A Retrospective Analysis of VeriStrat Status on Outcome of a Randomized Phase II Trial of First-Line Therapy with Gemcitabine, Erlotinib, or the Combination in Elderly Patients (Age 70 Years or Older) with Stage IIIB/IV Non–Small-Cell Lung Cancer

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Purpose: In a multicenter randomized phase II trial of gemcitabine (arm A), erlotinib (arm B), and gemcitabine and erlotinib (arm C), similar progression-free survival (PFS) and overall survival (OS) were observed in all arms. We performed an exploratory, blinded, retrospective analysis of plasma or serum samples collected as part of the trial to investigate the ability of VeriStrat (VS) to predict treatment outcomes.
Methods: Ninety-eight patients were assessable, and the majority had stage IV disease (81%), adenocarcinoma histology (63%), reported current or previous tobacco use (84%), and 26% had a performance status (PS) of 2.
Results: In arm A, patients with VS Good (n = 20) compared with VS Poor status (n = 8) had similar PFS (hazard ratio [HR]: 1.21; p = 0.67) and OS (HR: 0.82; p = 0.64). In arm B, patients with VS Good (n = 26) compared with VS Poor (n = 12) had a statistically significantly superior PFS (HR: 0.33; p = 0.002) and OS (HR: 0.40; p = 0.014). In arm C, patients with VS Good (n = 17) compared with Poor (n = 1 5) had a superior PFS (HR: 0.42; p = 0.027) and a trend toward superior OS (HR: 0.48; p = 0.051). In the multivariate analysis for PFS, VS status was statistically significant (p = 0.011); for OS, VS status (p = 0.017) and PS (p = 0.005) were statistically significant. A statistically significant VS and treatment interaction (gemcitabine versus erlotinib) was observed for PFS and OS.
Conclusions: Gemcitabine is the superior treatment for elderly patients with VS Poor status. First-line erlotinib for elderly patients with VS Good status may warrant further investigation.

Key Words: Proteomics, Biomarkers, Epidermal growth factor receptor tyrosine kinase inhibitors, Elderly.

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The management of elderly patients with stage IIIB or IV non–small-cell lung cancer (NSCLC) remains controversial. Cytotoxic chemotherapy remains the standard therapy for the majority of patients, but the optimal treatment for this heterogeneous patient population is unclear. Many "fit" elderly patients tolerate platinum-based therapy and are frequently enrolled in trials of platinum-based therapy. Other elderly patients have cardiopulmonary comorbidities related to tobacco use and comorbidities associated advanced age. These patients represent the "frail" elderly and have difficulty tolerating cytotoxic chemotherapy.[1] Trials investigating novel agents, optimal chemotherapy schedules and combinations, and developing biomarkers of efficacy and/or tolerance of therapy for the frail elderly patient population are a priority for the thoracic oncology community.

Beginning in 2005, we performed a noncomparative randomized phase II trial of gemcitabine, erlotinib, and erlotinib and gemcitabine in elderly patients (age 70 years or older) with stage IIIB or IV NSCLC.[2] At the time the study was designed, single-agent chemotherapy was a standard of care based on prospective phase III trials in elderly patients.[3–5] Erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), was a standard therapy in the second- and third-line settings, and a single arm phase II trial had revealed promising activity in elderly patients.[6,7] A phase III trial of gemcitabine and erlotinib compared with gemcitabine in advanced pancreatic cancer had revealed superior overall survival (OS) with the combination therapy.[8] The results of the intent-to-treat patient population have previously been published;[2] neither of the investigational arms

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(erlotinib alone or with gemcitabine) demonstrated sufficient activity to warrant further investigation. The role of *EGFR* mutation status in the selection of patients for first-line EGFR TKI therapy was not established at the time the trial was designed.[9–12]

VeriStrat is a commercially available serum or plasma test using matrix-assisted laser desorption ionization mass spectrometry methods. It was developed on a training set of pretreatment serum samples from patients with advanced NSCLC who experienced either long-term stable disease or early progression on gefitinib therapy.[13] Mass spectra (MS) from these patients' serum samples were used to define eight MS features (i.e., peaks), differentiating these two outcome groups. An algorithm utilizing these features and based on k-nearest neighbors classification scheme was created, and its parameters were optimized using additional spectra from the training cohort. The current commercial test uses the same fixed set of parameters established during the development phase. VeriStrat assigns each sample a classification of VeriStrat Good or VeriStrat Poor; when an unequivocal classification cannot be determined (<3% of samples), an indeterminate result is reported.

Validation studies of VeriStrat were performed in a blinded fashion using multiple single-arm cohorts of patients with NSCLC undergoing EGFR TKI therapy.[13] Retrospective analysis of available plasma samples from the phase III registrational trial of erlotinib, National Cancer Institute of Canada Clinical Trials Group BR.21, confirmed VeriStrat's ability to separate patients with advanced NSCLC into groups with better and worse outcomes with erlotinib therapy. VeriStrat status demonstrated prognostic properties and was predictive of response to erlotinib. This study confirmed previous results that VeriStrat classification is not significantly correlated with *EGFR* or *KRAS* mutation status, and the absence of a correlation with *EGFR* gene copy number.[14–16] Although VeriStrat classification significantly correlated with certain prognostic characteristics, such as performance status (PS), it maintained a significant correlation with outcomes independent of these potential confounding factors in multivariate analysis.[13,14]

In this study we performed a retrospective analysis of the clinical outcomes of patients classified as VeriStrat Good and Veristrat Poor in each treatment arm. Although the analysis in the erlotinib arm is similar to previous studies, those in the other treatment arms represent the first studies of VeriStrat testing in gemcitabine and gemcitabine plus erlotinib treated patients and therefore are exploratory.

PATIENTS AND METHODS

Eligibility Criteria

Patients were required to have histologic or cytologic diagnosis of NSCLC, AJCC 6th edition stage IIIB or IV disease, age 70 years or older, Eastern Cooperative Oncology Group PS of 0 to 2, and adequate bone marrow, renal, and hepatic function. Patients were required to have measureable disease according to Response Evaluation Criteria in Solid Tumors (RECIST).[17] Patients who were unable to provide informed consent or participate in the Health Related Quality of Life (HRQOL) questionnaires were not eligible. There were no eligibility requirements related to histology, history of tobacco use, or *EGFR* mutation status. This trial was reviewed by the institutional review board of all the participating centers, and patients were required to provide informed consent before any study related tests were performed. The study was registered with Clinicaltrials.gov (NCT00283244). The protocol was amended in December 2007, and a correlative science study with collection of peripheral blood samples was incorporated into the study. Participation was voluntary and patients who agreed to participate in the correlative science study signed a separate institutional review board approved informed consent document. Collection of tumor samples was not required; therefore, tumor samples are not available for analysis for *EGFR* and *KRAS* mutational status.

Treatment

Patients were randomly assigned to treatment arms A, B, or C; patients were stratified based on gender, smoking history (never or light smoking history versus current or former tobacco use), and PS (2 versus 0 or 1). Patients assigned to arm A received gemcitabine 1200 mg/m^2 intravenously on days 1 and 8 every 21 days until disease progression, unacceptable toxicity, or a maximum of four cycles. At the time of disease progression patients were offered erlotinib 150 mg daily until disease progression or unacceptable toxicity as part of the trial. Patients assigned to arm B received erlotinib 150 mg daily until disease progression or unacceptable toxicity. Patients assigned to arm C received gemcitabine 1000 mg/m^2 intravenously on days 1 and 8 every 21 days and erlotinib 100 mg daily; patients received gemcitabine until disease progression, unacceptable toxicity, or a maximum of four cycles. After four cycles (in the absence of disease progression or unacceptable toxicity), patients continued erlotinib until disease progression or unacceptable toxicity. Details about the dose adjustments for gemcitabine and erlotinib are available in the previous publication.[2]

Study Assessments

Patients were required to have a staging computed tomography scan of the chest and abdomen (including the liver and adrenals) within 4 weeks of trial enrollment. Bone scan, positron emission tomography, and computed tomography scan or magnetic imaging of the brain were not required and were performed if clinically indicated. Disease status according to RECIST was assessed after cycles 2 and 4 and at 6 months from the beginning of therapy, and then every 2 months or if clinically indicated. Disease status was assessed by the investigator. Patients underwent laboratory and physical examinations and toxicity assessment with each cycle.[2] Patients were evaluated using the Functional Assessment of Cancer Therapy for Lung Cancer (FACT-L) which consists of the FACT-General and the lung cancer–specific subscale (LCS).[18,19] The FACT-L was administered at the screening visit (within 2 weeks of the day 1 of the first treatment cycle) or day 1 of the first treatment cycle (baseline), after each cycle (21 days), after the completion of treatment or at the time the patient was withdrawn from the study. The Trial Outcome Index-Lung (TOI-L) was the primary HRQOL analyzed.

VeriStrat Analysis

Mass spectrometry was performed in a fully blinded manner on 110 available pretreatment plasma and serum samples sent to Biodesix (Boulder, CO). Sample aliquots were diluted 1:10 in HPLC-grade water and mixed (1:1 v/v) with matrix solution (25 mg/ml sinapinic acid dissolved in 50/50/0.1% acetonitrile:water:trifluoroacetic acid). The dilute sample-matrix mixture was spotted in triplicate on a matrix-assisted laser desorption ionization target in randomly assigned plate positions. Spectra were acquired on a Bruker Flextreme mass spectrometer. Each replicate spectrum consisted of an average of 2000 individual spectra collected from various locations within the spot. The MS were then processed by the VeriStrat classification algorithm, which is identical to the one previously described by Taguchi et al.[13] The VeriStrat test performed was the same as that provided commercially, and testing is conducted by Biodesix, Inc. in their Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. No adjustments were made to the test, which has remained fully locked since development in 2005. Testing was carried out blinded to all clinical information.

Statistical Methods and Study Design

This retrospective analysis was designed as an exploratory study of the use of the VeriStrat proteomic test in first-line elderly patients with advanced NSCLC treated with gemcitabine, erlotinib, or the combination of gemcitabine and erlotinib. Statistical analyses were performed using SAS 9.2 (Cary, NC) and PRISM (GraphPad, La Jolla, CA). Progression-free survival (PFS) and OS were summarized using the Kaplan–Meier method and compared between treatment arms and VeriStrat groups using the log-rank test. Hazard ratios (HRs) between groups for time-to-event variables were calculated using Cox proportional hazard methods. The impact of baseline prognostic factors on outcome was explored with Cox regression models using forward selection, backward elimination, or stepwise selection of covariates with a fixed selection parameter of $\alpha = 0.1$. Correlations of categorical variables with VeriStrat classification were assessed using Fisher's exact test or a χ^2 test. Statistical significance was set at a level of 0.05 for all analyses.

RESULTS

Between March 2006 and May 2010, 146 eligible patients were enrolled and initiated trial therapy. Plasma or serum samples were available from 110 patients, and 98 were assessable for analysis (Fig. 1). The clinical characteristics of the patients are presented in Table 1.[2] Of the 98 patients in the VeriStrat analysis cohort, 63 were classified as VeriStrat Good and 35 as Poor. Tumor samples were not available for *EGFR* and *KRAS* mutational status making an analysis of Veristrat Status and tumor mutational status impossible. Of the 28 patients in the gemcitabine arm, 12 patients received second-line erlotinib as part of the protocol therapy. In the erlotinib and gemcitabine and erlotinib combination arms, 14 and 13 patients received second-line therapy off of the protocol. An analysis of PFS and OS within the treatment arms was performed (Fig. 2 and Table 2). In the gemcitabine arm, patients classified as Good ($n = 20$) compared with Poor ($n = 8$) experienced similar PFS and OS. In contrast, in the erlotinib arm, patients classified as Good ($n = 26$) compared with Poor ($n = 12$) experienced significantly longer PFS (HR: 0.33; 95% CI: 0.16–0.70; log-rank $p = 0.002$; median PFS of 89 and 22 days, respectively) and OS (HR: 0.40; 95% CI: 0.19–0.85; log-rank $p = 0.014$; median OS of 255 and 51 days, respectively). In the gemcitabine and erlotinib arm, patients classified as Good ($n = 17$) compared with Poor ($n = 15$) experienced a statistically significantly longer PFS (HR: 0.42; 95% CI: 0.19–0.93; log-rank $p = 0.027$) and a trend toward an improvement in OS (HR: 0.48; 95% CI: 0.23–1.02; log-rank $p = 0.051$).

When outcomes between treatment the erlotinib alone and gemcitabine alone arms were compared, the HR for PFS between for the VeriStrat Good and Poor groups were 0.60 (95% CI: 0.31–1.15; log-rank $p = 0.12$) and 2.13 (95% CI: 0.83–5.52; log-rank $p = 0.11$), respectively (HR < 1 favors erlotinib). The corresponding results for OS for the VeriStrat Good and Poor groups between erlotinib and gemcitabine arms were HR = 0.66 (95% CI: 0.35–1.24; log-rank $p = 0.19$) and HR = 1.62 (95% CI: 0.64–4.07; log-rank $p = 0.30$), respectively. It should, however, be noted that in the gemcitabine monotherapy arm, nine of the patients classified as Good and three classified as Poor went on to receive erlotinib therapy as a second-line therapy. Outcomes on the erlotinib and gemcitabine combination arm lay numerically in between those of the two monotherapy arms for both the VeriStrat groups.

In the gemcitabine alone among patients with VeriStrat Good and Poor, the overall response rate (ORR) was 6% and 0%, respectively, and the disease control rate (DCR), defined as ORR and stable disease rate, was 60% and 62%, respectively. In the erlotinib arm, the ORR among patients with Veristrat Good and Poor was 5% and 0%, respectively, and the DCR was 62% and 25%, respectively. In the combination arm, the ORR among patients with VeriStrat Good and Poor was 15% and 10%, respectively, and the DCR was 65% and 47%, respectively. No evidence of association between VeriStrat classification and ORR or DCR was found in any of the treatment arms.

Analysis of the association of patient characteristics with VeriStrat classification revealed a statistically significant correlation between VeriStrat Good status and a PS of 0 or 1 as well as adenocarcinoma histology compared with other histologies (Table 3). To adjust for these and other possible confounding factors, multivariate analysis was performed for PFS and OS (Table 4). In the multivariate analysis for PFS, VeriStrat status (Good versus Poor) was associated with longer PFS (HR: 0.51; 95% CI: 0.30–0.86; $p = 0.011$). There was a statistical trend for shorter PFS associated with PS of 2 compared with PS 0 or 1 (HR: 1.69; 95% CI: 0.98–2.92; $p = 0.058$). In the multivariate analysis for OS, VeriStrat status (Good versus Poor) was associated with longer OS (HR: 0.53; 95% CI: 0.32–0.90; $p = 0.017$), and PS of 2 compared with 0 or 1 was associated with shorter OS (HR: 2.20; 95% CI: 1.27–3.83; $p = 0.005$). There was a borderline significant difference between stage IIIB and IV, with worse survival for patients with stage IV compared with stage IIIB disease (HR: 1.76; 95% CI: 0.93–3.32; $p = 0.080$).

When the clinical data from the gemcitabine and erlotinib arms were analyzed using adjusted multivariate analysis

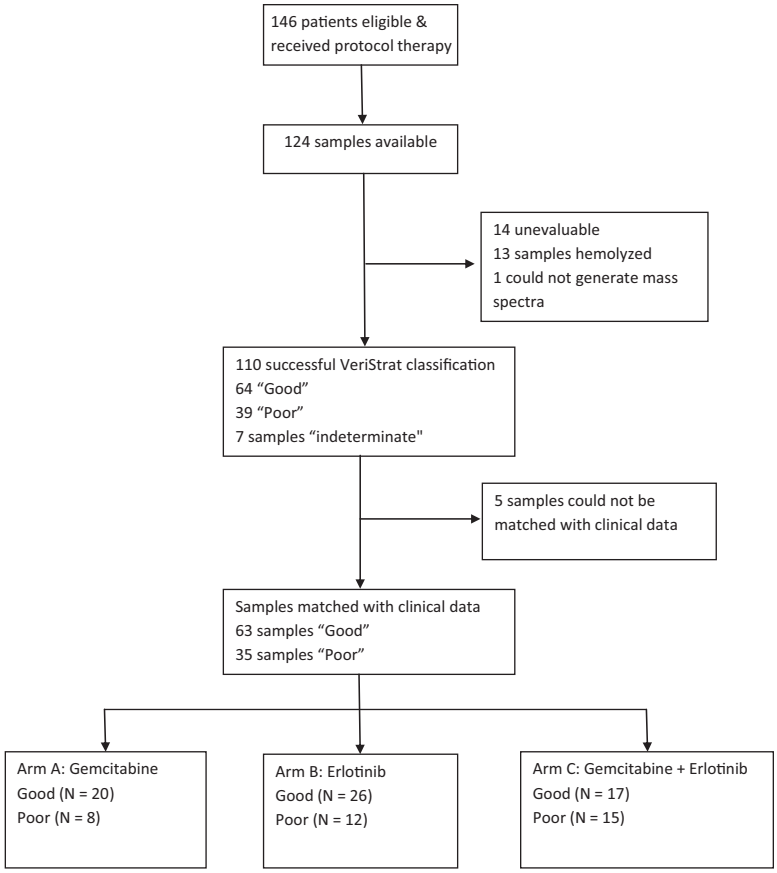

FIGURE 1. Consort diagram for the study.

with covariate selection, the interaction between treatment and VeriStrat classification was shown to be significant ($p < 0.001$), together with the treatment arm ($p = 0.028$) and sex ($p = 0.029$) for PFS (Table 5). Similar analysis for OS showed that the interaction was again significant ($p = 0.017$), this time together with PS ($p = 0.010$) and disease stage ($p = 0.047$) (Table 5). The significance of the interaction between erlotinib or gemcitabine treatment and VeriStrat classification indicates that there is a differential benefit from these therapies between patients with Good and Poor VeriStrat classification, that is, the VeriStrat Good group benefits more from erlotinib, whereas Veristrat Poor group benefits more from gemcitabine.

We performed an exploratory analysis investigating if VeriStrat Good status and the longer PFS were associated with an improvement in HRQOL or lung cancer symptoms. In the gemcitabine alone arm, the PFS was similar in patients with VeriStrat Good and Poor status, and we performed an exploratory analysis to see if there was a difference in HRQOL or lung cancer symptoms related to VeriStrat status without the potential confounding factor of difference in PFS. These analyses are retrospective and exploratory and were not designed to test a specific hypothesis. There did not appear to be any significant differences in best response to treatment analysis as assessed by the FACT-L, TOI-L, or the LCS (Table 6). In the gemcitabine arm ($n = 28$) and erlotinib arm ($n = 36$), statistically significant differences were not observed between Veristrat Good and Poor groups and also differences were not observed on the TOI-L, FACT-L, and LCS at any of the four individual time points or in the longitudinal HRQOL trend analysis (Fig. 3).

DISCUSSION

The development of predictive biomarkers for currently available therapies is an area of intense investigation in thoracic oncology. *EGFR* mutations and anaplastic lymphoma kinase rearrangements are predictive of clinical benefit of EGFR TKI therapy and crizotinib, respectively. It is, however, estimated that only approximately 20% of patients with adenocarcinoma will have these molecular characteristics.[20] Patients with EGFR mutant tumors derive tremendous benefit from EGFR TKI therapy, but there is a significant clinical need to further define who benefits from EGFR TKI therapy in patients with *EGFR* wild-type tumors. VeriStrat is a commercially available test in the United States; it has previously been demonstrated to be associated with longer PFS and OS in patients treated with EGFR TKIs and to be predictive of response to erlotinib. Our retrospective analysis confirmed that patients with a VeriStrat Good compared with Poor status have statistically significant longer PFS and OS when treated with erlotinib. The median PFS and OS observed among elderly patients with VeriStrat Good status suggests benefit for first-line EGFR TKI therapy in this patient population. This, however, is a retrospective analysis, and the number of patients in this cohort is small ($n = 26$). VeriStrat Good status was associated with good PS

TABLE 1. Patient Characteristics

Characteristic	Veristrat analysis	Gemcitabine	Erlotinib	Gemcitabine/erlotinib
Number	98	28	38	32
VeriStrat status				
Good/Poor	63/35	20/8	26/12	17/15
Median age, years (range)	76 (69–90)	74 (70–86)	76 (69–86)	78 (70–90)
Stage (%)				
IIIB	19 (19)	8 (29)	3 (8)	8 (25)
IV	79 (81)	20 (71)	35 (92)	24 (75)
Gender (%)				
Male	54 (55)	16 (57)	20 (53)	18 (56)
Female	44 (45)	12 (43)	18 (47)	14 (44)
Performance status (%)				
0	18 (18)	7 (25)	6 (16)	5 (16)
1	44 (45)	13 (46)	22 (58)	18 (56)
2	25 (26)	8 (29)	9 (24)	8 (25)
Missing	2 (2%)	0 (0)	1 (3)	1 (3)
Smoking history (%)				
Never or light	13 (13)	3 (11)	5 (13)	5 (16)
Current or former	82 (84)	23 (82)	32 (84)	27 (84)
Missing	3 (3)	2 (7)	1 (3)	0 (0)
Histology (%)				
Adenocarcinoma	63 (64)	17 (61)	24 (63)	22 (69)
Squamous	14 (14)	5 (18)	5 (13)	4 (12)
NOS[a]	20 (20)	5 (18)	9 (24)	6 (19)
Large cell carcinoma	1 (1)	1 (4)	0 (0)	0 (0)

[a]Includes one patient with giant cell histology.

and adenocarcinoma histology, which are also good prognostic factors. Unfortunately, we do not have additional clinical data to determine if there is an association with VeriStrat status with other clinical factors such as weight loss, site or number of metastases, and comorbidities. The association with VeriStrat Good status and good PS has been observed in other studies and warrants further investigation.[13,21]

Of concern, the patients in the erlotinib arm with Veristrat Poor status had poor median PFS and OS, 22 and 51 days, respectively. Importantly, only 14 of patients enrolled in the erlotinib arm received second-line therapy, and VeriStrat Poor status was associated with worse PS and nonadenocarcinoma histology.[2] Patients in this cohort experienced rapid disease progression on first-line erlotinib and may not have received second-line therapy related to poor PS, comorbidities, symptomatic decline, and patient and/or physician decision. The reasons for the poor efficacy are most likely multifactorial, but the data indicate erlotinib is not an acceptable first-line treatment option for this patient population. Patients with Veristrat Poor and Good status had similar PFS and OS with single agent gemcitabine, and a significant interaction of treatment and VeriStrat status was detected. These data suggest that the VeriStrat test is predictive with respect to treatment, not merely prognostic, and that the patients with a VeriStrat Poor status received greater clinical benefit from single agent gemcitabine compared with erlotinib than those with VeriStrat Good status. Patients in the gemcitabine and erlotinib arm with VeriStrat Good compared with VeriStrat Poor status experienced an improvement in PFS and a trend toward improvement in OS. The lack of the association between VeriStrat status and improved PFS and OS in the gemcitabine alone arm in this analysis and the absence of an association between VeriStrat status and chemotherapy observed in previous trials suggests that the erlotinib component of the therapy is responsible for this observation.

This analysis is exploratory and has several deficiencies. The retrospective nature of this analysis and the association of VeriStrat Good status with certain prognostic factors could have created imbalances of prognostic factors in the different subsets; however, multivariate analyses may have adequately adjusted for possible confounding factors. Imbalances in the rate and type of poststudy therapy may have impacted the OS results, and type of second-line therapy was only mandated in the single agent gemcitabine arm. The lack of mandatory tumor collection as part of the eligibility criteria makes assessment of any correlation between VeriStrat status and molecular characteristics such as *EGFR* or *KRAS* mutation status impossible. The majority of patients enrolled had a history of tobacco use (approximately 85% of patients), 40% of patients had a tumor with nonadenocarcinoma histology, and no responses were observed in the erlotinib alone arm. These data are suggestive that the rate of *EGFR* mutant NSCLC was low in this trial. There was no significant difference in the HRQOL outcomes in the initial trial, and

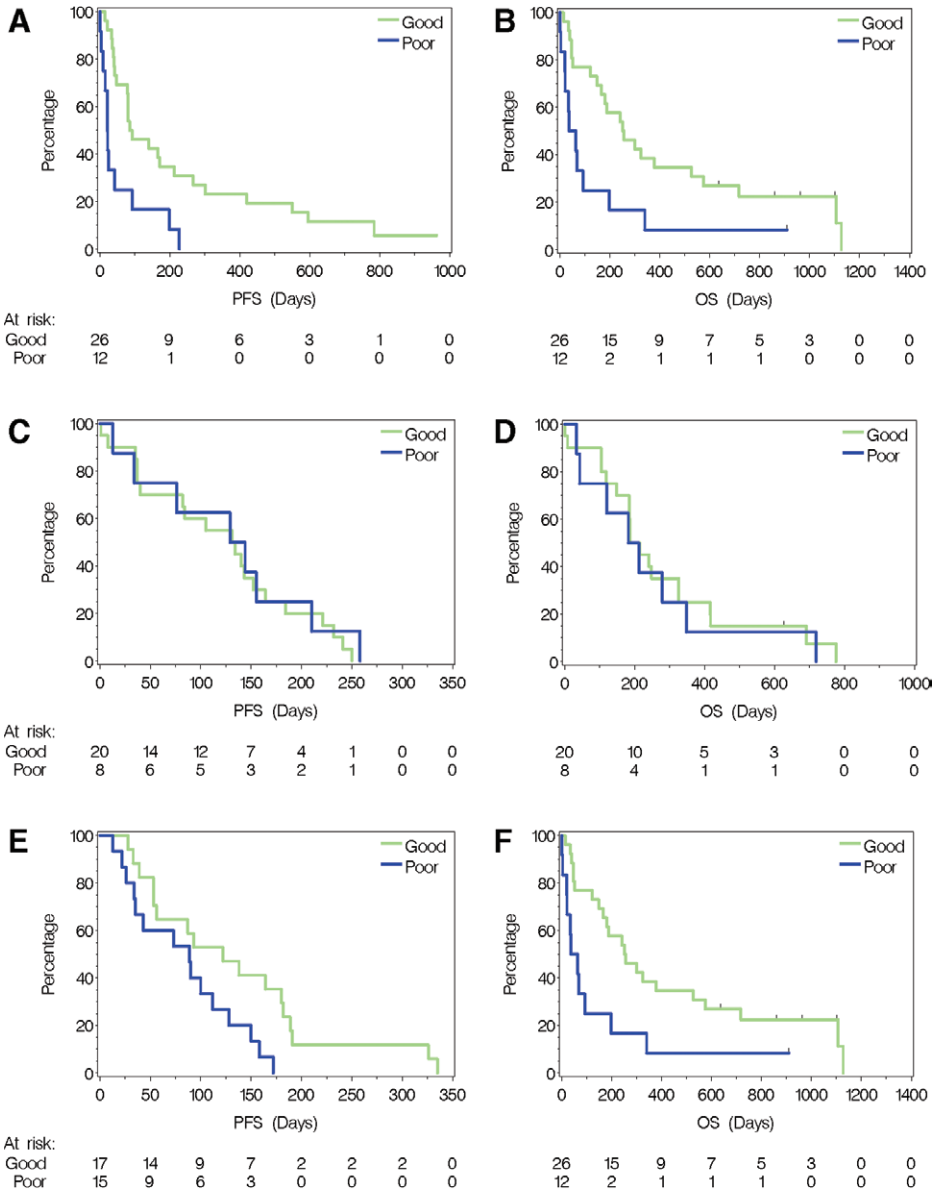

FIGURE 2. Kaplan–Meier plots by VeriStrat status (Good and Poor) for (*A*) PFS in the erlotinib arm, (*B*) OS in the erlotinib arm, (*C*) PFS in the gemcitabine arm, (*D*) OS in the gemcitabine arm, (*E*) PFS in the erlotinib+gemcitabine arm, (*F*) OS in the erlotinib+gemcitabine arm.

TABLE 2. Clinical Outcome of Veristrat Good compared to Poor

Treatment arm	No. of patients	Progression-free survival	Overall survival
Gemcitabine		HR: 1.21; 95% CI: 0.51–2.88; $p = 0.67$	HR: 0.82, 95% CI: 0.35–1.90; $p = 0.64$
	Good: 20	Median PFS Good: 133 days	Median OS Good: 201 days
	Poor: 8	Median PFS Poor: 137 days	Median OS Poor: 197 days
Erlotinib		HR: 0.33; 95% CI: 0.16–0.70; $p = 0.002$	HR = 0.40; 95% CI: 0.19–0.85; $p = 0.014$
	Good: 26	Median PFS Good: 89 days	Median OS Good: 255 days
	Poor: 12	Median PFS Poor: 22 days	Median OS Poor: 51 days
Gemcitabine/erlotinib		HR: 0.42; 95% CI: 0.19–0.93; $p = 0.027$	HR: 0.48; 95% CI: 0.23–1.02; $p = 0.051$
	Good: 17	Median PFS Good: 122 days	Median OS Good: 302 days
	Poor: 15	Median PFS Poor: 89 days	Median OS Poor: 106 days

TABLE 3. Patient characteristics by VeriStrat classification

	VeriStrat Good	VeriStrat Poor	*p* Value
Number	63	35	
Treatment arm			
Gemcitabine	20	8	0.27
Erlotinib	26	12	
Gemcitabine/erlotinib	17	15	
Gender			
Male	34	20	0.83
Female	29	15	
Ethnicity			
White	57	33	0.71
Nonwhite[a]	6	2	
Smoking history			
Ever[b]	50	32	0.13
Never	11	2	
ECOG PS			
0 or 1	52	19	0.004
2	10	15	
Histology			
Adenocarcinoma	45	17	0.03
Other histologies	18	18	
Stage			
IIIB	10	9	0.29
IV	53	26	

[a]Includes African American ($n = 6$), Asian ($n = 1$), unknown ($n = 1$).
[b]Defined as current or former.

TABLE 4. Multivariate Analysis for Progression-free survival and Overall Survival

Factor	Comparison	PFS hazard ratio	OS hazard ratio
VeriStrat status	Good vs. Poor	0.51 (95% CI: 0.30–0.86), $p = 0.011$	0.53 (95% CI: 0.32–0.90), $p = 0.017$
Histology	Other histologies vs. adenocarcinoma	0.95 (95% CI: 0.72–1.25), $p = 0.713$	0.87 (95% CI: 0.65–1.16), $p = 0.335$
Race	Nonwhite vs. white	0.93 (95% CI: 0.39–2.24), $p = 0.875$	0.86 (95% CI: 0.35–2.08), $p = 0.730$
Gender	Female vs. male	1.17 (95% CI: 0.74–1.84), $p = 0.497$	1.17 (95% CI: 0.73–1.88), $p = 0.522$
Treatment arm	Erlotinib vs. gemcitabine	0.65 (95% CI: 0.36–1.18), $p = 0.158$	0.71 (95% CI: 0.40–1.25), $p = 0.232$
Treatment arm	Gemcitabine/erlotinib vs. gemcitabine	0.86 (95% CI: 0.50–1.49), $p = 0.593$	0.76 (95% CI: 0.43–1.35), $p = 0.352$
Smoking history	Never vs. ever	0.94 (95% CI: 0.48–1.86), $p = 0.864$	0.78 (95% CI: 0.38–1.59), $p = 0.485$
Performance status	2 vs. 0 or 1	1.69 (95% CI: 0.98–2.92), $p = 0.058$	2.20 (95% CI: 1.27–3.83), $p = 0.005$
Stage	IV vs. III B	1.49 (95% CI: 0.82–2.71), $p = 0.197$	1.76 (95% CI: 0.93–3.32), $p = 0.080$

CI, confidence interval.

we wanted to test the hypothesis that the significant efficacy difference between the Veristrat Good and Poor subgroups in the erlotinib arm may have resulted in differences in HRQOL. The sample size for this analysis was small, and the short PFS observed in the VeriStrat Poor group treated with erlotinib limited the number of HRQOL assessments available for each patient. The utility of these analyses is limited and the purpose of including the results was to provide preliminary data for future studies.

This is the first report of the comparison of VeriStrat status in the elderly patients treated with erlotinib or with single-agent chemotherapy that demonstrates how a serum or plasma test, with no need of biopsy, may be particularly useful. Patients with VeriStrat Poor status should not receive erlotinib therapy but may be good candidates for gemcitabine treatment. Since this trial was developed in 2005, a phase III trial compared carboplatin and weekly paclitaxel to single-agent chemotherapy (gemcitabine or vinorelbine); a statistically significant improvement in PFS and OS was observed with the combination treatment.[22] This trial established double-agent platinum-based therapy as a standard therapy for appropriate patients. Many elderly patients are, however, "frail" and may

TABLE 5. Adjusted Interaction Analysis

Factor	Hazard ratio (95% CI)	*p* Value
Progression-free survival		
Gender (female vs. male)	1.85 (1.06–3.22)	0.029
Treatment arm (erlotinib vs. gemcitabine)	2.27 (1.09–4.73)	0.028
VeriStrat treatment interaction	0.20 (0.09–0.45)	<0.001
Overall survival		
PS (2 vs. 0/1)	2.24 (1.22–4.11)	0.010
Stage IV vs. IIIB	2.23 (1.01–4.93)	0.047
VeriStrat* treatment interaction	0.49 (0.27–0.88)	0.017

TABLE 6. Best Response to Treatment Analysis

		Gemcitabine		Erlotinib	
		Good	Poor	Good	Poor
Scale	Status	*n* = 20	*n* = 8	*n* = 26	*n* = 12
TOI-L	Improved	2	2	2	1
	No change	7	1	5	1
	Worsened	7	1	6	1
	Other	4	4	13	9
FACT-L	Improved	3	2	4	1
	No change	5	1	2	1
	Worsened	6	1	5	0
	Other	6	4	15	10
LCS	Improved	2	2	7	1
	No change	3	2	3	2
	Worsened	8	0	6	0
	Other	7	4	10	9

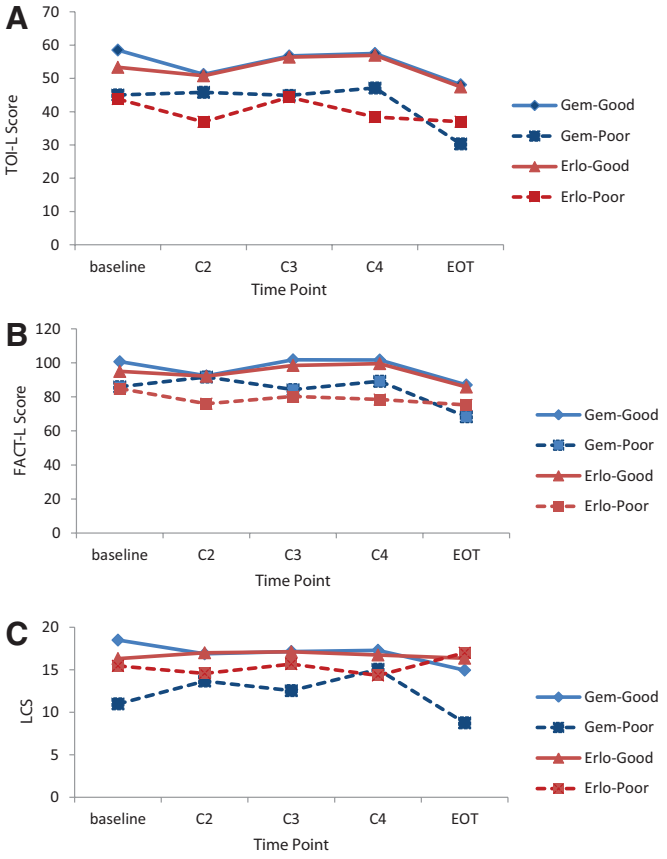

FIGURE 3. Plots of longitudinal quality of life scores: (*A*) TOI-L score, (*B*) FACT-L score, (*C*) LCS as measured from questionnaires completed at baseline, cycle 2 (C2), cycle 3 (C3), cycle 4 (C4), and at the end of the trial.

not be candidates for platinum-based therapy, and the optimal management for this patient population remains unclear. A prospective phase II trial comparing erlotinib to single-agent chemotherapy in elderly patients as first-line therapy who are not candidates for double-agent platinum-based therapy with VeriStrat Good status may be worth pursuing to further investigate the use of this minimally invasive test to select patients for therapy. Since this trial would be exploratory, a potential primary end point would be PFS with the goal of demonstrating an improvement in PFS of 1.5 times or greater than the control arm before pursing larger validation trials. An ongoing randomized trial in the second-line setting is prospectively stratifying patients based on VeriStrat status and is comparing erlotinib to docetaxel or pemetrexed.[23] Until the results of the prospective clinical trial are available, clinicians should not use VeriStrat status for selection erlotinib or chemotherapy in routine clinical practice.

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