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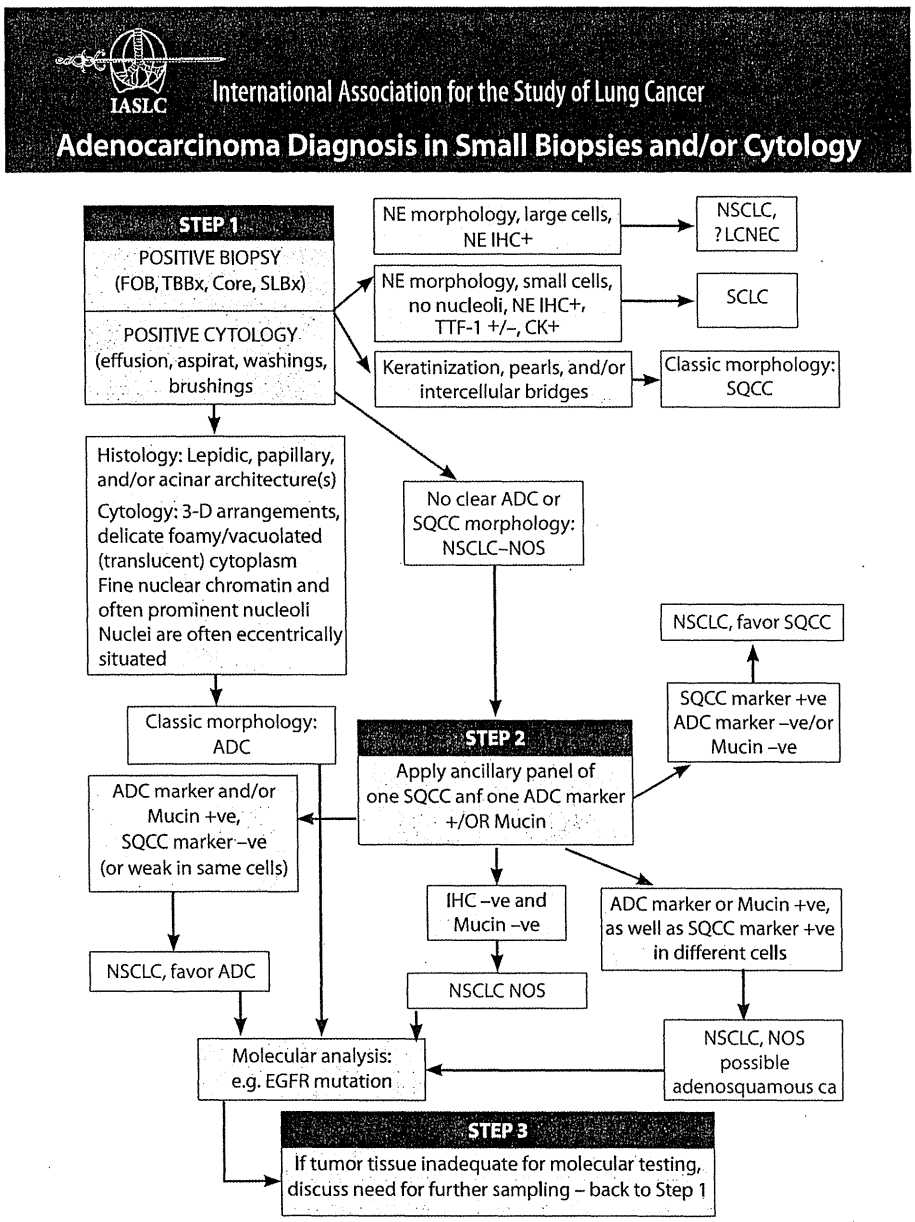
International Association for the Study of Lung Cancer

Proposed Terminology in Lung Adenocarcinoma Classification

2004 WHO Classification	SMALL BIOPSY/CYTOLOGY: IASLC/ATS/ERS
ADENOCARCINOMA Mixed subtype Papillary Acinar Solid	*Morphologic adenocarcinoma patterns clearly present:* Adenocarcinoma, describe identifiable patterns present (including micropapillary pattern not included in 2004 WHO classification)
Bronchioloalveolar carcinoma (nonmucinous)	Adenocarcinoma with lepidic pattern (if pure, add note: an invasive component cannot be excluded)
Bronchioloalveolar carcinoma (mucinous)	Mucinous adenocarcinoma (describe patterns present)
Fetal	Adenocarcinoma with fetal pattern
Mucinous (colloid)	Adenocarcinoma with colloid pattern
Signet ring	Adenocarcinoma with (describe patterns present) and signet ring features
Clear cell	Adenocarcinoma with (describe patterns present) and clear cell features
No 2004 WHO counterpart–most will be solid adenocarcinoma	*Morphologic adenocarcinoma patterns not present (supported by special stains):* Non-small cell carcinoma, favor adenocarcinoma
SQUAMOUS CELL CARCINOMA Papillary Small cell Clear cell Basaloid	*Morphologic squamous cell patterns clearly present:* Squamous cell carcinoma
No 2004 WHO counterpart	*Morphologic squamous cell patterns not present (supported by stains):* Non-small cell carcinoma, favor squamous cell carcinoma
SMALL CELL CARCINOMA	Small cell carcinoma
LARGE CELL CARCINOMA	Non-small cell carcinoma, not otherwise specified (NOS)
Large cell neuroendocrine carcinomas (LCNEC)	Non-small cell carcinoma with neuroendocrine (NE) morphology (positive NE markers), possible LCNEC
Large cell carcinoma with NE morphology (LCNEM)	Non-small cell carcinoma with NE morphology (negative NE markers)–see comment
ADENOSQUAMOUS CARCINOMA	*Morphologic squamous cell and adenocarcinoma patterns present:* Non-small cell carcinoma, with squamous cell and adenocarcinoma patterns
No counterpart in 2004 WHO classification	*Morphologic squamous cell and adenocarcinoma patterns not present but immunostains favor separate glandular and adenocarcinoma components* Non-small cell carcinoma, NOS, (specify the results of the immunohistochemical stains and the interpretation)
Sarcomatoid carcinoma	Poorly differentiated NSCLC with spindle and/or giant cell carcinoma (mention if adenocarcinoma or squamous carcinoma are present)



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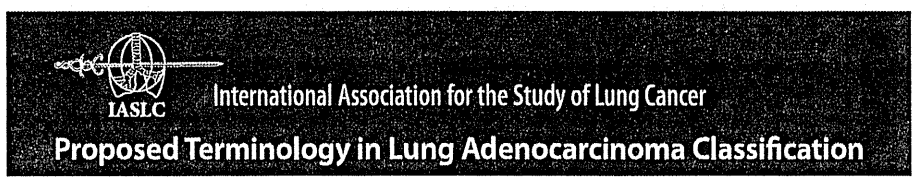

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SQUAMOUS CELL CARCINOMA Papillary Small cell Clear cell Basaloid	*Morphologic squamous cell patterns clearly present:* Squamous cell carcinoma
No 2004 WHO counterpart	*Morphologic squamous cell patterns not present (supported by stains):* Non-small cell carcinoma, favor squamous cell carcinoma
SMALL CELL CARCINOMA	Small cell carcinoma
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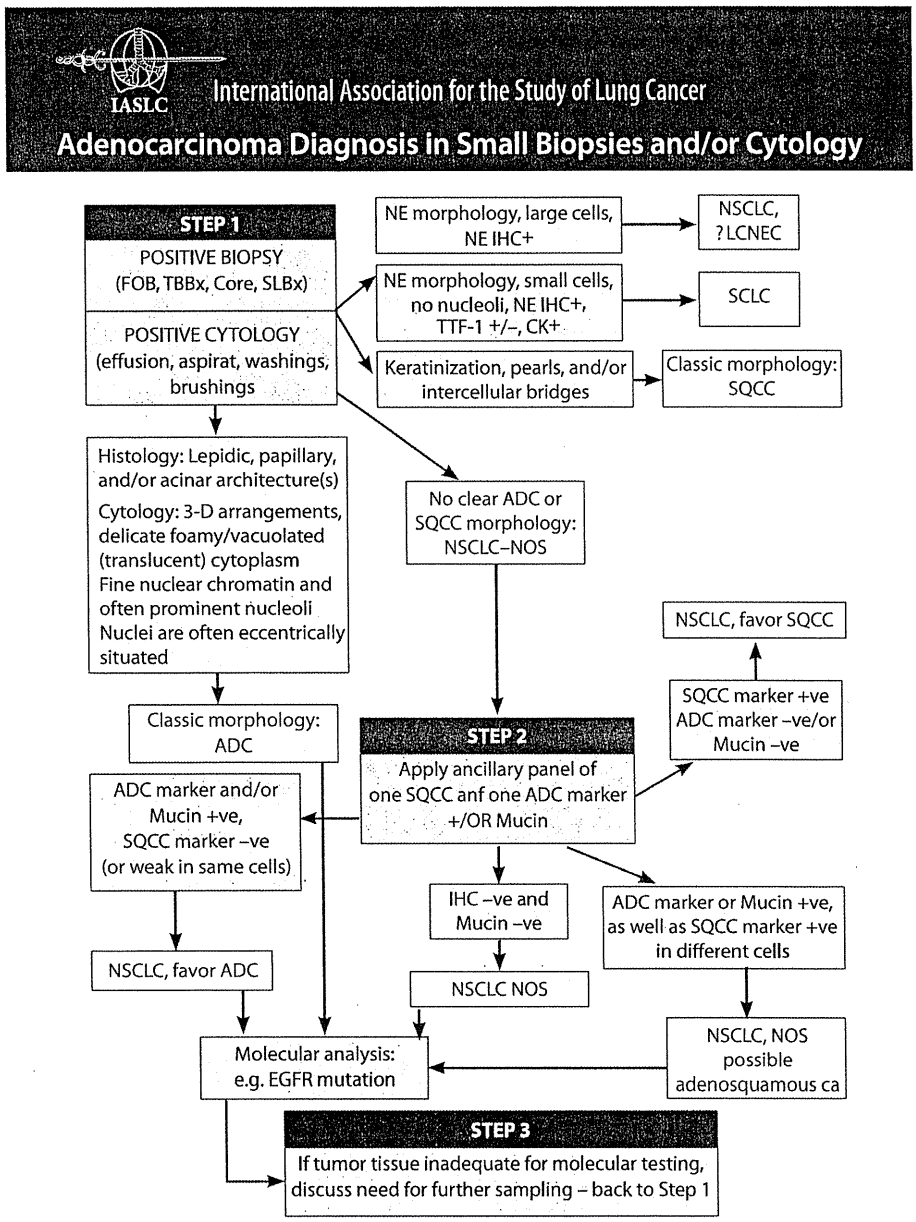

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Health-Related Quality-of-Life in a Randomized Phase III First-Line Study of Gefitinib Versus Carboplatin/Paclitaxel in Clinically Selected Patients from Asia with Advanced NSCLC (IPASS)

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Introduction: Evaluation of health-related quality-of-life (HRQoL) and symptom improvement were preplanned secondary objectives for the overall population and posthoc analyses for epidermal growth factor receptor (*EGFR*) mutation-positive/negative subgroups in IPASS.

Methods: HRQoL was assessed using the Functional Assessment of Cancer Therapy-Lung (FACT-L) and Trial Outcome Index (TOI); symptom improvement by the Lung Cancer Subscale (LCS). Improvements defined as: 6 or more (FACT-L; TOI), 2 or more (LCS) points increase maintained for 21 or more days.

Results: Overall (n = 1151/1217 evaluable), HRQoL improvement rates were significantly greater with gefitinib versus carboplatin/paclitaxel; symptom improvement rates were similar for both treatments. Significantly more patients recorded improvements in HRQoL and symptoms with gefitinib in the *EGFR* mutation-positive subgroup (n = 259; FACT-L 70.2% versus 44.5%; odds ratio, 3.01 [95% confidence interval, 1.79–5.07]; $p < 0.001$; TOI 70.2% versus 38.3%; 3.96 [2.33–6.71]; $p < 0.001$; LCS 75.6% versus 53.9%; 2.70 [1.58–4.62]; $p < 0.001$), and with carboplatin/paclitaxel in the *EGFR* mutation-negative subgroup (n = 169; FACT-L 14.6% versus 36.3%; odds ratio, 0.31 [0.15–0.65]; $p = 0.002$; TOI 12.4% versus 28.8%; 0.35 [0.16–0.79]; $p = 0.011$; LCS 20.2% versus 47.5%; 0.28 [0.14–0.55]; $p < 0.001$). Median time-to-worsening (months) FACT-L score was longer with gefitinib versus carboplatin/paclitaxel for the overall population (8.3 versus 2.5) and *EGFR* mutation-positive subgroup (15.6 versus 3.0), and similar for both treatments in the *EGFR* mutation-negative subgroup (1.4 versus 1.4). Median time-to-improvement with gefitinib was 8 days in patients with *EGFR* mutation-positive tumors who improved.

Conclusions: HRQoL and symptom endpoints were consistent with efficacy outcomes in IPASS and favored gefitinib in patients with *EGFR* mutation-positive tumors and carboplatin/paclitaxel in patients with *EGFR* mutation-negative tumors.

Key Words: Gefitinib, Non-small cell lung cancer, Quality-of-life.

(*J Thorac Oncol.* 2011;6: 1872–1880)

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Disclosure: This study was supported by AstraZeneca. Sumitra Thongprasert has received compensation from AstraZeneca to participate in a scientific symposium; Yi-Long Wu has received compensation from AstraZeneca, Roche, Eli Lilly, Pfizer and Glaxo Smith Kline for services as a speaker; James Chih-Hsin Yang has received compensation from AstraZeneca for services as a speaker and participation in an advisory board; Da-Tong Chu has received compensation from AstraZeneca for services as a speaker and participation in an advisory board; and Emma Duffield, Alison Armour and Patrick Magill are full-time employees of AstraZeneca and hold stock in AstraZeneca. All other authors declare no conflicts of interest.

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Presented, in part, in Mok et al. *N Engl J Med* 2009;361:947–957, and at the 2nd European Lung Cancer Conference, Geneva, Switzerland, April 28–May 1, 2010.

ISSN: 1556-0864/11/0611-1872

Non-small cell lung cancer (NSCLC) is associated with high morbidity, and a number of studies have reported that patients with NSCLC experience more symptom distress than with other types of cancer.[1,2] Improving the management of symptom distress is therefore particularly important,[3] and health-related quality-of-life (HRQoL) and symptom improvement are measures of clinical benefit that help to achieve this management.[3–5] HRQoL or symptoms are best assessed by the patient with the use of patient-reported outcome instruments.[6]

The phase III IRESSA Pan ASia Study (IPASS) evaluated the epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) gefitinib (IRESSA, AstraZeneca, UK) as first-line monotherapy for advanced NSCLC in clinically selected patients.[7] IPASS exceeded its primary objective of noninferiority and demonstrated superiority of gefitinib compared with carboplatin/paclitaxel for progression-free survival (PFS) in this clinically selected population. A strong relationship between *EGFR*-mutation status and treatment was evident for PFS (treatment-by-*EGFR*-mutation-status interaction test $p < 0.001$). Patients with *EGFR* mutation-positive tumors treated with gefitinib had significantly longer PFS (hazard ratio [HR] = 0.48; 95% confidence interval [CI], 0.36–0.64; $p < 0.001$; median PFS 9.5 versus 6.3 months), whereas patients with *EGFR* mutation-negative tumors treated with gefitinib had significantly shorter PFS (HR = 2.85; 95% CI, 2.05–3.98; $p < 0.001$; median PFS 1.5 versus 5.5 months) as compared with carboplatin/paclitaxel. Similarly, objective response rate (ORR) significantly favored gefitinib and carboplatin/paclitaxel in the *EGFR* mutation-positive (ORR, 71.2% versus 47.3%; odds ratio [OR], 2.75; 95% CI, 1.65–4.60; $p < 0.001$) and mutation-negative subgroups (ORR, 1.1% versus 23.5%; OR, 0.04; 95% CI, 0.01–0.27; $p = 0.001$), respectively.

Here, we present the full results of the HRQoL and symptom improvement evaluations in IPASS. These were preplanned secondary objectives in the overall population and the data were analyzed posthoc by *EGFR* mutation status. Additionally, posthoc summaries of time-to-worsening are also presented. Some HRQoL and symptom improvement data in the overall population[7] and by *EGFR* mutation status (Supplemental Digital Content Figures 1 and 2, http://links.lww.com/JTO/A123 and http://links.lww.com/JTO/A124 (7)) reported previously are included here for completeness.

METHODS

Study Design

Full details of the IPASS study design (ClinicalTrials.gov identifier NCT00322452) have been published previously.[7] Eligible patients had stage IIIB/IV pulmonary adenocarcinoma (including bronchoalveolar carcinoma), were either never-smokers (<100 cigarettes in their lifetime) or light former smokers (stopped smoking ≥15 years previously and smoked ≤10 pack-years), and had received no previous chemotherapy or biologic/immunologic therapy. Patients were randomized 1:1 to gefitinib (250 mg/d) or carboplatin/paclitaxel (Paraplatin/Taxol, Bristol-Myers Squibb, USA; paclitaxel 200 mg/m^2 intravenously over 3 hours on day 1, immediately followed by carboplatin area under the curve 5.0 or 6.0 intravenously for 15–60 minutes, in 3-weekly cycles for ≤6 cycles).

Patients provided written, informed consent with separate consent obtained for optional provision of tumor material for *EGFR* biomarker analysis. Study approval was obtained from independent ethics committees at each institution. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation/Good Clinical Practice, applicable regulatory requirements, and AstraZeneca's policy on bioethics.

EGFR Mutation Analyses

Details of the *EGFR* mutation analyses have been published previously.[7] Briefly, *EGFR* mutation status was determined by performing analyses on DNA extracted from paraffin-embedded archival tumor tissue. *EGFR* mutations were detected by amplification mutation refractory system (ARMS) using an *EGFR* mutation detection kit (DxS, Manchester, UK).[8,9] Patients were considered *EGFR* mutation-positive if at least one of 29 *EGFR* mutations was detected. Throughout the study, patients remained blinded to their mutation status.

Health-Related-Quality-of-Life and Symptom Improvement Analyses

HRQoL and symptom improvement were assessed using the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire.[10] The FACT-L comprises five domains: four evaluating physical, social-familial, emotional, and functional well-being, and one evaluating HRQoL aspects specifically related to lung cancer (the Lung Cancer Subscale [LCS]). HRQoL changes were assessed from the FACT-L total score (the sum of all five domains) and the Trial Outcome Index (TOI; the sum of the physical, functional well-being, and LCS domains). Symptom improvement was measured using the LCS domain of the FACT-L.

Patients completed the FACT-L questionnaire at baseline, at weeks 1 and 3, 3-weekly until week 18, 6-weekly until progression, and at treatment discontinuation. At each visit, an overall response was calculated for FACT-L, TOI, and LCS scores based on the changes from baseline.[11] In addition, the best overall response over the course of the assessments (and improvement rate) was calculated for FACT-L, TOI, and LCS scores ("improved," "no change," "worsened," or "other"). A clinically relevant improvement was defined as an increase from baseline of 6 or more points for FACT-L and TOI, and 2 or more points for LCS, maintained for 21 or more days. Clinically relevant worsening was defined as a decrease from baseline of 6 or more points for FACT-L and TOI, and 2 or more points for LCS, maintained for 21 or more days.

Time-to-Worsening

Time-to-worsening of FACT-L, TOI, and LCS was a supplementary evaluation in all patients and was defined as the interval from randomization to the first visit of "worsened," maintained for 21 or more days, or to the date of death, if the death was no more than 12 weeks after the last HRQoL assessment. Patients not experiencing either of these events were included in the analysis and censored at their last evaluable HRQoL assessment.

Mean Change from Baseline

Mean change from baseline in FACT-L, TOI, and LCS scores was calculated for each week that HRQoL was assessed.

Time-to-Improvement

Time-to-improvement was calculated for patients with *EGFR* mutation-positive tumors who improved (i.e., an increase from baseline of 6 or more points for FACT-L and TOI, or 2 or more points for LCS, maintained for at least 21 days). Time-to-improvement was calculated only for patients treated with gefitinib; between-treatment comparisons were considered inappropriate because whether a patient improved was affected by the randomized treatment they received. Therefore, any such comparisons would be nonrandomized and based on a postbaseline outcome (improvement), leading to potential biased analyses.

Compliance and Missing Data

The compliance rate for completion of the FACT-L questionnaire was defined as the number of evaluable forms divided by the number of expected forms (one from each questionnaire timepoint). A form was considered evaluable if all five subscale scores could be determined. For missing scores, if less than 50% of the FACT-L subscale scores were missing, the subscale score was divided by the number of completed items and multiplied by the total number of items on the subscale. If 50% or more of the items were missing, that subscale was treated as missing for that patient.

Survival Without CTC Grade 3 or 4 Toxicity

Analysis (preplanned in the overall population; posthoc by *EGFR* mutation status) of survival without Common Terminology Criteria (CTC) grade 3 or 4 toxicity (due to treatment, underlying disease, or comorbid conditions) was performed to help assess overall HRQoL.

Statistical Analyses

HRQoL and symptom data were assessed in the evaluable-for-health-related-quality-of-life (EFQ) population (patients with an evaluable baseline HRQoL assessment and at least one evaluable postbaseline HRQoL assessment). The changes from baseline for FACT-L total score, TOI, and LCS were summarized by randomized treatment group, for each week that HRQoL was assessed where 20 or more patients had available data. Mean change from baseline and 95% CIs were calculated. The primary HRQoL analysis was improvement rate and this was calculated for each randomized treatment group as a percentage of the total number of patients who had a best overall response of "improved." Improvement rates were compared between treatments using logistic regression, accounting for the effect of randomized treatment and the same covariates as used in the primary PFS analysis (World Health Organization performance status [WHO PS] (0, 1, versus 2), smoking history [never versus light former smoker], and gender [female versus male]). The OR (gefitinib:carboplatin/paclitaxel) was estimated along with 95% CIs and p values. Time-to-worsening was presented by treatment with median values and 95% CIs and by Kaplan-Meier plots.

For posthoc *EGFR* mutation analyses, patients were classified as positive, negative, or unknown. For each of these subgroups, ORs, 95% CIs, and p values were estimated for improvement rates (using logistic regression, accounting for the same covariates as above). Time-to-worsening was presented by mutation subgroup by treatment, with median values and associated 95% CIs and by Kaplan-Meier plots. Time-to-improvement (days) was calculated by *EGFR* mutation status for patients treated with gefitinib who improved and was presented with median, minimum, and maximum values.

Preplanned analysis of survival without grade 3 or 4 toxicity was carried out on the evaluable-for-safety (EFS) population (patients who received at least one dose of study medication). The time to an event was calculated from the date of the first dose to the earliest date of the following: (1) CTC grade 3 or 4 adverse event (as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0), (2) a worsening from baseline in any laboratory parameter to a CTC grade 3 or 4 toxicity, or (3) death. The analysis included all deaths regardless of when they occurred. Patients who did not experience any of the above types of events were censored at the last date they were known to be alive. Data were analyzed using a Cox proportional hazards model accounting for the effect of randomized treatment and the same covariates used in the primary PFS analysis. HRs, 95% CIs, and p values were estimated. The median survival time without CTC grade 3 or 4 toxicity was presented for each treatment group.

RESULTS

Patients

Of the 1217 patients randomized, 1151 had evaluable HRQoL data (EFQ; gefitinib, $n = 590$; carboplatin/paclitaxel, $n = 561$) (Figure 1). Of these, 428 patients (37.2% of EFQ; 35.2% of intent-to-treat [ITT]) had tumors of known *EGFR* mutation status (*EGFR* mutation-positive $n = 259$, *EGFR* mutation-negative [mutation not detected] $n = 169$), and *EGFR* mutation status was unknown in 723 (62.8% of EFQ; 59.4% of ITT; no consent provided, no sample provided, or sample unsuitable for analysis).

Key demographic and baseline characteristics for the EFQ population were comparable with the ITT study population (Table 1). Overall compliance rates for FACT-L questionnaire completion were 93.6% (gefitinib) and 85.3% (carboplatin/paclitaxel), with similar rates for patients with *EGFR* mutation-positive (94.8% and 89.5%, respectively) and mutation-negative (92.0% and 86.9%, respectively) tumors.

Overall Population

Best overall response by randomized treatment for FACT-L total score, TOI, and LCS in the EFQ population is shown in Supplemental Digital Content Table 1 (http://links.lww.com/JTO/A125). The rates of improvement in FACT-L total score, TOI, and LCS for the overall population were published previously and showed that significantly more patients experienced improvements with gefitinib versus carboplatin/paclitaxel in FACT-L total score (48.0% versus 40.8%; OR, 1.34; 95% CI, 1.06–1.69; $p = 0.02$) and TOI (46.4% versus 32.8%; OR, 1.78; 95% CI, 1.40–2.26; $p < 0.001$) (Supplemental Figure 1*A*). LCS improvement rates were similar for both treatments (51.5% versus 48.5%; OR, 1.13; 95% CI, 0.90–1.42; $p = 0.30$) (Supplemental Figure 1*A*).[7]

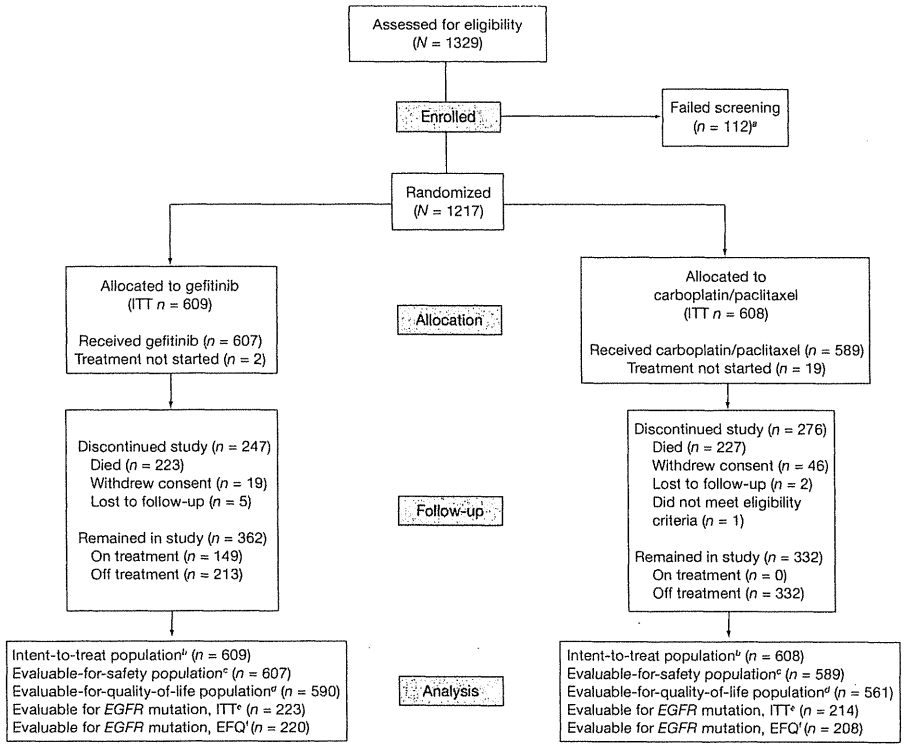

FIGURE 1. CONSORT diagram. [a]Among the 112 patients who failed screening, the main reasons for exclusion were abnormal serum creatinine (>1.5 times upper limit of reference range)/creatinine clearance (≤60 mL/min) levels; untreated central nervous system metastases; or low neutrophil ($<2.0 \times 10^9$/L), platelet ($<100 \times 10^9$/L), or hemoglobin (<10 g/dL) counts. [b]All patients who were randomly assigned to a study group were included in the ITT analysis. [c]All patients who received at least one dose of study treatment were included in the safety analysis. [d]All patients with a baseline and at least one postbaseline quality-of-life assessment that could be evaluated were included in the health-related quality-of-life analysis. [e]All patients in the intent-to-treat population with an evaluable tumor sample. Of 683 (56%) patients who provided samples, 118 were cytology samples, and 128 histologic samples were of insufficient quality, and were therefore not included in the main analysis. [f]All patients in the evaluable-for-quality-of-life population with an evaluable tumor sample. ITT, intent-to-treat; EFQ, evaluable-for-quality-of-life; *EGFR*, epidermal growth factor receptor; *n*, number of patients.

Time-to-worsening for the overall population was substantially longer with gefitinib than with carboplatin/paclitaxel for FACT-L total score (median 8.3 versus 2.5 months), TOI (median 9.7 versus 2.8 months), and LCS (median 7.1 versus 3.1 months) (Supplemental Digital Content Figures 2*A*, *C*, and *E*).

Mean changes from baseline for FACT-L total score, TOI, and LCS for the overall population are shown in Supplemental Digital Content Figures 3*A*, *C*, and *E* (http://links.lww.com/JTO/A126). Clinically meaningful improvements in FACT-L total score (≥6 points) and TOI (≥6 points) were seen with gefitinib. Mean change from baseline for LCS was similar for both treatments.

Survival without CTC grade 3 or 4 toxicity for the overall population was significantly longer with gefitinib than carboplatin/paclitaxel (HR, 0.34; 95% CI, 0.29–0.38; $p < 0.001$) (Supplemental Digital Content Figure 4*A*, http://links.lww.com/JTO/A127). The median survival without CTC grade 3 or 4 toxicity was 10.8 months with gefitinib and 0.5 months with carboplatin/paclitaxel.

Patients with EGFR Mutation-Positive Tumors (Posthoc Calculations)

The rates of improvement in FACT-L total score, TOI, and LCS for patients with *EGFR* mutation-positive tumors were published previously and significantly favored gefitinib over carboplatin/paclitaxel (FACT-L total score 70.2% versus 44.5%; OR, 3.01; 95% CI, 1.79–5.07; $p < 0.001$; TOI 70.2% versus 38.3%; OR, 3.96; 95% CI, 2.33–6.71; $p < 0.001$; LCS 75.6% versus 53.9%; OR, 2.70; 95% CI, 1.58–4.62; $p < 0.001$) (Figure 2*A*).[7]

Time-to-worsening was substantially longer with gefitinib than with carboplatin/paclitaxel for patients with *EGFR* mutation-positive tumors for FACT-L total score (median, 15.6 versus 3.0 months), TOI (median, 16.6 versus 2.9 months), and LCS (median, 11.3 versus 2.9 months) (Figures 3*A*, *C*, *E*).

There were clinically meaningful improvements in mean change from baseline with gefitinib in patients with *EGFR* mutation-positive tumors as early as week 1 in FACT-L total score (≥6 points) and week 3 in TOI (≥6

TABLE 1. Key Demographic and Baseline Characteristics (EFQ and ITT Populations)

	EFQ Population (n = 1151)		ITT Population (n = 1217)	
	Gefitinib (n = 590)	Carboplatin/Paclitaxel (n = 561)	Gefitinib (n = 609)	Carboplatin/Paclitaxel (n = 608)
Sex, n (%)				
Male	123 (20.8)	121 (21.6)	125 (20.5)	127 (20.9)
Female	467 (79.2)	440 (78.4)	484 (79.5)	481 (79.1)
Age, n (%)				
<65 yr	432 (73.2)	415 (74.0)	447 (73.4)	452 (74.3)
≥65 yr	158 (26.8)	146 (26.0)	162 (26.6)	156 (25.7)
WHO performance status, n (%)				
0, 1	535 (90.7)	508 (90.6)	548 (90.0)	543 (89.3)
2	55 (9.3)	53 (9.4)	61 (10.0)	65 (10.7)
Smoking history, n (%)				
Never smoker	553 (93.7)	524 (93.4)	571 (93.8)	569 (93.6)
Former smoker	37 (6.3)	37 (6.6)	38 (6.2)	39 (6.4)
Disease stage at screening,[a] n (%)				
Locally advanced	145 (24.6)	133 (23.7)	150 (24.6)	144 (23.7)
Metastatic	445 (75.4)	427 (76.1)	459 (75.4)	463 (76.2)

[a] One patient in the ITT and EFQ populations had unknown disease stage at screening.
EFQ, evaluable-for-health-related-quality-of-life; ITT, intent-to-treat; n, number of patients; WHO, World Health Organization.

points) and LCS (≥2 points) (Figures 4*A*, *C*, *E*). A clinically meaningful decrease was seen in FACT-L total score (≤−6 points) and TOI (≤−6 points) with carboplatin/paclitaxel at week 1 (not apparent at week 3), with no further improvement seen after week 3 (Figures 4*A*, *C*). There was no clinically meaningful change from baseline with carboplatin/paclitaxel in LCS (≤+/−2) for *EGFR* mutation-positive patients (Figure 4*E*).

For patients with *EGFR* mutation-positive tumors in the gefitinib arm who improved, median time-to-improvement was 8 days for FACT-L total score and LCS and 11 days for TOI (Table 2). Survival without CTC grade 3 or 4 toxicity for patients with *EGFR* mutation-positive tumors was significantly longer with gefitinib than carboplatin/paclitaxel (HR, 0.29; 95% CI, 0.21–0.39; $p < 0.001$) (Supplemental Digital Content Figure 4*B*). The median survival without CTC grade 3 or 4 toxicity was 12.1 months with gefitinib and 0.5 months with carboplatin/paclitaxel.

Patients with EGFR Mutation-Negative Tumors (Posthoc Calculations)

The rates of improvement in FACT-L total score, TOI, and LCS for patients with *EGFR* mutation-negative tumors were published previously and significantly favored carboplatin/paclitaxel over gefitinib (FACT-L: total score 36.3% versus 14.6%; OR, 0.31; 95% CI, 0.15–0.65; $p = 0.002$; TOI: 28.8% versus 12.4%; OR, 0.35; 95% CI, 0.16–0.79; $p = 0.011$; LCS: 47.5% versus 20.2%; OR, 0.28; 95% CI, 0.14–0.55; $p < 0.001$) (Figure 2*B*).[7]

Time-to-worsening with gefitinib was similar to carboplatin/paclitaxel for patients with *EGFR* mutation-negative tumors for FACT-L total score (median, 1.4 months both treatments) (Figure 3*B*). Time-to-worsening favored carboplatin/paclitaxel over gefitinib for TOI (median, 2.8 versus 1.4 months) and LCS (median, 4.2 versus 1.4 months) (Figures 3*D*, *F*).

There were clinically meaningful decreases in mean change from baseline with gefitinib in patients with *EGFR* mutation-negative tumors for FACT-L (≤−6 points), TOI (≤−6 points), and LCS (≤−2 points) (Figures 4*B*, *D*, *F*); there was no clinically meaningful mean change from baseline in FACT-L, TOI, or LCS with carboplatin/paclitaxel (Figures 4*B*, *D*, *F*).

Time-to-improvement with gefitinib was not calculated for patients with *EGFR* mutation-negative tumors as few patients in this subgroup experienced a meaningful improvement. Although improvement in survival without CTC grade 3 to 4 toxicity was observed for patients with *EGFR* mutation-negative tumors treated with gefitinib compared with carboplatin/paclitaxel, in the context of reduced efficacy that analysis becomes not meaningful and is therefore not presented.

Patients with EGFR Mutation-Unknown Tumors (Posthoc Calculations)

The rates of improvement in FACT-L total score, TOI, and LCS (Supplemental Digital Content Figure 1*B*), time to worsening in FACT-L total score, TOI, and LCS (Supplemental Digital Content Figures 2*B*, *D*, and *F*), change from baseline in FACT-L total score, TOI, and LCS (Supplemental Digital Content Figures 3*B*, *D*, and *F*), and survival without CTC grade 3 or 4 toxicity (Supplemental Digital Content Figure 4*C*) for patients with tumors of unknown *EGFR* mutation status are presented as Supplemental Digital Content.

DISCUSSION

HRQoL and symptom improvement are consistent with PFS and ORR outcomes previously reported in IPASS.[7] Significantly more patients in the gefitinib group recorded improve-

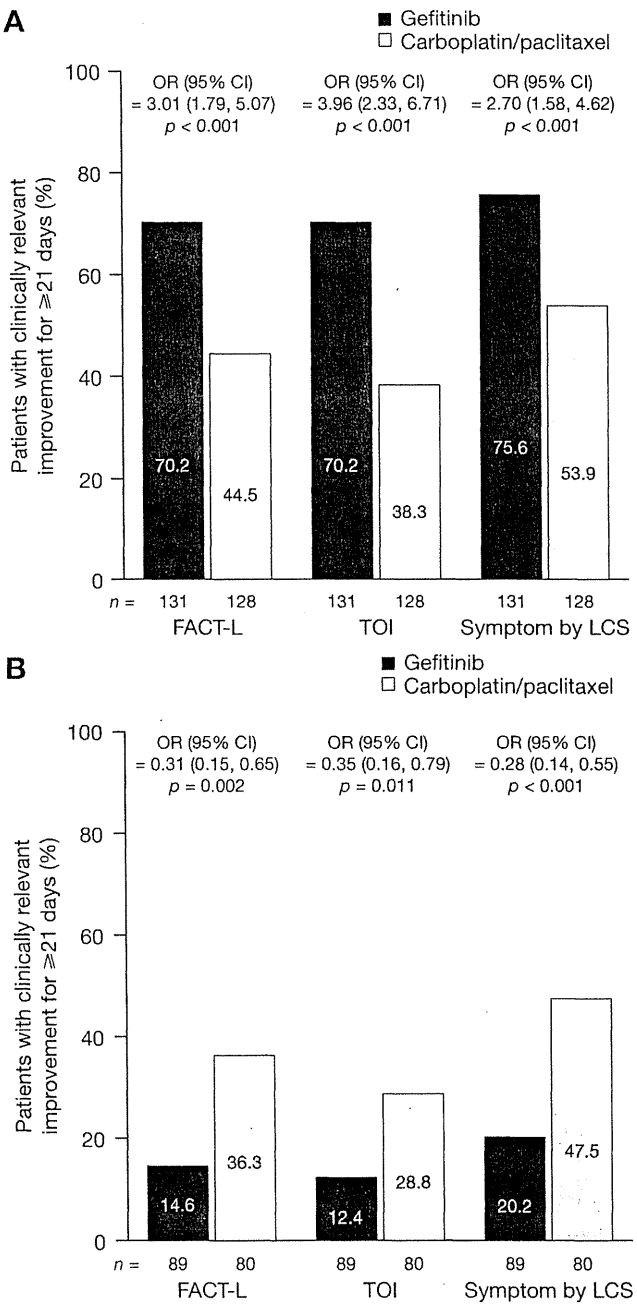

FIGURE 2. HRQoL and symptom improvement for FACT-L, TOI, and LCS for (*A*) patients with *EGFR* mutation-positive tumors and (*B*) patients with *EGFR* mutation-negative tumors (EFQ population). Posthoc analyses. HRQoL, health-related quality-of-life; FACT-L, Functional Assessment of Cancer Therapy-Lung; *EGFR*, epidermal growth factor receptor; TOI, Trial Outcome Index; LCS, Lung Cancer Subscale; EFQ, evaluable-for-quality-of-life; CI, confidence interval; OR, odds ratio.

ments in HRQoL compared with the carboplatin/paclitaxel group, with marked differences in the *EGFR* mutation-positive (favoring gefitinib) and mutation-negative (favoring carboplatin/paclitaxel) subgroups. Symptom improvement rates were similar for both treatments overall but were significantly higher with gefitinib in the *EGFR* mutation-positive subgroup and with carboplatin/paclitaxel in the *EGFR* mutation-negative subgroup. For *EGFR* mutation-positive patients who improved on gefitinib, median time-to-improvement in HRQoL was 8 days (FACT-L). These data, in conjunction with the previously reported PFS and ORR outcomes, indicate that patients with *EGFR* mutation-positive tumors will benefit most from first-line gefitinib therapy and highlight the importance of personalized medicine in advanced NSCLC. Survival without CTC grade 3 or 4 toxicity was significantly longer with gefitinib in the overall population (consistent with FACT-L and TOI HRQoL analyses) and in the *EGFR* mutation-positive subgroup. The higher incidence of toxicity in the chemotherapy group was consistent with the inclusion of worsening of neutropenia (laboratory measurement) to CTC grade 3 or 4 as part of the elements contributing to this variable.

Studies in patients with NSCLC have supported the hypothesis that tumor response and symptom improvement to treatment are related.[12–15] The IDEAL I study reported an improvement in disease-related symptoms in most patients whose tumors responded to gefitinib 250 mg,[14] with 70% of those with stable disease also reporting symptom improvement (versus 12% of patients with a best overall response of progression).[14] In the IDEAL II study, symptoms improved in 43% of patients treated with gefitinib 250 mg and improved in all patients with partial responses.[15] In addition, Cella et al.[3] report that the association of symptom improvement with partial response, PFS and survival seen in the IDEAL II study suggests that HRQoL and symptom improvement scores may provide early preradiological indications of a patient's disease status. In IPASS, early and sustained improvements in HRQoL were seen in patients with *EGFR* mutation-positive tumors treated with gefitinib. A significantly prolonged PFS and higher ORR was also seen in the gefitinib arm of the study when compared with patients treated with carboplatin/paclitaxel.

The HRQoL improvement results from previous randomized phase II and III studies in the pretreated setting of gefitinib versus chemotherapy favored gefitinib.[16–18] In the phase II SIGN study, symptom improvement rates were 36.8% with gefitinib (n = 68) and 26.0% with docetaxel (n = 71).[16] HRQoL improvement rates for FACT-L were 33.8% and 26.0% with gefitinib and docetaxel, respectively. The phase III INTEREST study reported significantly more patients with a sustained and clinically relevant improvement in HRQoL with gefitinib (n = 490) than docetaxel (n = 476), as assessed by FACT-L (25.1% versus 14.7%; OR, 1.99; 95% CI, 1.42–2.79; $p < 0.001$) and TOI (17.3% versus 10.3%; OR, 1.82; 95% CI, 1.23–2.69; $p = 0.003$).[17] Similar proportions of patients had improvements in symptoms (LCS 20.4% versus 16.8%; OR, 1.29; 95% CI, 0.93–1.79; $p = 0.133$). Similarly, in the phase III V-15-32 study, significantly more patients experienced a clinically relevant improvement in HRQoL with gefitinib (n = 185) versus docetaxel (n = 173): FACT-L 23% versus 14%; OR, 1.89; 95% CI, 1.09–3.28; $p = 0.023$; TOI 21% versus 9%; OR, 2.72; 95% CI, 1.44–

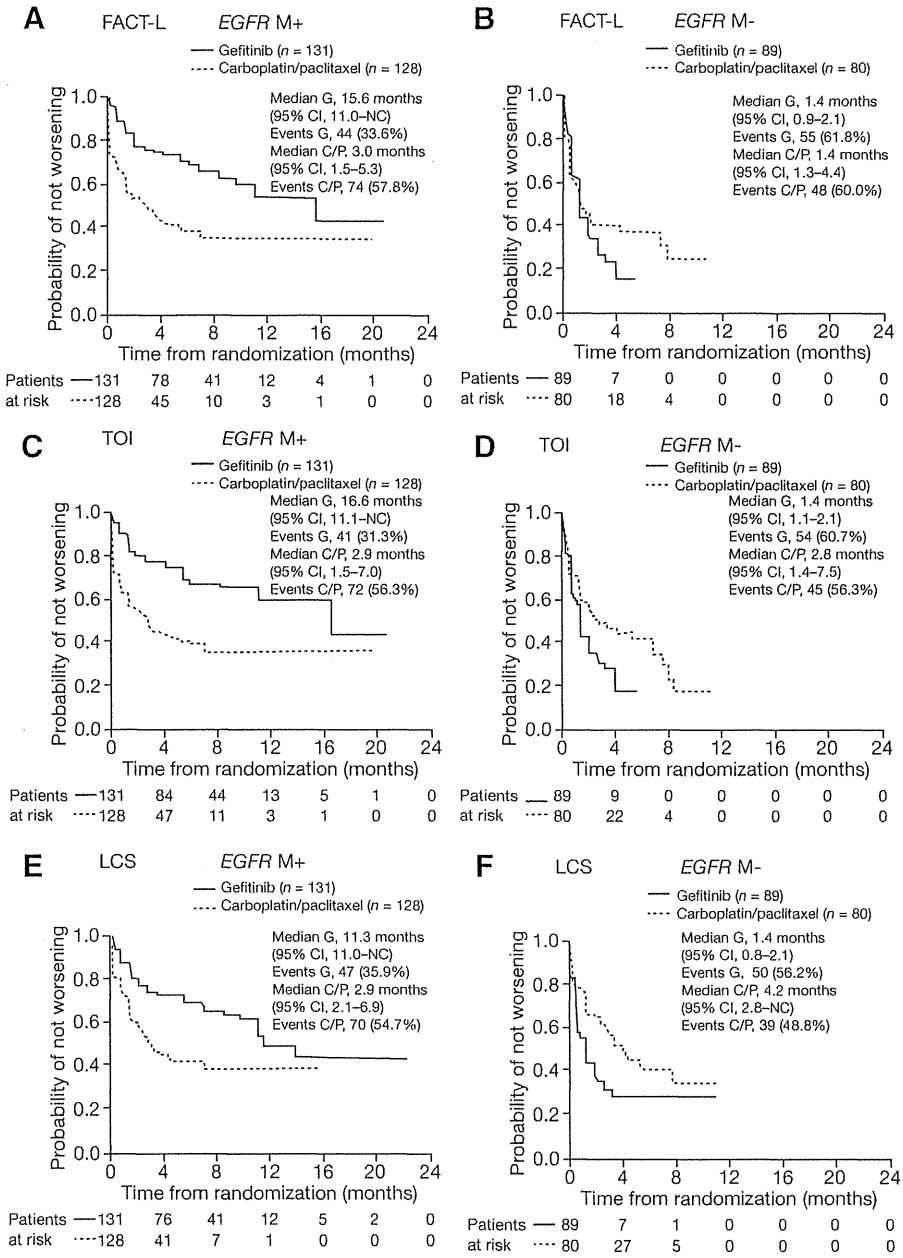

FIGURE 3. Time-to-worsening in HRQoL and symptoms for (*A*) FACT-L in patients with *EGFR* mutation-positive tumors, (*B*) FACT-L in patients with *EGFR* mutation-negative tumors, (*C*) TOI in patients with *EGFR* mutation-positive tumors, (*D*) TOI in patients with *EGFR* mutation-negative tumors, (*E*) LCS in patients with *EGFR* mutation-positive tumors, and (*F*) LCS in patients with *EGFR* mutation-negative tumors (EFQ population). Posthoc calculations. HRQoL, health-related quality-of-life; FACT-L, Functional Assessment of Cancer Therapy-Lung; *EGFR*, epidermal growth factor receptor; TOI, Trial Outcome Index; LCS, Lung Cancer Subscale; EFQ, evaluable-for-quality-of-life; M+, mutation-positive; *n*, number of patients; G, gefitinib; CI, confidence interval; NC, not calculated; C/P, carboplatin/paclitaxel; M−, mutation negative.

5.16; $p = 0.002$.[18] There was no significant difference between treatments in terms of symptom improvement rates (LCS 23% versus 20%; OR, 1.15; 95% CI, 0.72–1.81; $p = 0.562$). Consistent with the overall IPASS population, HRQoL and symptom improvement rates favored gefitinib over vinorelbine in the phase II, first-line, comparative INVITE study.[19] INVITE showed higher rates of improvement in HRQoL with gefitinib ($n = 70$) versus vinorelbine ($n = 64$) in elderly patients (FACT-L 24.3% versus 10.9%; OR, 2.97; 95% CI, 1.06–8.34; TOI 22.9% versus 6.3%; OR, 5.47; 95% CI, 1.61–18.56),[19] whereas symptom improvement rates were similar for both treatments (LCS 42.9% versus 39.1%; OR, 1.19; 95% CI, 0.57–2.48). The randomized, first-line, phase III First-SIGNAL study compared gefitinib ($n = 159$) with gemcitabine/cisplatin ($n = 150$) and reported better HRQoL with gefitinib compared with chemotherapy (global health status $p = 0.0007$; role function $p = 0.007$; social function $p = 0.002$).[20] Recently, the randomized, first-line, phase III NEJ002 study in patients with *EGFR* mutation-positive tumors, reported that in 148 patients, HRQoL was preserved much longer for those treated with gefitinib than those treated with carboplatin/paclitaxel.[21]

The significant improvement rates in HRQoL and symptoms reported in IPASS in patients with *EGFR* mutation-positive tumors treated with gefitinib have important clinical implications for the optimal management of patients