Quality of Life Analysis of TORCH, a Randomized Trial Testing First-Line Erlotinib Followed by Second-Line Cisplatin/Gemcitabine Chemotherapy in Advanced Non–Small-Cell Lung Cancer

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Introduction: The TORCH (*T*arceva *or Ch*emotherapy) trial randomized patients with advanced non–small-cell lung cancer to first-line erlotinib followed by second-line cisplatin/gemcitabine versus. standard inverse sequence. The trial, designed to test noninferiority in overall survival, was stopped at interim analysis because of inferior survival in the experimental arm. Quality of life (QoL), a secondary outcome, is reported here.

Methods: QoL was assessed at baseline and every 3 weeks during first-line, using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 and QLQ–lung cancer specific module (LC13). Mean changes from baseline within arms were reported. QoL response and time-to-deterioration of QoL using a competing-risk approach were compared between treatment arms.

Results: Six hundred and thirty patients (83%) completed baseline questionnaires. Compliance was affected by differential treatment efficacy, but was similar between arms for patients without progression or death. Significant differences in QoL responses were observed favoring chemotherapy for pain, sleeping, dyspnea, diarrhea, and favoring erlotinib for vomiting, constipation, sore mouth, and alopecia. In the small subset of patients with *EGFR*-mutated tumors, all selected items (global QoL, physical functioning, cough, dyspnea and pain) improved, whereas worsening or no change was observed in wild-type patients. Improvement was particularly evident in the first-line erlotinib arm as for global QoL and physical functioning.

Conclusions: QoL was impacted by differential toxicity and efficacy between arms. Functional domains and global QoL did not differ, although some symptoms were better controlled with chemotherapy in unselected non–small-cell lung cancer patients.

Key Words: Advanced non–small-cell lung cancer, Randomized trial, First-line treatment, Erlotinib, Chemotherapy, Health-related quality of life, EGFR.

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Lung cancer remains a leading global cause of cancer mortality and morbidity.[1] Most patients present with advanced disease, and modest gains in survival, symptom control, and health-related quality of life (QoL) are attained with chemotherapy,[2] and with second- or third-line erlotinib in unselected advanced non–small-cell lung cancer (NSCLC) patients after chemotherapy failure.[3,4] Therefore patients' preferences could be strongly affected by differences in toxicity profiles and convenience between parenteral chemotherapy and oral erlotinib.[5–7] The TORCH (*T*arceva *or Ch*emotherapy) randomized phase III trial tested noninferiority in overall survival with first-line erlotinib, followed by second-line doublet chemotherapy (cisplatin/gemcitabine), compared with the current inverse standard of first-line chemotherapy followed after progression by erlotinib, in unselected patients with advanced NSCLC.[8] We hypothesized that survival outcomes could be similar, but that advantages in terms of toxicity, convenience, and quality of life could also be expected with first-line erlotinib, even in an unselected NSCLC population. The study was prematurely stopped at the first interim analysis when inferiority of the experimental arm was demonstrated.[8]

In this article, we report results of QoL analyses during first-line treatment (cisplatin/gemcitabine versus erlotinib) in the TORCH trial, and an exploratory analysis of QoL differences between the two first-line strategies in the subgroup of patients with known *EGFR* mutation status.

PATIENTS AND METHODS

The TORCH trial (ClinicalTrials.gov number NCT00349219) was designed and conducted by the National Cancer Institute, Napoli, Italy, with collaborating centers in Italy and Canada. National Cancer Institute, Napoli, held and analyzed the data. Assessment of QoL during first-line treatment was a preplanned secondary outcome of this trial.

Study Population

Eligible patients had a confirmed pathologic diagnosis of advanced NSCLC (stage IV or IIIB with malignant pleural effusion or supraclavicular nodes), had Eastern Cooperative Oncology Group performance status 0 or 1, were aged less than 70 years (Canadian institutions did not apply age restriction), and were suitable for first-line cisplatin-based doublet chemotherapy. Details of trial eligibility and conduct are published elsewhere.[8] Study conduct was approved by the research ethics boards of all participating institutions, and all patients provided written informed consent to participate.

Study Procedures

Consenting patients completed baseline assessments including QoL evaluation, and were then randomized in a 1:1 ratio to either first-line erlotinib or first-line chemotherapy (cisplatin/gemcitabine). Patients randomized to the experimental arm received erlotinib (150 mg/day) orally until disease progression or the development of unacceptable toxicity. Patients randomized to the standard arm received cisplatin (80 mg/m^2 intravenously day 1) plus gemcitabine (1200 mg/m^2 intravenously days 1 and 8) every 3 weeks for a maximum of six cycles or until progression or unacceptable toxicity.

QoL Assessment

QoL assessment was mandatory for all study participants, but was limited to first-line treatment. This was to avoid expected selection bias of patients entering second-line therapy, given the unknown differential impact of first-line therapy in the two treatment arms.

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire - Core 30 (QLQ-C30) questionnaire[9] and the lung cancer specific module (EORTC QLQ-LC13)[10] were used to evaluate QoL at baseline and every 3 weeks in both arms (corresponding to end of cycles 1, 2, 3, 4, 5, and 6 in the standard arm).

The EORTC QLQ-C30[9] is a 30-item questionnaire composed of five multi-item functional subscales (physical, role, emotional, social, and cognitive functioning), three multi-item symptom scales (fatigue, pain, and emesis), a global health status subscale, and six single items to assess financial impact and symptoms such as dyspnea, sleep disturbance, appetite, diarrhea, and constipation, during the previous week. The EORTC QLQ-LC13 consists of 13 single items that evaluate specific symptoms of lung cancer.[10] Both questionnaires are designed to be completed by the patient. Scores for multi-item scales are calculated by deriving the mean raw scores of single items and transforming them linearly into scales ranging from 0 to 100[11]. For single items, only linear transformation is performed. For the five functional subscales, (physical, role, emotional, cognitive, and social functioning) and global health status, higher values represent better function. For symptom scales, higher values represent greater severity of symptoms (i.e., worse).

Baseline questionnaires had to be completed before the first treatment administration. Subsequent questionnaires were completed at weeks 3, 6, 9, 12, 15, and 18. In the event of delays in chemotherapy administration, questionnaires were accepted if completed at least 14 days after the previous administration of chemotherapy and before the subsequent chemotherapy cycle.

QoL Analysis

QoL missing data patterns were reported according to the National Cancer Institute of Canada Clinical Trials Group QoL framework.[12] Missing data fractions were reported under different scenarios: (1) rate of patients completing baseline assessments and the assessments at designated time points over the total number of patients eligible and entered into the trial; (2) rate of patients completing assessments at designated time points while on study over the total number completing assessment at baseline; and (3) rate of patients completing assessments at designated time points over the number of patients still on study, who were expected to complete questionnaires at each of those time points (excluding those who progressed or were dead at that time point).

For each domain or symptom, mean changes within arms from baseline to the six planned time points were reported to provide a complete picture of QoL behavior. A positive value represents an improvement in functional scales, and a worsening in symptom scales. Only patients with available values at baseline and at each time point were included in the analysis.

Two main QoL outcomes were compared between arms: (1) best QoL response and (2) time-to-deterioration of QoL. For best response, the first three questionnaires (3, 6, and 9 weeks) were evaluated; for time-to-deterioration, all available questionnaires were evaluated. Because of the exploratory nature of the QoL analysis, adjustment for multiple item comparisons was not performed.

Best QoL response from baseline was derived for each domain or symptom as follows: a change score of at least 10 points from baseline was defined as clinically relevant, as suggested by Osoba et al.[13]; patients were considered improved if they reported a score of 10 points or more better than baseline at any time, and were considered worsened if they reported a score 10 or more points worse than baseline (without improvement). Patients whose scores changed less than 10 points from baseline were considered stable. Only patients who had completed the baseline and at least one follow-up questionnaire within 9 weeks of treatment were included. An exact linear rank test was used to test whether the two study arms had the same underlying multinomial distribution of the ordered QoL response (Cytel Studio 9.0. 2010 Cytel Software Corp., Cambridge, MA).

Time-to-deterioration was defined as the time from randomization to QoL deterioration, using progression or death as competing events, that prevented the occurrence of QoL assessment. In the competing-risk approach,[14] the different types of events are not considered independent, and subjects who experienced progression or death before documented QoL deterioration were not censored at the time of progression/death. Accordingly, cumulative incidence functions, defined as the probability of deteriorating by the time t, were estimated for each domain and for each arm. Treatments were compared with the Gray method.[15] Deterioration of QoL was defined as a worsening of 10 or more points from baseline at any time during QoL assessment, irrespective of any improvement.

Analyses were repeated in the subgroup of patients with known *EGFR* mutation status for selected items that reflect disease-related effects (global QoL, physical functioning, cough, dyspnea, and pain). *EGFR* mutation analysis was performed retrospectively on all available tumor samples.

RESULTS

Seven hundred and sixty patients were accrued in the TORCH trial, 612 from Italy and 148 from Canada (Fig. 1); 630 completed baseline questionnaires, 315 (83%) in each arm (Fig. 1 and Fig. 2*A*). Patients with and without baseline QoL questionnaires were similar, with minor imbalances

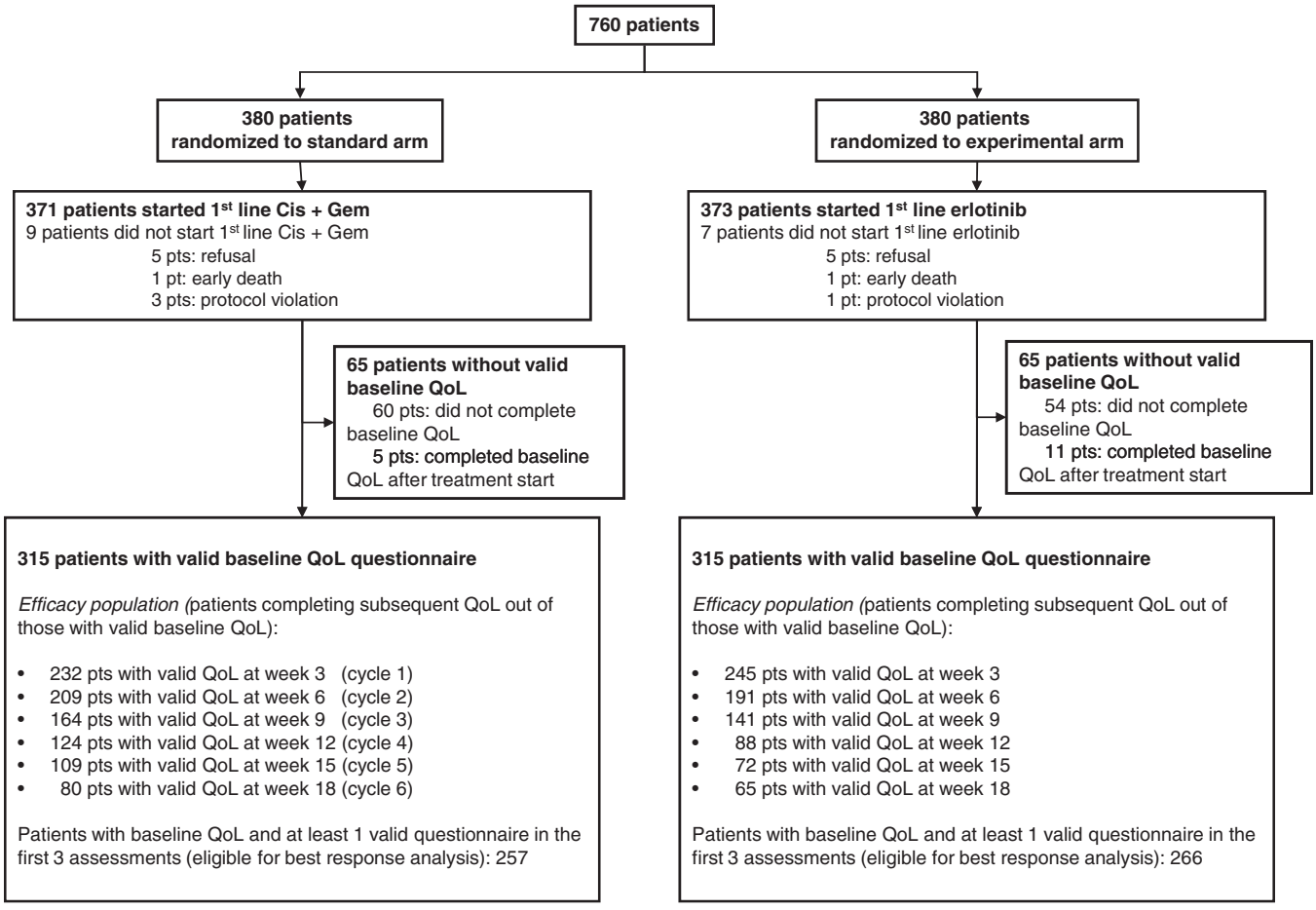

FIGURE 1. Flow-chart of TORCH study patients for QoL analysis. QoL, Quality of Life.

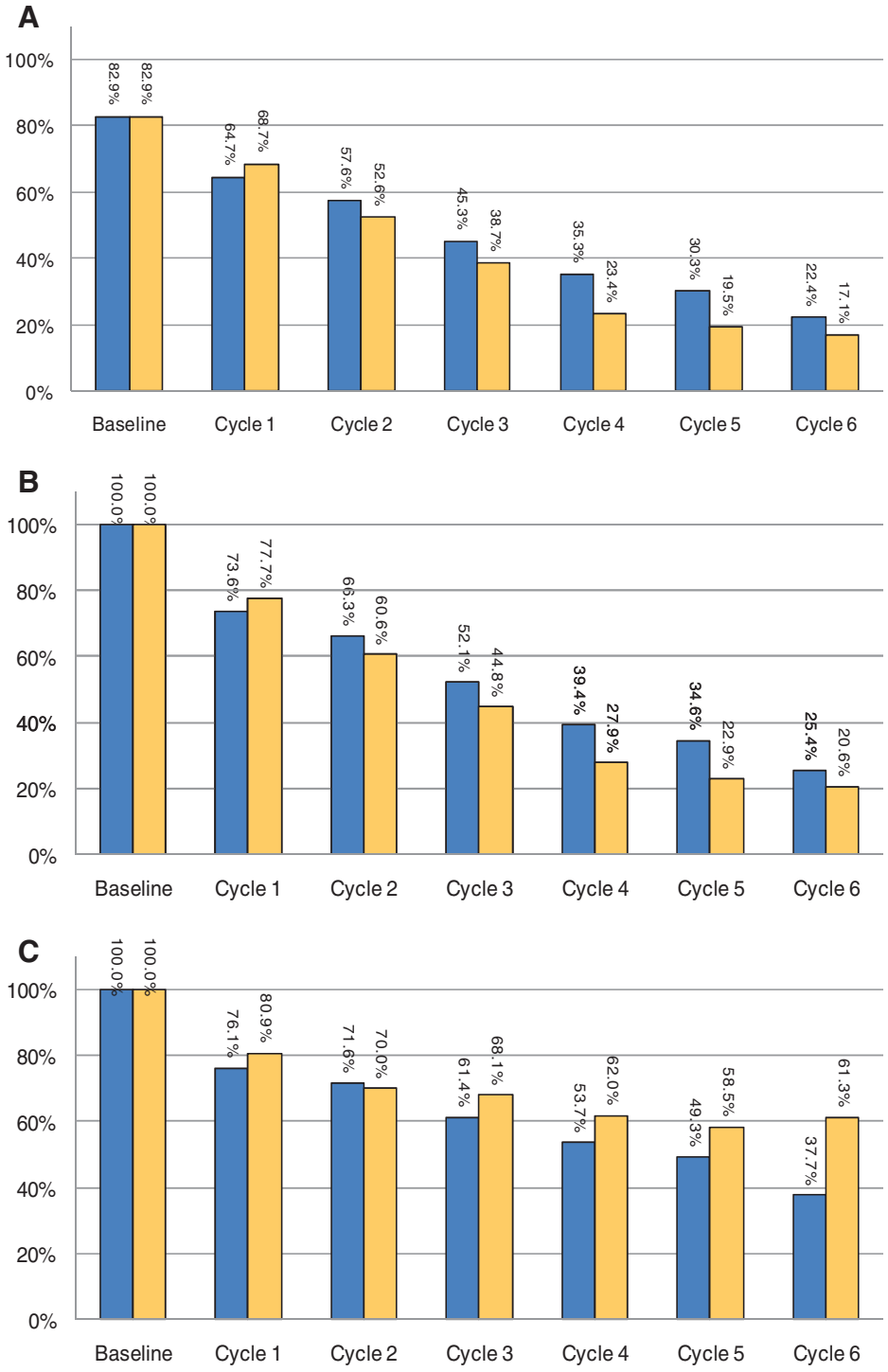

FIGURE 2. *A,* Rate of patients completing each Quality of Life assessment over the total number of patients entered into the trial *B,* over the total number completing assessment at baseline and *C,* over the number of patients without progression or death at each of those time points. Blue bars, cisplatin + gemcitabine; yellow bars, erlotinib.

by country, smoking status, and *EGFR* mutation status (Table 1). Baseline characteristics of patients included in QoL analyses were well balanced between study arms (Table 2). Thirty-five percent of the patients were women, 22% never smokers, and 56% had adenocarcinoma histology. For all QoL items, baseline values were similar between arms. *EGFR* mutation status was available for 275 patients (36.2%). Of these, 39 had tumors with activating *EGFR* mutations, 36 of whom were eligible for QoL analysis. Baseline characteristics did not differ between patients with or without *EGFR* assessment.[8]

Compliance with QoL questionnaire completion significantly decreased cycle after cycle, as expected in this poor-prognosis advanced-disease setting. In addition, compliance was significantly impacted by differing disease progression and survival rates between the two study arms. At 3,

TABLE 1. Baseline Characteristics of Patients With and Without Baseline Quality of Life Questionnaire

	All Patients	
	Patients With Baseline QoL (*n* = 630)	**Patients Without Baseline QoL (*n* = 130)**
Country *n* (%)		
Italy	493 (78%)	119 (92%)
Canada	137 (22%)	11 (8%)
Sex *n* (%)		
Male	412 (65%)	92 (71%)
Female	218 (35%)	38 (29%)
Age (yr) *n* (%)		
<70	592 (94%)	130 (100%)
>70 (only Canada)	38 (6%)	0
Ethnicity *n* (%)		
East Asian	22 (3%)	2 (2%)
Other	608 (97%)	128 (98%)
Smoking status *n* (%)		
Never smoker	141 (22%)	16 (12%)
Former or current smoker	489 (78%)	114 (88%)
ECOG performance status *n* (%)		
0	319 (51%)	63 (48%)
1	311 (49%)	67 (52%)
Stage, *n* (%)		
III B	70 (11%)	13 (10%)
IV	560 (89%)	117 (90%)
Histology, *n* (%)		
Squamous, large cell, mixed undefined	278 (44%)	60 (46%)
Adenocarcinoma (incl. BAC)	352 (56%)	70 (54%)
EGFR mutation status *n* (%)		
Not available	393 (62%)	92 (71%)
Available	237 (38%)	38 (29%)
Mutated	36 (15%)	3 (8%)
Wild type	201 (85%)	35 (92%)

QoL, Quality of Life questionnaire; BAC, bronchioloalveolar carcinoma; *EGFR*, epidermal growth factor receptor; ECOG, Eastern Cooperative Oncology Group.

TABLE 2. Baseline Characteristics and Quality of Life Values by Treatment Arm

	Standard Arm (*n* = 315)	**Experimental Arm (*n* = 315)**
Country, *n* (%)		
Italy	246 (78%)	247 (78%)
Canada	69 (22%)	68 (22%)
Sex, *n* (%)		
Male	205 (65%)	207 (66%)
Female	110 (35%)	108 (34%)
		(*Continued*)

TABLE 2. (Continued)

	Standard Arm (*n* = 315)	**Experimental Arm (*n* = 315)**
Age (yr), *n* (%)		
<70	296 (94%)	296 (94%)
>70	19 (6%)	19 (6%)
Ethnicity, *n* (%)		
East Asian	10 (3%)	12 (4%)
Other	305 (97%)	303 (96%)
Smoking status, *n* (%)		
Never smoker	68 (22%)	73 (23%)
Former or current smoker	247 (78%)	242 (77%)
ECOG PS, *n* (%)		
0	156 (50%)	163 (52%)
1	159 (50%)	152 (48%)
Stage, *n* (%)		
III B	32 (10%)	38 (12%)
IV	283 (90%)	277 (88%)
Histology, *n* (%)		
Squamous, large cell, mixed, undefined	136 (43%)	142 (45%)
Adenocarcinoma (incl. BAC)	179 (57%)	173 (55%)
EGFR mutation status, *n* (%)		
Not available	195	198
Mutated	18 (15%)	18 (15%)
Wild type	102 (85%)	99 (85%)
Mean baseline value (SD)		
Global QoL	56.7 (22.0)	58.0 (21.6)
Physical functioning	77.9 (20.5)	77.2 (20.0)
Role functioning	73.3 (27.8)	71.0 (28.5)
Emotional functioning	69.7 (22.5)	69.1 (22.4)
Cognitive functioning	88.6 (17.6)	88.3 (17.6)
Social functioning	79.9 (24.2)	81.1 (24.2)
Pain	27.2 (27.4)	24.7 (25.9)
Appetite	19.6 (27.0)	18.4 (25.8)
Constipation	14.3 (24.9)	14.4 (25.2)
Financial	11.1 (23.7)	15.0 (27.9)
Fatigue	30.6 (23.1)	30.7 (23.4)
Vomiting	7.3 (15.0)	7.3 (14.8)
Sleeping	25.7 (28.4)	24.2 (29.5)
Diarrhea	3.9 (12.3)	5.6 (14.8)
Dyspnea	24.4 (21.3)	25.9 (21.1)
Cough	32.9 (25.8)	35.8 (25.7)
Hemoptysis	3.6 (11.4)	4.3 (12.4)
Sore mouth	4.0 (14.5)	5.1 (14.7)
Swallowing	5.2 (15.0)	6.5 (18.0)
Neuropathy	7.8 (18.7)	8.0 (18.8)
Hair loss	4.2 (16.9)	5.1 (18.9)
Chest pain	14.2 (23.0)	13.6 (22.1)
Shoulder pain	16.0 (24.2)	17.7 (26.0)
Pain elsewhere	19.3 (28.8)	17.5 (25.8)
Analgesic use	47.9 (50.0)	42.7 (49.5)

ECOG, Eastern Cooperative Oncology Group; BAC, bronchioloalveolar carcinoma; PS, performance status;QoL, quality of life; SD, standard deviation.

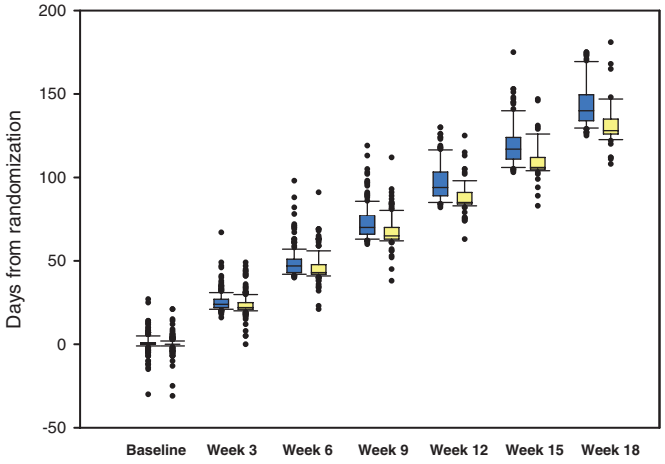

FIGURE 3. Box-plot of time distribution of Quality of Life assessments compared with date of randomization, by treatment arm. Line in the box, median value; box hinges, 25th to 75th percentiles; ends of the segments, 10th to 90th percentiles. Blue boxes: cisplatin/gemcitabine; yellow boxes: erlotinib.

6, and 9 weeks, 74%, 66%, and 52% reported QoL scores in the chemotherapy arm, compared with 78%, 61%, and 45% respectively in the erlotinib arm (Fig. 2*B*). When limiting to patients who were progression-free, compliance was similar between arms (Fig. 2*C*). Because of chemotherapy treatment delays time lag of questionnaire completion from randomization was slightly larger in the standard arm than in the experimental one (Fig. 3).

Observed Changes in QoL from Baseline

Absolute mean differences in QoL items from baseline are depicted in Figure 4. But for emotional functioning functional scales worsened during time for both arms (Fig. 4 *A*). Overall global QoL slightly improved with chemotherapy but slightly worsened in the experimental arm. Treatment-related symptoms including constipation, fatigue, vomiting, neuropathy, and hair loss, all expected side effects of chemotherapy, were worse in the standard arm. Diarrhea was worse in the erlotinib arm. Better control of cancer-related symptoms including pain, cough, and less use of analgesics was seen in patients receiving first-line chemotherapy (Fig. 4 *B* and *C*).

In the subset of patients with *EGFR*-mutated tumors (Fig. 5), all selected items improved in *EGFR*-mutated patients whereas worsening or no change was observed in wild-type patients. Improvement was particularly evident in the first-line erlotinib arm as for global QoL and physical functioning.

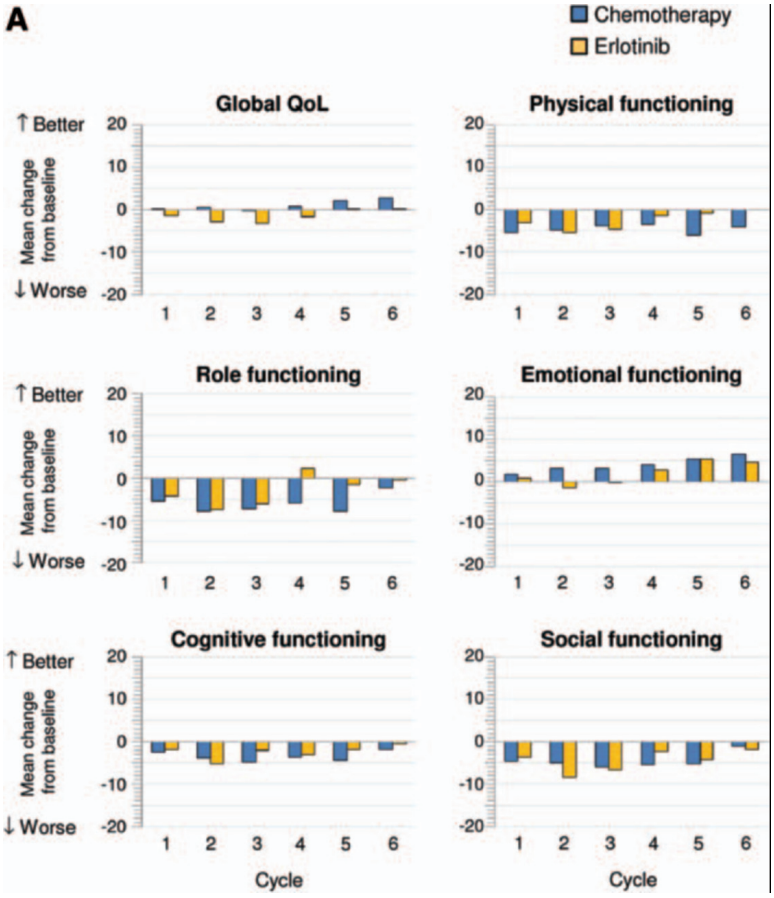

FIGURE 4. (Continued)

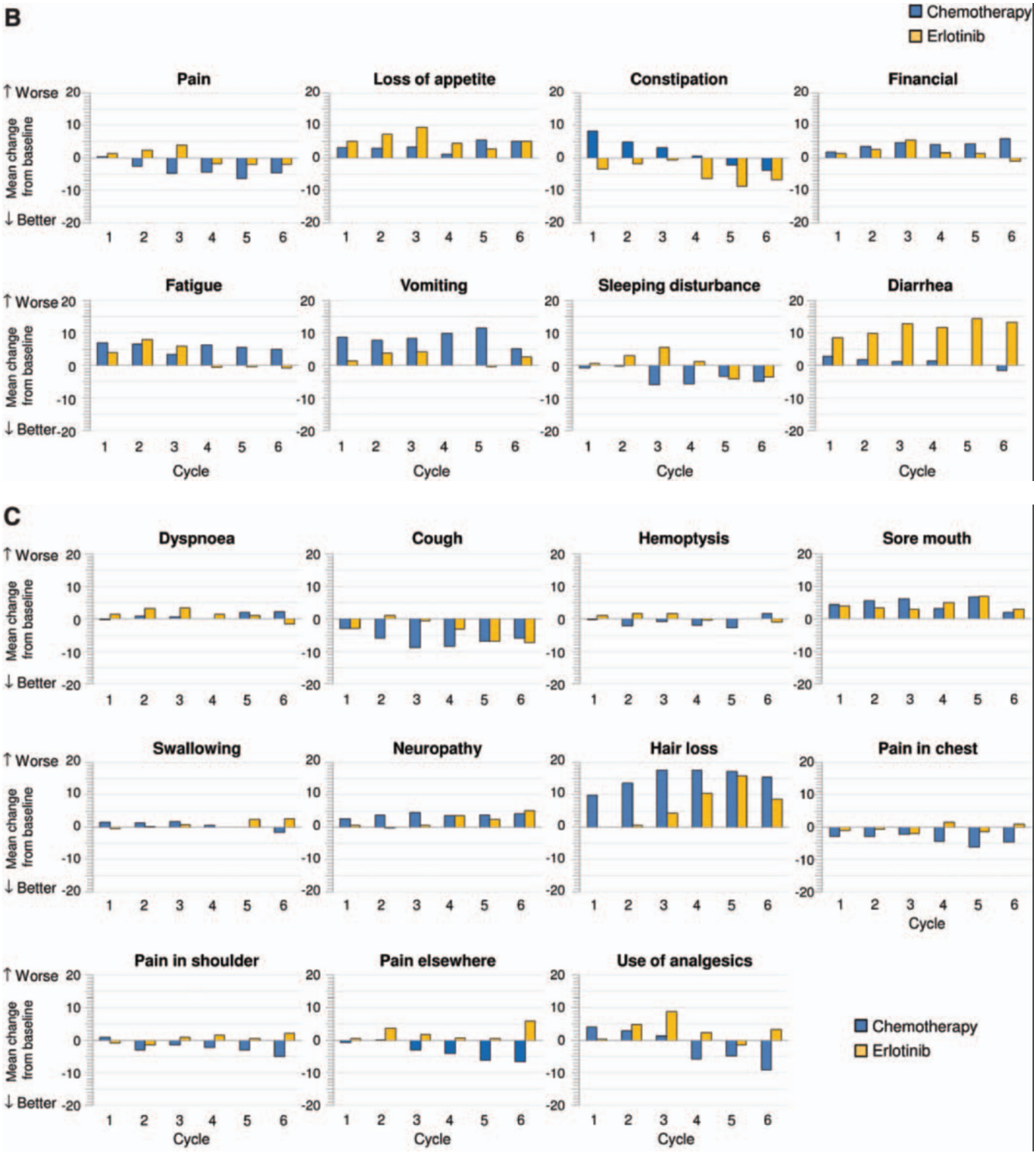

FIGURE 4. (Continued) Mean differences in QoL scores. *A*, QLQ-C30 functioning scales (positive indicate improvement). *B*, QLQ-C30 symptoms scales (negative indicate improvement). *C*, QLQ-LC13 symptoms scales (negative indicate improvement). Blue bars, cisplatin/gemcitabine; yellow bars, erlotinib. QoL, Quality of Life.

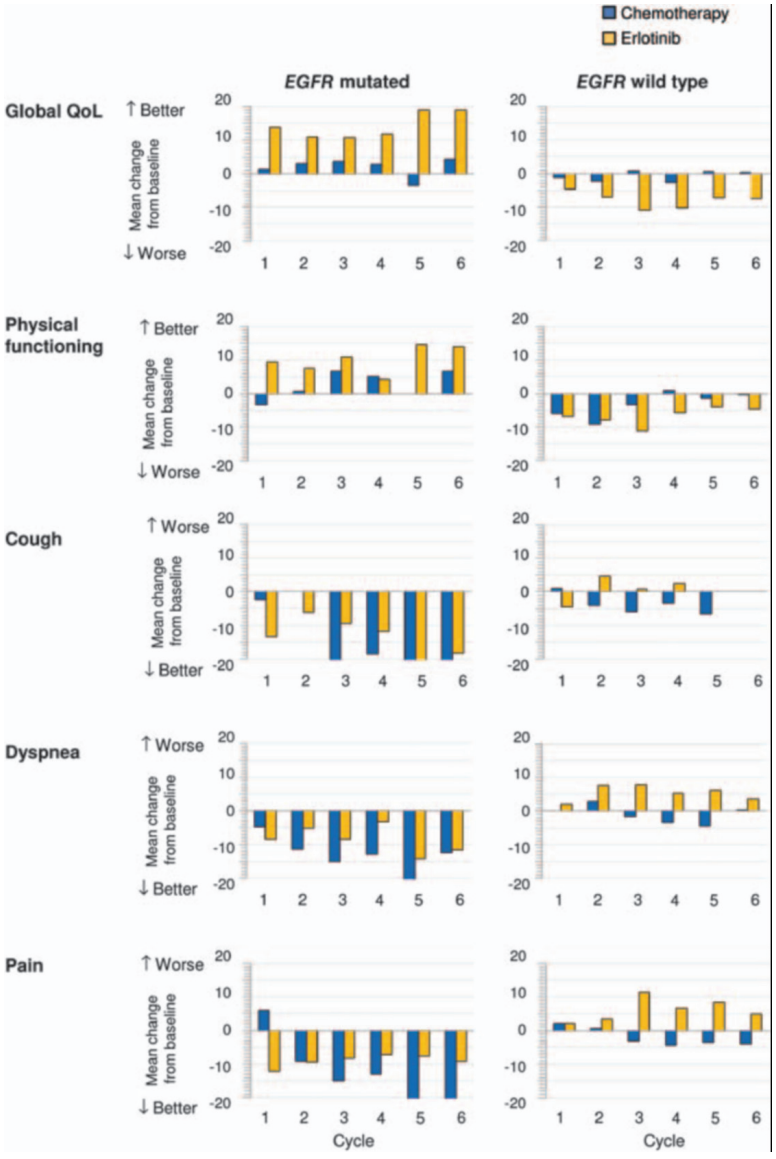

FIGURE 5. Mean differences in selected QoL items in patients with *EGFR* mutated tumor and in patients with *EGFR* wild-type tumor. Blue bars, cisplatin/gemcitabine; yellow bars, erlotinib. QoL, Quality of Life; *EGFR*, epidermal growth factor receptor.

Analysis of QoL Response

QoL response results by treatment arms are reported in Table 3. Clinically relevant differences favoring chemotherapy were seen for pain, dyspnea, and sleep disorders. In the subgroup with *EGFR*-mutated tumors, similar responses were observed in the two arms, whereas chemotherapy overcame the experimental arm in subjects with *EGFR* wild type (Table 4).

Analysis of Time-to-Deterioration

Cumulative incidence functions of time-to-deterioration are reported in Figure 6. Statistically significant differences in time-to-deterioration were observed for diarrhea, which was worse with erlotinib, and vomiting, constipation, sore mouth, and hair loss, which were worse with chemotherapy.

Cumulative incidence functions of time-to-deterioration of selected items according to *EGFR* mutational status are reported in Figure 7.

DISCUSSION

The TORCH trial demonstrates that, in unselected patients with advanced NSCLC, significantly better response rates, progression-free and overall survival are observed with first-line chemotherapy compared with first-line erlotinib.[8] In the QoL analyses, however, the differences in global QoL scores between the arms were not significantly different. Impact of standard treatment in terms of disease symptoms control and side effects was consistent with the expected effect of platinum-based chemotherapy as first-line treatment of advanced NSCLC, with mean changes from baseline showing a reduction in some symptoms (pain, cough) and an increase in several side effects (fatigue, vomiting, loss of appetite, sore mouth, neuropathy, hair loss). Toxicity differences between the arms were clearly reflected in the QoL analyses, with more fatigue, alopecia, constipation, and vomiting seen with chemotherapy, and diarrhea with erlotinib, as expected.

TABLE 3. Best Quality of Life Response by Treatment Arm

	Standard Arm (n = 266)[a]			Experimental Arm (n = 257)[a]			
Domain/Item	Improved (%)	Stable (%)	Worse (%)	Improved (%)	Stable (%)	Worse (%)	p
Global QoL	93 (36)	76 (30)	86 (34)	81 (31)	77 (29)	105 (40)	0.11
Physical functioning	56 (22)	102 (40)	96 (38)	50 (19)	112 (43)	100 (38)	0.65
Role functioning	71 (28)	76 (30)	108 (42)	71 (27)	77 (29)	116 (44)	0.72
Emotional functioning	92 (36)	99 (39)	64 (25)	70 (27)	113 (43)	78 (30)	0.04
Cognitive functioning	57 (23)	102 (40)	94 (37)	49 (18)	123 (46)	93 (35)	0.84
Social functioning	58 (23)	89 (35)	108 (42)	64 (24)	88 (33)	111 (42)	0.83
Pain	104 (41)	82 (32)	68 (27)	79 (30)	84 (32)	101 (38)	0.002
Appetite	61 (24)	95 (37)	100 (39)	46 (17)	115 (43)	104 (39)	0.39
Constipation	44 (17)	120 (47)	92 (36)	56 (21)	163 (62)	46 (17)	<0.0001
Financial	23 (9)	175 (68)	58 (23)	33 (13)	179 (69)	49 (19)	0.13
Fatigue	89 (35)	43 (17)	124 (48)	91 (35)	49 (19)	123 (47)	0.83
Vomiting	35 (14)	87 (34)	133 (52)	40 (15)	145 (55)	79 (30)	<0.0001
Sleeping	88 (35)	95 (37)	72 (28)	63 (24)	104 (39)	99 (37)	0.005
Diarrhea	21 (8)	182 (71)	53 (21)	21 (8)	133 (50)	110 (42)	<0.0001
Dyspnea	67 (27)	122 (49)	62 (25)	48 (18)	127 (48)	88 (33)	0.005
Cough	91 (36)	115 (45)	49 (19)	81 (31)	112 (42)	72 (27)	0.05
Hemoptysis	18 (7)	221 (87)	16 (6)	19 (7)	214 (81)	32 (12)	0.10
Sore mouth	10 (4)	175 (68)	71 (28)	21 (8)	185 (70)	59 (22)	0.05
Swallowing	19 (7)	192 (75)	45 (18)	29 (11)	192 (73)	43 (16)	0.30
Neuropathy	23 (9)	182 (72)	49 (19)	37 (14)	176 (67)	49 (19)	0.26
Hair loss	12 (5)	125 (49)	117 (46)	14 (5)	217 (82)	33 (12)	<0.0001
Chest pain	56 (22)	154 (60)	45 (18)	50 (19)	164 (62)	50 (19)	0.41
Shoulder pain	52 (21)	149 (59)	50 (20)	49 (19)	164 (63)	46 (18)	0.99
Pain elsewhere	60 (24)	129 (51)	62 (25)	57 (22)	126 (48)	77 (30)	0.27
Analgesic use	31 (13)	174 (70)	42 (17)	28 (11)	189 (73)	42 (16)	0.85

[a] According to Osoba et al.[13] based on patients with at least one questionnaire at 3, 6, or 9 weeks after baseline.
Number and row percentage are reported for each item and within each arm; small changes in the total number can depend on missing responses in each item.
QoL, quality of life.

Tumor-related symptom control was reflective of treatment efficacy, with better pain and dyspnea scores in the standard arm (chemotherapy). Compliance was slightly less in the experimental arm over time, related to greater clinical deterioration in the erlotinib arm compared with chemotherapy.

To compare QoL between treatment arms, we calculated the best QoL response (the proportion of patients with clinically meaningful differences for each item), which is the preferred analysis for health-related QoL data from clinical trials, according to the National Cancer Institute of Canada Clinical

TABLE 4. Quality of Life Response*[a] by Treatment Arm, by *EGFR* Mutational Status

	EGFR Mutated (*n*=31)[b]						*EGFR* Wild Type (*n* = 165)[b]					
	Standard Arm (*n*=15)			Experimental Arm (*n*=16)			Standard Arm (*n* = 82)			Experimental Arm (*n* = 83)		
Domain/item	Improved (%)	Stable (%)	Worse (%)	Improved (%)	Stable (%)	Worse (%)	Improved (%)	Stable (%)	Worse (%)	Improved (%)	Stable (%)	Worse (%)
Global QoL	6 (40)	5 (33)	4 (27)	8 (50)	4 (25)	4 (25)	28(35)	23 (28)	30 (37)	23 (28)	16 (20)	42 (52)
Physical functioning	5 (33)	6 (40)	4 (27)	8 (50)	3 (19)	5 (31)	19 (23)	29 (35)	34 (41)	10 (12)	29 (35)	43 (52)
Pain	7 (47)	5 (33)	3 (20)	9 (56)	4 (25)	3 (19)	31 (38)	20 (25)	30 (37)	20 (24)	25 (30)	38 (46)
Dyspnea	6 (40)	6 (40)	3 (20)	6 (38)	7 (44)	3 (19)	23 (29)	32 (41)	23 (29)	14 (17)	37 (45)	31 (38)
Cough	7 (47)	5 (33)	3 (20)	7 (44)	5 (31)	4 (25)	32 (40)	29 (36)	20 (25)	27 (33)	33 (40)	23 (28)

[a] According to Osoba et al.[13] based on patients with at least one questionnaire at 3, 6, or 9 weeks after baseline.
[b] Number and row percentage are reported for each item and within each arm; small changes in the total number can depend on missing responses in each item.
QoL, quality of life; *EGFR,* epidermal growth factor receptor.

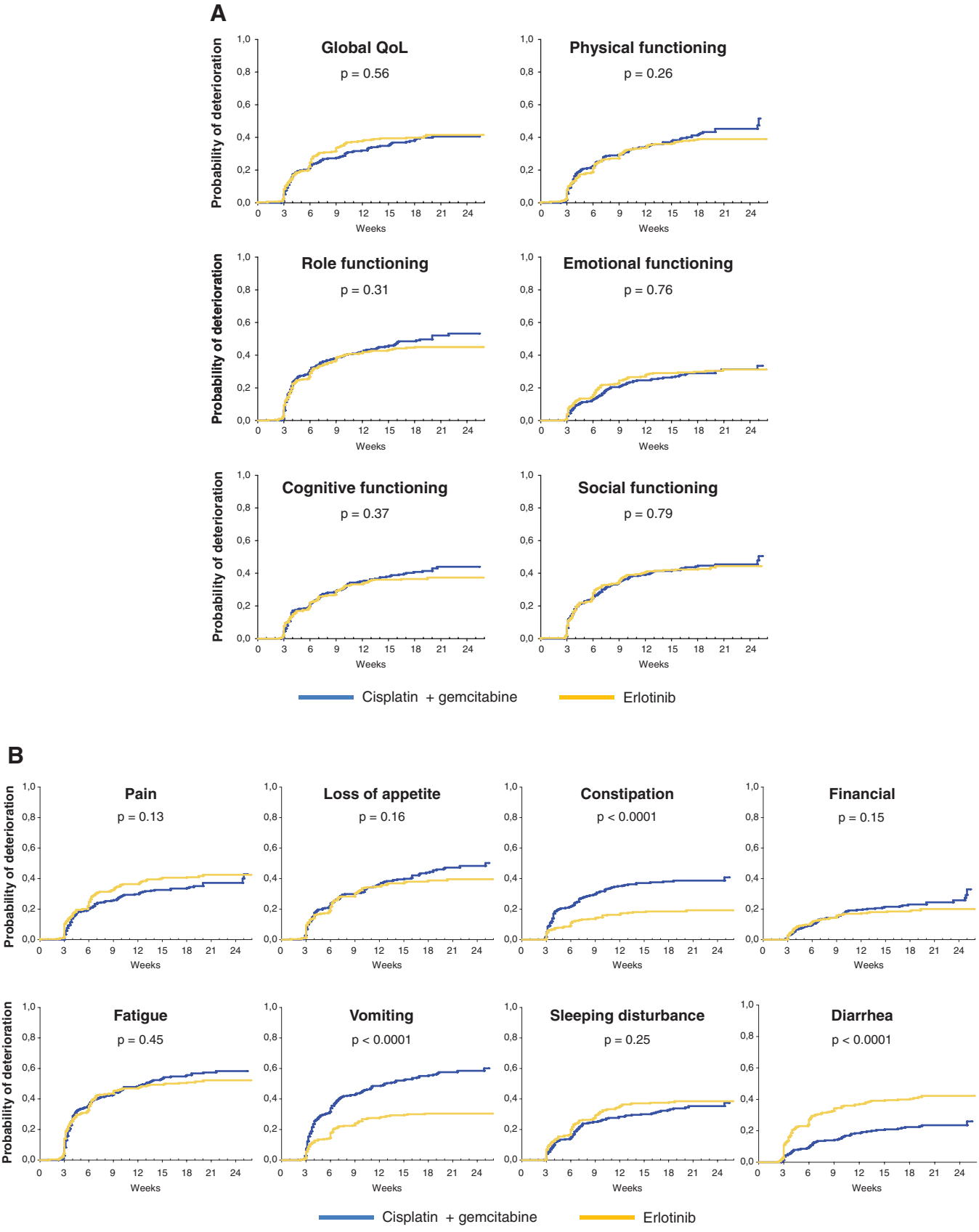

FIGURE 6. (Continued)

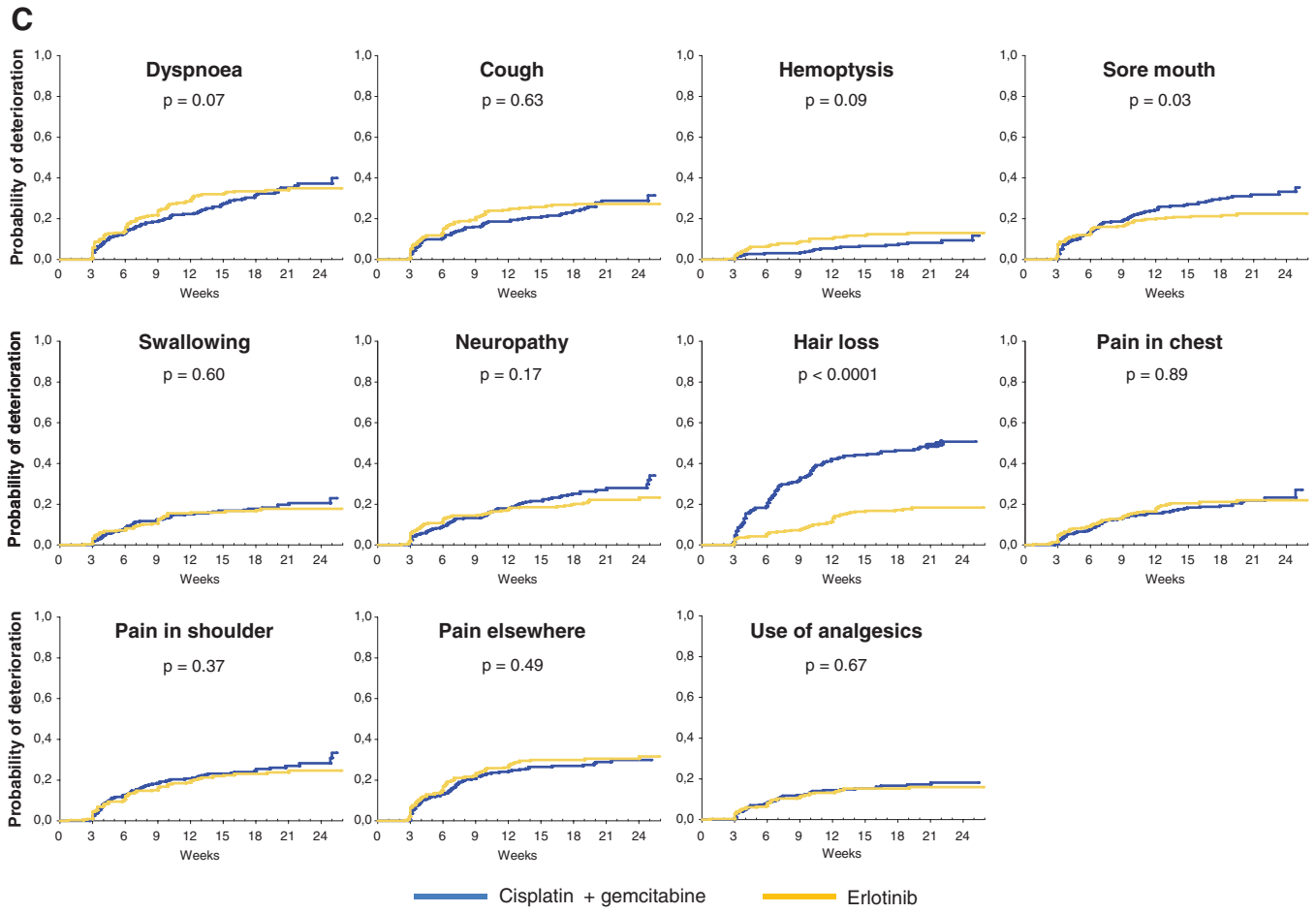

FIGURE 6. (Continued) Cumulative incidence functions of time-to-deterioration for QoL items. *A*, QLQ-C30 functioning scales. *B*, QLQ-C30 symptoms scales. *C*, QLQ–lung cancer specific module (LC13) symptoms scales. Blue curves, cisplatin/gemcitabine; yellow curves, erlotinib. QoL, Quality of Life.

Trials Group.[12] In addition, we hypothesized that time-to-deterioration analysis, including time to symptom worsening as defined by QoL response parameters, or disease progression or death, would better reflect the clinical differences between arms. However, despite the poor clinical outcomes in the experimental arm, we did not find a significant difference in time to global QoL or disease-related symptom deterioration.

On the basis of these results, the QoL analyses in this trial were reflective of differing treatment toxicity profiles, and able to capture greater symptom improvement in the chemotherapy arm. However, the analyses of global QoL do not reflect the significant differences in efficacy between arms, as would have been expected. It is unclear whether this is related to the measures used. The EORTC QLQ-C30 and LC13 may be better instruments to capture treatment toxicity and elements of lung cancer symptom control. Or, despite evidence that systemic therapy improves QoL despite treatment toxicity,[16] the impact of toxicity may overshadow potential QoL benefit in the standard arm.

The difference in QoL compliance, affected by differing disease progression and survival rates between study arms, reverberates differently on the two outcomes. It should not affect best QoL response, because it is very unlikely that patients progressed could subsequently experience clinical improvement in one or more items of QoL questionnaire. Conversely, it could affect time-to-deterioration, and for this reason we used the competing-risk approach, to speculate whether there would be differences between arms once the effect of competing events that prevent the outcome of interest is removed.

After initiation of the TORCH trial, several randomized trials have been reported comparing first-line EGFR tyrosine kinase inhibitor (gefitinib or erlotinib) with platinum-based chemotherapy in patients selected (by subgroup analysis[17,18] or as inclusion criteria)[19–22] for the presence of *EGFR* activating mutations. In the first of these trials, Mok et al.[17] compared first-line carboplatin plus paclitaxel versus gefitinib in good performance status patients with lung adenocarcinoma and a light- or never-smoking history. In the subset analysis of patients with somatic *EGFR* activating mutations, better response rates and progression-free survival were seen in those treated with first-line gefitinib compared with chemotherapy. QoL scores were also better with gefitinib in the mutation-positive subgroup, compared with scores for those treated with first-line chemotherapy. A clinically relevant improvement in global QoL was observed in 70% of *EGFR* mutation-positive patients

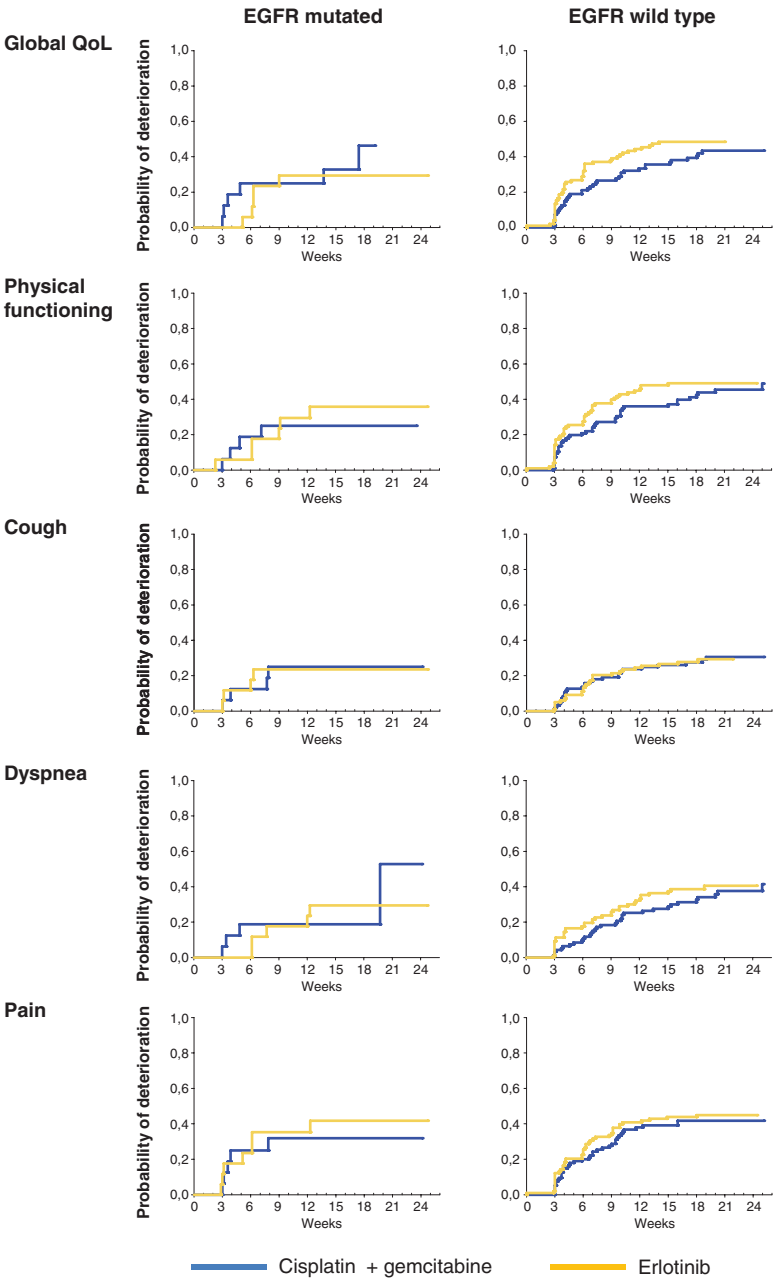

FIGURE 7. Cumulative incidence functions of time-to-deterioration for selected QoL items in patients with *EGFR* mutated tumor and in patients with *EGFR* wild-type tumor. Blue curves, cisplatin/gemcitabine; yellow curves, erlotinib. QoL, Quality of Life; *EGFR*, epidermal growth factor receptor.

treated with gefitinib, compared with 45% of patients receiving chemotherapy (odds ratio 3.01, 95% confidence interval 1.79–5.07, $p < 0.0001$). A significant interaction with *EGFR* mutation status was also demonstrated in the Trial Outcome Index,[23] which combines scores on physical well-being, functional well-being, and lung cancer subscale of the Functional Assessment of Cancer Therapy-Lung instrument and in the analysis of items related to lung cancer symptoms. Of note, both in terms of global QoL and in terms of lung cancer symptoms, improvements with gefitinib were usually rapid. In the First-SIGNAL trial, comparing chemotherapy to gefitinib in never smokers with lung adenocarcinoma, quality of life was assessed by the same measures used in TORCH, the EORTC QLQ-C30 and LC-13[18]. Gefitinib was associated with significantly better physical role and social function, compared with standard first-line chemotherapy. As for lung cancer symptoms, in the subgroup of patients with *EGFR* mutation positive tumors, gefitinib was associated with a better outcome in terms of hemoptysis, dysphagia, and pain compared with chemotherapy treatment.

In the TORCH trial, *EGFR* mutation status was known in only one third of the patients. With the low prevalence of *EGFR* mutations in Western patients, the absolute number of mutation-positive cases is low although well balanced between treatment arms. Mean differences from baseline in global QoL clearly show a differential impact of treatment, with erlotinib producing a consistent improvement of global QoL at all time points in mutation-positive cases, and a consistent deterioration of global QoL at all time points in wild-type cases. A

similar effect is seen for erlotinib also in physical functioning and in the three symptoms analyzed (cough, dyspnea, and pain). For patients with wild-type tumors, administration of erlotinib was associated with a worse outcome compared with chemotherapy in all items studied. Interestingly, there was a better symptom control in *EGFR*-mutated patients, compared with wild-type cases, also for those assigned to chemotherapy. Thus, our subanalyses confirm existing evidence that for *EGFR* wild-type patients, first-line erlotinib produces inferior clinical efficacy and inferior quality of life outcomes compared with chemotherapy, despite a more favorable toxicity profile. Similarly, patients with *EGFR* mutation-positive tumors derive dramatic clinical and QoL benefit from first-line EGFR tyrosine kinase inhibitor treatment, but also derive good clinical efficacy from chemotherapy, also reflected in favorable symptom-control scores.

First-line treatment with an EGFR tyrosine kinase inhibitor (gefitinib or erlotinib) in patients with *EGFR* mutation-positive advanced NSCLC has become standard worldwide.[17–22] For those with *EGFR* wild type or unknown *EGFR* genotype, chemotherapy remains the first-line standard. QoL analyses, including those from the TORCH trial, support this treatment algorithm. In unselected patients with advanced NSCLC, QoL scores reflect not only treatment toxicity, but also better symptom control with chemotherapy.

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APPENDIX

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