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ORIGINAL REPORT

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

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ABSTRACT

Purpose
This phase III study investigated whether continuation maintenance with gemcitabine or switch maintenance with erlotinib improves clinical outcome compared with observation in patients with advanced non–small-cell lung cancer (NSCLC) whose disease was controlled after cisplatin-gemcitabine induction chemotherapy.

Patients and Methods
Four hundred sixty-four patients with stage IIIB/IV NSCLC without tumor progression after four cycles of cisplatin-gemcitabine were randomly assigned to observation or to gemcitabine (1,250 mg/m^2 days 1 and 8 of a 3-week cycle) or daily erlotinib (150 mg/day) study arms. On disease progression, patients in all three arms received pemetrexed (500 mg/m^2 once every 21 days) as predefined second-line therapy. The primary end point was progression-free survival (PFS).

Results
PFS was significantly prolonged by gemcitabine (median, 3.8 *v* 1.9 months; hazard ratio [HR], 0.56; 95% CI, 0.44 to 0.72; log-rank $P < .001$) and erlotinib (median, 2.9 *v* 1.9 months; HR, 0.69; 95% CI, 0.54 to 0.88; log-rank $P = .003$) versus observation; this benefit was consistent across all clinical subgroups. Both maintenance strategies resulted in a nonsignificant improvement in overall survival (OS); patients who received second-line pemetrexed or with a performance status of 0 appeared to derive greater benefit. Exploratory analysis showed that magnitude of response to induction chemotherapy may affect the OS benefit as a result of gemcitabine maintenance. Maintenance gemcitabine and erlotinib were well tolerated with no unexpected adverse events.

Conclusion
Gemcitabine continuation maintenance or erlotinib switch maintenance significantly reduces disease progression in patients with advanced NSCLC treated with cisplatin-gemcitabine as first-line chemotherapy. Response to induction chemotherapy may affect OS only for continuation maintenance.

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INTRODUCTION

The standard of care for patients with stage IV, epidermal growth factor receptor (EGFR), wild-type, non–small-cell lung cancer (NSCLC) is based on the watch-and-wait strategy.[1] This involves administration of multiple treatment lines that are initiated at the onset of disease progression and separated by treatment-free intervals.[2-4] The treatment break after first-line therapy is generally short (median duration, 2 to 3 months)[5] and carries a risk of rapid clinical deterioration, which often rules out second-line treatment. Indeed, only two thirds of patients who experience objective response or disease stabilization after platinum-based doublet therapy subsequently receive second-line therapy during routine clinical practice.[6,7] This lost opportunity for effective therapy after first-line treatment may lead to a reduction in overall survival (OS).[8]

Maintenance therapy is defined as the continuation of a treatment after achieving a clinical response to platinum-based chemotherapy, including

disease stabilization.[5,9] The objective is to increase the duration of disease control and, ultimately, improve survival. The availability of better tolerated drugs (eg, novel cytotoxic drugs or EGFR tyrosine-kinase inhibitors) has made the maintenance strategy a feasible option because, previously, prolongation of first-line platinum doublet therapy led to cumulative toxicity issues that precluded use of this approach.[10-14]

Two methods for delivering maintenance therapy have been explored[5]: continuation maintenance involves continuing the non-platinum component of the first-line regimen, whereas switch maintenance requires introducing a drug with proven efficacy in the second-line setting immediately after the end of induction chemotherapy, thereby ensuring patients have the opportunity to receive an additional treatment. Continuation maintenance with gemcitabine[15] and, recently, pemetrexed[16] have both demonstrated significant prolongation of progression-free survival (PFS) with potential improvement in OS,[15] whereas both erlotinib[17] and pemetrexed[18] have demonstrated improvements in PFS and OS in the switch maintenance setting. The mechanism of OS benefit in these trials has been widely discussed.[5,19] It has been questioned whether an imbalance in second-line drug exposure between the control and experimental arms may have led to an overestimation of OS benefit in both pemetrexed and erlotinib trials or whether the OS benefit was entirely as a result of the maintenance strategy (ie, to an increase in treatment duration). The trial by Fidias et al,[20] assessed docetaxel as either switch maintenance or conventional second-line therapy and found that the survival benefit from the switch maintenance strategy was mainly owing to more patients receiving docetaxel in the maintenance arm. Another important issue is the selection of patients who will benefit most from a maintenance strategy, especially regarding continuation versus switch maintenance. Patients with stable disease after first-line chemotherapy seem to benefit more from switch maintenance,[21] whereas continuation maintenance may be more effective for responders.

Our phase III, IFCT-GFPC 0502 trial was designed to investigate two maintenance strategies: continuation maintenance with gemcitabine or switch maintenance with erlotinib compared with observation in patients with advanced NSCLC whose disease was controlled after cisplatin-gemcitabine induction chemotherapy. The study design imposed the same second-line treatment (pemetrexed) in all three arms to avoid bias in the survival analysis, as a result of an imbalance in subsequent treatments.

PATIENTS AND METHODS

Patients

Patients were enrolled onto the study at the beginning of induction chemotherapy and were eligible for study entry if they met the following criteria: age 18 to 70 years with histologically or cytologically documented stage IV NSCLC or stage IIIB NSCLC with documented pleural involvement, measurable disease according to Response Evaluation Criteria In Solid Tumors 1.0[22] and an Eastern Cooperative Oncology Group performance status (PS) of

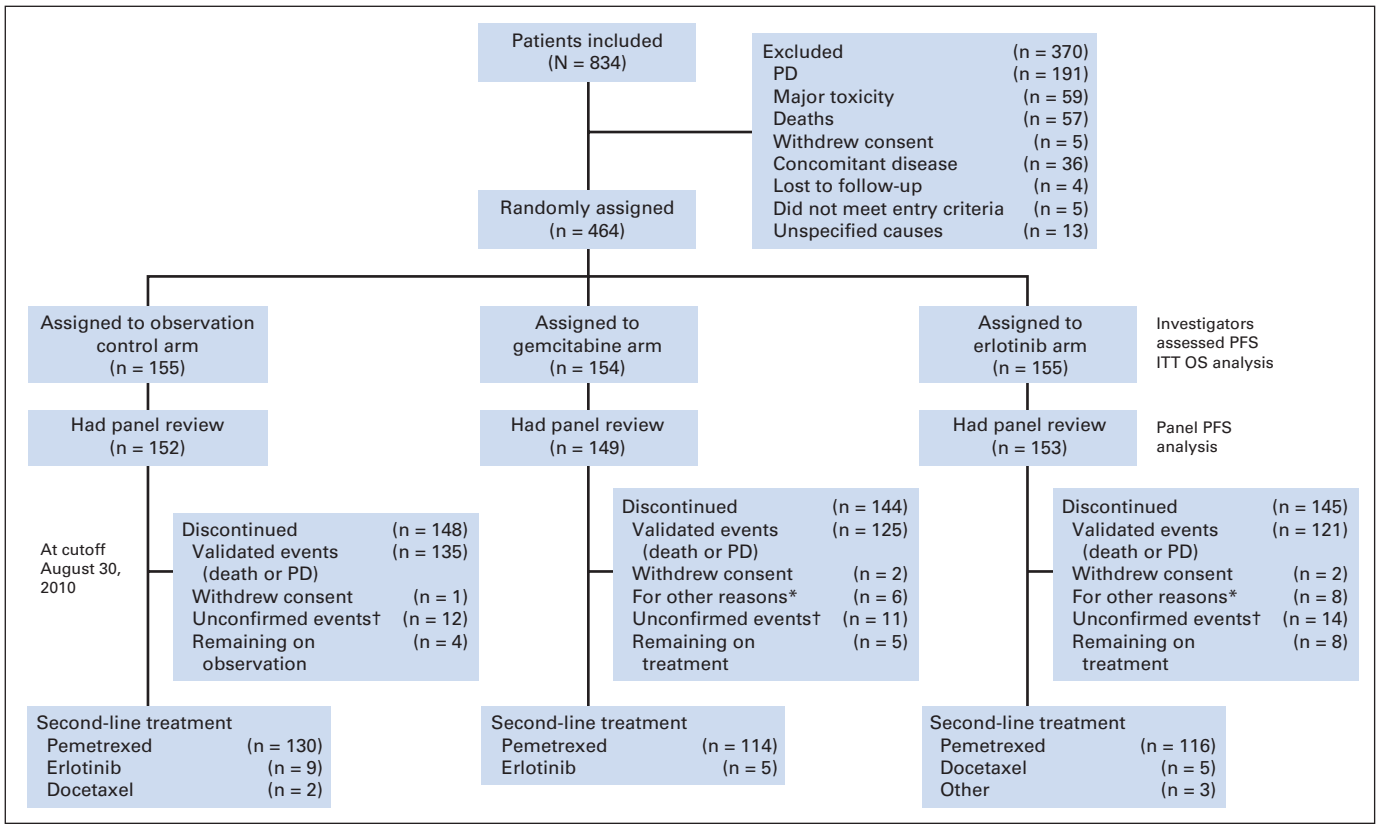

Fig 1. Patient disposition. (*) Other reasons, including protocol violation, loss to follow-up, and physician decision. (†) Patients who were initiated on second-line therapy by the investigator without confirmed disease progression; these patients were censored at the time of initiation of second-line treatment for progression-free survival (PFS) analysis. ITT, intent-to-treat; OS, overall survival; PD, progressive disease.

0 or 1. Exclusion criteria included prior therapy with an EGFR inhibitor, concurrent radiotherapy except for bone metastasis, pre-existing interstitial lung disease, any other malignancies within the previous 5 years (except for treated carcinoma in situ of the cervix or basal cell skin cancer), and symptomatic brain metastasis.

All patients provided written informed consent for participation in the study and consent for tumor sample collection. The study was approved by the Ethics Committee of Lyon, France and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Participating institutions are listed in the Data Supplement, section 1 (online only).

Study Design

After screening and enrolment, patients received four cycles of induction chemotherapy (cisplatin 80 mg/m^2 day 1 plus gemcitabine 1,250 mg/m^2 day 1, day 8 of a 3-week cycle). Disease status was reassessed after completion of four treatment cycles; patients without evidence of disease progression or unacceptable toxicity were then randomly assigned in a 1:1:1 ratio to observation (control arm), continuation maintenance with gemcitabine (1,250 mg/m^2 day 1, day 8 of a 3-week cycle), or switch maintenance with erlotinib (150 mg/d). Maintenance treatment was continued until disease progression, unacceptable toxicity, or death. On disease progression, patients in all three treatment arms received pemetrexed (500 mg/m^2 every 21 days) as predefined second-line therapy with vitamin B12/folic acid supplementation and corticosteroid premedication. Our study was designed and conducted before the labeling restriction of pemetrexed to nonsquamous cell carcinoma.

Patient randomization was stratified by center, gender, histology (adenocarcinoma/other), smoking status (current and former *v* never), and response to cisplatin-gemcitabine induction chemotherapy (objective response/stable disease) using a minimization adaptive randomization method to ensure a well-balanced distribution of patients in each stratum.[23] Randomization was computerized and centrally located.

Assessments

Tumor response (according to Response Evaluation Criteria In Solid Tumors 1.0) was assessed using computed tomography after two and four cycles (study baseline) of cisplatin-gemcitabine induction therapy, at 6 and 12 weeks after randomization during the maintenance phase, and then once every 9 weeks until disease progression or death. On disease progression, tumor assessments were performed after every two cycles (6 weeks) of pemetrexed. Disease progression was reviewed by a panel of investigators who were blinded to randomization, independently of the treating investigator.

Adverse events (AEs) and serious AEs were graded according to the National Cancer Institute Common Terminology Criteria, version 3.0. Dose modifications in case of AE during the maintenance phase are detailed in the Data Supplement, section 2 (online only). Evaluation of symptoms was performed from randomization at each tumor assessment using the Lung Cancer Symptom Scale[24] (Data Supplement, section 4).

Whenever possible, tumor samples were collected for biomarker analysis to determine possible correlations with treatment outcome. Expression of EGFR was assessed by immunohistochemistry (IHC; Zymed Laboratories, San Francisco, CA) using a semiquantitative score.[25] Analysis of *EGFR* mutations was restricted to exon 19 deletions and L858R point mutations in exon 21[26] (for additional details, see Data Supplement, section 3).

Statistical Analysis

The primary end point was PFS, that is, the time to progression or death from any cause from the date of randomization assessed by a panel of investigators. Secondary end points included OS (time from randomization to death from any cause), tolerability, prognostic/predictive effects of EGFR protein expression and *EGFR* mutations.

The study design provided 80% power to detect a 50% improvement in median PFS from 3.0 to 4.5 months (hazard ratio [HR], 0.66) for the comparison of each maintenance arm with the observation control arm. Assuming an accrual and follow-up period of 36 and 6 months, respectively, and using a two-sided log-rank test with a 5% α level, 191 events were required for the first comparison (gemcitabine *v* observation) needing an accrual of 290 patients. For the second comparison (erlotinib *v* observation), 87 further events were required, corresponding to an accrual of 145 additional patients in the third arm. Thus, a total of 278 events and 435 randomly assigned patients were required for the entire trial. As the answer to each of these two questions was unrelated to the other, and as the two comparisons were independently calibrated, multiplicity adjustment to control for the overall probability of a false-positive result being .05 (type I error) was not required.[27] Two successive interim analyses of PFS (assessed by an independent data safety monitoring committee) were based on the O'Brien-Fleming boundary[28] with significance thresholds of $P < .0005$ and $P < .014$, respectively, and were planned after documented events in the first 93 and 185 patients, respectively.

All survival analyses were performed on the intent-to-treat population. PFS and OS were analyzed using Cox proportional hazards regression model and presented as Kaplan-Meier estimates[29] with HR and 95% CIs. Median follow-up was calculated using a reverse Kaplan-Meier estimate.[30] Differences in survival estimates between the maintenance and observation arms were assessed using a two-sided log-rank test. Planned exploratory subgroup analyses of PFS and OS were performed using stratification variables and predefined prognostic variables (ie, PS and second-line pemetrexed). All patients who received at least one dose of study drug were included in the safety analyses. Our study was designed by D.P. and Sylvie Chabaud, senior

Table 1. Baseline Characteristics of Randomly Assigned Patients

Characteristic	Observation Group (n = 155)		Gemcitabine Group (n = 154)		Erlotinib Group (n = 155)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years						
Median	59.8		57.9		56.4	
Range	37-72		29-71		36-71	
Sex						
Male	113	72.9	113	73.4	113	72.9
Female	42	27.1	41	26.6	42	27.1
ECOG PS at inclusion						
0	78	50.3	73	47.4	81	52.3
1	77	49.7	81	52.6	74	47.7
ECOG PS at random assignment						
0	68	44.2	61	40.1	58	37.9
1	81	52.6	82	53.9	85	55.6
2	4	2.6	7	4.6	8	5.2
3	1	0.6	2	1.3	2	1.3
Unknown	1	0.6	2	1.3	2	1.3
Stage						
IIIB	14	9.2	14	9.3	11	7.4
IV	139	90.8	137	90.7	137	92.6
Unknown	2	1.3	3	1.9	7	4.5
Brain metastases	1	0.6	5	3.2	2	1.3
Smoking status						
Current and former smokers	143	92.3	137	89.0	138	89.0
Never smoker*	12	7.7	17	11.0	17	11.0
Histology						
Adenocarcinoma	103	66.5	101	65.6	97	62.6
Squamous cell carcinoma	30	19.4	34	22.1	27	17.4
Unknown	22	14.2	19	12.3	31	20.0
Response to induction chemotherapy						
Objective response	82	52.9	81	52.6	82	52.9
Stable disease	73	47.1	73	47.4	73	47.1

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status.
*Defined as consumption of < 100 cigarettes during a whole lifetime.

statistician, in the Biostatistics and Treatment Evaluation Unit of the Cancer Center Léon Bérard in Lyon. Analyses were performed using the SAS software (version 9.2, Cary, NC) by C.S-F., a second statistician of the Cancer Center Léon Bérard.

RESULTS

Patients

Between July 2006 and June 2009, 834 patients were enrolled onto 73 centers in France and received cisplatin-gemcitabine induction chemotherapy. A total of 464 patients were subsequently randomly assigned to observation (n = 155), gemcitabine (n = 154), or erlotinib (n = 155) maintenance therapy. The main reasons for nonrandomization were disease progression (22.9%), toxicity (7.1%), and death (6.8%; Fig 1). Baseline characteristics were well balanced among the treatment arms (Table 1). At data cutoff for the primary end point (August 30, 2010), 454 (97.8%) of 464 randomly assigned patients' files had been reviewed and 381 patients experienced disease progression or death (Fig 1). The median follow-up period for all patients was 25.6 months.

Study Treatment

The median number of maintenance gemcitabine treatment cycles was four (range, 1 to 19), whereas the median duration of treatment was 10.9 and 12.1 weeks for gemcitabine and erlotinib, respectively.

Efficacy

Continuation maintenance with gemcitabine significantly prolonged PFS versus observation alone (median PFS, 3.8 *v* 1.9 months; HR, 0.56; 95% CI, 0.44 to 0.72; log-rank $P < .001$; Fig 2A). Planned subgroup analysis revealed a consistent PFS benefit across all patient subgroups (Fig 2B). However, there was a trend toward a larger PFS benefit among patients who received second-line pemetrexed and those with an objective response to cisplatin-gemcitabine.

Switch maintenance with erlotinib also significantly improved PFS compared with observation (median PFS, 2.9 *v* 1.9 months; HR, 0.69; 95% CI, 0.54 to 0.88; log-rank $P = .003$; Fig 2C). Exploratory

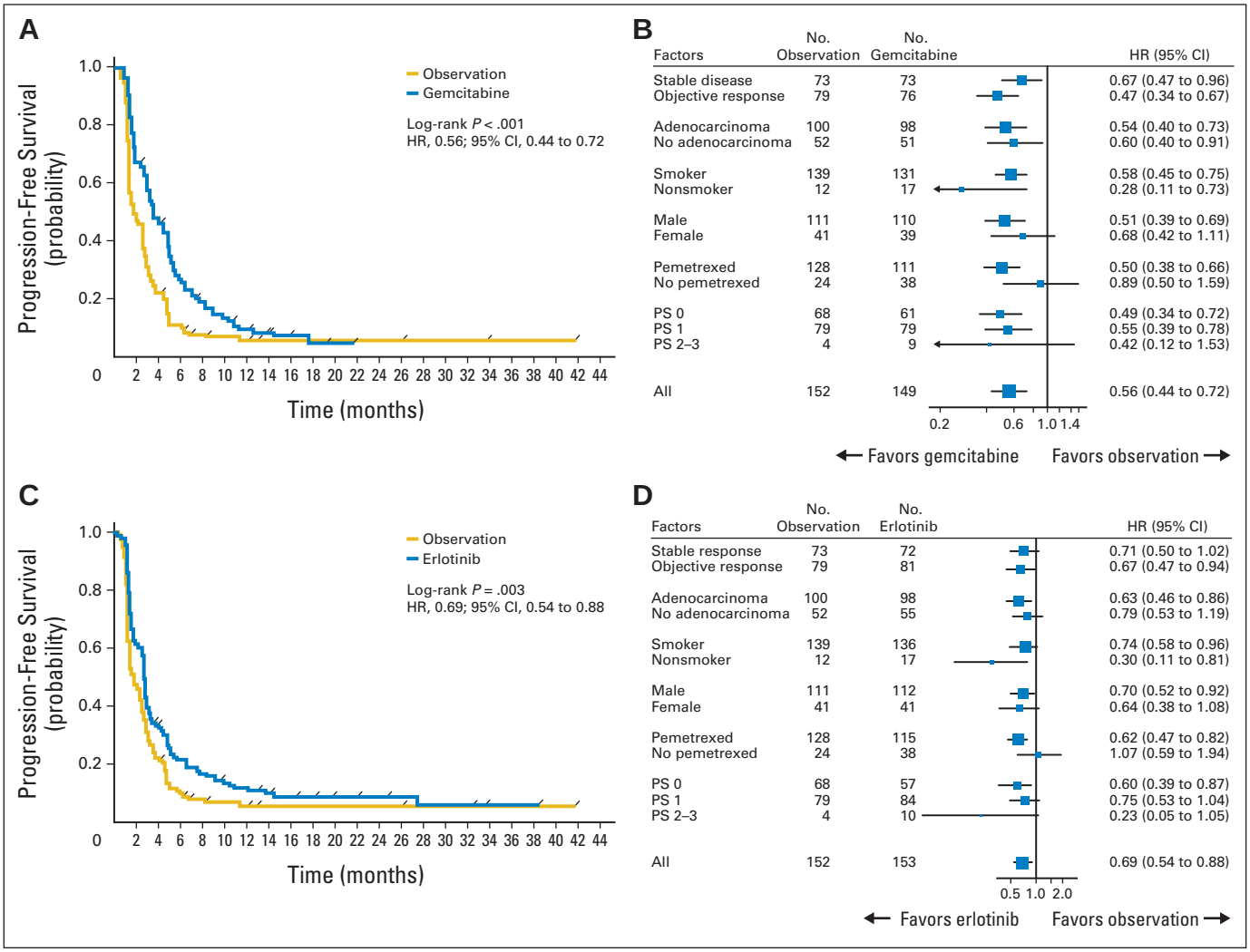

Fig 2. (A) Progression-free survival (PFS; panel review) and (B) PFS subgroup univariate analysis for patients treated with gemcitabine maintenance versus observation, and (C) PFS (panel review) and (D) PFS subgroup univariate analysis for patients treated with erlotinib maintenance versus observation. HR, hazard ratio; PS, performance status.

subgroup analysis demonstrated a consistent PFS benefit across patient subgroups irrespective of gender, smoking status, and response to induction chemotherapy (Fig 2D); however, there was a trend toward a larger benefit among never-smokers and patients who received second-line pemetrexed.

At data cutoff, 355 of 464 randomly assigned patients had died. The PFS benefit with gemcitabine continuation maintenance did not translate into a significant OS advantage versus observation alone (median OS, 12.1 *v* 10.8 months; HR, 0.89; 95% CI, 0.69 to 1.15; log-rank $P = .3867$; Fig 3A). An exploratory subgroup analysis showed that OS benefit may concern patients with a PS of 0, patients with an objective response to cisplatin-gemcitabine induction chemotherapy, and those treated with second-line pemetrexed (Fig 3B). Among patients with an objective response to induction chemotherapy, the HR for OS was 0.72 (95% CI, 0.51 to 1.04), with a median OS of 15.2 months with gemcitabine versus 10.8 months with observation.

Erlotinib switch maintenance also failed to provide an OS advantage over observation alone (median OS, 11.4 *v* 10.8 months; HR, 0.87; 95% CI, 0.68 to 1.13; log-rank $P = .3043$; Fig 3C). Subgroup analysis did not show any impact of magnitude of response to induction chemotherapy on OS benefit as a result of erlotinib maintenance. Similar to the patients on the gemcitabine arm, patients with a PS of 0 and patients who received second-line pemetrexed therapy seemed to benefit more from erlotinib maintenance (Fig 3D).

Second- and Third-Line Treatment

Overall, 90.9% of patients received second-line treatment (any type) in the observation arm compared with 77.2% and 79.9% on gemcitabine and erlotinib, respectively. As specified, pemetrexed was the most common second-line therapy (Table 2). The most common third-line treatment was erlotinib in the observation and gemcitabine-maintenance arms and docetaxel in the erlotinib-maintenance arm. Activity of second-line pemetrexed did not seem to differ between the three arms (Table 3).

Biomarker Analyses

Among the samples evaluable for EGFR IHC analysis (n = 261), 149 samples (57.1%) were IHC positive and 112 (42.9%) were IHC negative. Prognostic factors were well balanced, and EGFR IHC status had no significant effect on PFS benefit with either gemcitabine or

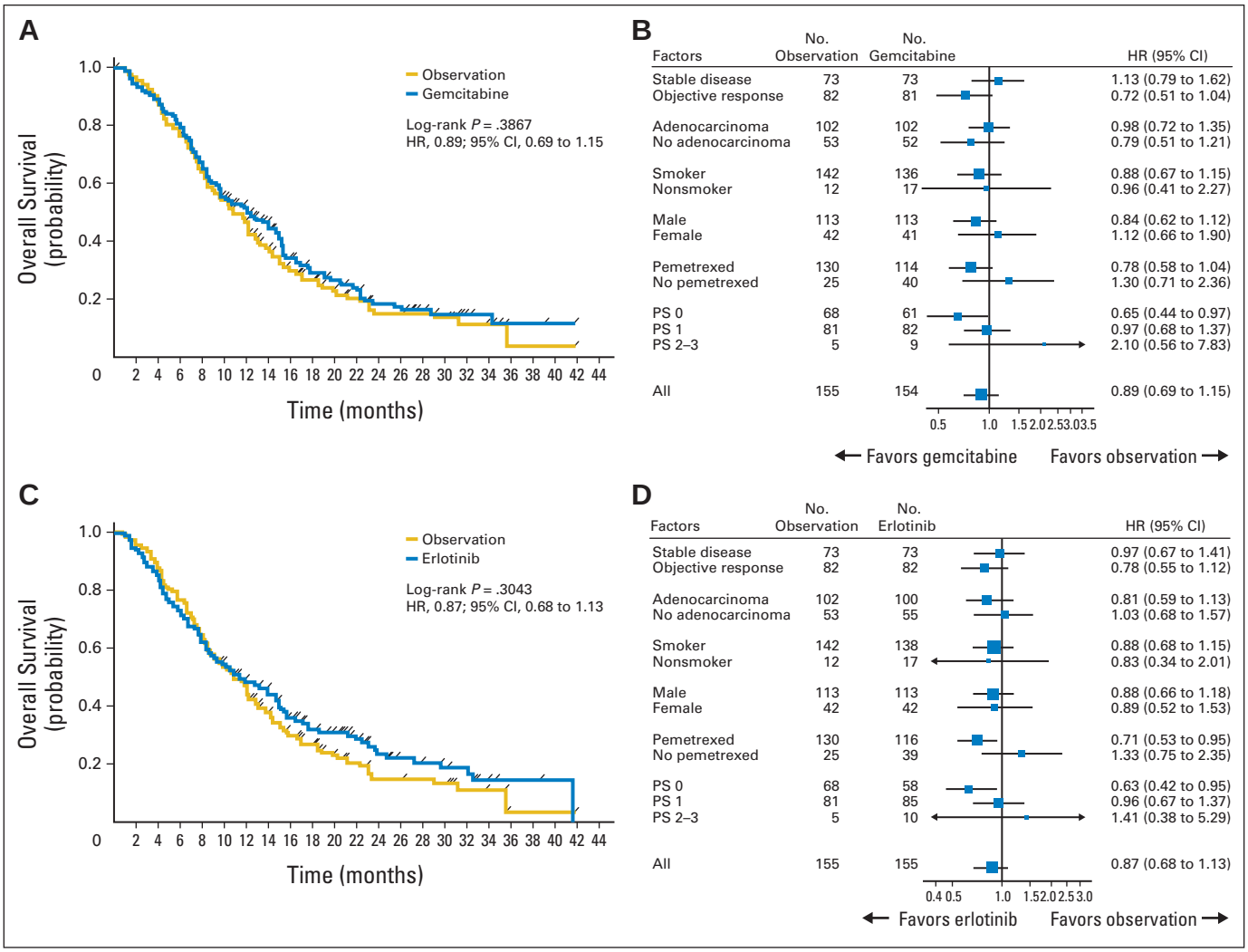

Fig 3. (A) Overall survival (OS) and (B) OS subgroup univariate analysis for patients treated with gemcitabine maintenance versus observation, and (C) OS and (D) OS subgroup univariate analysis for patients treated with erlotinib maintenance versus observation. HR, hazard ratio; PS, performance status.

Table 2. Postmaintenance Therapy Treatments

Treatment	Observation Group		Gemcitabine Group		Erlotinib Group	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Second-line treatment						
Total	155		154		155	
Pemetrexed	130	83.8	114	74.0	116	74.8
Erlotinib	9	5.8	5	3.2	0	
Docetaxel	2	1.3	0		5	3.2
Other	0		0		3	1.9
No second-line treatment	14	9.0	35	22.7	31	20.0
Third-line treatment						
Total	141		119		124	
No further treatment	21	14.9	18	15.1	21	16.9
Erlotinib	64	45.4	48	40.3	3	2.4
Docetaxel	12	8.5	19	16.0	42	33.9
Other	6	4.3	5	4.2	20	16.1
Still on pemetrexed	8	5.7	4	3.4	7	5.6
NA	30	21.2	25	21.0	31	25.0

Abbreviation: NA, data not available.

erlotinib maintenance (EGFR IHC–positive tumors: HR 0.67; 95% CI, 0.45 to 1.02 for gemcitabine; HR, 0.76; 95% CI, 0.49 to 1.18 for erlotinib; EGFR IHC–negative tumors: HR, 0.35; 95% CI, 0.20 to 0.60 for gemcitabine; HR, 0.77; 95% CI, 0.47 to 1.28 for erlotinib).

Fourteen activating *EGFR* mutations were identified from 188 evaluable samples (exon 19, n = 10; exon 21, n = 4); however, the number was insufficient for analysis according to *EGFR* mutational status.

Safety

There were no unexpected AEs during gemcitabine and erlotinib maintenance therapy (Table 4). The most common AEs with gemcitabine were hematologic, with 20.8% of patients experiencing grade 3/4 treatment-related neutropenia and two treatment-related deaths. Rash was the most frequent AE in the erlotinib arm, with 9% of patients experiencing a grade 3/4 treatment-related skin rash. Hematologic supportive care was only necessary in the gemcitabine arm, with 24.7% of patients requiring erythropoietin therapy and 11.7% requiring an RBC transfusion. Platelet transfusion was necessary in less than 1% of patients.

Table 3. Activity of Second-Line Pemetrexed Treatment

Activity	Observation Group (n = 155)		Gemcitabine Group (n = 154)		Erlotinib Group (n = 155)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Pemetrexed	130	83.8	114	74.0	116	74.8
No. of cycles						
Median	3		3		3	
Range	1-14		1-21		1-14	
Response to pemetrexed						
Total No. of patients evaluable for response	111		101		101	
CR	0		0		1	1.0
PR	11	9.9	8	7.9	10	9.9
SD	36	32.4	36	35.6	25	24.8
PD	64	57.7	57	56.4	65	64.4

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

DISCUSSION

To our knowledge, our study is the first trial to simultaneously explore both switch and continuation maintenance therapy, providing the opportunity to identify which patients stand to benefit most from either strategy. Our study is also the only maintenance trial to predefine second-line therapy, thereby preventing bias owing to second-line imbalances. Our study met its primary end point, demonstrating that both gemcitabine and erlotinib maintenance treatment provide a statistically significant and clinically meaningful improvement in the duration of disease control with manageable toxicity. One potential limitation of the study was that PFS was not assessed by external review, but was evaluated independently of the investigator in charge of the patient by a panel of other investigators blinded to randomization.

Despite the large improvement in PFS with gemcitabine, there was no significant impact on OS. However, the study was not powered to assess survival differences. Analysis of the impact of second-line pemetrexed therapy was not suggestive of a negative interaction between gemcitabine maintenance and second-line pemetrexed that could compromise improvement in OS. The exploratory subgroup analysis suggested that patients with a PS of 0 after induction chemotherapy and patients with an objective response to cisplatin-gemcitabine chemotherapy might achieve OS benefit from continuation maintenance with gemcitabine. Conversely, patients with stable disease did not seem to benefit from continuation maintenance. These results are analogous to those observed in the trial conducted by Brodowicz et al,[15] which showed similar PFS gains and an OS benefit predominantly in patients with a good Karnofsky index treated with maintenance gemcitabine; however, the study did not provide data according to response to cisplatin-gemcitabine. A United States study[31] also assessed gemcitabine continuation maintenance after carboplatin-gemcitabine induction chemotherapy but, contrary to both European studies, failed to show a PFS or OS benefit; the main difference being that 64% of patients in this study had a PS of ≥ 2 at the time of random assignment.[31] If these results are confirmed in other trials, continuation maintenance with gemcitabine might be a useful option for patients with good PS who have an objective response to cisplatin-gemcitabine.

Switch maintenance with erlotinib also provided a significant prolongation of PFS, which was similar in magnitude to that reported in the SATURN (Sequential Tarceva in Unresectable NSCLC)[17] and ATLAS (A randomized, double-blind, placebo controlled, phase IIIb trial)[32] studies. Survival analysis did not reveal a significant improvement in OS, contrary to the SATURN trial,[17] taking into account the lower power of our trial.

As a result of predefined second-line therapy, more than 90% of patients in the control arm received second-line therapy at disease

Table 4. AEs During Maintenance Phase

AE	Observation Group (n = 155)				Gemcitabine Group (n = 154)				Erlotinib Group (n = 155)			
	All Grades		Grade 3/4		All Grades		Grade 3/4		All Grades		Grade 3/4	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
≥ 1 serious AE unrelated to disease progression	29	18.7			35	22.7			36	23.2		
≥ 1 grade 3/4 AE related to treatment	4	2.6			43	27.9			24	15.5		
AE												
Anemia	12	7.7	1	0.6	59	38.3	4	2.6	24	15.5	2	1.3
Neutropenia	7	4.5	1	0.6	65	42.2	32	20.8	5	3.2	1	0.6
Thrombocytopenia	2	1.3	0		60	39.0	10	6.5	2	1.3	0	
Rash	0		0		6	3.9	0		98	63.2	14	9.0
Diarrhea	1	0.6	0		8	5.2	1	0.6	31	20.0	1	0.6
Anorexia	4	2.6	1	0.6	11	7.1	1	0.6	8	5.2	2	1.3
Asthenia	11	7.1	0		42	27.3	3	1.9	27	17.4	2	1.3
Deterioration of general condition	9	5.8	6	3.9	10	6.5	5	3.2	10	6.5	3	1.9
Infection	2	1.3	0		10	6.5	2	1.3	8	5.2	4	2.6
Renal failure	2	1.3	0		7	4.5	1	0.6	8	5.2	2	1.3
Pneumonia	4	2.6	2	1.3	7	4.5	5	3.2	9	5.8	4	2.6
Treatment-related deaths	0				2*				0			

Abbreviation: AE, adverse event.
*One death as a result of bacterial pneumonia and one as a result of renal failure and pneumonia.

progression, which is higher than seen in clinical practice[6,7] and the SATURN trial.[17] Moreover, more than 45% of control patients were subsequently treated with erlotinib, compared with 21% of patients treated with EGFR tyrosine-kinase inhibitors in SATURN.[17] As the OS benefit from switch maintenance therapy is partly because of an increase in the proportion of patients exposed to active drug in the second-line setting,[5,9,17] optimization of second-line therapy in the control arm may have contributed to a reduction in the magnitude of the OS benefit in the current study compared with the SATURN trial. However, maintenance erlotinib was still associated with a slight OS benefit in our study, despite the fact that nearly all patients received second-line therapy in the control arm. The exploratory subgroup analysis for OS showed that patients who received the entire therapeutic sequence (ie, first- and second-line therapies in the control arm, first-line maintenance, and second-line therapies in the erlotinib arm) seemed to benefit most from erlotinib maintenance, linking the prolongation of survival to the PFS benefit. Notably, we did not observe a similar impact of response to induction chemotherapy on OS benefit with erlotinib maintenance as in the SATURN trial.[21]

The tolerability profile of erlotinib was similar to that observed in the BR.21[4] and SATURN trials,[17] with skin toxicity and diarrhea the main AEs; however, as expected, grade 3/4 toxicities were infrequent. Treatment-related grade 3/4 AEs were approximately half as frequent with erlotinib versus gemcitabine.

In conclusion, continuation maintenance with gemcitabine or switch maintenance with erlotinib significantly improves duration of disease control in patients with advanced NSCLC treated with cisplatin-gemcitabine as first-line chemotherapy, irrespective of smoking status, histology, gender, and EGFR expression. AEs are manageable with both maintenance treatments. Neither of the maintenance strategies significantly improved OS, but optimization of subsequent treatments with predefined second-line therapy might explain a smaller benefit than that observed in the SATURN[17] and JMEN[18] trials. Response to cisplatin-gemcitabine chemotherapy seems to influence benefit only from gemcitabine, suggesting that continuation maintenance should only be proposed for patients with a good PS and objective response to induction chemotherapy. In contrast, erlotinib maintenance therapy might be prescribed, irrespective of response to induction chemotherapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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REFERENCES

1. Azzoli CG, Baker S Jr, Temin S, et al: 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
2. Shepherd FA, Dancey J, Ramlau R, et al: Prospective randomized trial of docetaxel versus best supportive care in patients with non–small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 18:2095-2103, 2000
3. Hanna N, Shepherd FA, Fossella FV, et al: Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 22:1589-1597, 2004
4. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al: Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 353:123-132, 2005
5. Fidias P, Novello S: Strategies for prolonged therapy in patients with advanced non–small-cell lung cancer. J Clin Oncol 28:5116-5123, 2010
6. Sun JM, Park JO, Won YW, et al: Who are less likely to receive subsequent chemotherapy beyond first-line therapy for advanced non-small cell lung cancer? Implications for selection of patients for maintenance therapy. J Thorac Oncol 5:540-545, 2010
7. Gerber DE, Rasco DW, Le P, et al: Predictors and impact of second-line chemotherapy for advanced non-small cell lung cancer in the United States: Real word considerations for maintenance therapy. J Thorac Oncol 6:365-371, 2011
8. Stinchcombe TE, West HL: Maintenance therapy in non-small-cell lung cancer. Lancet 374: 1398-1400, 2009
9. Stinchcombe TE, Socinski MA: Maintenance therapy in advanced non-small cell lung cancer: Current status and future implications. J Thorac Oncol 6:174-182, 2011
10. Smith IE, O'Brien ME, Talbot DC, et al: Duration of chemotherapy in advanced non–small-cell lung cancer: A randomized trial of three versus six courses of mitomycin, vinblastine and cisplatin. J Clin Oncol 19:1136-1143, 1991
11. von Plessen C, Bergman B, Andresen O, et al: Palliative chemotherapy beyond three courses conveys no survival or consistent quality-of-life benefits in advanced non-small-cell lung cancer. Br J Cancer 95:966-973, 2006
12. Socinski MA, Schell MJ, Peterman A, et al: Phase III trial comparing a defined duration of therapy versus continuous therapy followed by second-line therapy in advanced-stage IIIB/IV non–small-cell lung cancer. J Clin Oncol 20:1335-1343, 2002
13. Park JO, Kim SW, Ahn JS, et al: Phase III trial of two versus four additional cycles in patients who are nonprogressive after two cycles of platinum-based chemotherapy in non–small-cell lung cancer. J Clin Oncol 25:5233-5239, 2007
14. Lima JP, dos Santos LV, Sasse EC, et al: Optimal duration of first-line chemotherapy for advanced non-small cell lung cancer: A systematic review with meta-analysis. Eur J Cancer 45:601-607, 2009
15. Brodowicz T, Krzakowski M, Zwitter M, 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 52:155-163, 2006
16. Paz-Ares L, de Marinis F, Dediu M, 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 13:247-255, 2012
17. Cappuzzo F, Ciuleanu T, Stelmakh L, et al: Erlotinib as maintenance treatment in advanced, non-small-cell lung cancer: A multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol 11:521-529, 2010
18. Ciuleanu T, Brodowicz T, Zielinski C, 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 374:1432-1440, 2009
19. Socinski MA: Re-evaluating duration of therapy in advanced non–small-cell lung cancer: Is it really duration or is it more about timing and exposure? J Clin Oncol 27:3268-3270, 2009
20. Fidias PM, Dakhil SR, Lyss AP, 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 27:591-598, 2009
21. Coudert B, Ciuleanu T, Park K, et al: Survival benefit with erlotinib maintenance therapy in patients with advanced non-small-cell lung cancer (NSCLC) according to response to first-line chemotherapy. Ann Oncol 23:388-394, 2012
22. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205-216, 2000
23. Pocock SJ, Simon R: Sequential treatment assessment with balancing for prognostic factors in the controlled clinical trial. Biometrics 31:103-115, 1975
24. Hollen PJ, Gralla RJ, Kris MG, et al: Quality of life during clinical trials: Conceptual model for the Lung Cancer Symptom Scale (LCSS). Support Care Cancer 2:213-222, 1994
25. Hirsch FR, Varella-Garcia M, Bunn PA Jr, et al: Epidermal growth factor receptor in non–small-cell lung carcinomas: Correlation between gene copy number and protein expression and impact on prognosis. J Clin Oncol 21:3798-3807, 2003
26. Molina-Vila MA, Bertran-Alamillo J, Reguart N, et al: A sensitive method for detecting EGFR mutations in non-small cell lung cancer samples with few tumor cells. J Thorac Oncol 3:1224-1235, 2008
27. Freidlin B, Korn EL, Gray R, et al: Multi-arm clinical trials of new agents: Some design considerations. Clin Cancer Res 14:4368-4371, 2008
28. O'Brien PC, Fleming TR: A multiple testing procedure for clinical trials. Biometrics 35:549-556, 1979
29. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958
30. Schemper M, Smith TL: A note on quantifying follow-up in studies of failure time. Control Clin Trials 17:343-346, 1996
31. Belani CP, Waterhouse DM, Ghazal H, 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 28:540s, 2010 (suppl 15; abstr 7506)
32. Kabbinavar FF, Miller VA, Johnson BE, et al: Overall survival (OS) in ATLAS, a phase IIIb trial comparing bevacizumab (B) therapy with or without erlotinib (E) after completion of chemotherapy (chemo) with B for first-line treatment of locally advanced, recurrent, or metastatic non–small cell lung cancer (NSCLC). J Clin Oncol 28:544s, 2010 (suppl 15; abstr 7526)

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