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Similar survival rates with first-line gefitinib, gemcitabine, or docetaxel in a randomized phase II trial in elderly patients with advanced non-small cell lung cancer and a poor performance status (IFCT-0301)

G. Des Guetz[a,b], T. Landre[a,b,*], V. Westeel[a], B. Milleron[a], F. Vaylet[a], T. Urban[a], F. Barlesi[a], P.J. Souquet[a], D. Debieuvre[a], D. Braun[a], G. Fraboulet[a], I. Monnet[a], B. Uzzan[a], O. Molinier[a], F. Morin[a], D. Moro-Sibilot[a], J.F. Morère[a]

[a]Intergroupe Francophone de Cancérologie Thoracique (IFCT), Paris, France
[b]Unité de Coordination Onco — Gériatrique (UCOG 93), HUPSSD — APHP, France

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ABSTRACT

Objectives: We evaluated the impact of age in a randomized phase II trial that compared three first-line drugs in elderly patients with advanced non-small cell lung cancer (NSCLC) and a poor performance status (PS).

Materials and Methods: Patients with advanced NSCLC with a PS of 2 or 3 were enrolled into a multicenter randomized trial: arm A, gefitinib; arm B, gemcitabine; and arm C, docetaxel. We performed subgroup analyses according to age.

Results: Between December 2004 and June 2007, 127 patients were enrolled. Analyses were performed between the two subgroups aged <70 years (younger, $n = 56$) and ≥70 years (older, $n = 71$). Patients mainly had adenocarcinoma (46% young vs. 51%: elderly), of which 62% vs. 75% had a PS of 2, respectively. Significantly more elderly patients were women and non-smokers, and there was a non-significant trend towards more PS-2 among the elderly. Progression-free survival (PFS) was 1.4 months (95% CI: 1.1–1.9) for younger compared to 2.3 months (95% CI: 2.1–2.9) for elderly patients. Overall survival (OS) was 2.0 months (95% CI: 1.5–2.4) and 3.7 months (95% CI: 2.4–4.8), respectively. Toxicity did not differ between younger and older patients. NSCLC was better controlled in elderly patients after three cycles of monotherapy compared to younger patients ($p = 0.034$). When adjusted for stratification criteria, age was the main prognostic factor for PFS. Adjusted HRs for PFS was 0.57 (95% CI: 0.38–0.85) for the elderly compared to patients aged <70 years ($p = 0.004$).

Conclusions: Older patients had a decreased risk of progression/death compared to younger patients. Single-agent chemotherapy can be considered for patients aged ≥70 years with a PS of 2.

* *Corresponding author at: UCOG 93, Hôpital René Muret, avenue du Dr Schaeffner, 93270 Sevran, France.* Tel.:+33 1 41 52 59 46; fax: +33 1 41 52 55 66.
E-mail address: thierry.landre@rmb.aphp.fr (T. Landre).

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1. Introduction

The elderly are considered a frail population, and this subgroup of patients is numerically growing and becoming predominant. Approximately two-thirds of patients diagnosed with non-small cell lung cancer (NSCLC) are ≥65 years, and nearly 50% are aged ≥70 years.[1] Treatment for older patients and patients with a performance status (PS) score of 2 is often the same. These patients usually have comorbidities and their treatments are controversial. Because of feared hematological side effects with doublet chemotherapies, single-agent chemotherapies are usually proposed. In the SEER database, only 25.8% of the 21,285 patients with NSCLC and aged ≥66 years received first-line chemotherapy.[6]

Patients with PS 2 or 3 represent a substantial fraction of patients with advanced NSCLC,[2] yet these patients have been largely excluded from clinical research in the past decade. These patients tend to tolerate treatment poorly and have significantly inferior survival rates compared to patients with a PS of 0 or 1.[3–5] Patients with PS 2 or 3 NSCLC are particularly difficult to manage.

Intergroupe Francophone de Cancérologie Thoracique ([IFCT]-0301) phase-II randomized trial that prospectively evaluated three different single therapies in unselected NSCLC patients with PS 2 or 3.[6] In the IFCT-0301 study, gefitinib, gemcitabine, and docetaxel achieved similar results. Median progression-free survival (PFS) was 1.9 months in the gefitinib arm, 2.0 months in the gemcitabine arm, and 2.0 months in the docetaxel arm (Hazard Ratio [HR] for gemcitabine vs. gefitinib: 0.74, 95% CI: 0.48–1.16, HR for docetaxel vs. gefitinib: 0.69, 95% CI: 0.43–1.05). Docetaxel was associated with higher rates of adverse events.

Considering the benefit:risk ratios for these frail older patients with NSCLC seems crucial.[7] The choice between single-drug and doublet chemotherapy, or even of palliative treatment, remains a challenge. Elderly patients with a PS of 2 have not been thoroughly assessed in published studies.

This present study reports the post-hoc analyses of data from the IFCT-0301 study to assess the impact of age on prognosis and to compare the efficacy and tolerance of a single-drug treatment with a targeted therapy (gefitinib)[8] or two single-drug chemotherapies (gemcitabine and docetaxel).

2. Patients and Methods

2.1. Study Design

A subgroup analysis was conducted according to age (<70 vs. ≥70 years) using the database constructed for the patients enrolled in the IFCT-0301 study.

Patients, aged 18–80 years, with cytological or pathological confirmation of stage IIIB (malignant effusion) or IV NSCLC were included in the IFCT-0301 study if they had a measurable disease that could be assessed and a PS of 2 or 3, according to Eastern Cooperative Oncology Group (ECOG) criteria. Patients, who were enrolled from all participating institutions, were randomly assigned to receive gefitinib (250 mg orally once daily) or gemcitabine IV (1250 mg/m^2 on days 1 and 8, and then every 3 weeks), or docetaxel IV (75 mg/m^2 on day 1 and then every 3 weeks). The randomized treatment was given until progression or toxicity. Patients were followed for survival. Patients who experienced progression, did not tolerate treatment, or refused further chemotherapy were allowed to cross-over to gefitinib provided that they still met the initial eligibility criteria. Patients who progressed after gefitinib were treated with docetaxel (75 mg/m^2 on day 1 and then every 3 weeks).

Patients who had undergone previous therapy to inhibit epidermal growth-factor receptors (EGFR) or prior thoracic radiotherapy were excluded. Patients with locally advanced disease amenable to a combined-modality therapy were also excluded. Adequate organ function was required. Patients with any other serious medical condition that might impair their ability to receive the scheduled protocol therapy were excluded. Patients with prior or concurrent active malignancies, except for in situ carcinoma of the cervix, basal-cell carcinoma of the skin, or a tumor in complete remission at >5 years after surgery, were also excluded. All types of histology were included because of the rather small number of eligible patients and to obtain more data. The Charlson comorbidity index was evaluated for each patient.[9] All patients provided their written informed consent.

Random assignment was performed by the IFCT data center. The random assignment of patients was done according to block-stratified performance status (PS 2 vs. PS 3) and pathological diagnosis (adenocarcinoma vs. non-adenocarcinoma).

Toxicity was assessed every cycle using the National Cancer Institute Common Toxicity Criteria (NCI CTC), version 3.0. No dose modification of gefitinib was allowed. For gemcitabine, the first dose reduction was to 940 mg/m^2; growth factors were also allowed in cases of neutropenia after this dose reduction. Further reductions were not allowed. For docetaxel, the first dose reduction was to 60 mg/m^2 associated with growth factors. Further reductions were not allowed. Unfortunately, the numbers of patients who had dose reductions were not recorded. Similarly, the numbers of hospitalizations were not recorded. Response to treatment was assessed by imaging every 9 weeks and was evaluated by Response Evaluation Criteria In Solid Tumors.

2.2. Statistical Analysis

The primary goal was to assess the efficacy of gefitinib (a targeted anti-EGFR therapy) and of standard single-drug chemotherapy in PS 2–3 populations. The primary end point was PFS, defined as the time from the first day of treatment until the first day of progression, or until death in the absence of progression. The tested hypothesis was an increase in median PFS from 9 weeks (referent treatment with best supportive care [BSC]) to 18 weeks. To obtain a 95% confidence interval (95% CI) from 13 to 24 weeks, with a two-sided alpha of 5% and a power of 80%, 40 patients were needed in each arm. Assuming that 5% of patients would not be assessed, 42 patients in each arm would be needed. Additional endpoints included response rates, overall survival (OS), and toxicities. OS was calculated as the time from random assignment into the study until the date of death resulting from any cause.

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All patients who received at least one dose of gefitinib, gemcitabine, or docetaxel were considered for assessment of PFS, OS, and safety (modified intent-to-treat analysis).

Patients who received at least 21 days of gefitinib or one cycle of chemotherapy and had disease reassessed were considered evaluable for response. The median time to an event and 95% CIs were estimated from Kaplan–Meier curves. A log-rank test was used to explore time-to-event outcomes. Analyses of patients' baseline characteristics were performed for eligible patients. Adverse events were based on the investigator's attribution of causality. Differences in proportions were analyzed by the chi-squared test or Fisher's exact test (or the Freeman–Halton test), as necessary. Differences in median age were analyzed by the Wilcoxon test. Statistical analyses were carried out using SAS software, version 9.1 (SAS Institute Inc., Cary, NC, USA). Regression analysis, using Cox's model, was conducted to determine the prognostic factors associated with survival.

3. Results

3.1. *Patient Characteristics*

From December 2004 to June 2007, 127 patients were randomized to receive gefitinib (43 patients), gemcitabine (42 patients), or docetaxel (42 patients). A total of 71 patients (56%) were aged ≥70 years and 56 patients (44%) were aged <70 years. Baseline clinical and demographic data are summarized in Table 1. Median age was 73 years in the elderly group (range: 70–80) and 62 years in the younger group (range: 30–69). Prognostic characteristics were well balanced between the elderly and younger patients: i.e., regarding stage IIIb/IV, histology, and treatment arm. Gender ratio was different for the elderly population, with more women. There were significantly more non-smokers among elderly patients and a non-significant trend for more patients with PS of 2 compared to PS of 3 among the elderly. Among patients aged >70 years, 36% were aged >75 years, but only three patients were aged 80 years.

3.2. *Efficacy*

Anti-tumor activities in the two age groups are summarized in Figs. 1 and 2. In the intention-to-treat analysis, overall response rates for patients aged ≥70 and <70 years were 34.9% (95% CI: 26.0–43.9) and 44.7% (95% CI: 38.3–51.1), respectively ($p = 0.081$). Tumor-growth control in the two age groups was 58.8% and 73.0%, respectively. For evaluable patients, response rate and tumor-growth control were 41.8% (95% CI: 31.7–51.9) and 70.4% in the elderly group, respectively, and 48.6% (95% CI: 41.9–55.3) and 74% in the younger group ($p = 0.386$). Median duration of response was similar among both groups of patients: 9.3 weeks for elderly patients and 9.2 weeks for younger patients, respectively.

PFS was 1.4 months (95% CI: 1.1–1.9) for the younger patients and 2.3 months (95% CI: 2.1–2.9) for the elderly patients (Fig. 3). OS was 2.0 months (95% CI: 1.5–2.4) for the younger patients and 3.7 months (95% CI: 2.4–4.8) for the older patients (Fig. 4). Toxicity did not vary between the younger and older patients (Table 2).

Disease was significantly better controlled in elderly patients after three cycles of monotherapy when compared to younger patients ($p = 0.034$). Adjusted for stratification criteria (PS and histology), treatment arm, weight loss, and brain metastasis; age was the preponderant prognostic factor for PFS (Table 3). Adjusted HRs for PFS were 0.57 (95% CI: 0.38–0.85) for patients aged ≥70 years compared to patients aged <70 years ($p = 0.004$). Elderly patients had a decreased risk (40%) of progression/death compared to younger patients.

Table 1 – Population characteristics by age (eligible population).

		<70 years (n = 56)	≥70 years (n = 71)	Total (n = 127)	*p*
Age	(Median, range)	62 [30–69]	73 [70–80]	71 [30–80]	
Gender	Female	5 (8.93%)	17 (23.9%)	22 (17.3%)	0.02
	Male	51 (91.1%)	54 (76.1%)	105 (82.7%)	
Never smoker	No	56 (100%)	63 (88.7%)	119 (93.7%)	0.008
	Yes	0 (0%)	8 (11.3%)	8 (6.3%)	
Arm	A	21 (37.5%)	22 (31%)	43 (33.9%)	0.72
	B	18 (32.1%)	24 (33.8%)	42 (33.1%)	
	C	17 (30.4%)	25 (35.2%)	42 (33.1%)	
Performance status	2	35 (62.5%)	53 (74.6%)	88 (69.3%)	0.14
	3	21 (37.5%)	18 (25.4%)	39 (30.7%)	
Weight loss ≥5%	No	10 (18.9%)	19 (28.4%)	29 (24.2%)	0.22
	Yes	43 (81.1%)	48 (71.6%)	91 (75.8%)	
Charlson Score	0	17 (30.4%)	18 (25.3%)	35 (27.6%)	0.50
	1	21 (37.5%)	25 (35.2%)	46 (36.2%)	
	2	13 (23.2%)	15 (21.1%)	28 (22.0%)	
	≥3	5 (8.9%)	13 (18.3%)	18 (14.2%)	
Brain metastasis	Yes	6 (13.0%)	4 (6.9%)	10 (9.62%)	0.29
Stage	IIIb	10 (17.9%)	13 (18.3%)	23 (18.1%)	0.95
	IV	46 (82.1%)	58 (81.7%)	104 (81.9%)	
Histology	Adenocarcinoma	26 (46.4%)	36 (50.7%)	62 (48.8%)	0.50
	Squamous	14 (25.0%)	21 (29.6%)	35 (27.6%)	
	Other	16 (28.6%)	14 (19.7%)	30 (23.6%)	

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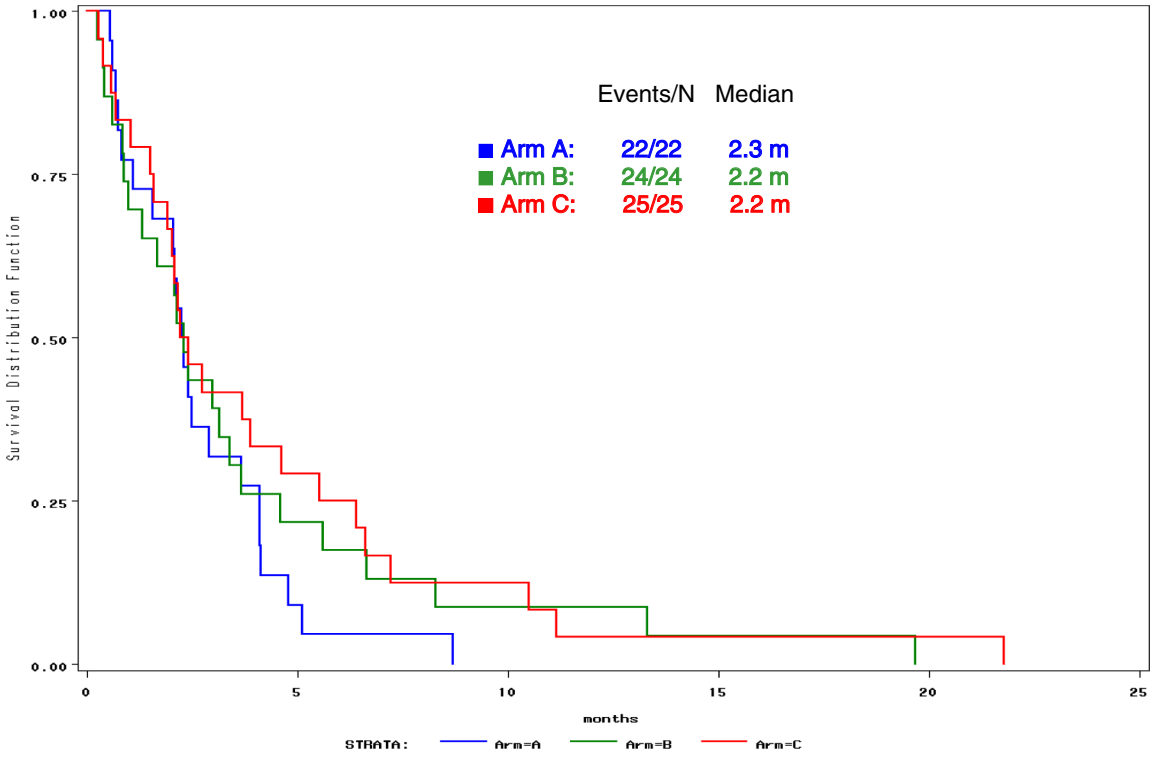

Fig. 1 – Progression-free survival by arm: aged ≥70 years.

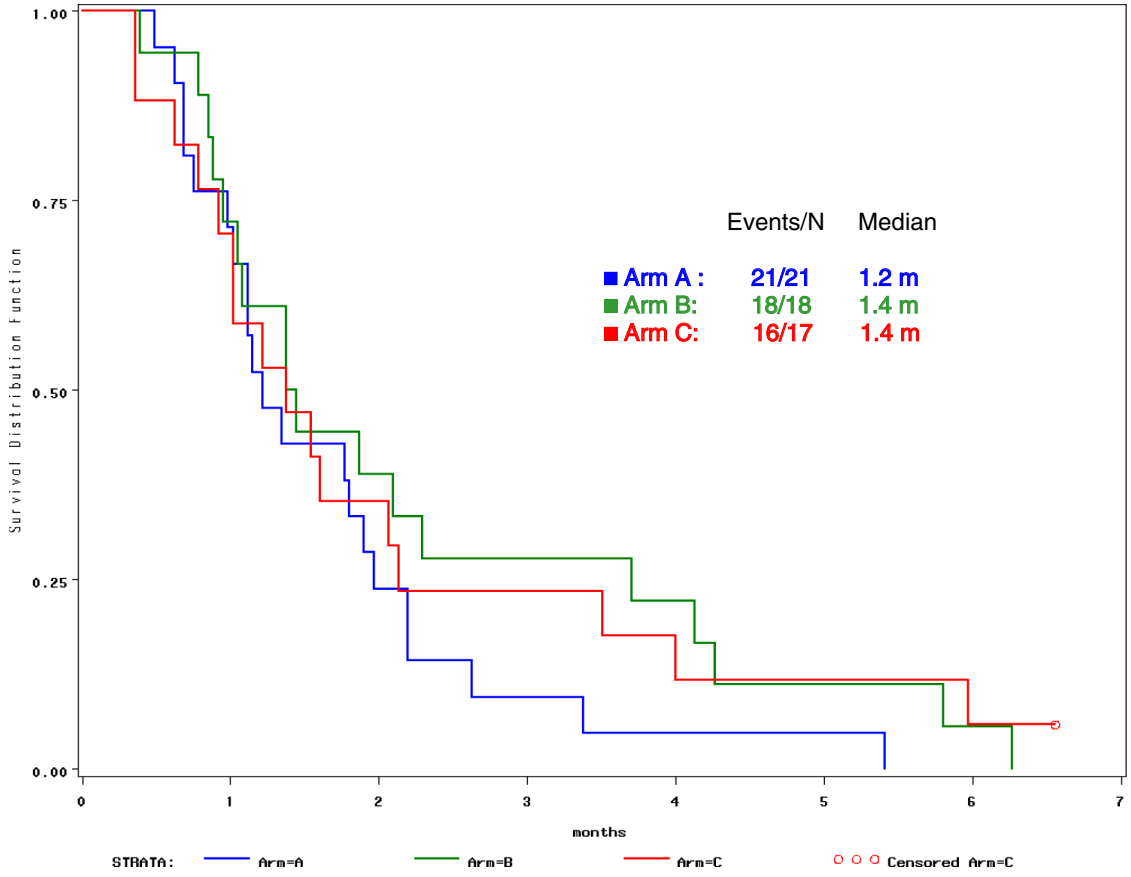

Fig. 2 – Progression-free survival by arm: aged <70 years.

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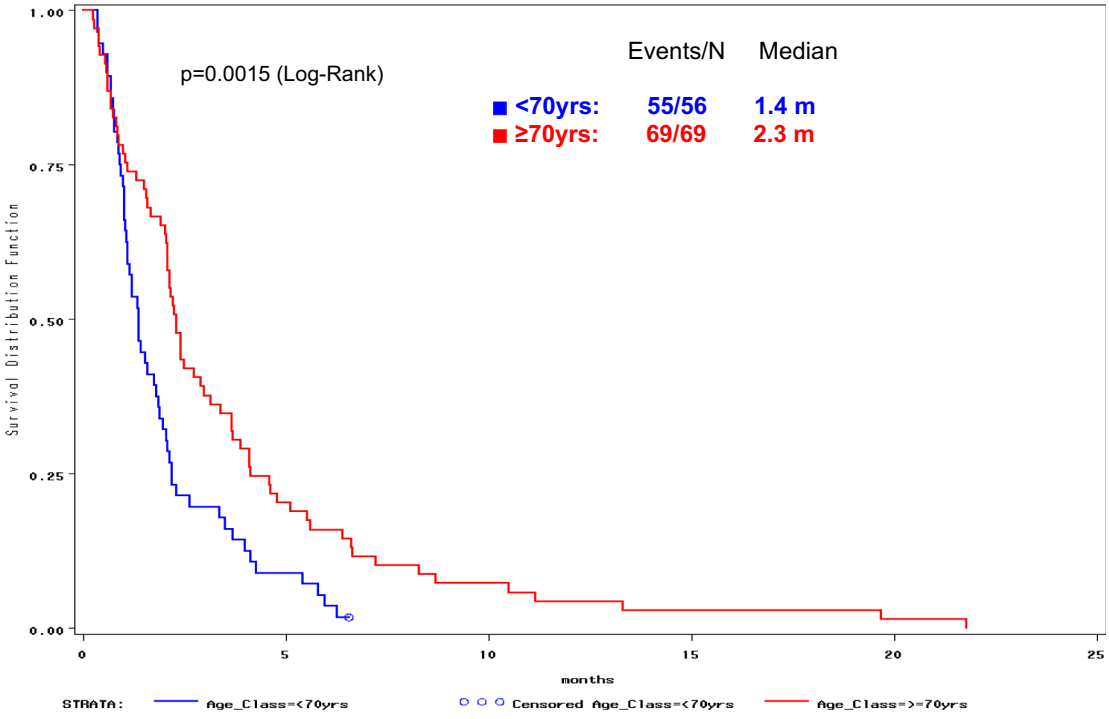

Fig. 3 – Progression-free survival by age.

4. Discussion

The main result of this substudy on frail elderly patients is that a single-drug therapy is feasible and beneficial for these patients at the expense of acceptable toxicity. To our knowledge, this is the first study to specifically address this issue. Accordingly, PFS and OS were very short among patients with an aggressive disease that was resistant to chemotherapy.

The multivariate analysis showed that being older was beneficial in terms of survival. In this study, there was no difference in toxicity between older and younger patients. Tolerance was rather good in both groups, although tolerance

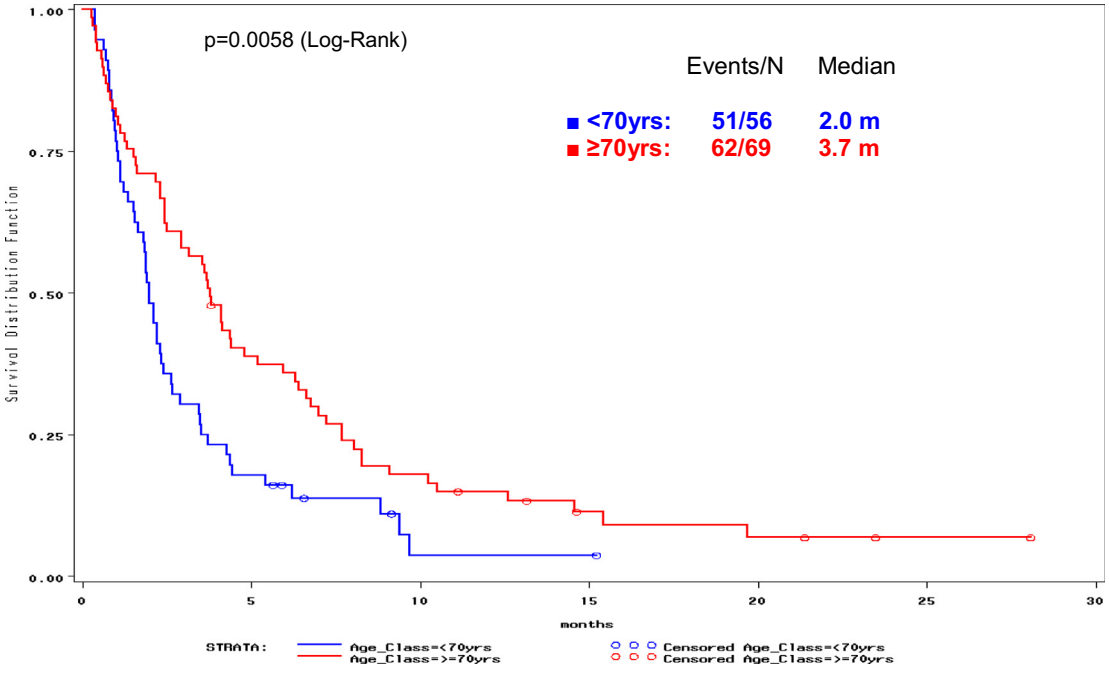

Fig. 4 – Overall survival according to age.

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Table 2 – Toxicity by age.

	<70 years (n = 56)				≥70 years (n = 69)				p
	All grades		3/4 Grade		All grades		3/4 Grade		
	N	%	N	%	N	%	N	%	
All	41	73.2	21	37.5	52	73.2	24	33.8	0.784
Alopecia	3	5.4	0	0.0	5	7.0	0	0.0 -	
Anemia	12	21.4	3	5.4	12	16.9	4	5.6	0.569
Anorexia	2	3.6	1	1.8	2	2.8	0	0.0 -	
Constipation	4	7.1	1	1.8	4	5.6	0	0.0 -	
Diarrhea	9	16.1	2	3.6	14	19.7	1	1.4	0.545
Fatigue	6	10.7	2	3.6	5	7.0	3	4.2 -	
Myalgia	0	0.0	0	0.0	1	1.4	0	0.0 -	
Nausea/Vomiting	7	12.5	2	3.6	14	19.7	0	0.0	0.246
Neuropathy peripheral	3	5.4	3	5.4	4	5.6	3	4.2 -	
Neutropenia	10	17.9	7	12.5	17	23.9	12	16.9	0.360
Rash	11	19.6	1	1.8	14	19.7	2	2.8	0.928
Respiratory	5	8.9	2	3.6	2	2.8	2	2.8 -	
Thrombocytopenia	2	3.6	0	0.0	6	8.5	3	4.2 -	

to chemotherapy is usually considered to be poorer in elderly patients, particularly hematological toxicities. In the IFCT-0301 study,[6] docetaxel was significantly more toxic than the other two treatments. Diarrhea was more frequent in the gefitinib group and neutropenia in the docetaxel group.[6] Hematological toxicity is reported to be slightly greater in younger compared to older patients with NSCLC.[10] In a retrospective study that included 976 patients, hematological toxicity was mainly observed during the first cycle of chemotherapy for all age groups.[11] Generally, doses of chemotherapy are reduced in older patients with NSCLC.

The main limitation of our study is that it was retrospective. However, the choice of a cut-off age of 70 years limits the consequences of the retrospective nature of this study, as median age was 71 years. A prospective study would probably have chosen a cut-off of 75 years. Another limitation is the rather small sample size.

The National Comprehensive Cancer Network (NCCN) guidelines classify older patients into three categories: patients aged 65–75 years, older patients aged 76–85 years, and the oldest patients aged >85 years. In this study, the cut-off for age was chosen close to the median age to facilitate statistical analyses. It should be noted that no patients were aged >80 years and that elderly patients in this study had a somewhat lower PS score compared to younger patients (37% PS3 for younger patients vs. 25% for older patients). Elderly patients also had less weight loss: this implies that the elderly patients were relatively "fit" in our study.

Geriatric assessment was not initially scheduled, but several items have been included as part of this geriatric

Table 3 – Progression-free survival: Cox's model univariate and multivariate analyses.

		Univariate		Multivariate	
		HR [95% CI]	p	HR [95% CI]	p
Arm	A	1.49 [0.95–2.32]	0.080	1.27 [0.79–2.05]	0.324
	B	1.11 [0.72–1.73]	0.633	0.83 [0.51–1.34]	0.448
	C	1.00	–	1.00	–
Age	**≥70 years**	**0.55 [0.38–0.80]**	**0.002**	**0.60 [0.40–0.91]**	**0.015**
	<70 years	**1.00**	–	**1.00**	–
PS	3	1.41 [0.96–2.06]	0.081	1.27 [0.82–1.97]	0.276
	2	1.00	–	1.00	–
Histology	SCC	0.92 [0.61–1.40]	0.710	0.76 [0.47–1.23]	0.267
	Other	1.05 [0.67–1.64]	0.842	0.78 [0.45–1.35]	0.369
	ADC	1.00	–	1.00	–
Weight loss ≥5%	Yes	1.30 [0.84–2.00]	0.238	1.14 [0.72–1.81]	0.568
	No	1.00	–	1.00	–
Brain metastasis	Yes	1.10 [0.58–2.11]	0.767	1.09 [0.55–2.14]	0.808
	No	1.00	–	1.00	–
Never smoker	**No**	**2.46 [1.14–5.31]**	**0.022**	2.55 [0.86–7.57]	0.092
	Yes	**100**		1.00	
Gender	Male	1.41 [0.87–2.29]	0.158	0.69 [0.36–1.31]	0.262
	Female	1.00		1.00	
Charlson score	≥2	0.96 [0.67–1.39]	0.849	0.95 [0.61–1.49]	0.828
	<2	1.00		1.00	

Abbreviations: SCC, squamous cell carcinoma; ADC, adenocarcinoma.

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study. Weight loss is part of nutritional assessment and was recorded for each patient. Patients had to provide an informed consent, which consequently excluded patients with severe dementia. The Charlson comorbidity score was also included in the assessment. As expected, this score was higher among elderly patients (18.3% older vs. 8.9% younger patients that had >3 comorbidities). In addition, the elderly patients included in our trial did not have a major loss of autonomy.

Assessment of EGFR mutation status was not initially scheduled, which represents a limitation of this study, but there were probably few mutated adenocarcinomas in our population. Results could have been better for the subgroup treated with gefitinib if more patients in this subgroup had presented with EGFR mutations.

In this study, three cycles of single-drug therapy resulted in better disease control in elderly patients compared to the younger patients, with no significant differences between the three drugs (gefitinib, gemcitabine, docetaxel). These rather paradoxical results might be explained by an imbalance in some of the patients' characteristics between the elderly and younger patients. After adjustment for stratification criteria, treatment arm, weight loss, and the presence or absence of brain metastasis, elderly patients had similar benefits from the treatments.

PS score is an imperfect reflection of well-being and impact on daily-living activities because it is indirectly influenced by age and the resultant decreased activity. Therefore, the better results for OS and PFS observed among our elderly patients could be explained, at least in part, by improper interpretation of PS scores in elderly patients. Functional status and performance status do not always correlate well.

The ELVIS study on elderly patients with NSCLC (where patients with a PS of 2 represented 25–30% of the cohort) was the first to compare vinorelbine and best supportive care (BSC), and found a statistically better OS, although this benefit was clinically moderate with vinorelbine (6 months vs. 5 months).[12] Our study included a greater number of older patients with a PS 2 score (i.e., 65%) with a poor survival. It did not include a treatment arm with BSC only. Our results suggest that BSC could represent an alternative to chemotherapy or targeted therapy.

A meta-analysis, published in 2013,[13] evaluated BSC alone or with chemotherapy. OS varied from 2.7 to 5.9 months in patients who received BSC alone: this is in accordance with our results where OS was 3.7 months among the elderly. It should be noted that none of the meta-analysis studies included patients with a PS of 2 or 3. In a phase-III study, Zukin et al.[14] compared carboplatin/pemetrexed with pemetrexed alone in metastatic cases of PS 2 lung adenocarcinoma and found better overall survival after a bitherapy (9 months vs. 5 months). This result is at variance with ours, which included frail and older patients with a PS 2 and PS 3. These data should be considered in future studies on the elderly population.

According to our results, patients aged ≥70 years had a 40% decreased risk of disease progression/death compared to younger patients: this may be partly explained by selection bias of the elderly patients. Thus, despite the limitations of this study, age per se does not appear to be an adverse prognostic factor or a contra-indication for single-drug chemotherapy in this PS 2 population.

Conflict of Interest Statement

Milleron Bernard: consultancies (Astra Zeneca, Eli Lilly, Sanofi-Aventis). Moro-Sibilot Denis: consultancies (Astra Zeneca, Roche Eli Lilly), honoraria (Astra Zeneca, Roche Eli Lilly), other funding (Sanofi-Aventis). Remaining authors have no conflict of interest.

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Pr Virginie Westeel CHU Besançon, Bobigny, Pr Jean-Francois Morere CHU Avicenne Bobigny, Dr Bernard Milleron CH Tenon Paris, Pr Bernard Lebeau CH Saint-Antoine Paris, Dr Fabien Vaylet HIA Clamart–Percy, Dr Fabrice Barlesi Hôpital Sainte Marguerite APHM Marseille, Pr Thierry Urban CHU Angers, Pr Denis Moro-Sibilot CHU Grenoble, Dr Pierre-Jean Souquet CH Lyon–Sud, Dr Didier Debieuvre CHI Vesoul, Dr Denis Braun CH Briey, Dr Gislaine Fraboulet CH Pontoise, Dr Alain Riviere CAC Caen, Pr Gérard Zalcman CHU Caen, Dr Isabelle Monnet CHI Créteil, Dr Olivier Molinier CHG Le Mans, Dr Jean-Philippe Oster CH Colmar, Dr Philippe David CHI Elbeuf, Pr Elisabeth Quoix CH Lyautey Strasbourg,Dr Lionel Uwer CAC Vandoeuvre-lès-Nancy, Dr Philippe Bonnefoy CH Jonzac, Dr Gérard Oliviero CH Longjumeau, Dr Paul Rebattu CAC Lyon, Dr Jacques Hermann CH Metz–Belle-Isle, Dr Xu-Shan Sun CH Montbéliard, Dr Jean-Francois Bic Polyclinique Gentilly Nancy, Dr Alain Prevost CAC Reims, Dr Alain Ducolone CH Haute Pierre Strasbourg, Dr Laurence Bigay-Game CHU Larrey Toulouse.

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