

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

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

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A B S T R A C T

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.

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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 treat-

ments.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, multi-center, 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/ μ L, platelets < 100,000/ μ 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* \geq 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/m² intravenously on day 1 plus gemcitabine 1,200 mg/m² 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 \geq 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 \geq 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.

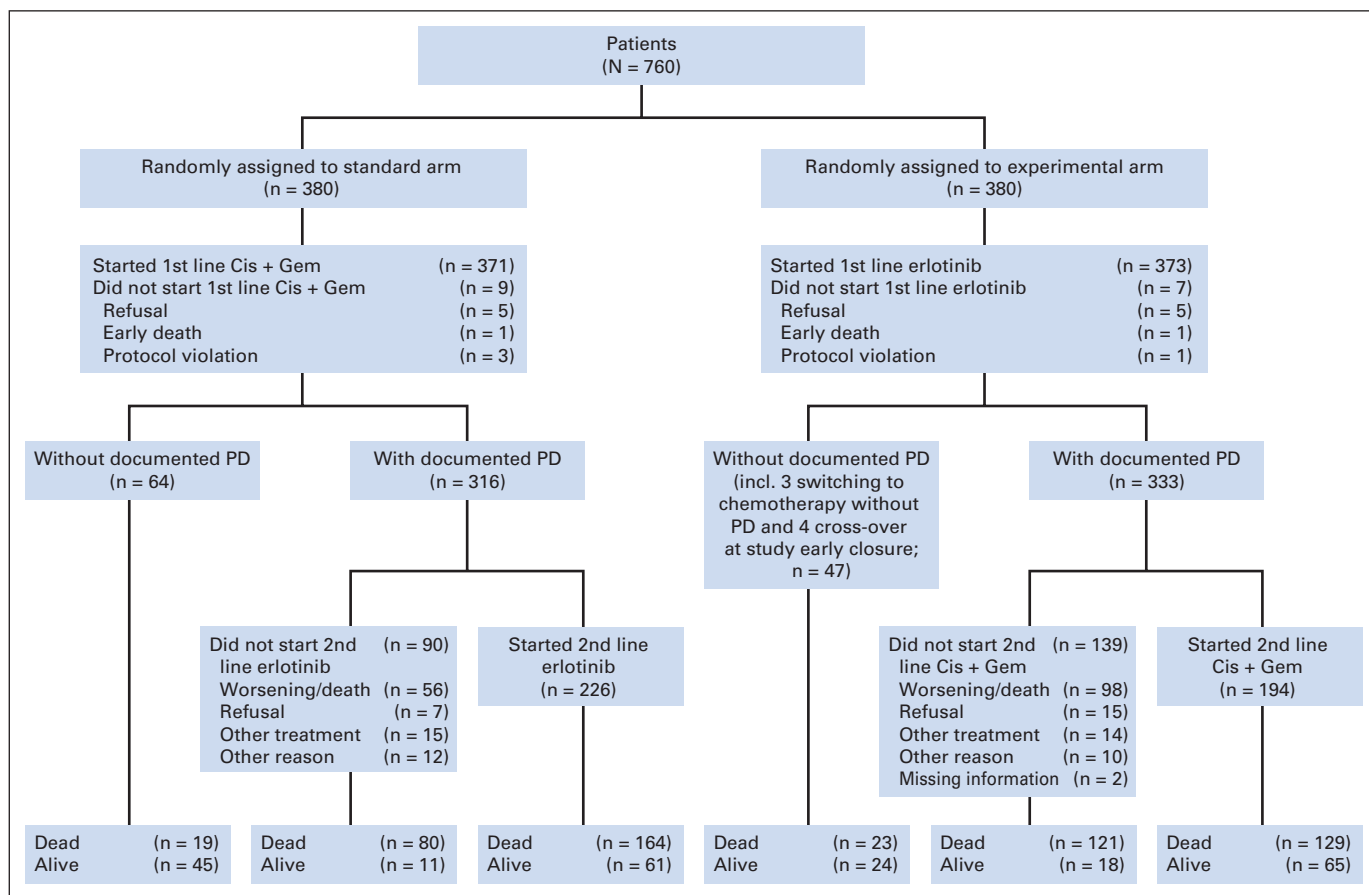


Fig 1. Patients' study flow by treatment arm. Cis, cisplatin; Gem, gemcitabine; PD, progressive disease.

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 pro-

gression, 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.

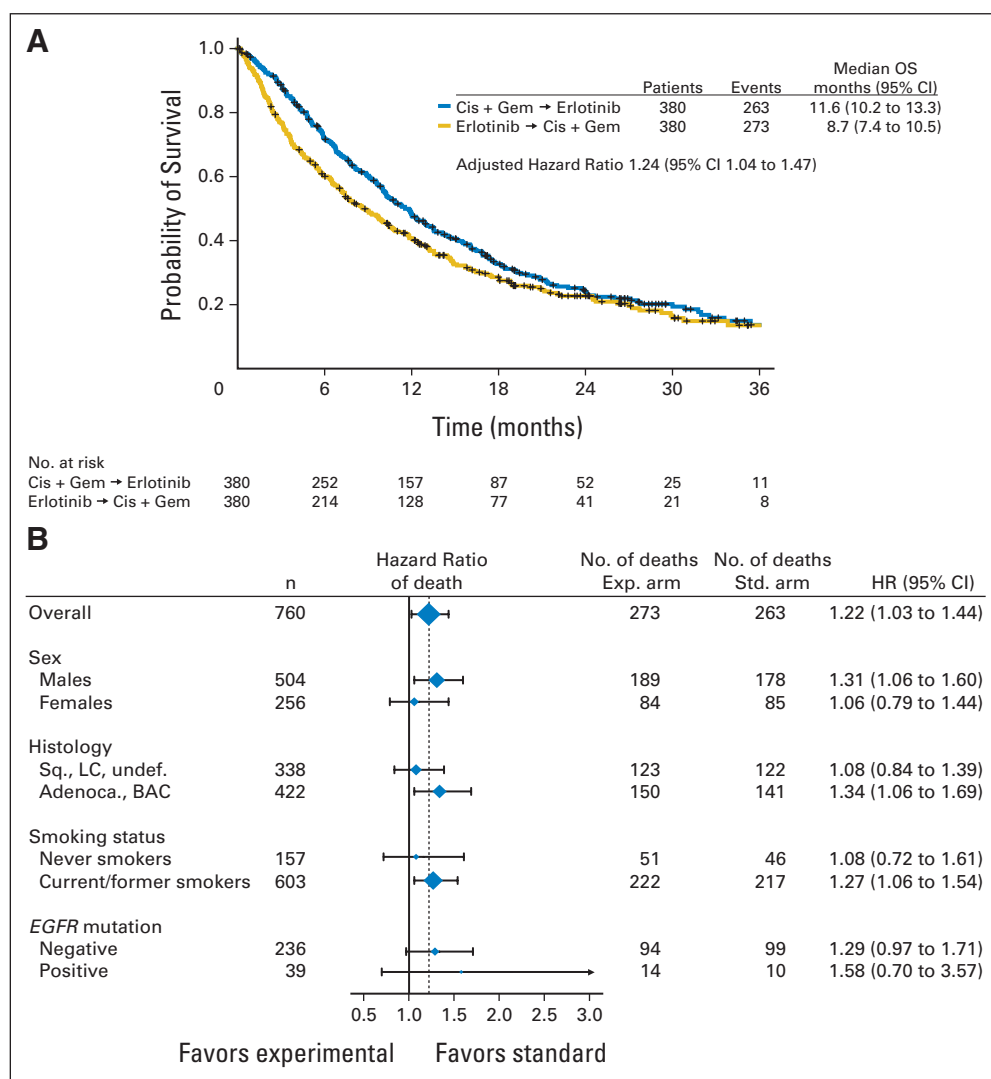


Fig 2. (A) Overall survival (OS) curves by treatment arm. (B) Treatment effect (unadjusted experimental [Exp.] v standard hazard ratios [HRs]) on OS within major patient subgroups (vertical dotted line represents unadjusted HR in the overall study population). Adenoca., adenocarcinoma; BAC, bronchioloalveolar 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

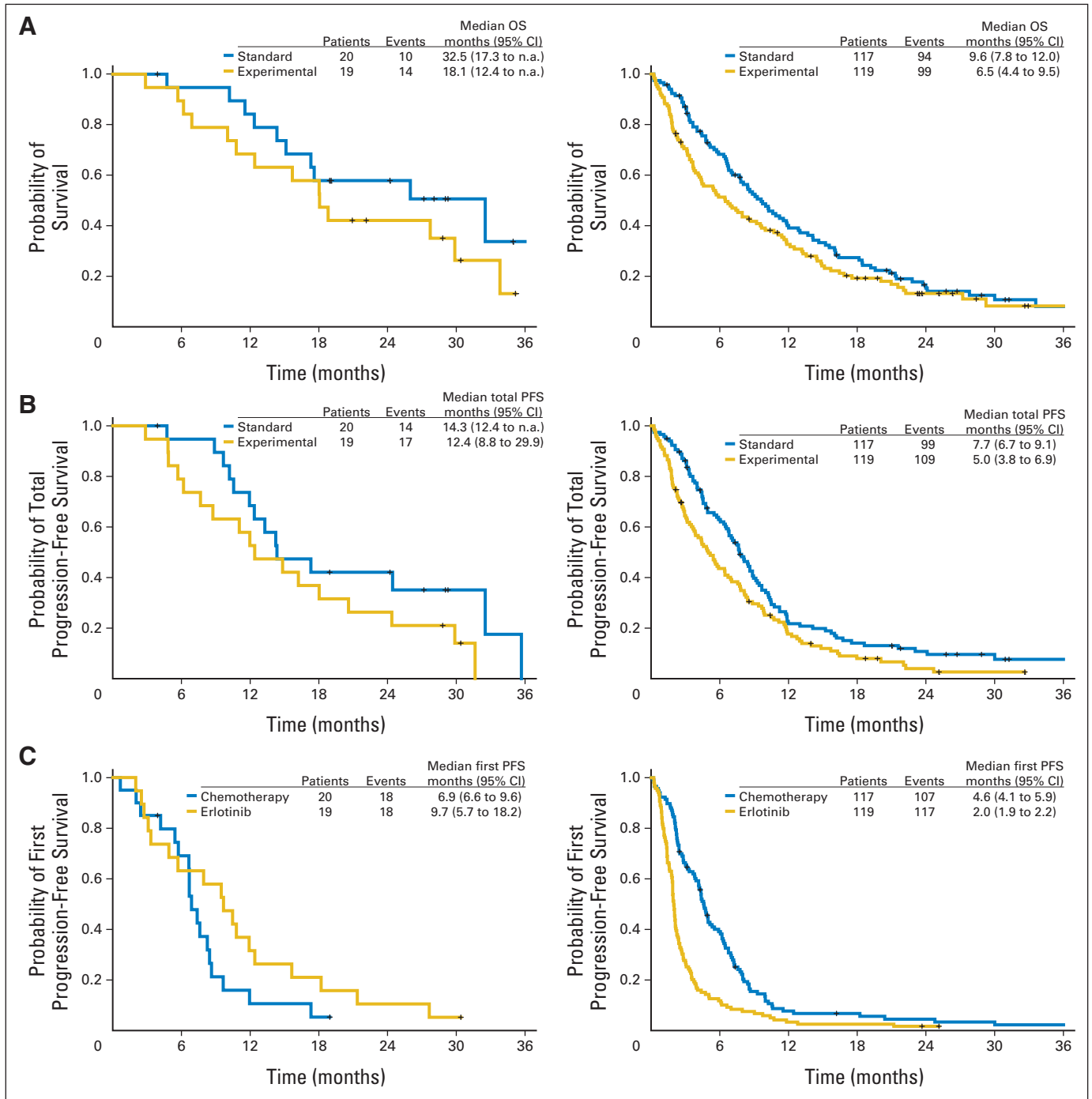


Fig 3. (A) Overall survival (OS), (B) total progression-free survival (PFS), and (C) first PFS curves by treatment arm according to epidermal growth factor receptor (*EGFR*) mutation status (left panel: *EGFR* mutation-positive patients, right panels: *EGFR* mutation-negative patients). n.a., not achieved.

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.

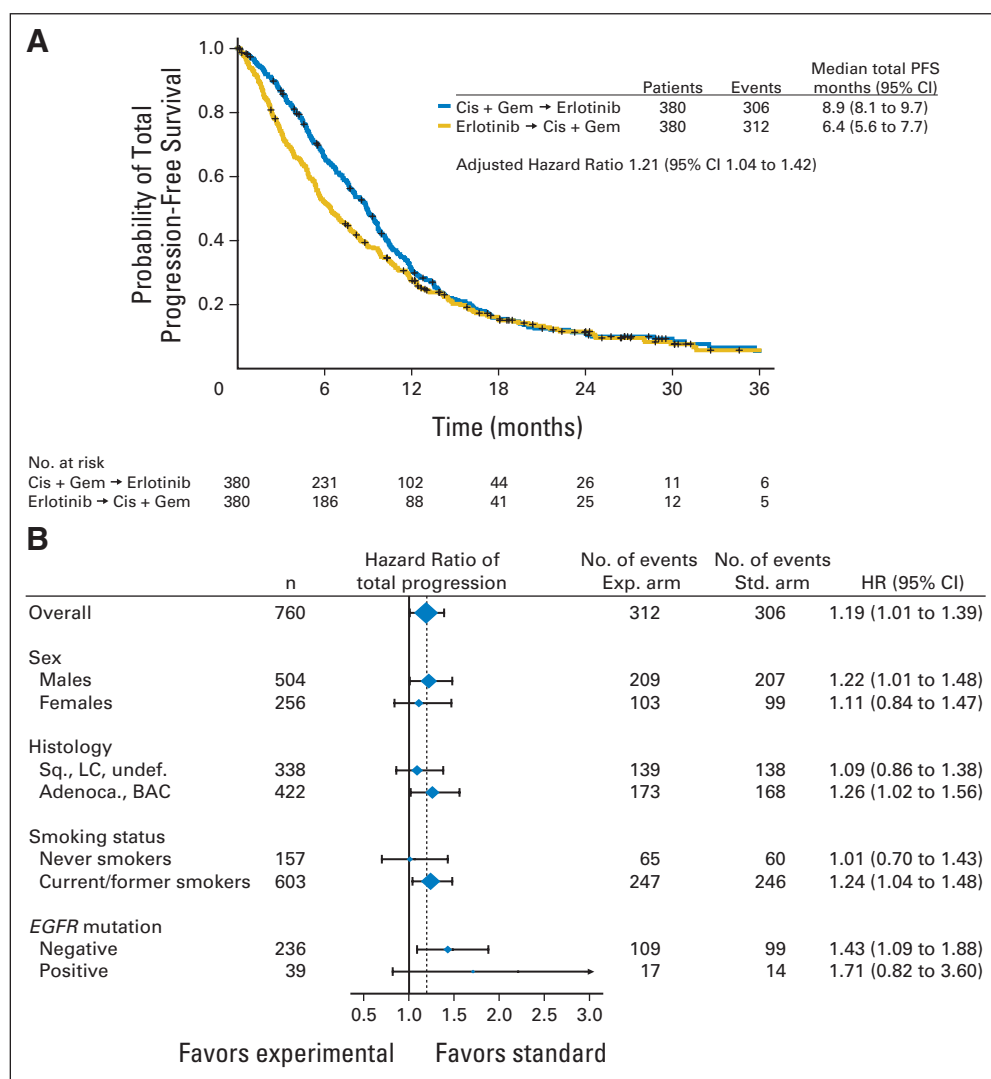


Fig 4. (A) Total progression-free survival (PFS) curves by treatment arm. (B) Treatment effect (unadjusted experimental [Exp.] v standard hazard ratios [HRs]) on total PFS within major patient subgroups (vertical dotted line represents unadjusted HR in the overall study population). Adenoca., adenocarcinoma; 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.

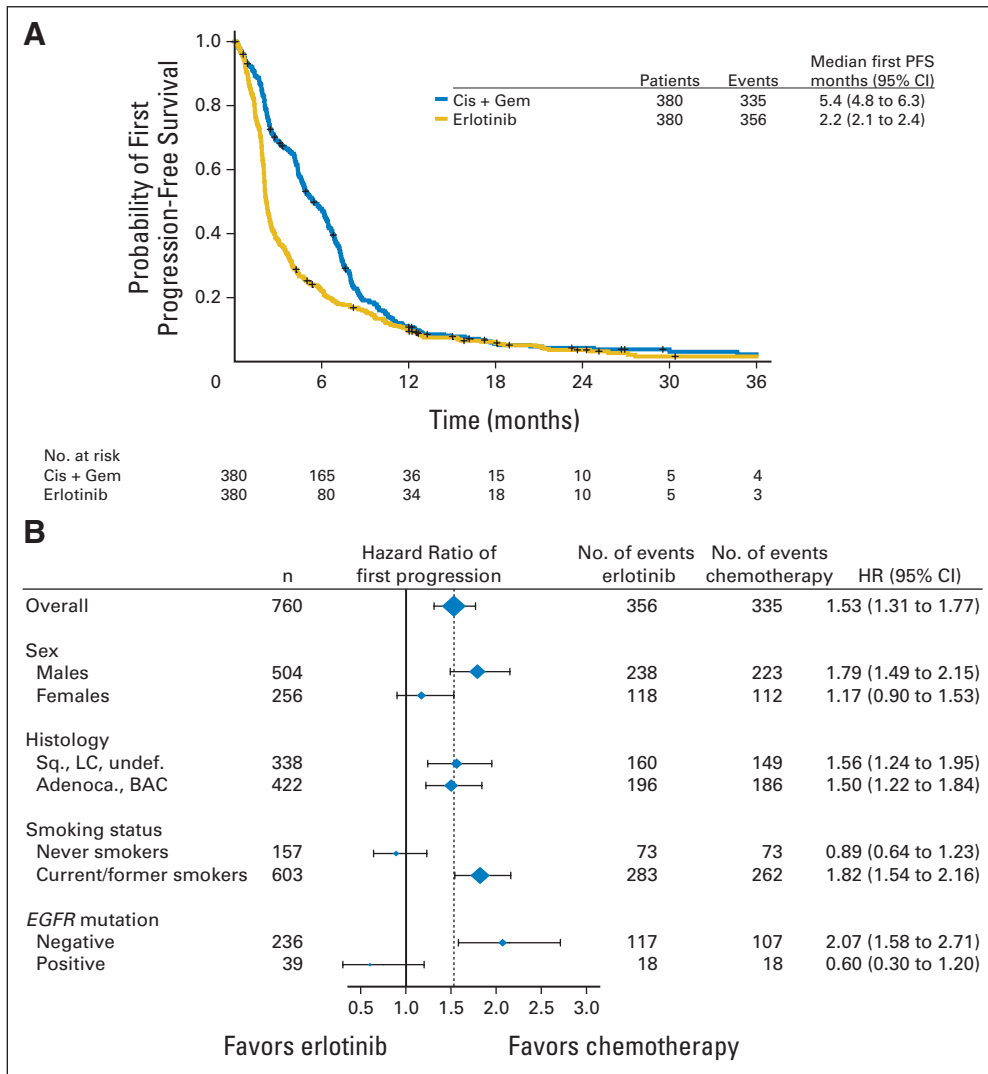


Fig 5. (A) First progression-free survival (PFS) curves by treatment arm. (B) Treatment effect (unadjusted experimental v standard hazard ratios [HRs]) on first PFS within major patient subgroups (vertical dotted line represents unadjusted HR in the overall study population). Adenoca., adenocarcinoma; BAC, bronchioloalveolar carcinoma; chemo, chemotherapy; Cis, cisplatin; *EGFR*, epidermal growth factor receptor; Gem, gemcitabine; Sq., LC, undef., squamous, 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 adult¹² and elderly¹³ 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)

Adverse Event	CTC-AE Grade																				P*	Pt†						
	Standard Arm (n = 368)										Experimental Arm (n = 372)																	
	0		1		2		3		4		5		0		1		2		3				4		5			
No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%					
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) trial¹⁹ 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 study¹⁹ 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 trial²⁸ 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.

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Table A1. Baseline Characteristics of Patients With and Without *EGFR* Mutational Analysis

Characteristic	Standard Arm				Experimental Arm				Whole Study Population				P*
	Patients With <i>EGFR</i> Mutation Analysis (n = 137)		Patients Without <i>EGFR</i> Mutation Analysis (n = 243)		Patients With <i>EGFR</i> Mutation Analysis (n = 138)		Patients Without <i>EGFR</i> Mutation Analysis (n = 242)		Patients With <i>EGFR</i> Mutation Analysis (n = 275)		Patients Without <i>EGFR</i> Mutation Analysis (n = 485)		
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
Country													< .001
Italy	96	70	210	86	89	64	217	90	185	67	427	88	
Canada	41	30	33	14	49	36	25	10	90	33	58	12	
Sex													.12
Male	98	72	154	63	94	68	158	65	192	70	312	64	
Female	39	28	89	37	44	32	84	35	83	30	173	36	
Age, years													< .001
< 70	126	92	235	97	124	90	237	98	250	91	472	97	
≥ 70 (Canada only)	11	8	8	3	14	10	5	2	25	9	13	3	
Ethnicity													< .001
East Asian	6	4	6	2	11	8	1	< 1	17	6	7	1	
Other	131	96	237	98	127	92	241	99	258	94	478	99	
Smoking status†													.47
Never smoker	25	18	54	22	28	20	50	21	53	19	104	21	
Former/current smoker	112	82	189	78	110	80	192	79	603	81	222	79	
ECOG performance status													.27
0	65	47	120	49	66	48	131	54	131	48	251	52	
1	72	53	123	51	72	52	111	46	144	52	234	48	
Stage													.81
IIIB	15	11	22	9	16	12	30	12	31	11	52	11	
IV	122	89	221	91	122	88	212	88	244	89	433	89	
Histology													.91
Adenocarcinoma (including BAC)	76	55	136	56	76	55	134	55	152	55	270	56	
Other	61	45	107	44	62	45	108	45	123	45	215	44	

Abbreviations: BAC, bronchioloalveolar carcinoma; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.

*From the comparison of patients with and without *EGFR* mutation analysis in the whole study population.

†Never smokers: < 100 cigarettes per lifetime; former smoker: ≥ 100 cigarettes per lifetime but nonsmoker when entering the study.

First-Line Erlotinib in Unselected Patients With Advanced NSCLC

Table A2. Worst Grade of Adverse Events According to Treatment Arm (first line only)

Adverse Event	CTC-AE Grade																				P*	Pt†					
	Cisplatin Plus Gemcitabine (n = 368)										Erlotinib (n = 372)																
	0		1		2		3		4		5		0		1		2		3				4		5		
No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%				
Anemia	152	41	86	23	100	27	30	8	—	—	—	—	243	65	60	16	52	14	15	4	2	1	—	—	<.001	.046	
Neutropenia	208	57	33	9	48	13	52	14	27	7	—	—	365	81	4	1	2	1	—	—	1	<1	—	—	<.001	<.001	
Febrile neutropenia	360	98	—	—	—	—	—	6	2	2	1	—	—	371	99	—	—	—	—	1	<1	—	—	—	—	.02	.02
Infection	367	99	—	—	1	<1	—	—	—	—	—	—	371	99	—	—	1	<1	—	—	—	—	—	—	1.00	N/A	
Thrombocytopenia	248	67	48	13	30	8	28	8	14	4	—	—	367	99	4	1	1	<1	—	—	—	—	—	—	<.001	<.001	
Coagulation	365	99	1	<1	—	—	2	1	—	—	—	—	366	98	2	1	2	1	2	1	—	—	—	—	.47	.99	
Bleeding	348	95	14	4	3	1	2	1	—	—	1	<1	343	92	21	6	4	1	—	—	1	<1	3	1	.21	1.00	
Allergy	357	97	8	2	2	1	1	<1	—	—	—	—	367	98	2	1	3	1	—	—	—	—	—	—	.13	.50	
Renal toxicity	328	89	26	7	11	3	3	1	—	—	—	—	354	95	9	2	6	2	3	1	—	—	—	—	.003	.69	
Heart rhythm	358	97	4	1	5	1	1	<1	—	—	—	—	361	97	3	1	5	1	2	1	1	<1	—	—	.87	.37	
Heart, general	343	93	1	<1	12	3	7	2	5	1	—	—	354	95	5	1	6	2	1	<1	4	1	2	1	.23	.24	
Vascular	354	96	—	—	2	1	4	1	4	1	4	1	362	97	2	1	3	1	1	<1	2	1	2	1	.31	.08	
Fatigue	150	41	71	19	101	27	42	11	4	1	—	—	210	56	57	15	73	20	31	8	1	<1	—	—	<.001	.08	
Fever	329	89	29	8	9	2	1	<1	—	—	—	—	342	92	17	5	13	3	—	—	—	—	—	—	.27	.50	
Weight loss	329	89	27	7	11	3	1	<1	—	—	—	—	318	85	39	10	15	4	—	—	—	—	—	—	.12	.50	
Hair loss	320	87	30	8	18	5	—	—	—	—	—	—	346	93	20	5	6	2	—	—	—	—	—	—	.005	—	
Skin rash	346	94	14	4	7	2	1	<1	—	—	—	—	121	33	116	31	95	26	40	11	—	—	—	—	<.001	<.001	
Skin other	347	94	13	3	7	2	1	<1	—	—	—	—	228	61	85	23	47	13	12	3	—	—	—	—	<.001	.002	
Anorexia	273	74	42	11	48	13	4	1	1	<1	—	—	276	74	36	10	48	13	10	3	2	1	—	—	.83	.09	
Constipation	264	72	61	17	38	10	5	1	—	—	—	—	330	89	22	6	14	4	5	1	1	<1	—	—	<.001	.77	
Diarrhea	321	87	27	7	18	5	1	<1	—	—	1	<1	231	62	83	22	41	11	16	4	1	<1	—	—	<.001	<.001	
Nausea	157	43	102	28	96	26	13	3	—	—	—	—	293	79	45	12	26	7	8	2	—	—	—	—	<.001	.26	
Vomiting	224	61	64	17	65	18	14	4	1	<1	—	—	338	91	15	4	15	4	3	1	1	<1	—	—	<.001	.01	
Mucositis	327	89	30	8	10	3	1	<1	—	—	—	—	341	92	19	5	11	3	1	<1	—	—	—	—	.22	1.00	
Liver toxicity	325	88	25	7	12	3	4	1	2	1	—	—	324	87	28	8	13	3	6	2	1	<1	—	—	.62	.79	
Pulmonary toxicity	248	67	55	15	42	11	19	5	1	1	3	1	241	65	50	13	48	13	26	7	5	1	2	1	.30	.18	
Neurological toxicity	288	78	44	12	24	7	9	2	—	—	3	1	320	86	21	6	18	5	8	2	3	1	2	1	.01	.86	
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).

Table A3. Percentage of Patients With EGFR Mutational Analysis in Major Trials Testing Efficacy of Gefitinib or Erlotinib in Unselected Patients With Advanced NSCLC

Trial	Reference	Drug	Study Sample Size	EGFR Mutational Analysis	
				No.	%
INTACT					
INTACT1	Bell et al: J Clin Oncol 23:8081-8092, 2005; Giaccone et al: J Cancer Res Clin Oncol 135:467-476, 2009	Gefitinib	1,093	312	15 combined
INTACT2	Bell et al: J Clin Oncol 23:8081-8092, 2005; Giaccone et al: J Cancer Res Clin Oncol 135:467-476, 2009	Gefitinib	1,037		
TALENT	Gatzemeier et al ¹⁰ ; Gatzemeier et al: J Clin Oncol 23:627s, 2005 (suppl; abstr 7028)	Erlotinib	1,172	293	25
TRIBUTE	Herbst et al ¹¹ ; Eberhard et al: J Clin Oncol 23:5900-5909, 2005; Hirsch et al: Clin Cancer Res 14:6317-6323, 2008	Erlotinib	1,079	274	25
BR.21	Shepherd et al ⁸ ; Tsao et al ⁹ ; Zhu et al: J Clin Oncol 26:4268-4275, 2008	Erlotinib	731	204	28
ISEL	Thatcher et al ¹⁷ ; Hirsch et al: J Clin Oncol 24:5034-5042, 2006	Gefitinib	1,692	215	13
INTEREST	Kim et al: Lancet 372:1809-1818, 2008; Douillard et al: J Clin Oncol 26:424s, 2008 (suppl; abstr 8001)	Gefitinib	1,466	297	20
IPASS	Fukuoka et al ¹⁸	Gefitinib	1,217	437	36
TORCH		Erlotinib	760	275	36

Abbreviations: EGFR, endothelial growth factor receptor; NSCLC, non-small-cell lung cancer.