VOLUME 34 · NUMBER 13 · MAY 1, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Use of a Comprehensive Geriatric Assessment for the Management of Elderly Patients With Advanced Non–Small-Cell Lung Cancer: The Phase III Randomized ESOGIA-GFPC-GECP 08-02 Study

Romain Corre, Laurent Greillier, Hervé Le Caër, Clarisse Audigier-Valette, Nathalie Baize, Henri Bérard, Lionel Falchero, Isabelle Monnet, Eric Dansin, Alain Vergnenègre, Marie Marcq, Chantal Decroisette, Jean-Bernard Auliac, Suzanna Bota, Régine Lamy, Bartomeu Massuti, Cécile Dujon, Maurice Pérol, Jean-Pierre Daurès, Renaud Descourt, Hervé Léna, Carine Plassot, and Christos Chouaïd

See accompanying article on page 1438

Author affiliations appear at the end of this article.

Published online ahead of print at www.jco.org on February 16, 2016.

Written on behalf of Groupe Français de Pneumo-Cancérologie and Grupo Espanol de Cancer de Pulmon.

Supported by grants from Eli Lilly, Sanofi, Roche, and Chugaï.

Groupe Français de Pneumo-Cancérologie had full responsibility for the study design, data collection, data analysis, and data interpretation. R.C. had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Corresponding author: Romain Corre, MD, Service de Pneumologie, Centre Hospitalier Universitaire de Rennes, 2 rue Henri Le Guilloux, Rennes 35000, France; e-mail: romain.corre@chu-rennes.fr.

0732-183X/16/3413w-1476w/$20.00

DOI: 10.1200/JCO.2015.63.5839

ABSTRACT

Purpose

Comprehensive geriatric assessment (CGA) is recommended to assess the vulnerability of elderly patients, but its integration in cancer treatment decision making has never been prospectively evaluated. Here, in elderly patients with advanced non–small-cell lung cancer (NSCLC), we compared a standard strategy of chemotherapy allocation on the basis of performance status (PS) and age with an experimental strategy on the basis of CGA.

Patients and Methods

In a multicenter, open-label, phase III trial, elderly patients ≥ 70 years old with a PS of 0 to 2 and stage IV NSCLC were randomly assigned between chemotherapy allocation on the basis of PS and age (standard arm: carboplatin-based doublet if PS ≤ 1 and age ≤ 75 years; docetaxel if PS = 2 or age > 75 years) and treatment allocation on the basis of CGA (CGA arm: carboplatin-based doublet for fit patients, docetaxel for vulnerable patients, and best supportive care for frail patients). The primary end point was treatment failure free survival (TFFS). Secondary end points were overall survival (OS), progression-free survival, tolerability, and quality of life.

Results

Four hundred ninety-four patients were randomly assigned (standard arm, n = 251; CGA arm, n = 243). Median age was 77 years. In the standard and CGA arms, 35.1% and 45.7% of patients received a carboplatin-based doublet, 64.9% and 31.3% received docetaxel, and 0% and 23.0% received best supportive care, respectively. In the standard and CGA arms, median TFFS times were 3.2 and 3.1 months, respectively (hazard ratio, 0.91; 95% CI, 0.76 to 1.1), and median OS times were 6.4 and 6.1 months, respectively (hazard ratio, 0.92; 95% CI, 0.79 to 1.1). Patients in the CGA arm, compared with standard arm patients, experienced significantly less all grade toxicity (85.6% *v* 93.4%, respectively $P = .015$) and fewer treatment failures as a result of toxicity (4.8% *v* 11.8%, respectively; $P = .007$).

Conclusion

In elderly patients with advanced NSCLC, treatment allocation on the basis of CGA failed to improve the TFFS or OS but slightly reduced treatment toxicity.

J Clin Oncol 34:1476-1483. © 2016 by American Society of Clinical Oncology

INTRODUCTION

Lung cancer is the most common malignancy worldwide and the leading cause of cancer-related deaths in Western countries.[1] Approximately 50% of patients with non–small-cell lung cancer (NSCLC) are 70 years of age or older at diagnosis.[2] Concerning advanced NSCLC, international treatment guidelines have evolved significantly over the past 15 years.[3,4] In 2004, the American Society of Clinical Oncology guidelines recommended single-agent chemotherapy.[5] Guidelines published in 2009 considered there was no evidence to support the use of a particular first-line drug or combination on the basis of age alone and that both physiologic age and performance status

(PS) should be taken into account.[6] At that time, subgroup analyses of clinical trials of platinum-based doublets in patients unselected for age suggested that carefully selected elderly patients could receive this treatment.[7,8] In 2011, a phase III trial in fit elderly patients demonstrated the superiority of a monthly carboplatin and weekly paclitaxel doublet over vinorelbine or gemcitabine monotherapy in terms of overall survival (OS).[9] Consequently, current guidelines recommend first-line treatment with a carboplatin-based doublet for fit elderly patients and consider that single-agent treatment is an option for less fit patients; no specific recommendations are made for octogenarians.[10] However, there is no consensus definition of fit or less fit patients. In clinical practice, elderly patients form a heterogeneous population with baseline organ dysfunctions and with variable numbers of comorbidities correlating poorly with functional status.[11] These patients are often taking several medications and may also have a geriatric syndrome and suffer from social isolation, including poor caregiver support. This makes it difficult for clinicians to follow these recommendations.

Comprehensive geriatric assessment (CGA) is based on a multidisciplinary and global approach to elderly patients, covering functional status, cognitive capacities, emotional status, comorbidities, nutritional status, polypharmacy, social and environmental situations, and a possible geriatric syndrome. CGA can predict morbidity and mortality in elderly patients with cancer[11] and can help to adapt cancer management to each patient's fitness or frailty.[12] Balducci and Extermann[13] used a practical CGA-based approach to define the following three therapeutic groups of elderly patients: standard therapy for fit patients, adjusted therapy for vulnerable patients, and best supportive care (BSC) for frail patients. Our group (Groupe Français de Pneumo-Cancérologie) showed in phase II studies that CGA can identify homogenous groups of fit and frail patients.[14-17] However, even if the use of CGA is encouraged in several guidelines,[10,18] there is no firm evidence of its feasibility or utility in routine clinical practice.[19]

We conducted a multicenter, randomized, phase III trial in elderly patients (≥ 70 years) with stage IV NSCLC, comparing a standard strategy of treatment allocation (carboplatin-based doublet or single agent on the basis of PS and age) with experimental CGA-based allocation of the same chemotherapies or BSC. In both arms, the associated drug included in the carboplatin doublet was based on histologic findings. Single-agent therapy consisted of weekly docetaxel because previous studies have demonstrated its efficacy and favorable safety profile.[14,20,21]

PATIENTS AND METHODS

Patients

The main eligibility criteria were age ≥ 70 years, histologically or cytologically proven advanced NSCLC, measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.0, and Eastern Cooperative Oncology Group PS of 0 to 2. Adequate hematologic, renal (creatinine clearance ≥ 45 mL/min using Modification of Diet in Renal Disease equation), and hepatic function was required. At inclusion, *EGFR* and *ALK* status was wild type or unknown. The main exclusion criteria were severe concurrent disorders, active malignancy within the past 5 years, and symptomatic brain metastases. Patients with a bronchoalveolar, neuroendocrine, or composite cancer histology were not eligible. All enrolled patients gave their written informed consent. The study was approved by the Rennes Ethics Committee and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

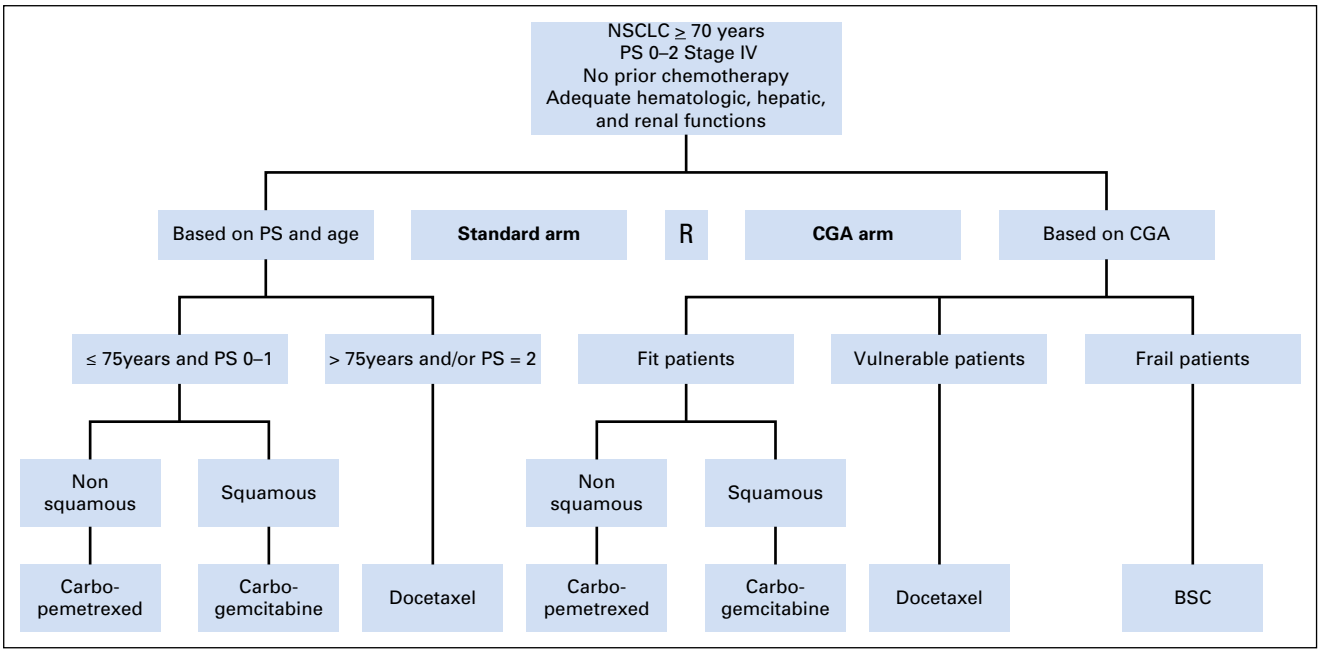

Fig 1. Study design and chemotherapy schedules. Four cycles of chemotherapy were to be administered every 3 weeks; chemotherapy involved a carboplatin (Carbo)–based doublet (for nonsquamous histology: Carbo [area under the curve 5 on day 1] plus pemetrexed [500 mg/m^2 on day 1]; for squamous histology: Carbo [area under the curve 5 on day 1] plus gemcitabine [1,000 mg/m^2 on days 1 to 8]) or single-agent treatment (docetaxel 38 mg/m^2 on days 1 to 8). BSC, best supportive care; CGA, comprehensive geriatric assessment; NSCLC, non–small-cell lung cancer; PS, performance status; R, random assignment.

Table 1. Definition of Fit, Vulnerable, and Frail Patients in the CGA Arm

Geriatric Parameters	Fit: All Criteria	Vulnerable: One of the Bold Criteria	Frail: One of the Bold Criteria
PS	0 or 1	**2**	0-2
ADL (0-6)	6	6	**≤ 5**
IADL (0-4)	0	**1**	**≥ 2**
Schultz-Larsen MMSE (0-11)	≥ 9		
Folstein MMSE (0-30)		> 23	**≤ 23**
Geriatric syndrome	No	No	**Yes**
Charlson comorbidity index	0-1	**2-3**	**≥4 (≥ 3 if > 80 years)**
GDS5 (0-5)	0-1	**2-3**	**4-5**

NOTE. Patients were considered fit if they met all the following criteria that constitute an abbreviated geriatric assessment: PS of 0-1, ADL score of 6, IADL score of 0, Schultz-Larsen MMSE ≥ 9, no geriatric syndrome (confirmed dementia, repeated falls, or urinary or fecal incontinence), Charlson comorbidity index ≤ 1, GDS5 score of 0 to 1. If patients were not fit, the Folstein MMSE was also considered. Patients were considered vulnerable if they met one or more of the following criteria: PS of 2, IADL score of 1, Charlson comorbidity index of 2 to 3, or GDS5 score of 2 to 3. Patients were considered frail if they met one or more of the following criteria: ADL score ≤ 5, IADL score ≥ 2, Folstein MMSE ≤ 23, presence of geriatric syndrome (confirmed dementia, repeated falls, or urinary or fecal incontinence), Charlson comorbidity index ≥ 4 (or ≥ 3 if > 80 years), or GDS5 of 4 to 5.

Abbreviations: ADL, activities of daily living; CGA, comprehensive geriatric assessment; GDS5, Geriatric Depression Scale 5; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination; PS, performance status.

Study Design

All patients had a CGA performed by their regular cancer physician. The domains explored and the scales used are described in Appendix Table A1 (online only). The protocol included no specific interventions to improve problems detected by the CGA. The patients were stratified by center and randomly assigned at a 1:1 ratio to the two arms (Fig 1). In the standard arm, patients with PS ≤ 1 and age ≤ 75 years received a carboplatin-based doublet according to their tumor histology, namely carboplatin (area under the curve 5 on day 1) plus pemetrexed (500 mg/m^2 on day 1) for nonsquamous carcinoma and carboplatin (area under the curve 5 on day 1) plus gemcitabine (1,000 mg/m^2 on days 1 to 8) for squamous carcinoma. Patients with a PS of 2 and/or age greater than 75 years received single-agent docetaxel (38 mg/m^2 on days 1 to 8). In the CGA arm, the following three groups of patients were defined according to the CGA (Table 1): fit patients received the same histology-based carboplatin doublet as in the standard arm; vulnerable patients received single-agent docetaxel; and frail patients received BSC (Fig 1). The maximum allowed delay between random assignment and initiation of treatment was 10 days. In both arms, four cycles of chemotherapy every 3 weeks were planned for patients receiving chemotherapy; maintenance therapy was not offered. Growth factor support was not recommended as primary prophylaxis but was authorized as secondary prophylaxis.

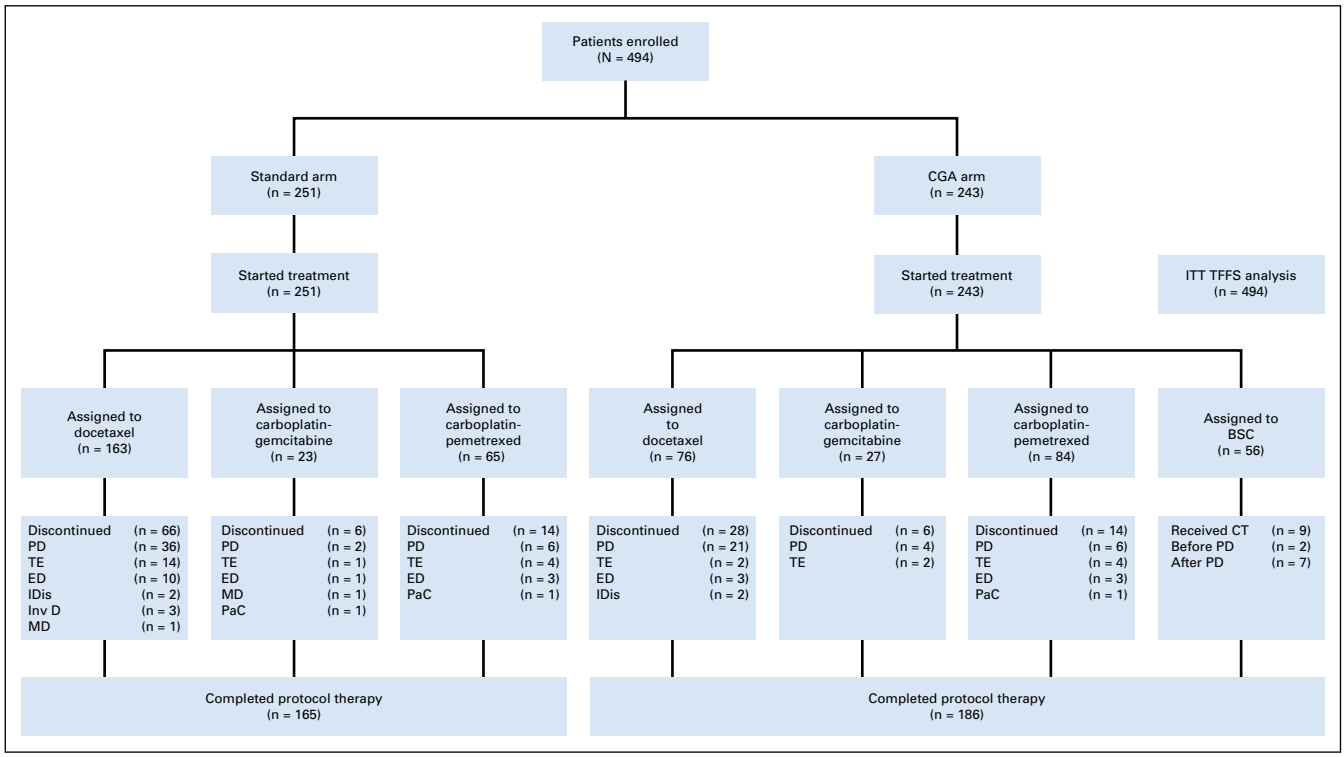

Fig 2. CONSORT diagram showing patient registration, treatment arm assignments, and reasons for discontinuation. Discontinued indicates patients who did not receive the four planned cycles. BSC, best supportive care; CT, chemotherapy; ED, early death; IDis, intercurrent disease; InvD, investigator's decision; ITT, intention to treat; MD, missing data; PaC, patient's choice; PD, progressive disease; TE, toxic effect; TFFS, treatment failure–free survival.

Outcome Measures

The primary end point was the treatment failure–free survival (TFFS), which was defined as the time elapsing between random assignment and early treatment discontinuation as a result of any reason (including disease progression, treatment toxicity, or early death), disease progression, or death (resulting from any cause). Secondary end points included OS, progression-free survival (PFS; defined as the time from random assignment to progression or death), overall response rate, tolerability, quality of life (QoL), and QoL-adjusted survival. The tumor response was assessed by computed tomography 6 and 12 weeks after random assignment and then every 8 weeks until disease progression, trial exit for toxicity, death, or withdrawal of consent. Disease progression was assessed by a panel of investigators blinded to the group allocation, independently of the treating investigator. Adverse events (Aes) and serious Aes were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Symptoms and QoL were evaluated from random assignment to each tumor assessment using the Lung Cancer Symptom Scale and the EuroQol EQ-5D questionnaires.

Statistical Analysis

This study was designed to detect a 30% improvement in TFFS, with an assumed median TFFS time of 3.4 months in the standard arm and 4.5 months in the CGA arm, with a statistical power of 80%, a two-sided type I error of 5%, and a 5% rate of loss to follow-up. This required 490 patients to be enrolled over 3 years with a minimum follow-up of 12 months. Efficacy analyses were performed on an intent-to-treat basis. TFFS, OS, and PFS were analyzed using Cox proportional hazards regression models and are reported as Kaplan-Meier estimates with hazard ratios and 95% CIs. Differences between the arms were assessed using a two-sided log-rank test. Subgroup analyses of TFFS were performed using baseline characteristics (sex, age, and PS) and geriatric characteristics (eg, Mini-Mental State Examination and activities of daily living [ADL] scores) as stratification variables. To identify factors potentially influencing TFFS, a multivariate Cox model was constructed with stepwise variable selection. We used univariate Cox models to select baseline variables ($P = .20$) for the multivariate analysis. Given the longitudinal nature of the QoL data, a linear mixed-effects model was used to compare the utility score and, therefore, QoL between the standard and CGA arms. Finally, QoL-adjusted survival was estimated, and the average QoL-adjusted survival time was compared between the arms.[22,23] Usual statistical tests (χ^2 test, Fisher's exact test, and Wilcoxon Mann-Whitney U test) were used to compare variables between the arms. A value of $P < .05$ was considered statistically significant. Data were analyzed using SAS software 9.3 (SAS Institute, Cary, NC). The trial is registered with ClinicalTrials.gov (identifier: NCT 01257139).

RESULTS

Between January 2010 and January 2013, 494 patients were enrolled by 45 centers in France and Spain (14 university hospitals, four cancer centers, and 27 community hospitals), and 251 and 243 patients were assigned to the standard and CGA arms, respectively (Fig 2). Median age was 77 years. Baseline characteristics (Table 2) were well balanced, except that more patients in the CGA arm than the standard arm had an ADL score of 6 (89.3% *v* 82.1%, respectively). Median follow-up was 4.5 months (range, 0 to 36.7 months), and the final cutoff date was March 2014. Median time spent on CGA administration was 35 minutes. In the standard arm, 35.1% of patients received a carboplatin doublet and 64.9% received docetaxel. In the CGA arm, 45.7%, 31.3%, and 23.0% of patients received a carboplatin doublet, single-agent therapy, and BSC, respectively (Table 3). The median number of treatment cycles was four (range, one to four cycles) in both arms after excluding patients assigned to BSC in the CGA arm.

There was no significant difference between the arms with respect to TFFS time (3.2 *v* 3.1 months in the standard and CGA arms, respectively; hazard ratio, 0.91; 95% CI, 0.76 to 1.1; $P = .32$). In the standard arm, the median TFFS times among patients treated with a carboplatin doublet and with docetaxel were 4.4 and 2.9 months, respectively (Fig 3). In the CGA arm, the median TFFS times among patients treated with a carboplatin doublet, single-agent docetaxel, and BSC were 4.8, 2.6, and 1.3 months, respectively (Table 3). The reasons for treatment failure (Table 3) were not significantly different between the arms, except that failures as a result of toxicity were more frequent in the standard arm than the CGA arm (11.8% *v* 4.8%, respectively; $P = .007$). This difference persisted when patients managed with BSC in the CGA arm were excluded, but it was no longer statistically significant (11.8% *v* 6.3% in the standard and CGA arms, respectively; $P = .06$).

PFS did not differ significantly between the standard and CGA arms (3.7 *v* 3.4 months, respectively; $P = .59$; Appendix Fig A1, online only). After progression, 40.6% and 41.1% of patients in the standard and CGA arms, respectively, received a further line of treatment (more frequently after doublet therapy in both arms; Appendix Table A2, online only), and 17.6% of the patients managed exclusively with BSC received a systemic treatment after progression. OS was not significantly different between the standard and CGA arms (6.4 *v* 6.1 months, respectively; $P = .87$; Appendix Fig A2, online only). In the standard arm, median OS times among patients treated with a carboplatin doublet and with docetaxel were 8.6 and 5.7 months, respectively. In the CGA arm, median OS times among patients treated with a carboplatin doublet, single-agent docetaxel, and BSC were 10.0, 4.9, and

Table 2. Baseline Patient Characteristics

Characteristic	Standard Arm (n = 251)	CGA Arm (n = 243)
Age, years		
Median	76	77
Range	70-91	70-87
Men, %	74.5	74.1
Histology, %		
Squamous	27.1	28.8
Nonsquamous	72.9	71.2
Never-smokers, %	20.8	19.6
BMI < 20 kg/m^2, %	16.3	13.2
Performance status, %		
0-1	80.9	81.5
2	19.1	18.5
ADL score = 6, %	82.1	89.3
IADL score, %		
0	71.7	71.2
1	16.3	20.2
≥ 2	12.0	8.6
Folstein MMSE > 23, %	83.7	85.6
No geriatric syndrome, %	90	91.4
Charlson comorbidity index		
0-1	76.5	75.7
≥ 2	23.5	24.3
GDS5		
0-1	85.7	83.5
2-3	12.7	12.0
4-5	1.6	4.5

Abbreviations: ADL, activities of daily living; BMI, body mass index; CGA, comprehensive geriatric assessment; GDS5, Geriatric Depression Scale 5; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination.

Table 3. Treatments and Outcomes

Treatment and Outcome	Standard Arm (n = 251)	CGA Arm (n = 243)	*P* (Log-Rank Test)
Treatment allocation, No. (%)			< .001
Monotherapy	163 (64.9)	76 (31.3)	
Doublet	88 (35.1)	111 (45.7)	
BSC		56 (23.0)	
Median TFFS, months			.32
All	3.2	3.1	
Doublet	4.4	4.8	
Monotherapy	2.9	2.6	
BSC	—	1.3	
Reasons for treatments failures, No. (%)			
Missing data	14	15	
Progression	156 (65.8)	158 (69.3)	.42
Toxicity	28 (11.8)	11 (4.8)	.01
Toxicity except for BSC in the CGA arm	28 (11.8)	11 (6.3)	.06
Withdrawal of consent	9 (3.8)	7 (3.1)	.67
Death	31 (13.1)	32 (14.0)	.76
Other	13 (5.5)	20 (8.8)	.17
Median PFS, months			.59
All	3.7	3.4	
Doublet	4.7	4.8	
Monotherapy	3.1	2.7	
BSC	—	1.3	
Median OS, months			.87
All	6.4	6.1	
Doublet	8.6	10.0	
Monotherapy	5.7	4.9	
BSC	—	2.8	
Mean life expectancy adjusted on QoL, months	4.3	4.4	.51

Abbreviations: BSC, best supportive care; CGA, comprehensive geriatric assessment; OS, overall survival; PFS, progression-free survival; QoL, quality of life; TFFS, treatment failure–free survival.

2.8 months, respectively (Table 3). Central review of treatment responses, assessable in 75% and 71% of patients in the standard and CGA arms, respectively, showed no difference in the objective response rate (26.6% *v* 26.0%, respectively; $P = .89$) or the disease control rate (80.8% *v* 73.4%, respectively; $P = .09$).

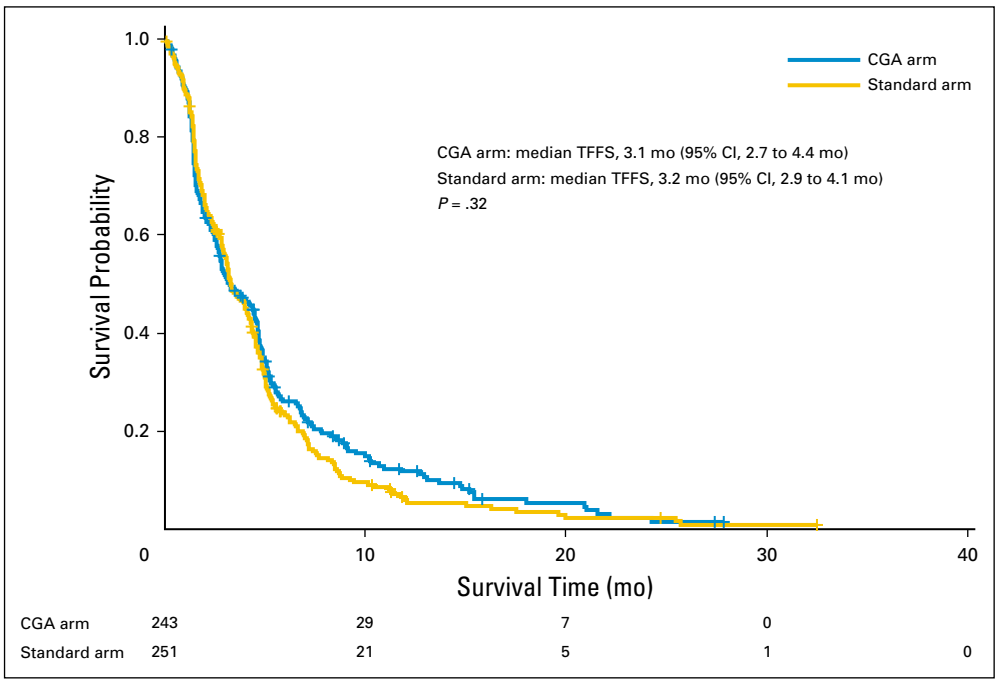

Fig 3. Treatment failure–free survival (TFFS) over the duration of the study. CGA, comprehensive geriatric assessment.

Table 4. Grade 3 or 4 Toxicities

Toxicity	% of Patients: Standard Arm (n = 251)	% of Patients: CGA Arm (n = 243)	*P*
All grades	93.4	85.6	.01
Grade 3-4	71.3	67.9	.41
Grade 3-4 neutropenia			.41
All	11.1	13.2	
Doublet	16.0	25.2	
Monotherapy	8.0	5.3	
BSC	—	0	
Grade 3-4 febrile neutropenia			.22
All	5.6	3.3	
Doublet	11.0	5.4	
Monotherapy	2.4	2.6	
BSC	—	0	
Grade 3-4 anemia			.87
All	11.2	10.7	
Doublet	21.6	16.2	
Monotherapy	5.5	6.6	
BSC	—	5.3	
Grade 3-4 thrombocytopenia			.04
All	3.6	7.8	
Doublet	7.9	17.1	
Monotherapy	1.2	0	
BSC	—	0	
Grades 3-4 asthenia			.34
All	10.8	13.6	
Doublet	7.9	14.4	
Monotherapy	12.3	15.8	
BSC	—	8.9	
Grade 3-4 anorexia			.27
All	4.0	6.2	
Doublet	0	10	
Monotherapy	6.0	5.3	
BSC	—	0	
Grade 3-4 nausea/vomiting			.46
All	3.6	4.9	
Doublet	1.1	8.1	
Monotherapy	4.9	2.6	
BSC	—	1.8	
Grade 3-4 peripheral sensory neuropathy			.62
All	1.2	0.4	
Doublet	0	0	
Monotherapy	1.8	1.3	
BSC	—	0	

Abbreviations: BSC, best supportive care; CGA, comprehensive geriatric assessment.

The percentage of patients who experienced all grade Aes was significantly higher in the standard arm than in the CGA arm (93.4% *v* 85.6%, respectively; $P = .015$), but this difference was no longer significant when the analysis was restricted to grade 3 or 4 Aes (71.3% *v* 67.9%, respectively; $P = .41$). The most common grade 3 or 4 Aes were neutropenia, anemia, and asthenia (Table 4). QoL utility scores at baseline did not differ between the arms. At each subsequent evaluation, the utility score was always higher in the CGA arm than in the standard arm (data not shown), but the difference was significant only at week 36 ($P = .02$). Utility scores tended to decline over time and were not significantly different between the arms ($P = .85$). Life expectancies adjusted on QoL were 4.3 and 4.4 months in the standard and CGA arms, respectively (Table 3). Several factors negatively influenced TFFS in univariate analysis (Appendix Table A3, online only), but only body mass index ≤ 20 kg/m^2, former or current smoking status, less than four chemotherapy cycles, Charlson comorbidity index ≥ 2, and the existence of a geriatric syndrome remained independent unfavorable prognostic factors for TFFS in multivariate analysis.

DISCUSSION

To our knowledge, this is the first randomized trial in which a CGA was integrated into the treatment allocation for elderly patients with advanced NSCLC and that prospectively studied its impact on survival outcomes. The Elderly Selection on Geriatric Index Assessment (ESOGIA) study demonstrates the feasibility of CGA in a large cohort of elderly patients, although no resulting improvement in TFFS or OS was observed. Several explanations for these negative results can be envisaged. First, TFFS is a combined primary end point particularly adapted to elderly patients, taking into account not only progression but also tolerability.[24] This is a good option for cancers with an indolent course or in case of patients with significant comorbidities who are likely to die of causes other than cancer. However, as was the case in this study, patients with NSCLC are more likely to have treatment interruptions as a result of progressive disease or death and less likely as a result of toxicity. Second, even if more patients in the CGA arm received a carboplatin doublet, the difference compared with the standard arm was small (Table 3) and was counterbalanced by the 23% of patients who received BSC alone. (Appendix Table A4 [online only] indicates what would have been the allocations of treatment based on CGA parameters in the standard arm.) Moreover, the cutoffs used to define fit, vulnerable, and frail patients may not be the most relevant in the advanced NSCLC setting, even if the domains explored here were consistent with recent recommendations.[18] The impact of comorbidities on outcome could be lesser in patients with advanced NSCLC, most of whom die of NSCLC rather than comorbidities. Nevertheless, comorbidities provide information independent of functional status; they are associated with worse survival among elderly patients with advanced NSCLC and also with a variety of other tumors.[11,25,26] In our study, a Charlson comorbidity index ≥ 2 and the presence of a geriatric syndrome were unfavorable independent predictors of TFFS in multivariate analysis. The type and severity of comorbidities, rather than just their number, should probably be considered for treatment allocation in this setting.

CGA on the basis of the ADL and instrumental ADL scores adds substantial information to functional assessment on the basis of PS alone.[18,27] Maione et al[28] demonstrated that the instrumental ADL score but not the ADL score had independent prognostic value for survival, especially in frail patients. However, neither score was an independent prognostic factor for TFFS in our multivariate analysis. One possible drawback in our definition of the CGA groups is that we did not integrate nutritional parameters. Indeed, body mass index ≤ 20 kg/m^2 was an independent unfavorable prognostic factor for TFFS in multivariate analysis, and recent studies have shown that poor nutritional status is associated with a poor prognosis in elderly patients with cancer.[29,30] As suggested by previous studies, geriatric assessment might help with the choice of well-tolerated treatments.[18] The

patients in the CGA arm showed a modest but statistically significant lower incidence of all grade Aes and treatment failures as a result of toxicity (Table 3), possibly because 23% of them received BSC alone. Nevertheless, a nonsignificant difference persisted when patients who received BSC were excluded from the analysis (6.3% *v* 11.8% in CGA and standard arms, respectively), even though more and older patients received doublet therapy in the CGA arm. The median OS among fit patients treated with a carboplatin doublet in the CGA arm was 10.0 months, in line with median values reported in previous studies including fit elderly patients with advanced NSCLC treated with various carboplatin doublets.[9,31] In our study, these fit patients had a favorable safety profile, with grade 3 or 4 neutropenia, febrile neutropenia, and treatment-related death in 23.8%, 5.5%, and 0.9% of patients, respectively; the corresponding rates were 48.4%, 9.4%, and 4.4%, respectively, among the 225 patients treated with carboplatin-paclitaxel in the Intergroupe Francophone de Cancérologie Thoracique 05.01 trial.[9] Our favorable results may be related to the chemotherapy regimens used, but the median OS among the 88 patients in the standard arm (all ≤ 75 years old) was 8.6 months, and the toxicity profile was similar, suggesting that CGA can help to select fit elderly patients who can be treated safely and effectively with a carboplatin-based doublet. The 73 vulnerable patients treated with weekly docetaxel in the CGA arm had a short median OS of 4.9 months, compared with 5.1 to 8.5 months in trials of first-line single-agent chemotherapy.[3,21,32,33] This difference may be a result of subsequent-line treatments but also of the fact that patients in the CGA arm were selected according to frailty criteria. As a matter of fact, median OS was better (5.7 months) among patients treated by docetaxel in the standard arm and selected on the basis of PS and age. Median OS among frail patients managed exclusively with BSC was only 2.8 months, which clearly is lower than the OS of 5.2 months among patients ≥ 70 years old with a PS of 0 to 2 who received BSC alone in the Elderly Lung Cancer Vinorelbine Italian Study trial.[3] This suggests that the CGA identified patients with a poor natural prognosis, but our study design did not allow us to validate the appropriateness of exclusive BSC for these patients. Interestingly, although Qol utility scores at baseline were not different between the arms, they always were higher (although not significantly so) in the CGA arm than in the standard arm at each subsequent evaluation, with no evident negative impact of the 23% of patients who received exclusive BSC.

In our study, as recommended in 2009, none of the patients ≥ 75 years old in the standard arm or with a PS of 2 in either arm received a carboplatin doublet. However, recent trials have shown that selected patients ≥ 75 years old and/or with a PS of 2 can be treated with a carboplatin doublet.[9,34] As a consequence, some of these patients may have been undertreated in both arms, and geriatric parameters in the CGA arm could have had less impact on the treatment allocation.

CGA-based allocation of chemotherapy did not improve the survival outcomes of elderly patients with advanced NSCLC. Consequently, the use of CGA in this setting cannot be routinely advised in clinical practice. Further research is needed to better identify within CGA the most relevant tools in patients with advanced NSCLC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Romain Corre, Hervé Le Caër, Isabelle Monnet, Alain Vergnenègre, Marie Marcq, Chantal Decroisette, Suzanna Bota, Régine Lamy, Maurice Pérol, Jean-Pierre Daurès, Renaud Descourt, Hervé Léna, Carine Plassot, Christos Chouaïd

Provision of study materials or patients: Romain Corre, Laurent Greillier, Hervé Le Caër, Clarisse Audigier-Valette, Nathalie Baize, Henri Bérard, Lionel Falchero, Isabelle Monnet, Eric Dansin, Alain Vergnenègre, Marie Marcq, Chantal Decroisette, Jean-Bernard Auliac, Suzanna Bota, Régine Lamy, Bartomeu Massuti, Cécile Dujon, Maurice Pérol, Renaud Descourt, Hervé Léna, Christos Chouaïd

Collection and assembly of data: Romain Corre, Laurent Greillier, Eric Dansin, Cécile Dujon, Jean-Pierre Daurès, Carine Plassot

Data analysis and interpretation: Romain Corre, Laurent Greillier, Hervé Le Caër, Clarisse Audigier-Valette, Nathalie Baize, Henri Bérard, Lionel Falchero, Alain Vergnenègre, Jean-Bernard Auliac, Bartomeu Massuti, Maurice Pérol, Jean-Pierre Daurès, Renaud Descourt, Hervé Léna, Carine Plassot, Christos Chouaïd

Manuscript writing: All authors

Final approval of manuscript: All authors

REFERENCES

1. Ferlay J, Shin H-R, Bray F, et al: Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 127:2893-2917, 2010
2. Altekruse S, Kosary S, Krapcho M, et al: SEER cancer statistics review, 1975–2007. http://seer.cancer.gov/archive/csr/1975_2007/
3. The Elderly Lung Cancer Vinorelbine Italian Study Group: Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. J Natl Cancer Inst 91:66-72, 1999
4. Gridelli C, Maione P, Illiano A, et al: Cisplatin plus gemcitabine or vinorelbine for elderly patients with advanced non small-cell lung cancer: The MILES-2P studies. J Clin Oncol 25:4663-4669, 2007
5. Pfister DG, Johnson DH, Azzoli CG, et al; American Society of Clinical Oncology: American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: Update 2003. J Clin Oncol 22:330-353, 2004
6. Azzoli CG, Baker S Jr, Temin S, et al; American Society of Clinical Oncology: American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. J Clin Oncol 27:6251-6266, 2009
7. Belani CP, Fossella F: Elderly subgroup analysis of a randomized phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for first-line treatment of advanced nonsmall cell lung carcinoma (TAX 326). Cancer 104:2766-2774, 2005
8. Ansari RH, Socinski MA, Edelman MJ, et al; Alpha Oncology Research Network: A retrospective analysis of outcomes by age in a three-arm phase III trial of gemcitabine in combination with carboplatin or paclitaxel vs. paclitaxel plus carboplatin for advanced non-small cell lung cancer. Crit Rev Oncol Hematol 78:162-171, 2011
9. Quoix E, Zalcman G, Oster J-P, et al; Intergroupe Francophone de Cancérologie Thoracique: 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 378:1079-1088, 2011
10. Pallis AG, Gridelli C, Wedding U, et al: Management of elderly patients with NSCLC; updated expert's opinion paper: EORTC Elderly Task Force, Lung Cancer Group and International Society for Geriatric Oncology. Ann Oncol 25:1270-1283, 2014

11. Extermann M, Hurria A: Comprehensive geriatric assessment for older patients with cancer. J Clin Oncol 25:1824-1831, 2007

12. Girre V, Falcou M-C, Gisselbrecht M, et al: Does a geriatric oncology consultation modify the cancer treatment plan for elderly patients? J Gerontol A Biol Sci Med Sci 63:724-730, 2008

13. Balducci L, Extermann M: Management of cancer in the older person: A practical approach. Oncologist 5:224-237, 2000

14. LeCaer H, Barlesi F, Robinet G, et al: An open multicenter phase II trial of weekly docetaxel for advanced-stage non-small-cell lung cancer in elderly patients with significant comorbidity and/or poor performance status: The GFPC 02-02b study. Lung Cancer 57:72-78, 2007

15. LeCaer H, Fournel P, Jullian H, et al: An open multicenter phase II trial of docetaxel-gemcitabine in Charlson score and performance status (PS) selected elderly patients with stage IIIB pleura/IV non-small-cell lung cancer (NSCLC): The GFPC 02-02a study. Crit Rev Oncol Hematol 64:73-81, 2007

16. LeCaer H, Greillier L, Corre R, et al; GFPC 0505 Team: A multicenter phase II randomized trial of gemcitabine followed by erlotinib at progression, versus the reverse sequence, in vulnerable elderly patients with advanced non small-cell lung cancer selected with a comprehensive geriatric assessment (the GFPC 0505 study). Lung Cancer 77:97-103, 2012

17. LeCaer H, Barlesi F, Corre R, et al; GFPC 0504 Team: A multicentre phase II randomised trial of weekly docetaxel/gemcitabine followed by erlotinib on progression, vs the reverse sequence, in elderly patients with advanced non small-cell lung cancer selected with a comprehensive geriatric assessment (the GFPC 0504 study). Br J Cancer 105:1123-1130, 2011

18. Wildiers H, Heeren P, Puts M, et al: International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol 32:2595-2603, 2014

19. Puts MTE, Santos B, Hardt J, et al: An update on a systematic review of the use of geriatric assessment for older adults in oncology. Ann Oncol 25:307-315, 2014

20. Kudoh S, Takeda K, Nakagawa K, et al: Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non-small-cell lung cancer: Results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). J Clin Oncol 24: 3657-3663, 2006

21. Karampeazis A, Vamvakas L, Agelidou A, et al: Docetaxel vs. vinorelbine in elderly patients with advanced non–small-cell lung cancer: A hellenic oncology research group randomized phase III study. Clin Lung Cancer 12:155-160, 2011

22. Fairclough DL: Design and Analysis of Quality of Life Studies in Clinical Trials. Boca Raton, FL, CRC Press, 2010

23. Crowley J, Hoering A: Handbook of Statistics in Clinical Oncology. Boca Raton, FL, CRC Press, 2012 doi:10.1201/b11800

24. Wildiers H, Mauer M, Pallis A, et al: End points and trial design in geriatric oncology research: A joint European Organisation for Research and Treatment of Cancer Alliance for Clinical Trials in Oncology International Society of Geriatric Oncology position article. J Clin Oncol 31:3711-3718, 2013

25. Frasci G, Lorusso V, Panza N, et al: Gemcitabine plus vinorelbine versus vinorelbine alone in elderly patients with advanced non-small-cell lung cancer. J Clin Oncol 18:2529-2536, 2000

26. Asmis TR, Ding K, Seymour L, et al; National Cancer Institute of Canada Clinical Trials Group: Age and comorbidity as independent prognostic factors in the treatment of non small-cell lung cancer: A review of National Cancer Institute of Canada Clinical Trials Group trials. J Clin Oncol 26: 54-59, 2008

27. Repetto L, Fratino L, Audisio RA, et al: Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: An Italian Group for Geriatric Oncology Study. J Clin Oncol 20:494-502, 2002

28. Maione P, Perrone F, Gallo C, et al: Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: A prognostic analysis of the multicenter Italian lung cancer in the elderly study. J Clin Oncol 23:6865-6872, 2005

29. Kanesvaran R, Li H, Koo K-N, et al: Analysis of prognostic factors of comprehensive geriatric assessment and development of a clinical scoring system in elderly Asian patients with cancer. J Clin Oncol 29:3620-3627, 2011

30. Aaldriks AA, Maartense E, le Cessie S, et al: Predictive value of geriatric assessment for patients older than 70 years, treated with chemotherapy. Crit Rev Oncol Hematol 79:205-212, 2011

31. Zhu J, Sharma DB, Chen AB, et al: Comparative effectiveness of three platinum-doublet chemotherapy regimens in elderly patients with advanced non-small cell lung cancer. Cancer 119: 2048-2060, 2013

32. Quoix E, Breton J-L, Ducoloné A, et al: First line chemotherapy with gemcitabine in advanced non-small cell lung cancer elderly patients: A randomized phase II study of 3-week versus 4-week schedule. Lung Cancer 47:405-412, 2005

33. Gridelli C, Perrone F, Gallo C, et al; MILES Investigators: Chemotherapy for elderly patients with advanced non-small-cell lung cancer: The Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. J Natl Cancer Inst 95: 362-372, 2003

34. Zukin M, Barrios CH, Pereira JR, et al: Randomized phase III trial of single-agent pemetrexed versus carboplatin and pemetrexed in patients with advanced non-small-cell lung cancer and Eastern Cooperative Oncology Group performance status of 2. J Clin Oncol 31:2849-2853, 2013

Affiliations

Romain Corre and Hervé Léna, Centre Hospitalier Universitaire de Rennes, Rennes; Laurent Greillier, Université de Médecine, Marseille; Hervé Le Caër, Centre Hospitalier de Draguignan, Draguignan; Clarisse Audigier-Valette, Centre Hospitalier Intercommunal de Toulon; Henri Bérard, Hôpital Inter Armées Sainte-Anne, Toulon; Nathalie Baize, Centre Hospitalier Universitaire d'Angers, Angers; Lionel Falchero, Centre Hospitalier de Villefranche sur Saône, Villefranche sur Saône; Isabelle Monnet and Christos Chouaïd, Centre Hospitalier Intercommunal de Créteil, Créteil; Eric Dansin, Centre Oscar Lambret, Lille; Alain Vergnenègre, Centre Hospitalier Universitaire du Cluzeau, Limoges; Marie Marcq, Centre Hospitalier Départemental les Oudairies, La Roche-sur-Yon; Chantal Decroisette, Centre Hospitalier d'Annecy, Annecy; Jean-Bernard Auliac, Centre Hospitalier de Mantes La Jolie, Mantes la Jolie; Suzanna Bota, Centre Hospitalier Universitaire Charles Nicolle, Rouen; Régine Lamy, Centre Hospitalier de Bretagne Sud, Lorient; Cécile Dujon, Hôpital A. Mignot, Le Chesnay; Maurice Pérol, Centre Léon Bérard, Lyon; Jean-Pierre Daurès and Carine Plassot, Université Montpellier 1, Montpellier; Renaud Descourt, Centre Hospitalier Universitaire de Brest, Brest, France; and Bartomeu Massuti, Hospital General Universitario de Alicante, Alicante, Spain.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Use of a Comprehensive Geriatric Assessment for the Management of Elderly Patients With Advanced Non–Small-Cell Lung Cancer: The Phase III Randomized ESOGIA-GFPC-GECP 08-02 Study

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Romain Corre
Consulting or Advisory Role: Eli Lilly, Roche, Bristol-Myers Squibb, Boehringer Ingelheim
Travel, Accommodations, Expenses: Eli Lilly, Roche, Amgen, Bristol-Myers Squibb

Laurent Greillier
Consulting or Advisory Role: Roche, Eli Lilly, Boehringer Ingelheim
Research Funding: Roche
Travel, Accommodations, Expenses: Eli Lilly, Roche

Hervé Le Caër
No relationship to disclose

Clarisse Audigier-Valette
Consulting or Advisory Role: Roche, Eli Lilly, Pfizer, Boehringer Ingelheim, AstraZeneca
Research Funding: Roche, Boehringer Ingelheim, Bristol-Myers Squibb, Novartis
Travel, Accommodations, Expenses: Roche, Eli Lilly, Pfizer, Boehringer Ingelheim, AstraZeneca

Nathalie Baize
No relationship to disclose

Henri Bérard
Travel, Accommodations, Expenses: Novartis, Boehringer Ingelheim

Lionel Falchero
No relationship to disclose

Isabelle Monnet
No relationship to disclose

Eric Dansin
Honoraria: Roche, Novartis, AstraZeneca, Pfizer, Boehringer Ingelheim
Consulting or Advisory Role: Vivactis, Publiclin
Research Funding: Roche
Travel, Accommodations, Expenses: Eli Lilly, Ipsen

Alain Vergnenègre
Consulting or Advisory Role: AstraZeneca, Merck Sharp & Dohme, Bristol-Myer Squibb, Teva, Eli Lilly, Clovis Oncology
Research Funding: Chugai, Boehringer Ingelheim, Roche
Travel, Accommodations, Expenses: Roche, Boehringer Ingelheim, AstraZeneca

Marie Marcq
No relationship to disclose

Chantal Decroisette
No relationship to disclose

Jean-Bernard Auliac
Consulting or Advisory Role: Roche, Boehringer Ingelheim, Pfizer, Clovis
Travel, Accommodations, Expenses: Eli Lilly, Boehringer Ingelheim, Roche

Suzanna Bota
No relationship to disclose

Régine Lamy
No relationship to disclose

Bartomeu Massuti
No relationship to disclose

Cécile Dujon
Travel, Accommodations, Expenses: Boehringer Ingelheim

Maurice Pérol
Consulting or Advisory Role: Eli Lilly
Speakers' Bureau: Eli Lilly

Jean-Pierre Daurès
No relationship to disclose

Renaud Descourt
No relationship to disclose

Hervé Léna
Honoraria: Genentech, Eli Lilly, Bristol-Myers Squibb, AstraZeneca, Boehringer Ingelheim, MSD Oncology, Pierre Fabre, Pfizer, Novartis
Consulting or Advisory Role: Bristol-Myers Squibb, Novartis
Research Funding: Genentech
Travel, Accommodations, Expenses: Boehringer Ingelheim, Eli Lilly, Amgen, Genentech

Carine Plassot
No relationship to disclose

Christos Chouaïd
Consulting or Advisory Role: Eli Lilly, Roche, Amgen
Travel, Accommodations, Expenses: AstraZeneca

Acknowledgment

We are indebted to Anne Hespel, Catherine Mouchel, and Yves Rayer from the Direction de la Recherche Clinique of the Centre Hospitalier Universitaire de Rennes, France, who provided substantial administrative help. We thank Solenne Daubresse for her substantial contribution to the study. We also thank Sophie Lecanuet and Veronique Blanc, who did data quality checks during the study; Willy Lambert and Thomas Perraudin, who designed the electronic case report form; and David Young, for helping us to improve our use of English. We especially thank all of the patients and families.

Appendix

Study Investigators

The following investigators participated in this study: Pierre Fournel (Institut de Cancérologie de la Loire à Saint Priez en Jarez), Ghislaine Fraboulet (Centre Hospitalier de Cergy-Pontoise), Laurence Bigay Game (Centre Hospitalier Universitaire de Toulouse), Jacques Le Treut (Centre Hospitalier d'Aix en Provence), Michel André (Hôpital Inter Armées de Brest), Géraldine François (Centre Hospitalier Universitaire d'Amiens), Sana Kalhout (Centre Hospitalier d'Antibes), Bénédicte Etienne-Mastroianni (Centre Hospitalier de Lyon Monchat), Radj Gervais (Centre de Recherche et de Lutte Contre le Cancer de Caen), Gwenaëlle Le Garff (Centre Hospitalier de Saint-Brieuc, Saint-Brieuc), Christine Raynaud (Centre Hospitalier d'Argenteuil), Stéphane Chouabe (Centre Hospitalier de Charleville Mézières), Jacky Crequit (Centre Hospitalier de Beauvais), Magali Roa (Centre Hospitalier de Fréjus), Pascal Thomas (Centre Hospitalier de Gap), Samir Abdiche (Centre Hospitalier de Libourne), Pilar Mut Sanchis (Hospital Son Llàtzer, Illes Balears), A. Madroszyk (Centre de Recherche et de Lutte Contre le Cancer de Marseille), Chrystele Locher (Centre Hospitalier de Meaux), Jean-Yves Delhoume (Centre Hospitalier de Périgueux), Daniel Castera (Centre Hospitalier de Perpignan), Valérie Grangeon (Centre Hospitalier de Roanne), Dominique Paillotin (Centre Hospitalier Universitaire de Rouen), Roland Schott (Centre de Recherche et de Lutte Contre le Cancer de Strasbourg), Sophie Bayle Bleuez (Centre Hospitalier Universitaire de Saint Etienne).

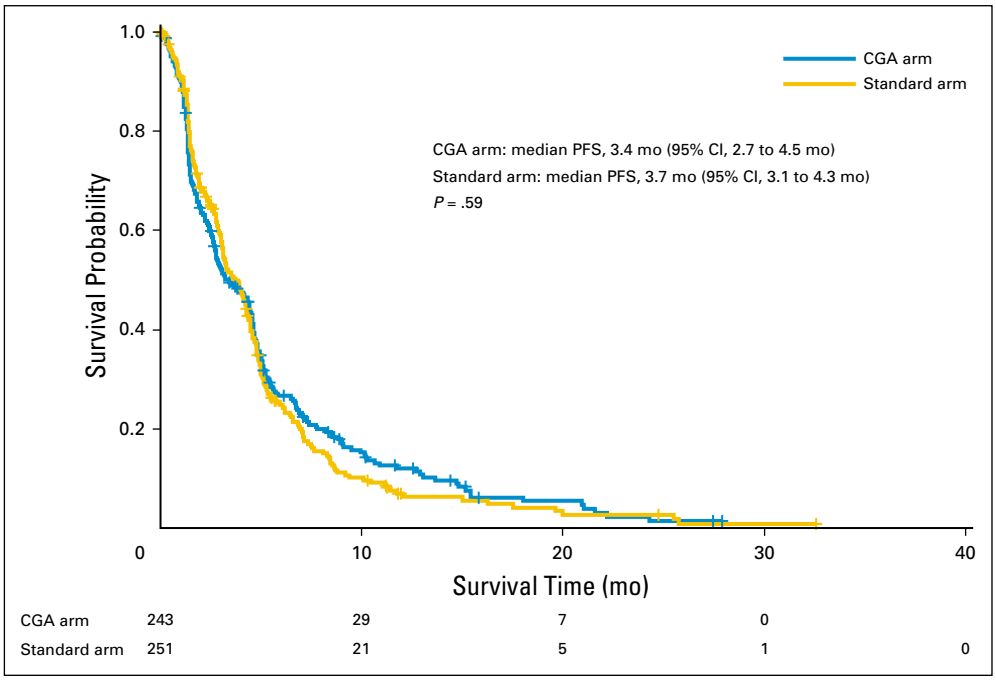

Fig A1. Progression-free survival (PFS) over the duration of the study. CGA, comprehensive geriatric assessment.

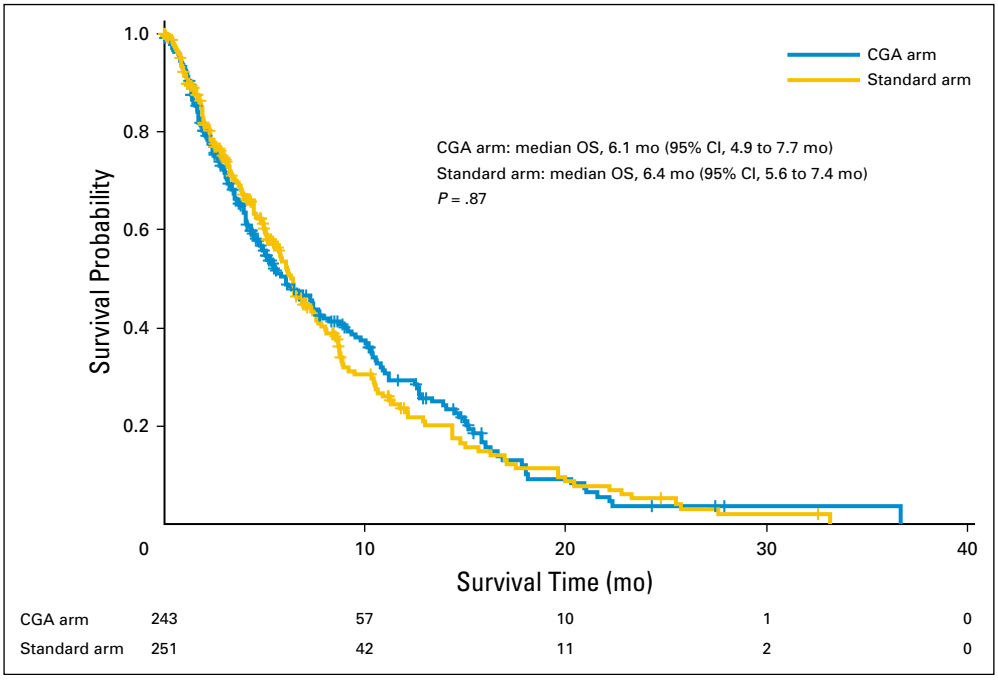

Fig A2. Overall survival (OS) over the duration of the study. CGA, comprehensive geriatric assessment.

Table A1. Domains Explored by the Comprehensive Geriatric Assessment

Domain	Scales
Functional status	Eastern Cooperative Oncology Group performance status, Katz basic Activities of Daily Living Scale, Simplified Lawton's Instrumental Activities of Daily Living Scale
Comorbidities	Charlson comorbidity index
Medications	Number, type, indication
Cognitive function	Folstein Mini-Mental State Examination, Schultz-Larsen Mini-Mental State Examination
Geriatric syndrome	Repeated falls, fecal and/or urinary incontinence
Depression/ mood	Geriatric Depression Scale 5, Emotional questionnaire
Nutrition	Body mass index
Mobility	Timed Up and Go test
Situational assessment	Accessibility of services, mobility, social environment, accessibility of home rooms

Table A2. Treatment Received After Progression

Treatment	% of Patients	
	Standard Arm (n = 251)	CGA Arm (n = 243)
Patients who received second-line treatment	40.6	41.1
Patients who received a second-line treatment according to the first-line treatment received		
Monotherapy	37.3	39.6
Carboplatin doublet	50	55
BSC	—	17.6
Types of second-line treatment received		
Tyrosine kinase inhibitor	69.5	66.6
Pemetrexed monotherapy	14.5	15.3
Gemcitabine, docetaxel, or vinorelbine monotherapy	16	18.1

Abbreviation: BSC, best supportive care.

Table A3. Univariate and Multivariable Analyses of Treatment-Failure-Free Survival

Variable	No. of Patients	Univariate Analysis		Multivariable Analysis	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Arm					
Standard arm	251	1		—	—
CGA arm	243	0.91 (0.76 to 1.1)	.3231	—	—
BMI (kg/m^2)					
20-25	223	1		1	
≤ 20	73	1.56 (1.19 to 2.05)	.0014	2.38 (1.53 to 3.71)	.0001
26-30	123	1.07 (0.85 to 1.35)	.5803	1.12 (0.79 to 1.58)	.5288
> 30	39	0.82 (0.57 to 1.18)	.2874	1.09 (0.65 to 1.82)	.7453
Smoker status					
Never-smokers	74	1		1	
Former smokers	60	1.17 (0.81 to 1.7)	.3935	1.97 (1.18 to 3.31)	.0098
Current smokers	233	1.38 (1.05 to 1.819)	.0216	1.71 (1.16 to 2.53)	.0071
No. of chemotherapy cycles					
< Four	149	1		1	
Four	276	0.34 (0.28 to 0.42)	< .0001	0.28 (0.20 to 0.38)	< .0001
Treatment					
Monotherapy	239	1		—	—
Carboplatin doublet	199	0.67 (0.55 to 0.82)	< .0001	—	—
Best supportive care	56	1.51 (1.11 to 2.04)	.0084	—	—
Albumin (g/L)					
> 30	94	1		—	—
≤ 30	254	1.7 (1.33 to 2.17)	< .0001	—	—
ECOG PS					
0	136	1		—	—
1	265	1.35 (1.08 to 1.68)	.0079	—	—
2	93	2.72 (2.05 to 3.60)	< .0001	—	—
ADL score					
0	423	1		—	—
≥ 1	71	1.53 (1.18 to 1.98)	.0012	—	—
IADL score					
0	353	1		—	—
1	90	1.27 (0.99 to 1.63)	.0565	—	—
≥ 2	51	2.77 (2.05 to 3.75)	< .0001	—	—
Charlson comorbidity index					
0	215	1		1	
1	161	1.17 (0.95 to 1.45)	.1489	1.10 (0.79 to 1.53)	.5705
≥ 2	118	1.72 (1.36 to 2.18)	< .0001	1.75 (1.17 to 2.62)	.0064
GDS 5 score					
0-1	417	1		—	—
2-3	61	1.47 (1.1 to 1.96)	.0089	—	—
4-5	15	1.68 (0.98 to 2.87)	.0571	—	—
Folstein's MMSE score					
> 23	418	1		—	—
≤ 23	76	1.46 (1.13 to 1.89)	.0037	—	—
Falls during the last year					
No	420	1		—	—
Several	24	1.77 (1.16 to 2.7)	.0081	—	—
One	50	1.24 (0.91 to 1.70)	.1686	—	—
Continence					
Yes	469	1		1	
No	25	1.39 (0.92 to 2.09)	.1200	5.15 (1.84 to 14.46)	.0013
Recent weight loss (at least 3 kg)					
No	215	1		—	—
Yes	270	1.33 (1.1 to 1.61)	.0029	—	—
Loss of appetite					
No	429	1		—	—
Yes	65	1.54 (1.17 to 2.03)	.0022	—	—
Get up and go test					
Normal	359	1		—	—
Abnormal	132	1.3 (1.05 to 1.6)	.0140	—	—
Autonomy					
Yes	409	1		—	—
No	83	1.96 (1.53 to 2.52)	< .0001	—	—

(continued on following page)

Table A3. Univariate and Multivariable Analyses of Treatment-Failure-Free Survival (continued)

Variable	No. of Patients	Univariate Analysis		Multivariable Analysis	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Social environment					
Good social environment	440	1		—	—
Social isolation/insufficient environment	54	1.35 (1.01 to 1.81)	.0442	—	—

NOTE. All baseline variables with $P < .20$, univariate Cox model were included in the multivariate analysis, but only the "best subset of predictors" were retained in the final model after stepwise selection. Dashes indicate nonsignificant results.

Abbreviations: ADL, Activities of Daily Living; BMI, body mass index; CGA, comprehensive geriatric assessment; ECOG PS, Eastern Cooperative Oncology Group performance status; GD5, Geriatric Depression Scale 5; IADL, Instrumental Activities of Daily Living; MMSE, Mini-Mental State Examination.

Table A4. Allocations of Treatment Based on CGA Parameters in the Standard Arm

Treatment based on CGA	Treatment Based on PS and Age	
	Single Therapy (n = 163), No. (%)	Double Therapy (n = 88), No. (%)
Double-agent therapy	51 (31.3)	45 (51.1)
Single-agent therapy	37 (22.7)	19 (21.6)
Best supportive care	75 (46.0)	24 (27.3)

Abbreviations: CGA, comprehensive geriatric assessment; PS, performance status.