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Original article

Second-line therapy in elderly patients with advanced non-small cell lung carcinoma: analysis of the IFCT-0501 Phase III study comparing single-agent therapy to carboplatin-based doublet therapy with fixed second-line erlotinib therapy

E. Quoix[1], V. Westeel[2], L. Moreau[3], E. Pichon[4], A. Lavolé[5], J. Dauba[6], D. Debieuvre[7], P.J. Souquet[8], L. Bigay-Game[9], E. Dansin[10], M. Poudenx[11], O. Molinier[12], F. Vaylet[13], D. Moro-Sibilot[14], D.Herman[15], H. Sennelart[16], J. Tredaniel[17], B. Mennecier[1], F. Morin[18], L. Baudrin[18], B. Milleron[18], and G. Zalcman[18,19] on behalf of *Intergroupe Francophone de CancérologieThoracique*

1 Department of Pulmonology, CHU Strasbourg, France
2 Department of Pulmonology CHU Besançon, France
3 Department of Pulmonology, CHG, Colmar, France
4 Department of Pulmonology , CHU, Tours, France
5 Department of Pulmonology, Tenon hospital, Paris, France
6 Department of Medical Oncology, CHG, Mont de Marsan, France
7 Department of Pulmonology, CHG, Mulhouse, France
8 Department of Pulmonology, CHU, Pierre-Bénite, France
9 Department of Pulmonology, Larrey Hospital, Toulouse, France
10 Department of Medical Oncology, CLCC Oscar Lambret, Lille, France
11 Department of Medical Oncology, CLCC Antoine Lacassagne, Nice, France
12 Department of Pulmonology, CHG, Le Mans, France
13 Department of Pulmonology, Instruction hospital of the armies, Percy-Clamart, France
14 Department of Pulmonology, CHU La Tronche, Grenoble, France
15 Department of Pulmonology, CHG, Nevers, France
16 Department of Medical Oncology , CLCC René Gauducheau, Nantes, France
17 Department of Medical Oncology, St Joseph Hospital, Paris, France
18 IFCT, Paris
19Department of Pulmonology and Thoracic Oncology, CHU, Caen, France

Corresponding author: Pr E. Quoix,
Department of Pneumology,
University Hospital,
1 Place de l'hôpital, F - 67091 Strasbourg Cedex
Phone: +(33)369550644; Mail: elisabeth.quoix@chru-strasbourg.fr

Abstract

Background: There is no dedicated study on second-line treatment for elderly patients with advanced non-small cell lung cancer (NSCLC). We report the results on second-line erlotinib therapy from our previously published Phase III study comparing single-agent therapy withplatin-based doublet (carboplatin + paclitaxel) therapy in 451elderly patients.

Patients and Methods:Erlotinib was given to patients exhibiting disease progression (PD) or experiencing excessive toxicity during first-line therapy, until further PD or non-acceptable toxicity.

Results: In total, 292 (64.7%) patients received erlotinib in second-line. Initial performance status (PS) 0-1, Stage IV NSCLC, and ADL6 were independent factors for receiving erlotinib. Median overall survival was 4 months (95% CI: 3.2-6.7) *vs.* 6.8 months (95% CI: 5.0-8.3) in single-agent arm and doublet arm, respectively(p=0.089). PS 0-1, never-smoking, adenocarcinoma, and weight loss ≤5% were favorable independent prognostic factors of survival, whereas the randomization arm had no significant impact. Among the 292 patients who received erlotinib, 60 (20.5%) experienced Grade 3-4 toxic effects, the most frequent beingrash.

*Conclusion:*Erlotinib as second-line therapy is feasible, leading to efficacy results similar to those obtained in a previous randomized study that was not dedicated to elderly patients, with acceptable toxicity.

Key words: advanced non-small cell lung cancer, elderly,erlotinib,and second-line

There is a notable rise in the incidence of lung cancer in elderly patients, with a median age at diagnosis of around 70 years. This rise reflects increasing life-expectancy, increasing risk of developing cancer with age, and perhaps decreasing nihilism among patients and doctors. As documented in younger counterparts, non-small cell lung cancer (NSCLC) represents approximately 85% of all diagnoses [1], and around two-thirds of patients are diagnosed with advanced disease.

For fit, chemo-naïve non-elderly patients with advanced NSCLC not amenable to chemo-radiation, platinum-based doublet is considered the standard first-line treatment. Single-agent therapy has long been recommended for first-line chemotherapy in elderly patients (aged ≥70 years), gemcitabine and vinorelbine being the most frequently studied agents [2]. However, subgroup analyses of several Phase III trials,which were not focused on elderly patients, suggested that patients aged ≥70 years derived similar benefits from a platin-based doublet as their younger counterparts [3-5]. In 2006, our group conducted a Phase III study comparing single-agent therapy (gemcitabine or vinorelbine according to the center's choice) to carboplatin and weekly paclitaxel in elderly NSCLC patients [6]. There was considerable benefit derived from the carboplatin-based doublet compared tothe single-agent therapyin terms of overall survival (OS). These results led to a modified paradigm of first-line treatment in performance status (PS) 0-2 elderly patients with advanced NSCLC, as illustrated by the recently published NCCN recommendations [7].

At the present time, three drugs (docetaxel, pemetrexed, and erlotinib) have been authorized for second-line therapy in advanced NSCLC patients, previously treated with at least one line of a platinum-based combination chemotherapy [8-10]. In particular, the BR21 study showed that erlotinib significantly increased OScompared with best supportive care for non-selected advanced NSCLC [10]. There have been no randomized trials dedicated to elderly patients

with second-line epidermal growth factor receptor (EGFR) - tyrosine kinase inhibitor (TKI). However, subgroup analysis of elderly patients included in the BR21 study showed that there was no differential effect of erlotinib according to age ≥70 *versus*<70 years [11]. Due to its good tolerability profile, erlotinib was chosen as systematic second-line therapy in the IFCT 0501 trial, after either single-agent or carboplatin-paclitaxel doublettherapy. In this article,we report the mature efficacy and toxicity data pertaining toerlotinib second-line therapy in all-comers aged ≥70 years, included in the IFCT0501 Phase 3 trial, who progressed after induction therapy with either a weekly paclitaxel-carboplatin doublet or monotherapy (either gemcitabine or vinorelbine).

The protocol was approved by the Ethics Committee of Paris, and the trial was authorized by French Health authorities (NCT00298415). All enrolled patients provided written informed consent.

Patients and methods

Details regarding patient selection criteria were provided in the first publication on the current study [6]. Briefly, 451 patients were enrolled between April 2006 and December 2009 by 61 institutions. The main eligibility criteria were: locally advanced NSCLC with contraindication to radiation therapy or Stage IV disease, age between 70 and 89 years, PS 0-2, adequate hematologic, hepatic, and renal function, as well as life-expectancy of at least 12 weeks. Patients were randomized 1:1 to the two treatment groups using minimization andstratification by center, PS (0-1 *vs.* 2), Stage (III *vs*. IV), and age (≤ 80 *vs*. >80). Patients assigned to the single-agent therapyreceived either vinorelbine or gemcitabine (according to the center's initial choice),while those assigned to doublet therapy received carboplatin and paclitaxel (Fig 1). A maximum of five cycles were delivered in the single-agent group versus four in the doublet group. For patients exhibiting disease progression (PD) anytime during or

afterinduction treatment or for those experiencing excessive toxicity during first-line therapy, treatment was replaced by erlotinib at 150 mg/day until further PD or non-acceptable toxicity. Third-line therapy could be employed at the discretion of the investigators. Baseline disease assessment was performed using chest X-ray, thoracic computed tomography (CT) scan, bronchial endoscopy, brain CT or magnetic resonance imaging (MRI), and abdominal ultrasonography or CTscan. EGFR mutational status was not available when the trial was designed (2005), and therefore not systematically recorded for patients undergoing erlotinib second-line therapy. During second-line therapy, disease was assessed using the same imaging procedures every 2 months during the first 6 months, and every 3 months thereafter using the WHO criteria [12]

The current study aimed to describe compliance to second-line erlotinib, median duration of second-line therapy, progression-free survival (PFS), OS, as well as prognostic factors, starting from the initiation of erlotinib in the two arms.

Baseline characteristics (at time of randomization) of patients receiving second-line therapy or not were analyzed using logistic regression, with the following factors analyzed: first-line treatment arm (monotherapy *vs.* doublet), PS (0-1 *vs.* 2), weight loss before randomization (≤5% *vs.*>5%), body-mass index (BMI) (<20 kg/m², 20-≤26 kg/m², >26-≤30 kg/m², and >30 kg/m²), age (≤80 *vs.*>80 yrs), smoking status (never-smoker *vs.* ever-smoker), disease stage (III *vs.* IV), histology (adenocarcinoma *vs.* squamous or other), Charlson's comorbidity index score (≤2 *vs.*>2), mini-mental state examination score (MMS: ≤23 *vs*>23), and activities of daily living score (ADL:<6 *vs.* 6). Variables with a $p<0.2$ were included in the multivariate logistic regression and then selected by a backward procedure, with a stay significance level of 0.05.

Median times on second-line therapy according to the first-line treatment arm were compared using the Mood median test.

OS was defined as the time from first erlotinib administration to death from any cause, or was censored at the last follow-up. PFS was defined as the time from first erlotinib administration to documented PD or death, whichever occurred first, or was censored at the last follow-up. The end-point date was April 1st, 2012. Cumulative incidence curves for PFS and OS were estimated using the Kaplan-Meier method. Median and 1-year OS were reported with their respective 95% CI, and the medians were compared using the log-rank test. The associations between OS and each potential prognostic factor, as shown above, were assessed using the univariate Cox model. As with the logistic regression analysis, variables with a $p<0.2$ were included in a multivariate Cox model and then selected by a backward procedure, with a stay significance level of 0.05.

Fisher's exact test was used to compare Grade 3 and 4 toxicity rates during erlotinib therapy between treatment arms.

Analyses were performed on all patients who received at least one dose of erlotinib. Statistical analyses were perfomed using SAS Version 9 (SAS Institute, Cary, NC). A two-sided p value < 0.05 was considered to be statistically significant.

Results

In total, 451 patients were randomly assigned to this study, with 448 receiving at least one injection of first-line therapy. As illustrated in flow chart diagram (Fig 2), of the 444 patients who completed first-line therapy (four patients were still undergoing first-line therapy at the end-point date, three in the doublet and one in the monotherapy arm), 152 (34.2%) did not continue on with second-line therapy (causes being: 78 deaths, 40 general condition deteriorations, 16 protocol violations, seven patient refusals, five consent withdrawals, three

major toxicities during first-line therapy precluding any possibility of second-line therapy, and three other causes).

Finally, 292 patients received second-line therapy according to protocol. The proportion of patients who actually received second-line erlotinib did not differ between the two arms (144/226 [63.7%] in the single-agent arm and 148/225 [65.8%] in the doublet arm, p=0.60). Of the 292 patients, four were considered ineligible at baseline assessment (one patient with oxygen dependence, two with other cancer diagnosis within the last 5 years, and one patient with previous chemotherapy and radiation therapy). The reason for undergoing second-line therapy was PD for 93.8% of the 292 patients, (95.1% in the single-agent arm and 92.6% in the doublet arm), excessive chemotherapy toxicity for 4.1% (2.8% and 5.4%, respectively), and other reasons in 2.1% of cases. Baseline characteristics differed greatly between patients who received second-line therapy according to protocol and those who did not, with the former exhibiting significantly better PS, less weight loss, higher MMS and ADL scores, and a higher proportion of Stage IV disease. (Table I). Multivariate logistic regression showed that initial PS 0-1, Stage IV, and ADL 6 were independent factors of receiving second-line erlotinib therapy.

Of the 292 patients treated with erlotinib, two in the doublet arm were still undergoing treatment at time of analysis. The reasons for discontinuing erlotinibin the 290 remaining patients are detailed in Table II, with the most common cause being PD for both arms (63.1%). Median duration of erlotinib treatment was 2.0 months (95% CI: 1.8-2.3) in the single-agent arm (arm A) and 2.2 months (95% CI: 2.0-2.8) in the doublet arm (arm B) (p = 0.66). In 23.6% and 25% of cases, respectively (p = 0.78), the erlotinib dose had to be reduced.

PFS from first erlotinib administration was 2.2 months (95% CI: 1.9-2.8) in arm A and 2.6 months (95% CI: 2.4-3.0) in arm B (p = 0.30). Median OS was 4 months (95% CI: 3.2-6.7) versus 6.8 months (95% CI: 5.0-8.3), respectively, (p=0.089). The 1-year survival rate

was 26.4% (95% CI: 19.5%-33.8%) and 33.8% (95% CI: 26.3%-41.4%), respectively (p=0.167).

Univariate analysis of OS since first erlotinib administrationaccording to baseline characteristics is displayed in Table III. PS 0-1, female gender, never-smoking, adenocarcinoma histology, and weight loss ≤5% were favorable prognostic factors. Multivariate analysis of OSrevealed that PS 0-1, never-smoking, adenocarcinoma, and weight loss ≤5% were all favorable independent prognostic factors, whereas the randomization arm showed no significant impact. We used initial PS and weight loss since a substantial number of data were missing at the beginning of second line therapy (83 and 116 respectively out of 292). However survival multivariate analysis performed on the 159 patients without missing data, using the unchanged baseline characteristics but PS and weight loss registered at time of second line therapy, gave similar results, with PS 0-1, weight loss <=5%, adenocarcinoma histology still being independent favorable prognostic factors (online supplementary Table I).There was a quantitative interaction between histology and smoking status, (interaction test, p=0.0013), which remained significant when adjusted for PS and weight loss (interaction test, p=0.0011). Indeed, after adjustment, there was highly significant difference in OS according to histology for never-smokers, whereas ever-smoker adenocarcinoma patients demonstrated no significantly longer survival rates (Fig4A and 4B).

Of the 292 patients who received erlotinib, 60 (20.5%) experienced Grade 3 or 4 toxic effects (Table V), 28 in the single-agent arm (19.4%), and 32 in the doublet arm (21.6%). The most frequent toxic effects were rash (26 patients), asthenia (12 patients), anorexia (10 patients), and diarrhea (eight patients), withanorexia significantly more common in the monotherapy group, (p=0.032). Three patients experienced a Grade 4 toxicity (one gastric hemorrhage and one interstitial pneumonitis in the single-agent arm, and one folliculitis in the doublet arm).

Discussion

In our study, 292 out of 451 patients (64.7%) were eligible to receive the assigned second-line therapy. This figure compares favorably to that of 49% reported for a cohort of 406 unselected patients [13], but less favorably to the maintenance Phase 3 trial study conducted by our intergroup in which more than 77% of the randomized patients(aged 18-70, median age=56.4 to 59.8) received the predefined second-line therapy[14]. These patients were, however,*i)* younger (maximum age for inclusion: 75 years) and*ii)* highly selected (all were without PD after induction treatment). In our study, the strategy, as in the cohort of unselected patients[13], differed because second-line therapy was proposed when PD occurred, regardless of whether it was during or after the induction phase. As reported in a previous study, the likelihood of receiving second-line chemotherapy was strongly determined by PS [15]. Furthermore, in our study, several geriatric indexeshad a significant influence on being selected to receive second-line chemotherapy (MMS and ADL),which, to the best of our knowledge, has not been described elsewhere. Median duration of treatment was around 2 months, with no significant difference documented between the initial arms (monotherapy or carboplatin doublet). This duration is similar to that of the BR21 trial. Moreover, the median OS of 6.8 months (95% CI 5.0-8.3) recordedin our study patients who were initially randomized to the doublet arm was similar to that observed in the BR21 study for those treated with erlotinib (6.7 months) [10]. In both instances, erlotinib was administeredfollowing a platin-based doublet, regardless of EGFR mutational status. Median survival of our study patients previously treated with monotherapy was inferior to that observed when they first received the carboplatin-weekly paclitaxel doublet. This difference, however, was not statistically significant. Moreover, the randomization arm was not a significant prognostic factor for OS undererlotinib treatment. The trend observed toward a longer survival under erlotinib for the doublet arm patients might be explained by a

significant higher response rate and a longer time to progression under first line therapyin the doublet arm [6],possibly providing a better general condition at the beginning of erlotinib. As a matter of fact, even if data were missing in 30 to 40% of the patients, there still was a trend toward a better PS, and a significant higher BMI, in patients initially included in the doublet arm, but no difference in weight loss between randomization and the beginning of erlotinib (online supplementary tables II and III). Multivariate analysis of survival revealed that initial PS (before induction treatment) remained a strong prognostic factor. Other independent favorable prognostic factors were never-smoker status, adenocarcinoma histology, and no significant weight loss prior to induction treatment. The interaction between smoking status and histology may show that these clinical features do have an impact on erlotinib efficacy, as could be expected. In smokers with adenocarcinoma, however, at least one-third of patients likely exhibit K-RAS mutations [16], which preclude any efficacy of tyrosine kinase inhibitors. As analyses of EGF-R and K-RAS mutations were not routinely performed in France when we initiated this study, we cannot retrospectively verify such hypotheses.

Grade 3-4 toxicity due to erlotinib was somewhat lower than that observed in the BR21 study [11], in which Grade 3-4 toxicity was observed in 35% of elderly patients versus 18% of their younger counterparts ($p<0.001$).In our study, only 20.5% of patients experienced Grade 3-4 toxicity, and treatment was discontinued due to excessive toxicity in 9.7% versus 12% in the BR21 study.

Our study did not examine the role of maintenance therapy. In the SATURN study, which evaluated the value of maintenance erlotinib versus placebo using a randomized design, following four induction cycles with a platin-based doublet, regardless of EGFR mutational status, maintenanceerlotinib therapy proved to be of value[17] in terms of OS for patients with stabilized disease (SD) at the end of induction therapy. Through an exploratory subgroup analysis, however, no benefit was found for patients aged 65 and over. One element that is

missing from the SATURN study is the type of second-line therapy assigned to the placebo group. It would have been interesting to find out if, at least in a subgroup analysis, patients receiving delayed erlotinib (in the placebo arm) fared similarly to patients in the maintenance arm.

In conclusion, our study confirmed the feasibility of second-line erlotinib therapy in elderly patients, with an acceptable Grade 3-4 toxicity rate. Although our study was not designed to reconfirm the survival benefit induced by this second-line therapy, we are now in the position to confirm the prognostic role of initial PS, smoking status, initial weight loss, and histology in elderly patients receiving second-line therapy. On the other hand, although we provide original data on the efficacy of geriatric indexes used in this study (MMS, ADL) in predicting the probability of receiving second-line erlotinib, these indexes did, in fact, fail to significantly influence the probability of survival.

Table I Results of univariate and multivariate logistic regression analyses assessing the eligibility to receive erlotinib as second-line therapy (L2) according to baseline patient characteristics (prior to induction therapy)

	Patients receiving L2 N (%)	Univariate analysis (n=444)		Multivariate analysis (n=421)	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Treatment arm					
Doublet chemotherapy	144 (64.3)	1.14 (0.77-1.69)	0.5073		
Monotherapy	148 (67.3)	1			
Sex					
Male	210 (64.4)	1			
Female	82 (69.5%)	1.26 (0.80-1.98)	0.3201		
Age (years)					
≤80	217 (65.4)	0.93 (0.59-1.47)	0.7572		
>80r	75 (67.0)	1			
Performance status					
0-1	234 (72.9)	2.97 (1.93-4.57)	<0.0001	2.45 (1.55-3.88)	0.0001
2*	58 (47.6)	1		1	
Stage					
IIIA-IIIB	47 (56.0)	1			
IV	245 (68.1)	1.67 (1.03-2.72)	0.0364	1.67 (1.00-2.79)	0.0497
Histology					
Squamous-Other	142 (65.1)	1			
Adenocarcinoma	150 (66.4)	1.06 (0.71-1.56)	0.7841		
Smoking status					
Never-smoked	68 (72.3)	1.47 (0.89-2.43)	0.1317		
Ever-smoked	224 (64.0)	1			
MMSE					
≤23	34 (52.3)	1			
>23	250 (67.8)	1.92 (1.12-3.27)	0.0169		
ADL score					
<6	42 (48.8)	1			
6	239 (69.7)	2.41 (1.49-3.90)	0.0003	1.82 (1.08-3.05)	0.0242
CCI					
≤2	226 (67.7)	1.40 (0.89-2.18)	0.1426		
>2	66 (60.0)	1			
BMI (kg/m²)					
≤20	32 (61.5)	1			
]20;26[	156 (63.7)	1.10 (0.59-2.03)	0.7718		
[26;30]	70 (72.2)	1.62 (0.79-3.31)	0.1850		
>30	34 (68.0)	1.33 (0.59-3.00)	0.4953		
Weight loss before randomization					
≤5%	144 (72.4)	1.73 (1.15-2.59)	0.0081		
>5%	144 (60.3)	1			

MMSE=mini-mental state examination questionnaire/ADL=activities of daily living questionnaire/CCI=Charlson's comorbidity index

* Patients who completed first-line therapy

** Six patients of those who had not received L2 had an initial WHO performance status score of 3

Table II Reasons for discontinuing second-line therapy in both arms

	All patients (N=290)	Monotherapyarm (N=143)	Doublet chemotherapy arm (N=147)
Reason for stopping L2			
Death	49 (16.9%)	26 (18.1%)	23 (15.6%)
Due to cancer	39 (79.6%)	22 (84.6%)	17 (73.9%)
Intercurrent disease	9 (18.4%)	4 (15.4%)	5 (81.7%)
Unknown reason	1 (2.04%)	0 (0%)	1 (4.35%)
Disease progression	183 (63.1%)	92 (64.3%)	91 (61.9%)
Consent withdrawal	3 (1.0%)	2 (1.4%)	1 (0.7%)
Excessive toxicity	28 (9.7%)	11 (7.6%)	17 (11.6%)
Protocol violation	2 (0.7%)	0	2 (1.4%)
Other	25 (8.6%)	12 (8.3%)	13 (8.8%)
General condition deterioration	15	6	9
Patient refusal	6	3	3
Other	4	3	1

Table III Univariate and multivariate analyses of overall survival under L2

	No. of patients	Univariate analysis (n=292)		Multivariate analysis (n=288)	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Treatment arm					
Doublet chemotherapy	148	0.81 (0.64-1.03)	0.0897		
Monotherapy	144	1			
Sex					
Male	210	1			
Female	82	0.67 (0.51-0.88)	0.004		
Age (years)					
≤80	217	0.92 (0.70-1.20)	0.530		
>80r	75	1			
Performance status					
0-1	234	0.56 (0.42-0.76)	0.0002	0.63 (0.47-0.86)	0.0034
2	58	1		1	
Stage					
IIIA-IIIB	47	0.82 (0.59-1.13)	0.218		
IV	245	1			
Histology					
Squamous-other	142	1		1	
Adenocarcinoma	150	0.53 (0.42-0.68)	<0.0001	0.68 (0.52-0.88)	0.0039
Smoking status					
Never-smoked	68	0.50 (0.37-0.67)	<0.0001	0.62 (0.45-0.85)	0.0034
Ever-smoked	224	1		1	
MMSE					
≤23	34	1			
>23	250	0.91 (0.63-1.31)	0.598		
ADL score					
<6	42	1			
6	239	0.82 (0.59-1.15)	0.252		
CCI					
≤2	226	0.79 (0.59-1.05)	0.099		
>2	66	1			
BMI (kg/m²)					
≤20	32	1			
[20;26]	156	0.91 (0.62-1.35)	0.651		
[26;30]	70	0.75 (0.49-1.15)	0.180		
>30	34	0.88 (0.53-1.45)	0.606		
Weight loss before randomization					
≤5%	144	0.66 (0.52-0.84)	0.0008	0.76 (0.60-0.98)	0.0337
>5%	144	1		1	

HR=hazard ratio. MMSE=mini-mental state examination questionnaire/ADL=activities of daily living questionnaire/CCI=Charlson's comorbidity index

Table IV Grade 3-4 toxic effects in patients who received at least one-dose of second-line therapy

	Monotherapy group (n=28)		Doublet chemotherapy (n=32)	
	Grade 3 (n=26)	Grade 4 (n=2)	Grade 3 (n=32)	Grade 4 (n=1)
Skin disorders	15 (58%)		16 (50%)	1
Alanine aminotransferase increase	0		1 (3%)	
Anorexia	8 (31%)		2 (6%)	
Asthenia	7 (27%)		5 (16%)	
Conjunctivitis	1 (4%)		1 (3%)	
Depression	0		1 (3%)	
Diarrhea	3 (12%)		5 (16%)	
Edema limbs	0		1 (3%)	
Gamma-glutamyltransferase increase	0		1 (3%)	
Gastric hemorrhage		1		
Gastrointestinal disorder	1 (4%)		0	
Hemiplegia	1 (4%)		0	
Hemoglobin decrease	0		1 (3%)	
Interstitial pneumonitis		1		
Mouth irritation	2 (8%)		1 (3%)	
Nail infection	0		1 (3%)	
Nausea	1 (4%)		1 (3%)	
Rectal hemorrhage	0		1 (3%)	
Reduced general condition	0		2 (6%)	
Sensory neuropathy	0		1 (3%)	
Subcutaneous emphysema	0		1 (3%)	
Vomiting	0		1 (3%)	

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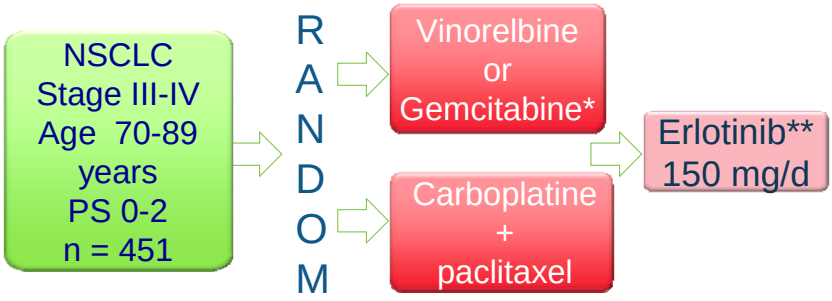
Fig 1 Treatment scheme



* Institution choice

** In case of progressive disease or excessive toxicity

Doses: vinorelbine 30 mg/m², D1 and 8, D1 = D22; gemcitabine 1150 mg/m² D1 and 8, D1 = D22; carboplatine D1 AUC 6, D1 = D29; paclitaxel 90 mg/m² D1, 8 and 15.

Fig 2: Study profile

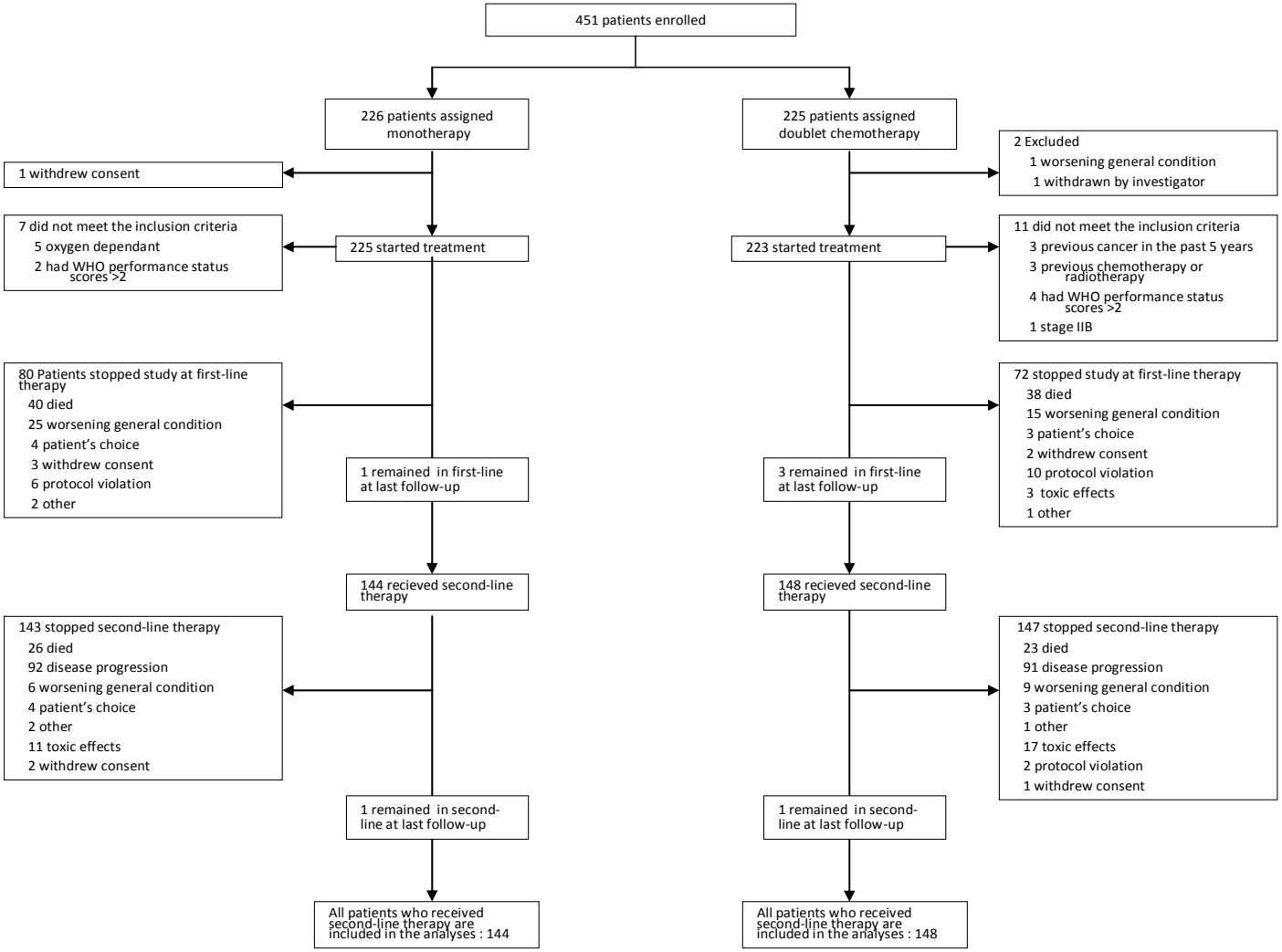


Fig 3: Overall survival with erlotinib according to treatment arm

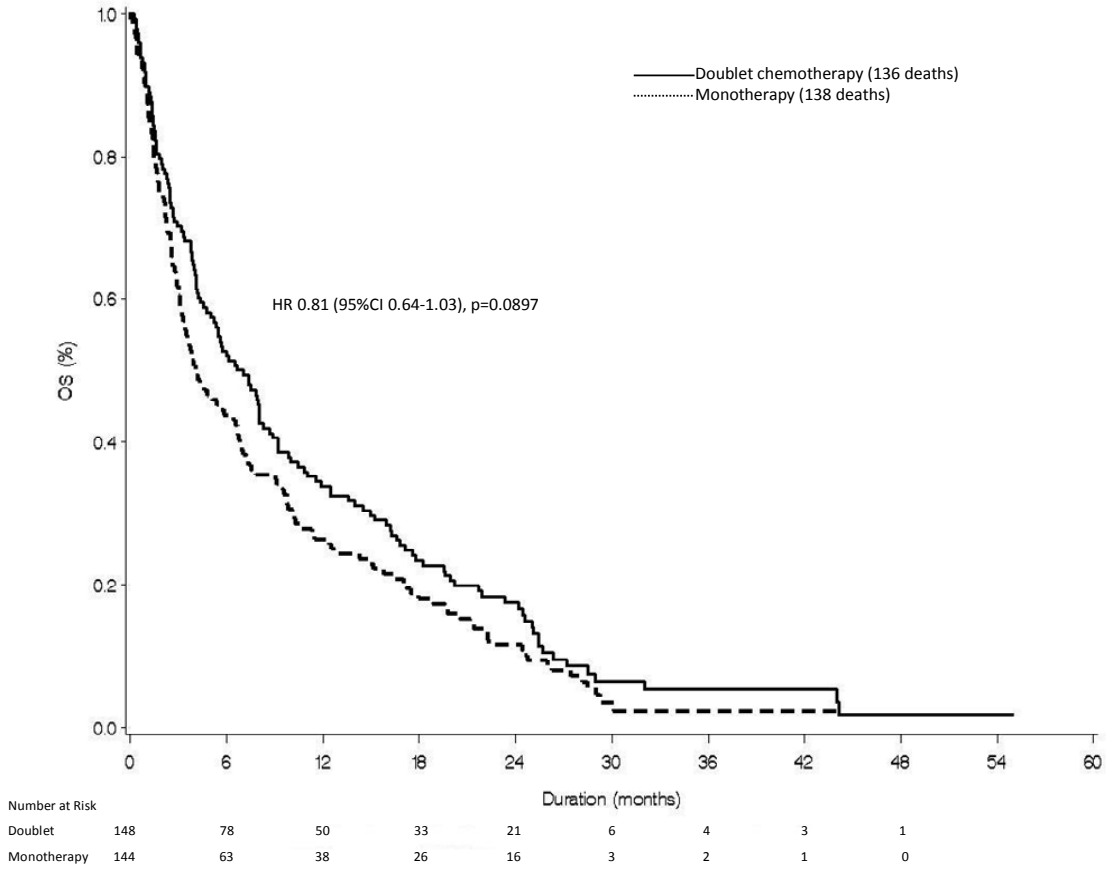


Fig 4A: Overall survival with erlotinib according to histology – Never-smoker

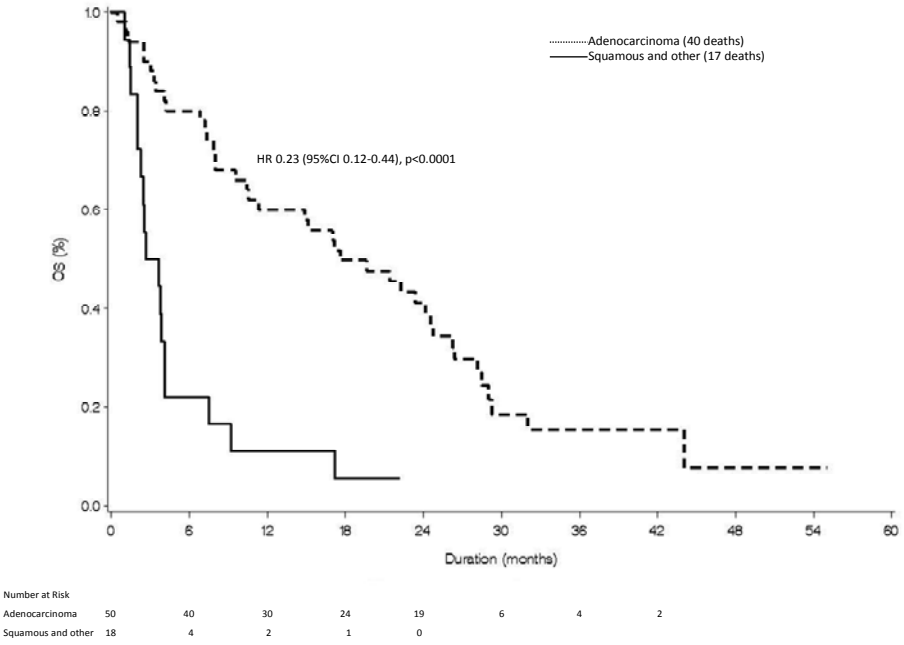
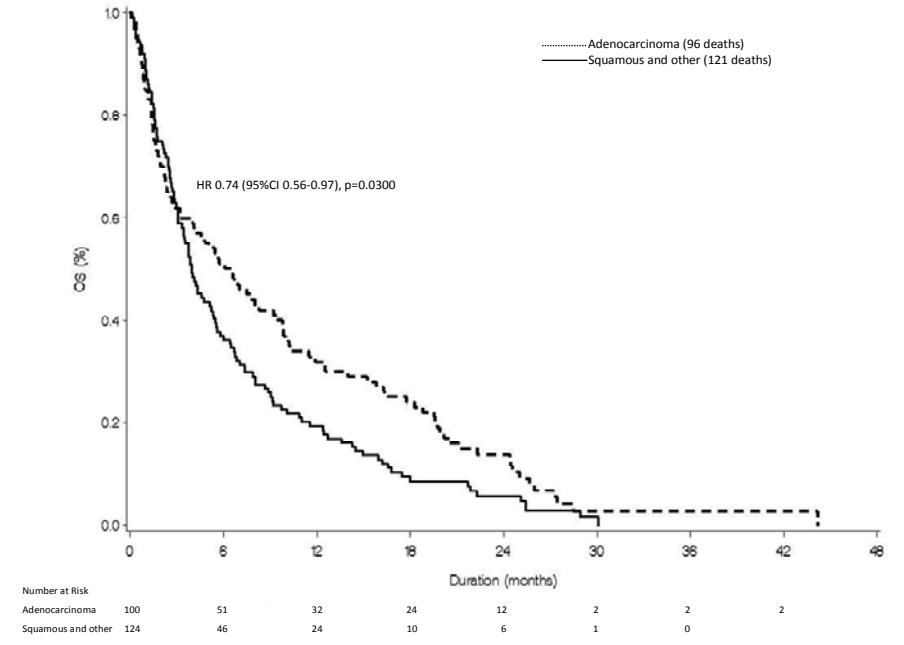


Fig 4B: Overall survival under erlotinib according to histology – Ever-smoker



Interaction test, p=0.0013 / Adjusted interaction test over the Performance status and Weight loss, p=0.0011.
HR are presented crude.
Adjusted over the Performance status and Weight loss for Never-smoker: HR 0.23 (95% CI 0.0.12-0.45), p<0.0001
Adjusted over the Performance status and Weight loss for Ever-smoker: HR 0.80 (95% CI 0.60-1.05), p=0.1091

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