BRIEF REPORT

Randomized Phase III Trial of Erlotinib versus Docetaxel in Patients with Advanced Squamous Cell Non–Small Cell Lung Cancer Failing First-Line Platinum-Based Doublet Chemotherapy Stratified by VeriStrat Good versus VeriStrat Poor. The European Thoracic Oncology Platform (ETOP) EMPHASIS-lung Trial

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ABSTRACT

Introduction: Docetaxel and erlotinib are registered second-line treatments for wild-type *EGFR* NSCLC. Previous studies suggested a predictive value of the VeriStrat test in second-line therapy of NSCLC, classifying patients as either VeriStrat good or VeriStrat poor. EMPHASIS-lung aimed at exploring this predictive effect in patients with squamous cell NSCLC. The trial closed prematurely because of low accrual and results from other trials. Our analysis includes an exploratory combined analysis with results from the PROSE trial.

Methods: EMPHASIS-lung was a randomized phase III multicenter trial exploring the differential effect of second-line erlotinib versus docetaxel on progression-free survival (PFS) in VeriStrat good versus VeriStrat poor patients with squamous cell NSCLC.

Results: A total of 80 patients were randomized, with 72.5% categorized as VeriStrat good. Patient characteristics were balanced between VeriStrat status and treatment groups. The median PFS times with docetaxel and erlotinib treatment in the VeriStrat good cohort were 4.1 and 1.6 months, respectively, versus 1.9 and 2.1 months, respectively, in the VeriStrat poor cohort. The median overall survival (OS) times with docetaxel and erlotinib treatment in the VeriStrat good cohort were 7.8 and 8.4 months, respectively, and 4.4 and 5.2 months, respectively, in the VeriStrat poor cohort. An additional exploratory analysis was performed; in it, 47 patients from the squamous cell subgroup of PROSE were included in a combined analysis, contributing with 45 PFS and 41 OS events.

Conclusions: The final analysis of EMPHASIS-lung did not show a differential effect on PFS for erlotinib versus docetaxel stratified by VeriStrat status. Similarly, in the combined analysis, no significant treatment by VeriStrat status interaction was observed (interaction $p = 0.24$ for PFS and 0.45 for OS, stratified by study).

Keywords: NSCLC; Squamous; Erlotinib; Docetaxel; ETOP; VeriStrat

Introduction

NSCLC accounts for 80% to 85% of lung cancers. The prevalence of the squamous cell histological subtype accounts for 25% to 30% of NSCLC.[1,2] Although the molecular characterization of lung tumors has revolutionized the treatment strategies for oncogene-addicted nonsquamous cell NSCLC, an unmet need exists for effective treatment of patients with squamous cell NSCLC, especially in the second- and third-line settings.

Single-agent chemotherapy can improve disease-related symptoms and survival.[3–5] Docetaxel and erlotinib are comparable and registered as second-line treatment options for squamous cell NSCLC. Erlotinib was shown to improve overall survival (OS) as second-line or third-line therapy in unselected NSCLC, whereas gefitinib and docetaxel demonstrated equivalent activity in terms of progression-free survival (PFS) and OS.[3,6]

In refractory patients, erlotinib was shown to be equivalent to docetaxel and both compounds demonstrated equivalence in patients with *EGFR* wild-type NSCLC with respect to OS, with modest improvement of PFS for docetaxel.[7,8] This is in good agreement with the findings for erlotinib as second- or third-line therapy, in which superior PFS but not OS for docetaxel was demonstrated.[9] In advanced-stage squamous cell NSCLC progressing after chemotherapy, afatinib demonstrated a modest benefit in terms of PFS and OS compared with erlotinib.[10]

Recently, the programmed cell death 1–targeting immune checkpoints inhibitors nivolumab and pembrolizumab have been shown to result in prolonged OS as compared with docetaxel in the second- or third-line setting,[11,12] and where available, these agents are more and more replacing docetaxel or erlotinib as second-line therapies.

The clinically validated serum proteomic test VeriStrat (Biodesix, Boulder, CO) is used to classify patients as either VeriStrat good or VeriStrat poor by using the intensity of eight mass-to-charge ratio features in the mass spectra obtained from pretreatment serum samples.[13] Retrospective studies showed that VeriStrat good patients have significantly better outcomes than VeriStrat poor patients when treated with EGFR tyrosine kinase inhibitors (TKIs).[14–18] In the randomized phase III study PROSE, 285 patients with stage IIIB or IV NSCLC after first-line therapy were randomly assigned to either chemotherapy or erlotinib. Patients were stratified on the basis of VeriStrat status.[19] A significant interaction between treatment and proteomic classification was documented in this trial, with VeriStrat poor patients having worse OS when receiving erlotinib than when receiving chemotherapy, whereas for VeriStrat good patients no significant difference in OS between treatments was detected.

The EMPHASIS-lung trial aimed to explore the predictive value of VeriStrat with respect to PFS in patients with squamous cell NSCLC treated with erlotinib versus treated with docetaxel. The trial was closed prematurely on account of low accrual and release of the results from the PROSE and TAILOR trials.[20]

Here we present the final results regarding PFS and OS for the EMPHASIS-lung trial as well as for an exploratory combined analysis that included the squamous cell NSCLC cohort of the PROSE trial.

Methods

Study Design, Key Eligibility Criteria, and Trial Treatment

This clinical trial was a randomized, open label phase III trial exploring the differential effect of erlotinib versus docetaxel on PFS in VeriStrat good versus VeriStrat poor patients.

The eligibility criteria comprised stage IIIB squamous cell NSCLC not amenable to radical radiotherapy or metastatic stage IV disease (according to the seventh TNM classification); documented progressive disease during or after a previous line of chemotherapy (including platinum-doublet therapy); an Eastern Cooperative Oncology Group performance status of 0 to 2; and adequate hematological, hepatic, and renal function. Patients with activating *EGFR* mutation and patients previously exposed to EGFR TKIs or docetaxel were excluded. Written informed consent was obtained from all patients.

Patients were randomized 1:1 to receive either erlotinib, 150 mg/d orally, or docetaxel, 75 mg/m^2 intravenously, on day 1 of every 21-day cycle. Serum samples were collected from each patient for further VeriStrat testing in the central laboratory at Biodesix. The investigative sites and personnel were blinded to the result of the VeriStrat test, which was used only for randomization. Tumor response or disease progression was assessed with thorax-abdomen computed tomography scans at 6-week intervals according to the Response Evaluation Criteria in Solid Tumors.

Block-stratified randomization balanced by center using a minimization algorithm[21] was used, with the stratification factors VeriStrat status (VeriStrat good versus VeriStrat poor) and performance status (0–1 versus 2). The protocol was approved by institutional review boards at each site, and the trial was conducted in accordance with the Declaration of Helsinki, the Guideline for Good Clinical Practice, and the International Conference on Harmonization Tripartite Guideline. Safety was reviewed by the European Thoracic Oncology Platform independent data monitoring committee.

Statistical Analysis

The primary end point was PFS, defined as the time from randomization until documented progression or death if occurring without documented progression for all randomized patients (the intent-to-treat population).

The statistical design was based on an expected hazard ratio (HR) of erlotinib versus docetaxel of 0.675 for the VeriStrat good patients (median PFS of 4.0 months with erlotinib and 2.7 months with docetaxel), and 1.23 for the VeriStrat poor patients (median PFS of 2.2 months with erlotinib and 2.7 months with docetaxel). A sample size of 500 was needed to achieve 86% power for testing the expected interaction HR of 1.82 at the 0.05 two-sided significance level.

Baseline characteristics were compared between treatments and VeriStrat groups by Fisher's exact test (categorical variables) and the Mann-Whitney test (continuous variables). The log-rank test was used to detect differences in PFS and OS between the treatment arms within each VeriStrat population (Veristrat

stratified log-rank was used in the total population). The impact of treatment and VeriStrat status and their interaction on PFS and OS was explored through appropriate Cox proportional hazards models adjusted for variables of clinical interest (sex, age, performance status, and smoking status).

A stochastic curtailment approach was applied to estimate the conditional power at the end of the study if it were to be continued to completion. In addition, a combined analysis of the EMPHASIS-lung data with data for the squamous cell cohort of the PROSE trial was included.

All analyses were performed with the SAS 9.3 statistical package (SAS Institute Inc., Cary, NC), and R software (R Foundation for Statistical Computing, Vienna, Austria) was used for the stochastic curtailment simulations.

PROSE Squamous Cell Cohort

The primary end point in the PROSE trial was OS, with PFS as a secondary end point. Patients were randomized to receive either erlotinib (150 mg orally daily) or chemotherapy (up to six cycles of docetaxel, 75 mg/m^2 intravenously) and stratified by VeriStrat status, performance status, smoking, and center. Tumor response or disease progression was assessed with thorax-abdomen computed tomography scans at 8-week intervals according to the Response Evaluation Criteria in Solid Tumors. The squamous cell cohort of the PROSE trial population was used as a subgroup in the combined analysis.

Combined EMPHASIS-lung and PROSE Squamous Cell Cohort Analysis

The evaluation of the combined cohort (EMPHASIS-lung patients and squamous cell cohort of the PROSE trial) was stratified by trial, with OS as the primary efficacy measure. The baseline characteristics were compared and the data were combined through the appropriate multivariate Cox proportional hazards model for OS, with variables of clinical interest and the data source used as possible covariates.

Results

Study Cohorts

Two trial cohorts were analyzed: the EMPHASIS-lung cohort of 80 patients randomized from January 2013 and January 2014 (CONSORT diagram in Fig. 1) and the PROSE cohort comprising 47 patients with the squamous cell histological subtype (randomized from 2008–2012). A combined data set was used for outcome evaluation.

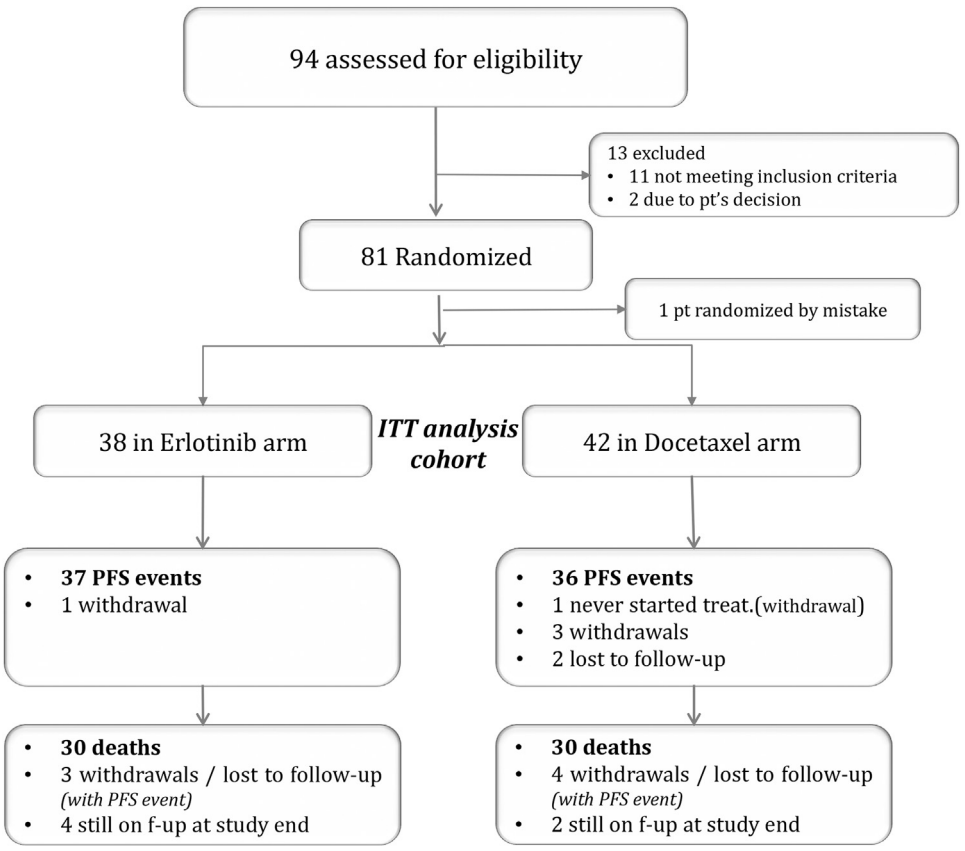

Figure 1. CONSORT diagram of the EMPHASIS trial. pt, patient; ITT, intent-to-treat; PFS; progression-free survival; f-up, follow-up.

Table 1. Patient Baseline Characteristics

	EMPHASIS-lung Cohort							PROSE Cohort			
	Treatment Arm			VeriStrat Status				VeriStrat Status			
	Erlotinib (n = 38)	Docetaxel (n = 42)	*p* Value	VeriStrat Good (n = 58)	VeriStrat Poor (n = 22)	*p* Value	All Patients (N = 80)	VeriStrat Good (n = 29)	VeriStrat Poor (n = 18)	*p* Value	All Patients (N = 47)
Categorical Characteristics								**Categorical Characteristics**			
Sex, n (%)											
Male	31 (81.6)	35 (83.3)	>0.99[a]	46 (79.3)	20 (90.9)	0.33	66 (82.5)	21 (72.4)	17 (94.4)	0.12[a]	38 (80.9)
Female	7 (18.4)	7 (16.7)		12 (20.7)	2 (9.1)		14 (17.5)	8 (27.6)	1 (5.6)		9 (19.1)
Smoking history, n (%)											
Current	16 (42.1)	12 (28.6)	0.41[a]	22 (37.9)	6 (27.3)	0.76[a]	28 (35.0)	6 (20.7)	11 (61.1)	0.013[a]	17 (36.2)
Former (>100 cigs and >12 mo smoke-free)	20 (52.6)	28 (66.7)		33 (56.9)	15 (68.2)		48 (60.0)	21 (72.4)	7 (38.9)		28 (59.6)
Never	2 (5.3)	2 (4.8)		3 (5.2)	1 (4.5)		4 (5.0)	2 (6.9)	0 (0.0)		2 (4.3)
ECOG performance status, n (%)											
0	12 (31.6)	15 (35.7)	0.52[a]	16 (27.6)	11 (50.0)	0.12[a]	27 (33.8)	19 (65.5)	7 (38.9)	0.17[a]	26 (55.3)
1	24 (63.2)	22 (52.4)		37 (63.8)	9 (40.9)		46 (57.5)	8 (27.6)	9 (50.0)		17 (36.2)
2	2 (5.3)	5 (11.9)		5 (8.6)	2 (9.1)		7 (8.8)	2 (6.9)	2 (11.1)		4 (8.5)
VeriStrat status, n (%)											
Good	28 (73.7)	30 (71.4)	>0.99[a]				58 (72.5)				
Poor	10 (26.3)	12 (28.6)					22 (27.5)				
Continuous characteristic								**Continuous characteristic**			
Age, y											
Mean (95% CI)	66.3 (63.5-69.2)	69.7 (67.3-72.1)	0.065[b]	69.3 (67.4-71.3)	64.9 (60.4-69.3)	0.11[b]	68.1 (66.3-70.0)	68.1 (65.2-70.9)	69.1 (65.0-73.2)	0.51[b]	68.5 (66.2-70.7)
Median (Min-Max)	66.7 (44.4-81.9)	70.1 (53.3-84.0)		69 (56.1-84.0)	65.3 (44.4-81.9)		68.7 (44.4-84.0)	67 (50.0-84.0)	68 (53.0-84.0)		68 (50.0-84.0)

[a]Fisher's exact test.
[b]Mann-Whitney test.
cig, cigarette; ECOG, Eastern Cooperative Oncology Group; CI, confidence interval; Min-Max, minimum-maximum.

Table 2. Patient baseline characteristics by treatment and VeriStrat group for the EMPHASIS-lung Cohort

	VeriStrat Good (n = 58)			VeriStrat Poor (n = 22)		
	Treatment Arm			Treatment Arm		
	Erlotinib (n = 28)	Docetaxel (n = 30)	*p* Value	Erlotinib (n = 10)	Docetaxel (n = 12)	*p* Value
Categorical Characteristics				Categorical Characteristics		
Sex, n (%)						
Male	22 (78.6)	24 (80.0)	>0.99[a]	9 (90.0)	11 (91.7)	>0.99[a]
Female	6 (21.4)	6 (20.0)		1 (10.0)	1 (8.3)	
Smoking history, n (%)						
Current	12 (42.9)	10 (33.3)	0.55[a]	4 (40.0)	2 (16.7)	0.35[a]
Former (>100 cigs and >12 mo smoke-free)	14 (50.0)	19 (63.3)		6 (60.0)	9 (75.0)	
Never	2 (7.1)	1 (3.3)		0 (0.0)	1 (8.3)	
ECOG performance status, n (%)						
0	7 (25.0)	9 (30.0)	0.85[a]	5 (50.0)	6 (50.0)	0.57[a]
1	19 (67.9)	18 (60.0)		5 (50.0)	4 (33.3)	
2	2 (7.1)	3 (10.0)		0 (0.0)	2 (16.7)	
Continuous characteristic				Continuous characteristic		
Age, y						
Mean (95% CI)	68.1 (65.4-70.7)	70.5 (67.7-73.3)	0.18[b]	61.4 (53.1-69.7)	67.8 (62.8-72.8)	0.14[b]
Median (Min-Max)	67.1 (58.3-81.8)	70.1 (56.1-84.0)		60.1 (44.4-81.9)	69.8 (53.3-77.5)	

[a]Fisher's exact test.
[b]Mann-Whitney test.
cig, cigarette; ECOG, Eastern Cooperative Oncology Group; CI, confidence interval; Min-Max, minimum-maximum.

Baseline Characteristics

EMPHASIS-lung Cohort. The baseline characteristics are summarized in Table 1. Median age was 68.7 years, with most patients being male (82.5%), being former or current smokers (95.0%), and having good performance status (91.3% with a performance status of $\leq$1). Patient characteristics for the different treatment arms and VeriStrat groups were similar (Tables 1 and 2).

The overall proportion of VeriStrat good patients was 72.5% (exact binomial 95% confidence interval [CI]: 61.4–81.9), which was higher than the anticipated 50% used for the study design.

Combined EMPHASIS-lung and PROSE squamous cell cohort. The distribution of baseline characteristics in the PROSE cohort (see Table 1) with respect to VeriStrat status was well balanced between treatment arms except for smoking history (among current smokers, six patients (20.7%) were classified as VeriStrat good and 11 patients (61.1%) were classified as VeriStrat poor [$p = 0.013$]).

The distribution of the patient characteristics was similar in the two trials. This justified addressing the main question regarding a predictive value of VeriStrat in the combined cohort.

Outcome

EMPHASIS-lung cohort. As of the data cutoff date of 31 December 2015, at a median follow-up time of 20.5 months (interquartile range 13.7–23.8 months), all patients had stopped trial treatment (median time on treatment 2.1 months, interquartile range 1.2–4.3 months). Seventy-three patients had experienced a PFS event (median PFS 2.7 months, 95% CI: 1.6–3.8) and 60 patients had died (median OS 7.1 months, 95% CI: 6.0–8.6). Seven patients were lost to follow-up before experiencing a PFS event.

PFS showed no difference by treatment (the median PFS times for erlotinib versus docetaxel were 1.6 versus 3.0 months stratified by VeriStrat status [$p = 0.32$]). In the VeriStrat good cohort, 51 patients (87.9%) experienced a progression-defining event (the median PFS times for erlotinib versus docetaxel were 1.6 versus 4.1 months [$p = 0.37$]), whereas all 22 patients (100%) in the VeriStrat poor group experienced a PFS event (the median PFS times for erlotinib versus docetaxel were 2.1 versus 1.9 months [$p = 0.66$]). No significantly different PFS was found by VeriStrat status or by any other variable of clinical interest in univariate or multivariate model analyses. In the primary analysis for PFS, no significant interaction between treatment and VeriStrat status was found ($p = 0.80$) (Fig. 2*A*).

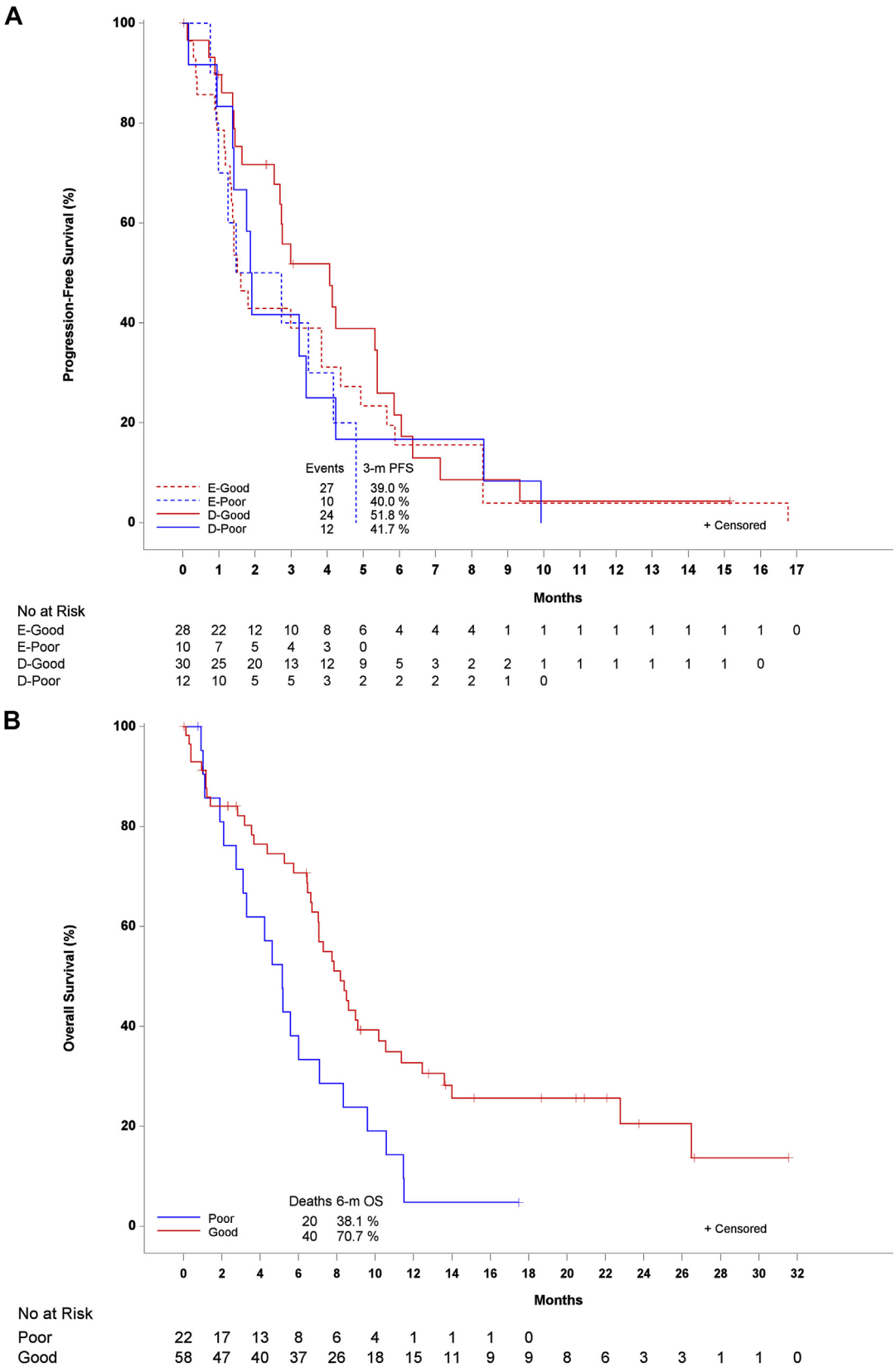

Figure 2. Kaplan-Meier survival curves for progression-free survival (PFS) and overall survival (OS) in the EMPHASIS-lung cohort (N = 80). (*A*) PFS by treatment arm and VeriStrat status. (*B*) OS by VeriStrat status. (*C*) OS by treatment arm and VeriStrat status. E-Good, VeriStrat good patients in the erlotinib arm; E-Poor, VeriStrat poor patients in the erlotinib arm; D-Good, VeriStrat good patients in the docetaxel arm; D-Poor, VeriStrat poor patients in the docetaxel arm.

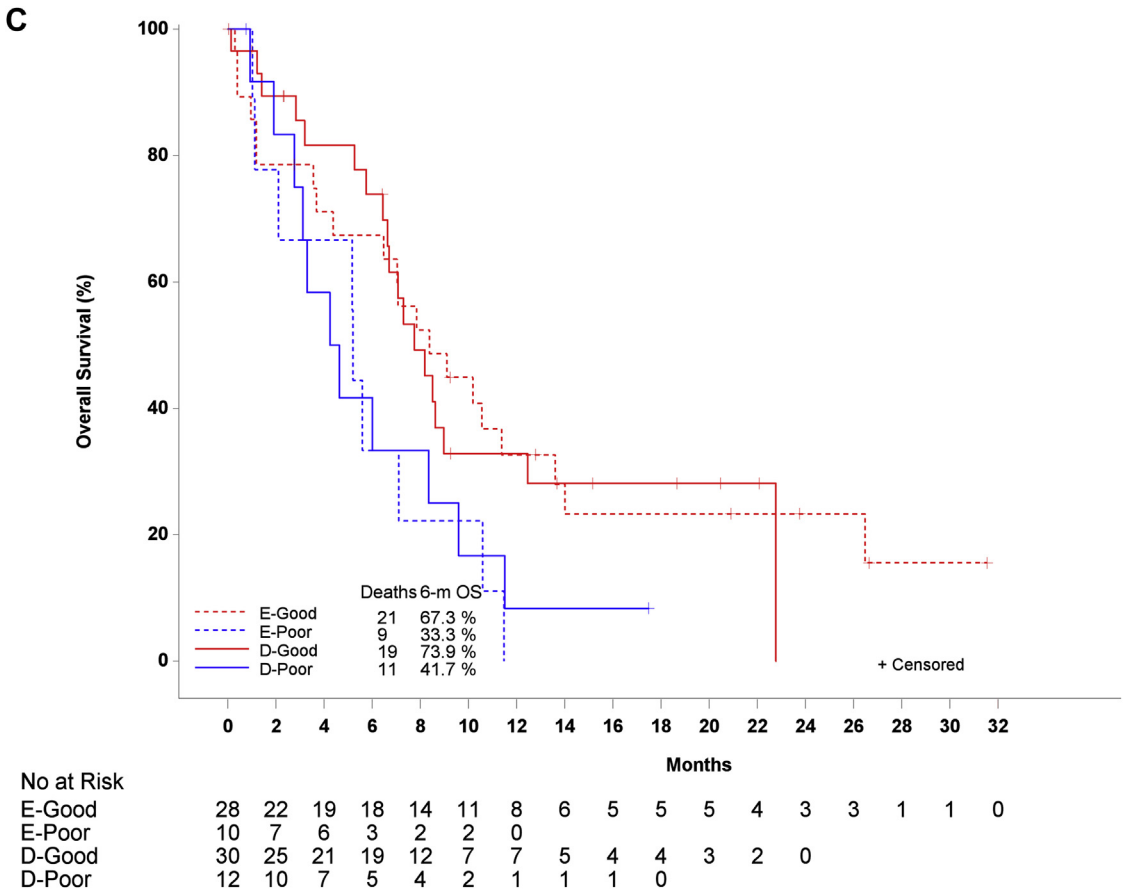

Figure 2. (*continued*).

The difference in OS between the two treatment arms was not significant either overall (median OS was 7.1 months for both erlotinib and docetaxel stratified by VeriStrat status [$p = 0.91$]) or within each VeriStrat group (OS of 8.4 versus 7.8 months for erlotinib versus for docetaxel in patients with VeriStrat good status [$p = 0.88$] as opposed to 5.2 versus 4.4 months in patients with VeriStrat poor status [$p = 0.68$]), but the difference was significant by VeriStrat status ($p = 0.012$). In the VeriStrat good population, 69.0% of patients died (40 deaths) with a median OS of 8.2 months (95% CI: 6.7–10.6), whereas in the VeriStrat poor group the corresponding proportion was 90.9% (20 deaths) with a median OS of 5.2 months (95% CI: 3.1–7.1). VeriStrat good patients experienced a statistically significant reduced risk for death compared with VeriStrat poor patients irrespective of the treatment (HR for Veristrat good versus Veristrat poor status = 0.50, 95% CI 0.29–0.86) (Fig. 2*B*). This also applied when adjustment was made for clinical variables of interest (model adjusted for sex: HR for Veristrat good versus Veristrat poor status = 0.53, 95% CI: 0.30–0.92, $p = 0.023$). The interaction of treatment arm and VeriStrat status was not found to be significant either for OS or for PFS (interaction $p = 0.72$) (Fig. 2*C*).

Combined EMPHASIS-lung and PROSE squamous cell cohort. No significant treatment by VeriStrat interaction was observed for the combined cohort ($p = 0.24$ and 0.45 for PFS/OS). Overall, 79.5% deaths with a median OS of 7.2 months was observed. No significant difference for OS could be observed either between the treatment arms overall (median OS with erlotinib versus with docetaxel, 7.0 versus 7.8 months [stratified $p = 0.13$]) or within each VeriStrat group separately ($p = 0.52$ for Veristrat good versus $p = 0.097$ for VeriStrat poor). A statistically significant difference in OS was observed between the VeriStrat groups ($p < 0.001$), with 73.6% deaths (median OS of 9.0 months) in the VeriStrat good population versus 92.5% (median OS of 4.6 months) in the VeriStrat poor population. The treatment and VeriStrat HRs for PFS/OS in the individual and combined cohorts are presented in Figure 3. No variable of clinical interest had a significant effect either on PFS or on OS. Results are estimated from the Cox models stratified by study.

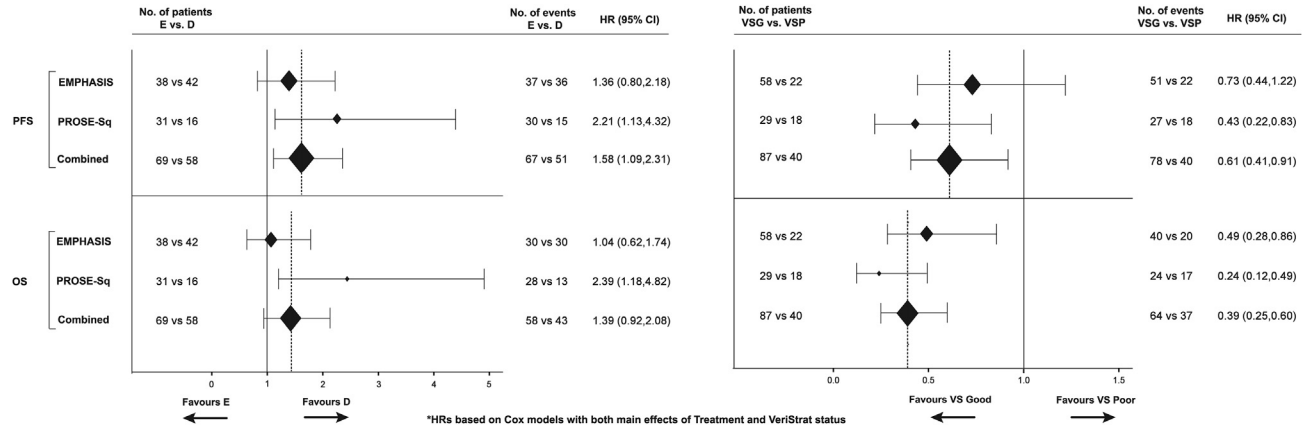

Figure 3. Forest plot of the effect of treatment and VeriStrat status (VS) on progression-free survival (PFS) and overall survival (OS) shown individually for each trial (EMPHASIS-lung and PROSE) and for the combined cohort. E, erlotinib; D, docetaxel; HR, hazard ratio; CI, confidence interval; PROSE-sq, squamous cell cohort from the PROSE trial; VSG, VeriStrat good; VSP, VeriStrat poor.

For the combined cohort, the impact of VeriStrat status was found to be significant for both PFS and OS ($p = 0.015$ and $p < 0.001$, respectively), whereas treatment was significant only for PFS ($p = 0.017$).

AEs

EMPHASIS-lung cohort. A total of 75 patients experienced at least one adverse event (AE) (36 and 39 in each treatment arm, respectively), whereas 26 patients had at least one serious AE (SAE), from a total of 35 reported SAEs. No unexpected SAE was observed. Ten fatal AEs were recorded, with seven deaths during erlotinib treatment and three during docetaxel treatment, all of which were unrelated or unlikely to be related to trial treatment.

Combined EMPHASIS-lung and PROSE Squamous Cell Cohort. The AEs for the PROSE cohort have been reported previously.[19] They were similar to those reported for the EMPHASIS-lung patients.

Discussion

In a series of clinical trials docetaxel was compared with erlotinib as standard second-line chemotherapy for unselected NSCLC, but no clear difference in antitumor activity could be demonstrated.[4,5,7–9] From a meta-analysis it can be concluded that treatment with a first-generation EGFR TKI compared with conventional chemotherapy was associated with improvement in PFS but not OS.[22] This is also reflected in the current guidelines,[23] which leave both options up to the treating oncologist's decision. Hence, the choice between docetaxel and an EGFR TKI is made on the basis of subjective arguments rather than scientific evidence in the face of the obstacle that only few patients will ever receive subsequent third-line therapy. This is especially true for advanced NSCLC of the squamous cell histological subtype, which is characterized by short OS,[24,25] and supporting data would help in deciding on a strategy in the second-line scenario for these patients.

In 2014, the PROSE trial showed a predictive ability of the VeriStrat classification to differentiate treatment benefits of chemotherapy versus erlotinib in the second-line treatment of unselected advanced NSCLC,[14] with a significant interaction between treatment and test classification with respect to OS. In particular, 30% of VeriStrat poor patients demonstrated poor OS when treated with erlotinib, whereas no treatment superiority was found within the population of VeriStrat good patients. These results, together with the presentation of the TAILOR trial[9] and a related meta-analysis,[22] did call into question the role of erlotinib in the second-line setting and hence also the aim of the EMPHASIS-lung trial.

The final analysis of EMPHASIS-lung did not show a differential effect of erlotinib versus docetaxel on PFS by VeriStrat status in patients with NSCLC of the squamous cell histological subtype, as is also clearly shown by the significant overlap in the HR CIs (see Fig. 3). These results are at variance with previous studies, the PROSE trial, and our trial assumptions. A plausible explanation is the lack of power in the EMPHASIS-lung trial owing to its early termination and low accrual. Indeed, conditional power calculations indicated that if the trial had proceeded to completion, the power of detecting a treatment by VeriStrat status interaction would still be greater than 60%.

In the EMPHASIS-lung analysis, it was confirmed that VeriStrat good patients had better OS than VeriStrat poor patients, but no treatment effect either on PFS or on OS was detected.

In the combined analysis of the EMPHASIS-lung patients and the squamous cell NSCLC cohort of the PROSE trial, treatment with erlotinib was associated with a significantly higher risk for progression and a numerical but not significantly higher risk for death compared with docetaxel for both VeriStrat good and VeriStrat poor patients, and importantly, VeriStrat good patients demonstrated a significantly lower risk for progression and death compared with VeriStrat poor patients.

In summary, although the prognostic ability of VeriStrat status could be confirmed, neither the EMPHASIS-lung results nor the combined EMPHASIS-lung and PROSE analysis results could show a predictive value of the VeriStrat test with respect to a differential effect of erlotinib versus docetaxel on the basis of the VeriStrat classification for advanced squamous cell NSCLC.

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