Second-line therapy in elderly patients with advanced nonsmall cell lung cancer

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ABSTRACT There is no dedicated study on second-line treatment for elderly patients with advanced nonsmall cell lung cancer (NSCLC). We report the results on second-line erlotinib therapy from our previously published phase III study comparing single-agent therapy with platinum-based doublet (carboplatin plus paclitaxel) therapy in 451elderly patients.

Erlotinib was given to patients exhibiting disease progression or experiencing excessive toxicity during first-line therapy, until further progression or unacceptable toxicity.

In total, 292 (64.7%) patients received erlotinib as second-line therapy. Initial performance status 0–1, stage IV NSCLC and an Activities of Daily Living score of 6 were independent factors for receiving erlotinib. Median (95% CI) overall survival was 4 (3.2–6.7) *versus* 6.8 (5.0–8.3) months in the single-agent and doublet arms, respectively (p=0.089). Performance status 0–1, never having smoked, adenocarcinoma and weight loss ⩽5% were favourable independent prognostic factors of survival, whereas the randomisation arm had no significant impact. Among the 292 patients who received erlotinib, 60 (20.5%) experienced grade 3–4 toxic effects, the most frequent being rash.

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

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Introduction

There has been a notable rise in the incidence of lung cancer in elderly patients, with a median age at diagnosis of ~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, nonsmall cell lung cancer (NSCLC) represents ~85% of all diagnoses [1] and around two-thirds of patients are diagnosed with advanced disease.

For fit, chemotherapy-naïve, nonelderly patients with advanced NSCLC not amenable to chemoradiotherapy, platinum-based doublets are 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 platinum-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 centre's choice) to carboplatin and weekly paclitaxel in elderly NSCLC patients [6]. There was considerable benefit derived from the carboplatin-based doublet compared with the single-agent therapy in terms of overall survival. These results led to a modified paradigm of first-line treatment in performance status 0–2 elderly patients with advanced NSCLC, as illustrated by the recently published National Comprehensive Cancer Network recommendations [7].

At the present time, three drugs (docetaxel, pemetrexed and erlotinib) have been authorised 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 overall survival compared with best supportive care for nonselected advanced NSCLC [10]. There have been no randomised trials dedicated to elderly patients with second-line epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs). 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 Intergroupe Francophone de Cancérologie Thoracique (IFCT)0501 trial, after either single-agent or carboplatin–paclitaxel doublet therapy. In this article, we report the mature efficacy and toxicity data pertaining to erlotinib second-line therapy in all-comers aged ⩾70 years, included in the IFCT0501 phase III trial, who progressed after induction therapy with either a weekly paclitaxel-carboplatin doublet or monotherapy (either gemcitabine or vinorelbine).

Patients and methods

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

Details regarding patient selection criteria were provided in the first publication from the current study [6]. Briefly, 451 patients were enrolled between April 2006 and December 2009 by 61 institutions. The main eligibility criteria were: 1) locally advanced NSCLC with contraindication to radiation therapy or stage IV disease; 2) age between 70 and 89 years; 3) performance status 0–2; 4) adequate haematological, hepatic and renal function; and 5) life expectancy of ⩾12 weeks. Patients were randomized 1:1 to the two treatment groups using minimisation and stratification by centre for performance status (0–1 *versus* 2), stage (III *versus* IV) and age (⩽80 *versus* >80 years). Patients assigned to the single-agent therapy received either vinorelbine or gemcitabine (according to the centre'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 at any time during or after induction treatment or for those experiencing excessive toxicity during first-line therapy, treatment

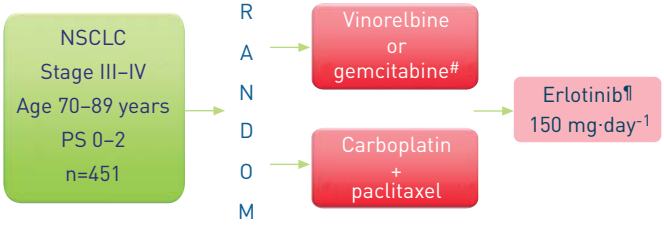

FIGURE 1 Treatment scheme. Doses: vinorelbine 30 mg·m^{-2}, day (D) 1 and 8, the cycle restarting on D22 (D1=D22); gemcitabine 1150 mg·m^{-2}, D1 and 8, D1=D22; carboplatin area under the curve 6, D1, D1=D29; paclitaxel 90 mg·m^{-2}, D1, 8 and 15. NSCLC: nonsmall cell lung cancer; PS: performance status. #: institution choice; ¶: in the case of progressive disease or excessive toxicity.

was replaced by erlotinib at 150 mg per day until further progression or unacceptable toxicity. Third-line therapy could be employed at the discretion of the investigators. Baseline disease assessment was performed using chest radiography, thoracic computed tomography, bronchial endoscopy, brain computed tomography or magnetic resonance imaging, and abdominal ultrasonography or computed tomography. *EGFR* mutational status was not available when the trial was designed (2005) and, therefore, was 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 World Health Organization criteria [12]

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

Baseline characteristics (at time of randomisation) of patients receiving second-line therapy or not were analysed using logistic regression, for the following factors: first-line treatment arm (monotherapy *versus* doublet), performance status (0–1 *versus* 2), weight loss before randomisation ($\leqslant$5% *versus* >5%), body mass index (BMI) (<20, 20 to $\leqslant$26, >26 to $\leqslant$30 and >30 $kg \cdot m^{-2}$), age ($\leqslant$80 *versus* >80 years), smoking status (never- *versus* ever-smoker), disease stage (III *versus* IV), histology (adenocarcinoma *versus* squamous or other), Charlson's comorbidity index score ($\leqslant$2 *versus* >2), mini-mental state (MMS) examination score ($\leqslant$23 *versus* >23) and activities of daily living (ADL) score (<6 *versus* 6). Variables with a p-value <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.

Overall survival 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 disease progression or death, whichever occurred first, or was censored at the last follow-up. The end-point date was April 1, 2012. Cumulative incidence curves for PFS and overall survival were estimated using the Kaplan–Meier method. Median and 1-year overall survival were reported with their respective 95% confidence intervals, and the medians were compared using the log-rank test. The associations between overall survival 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-value <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 performed using SAS version 9 (SAS Institute, Cary, NC, USA). 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 figure 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 (63.7%) out of 226 in the single-agent arm and 148 (65.8%) out of 225 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 disease progression 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 performance status, less weight loss, higher MMS and ADL scores, and a higher proportion of stage IV disease (table 1). Multivariate logistic regression showed that initial

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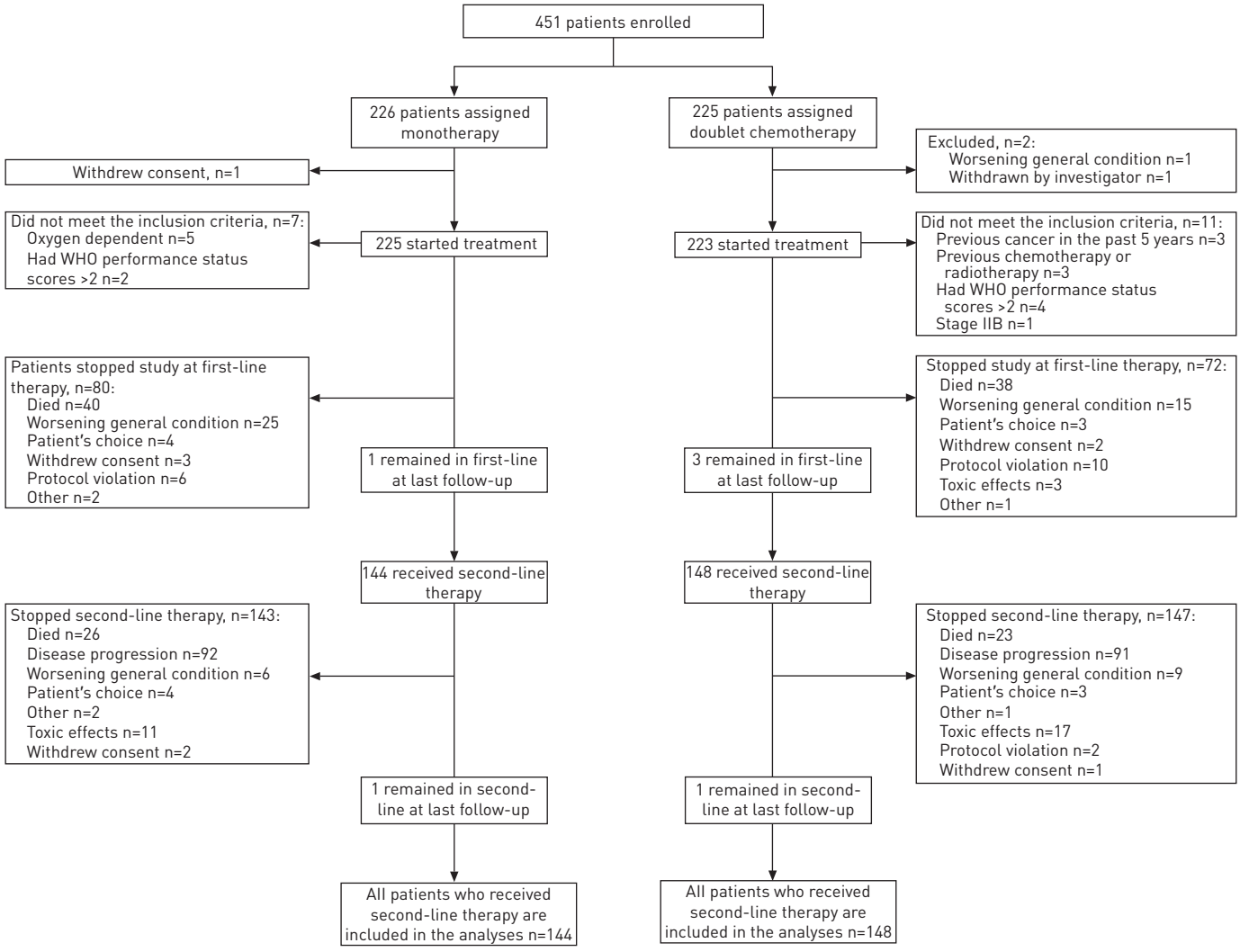

FIGURE 2 Study profile. WHO: World Health Organization.

performance status 0–1, stage IV disease and ADL score 6 were independent factors for receiving second-line erlotinib therapy.

Of the 292 patients treated with erlotinib, two in the doublet arm were still undergoing treatment at the time of analysis. The reasons for discontinuing erlotinib in the 290 remaining patients are detailed in table 2, with the most common cause being disease progression for both arms (63.1%). Median (95% CI) duration of erlotinib treatment was 2.0 (1.8–2.3) months in the single-agent arm (arm A) and 2.2 (2.0–2.8) months 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 (1.9–2.8) months in arm A and 2.6 (2.4–3.0) months in arm B (p=0.30). Median overall survival (fig. 3) was 4 (3.2–6.7) *versus* 6.8 (5.0–8.3) months, respectively, (p=0.089). The 1-year survival rate was 26.4 (19.5–33.8) and 33.8 (26.3–41.4)%, respectively (p=0.167).

Univariate analysis of overall survival since first erlotinib administration according to baseline characteristics is presented in table 3. Performance status 0–1, female sex, never having smoked, adenocarcinoma histology and weight loss $\leqslant$5% were favourable prognostic factors. Multivariate analysis of overall survival revealed that performance status 0–1, never having smoked, adenocarcinoma and weight loss $\leqslant$5% were all favourable independent prognostic factors, whereas the randomisation arm showed no significant impact. We used initial performance status and weight loss, as a substantial number of data were missing at the beginning of second-line therapy (83 and 116 out of 292, respectively). However, survival multivariate analysis performed on the 159 patients without missing data, using the unchanged baseline characteristics but performance status and weight loss registered at the time of second-line therapy, gave

TABLE 1 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#		Multivariate analysis¶	
		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		
>80	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 or 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			
MMS examination					
⩽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·m^{-2}					
⩽20	32 (61.5)	1			
20 to ⩽26	156 (63.7)	1.10 (0.59–2.03)	0.7718		
>26 to ⩽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 randomisation %					
⩽5	144 (72.4)	1.73 (1.15–2.59)	0.0081		
>5	144 (60.3)	1			

MMS: mini-mental state; ADL: activities of daily living questionnaire; CCI: Charlson's comorbidity index; BMI: body mass index. #: n=444; ¶: n=421; +: six patients who had not received L2 had an initial World Health Organization performance status of 3; §: patients who completed first-line therapy.

similar results, with performance status 0–1, weight loss ⩽5%, adenocarcinoma histology still being independent favourable prognostic factors (online supplementary table S1). There was a quantitative interaction between histology and smoking status (interaction test, p=0.0013), which remained significant when adjusted for performance status and weight loss (interaction test, p=0.0011). Indeed, after adjustment, there was highly significant difference in overall survival according to histology for never-smokers, whereas ever-smoker adenocarcinoma patients demonstrated no significantly longer survival rates (fig. 4).

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

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TABLE 2 Reasons for discontinuing second-line therapy (L2) in both arms

Reason for stopping L2	All patients[#]	Monotherapy arm[¶]	Doublet chemotherapy arm[+]
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 (5)	6 (4.1)	9 (6.3)
Patient refusal	6 (2)	3 (2.1)	3 (2.1)
Other	4 (1.5)	3 (2.1)	1 (0.7)

Data are presented as n (%) or n. [#]: n=290; [¶]: n=143; [+]: n=147.

Discussion

In our study, 292 (64.7%) out of 451 patients were eligible to receive the assigned second-line therapy. This figure compares favourably to that of 49% reported for a cohort of 406 unselected patients [13], but less favourably with the maintenance phase III trial study conducted by our intergroup in which >77% of the randomised patients (aged 18–70 years, median 56.4–59.8 years) received the predefined second-line therapy [14]. These patients were, however, 1) younger (maximum age for inclusion 75 years) and 2) highly selected (all were without disease progression after induction treatment). In our study, the strategy, as in the cohort of unselected patients [13], differed because second-line therapy was proposed when disease progression 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 performance status [15]. Furthermore, in our study, several geriatric indexes had 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 ~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 overall survival of 6.8 (5.0–8.3) months recorded in our study patients who were initially randomised 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 administered following a platinum-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 randomisation arm was not a significant prognostic factor for overall survival under erlotinib 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 therapy in

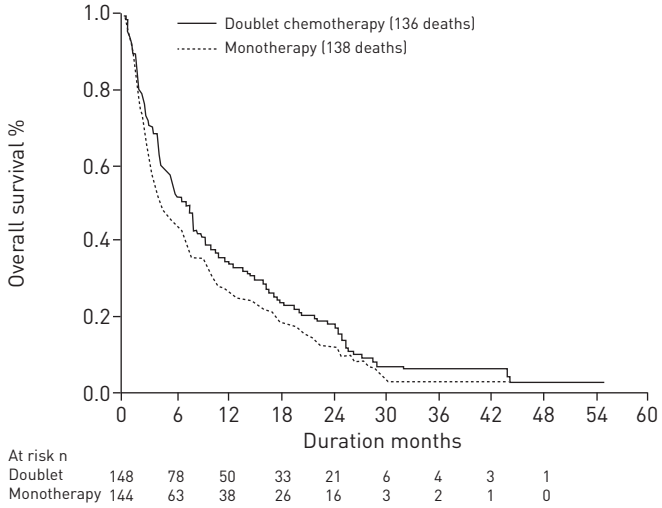

FIGURE 3 Overall survival with erlotinib according to treatment arm. Hazard ratio 0.81, 95% CI 0.64–1.03; p=0.0897.

TABLE 3 Univariate and multivariate analyses of overall survival under second-line therapy

	Patients n	Univariate[#]		Multivariate[¶]	
		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		
>80	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 or 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	
MMS examination					
⩽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·m^{-2}					
⩽20	32	1			
20 to ⩽26	156	0.91 (0.62–1.35)	0.651		
>26 to ⩽30	70	0.75 (0.49–1.15)	0.180		
>30	34	0.88 (0.53–1.45)	0.606		
Weight loss before randomisation %					
⩽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; MMS: mini-mental state; ADL: activities of daily living questionnaire; CCI: Charlson's comorbidity index; BMI: body mass index. [#]: n=292; [¶]: n=288.

the doublet arm [6], possibly providing a better general condition at the beginning of erlotinib. As a matter of fact, even though data were missing in 30–40% of the patients, there still was a trend toward a better performance status and a significantly higher BMI in patients initially included in the doublet arm, but no difference in weight loss between randomisation and the beginning of erlotinib (online supplementary tables S2 and S3). Multivariate analysis of survival revealed that initial performance status (before induction treatment) remained a strong prognostic factor. Other independent favourable 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 *KRAS* mutations [16], which precludes any efficacy of TKIs. As analyses of *EGFR* and *KRAS* 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.

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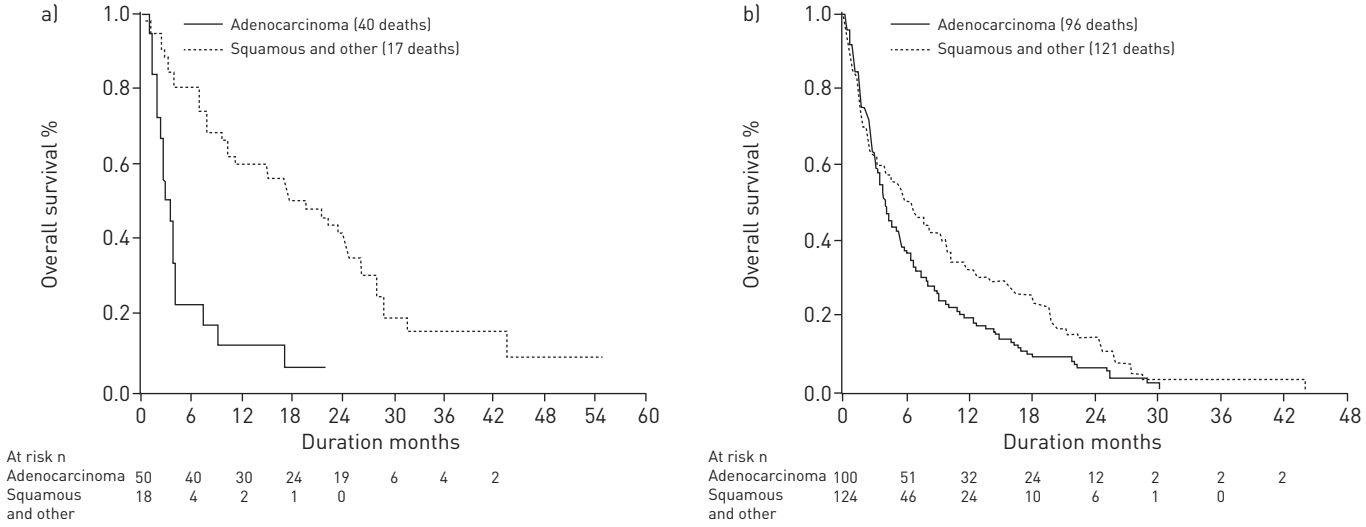

FIGURE 4 Overall survival with erlotinib according to histology. a) Never-smokers. Crude hazard ratio (HR) (95% CI) 0.23 (0.12–0.44), p<0.0001. HR adjusted for performance status and weight loss 0.23 (CI 0.12–0.45), p<0.0001. b) Ever-smokers. Crude HR 0.74 (0.56–0.97), p=0.0300. Adjusted HR 0.80 (0.60–1.05), p=0.1091. Interaction test, p=0.0013. Adjusted interaction test, p=0.0011.

Our study did not examine the role of maintenance therapy. In the Sequential Tarceva in Unresectable NSCLC (SATURN) study, which evaluated the value of maintenance erlotinib *versus* placebo using a randomised design, following four induction cycles with a platinum-based doublet, regardless of *EGFR* mutational status, maintenance erlotinib therapy proved to be of value in terms of overall survival for patients with stabilised disease at the end of induction therapy [17]. Through an exploratory subgroup

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

	Monotherapy arm[#]		Doublet chemotherapy arm[¶]	
	Grade 3	Grade 4	Grade 3	Grade 4
Subjects	26	2	32	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)	
Diarrhoea	3 (12)		5 (16)	
Limb oedema	0		1 (3)	
γ-glutamyltransferase increase	0		1 (3)	
Gastric haemorrhage		1		
Gastrointestinal disorder	1 (4)		0	
Hemiplegia	1 (4)		0	
Haemoglobin decrease	0		1 (3)	
Interstitial pneumonitis		1		
Mouth irritation	2 (8)		1 (3)	
Nail infection	0		1 (3)	
Nausea	1 (4)		1 (3)	
Rectal haemorrhage	0		1 (3)	
Reduced general condition	0		2 (6)	
Sensory neuropathy	0		1 (3)	
Subcutaneous emphysema	0		1 (3)	
Vomiting	0		1 (3)	

Data are presented as n or n (%). [#]: n=28; [¶]: n=32.

analysis, however, no benefit was found for patients aged $\geqslant$65 years. 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 performance status, smoking status, initial weight loss and histology in elderly patients receiving second-line therapy. However, although we provide original data on the efficacy of geriatric indexes used in this study (MMS and ADL), in predicting the probability of receiving second-line erlotinib, these indexes did, in fact, fail to significantly influence the probability of survival.

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