VOLUME 30 · NUMBER 24 · AUGUST 20 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

First-Line Erlotinib Followed by Second-Line Cisplatin-Gemcitabine Chemotherapy in Advanced Non–Small-Cell Lung Cancer: The TORCH Randomized Trial

Cesare Gridelli, Fortunato Ciardiello, Ciro Gallo, Ronald Feld, Charles Butts, Vittorio Gebbia, Paolo Maione, Floriana Morgillo, Giovenzio Genestreti, Adolfo Favaretto, Natasha Leighl, Rafal Wierzbicki, Saverio Cinieri, Yasmin Alam, Salvatore Siena, Giampaolo Tortora, Raffaella Felletti, Ferdinando Riccardi, Gianfranco Mancuso, Antonio Rossi, Flavia Cantile, Ming-Sound Tsao, Mauro Saieg, Gilda da Cunha Santos, Maria Carmela Piccirillo, Massimo Di Maio, Alessandro Morabito, and Francesco Perrone

Author affiliations appear at the end of this article.

Submitted December 30, 2011; accepted May 7, 2012; published online ahead of print at www.jco.org on July 9, 2012.

Written on behalf of the TORCH trial investigators.

Supported by the National Cancer Institute of Napoli, Italy; by Grant No. RO 0508231 from Roche (which also supplied erlotinib for nonregistered use); and by Grant No. 07008C from Hoffman-La Roche for the collection of samples and *EGFR* mutation analysis.

Presented as an oral presentation at the 46th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 4-8, 2010.

Roche had no role in trial design, conduction, analysis, interpretation, or presentation of results. Peripheral monitoring was performed by commercial clinical research organizations reporting to the National Cancer Institute of Napoli in Italy and to the University Health Network in Canada. University Health Network of Toronto coordinated the trial in Canada.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

Corresponding author: Cesare Gridelli, MD, Divisione di Oncologia Medica, Azienda Ospedaliera S.G. Moscati, Via Circumvallazione, 68, Contrada Amoretta, 83100 Avellino, Italy; e-mail: cgridelli@libero.it.

0732-183X/12/3024-3002/$20.00

DOI: 10.1200/JCO.2011.41.2056

ABSTRACT

Purpose
Erlotinib prolonged survival of unselected patients with advanced non–small-cell lung cancer (NSCLC) who were not eligible for further chemotherapy, and two phase II studies suggested it might be an alternative to first-line chemotherapy. A randomized phase III trial was designed to test whether first-line erlotinib followed at progression by cisplatin-gemcitabine was not inferior in terms of survival to the standard inverse sequence.

Patients and Methods
Patients with stage IIIB (with pleural effusion or supraclavicular nodes) to IV NSCLC and performance status of 0 to 1 were eligible. With a 95% CI upper limit of 1.25 for the hazard ratio (HR) for death, 80% power, a one-sided $\alpha = .025$, and two interim analyses, a sample size of 900 patients was planned.

Results
At the first planned interim analysis with half the events, the inferiority boundary was crossed, and the Independent Data Monitoring Committee recommended early termination of the study. Seven hundred sixty patients (median age, 62 years; range, 27 to 81 years) had been randomly assigned. Baseline characteristics were balanced between study arms. As of June 1, 2011, median follow-up was 24.3 months, and 536 deaths were recorded (263 in the standard treatment arm and 273 in the experimental arm). Median survival was 11.6 months (95% CI, 10.2 to 13.3 months) in the standard arm and 8.7 months (95% CI, 7.4 to 10.5 months) in the experimental arm. Adjusted HR of death in the experimental arm was 1.24 (95% CI, 1.04 to 1.47). There was no heterogeneity across sex, smoking habit, histotype, and epidermal growth factor receptor (*EGFR*) mutation.

Conclusion
In unselected patients with advanced NSCLC, first-line erlotinib followed at progression by cisplatin-gemcitabine was significantly inferior in terms of overall survival compared with the standard sequence of first-line chemotherapy followed by erlotinib.

J Clin Oncol 30:3002-3011. © 2012 by American Society of Clinical Oncology

INTRODUCTION

Non–small-cell lung cancer (NSCLC) is a major cause of death related to cancer around the world.[1] Most patients have advanced disease at diagnosis and are candidates for systemic therapy. Platinum-based chemotherapy is the standard first-line treatment, and it is associated with a modest survival benefit compared with best supportive care,[2,3] with substantial toxicity. Phase III trials suggest that no major efficacy differences exist between approved platinum-based treatments.[4] Gemcitabine plus cisplatin is among the most used combinations.[5,6]

Epidermal growth factor receptor (EGFR) is involved in development and progression of human epithelial malignancies and it is often found in NSCLC cells; EGFR inhibitors have been developed.[7] Erlotinib is an oral EGFR tyrosine kinase inhibitor (EGFR-TKI). The BR.21 study[8,9] evaluated the efficacy of erlotinib versus placebo in patients with locally advanced or metastatic NSCLC after failure of one or more prior chemotherapy treatments and found a significant survival benefit

for patients treated with erlotinib; therefore, erlotinib was registered for second- and third-line therapy of unselected patients with NSCLC.

In first-line treatment, erlotinib added to chemotherapy did not prolong survival.[10,11] However, two phase II studies suggested that first-line therapy with erlotinib might be an alternative to chemotherapy in patients with advanced NSCLC. In the first study,[12] single-agent erlotinib produced a 23% response rate, 53% nonprogression rate at 6 weeks, and median overall survival (OS) of 13 months. In the second study,[13] which was dedicated to elderly patients, disease control rate was 51%, and median OS was 11 months.

Thus, we planned a phase III trial to evaluate whether first-line erlotinib followed at progression by cisplatin plus gemcitabine was not inferior in OS compared with the reverse standard treatment sequence in patients with advanced NSCLC. Recently, advances in selection of patients for the use of EGFR-TKI have been reported; however, when the study was planned, erlotinib was registered for unselected patients, there was no clear evidence on predictive factors, and no general agreement on patient selection. In addition, in the BR.21 trial, erlotinib efficacy seemed to be independent of most clinical and biologic factors.[8,9] Therefore, clinical or biologic factors were not applied in the selection of the study population.

PATIENTS AND METHODS

Patients

TORCH (Tarceva or Chemotherapy) was an international, multicenter, open-label, randomized phase III trial conducted in Italy and Canada. Eligibility criteria were histologically or cytologically confirmed NSCLC stage IIIB (with malignant pleural effusion or supraclavicular nodes) or IV, at least one target or nontarget lesion according to Response Evaluation Criteria in Solid Tumors (RECIST), age younger than 70 years (no age limits for Canadian centers), and Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 1. Patients at first diagnosis and those with recurrence after surgery were eligible. Prior neoadjuvant or adjuvant chemotherapy was permitted if it did not contain gemcitabine and at least 1 year had elapsed from last administration to relapse. Prior

Table 1. Baseline Characteristics

Characteristic	Standard Arm (n = 380)		Experimental Arm (n = 380)		Overall (N = 760)	
	No.	%	No.	%	No.	%
Country						
Italy	306	80.5	306	80.5	612	80.5
Canada	74	19.5	74	19.5	148	19.5
Sex						
Male	252	66.3	252	66.3	504	66.3
Female	128	33.7	128	33.7	256	33.7
Age, years						
Median	62		63		62	
Range	34-81		27-79		27-81	
< 70	361	95.0	361	95.0	722	95.0
≥ 70	19	5.0	19	5.0	38	5.0
Ethnicity						
East Asian	12	3.2	12	3.2	24	3.2
Other	368	96.8	368	96.8	736	96.8
Smoking status*						
Never smoker	79	20.8	78	20.5	157	20.7
Former or current smoker	301	79.2	302	79.5	603	79.3
ECOG performance status						
0	185	48.7	197	51.8	382	50.3
1	195	51.3	183	48.2	378	49.7
Stage						
III B	37	9.7	46	12.1	83	10.9
IV	343	90.3	334	87.9	677	89.1
Previous surgery						
Yes	92	24.2	90	23.7	182	23.9
No	288	75.8	290	76.3	578	76.1
Histology						
Squamous, large cell, mixed, undefined	168	44.2	170	44.7	338	44.5
Adenocarcinoma, bronchioloalveolar	212	55.8	210	55.3	422	55.5
EGFR mutation status						
Not available	243		242		485	
Mutated	20	14.6	19	13.8	39	14.2
Wild type	117	85.4	119	86.2	236	85.8

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.
*Never smokers: < 100 cigarettes per lifetime; former smoker: ≥ 100 cigarettes per lifetime but nonsmoker when entering the study.

radiotherapy was permitted. Patients with asymptomatic brain metastases were eligible if surgical and/or radiation treatments were completed and if the patients were not receiving concurrent steroids. Exclusion criteria were prior treatment with anti-EGFR agents; history of prior invasive malignancy or inadequate bone marrow (neutrophils $< 1{,}500/\mu L$, platelets $< 100{,}000/\mu L$, hemoglobin < 9 g/dL), hepatic (bilirubin $> 1.5 \times$ upper limit of normal [ULN], ALT or AST $> 2.5 \times$ ULN in the absence of liver metastases, ALT or AST $> 5 \times$ ULN with liver metastases), or renal (serum creatinine $> 1.5 \times$ ULN) function; or any unstable systemic disease, including active infections and significant cardiovascular, hepatic, renal, or metabolic disease. Patients with inflammatory eye surface changes and those who could not take or absorb oral medications were excluded.

The ethics committee of each participating institution approved the study. All patients provided written informed consent. An independent data monitoring committee (IDMC) was nominated by the Steering Committee in April 2008.

Random Assignment

Patients were centrally randomly assigned to the two treatment arms (1:1 ratio) through a centralized automated minimization procedure by using histology (adenocarcinoma *v* other), smoking status (never *v* ever smoker), sex, age (< 70 *v* ≥ 70 years), center, and PS (0 *v* 1) as strata.

Treatments

Patients randomly assigned to the experimental arm received erlotinib 150 mg per day orally until disease progression. After progression, patients received second-line cisplatin 80 mg/m^2 intravenously on day 1 plus gemcitabine 1,200 mg/m^2 intravenously per day on days 1 and 8 every 3 weeks for a maximum of six cycles. Patients randomly assigned to the standard arm received cisplatin plus gemcitabine at the same doses. After progression, patients received second-line erlotinib 150 mg per day until progression.

Dose reductions for chemotherapy were planned on day 8 for grade 2 neutropenia or thrombocytopenia, and chemotherapy was withheld for hematologic toxicity grade ≥ 3. Dose reductions for day 1 were not planned, but chemotherapy could be postponed for up to 14 days for persistent hematologic and nonhematologic toxicities grade ≥ 2. Erlotinib dose could be reduced up to two levels (100 mg at first reduction, 50 mg at second reduction) or could be interrupted for up to 2 weeks. Dose re-escalation was not permitted except in the case of erlotinib-related rash.

Assessment Procedures

Patients were evaluated at baseline with a complete history and physical examination, routine hematology and biochemistry, chest x-ray, computed tomography scans of head, chest, and abdomen, and bone scan. During first-line treatment, routine hematology, biochemistry, and physical examination were performed every 3 weeks, before each cycle in both arms. Hematology was also repeated before chemotherapy on day 8 of each cycle. Chest x-ray, computed tomography scans, and bone scans were repeated after three and six cycles. Clinical evaluation, routine hematology, biochemistry, and radiologic examinations were required every 12 weeks after completion of six cycles of therapy.

Objective response was determined by using RECIST (version 1.0). Toxicity was codified according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTC-AE) version 3. Baseline and follow-up evaluations for patients receiving second-line treatment were performed on the same schedule as for first-line therapy.

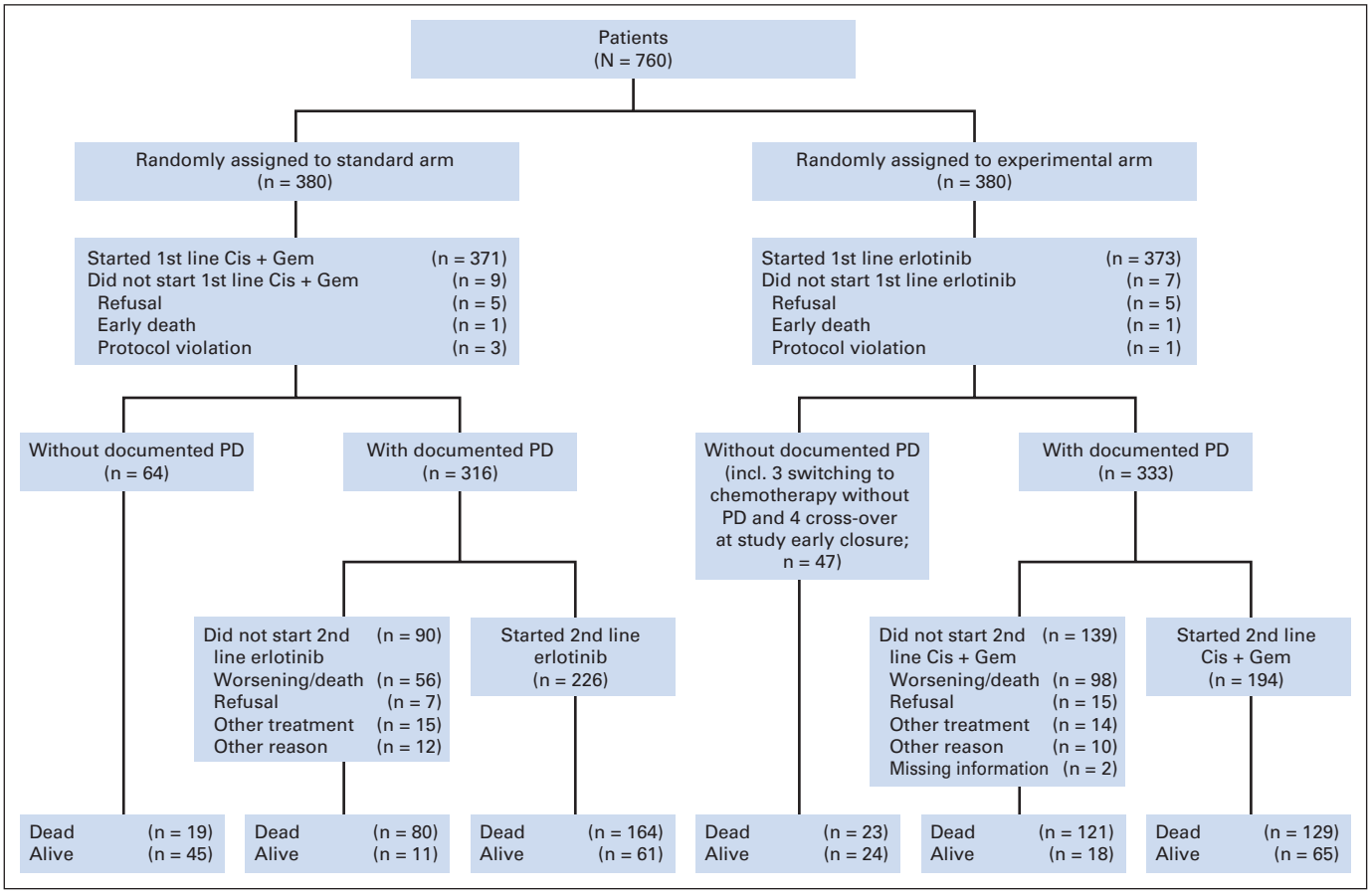

Fig 1. Patients' study flow by treatment arm. Cis, cisplatin; Gem, gemcitabine; PD, progressive disease.

EGFR *Mutation Analysis*

EGFR mutation analysis was performed on available tumor samples after study closure. Samples included paraffin blocks or unstained sections. The hematoxylin and eosin–stained sections were evaluated first for presence and abundance of tumor cells; then, the tumor-enriched areas were marked for macrodissection. *EGFR* exon 19 deletion was analyzed by using the polymerase chain reaction fragment analysis method[14,15]; positive cases were confirmed by capillary sequencing of independent polymerase chain reaction products by ABI 3130 sequence analyzer (Applied Biosystems, Foster City, CA). Capillary sequencing was also used to identify mutations on *EGFR* exon 21.[15] Negative cases were further confirmed by MassARRAY (Sequenom, San Diego, CA) by using primers designed specifically for L858R mutation.

Outcomes

The primary end point was OS, defined as the time from random assignment to death or to last follow-up visit for living patients. Secondary end points reported in this article included total progression-free survival (total PFS), PFS after first-line therapy (first PFS), tumor response, and toxicity.

Total PFS was defined as the time from random assignment to progression after second-line treatment or death if it occurred before second progression, or last follow-up visit for patients who were not included in the previous two categories. First PFS was defined as the time from random assignment to progression after first-line treatment, or death if it occurred before first progression, or last follow-up visit for patients who were not included in the previous two categories.

Overall response rate (ORR) was defined as the number of patients with complete or partial response at any time divided by the total number of patients enrolled onto each arm. Further secondary end points not reported in this article included quality of life, comparisons of resource use, and studies of exploratory biomarkers in tumor and blood samples.

Statistical Considerations

The study was designed to test whether OS in the experimental arm was not inferior to that in the standard arm. Noninferiority was defined as a 95% CI with an upper limit of 1.25 or less for the hazard ratio (HR) of death for the experimental arm. With statistical power of 80%, one-sided $\alpha = .025$ probability of error, two interim analyses, and 900 patients, 669 events (deaths) were required for the final analysis (East 3.1 software; Cytel, Cambridge, MA).

The two interim analyses were planned after approximately 50% and 75% of the events were observed by using O'Brien-Fleming stopping boundaries accounting for both alpha and beta spending functions. Therefore, the trial could be stopped early either because noninferiority of the experimental arm was demonstrated or because inferiority of the experimental treatment was so clear that trial continuation would be unethical.

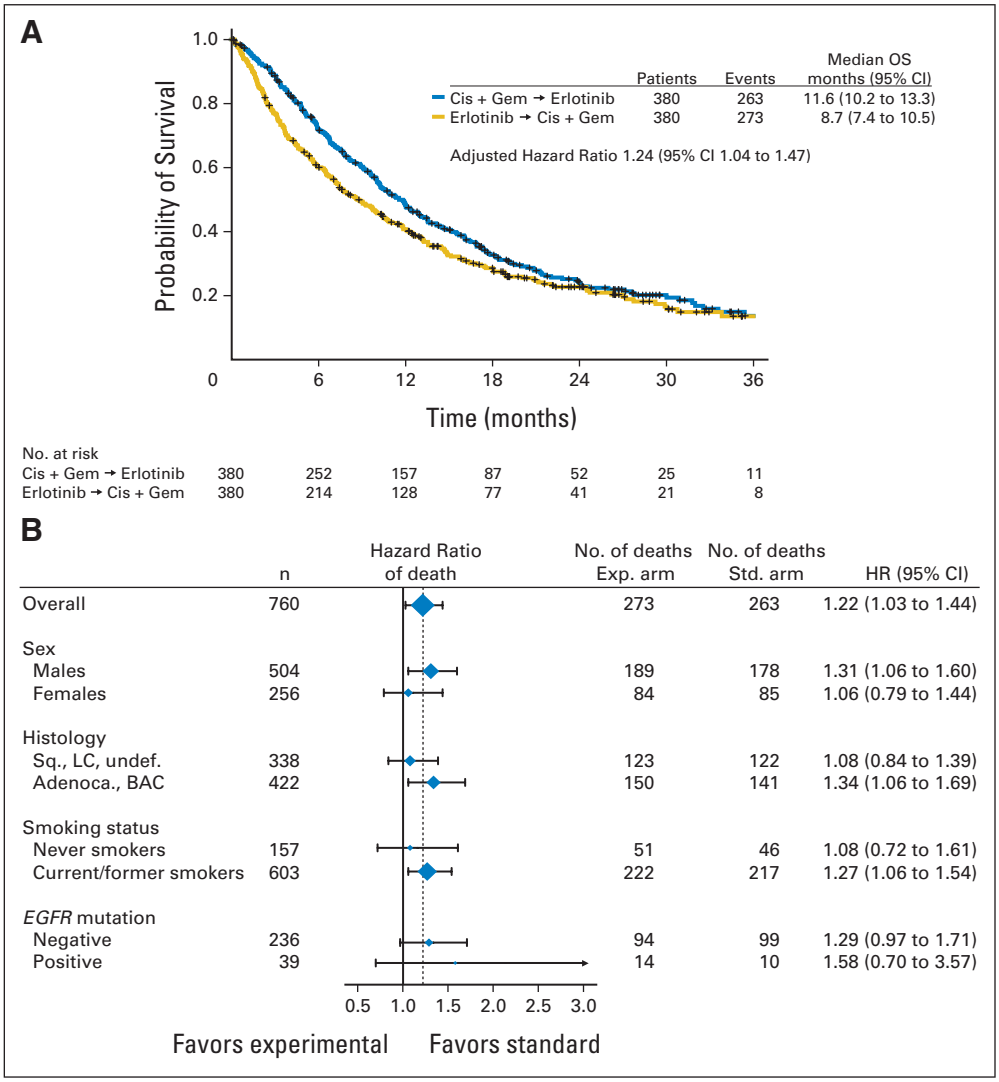

Fig 2. (A) Overall survival (OS) curves by treatment arm. (B) Treatment effect (unadjusted experimental [Exp.] *v* standard hazard ratios [HRs]) on OS within major patient subgroups (vertical dotted line represents unadjusted HR in the overall study population). Adenoca., adenocarcinoma; BAC, bronchioloalveolar carcinoma; Cis, cisplatin; EGFR, epidermal growth factor receptor; Gem, gemcitabine; Sq., LC, undef., squamous, large cell, undefined; Std., standard.

An early analysis of activity was planned only in the experimental arm, according to Fleming's single-stage phase II design. With a 0.05 type I error, 95% power, lowest acceptable proportion of progression-free patients of 0.25, and predicted alternative proportion of 0.40, at least 33 patients (32%) of the first 103 assigned to first-line erlotinib had to be progression-free 9 weeks after random assignment to allow continuation of the study. Failure was defined as progression, death, or any event that led to stopping erlotinib within 9 weeks from random assignment.

Efficacy analyses were planned on an intent-to-treat basis. OS and total-PFS curves were drawn according to the Kaplan-Meier product limit method. Comparison of curves was planned with a nonstratified log-rank test. The application of a multivariable Cox model was planned to estimate HRs adjusted by histology, smoking status, sex, age, ethnicity, PS, country, and size of center as covariates. First-PFS curves were drawn according to the Kaplan-Meier product limit method but were not further compared. Median follow-up was calculated according to the reverse Kaplan-Meier technique.[16]

Prompted by studies published after protocol planning, unplanned interaction tests were performed for clinical factors and *EGFR* mutation status that could possibly affect efficacy analyses, and Forest plots were

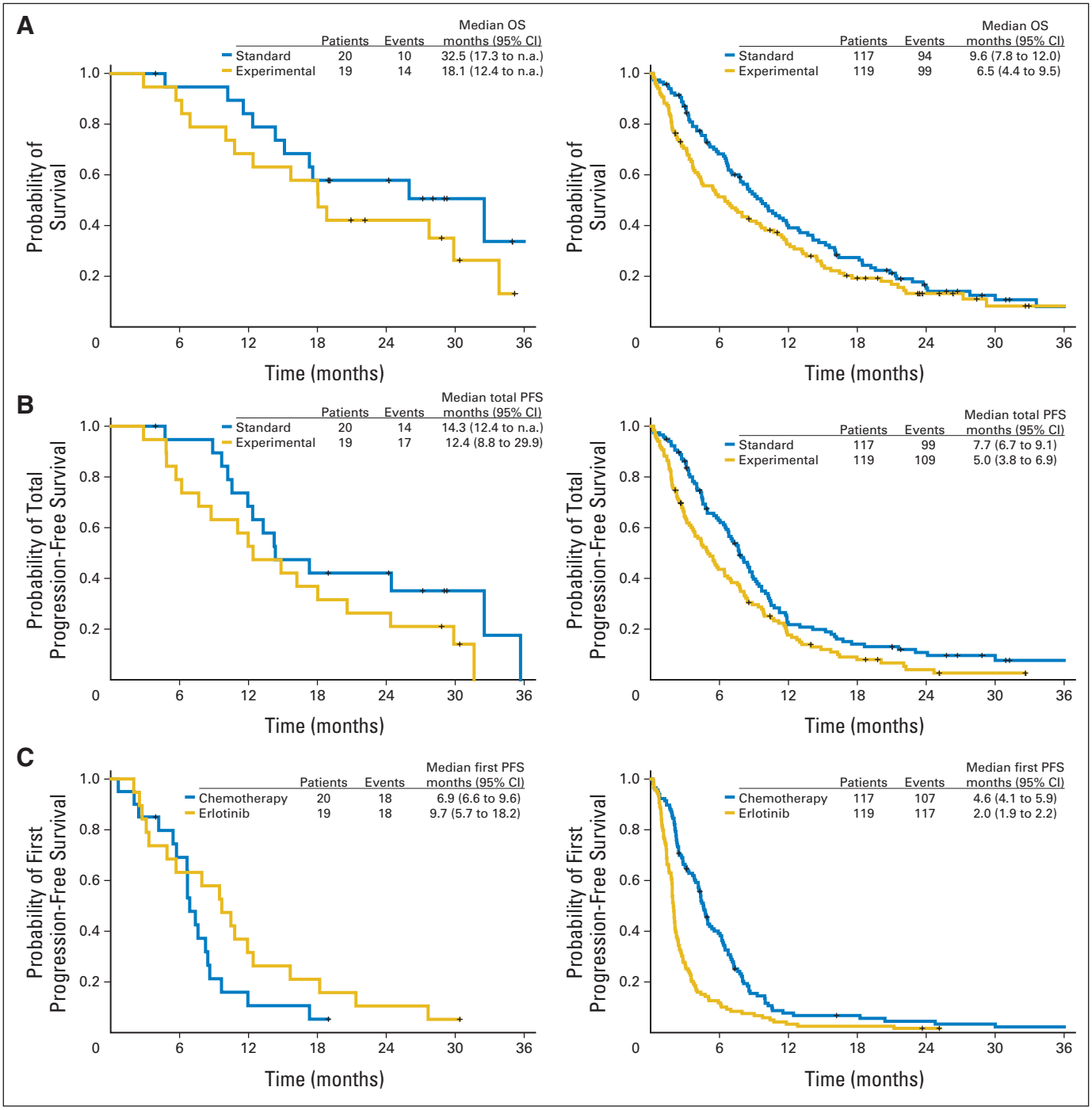

Fig 3. (A) Overall survival (OS), (B) total progression-free survival (PFS), and (C) first PFS curves by treatment arm according to epidermal growth factor receptor (*EGFR*) mutation status (left panel: *EGFR* mutation–positive patients, right panels: *EGFR* mutation–negative patients). n.a., not achieved.

drawn reporting unadjusted HRs within subgroups. All enrolled patients were considered for the evaluation of response. ORRs were compared with a χ^2 test.

All patients who started first-line treatment were considered for toxicity analyses. First, an exact linear permutation test was used to allow for the ordinal nature of toxicity grades (Cytel Studio 7 software; Cytel). Second, χ^2 test (or Fisher's exact test, if appropriate) was used to compare severe (grades 3 to 5) versus not severe (grades 0 to 2) toxicity.

The study is registered with ClinicalTrials.gov. The protocol is available on request to the corresponding author. Statistical plan and analyses were done by the study statistician (C.G.) at the Second University of Naples in Naples, Italy.

RESULTS

Between December 2006 and November 2009, 760 patients were randomly assigned, 612 in Italy (80.5%) and 148 in Canada (19.5%). Baseline characteristics were balanced between arms (Table 1). Median age was 62 years (range, 27 to 81 years), 33.7% were females, 20.7% were never smokers, and 55.5% had adenocarcinoma. Most patients were white, with 3.2% having East Asian ethnicity. *EGFR* mutational status for exon 19 and exon 21 was known in 275 patients (36.2%); baseline characteristics of these patients are reported in Appendix Table A1 (online only), also scattered by treatment arm. Thirty-nine patients (14.2%) had *EGFR* mutation–positive tumor: 20 in the standard arm and 19 in the experimental arm.

Patient flow is reported in Figure 1. In the standard arm, 371 patients (97.6%) received at least one cycle of first-line cisplatin plus gemcitabine, with a median number of five cycles received. Of 316 patients with documented progression during or after first-line therapy, 90 patients (28.5%) did not receive second-line erlotinib, mostly because of worsening conditions or death. In the experimental arm, 373 patients (98.2%) received at least one dose of first-line erlotinib. Of 333 patients with documented progression with first-line erlotinib, 139 patients (41.7%) did not receive second-line cisplatin plus gemcitabine, mostly because of worsening conditions or death.

The early activity analysis was performed in May 2008. Of the first 101 patients assigned to first-line erlotinib (two patients withdrew consent), 38 (38%) were progression-free 9 weeks after random assignment. The IDMC agreed that the study should continue according to study protocol.

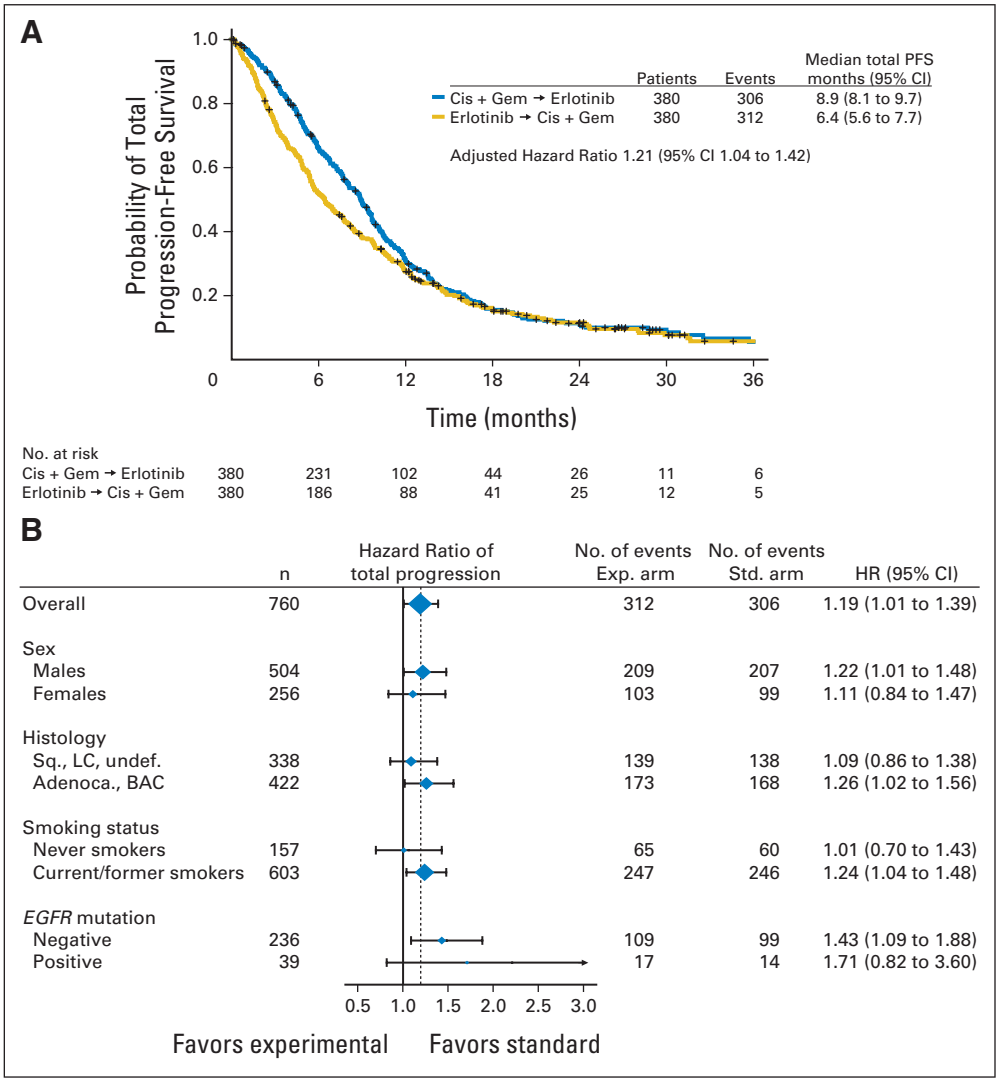

Fig 4. (A) Total progression-free survival (PFS) curves by treatment arm. (B) Treatment effect (unadjusted experimental [Exp.] *v* standard hazard ratios [HRs]) on total PFS within major patient subgroups (vertical dotted line represents unadjusted HR in the overall study population). Adenoca., adenocarcinoma; BAC, bronchioloalveolar carcinoma; Cis, cisplatin; EGFR, epidermal growth factor receptor; Gem, gemcitabine; Sq., LC, undef., squamous, large cell, undefined; Std, standard.

The first planned interim analysis was performed with blinded data in November 2009 on the basis of 340 deaths: 151 in the standard arm and 189 in the experimental arm. At that time, 760 patients had been enrolled, with median follow-up of 8.3 months. The test statistic was equal to −1.030, far lower than the boundary limit of 0.583 for claiming the inferiority of the experimental arm. The IDMC recommended early study termination. Crossover to cisplatin plus gemcitabine was suggested for patients who were still in their first 9 weeks of first-line erlotinib (before the first restaging); four patients agreed to stop erlotinib and start chemotherapy. All time-to-event analyses that follow refer to 760 patients, updated as of June 1, 2011.

OS

After a median follow-up of 24.3 months, 536 deaths were recorded: 263 in the standard arm and 273 in the experimental arm. Median survival was 11.6 months (95% CI, 10.2 to 13.3 months) in the standard arm and 8.7 months (95% CI, 7.4 to 10.5 months) in experimental arm (Fig 2). Unadjusted HR of death for the experimental arm was 1.22 (95% CI, 1.03 to 1.44). After adjustment for known prognostic covariates, the estimated HR of death for the experimental arm was 1.24 (95% CI, 1.04 to 1.47). There was no significant heterogeneity of treatment effect among subgroups defined by sex, histology, smoking status, and *EGFR* mutations (Fig 2); OS curves by *EGFR* mutation status are presented in Figure 3.

PFS

With 618 events, median total PFS was 8.9 and 6.4 months in the standard arm and the experimental arm, respectively (Fig 4); adjusted HR of progression was 1.21 (95% CI, 1.04 to 1.42). There was no significant heterogeneity of treatment effect among subgroups defined by sex, histology, smoking status, and *EGFR* mutations (Fig 4).

With 691 events, median first PFS was 5.4 and 2.2 months after first-line chemotherapy and first-line erlotinib, respectively (Fig 5). There was a statistically significant interaction of treatment effect with sex ($P = .014$), smoking status ($P < .001$), and *EGFR* mutation status ($P = .006$), although there was no significant interaction of treatment effect with histology (Fig 5). Total-PFS and first-PFS curves by *EGFR* mutation status are given in Figure 3.

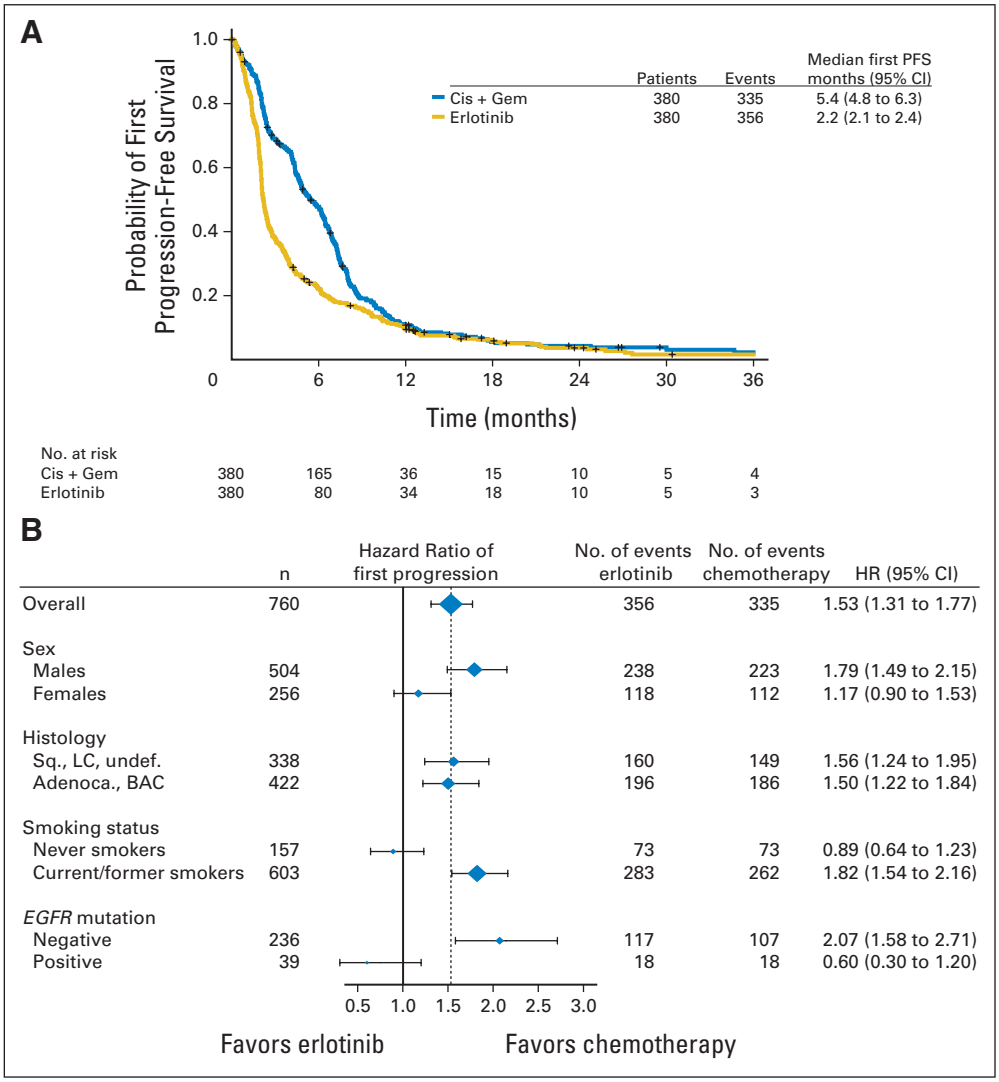

Fig 5. (A) First progression-free survival (PFS) curves by treatment arm. (B) Treatment effect (unadjusted experimental *v* standard hazard ratios [HRs]) on first PFS within major patient subgroups (vertical dotted line represents unadjusted HR in the overall study population). Adenoca., adenocarcinoma; BAC, bronchioloalveolar carcinoma; chemo, chemotherapy; Cis, cisplatin; EGFR, epidermal growth factor receptor; Gem, gemcitabine; Sq., LC, undef., sqamous, large cell, undefined.

Objective Response

Among 380 patients assigned to the standard arm, 124 (32.6%; 95% CI, 27.9% to 37.3%) obtained an objective response: 97 (25.6%) with first-line chemotherapy, 18 (4.7%; 8.0% of those treated) with second-line erlotinib, and nine (2.4%; 4.0% of those treated) with both lines.

Among 380 patients assigned to the experimental arm, 77 (20.3%; 95% CI, 16.2% to 24.3%) obtained an objective response: 33 (8.7%) with first-line erlotinib, 40 (10.5%; 20.6% of those treated) with second-line chemotherapy, and four with both lines (1.1%; 2.1% of those treated). ORRs were significantly different between study arms ($P < .001$).

Among patients with *EGFR* mutations, response rate after first-line treatment was 25.0% with chemotherapy and 42.1% with erlotinib. ORR (after both lines of therapy) was 45.0% in the standard arm and 42.1% in the experimental arm.

Toxicity

Information about toxicity was available for 740 patients of 744 who started the assigned first-line therapy; there were three patients in the standard arm and one patient in the experimental arm with missing data. Worst toxicity experienced during the whole treatment is reported in Table 2; worst toxicity experienced with first-line treatment alone is reported in Appendix Table A2 (online only).

Hematologic toxicity was more frequent and severe among patients assigned to the standard arm; they experienced more anemia, neutropenia, and thrombocytopenia. Patients assigned to the standard arm experienced significantly more allergy, constipation, nausea, vomiting, hair loss, neurotoxicity, and renal toxicity; diarrhea and skin toxicity were more frequent and severe in the experimental arm.

DISCUSSION

Erlotinib and gefitinib were the first targeted drugs approved for treatment of NSCLC.[7] To the best of our knowledge, TORCH is the first trial testing the hypothesis that single-agent erlotinib might be an alternative to first-line chemotherapy in unselected patients with advanced NSCLC. This hypothesis was prompted by results of the BR.21 trial,[8] in unselected patients pretreated with chemotherapy and by two phase II studies of erlotinib in untreated and unselected adult[12] and elderly[13] patients. TORCH shows that a strategy based on first-line erlotinib followed at progression by cisplatin plus gemcitabine is inferior to the standard reverse sequence. Indeed, a statistically significant and clinically relevant inferior median survival of 2.9 months was found. Crossover design confounds the interpretation of treatment

Table 2. Worst Grade of Adverse Events According to Treatment Arm (both lines of treatment)

	CTC-AE Grade																							
	Standard Arm (n = 368)												Experimental Arm (n = 372)											
	0		1		2		3		4		5		0		1		2		3		4		5			
Adverse Event	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	*P**	*P*†
Anemia	145	39	90	24	101	27	32	9	—	—	—	—	231	62	65	17	58	16	15	4	3	1	—	—	< .001	.04
Neutropenia	208	57	33	9	48	13	52	14	27	7	—	—	286	77	16	4	28	8	29	8	13	4	—	—	< .001	< .001
Febrile neutropenia	359	98					7	2	2	1	—	—	365	98					4	1	3	1	—	—	.61	.60
Infection	367	99			1	< 1	—	—	—	—	—	—	369	99			2	1	—	—	1	< 1	—	—	.56	.50
Thrombocytopenia	245	67	48	13	31	8	29	8	14	4	1	< 1	302	81	23	6	8	2	26	7	13	3	—	—	< .001	.53
Coagulation	364	99	1	< 1	1	< 1	2	1	—	—	—	—	364	98	2	1	3	1	3	1	—	—	—	—	.35	.69
Bleeding	344	93	16	4	4	1	3	1	—	—	1	< 1	337	91	25	7	5	1	—	—	2	1	3	1	.16	1.00
Allergy	353	96	11	3	3	1	1	< 1	—	—	—	—	367	99	2	1	3	1	—	—	—	—	—	—	.02	.50
Renal toxicity	317	86	29	8	17	5	5	1	—	—	—	—	341	92	13	3	12	3	6	2	—	—	—	—	.02	.78
Heart rhythm	355	96	4	1	8	2	1	< 1	—	—	—	—	360	97	4	1	5	1	2	1	1	< 1	—	—	.79	.37
Heart, general	338	92	2	1	14	4	9	2	5	1	—	—	346	93	8	2	9	2	1	< 1	6	2	2	1	.50	.28
Vascular	352	96	—	—	2	1	4	1	5	1	5	1	357	96	2	1	7	2	1	< 1	3	1	2	1	.72	.07
Fatigue	130	35	68	18	113	31	50	14	7	2			159	43	64	17	98	26	46	12	5	1			.05	.49
Fever	318	86	35	10	14	4	1	< 1	—	—	—	—	325	87	33	9	14	4	—	—	—	—	—	—	.70	.50
Weight loss	309	84	37	10	20	5	2	1					301	81	47	13	22	6	2	1					.30	.62
Hair loss	312	85	38	10	18	5							340	91	24	7	8	2							.004	N/A
Skin rash	233	63	51	14	58	16	26	7	—	—	—	—	120	32	116	31	96	26	40	11	—	—	—	—	< .001	.08
Skin other	285	77	46	12	33	9	4	1	—	—	—	—	225	60	86	23	49	13	12	3	—	—	—	—	< .001	.04
Anorexia	246	67	47	13	62	17	12	3	1	< 1	—	—	245	66	46	12	62	17	16	4	3	1	—	—	.67	.29
Constipation	259	70	63	17	41	11	5	1	—	—	—	—	296	80	38	10	29	8	8	2	1	< 1	—	—	.008	.29
Diarrhea	277	75	56	15	33	9	1	< 1	—	—	1	< 1	220	59	82	22	50	13	19	5	1	< 1	—	—	< .001	< .001
Nausea	149	40	102	28	102	28	14	4	1	< 1			216	58	72	19	72	19	12	3	—	—			< .001	.54
Vomiting	214	58	69	19	70	19	14	4	1	< 1	—	—	281	76	42	11	36	10	12	3	1	< 1	—	—	< .001	.68
Mucositis	316	86	36	10	14	4	2	1	—	—	—	—	327	88	26	7	16	4	3	1	—	—	—	—	.46	.69
Liver toxicity	311	85	34	9	16	4	5	1	2	1	—	—	309	83	34	9	20	5	8	2	1	< 1	—	—	.56	.63
Pulmonary toxicity	227	62	51	14	49	13	34	9	3	1	4	1	217	58	56	15	60	16	29	8	6	2	4	1	.42	.77
Neurologic toxicity	262	71	53	14	28	8	21	6	1	< 1	3	1	292	78	29	8	30	8	14	4	5	1	2	1	.04	.52
Death NOS	368	100									—	—	368	99									4	1	N/A	.12

Abbreviations: CTC-AE, Common Terminology Criteria for Adverse Events; N/A, not applicable; NOS, not otherwise specified.
*Test for linear trend including all grades.
†χ^2 test (or Fisher exact test if appropriate) comparing severe (grade ≥ 3) *v* not severe (grade ≤ 2).

interaction with clinical factors and *EGFR* mutation when OS is considered; however, a significant qualitative interaction was found in first-PFS analysis, showing higher efficacy of erlotinib in the presence of *EGFR* mutation and higher efficacy of chemotherapy in the case of *EGFR* wild-type tumor. This finding might be affected by the limited proportion of patients (36.2%) for whom mutation was studied; however, this rate is the highest among published clinical trials without mandatory tumor sample collection and the same as that in the Iressa Pan-Asia Study (IPASS) trial[19] that led to gefitinib registration (Appendix Table A3, online only).

This result, of course, does not negate that erlotinib can be beneficial for unselected patients pretreated with chemotherapy, as demonstrated by the BR.21 trial in second- or third-line therapy and by the SATURN trial (SequentiAl Tarceva in UnResectable NSCLC) as maintenance treatment.[20]

Convincing evidence has been reported on first-line therapy with EGFR inhibitor in patients selected by *EGFR* mutations.[19,21-25] The first evidence came from the phase III IPASS study[19] conducted in East Asian patients that compared first-line gefitinib with carboplatin plus paclitaxel in patients with advanced NSCLC selected by clinical characteristics (no or light smoking, with adenocarcinoma). In the overall population, gefitinib was superior to carboplatin plus paclitaxel in PFS, the primary end point. However, benefit was limited to *EGFR* mutation–positive tumors, in which gefitinib produced a response rate of 71% and significantly prolonged PFS, although it was inferior for patients without mutations.

Confirmatory evidence came from two randomized trials[26,27] conducted in Japanese patients with *EGFR* mutation–positive tumors. In these studies, first-line gefitinib improved PFS compared with chemotherapy. Similar results have also been obtained with erlotinib in two phase III trials: the Chinese Optimal trial[28] and the European EURTAC trial (European Tarceva versus Chemotherapy).[29] The latter compared erlotinib therapy with platinum-based chemotherapy, representing the first head-to-head comparison of an EGFR-TKI versus chemotherapy in Western patients with *EGFR* mutation–positive tumors.

However, whether PFS prolongation translates into survival gain is not yet clear: mature IPASS data showed no survival difference between first-line gefitinib and chemotherapy, probably as a result of treatment crossover in patients with tumors harboring *EGFR* mutation.[18]

Given the critical role played by *EGFR* mutations in predicting efficacy of TKIs, the negative result of TORCH in a Western unselected population is consistent with the prevalence of such mutations that is substantially lower than that in East Asian patients: the proportion of patients with *EGFR* mutations was 16.6% in a series of 2,105 Western patients with nonsquamous cancer.[30] TORCH data (with only 3% of East Asian patients) confirm this low prevalence (14.2%).

In conclusion, according to the results of the studies we reported here, EGFR-TKIs can be used as first-line treatment in patients with tumors harboring *EGFR* mutations, although TORCH results show that first-line erlotinib followed by second-line chemotherapy is not recommended compared with the reverse sequence in the treatment of unselected patients with advanced NSCLC.

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.

Employment or Leadership Position: None **Consultant or Advisory Role:** Cesare Gridelli, Eli Lilly (C), Roche (C); Ronald Feld, Roche (C); Charles Butts, Roche (C); Paolo Maione, Eli Lilly (C), Roche (C); Antonio Rossi, Eli Lilly (C), Roche (C); Ming-Sound Tsao, AstraZeneca (C), F. Hoffman-La Roche (C), OSI Pharmaceuticals (C); Massimo Di Maio, Eli Lilly (C) **Stock Ownership:** None **Honoraria:** Cesare Gridelli, Eli Lilly, Roche; Ronald Feld, Roche; Charles Butts, Roche; Paolo Maione, Eli Lilly, Roche; Saverio Cinieri, Roche; Antonio Rossi, Eli Lilly, Roche; Ming-Sound Tsao, AstraZeneca, F. Hoffman-La Roche; Massimo Di Maio, Eli Lilly, Roche; Alessandro Morabito, Roche; Francesco Perrone, Roche **Research Funding:** Ronald Feld, Roche; Natasha Leighl, Roche; Ming-Sound Tsao, F. Hoffman-La Roche; Francesco Perrone, Roche **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Cesare Gridelli, Fortunato Ciardiello, Ciro Gallo, Ronald Feld, Charles Butts, Francesco Perrone

Provision of study materials or patients: Cesare Gridelli, Fortunato Ciardiello, Ronald Feld, Charles Butts, Vittorio Gebbia, Paolo Maione, Floriana Morgillo, Giovenzio Genestreti, Adolfo Favaretto, Natasha Leighl, Rafal Wierzbicki, Saverio Cinieri, Yasmin Alam, Salvatore Siena, Giampaolo Tortora, Raffaella Felletti, Ferdinando Riccardi, Antonio Rossi, Flavia Cantile, Alessandro Morabito

Collection and assembly of data: Vittorio Gebbia, Paolo Maione, Floriana Morgillo, Giovenzio Genestreti, Adolfo Favaretto, Natasha Leighl, Rafal Wierzbicki, Saverio Cinieri, Yasmin Alam, Salvatore Siena, Giampaolo Tortora, Raffaella Felletti, Ferdinando Riccardi, Gianfranco Mancuso, Antonio Rossi, Flavia Cantile, Ming-Sound Tsao, Mauro Saieg, Gilda da Cunha Santos, Maria Carmela Piccirillo, Massimo Di Maio, Alessandro Morabito, Francesco Perrone

Data analysis and interpretation: Cesare Gridelli, Fortunato Ciardiello, Ciro Gallo, Ronald Feld, Charles Butts, Natasha Leighl, Ming-Sound Tsao, Mauro Saieg, Gilda da Cunha Santos, Maria Carmela Piccirillo, Massimo Di Maio, Alessandro Morabito, Francesco Perrone

Manuscript writing: All authors

Final approval of manuscript: All authors

REFERENCES

1. Jemal A, Siegel R, Ward E, et al: Cancer statistics, 2009. CA Cancer J Clin 59:225-249, 2009

2. [No authors listed]: Chemotherapy in non-small cell lung cancer: A meta-analysis using updated data on individual patients from 52 randomised clinical trials. BMJ 311:899-909, 1995

3. NSCLC Meta-Analyses Collaborative Group: Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: A systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. J Clin Oncol 26:4617-4625, 2008

4. Schiller JH, Harrington D, Belani CP, et al: Comparison of four chemotherapy regimens for

advanced non-small-cell lung cancer. N Engl J Med 346:92-98, 2002

5. Cardenal F, López-Cabrerizo MP, Antón A, et al: Randomized phase III study of gemcitabine-cisplatin versus etoposide-cisplatin in the treatment of locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 17:12-18, 1999

6. Sandler AB, Nemunaitis J, Denham C, et al: Phase III trial of gemcitabine plus cis-platin versus cisplatin alone in patients with locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 18:122-130, 2000

7. Ciardiello F, Tortora G: EGFR antagonists in cancer treatment. N Engl J Med 358:1160-1174, 2008

8. 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

9. Tsao MS, Sakurada A, Cutz JC, et al: Erlotinib in lung cancer: Molecular and clinical predictors of outcome. N Engl J Med 353:133-144, 2005

10. Gatzemeier U, Pluzanska A, Szczesna A, et al: Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: The Tarceva Lung Cancer Investigation Trial. J Clin Oncol 25:1545-1552, 2007

11. Herbst RS, Prager D, Hermann R, et al: TRIBUTE: A phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 23:5892-5899, 2005

12. Giaccone G, Gallegos Ruiz M, Le Chevalier T, et al: Erlotinib for frontline treatment of advanced non-small cell lung cancer: A phase II study. Clin Cancer Res 12:6049-6055, 2006

13. Jackman DM, Yeap BY, Lindeman NI, et al: Phase II clinical trial of chemotherapy-naive patients > or = 70 years of age treated with erlotinib for advanced non-small-cell lung cancer. J Clin Oncol 25:760-766, 2007

14. Pan Q, Pao W, Ladanyi M: Rapid polymerase chain reaction-based detection of epidermal growth factor receptor gene mutations in lung adenocarcinomas. J Mol Diagn 7:396-403, 2005

15. Lara-Guerra H, Waddell TK, Salvarrey MA, et al: Phase II study of preoperative gefitinib in clinical stage I non-small-cell lung cancer. J Clin Oncol 27:6229-6236, 2009

16. Schemper M, Smith TL: A note on quantifying follow-up in studies of failure time. Control Clin Trials 17:343-346, 1996

17. Thatcher N, Chang A, Parikh P, et al: Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: Results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet 366:1527-1537, 2005

18. Fukuoka M, Wu YL, Thongprasert S, et al: Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). J Clin Oncol 29: 2866-2874, 2011

19. Mok TS, Wu YL, Thongprasert S, et al: Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 361:947-957, 2009

20. 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

21. Sequist LV, Martins RG, Spigel D, et al: First-line gefitinib in patients with advanced non-small-cell lung cancer harboring somatic EGFR mutations. J Clin Oncol 26:2442-2449, 2008

22. Lynch TJ, Bell DW, Sordella R, et al: Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 350:2129-2139, 2004

23. Paez JG, Jänne PA, Lee JC, et al: EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy. Science 304:1497-1500, 2004

24. Mitsudomi T, Kosaka T, Endoh H, et al: Mutations of the epidermal growth factor receptor gene predict prolonged survival after gefitinib treatment in patients with non-small-cell lung cancer with postoperative recurrence. J Clin Oncol 23:2513-2520, 2005

25. Park K, Goto K: A review of the benefit-risk profile of gefitinib in Asian patients with advanced non-small-cell lung cancer. Curr Med Res Opin 22: 561-573, 2006

26. Mitsudomi T, Morita S, Yatabe Y, et al: Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): An open label, randomised phase 3 trial. Lancet Oncol 11:121-128, 2010

27. Maemondo M, Inoue A, Kobayashi K, et al: Gefitinib or chemotherapy for non-small cell lung cancer with mutated EGFR. N Engl J Med 362:2380-2388, 2010

28. Zhou C, Wu YL, Chen G, et al: Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): A multicentre, open-label, randomised, phase 3 study. Lancet Oncol 12:735-742, 2011

29. Rosell R, Carcereny E, Gervais R, et al: Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. Lancet Oncol 13:239-246, 2012

30. Rosell R, Moran T, Queralt C, et al: Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med 361:958-967, 2009

Affiliations

Cesare Gridelli, Paolo Maione, and Antonio Rossi, S.G. Moscati Hospital, Avellino; Fortunato Ciardiello, Ciro Gallo, Floriana Morgillo, and Flavia Cantile, Second University; Giampaolo Tortora, Federico II University; Ferdinando Riccardi, Cardarelli Hospital; Maria Carmela Piccirillo, Massimo Di Maio, Alessandro Morabito, and Francesco Perrone, National Cancer Institute, Napoli; Giampaolo Tortora, University of Verona, Verona; Vittorio Gebbia and Gianfranco Mancuso, Casa di Cura La Maddalena, Palermo; Giovenzio Genestreti, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola; Adolfo Favaretto, Istituto Oncologico Veneto, Padova; Saverio Cinieri, A. Perrino Hospital, Brindisi and European Institute of Oncology; Salvatore Siena, Niguarda Ca' Granda Hospital, Milano; Raffaella Felletti, San Martino Hospital, Genova, Italy; Ronald Feld, Natasha Leighl, Ming-Sound Tsao, Mauro Saieg, and Gilda da Cunha Santos, Princess Margaret Hospital/University Health Network, Toronto; Rafal Wierzbicki, Oncology Clinical Trials-Durham Regional Cancer Centre, Oshawa; and Yasmin Alam, Windsor Regional Cancer Centre, Windsor, Ontario; and Charles Butts, Cross Cancer Institute, Edmonton, Alberta, Canada.

