deaths were reported.

**Table 2** Prognostic factors related to TTP and OS ($n = 66$)

| Variable | Time to progression (months) | | Overall survival (months) | |
|---|---|---|---|---|
| | Median (95 % CI) | | Median (95 % CI) | |
| Age | | | | |
| ≤60 | 5.9 (3.7; 10.3) | $p = 0.1389$ | 22.3 (11.8; 52.5) | $p = 0.3$ |
| >60 | 10 (6.5; 22.6) | | 32.0 (17.3; NA) | |
| Histology | | | | |
| squamous | 6.9 (5.6; 13.1) | $p = 0.7571$ | 23.2 (16.7; 40.9) | $p = 0.5$ |
| Non-squamous | 10 (4.2; 21.1) | | 48.6 (15.6; 48.6) | |
| ECOG | | | | |
| 0 | 10 (4.9; 21.1) | $p = 0.6576$ | 27.1 (13.5; 52.5) | $p = 0.9$ |
| 1 or 2 | 9.9 (6.2; 13.1) | | 22.3 (15.6; 48.6) | |
| Past smoker | | | | |
| Yes | 10.1 (6.4; 14.8) | $p = 0.02$* | 39.9 (18.5; 52.5) | $p = 0.004$* |
| No | 4.6 (1.7; 9.9) | | 10.4 (3.4; 32.0) | |

* Statistically significant according to log-rank test

## Discussion

When our study was initiated, the standard of care for unresectable stage III NSCLC was the administration of 2–4 cycles of cCRT followed by the observation of patient until disease progression. Expected median OS was about 17 months, with 5-year survival rates of ≤15 % [6, 8]. Thus, this single arm, phase II study was designed to assess if erlotinib was able to prolong PFS and OS in patients with advanced NSCLC who has not progressed after initial treatment with a standard platinum-based cCRT regimen with curative intent.

Our study met its primary objective, observing that 63.5 % of patients continued progression-free 6 months after starting erlotinib treatment. Moreover, secondary efficacy results, TTP (median: 9.9 months) and OS (median: 24.0 months), were reasonable. Maintenance treatment with erlotinib assured that systematic second-line CT was given in almost all (77.4 %, 41 out of 53) patients who observed progression after initial therapy. Although comparisons over time and studies may be problematic, survival rates seem to be in line to those observed by Rigas et al. [20] in a randomized, placebo-controlled phase III study (D0410 study) in patients with unresectable stage III NSCLC following cCRT. The study preliminary results in 223 patients found a trend in benefit for maintenance erlotinib versus placebo for mean TTP (13.5 vs. 10.4 months) and OS (30.4 vs. 25.1 months), but neither difference was statistically significant. The results from this study were not conclusive because the study was closed very prematurely for reasons of poor recruitment.

Noteworthy, most patients included in our study were males (90.9 %) with squamous cell carcinoma histology (63.1 %) which are factors not favorable for erlotinib efficacy [21]. Despite these unfavorable features, the open design of our study or good baseline characteristics of patients (e.g., 92.3 % patients with ECOG PS 0/1) following initial therapy might have contributed favorably to the good results observed in our study.

Even if a subgroup analysis by smoking status, sex, squamous histology or age might have been of interest, our study was not powered enough to draft any conclusion from these subgroup analysis. Actually, in the analysis of the prognostic factors, only a statistically significant difference was noted for former smokers.

A subgroup analysis by EGFR mutation status might have been done in view of the larger survival benefit for patients with EGFR mutation-positive tumors observed in other studies such as the SATURN trial [13]. However, since that biomarker analysis was not mandatory when our study was initiated, EGFR mutation status was not analyzed.

Nowadays, the use of the word “maintenance” or “consolidation” therapy is a matter of debate, as it is the choice and the duration of the maintenance agent [22]. To date, the results from studies in the localized stages of NSCLC patients have been unsatisfactory [23–26]. A median OS of 26 months and a 3-year survival rate of 37 % were achieved with cCRT followed by consolidation with docetaxel, inoperable stage III NSCLC patients in a phase II study by Gandara et al. [24] (SWOG 9504). However, a subsequent randomized phase III study of consolidation with docetaxel (HOG LUN 01-24/USO-023) [25] failed to demonstrate an improvement in survival over the control arm (observation). A recent randomized phase III study with paclitaxel as additional maintenance therapy versus observation after cCRT found similar results, with survival results favoring the standard arm (26.9 months) [23]. Similarly, a phase III study of maintenance treatment with gefitinib (SWOG S0023) in inoperable stage III NSCLC patients failed to demonstrate an improvement in survival over placebo (with a median survival of 23 compared with 35 months (HR 0.63, 95 % CI 0.44–0.91; $p = .013$) [26]. Finally, no survival advantage has been observed for consolidation chemotherapy with vinorelbine plus cisplatin and best supportive care (BSC) over BSC alone after definitive therapy with cCRT in a phase III study in locally advanced NSCLC patients recently presented at the 2012 ASCO meeting [27].

In our study, a mean OS of 24 months and the observed high rate of progression-free patients at 6 months substantiate the efficacy of erlotinib as maintenance treatment in patients with locally advanced NSCLC, being a useful hypothesis generator for further larger well-controlled studies. Noteworthy, treatment duration in our study is limited to 6 months, whereas treatment duration is around 2 years in the other studies in inoperable stage III NSCLC patients [20, 24–26]. Future studies might consider the prolongation of the maintenance treatment with erlotinib beyond 6 months.

Side effects of erlotinib treatment were generally less severe than with conventional cytotoxic CT such as intravenous CT. The most common AEs were rash (78.8 %) and diarrhea (28.8 %), which were within the rates reported in other studies with erlotinib in monotherapy (*prescribing information for Tarceva*). Grade 3 treatment-related rash and diarrhea occurred in 16.7 and 1.5 % of patients, respectively. However, rash and diarrhea resulted in study discontinuation in one patient (1.5 %) each. The incidence of skin rashes in patients treated with EGFR inhibitors varies from 50 to 100 %, depending on the agent and cancer type, and the median onset tends to be within 1–2 weeks of the start of therapy [28]. Some researchers have shown that erlotinib-induced skin rashes may be linked to a survival advantage [29]. The advantage of erlotinib is that the toxicity generally decreases over time and is not cumulative, which may overcome the undesirable cumulative toxicity caused by cytotoxic agents administered in first-line setting. In addition, erlotinib has a more convenient oral administration for patients.

In conclusion, single agent erlotinib as maintenance therapy is an active treatment after cCRT in patients with stage III NSCLC, reaching a PFR of 63.5 % at 6 months and a promising median OS of 24 months. The safety profile of maintenance erlotinib was as expected and manageable.

**Acknowledgments** This study was supported by Roche Farma S.A., Madrid, Spain.

**Conflict of interest** The authors declare not having conflict of interest regarding this study.

## References


1. Jemal A, Bray F, Center MM et al (2011) Global cancer statistics. CA Cancer J Clin 61:69–90
2. Crino L, Weder W, van Meerbeeck J et al (2010) Early stage and locally advanced (non-metastatic) non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 21(Suppl 5):v103–v115
3. American Joint Committee on Cancer (2010) TNM classification of malignant tumours, lung. In: Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A (eds) American Joint Committee on Cancer: AJCC cancer staging manual, 7th edn. Springer, New York, pp 253–270
4. Ramalingam SS, Owonikoko TK, Khuri FR (2011) Lung cancer: new biological insights and recent therapeutic advances. CA Cancer J Clin 61:91–112
5. Auperin A, Le PC, Rolland E et al (2010) Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 28:2181–2190
6. Auperin A, Pechoux C, Pignon J et al (2006) Concomitant radiochemotherapy base on platin compounds in patients with locally advanced non-small-cell lung cáncer (NSCLC): a meta-analysis of individual data from 1764 patients. Ann Oncol 17:473–483
7. Curran WJ Jr, Paulus R, Langer CJ et al (2011) Sequential vs concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst 103:1452–1460
8. O'Rourke N, Roque IF, Farre BN et al (2010) Concurrent chemoradiotherapy in non-small cell lung cancer. Cochrane Database Syst Rev CD002140
9. Vokes EE, Herndon JE, Crawford J et al (2002) Randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage III non-small-cell lung cancer: Cancer and Leukemia Group B study 9431. J Clin Oncol 20:4191–4198
10. Yamammoto N, Nakagawa K, Nishimura Y et al (2010) Phase III study comparing second and third generation regimens with concurrent Thoracic Radiotherapy in patients with unresectable stage III non-small-cell lung cáncer: West Japan Thoracic Oncology Group WJTOG0105. J Clin Oncol 28:3739–3745
11. Huber RM, Flentje M, Schmidt M et al (2006) Simultaneous chemoradiotherapy compared with radiotherapy alone after induction chemotherapy in inoperable stage IIIA or IIIB non-small-cell lung cancer: study CTRT99/97 by the Bronchial Carcinoma Therapy Group. J Clin Oncol 24(27):4397–4404
12. Rivera S, Quero L, Wong Hee KS et al (2011) Targeted therapies and radiation therapy in non-small cell lung cancer. Cancer Radiother 15:527–535
13. Cappuzzo F, Ciuleanu T, Stelmakh L et al (2010) Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol 11:521–529
14. Perol M, Chouaid C, Perol D et al (2012) Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 30:3516–3524
15. Kim JC, Ali MA, Nandi A et al (2005) Correlation of HER1/EGFR expression and degree of radiosensitizing effect of the HER1/EGFR-tyrosine kinase inhibitor erlotinib. Indian J Biochem Biophys 42:358–365
16. Wang M, Morsbach F, Sander D et al (2011) EGF receptor inhibition radiosensitizes NSCLC cells by inducing senescence in cells sustaining DNA double-strand breaks. Cancer Res 71:6261–6269
17. Sacco PC, Maione P, Rossi A et al (2011) Combination of radiotherapy and targeted therapies in the treatment of locally advanced non-small cell lung cancer. Target Oncol 6:171–180
18. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
19. Simon R (1989) Optimal two-stage designs for phase II clinical trials. Control Clin Trials 10:1–10
20. Rigas JR, Carey MA, Rubin MS (2009) Efficiency of maintenance erlotinib versus placebo in patients with unresectable stage III non-small lung cancer (NSCLC) following concurrent chemoradiation (D0410, NCT00153803). J Thoracic Oncol 4:S371
21. Petrelli F, Borgonovo K, Cabiddu M et al (2011) Erlotinib as maintenance therapy in patients with advanced non-small cell lung cancer: a pooled analysis of three randomized trials. Anticancer Drugs 22:1010–1019
22. Novello S, Milella M, Tiseo M et al (2011) Maintenance therapy in NSCLC: why? To whom? Which agent? J Exp Clin Cancer Res 30:50
23. Carter DL, Garfield D, Hathorn J et al (2012) A randomized phase III trial of combined paclitaxel, carboplatin, and radiation therapy followed by weekly paclitaxel or observation for patients with locally advanced inoperable non-small-cell lung cancer. Clin Lung Cancer 13:205–213
24. Gandara DR, Chansky K, Albain KS et al (2003) Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non-small-cell lung cancer: phase II Southwest Oncology Group Study S9504. J Clin Oncol 21:2004–2010
25. Hanna N, Neubauer M, Yiannoutsos C et al (2008) Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and US Oncology. J Clin Oncol 26:5755–5760
26. Kelly K, Chansky K, Gaspar LE et al (2008) Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. J Clin Oncol 26:2450–2456
27. Huber RM, Engel-Riedel W, Kollmeier J et al (2012) GILT study: oral vinorelbine (NVBo) and cisplatin (P) with concomitant radiotherapy (RT) followed by either consolidation (C) with NVBo plus P plus best supportive care (BSC) or BSC alone in stage (st) III non-small cell lung cancer (NSCLC): final results of a phase (ph) III study. ASCO Annual Meeting, Chicago (abstr No. 7001)
28. Segaert S, Van CE (2005) Clinical signs, pathophysiology and management of skin toxicity during therapy with epidermal growth factor receptor inhibitors. Ann Oncol 16:1425–1433
29. Wacker B, Nagrani T, Weinberg J et al (2007) Correlation between development of rash and efficacy in patients treated with the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib in two large phase III studies. Clin Cancer Res 13:3913–3921