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Original Research

Switch maintenance chemotherapy versus observation after carboplatin and weekly paclitaxel doublet chemotherapy in elderly patients with advanced non–small cell lung cancer: IFCT-1201 MODEL trial

Elisabeth Quoix [a,*], Clarisse Audigier-Valette [b], Armelle Lavolé [c], Olivier Molinier [d], Virginie Westeel [e], Fabrice Barlesi [f], Jacques Le Treut [g], Eric Pichon [h], Jérôme Dauba [i], Josiane Otto [j], Lionel Moreau [k], Jeannick Madelaine [l], Patrick Dumont [m], Jacques Margery [n], Didier Debieuvre [o], Patrick Aldo Renault [p], Jean-Louis Pujol [q], Alexandra Langlais [r], Franck Morin [r], Denis Moro-Sibilot [s], Pierre-Jean Souquet [t]

[a] *Department of Pneumology, University Hospital of Strasbourg, Strasbourg, France*
[b] *Department of Pneumology, Toulon Sainte-Musse Hospital, Toulon, France*
[c] *Department of Pneumology, Tenon Hospital, Paris, France*
[d] *Department of Pneumology, Hospital of Le Mans, Le Mans, France*
[e] *Department of Pneumology, University Hospital of Besançon, Besançon, France*
[f] *Multidisciplinary Oncology and Therapeutic Innovations Department, Aix Marseille University, CNRS, INSERM, CRCM, APHM, Marseille, France*
[g] *Department of Pneumology, Pays D'Aix Hospital, Aix-en-Provence, France*
[h] *Department of Pneumology, University Hospital of Tours, Tours, France*
[i] *Department of Medical Oncology, Hospital Layné, Mont-de-Marsan, France*
[j] *University of Côte D'Azur, Nice, France*
[k] *Department of Pneumology, Louis Pasteur Hospital, Colmar, France*
[l] *Department of Pneumology, University Hospital of Caen Normandie, Caen, France*
[m] *Department of Pneumology, Hospital of Chauny, Chauny, France*
[n] *Department of Pneumology, Hôpital D'Instruction des Armées Percy, Clamart, France*
[o] *Department of Pneumology, GHRMSA, Emile Miller Hospital, Mulhouse, France*
[p] *Department of Pneumology, Hospital of Pau, Pau, France*
[q] *Department of Thoracic Oncology, Montpellier Regional University Hospital, Montpellier, France*
[r] *Intergroupe Francophone de Cancérologie Thoracique, Paris, France*
[s] *Thoracic Oncology Unit, Grenoble-Alpes University Hospital, Grenoble, France*
[t] *Department of Pneumology and Thoracic Oncology, Hospital of Lyon Sud, Lyon, France*

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* *Corresponding author*: Service de pneumologie, Pôle de pathologie thoracique, Hôpitaux universitaires de Strasbourg, 1 place de l'Hôpital, BP 426, 67091 Strasbourg Cedex, France.
E-mail address: equoix@gmail.com (E. Quoix).

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KEYWORDS
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Abstract ***Purpose:*** Maintenance chemotherapy is a reasonable choice for patients with metastatic non–small cell lung carcinoma (NSCLC) not progressing after induction therapy with a platinum-based doublet. Nevertheless, there have been no studies dedicated to elderly patients.
Patients and methods: We conducted a randomised trial in patients aged 70–89 years, with advanced NSCLC (with neither EGFR mutation nor ALK rearrangement), who had not progressed after four cycles of monthly carboplatin and weekly paclitaxel in order to compare maintenance with either pemetrexed (500 mg/m^2 d1, 22) in patients with non–squamous cell carcinoma or gemcitabine (1,150 mg/m^2 d1, 8, 22) in squamous cell carcinoma to simple observation. The patients were required to have a performance status (PS) 0–2, mini-mental score >23, and creatinine clearance ≥45 mL/min. The primary end-point was overall survival (OS).
Results: 632 patients were enrolled from May 2013 to October 2016. Of the 328 (52.3%) patients randomised after induction therapy, 166 patients were assigned to the observation arm, versus 162 to the switch maintenance arm, 119 of whom received pemetrexed and 43 gemcitabine. The median OS from randomisation was 14.1 months (95% confidence interval [CI]: 12.0–17.0) in the observation arm and 14 months (95% CI: 10.9–16.9) in the maintenance arm ($p = 0.72$). The median progression-free survival (PFS) from randomisation was 2.7 months (95% CI: 2.6–3.1) in the observation arm versus 5.7 months (95% CI: 4.8–7.1) in the maintenance arm ($p < 0.001$).
Conclusion: Switch maintenance therapy significantly prolonged PFS but not OS and, thus, should not be proposed to elderly patients with advanced NSCLC.

1. Introduction

Almost 50% of non–small cell lung carcinoma (NSCLC) is diagnosed at an advanced stage. Although significant survival improvements have been evidenced for patients with a driver mutation or rearrangement and, more recently, for those receiving checkpoint inhibitors with or without chemotherapy, a significant number of patients with a stage IV disease continue to be treated with a platinum-based doublet as recommended since 2009 [1]. For elderly patients, the first-line chemotherapy choice should not be based on age alone. In 2011, an updated recommendation addressed the issue of 'switch maintenance' therapy [2], based on five randomised clinical trials [3–7], recommending it for patients with stable disease or response after four cycles of induction. However, there was either no subgroup analysis of age impact [3,4] or an upper limit of age of 70 years [7] and 75 years [6].The PARAMOUNT study randomly assigned patients who did not progress after 4 cycles of cisplatin–pemetrexed to either follow-up or pemetrexed maintenance therapy [8]. More than 1000 patients were enrolled, and progression-free survival (PFS) and overall survival (OS) benefits were noted in the maintenance arm. In the subgroup analysis on patients aged ≥70 years, there was a PFS benefit that did not translate into an OS benefit.

The French Cooperative Thoracic Intergroup (IFCT) thus decided to conduct a randomised study in elderly patients with advanced NSCLC who did not progress after a four-cycle induction CT consisting of carboplatin + weekly paclitaxel [9,10], comparing observation and switch maintenance therapy with either pemetrexed for non–squamous cell carcinoma or gemcitabine for squamous cell carcinoma.

2. Methods

2.1. Study design and patients

Patients should have a histologically/cytologically confirmed stage IV or III not amenable to surgery or radiotherapy NSCLC, an age between 70 and 89 years, a performance status (PS) 0–2, a mini-mental score (MMS) > 23/30 and appropriate hepatic and renal functions and haematopoietic reserves.

The key exclusion criteria were as follows: *EGFR* mutations or *ALK* rearrangement; symptomatic brain metastases; previous anticancer treatment; severe and/or uncontrolled comorbidities; interstitial lung disease; peripheral neuropathy grade ≥2; previous history of cancer unless skin basal cell or *in situ* cervical cancer, or any other cancer treated curatively without progression over the last five years. At randomisation, the patients were eligible if they were either responders or stabilised

by induction treatment, if their PS was 0–2 with the biological requirements being the same as for induction treatment.

All patients provided their written informed consent before inclusion. The protocol was approved by the Committee of Protection of People Participating in Clinical Research on February 5, 2013 and registered under the following: N° EUDRACT: 2012-005520-15.

2.2. Randomisation and masking

An interactive web response system–generated random treatment allocation, with a 1:1 ratio. This randomisation was unblinded. A minimisation method (random factor of 0.8) was applied, with patients stratified based on response after four induction cycles (objective response versus stabilisation), PS at randomisation (0–1 vs 2), histology (non–squamous versus squamous), age (70–79 versus 80–89), and centre.

2.3. Procedures

During the induction phase, the patients were treated with carboplatin AUC 6 (day 1 every four weeks) and paclitaxel 90 mg/m^2 (days 1, 8, and 15 of each cycle) [9]. The maintenance schedule was pemetrexed 500 mg/m^2 every three weeks for patients with non–squamous cell carcinoma and gemcitabine 1150 mg/m^2 on days 1 and 8 of each three-week cycle for squamous cell carcinoma. Maintenance had to begin 42 days after the end of induction at the latest and was administered until progression, unacceptable adverse events, or patients' or doctors' decision to stop treatment. The patients were followed-up until death or study closure. Dose adjustments, delays, or omission of a treatment day during both induction and maintenance phases were allowed within the protocol guidelines.

After progression, the recommended second-line treatment (2L) was erlotinib 150 mg/d in both arms in accordance with its previous label in NSCLC without driver mutation [11].

A geriatric assessment (comprising MMS [12], instrumental activity daily living [IADL] [13], geriatric depression scale [GDS] [14], and ONCODAGE score [15]) was performed before induction and at randomisation (for the GDS and ONCODAGE). The indexes' cutoff values indicating abnormal scores were $\leq$23, $\leq$7, $\geq$5, and $\leq$14, respectively (appendix Tables 1–4). Quality of life results using the Lung Cancer Symptom Scale [16] will be provided in a dedicated publication.

All patients underwent within 4 weeks before the day 1 of induction therapy a thoracic and upper abdominal computed tomography (CT) scan, as well as CT scan or magnetic resonance imaging of the brain. Reassessments using RECIST1.1 were performed after 2 and 4 cycles of induction, after 2 and 4 cycles during maintenance, and every 3 cycles thereafter. In the observation arm, assessments were performed at the same intervals. During 2L, re-evaluations were performed at the same intervals as during maintenance therapy/observation.

2.4. Statistical analyses

The primary end-point was OS, defined as the time from randomisation to death from any cause. The secondary objectives were OS of the whole population of patients enrolled, the response rate to induction, feasibility of maintenance therapy (median number of cycles administered), PFS (defined as the time from randomisation to progression or death of any cause), response rate to maintenance therapy, toxicity (NCI CTC version 4.0), percent of patients receiving 2L, best response rate, PFS and OS since the beginning of 2L, and identification of prognostic factors of survival.

Demographic and OS analyses were performed on an intention-to-treat basis. All randomised patients were analysed for OS and PFS. All patients who had received at least one cycle of study treatment were included in the safety analyses. The primary OS analysis was based on the following assumptions [9]: median OS of elderly patients who received four cycles of carboplatin–paclitaxel and who had a disease control at the end of induction was 10.2 months from this time. To demonstrate a 4-month benefit of survival (14 months from randomisation) with a bilateral alpha risk of 5% and a power of 80%, 328 patients should be randomised. Given the hypothesis that 60% would be responding or stabilised by induction therapy, a total of 546 patients had to be enrolled. Overall, 278 events had to be observed.

The duration of inclusion was estimated to be 4 years, and the duration of follow-up was estimated at 3 years. After the inclusion of half of the randomised patients, an independent data monitoring committee comprising one statistician and three oncologists had a meeting to check the global quality of the trial.

PFS and OS were plotted with Kaplan–Meier curves and compared with Cox models. The follow-up was censored on July 01, 2018. We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) from a Cox model, adjusting for minimisation variables as appropriate [17]. Planned subgroup analyses for the primary outcome for known risk factors in a Cox model, adjusting for minimisation variables were performed. We tested the potential predictive factors of response by comparing randomised versus non–randomised patients using a logistic regression model. We included factors with a p value less than 0·20 in both multivariable models (Cox model and logistic regression). The SAS version 9.4 software was used for the statistical analyses; all p values and CIs were two-sided.

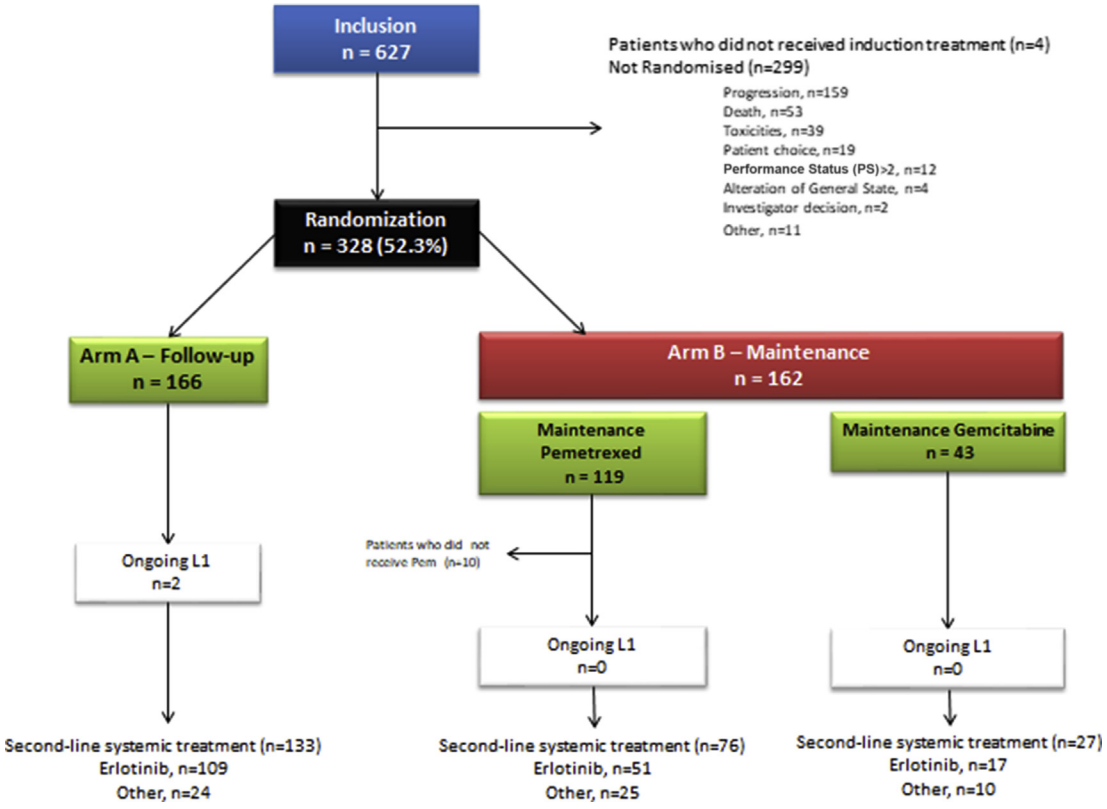

Fig. 1. Trial flow chart.

3. Results

Between May 2013 and October 2016, 632 patients were included at 67 centres. Because of 5 missing informed consents, 627 patients were finally analysed (Fig. 1). A median number of 4 induction cycles (range: 1–4) was administered to the 623 patients who received at least one injection of treatment. Three hundred and twenty-eight patients (52.3%) with non-progressive disease after induction could be randomised, 166 in the observation arm and 162 in the maintenance arm (119 to receive pemetrexed and 43 gemcitabine). The baseline characteristics of all 627 patients are displayed in Table 1. The patient characteristics differed between the randomised

Table 1
Patients characteristics at baseline.

Characteristics	All (N = 627)	Randomised (N = 328)	Non-randomised (N = 299)	p value
Performance status at inclusion N (%)				
0–1	535 (85.3)	289 (89.2)	246 (82.8)	0.02
2	86 (13.7)	35 (10.8)	51 (17.2)	
Stage N (%)				
III	62 (9.9)	39 (11.9)	23 (7.7)	0.08
IV	565 (90.1)	289 (88.1)	276 (92.3)	
Male N (%)	475 (75.8)	238 (72.6)	237 (79.3)	0.05
Age (years): Median (range)	76.4 [70.0–89.4]	76.5 [70.1–89.0]	76.2 [70.0–89.4]	NS
Age ≥80 years (%)	141 (22.5)	71 (21.6)	70 (23.4)	
Never smoker	92 (14.7)	59 (18.0)	33 (11.0)	0.01
Histology subtype N (%)				
Adenocarcinoma	401 (64.0)	216 (65·8)	185 (61·9)	NS
Squamous cell	178 (28.4)	90 (27·4)	88 (29·4)	
Large cell	13 (2·1)	2 (0·6)	11 (3·7)	
NOS	26 (4·1)	16 (4·9)	10 (3·3)	
Other	9 (1·4)	4 (1·2)	5 (1·7)	

NOS = not otherwise specified.

and non-randomised patients by two variables: PS 0–1 patients and never-smokers were more common among the randomized patients. Considering the geriatric assessment (appendix table 5), while there was no significant difference in MMS and IADL between the randomised and non-randomised patients, there were significantly more non-randomised patients with GDS 15 $\geq$ 5 along with ONCODAGE $\leq$14. The univariable analysis taking into account age, gender, PS, smoking history, disease stage, histology, and all geriatric indexes showed that PS 0–1, never-smokers, GDS 15 $<$ 5, and ONCODAGE $>$14 were all associated with the propensity to be randomised. However, the multivariable analysis demonstrated that the only independent variables associated with randomisation were GDS 15 $<$ 5 and ONCODAGE $>$14. The characteristics of the randomised patients are displayed in Table 2. A median of 4 cycles of maintenance therapy were administered, with a mean of 6.9 (range: 1–38) cycles for patients treated with pemetrexed and a mean of 6.3 (range: 1–31) for patients treated with gemcitabine.

The median follow-up of the 627 patients was 39.7 months (range: 20.4–61.5). Median OS of these patients (appendix Fig. 1) was 11 months (95% CI: 9.9–12.0). Multivariate analysis of overall survival taking into account all baseline geriatric indexes (MMS, IADL, GDS 15, ONCODAGE) shows that only PS 2 compared with PS 0–1 (HR: 1.51, 95% CI: 1.16–1.97, p value = 0.002), stage IV compared with stage III (HR = 1.60, 95% CI: 1.16–2.20, p value = 0.004) and ONCODAGE $\leq$ 14 (HR = 1.29, 95% CI: 1.02–1.62, p value = 0.033) were independent prognostic factors of shorter survival. The median OS estimated from the time of randomisation for the 328 randomised patients (Fig. 2) was 14.1 months (95% CI: 12.0–17.0) in the observation arm and 14.0 months (95% CI: 10.9–16.9) in the maintenance arm (p = 0.72). The adjusted HR was 0.91 (95% CI: 0.71–1.16). The forest plot with the adjusted HR for OS on each randomisation strata is illustrated in appendix

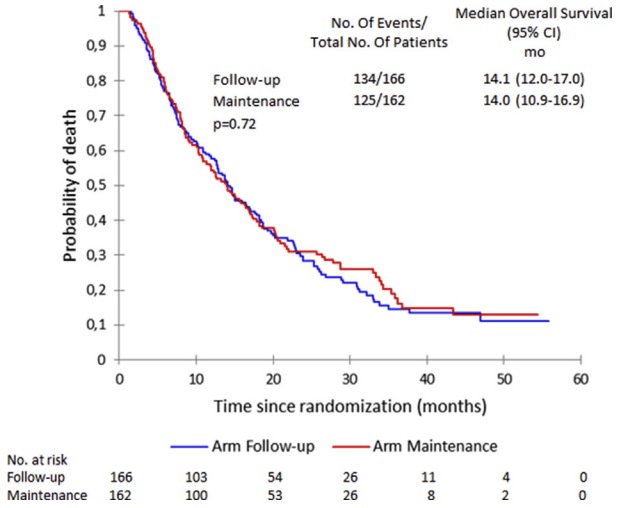

Fig. 2. Overall survival of the randomised patients (from randomisation). CI, confidence interval.

Fig. 2. No significant impact of age ($<$80 versus $\geq$80 years) or PS (0–1 versus 2) was noted. In addition, there was no significant impact of histology and of the response type observed during induction therapy (partial response or stabilisation). Looking at the impact of the two geriatric assessments performed at randomisation, in univariate analysis, the HR value was 1.28, 95% CI: 0.96–1.70, p value = 0.087 for GDS 15 and 1.38, 95% CI: 1.01–1.88, p value = 0.037 for ONCODAGE). In the multivariate analysis (appendix table 6), PS was the only significant determinant of OS whereas ONCODAGE was of borderline significance (p = 0.053).

Patients in the maintenance arm (appendix Fig. 3) had a longer PFS (5.7 months [95% CI: 4.8–7.1]) compared with the observation arm (2.7 months [95% CI: 2.6–3.1]) (p $<$ 0.001). The adjusted HR was 0.51 (95% CI: 0.40–0.64) (p $<$ 0.001). Tumour reduction during maintenance therapy was observed in 20/328 randomised patients (6.1%), namely 6 (3.6%) in the

Table 2
Patients' characteristics at randomisation.

Characteristics	Arm follow-up N = 166	Arm maintenance (N = 162)	Maintenance PEM (N = 119)	Maintenance GEM N = 43
Performance status at randomisation N (%)				
0-1	135 (81.3)	130 (80.2)	93 (78.2)	37 (86)
2	31 (18.7)	32 (19.8)	26 (21.8)	6 (14)
Age				
$<$ 80 years	130 (78.3)	127 (78.4)	92 (77.3)	35 (81.4)
$\geq$ 80	36 (21.7)	35 (21.6)	27 (22.7)	8 (18.6)
Histological subtype N (%)				
Squamous	46 (27.7)	44 (27.2)	1 (0.8)	43 (100)
Non-squamous	120 (72.3)	118 (72.8)	118 (99.2)	0 (0)
Response after four cycles of induction N (%)				
Complete response	1 (0.6)	1 (0.6)	0	1 (2.3)
Partial response	87 (52.4)	76 (46.9	49 (41.2)	27 (62.8)
Stabilisation	76 (45.8)	83 (51.2)	68 (57.1)	15 (34.9)
Progression	2 (1.2)	1 (0.6)	1 (0.8)	0
Not evaluable	0	1 (0.6)	1 (0.8)	0

PEM, pemetrexed; GEM, gemcitabine.

observation arm and 14 (8.6%) in the maintenance arm. The progression rates were 36.3%, 47%, and 25.3%, respectively (p = 0.0004).

During induction therapy, 579 (92.9%) patients had at least one drug-related adverse events, of which 357 (57.3%) had a grade ≥3. There were 12 toxic deaths (1.9%) mostly related to sepsis with or without neutropenia. Regarding randomised population, patients in the maintenance arm exhibited significantly more adverse events of any grade when compared with the observation arm (94.7% and 52.4% respectively, p < 0.001) and of grade ≥ 3 (50.0% vs. 2.4%, p < 0.001) (appendix table 7). The haematological and non-haematological drug-related adverse events are displayed in Tables 3 and 4. There were two deaths attributable to pemetrexed (one sepsis and one febrile neutropenia).

When compared with the maintenance arm, more patients in the observation arm (133: 81.1% vs. 103: 63.6%) were able to receive 2L. Of the 133 observation arm patients receiving 2L, 109 (82.0%) received erlotinib (recommended treatment), 11 (8.3%) nivolumab and 9 (6.8%) another therapy. Of the 103 maintenance arm patients receiving 2L, 68 (66%) received erlotinib, 22 (21.4%) nivolumab and 4 (3.9%) another therapy. The response rate to 2L was 7.8% in the observation arm and 9.4% in the maintenance arm (NS). The OS 2L was 11.7 months (95% CI: 8.8–14.9) in the observation arm and 9.2 months (95% CI: 5.9–13.2) in the maintenance arm (p = 0.48). The PFS 2L was 2.9 months (95% CI: 2.1–4) and 3.2 months (95% CI: 2.2–4.8), respectively.

4. Discussion

In this randomised phase III study comparing observation and switch maintenance chemotherapy, elderly patients in the maintenance arm did not experience OS benefit although they had longer PFS than the observation arm. Moreover, the higher toxicity in the maintenance arm jeopardised this small PFS advantage.

In a previous switch maintenance trial with pemetrexed after four cycles of platinum-based doublet [3], an improvement in both PFS and OS was noted. More drug-related grade ≥ 3 toxicities occurred in the maintenance arm (16% versus 4%) as this was also the case in the herein study; their frequency rates were even higher in our study, probably due to our patients' age and because PS 2 patients were allowed. As in our study, fewer patients in the pemetrexed arm received 2L than those in the observation arm. As for continuation maintenance, a subgroup analysis comparing patients

Table 3
Haematological treatment–related adverse events during maintenance.

Haematological adverse events	Arm follow-up (N = 166)		Maintenance pemetrexed (N = 109)		Maintenance gemcitabine (N = 43)	
	Any grade	Grade 3–4	Any grade	Grade 3–4–5	Any grade	Grade 3–4
Haematological adverse events	50 (30·1%)	2 (1·2%)	86 (78·9%)	39 (35·8%)[a]	37 (86%)	14 (32·6%)
Anaemia	46 (27·7%)	2 (1·2%)	80 (73·4%)	18 (16·5%)	33 (76·7%)	6 (14·0%)
Neutropenia	4 (2·4%)	0 (0%)	49 (45%)	25 (22·9%)	19 (44·2%)	6 (13·9%)
Lymphopenia	5 (3%)	0 (0%)	11 (10·1%)	3 (2·8%)	8 (18·6%)	0%
Thrombocytopenia	3 (1·8%)	0 (0%)	41 (37·6%)	16 (14·7%)	23 (53·5%)	3 (7%)
Febrile neutropenia	0 (0%)	0 (0%)	7 (6·4%)	7 (6·4%)[a]	2 (4·7%)	2 (4·7%)

[a] 1 toxic death.

Table 4
Non–haematological treatment–related adverse events during maintenance (more than 10% of patients except for sepsis).

Non haematological adverse events	Arm follow-up (N = 166)		Maintenance pemetrexed (N = 109)		Maintenance gemcitabine (N = 43)	
	Any grade	Grade 3–4	Any grade	Grade 3–4–5	Any grade	Grade 3–4
Asthenia	13 (7.8%)	1 (0.6%)	58 (53.2%)	14 (12.8%)	15 (34.9%)	4 (9.3%)
Neuropathy peripheral	28 (16.9%)	1 (0.6%)	20 (18.3%)	1 (0.9%)	10 (23.3%)	4 (9.3%)
Renal failure	8 (4.8%)	0 (0%)	23 (21.1%)	3 (2.8%)	4 (9.3%)	0 (0%)
Decreased appetite	5 (3%)	0 (0%)	21 (19.3%)	2 (1.8%)	3 (7%)	0 (0%)
Oedema peripheral	0 (0%)	0 (0%)	25 (22.9%)	2 (1.8%)	4 (9.3%)	0 (0%)
Nausea	0 (0%)	0 (0%)	27 (248%)	0 (0%)	1 (2·3%)	0 (0%)
Aspartate aminotransferase increase	0 (0%)	0 (0%)	18 (16.5%)	4 (3.7%)	3 (7%)	0 (0%)
Conjunctivitis	0 (0%)	0 (0%)	17 (15.6%)	1 (0·9%)	0 (0%)	0 (0%)
Constipation	1 (0.6%)	0 (0%)	12 (11%)	1 (0.9%)	3 (7%)	0 (0%)
Alanine aminotransferase increase	0 (0%)	0 (0%)	12 (11%)	2 (1.8%)	3 (7%)	0 (0%)
Diarrhoea	0 (0%)	0 (0%)	12 (11%)	2 (1.8%)	1 (2.3%)	0 (0%)
Pyrexia	0 (0%)	0 (0%)	7 (6.4%)	0 (0%)	5 (11.6%)	0 (0%)
Vomiting	0 (0%)	0 (0%)	11 (10.1%)	0 (0%)	1 (2.3%)	0 (0%)
Sepsis	0 (0%)	0 (0%)	2 (1.8%)	1 (0.9%)[a]	0 (0%)	0 (0%)

[a] One toxic death.

aged ≥ 70 years and those aged <70 years was performed in the PARAMOUNT study [18]. Only 92 patients (17%) during maintenance therapy were ≥ 70 years, and 17 were ≥ 75 years indicating that there were few very old patients in the PARAMOUNT study. Once again, this illustrates the need for dedicated studies involving elderly patients. Gemcitabine has been explored previously, mainly as a continuation maintenance therapy [7,19,20]. Although there was a significant PFS benefit in 2 studies [7,19], no survival benefit occurred in any of the three studies.

In our study, as expected, more patients in the observation arm could undergo 2L. The survival and PFS on 2L were in line with what was observed with erlotinib in our previous study and the BR21 study [11,21].

The relevance of geriatric indexes is still a matter of controversy. Adapted treatment based on geriatric assessment rather than PS and age did not result in significant outcome differences in a previous trial involving patients aged 70 years and over [22]. In our previous study [9], we incorporated geriatric indexes, such as the MMS and ADL, and we found a prognostic impact of these factors but not any predictive impact. In the herein study the MMS had to be > 23; this probably explains why this index did not exert any prognostic or predictive impact. IADL, GDS 15 and ONCODAGE were of prognostic value in univariate analysis of survival of the 627 patients, and GDS 15 and ONCODAGE (but not PS) had an independent impact on being randomised; however, only ONCODAGE also exhibited an independent prognostic value on OS, in addition to PS and disease stage. Comprehensive geriatric assessment is time-consuming and not easy to implement in a non-geriatric department. ONCODAGE could, thus, be a good surrogate [15].

Our study has several limitations. The choice of the geriatric indexes was somewhat arbitrary, primarily based on the following characteristics: not excessively time-consuming and well-recognised in the literature. The combination of ONCODAGE and IADL appears, in fact, to be of special interest [23]. Another study limitation is the relatively high number of missing values pertaining to the geriatric indexes at the time of randomisation. In addition, erlotinib is no longer recommended as salvage therapy in patients without *EGFR* mutations. Of note, several patients did not receive this recommended 2L, but rather immunotherapy. However, we do not believe that our study conclusions would have differed. It must be stressed that using immune checkpoint inhibitors in the elderly needs to be clarified with respect to the immunosenescence concept [24] and that, in the subgroup analyses of the 2L, patients aged ≥ 75 did not derive the same survival benefit compared with their younger counterparts [25,26]. When the cutoff was 65 years, instead, no outcome differences were observed [27].

In conclusion, 'stop and go' attitude appears more appropriate in elderly with advanced NSCLC, as more patients without maintenance can undergo 2L, which results in a similar survival rate with less toxicity. Given the possibility of maintenance with chemotherapy plus checkpoint inhibitors being one of the new standards of treatment in fit patients [28], this could possibly not be applied to elderly patients.

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Author contribution

EQ was the principal investigator of the trial and was involved in conception and study design. All investigators, including FM and AL, were involved in the data collection. All authors contributed to the data analysis, data interpretation, the writing and the approval of the final manuscript.

Conflict of interest statement

EQ reports grants from Roche, grants from Boehringer Ingelheim, during the conduct of the study; personal fees and non-financial support from Bristol Meyers Squibb, non-financial support from Roche, non-financial support from Takeda, and non-financial support from MSD, outside the submitted work. OM reports personal fees from Bristol Meyers Squibb, personal fees from AstraZeneca, personal fees from Takeda, and personal fees from Menarini, outside the submitted work. VW reports personal fees and other from Roche, personal fees and other from Bristol Meyers Squibb, personal fees and other from AstraZeneca, personal fees from MSD, personal fees from Takeda, other from Pfizer, personal fees and other from Boehringer Ingelheim, and personal fees from Lilly, outside the submitted work. FB reports personal fees from AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Lilly Oncology, Roche, Novartis, Merck, MSD, Pierre Fabre, Pfizer and Takeda and non-financial support from Abbvie, ACEA, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Eisai, Lilly Oncology, Roche, Genentech, Ipsen, Ignyta, Innate Pharma, Loxo, Novartis, Medimmune, Merck, MSD, Pierre Fabre, Pfizer, Sanofi-Aventis and Takeda, outside the submitted work. JMad reports personal fees from Pfizer SAS, personal fees from Boerhinger Ingelheim, personal fees from GSK, personal fees from Actelion, personal fees from Chugaï, personal fees from MSD, personal fees from AstraZeneca, personal fees from Novartis Pharma SAS, personal fees from Roche and personal fees from Bristol Meyers Squibb,

outside the submitted work. DD reports personal fees from AstraZeneca, Chugaï, Lilly, Roche, Novartis, Pfizer, MSD, Bristol Meyers Squibb and Boehringer Ingelheim, and grants from Roche, AstraZeneca, Lilly, Bristol Meyers Squibb, Boehringer Ingelheim, Chiesi, Chugaï, Pfizer, MSD, Novartis, GSK and Sandoz.

DMS reports personal fees and non-financial support from Bristol Meyers Squibb, grants, personal fees and non-financial support from Roche, personal fees and non-financial support from MSD, grants, personal fees and non-financial support from Abbvie, personal fees and non-financial support from Boehringer Ingelheim, personal fees from Novartis, personal fees and non-financial support from AstraZeneca, personal fees from Amgen, personal fees from Lilly, and grants, personal fees and non-financial support from Pfizer, during the conduct of the study. PJS reports grants, personal fees and non-financial support from Roche, grants from Lilly, during the conduct of the study.

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Appendix A. Supplementary data

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References

[1] Azzoli CG, Baker Jr S, Temin S, Pao W, Aliff T, Brahmer J, et al. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. J Clin Oncol 2009;27:6251–66.

[2] Azzoli CG, Temin S, Aliff T, Baker Jr S, Brahmer J, Johnson DH, et al. 2011 focused update of 2009 American society of clinical oncology clinical practice guideline update on chemotherapy for stage IV non-small-cell lung cancer. J Clin Oncol 2011;29:3825–31.

[3] Ciuleanu T, Brodowicz T, Zielinski C, Kim JH, Krzakowski M, Laack E, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet 2009;374:1432–40.

[4] Fidias PM, Dakhil SR, Lyss AP, Loesch DM, Waterhouse DM, Bromund JL, et al. Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer. J Clin Oncol 2009;27:591–8.

[5] Johnson EA, Marks RS, Mandrekar SJ, Hillman SL, Hauge MD, Bauman MD, et al. Phase III randomized, double-blind study of maintenance CAI or placebo in patients with advanced non-small cell lung cancer (NSCLC) after completion of initial therapy (NCCTG 97-24-51). Lung Cancer 2008;60:200–7.

[6] Takeda K, Hida T, Sato T, Ando M, Seto T, Satouchi M, et al. Randomized phase III trial of platinum-doublet chemotherapy followed by gefitinib compared with continued platinum-doublet chemotherapy in Japanese patients with advanced non-small-cell lung cancer: results of a west Japan thoracic oncology group trial (WJTOG0203). J Clin Oncol 2010;28:753–60.

[7] Pérol M, Chouaid C, Pérol D, Barlési F, Gervais R, Westeel V, et al. 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 2012;30:3516–24.

[8] Paz-Ares L, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol 2012;13:247–55.

[9] Quoix E, Zalcman G, Oster JP, Westeel V, Pichon E, Lavolé A, et al. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. Lancet 2011;378:1079–88.

[10] Masters GA, Temin S, Azzoli CG, Giaccone G, Baker Jr S, Brahmer JR, et al. Systemic therapy for stage IV non-small cell lung cancer : American society of clinical oncology clinical practice guideline update. J Clin Oncol 2015;33:3488–515.

[11] Quoix E, Westeel V, Moreau L, Pichon E, Lavolé A, Dauba J, et al. Second-line therapy in elderly patients with advanced non-small cell lung cancer. Eur Respir J 2014;43:240–9.

[12] Folstein MF, Robins LN, Helzer JE. The mini-mental state examination. Arch Gen Psychiatr 1983;40. 812.

[13] Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontol 1969;9:179–86.

[14] Nelson CJ, Cho C, Berk AR, Holland J, Roth AJ. Are gold standard depression measures appropriate for use in geriatric cancer patients? A systematic evaluation of self-report depression instruments used with geriatric, cancer, and geriatric cancer samples. J Clin Oncol 2010;28:348–56.

[15] Soubeyran P, Bellera C, Goyard J, Heitz D, Curé H, Rousselot H, et al. Screening for vulnerability in older cancer patients: the ONCODAGE prospective multicenter cohort study. PloS One 2014;9. e115060.

[16] Hollen PJ, Gralla RJ, Kris MG, Potanovich LM. Quality of life assessment in individuals with lung cancer: testing the Lung Cancer Symptom Scale (LCSS). Eur J Cancer 1993;29A(Suppl 1). S51–8.

[17] Kahan BC, Morris TP. Improper analysis of trials randomised using stratified blocks or minimisation. Stat *Med* 2012;31:328–40.

[18] Gridelli C, de Marinis F, Thomas M, Prabhash K, El Kouri C, Blackhall F, et al. Final efficacy and safety results of pemetrexed continuation maintenance therapy in the elderly from the PARAMOUNT phase III study. J Thorac Oncol 2014;9:991–7.

[19] Brodowicz T, Krzakowski M, Zwitter M, Tzekova V, Ramlau R, Ghilezan N, et al. Cisplatin and gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non-small cell lung cancer: a phase III trial. Lung Cancer 2006;52:155–63.

[20] Belani CP, Waterhouse DM, Ghazal H, Ramalingam S, Bordoni R, Greenberg R, et al. Phase III study of maintenance gemcitabine and best supportive care versus best supportive care following standard combination therapy with gemcitabine-carboplatin for patients with advanced non-small cell lung cancer. J Clin Oncol 2010;28. A7506.

[21] Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123–32.

[22] Corre R, Greillier L, Le Caer H, Audigier-Valette C, Baize N, Bérard H, et al. Use of a comprehensive geriatric assessment for the management of elderly patients with advanced non-small-cell lung cancer: the phase III randomized. J Clin Oncol 2016;34:1476–83.

[23] Petit-Moneger A, Rainfray M, Soubeyran P, Bellera CA, Mathoulin-Pelissier S. Detection of frailty in elderly cancer patients: improvement of the G8 screening test. J Geriatr Oncol 2016;7:99–107.

[24] Ferrara R, Mezquita L, Auclin E, Chaput N, Besse B. Immunosenescence and immunecheckpoint inhibitors in non-small cell lung cancer patients: does age really matter? Cancer Treat Rev 2017;60:60–8.

[25] Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced non-squamous non-small-cell lung cancer. N Engl J Med 2015;373:1627–39.

[26] Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2015;373:123–35.

[27] Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulöp A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 2016;375:1823–33.

[28] Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 2018;378:2078–92.