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European Perspectives

Retrospective Assessment of a Serum Proteomic Test in a Phase III Study Comparing Erlotinib plus Placebo with Erlotinib plus Tivantinib (MARQUEE) in Previously Treated Patients with Advanced Non-Small Cell Lung Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Non-small cell lung cancer • Proteomics • Biomarkers • Erlotinib • Tivantinib

Abstract

Background. The VeriStrat test provides accurate predictions of outcomes in all lines of therapy for patients with non-small cell lung cancer (NSCLC). We investigated the predictive and prognostic role of VeriStrat in patients enrolled on the MARQUEE phase III trial of tivantinib plus erlotinib (T+E) versus placebo plus erlotinib (P+E) in previously treated patients with advanced NSCLC.

Methods. Pretreatment plasma samples were available for 996 patients and were analyzed by matrix-assisted laser desorption/ionization-time of flight mass spectrometry to generate VeriStrat labels (good, VS-G, or poor, VS-P).

Results. Overall, no significant benefit in overall survival (OS) and progression-free survival (PFS) were observed for the addition of tivantinib to erlotinib. Regardless of treatment arm, patients who were classified as VS-G had significantly longer PFS (3.8 mo for T+E arm, 2.0 mo for P+E arm) and OS (11.6 mo for T+E, 10.2 mo for P+E arm) than patients classified as VS-P (PFS: 1.9 mo for both arms, hazard ratio [HR], 0.584; 95% confidence interval [CI], 0.468–0.733; $p < .0001$ for T+E, HR, 0.686; 95% CI, 0.546–0.870; $p = .0015$ for P+E; OS: 4.0 mo for both arms, HR, 0.333; 95% CI, 0.264–0.422; $p < .0001$ for T+E; HR, 0.449; 95% CI, 0.353–0.576; $p < .0001$ for P+E). The VS-G population had higher OS than the VS-P population within Eastern Cooperative Oncology Group (ECOG) performance score (PS) categories. VS-G patients on the T+E arm had longer PFS, but not OS, than VS-G patients on the P+E arm ($p = .0108$). Among EGFR mutation-positive patients, those with VS-G status had a median OS more than twice that of any other group (OS: 31.6 mo for T+E and 22.8 mo for P+E), whereas VS-P patients had similar survival rates as VS-G, EGFR-wild type patients (OS: 13.7 mo for T+E and 6.5 mo for P+E).

Conclusion. In these analyses, VeriStrat showed a prognostic role within EGOC PS categories and regardless of treatment arm and EGFR status, suggesting that VeriStrat could be used to identify EGFR mutation-positive patients who will have a poor response to EGFR tyrosine kinase inhibitors. ***The Oncologist*** 2018;23:1–9

Implications for Practice: This study suggests that VeriStrat testing could enhance the prognostic role of performance status and smoking status and replicates findings from other trials that showed that the VeriStrat test identifies EGFR mutation-positive patients likely to have a poor response to EGFR tyrosine kinase inhibitors (TKIs). Although these findings should be confirmed in other populations, VeriStrat use could be considered in EGFR mutation-positive patients as an additional prognostic tool, and these results suggest that EGFR mutation-positive patients with VeriStrat "poor" classification could benefit from other therapeutic agents given in conjunction with TKI monotherapy.

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Introduction

The VeriStrat test is a multivariate, mass-spectrometry based test that measures components of the circulating proteome in the serum of patients with non-small cell lung cancer (NSCLC). VeriStrat results assign a good (VS-G) or poor (VS-P) classification to a tested patient sample [1].

The test is prognostic and has been shown to predict outcomes in several settings. Fidler et al. recently published data on the association between circulating analytes and the VeriStrat test. The test was found to be significantly associated with 23 circulating biomarkers ($p \leq .05$); 6 out of 23 of the analytes had $p \leq .001$ (C-reactive protein, interleukin-6, serum amyloid A, CYFRA 21.1, IGF-II, osteopontin, and ferritin). Gene set enrichment analysis showed correlation between the VeriStrat test and acute phase response, which provides the mechanistic underpinning of the prognostic utility of the test. Taken together, these data indicate that VeriStrat is in fact a multivariate blood test that assesses multiple aspects of the patient's circulating proteome in assigning good and poor labels [2].

Two recent retrospective analyses of studies comparing erlotinib versus placebo in patients with advanced NSCLC demonstrated that VeriStrat testing is prognostic for overall survival (OS) in placebo-treated patients. The TOPICAL trial (first-line erlotinib in patients with advanced non-small cell lung cancer unsuitable for chemotherapy) enrolled patients unsuitable to receive front-line chemotherapy (VS-G median survival, 5.6 mo; VS-P median survival, 2.9 mo; hazard ratio [HR], 0.50; 95% confidence interval [CI], 0.37–0.66; $p < .001$) [3]. The BR.21 trial enrolled placebo-treated patients in second or higher line (VS-G median OS, 6.6 mo; VS-P median OS, 3.1 mo; HR, 0.44; 95% CI, 0.31–0.63; $p < .001$) [4]. In retrospective analyses of multiple cohorts, VeriStrat is prognostic for OS and progression-free survival (PFS) in patients treated with front-line platinum-based chemotherapy [5]. The prognostic and predictive capabilities have been replicated in prospective analyses, in patients treated with front-line platinum and pemetrexed (VS-G median PFS, 6.5 mo; VS-P median PFS, 1.6 mo; HR, 0.36; $p < .001$) [6], and VeriStrat has been shown to be predictive of differential therapeutic benefit between second-line chemotherapy and erlotinib [7].

The VeriStrat test analyzes several mass spectral regions that are associated with proteins, such as serum amyloid-A and other components of the circulating immune system. VS-P patients show an elevation in these components, representing a biological host response to the tumor that results in poor prognosis and diminished response to many therapies. This biological prognostic factor can be incorporated to enhance other common prognostic indicators, such as performance status (PS) and smoking status, given that it independently predicts outcome to therapies within these patient groups. In the placebo-treated patients in the TOPICAL trial, VS-P patients had significantly worse OS than VS-G patients within the same Eastern Cooperative Oncology Group (ECOG) categories (ECOG 0-1: VS-G median OS, 10.5 mo; VS-P median OS, 3.7 mo; ECOG 2–3: VS-G median OS, 4.9 mo; VS-P median OS, 3.5 mo; $p < .001$), suggesting that the prognostic capabilities of PS could be refined by including analysis of the patient's biological state [3].

The VeriStrat test is also predictive for outcomes to epidermal growth factor receptor (*EGFR*)-targeted therapies in patient cohorts in whom the *EGFR* mutation status is wild type (WT) or unknown. Multiple studies have demonstrated that VeriStrat testing can predict outcome to erlotinib [7–9], gefitinib [1, 10], and cetuximab [11], either as monotherapy or in combination with other treatments [12]. A retrospective analysis of the LUX-lung 8 study demonstrated that VeriStrat could also predict OS in patients with squamous cell carcinoma treated with afatinib (VS-G median OS, 11.5 mo; VS-P median OS, 4.7 mo; HR, 0.57; $p = .0001$) [13].

Tivantinib is a small molecule MET inhibitor with potential additional activity as a microtubule inhibitor [13, 14]. Clinical trials of tivantinib have been conducted in a variety of cancers, including hepatocellular carcinoma (HCC) [15], breast cancer [16], gastric cancer [17], pancreatic cancer (NCT00558207), and NSCLC [18]. However, in all these trials, tivantinib alone or in combination did not provide significant benefit relative to standard of care, and the drug currently is not approved for any indication.

The MARQUEE trial was a phase III clinical trial, designed to demonstrate improvement in OS in patients with advanced NSCLC treated in the second or third line with tivantinib plus erlotinib (T+E) compared with placebo plus erlotinib (P+E) [19]. Patients were *EGFR* tyrosine kinase inhibitor (TKI) naïve and enrolled independent of *EGFR* mutation status. The trial enrolled 1,048 patients, and at the futility interim analysis, the addition of tivantinib to erlotinib did not show any significant OS advantage [20]. Post hoc exploratory analysis identified some benefit from tivantinib in a high MET population [20]. However, two prospective trials in selected patients with MET-high HCC failed to show a significant benefit of tivantinib for patients with high MET expression (MET-ICC [21] and JET-ICC [22]), and development of tivantinib is currently halted.

The current retrospective investigation reports VeriStrat analyses of pretreatment serum samples available from the MARQUEE trial. In this analysis, VeriStrat was prognostic for both OS and PFS, independent of other clinical variables (e.g., PS, smoking status, and line of therapy), and prognostic in both *EGFR* WT and *EGFR* mutation-positive (MUT) subgroups.

Materials and Methods

Trial Cohort

Patients enrolled in the MARQUEE study were adult patients with confirmed advanced (stage IIIB or stage IV) NSCLC and an ECOG PS of 0 or 1. Patients had already received one or two prior systemic anticancer regimens and were randomized, after consenting, to receive T+E or P+E. Further details are available in the original publication of the trial [23].

Sample Collection and Proteomic Analysis

Available pretreatment serum samples from 996 patients enrolled in the clinical trial were analyzed by matrix-assisted

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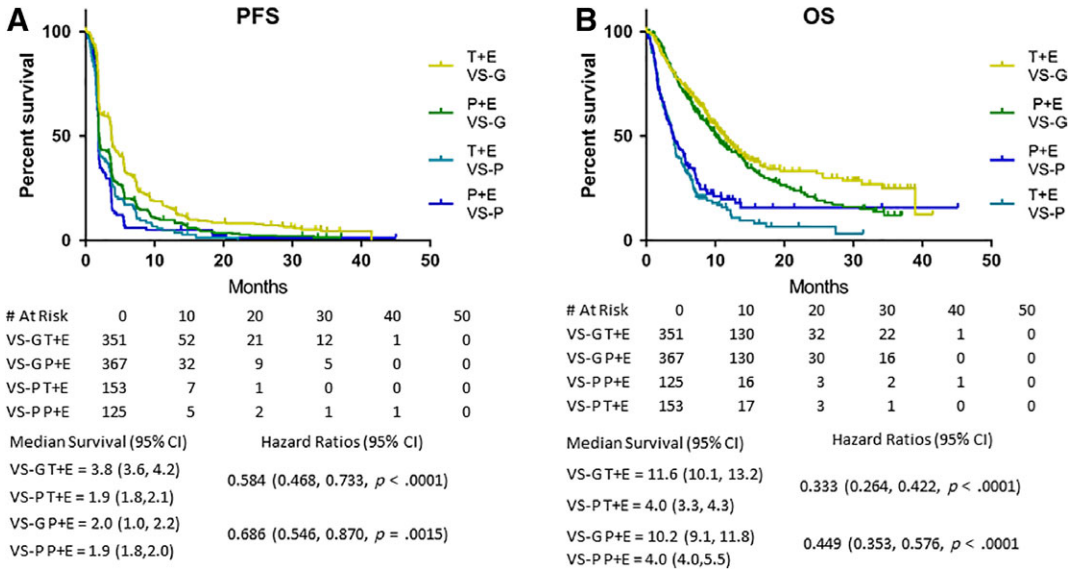

Figure 1. PFS and OS per treatment arm, stratified by VeriStrat. VS-P patients have significantly worse OS and PFS in each treatment arm (all $p < .0001$, except E+P PFS, which is $p < .0015$) in all comers population, including *EGFR* wild type and mutation positive.

Abbreviations: CI, confidence interval; OS, overall survival; P+E, placebo plus erlotinib; PFS, progression-free survival; T+E, tivantinib plus erlotinib, VS-G, VeriStrat "good" category; VS-P, VeriStrat "poor" category.

laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry to generate VeriStrat labels (VS-G or VS-P) according to standard protocols in the Biodesix Clinical Laboratory Improvement Amendments-accredited laboratory (Boulder, CO). Briefly, samples were analyzed by MALDI-TOF (Autoflex Speed, Bruker, Billerica, MA), and resulting spectra were processed and classified by the VeriStrat algorithm [1] blinded to all clinical data.

Statistical Analysis

This retrospective analysis of samples collected prospectively in the MARQUEE study was performed following a statistical analysis plan defined prior to blinded VeriStrat testing. The analysis population was defined as all patients in the intent-to-treat population with VeriStrat classification of VS-G or VS-P. Associations between categorical variables were assessed by Fisher's exact test, associations between continuous and categorical variables by Wilcoxon test, and differences in time-to-event outcomes between groups by Cox proportional hazard analysis stratified by line of treatment, gender, and smoking history. Covariates used in multivariate analysis were prespecified, as were *EGFR* and *KRAS* mutation status and performance status subgroup analyses. All calculations were carried out using SAS 9.3 (SAS Institute, Cary, NC). *P* values are two sided and uncorrected for multiple comparisons.

Results

One thousand forty-eight patients were recruited to the trial, 526 patients in the T+E arm and 522 in the P+E arm. VeriStrat labels of either VS-G or VS-P were successfully generated for 504 patients in the T+E arm and for 492 patients in the P+E arm. The evaluable cohort showed similar characteristics as the entire intent-to-treat patient population enrolled on the trial (supplemental online Fig. 1).

In the analysis population, patients with ECOG PS 0 were significantly more likely to be VS-G ($p = .0001$), as were patients with only one line of prior treatment ($p = .0035$), patients with an *EGFR* activating mutation ($p = .0099$), and female patients ($p = .0025$). Patients with progressive disease (according to RECIST) on a previous line of therapy were significantly more likely to be VS-P ($p < .0001$). Demographic characteristics were well balanced when characterized by both treatment arm and VeriStrat status (Table 1 and supplemental online Table 1).

Overall, the addition of tivantinib to erlotinib showed no significant improvement in either PFS or OS. Regardless of treatment arm in this retrospective analysis, patients who were classified as VS-G had significantly longer PFS (3.8 mo for T+E arm, 2.0 mo for P+E arm) and OS (11.6 mo for T+E, 10.2 mo for P+E arm) than patients classified as VS-P (PFS: 1.9 mo for each arm, OS: 4.0 mo for each arm; Fig. 1). VS-G patients on the T+E arm had significantly longer PFS than VS-G patients on the P+E arm ($p = .0108$). In the prespecified multivariate analysis, adjusting for multiple possible confounding factors, including ECOG PS, *EGFR* mutation status, and smoking status, VeriStrat classification remained an independent predictor of survival (supplemental online Table 2; $p < .001$). In addition, the independent prognostic value of VeriStrat was also maintained when *KRAS* mutation status was added to the multivariate analysis (supplemental online Table 3)

An unplanned analysis by smoking status within the *EGFR* WT population showed that VS-G patients had better survival than VS-P patients within each treatment arm for both ever smokers (P+E: VS-G OS, 9.0 mo; 95% CI, 7.5–9.9; VS-P OS, 3.7 mo; 95% CI, 2.7–5.3; HR, 0.339; 95% CI, 0.260–0.442; $p < .0001$; T+E: VS-G OS, 9.3 mo; 95% CI, 8.5–10.8; VS-P OS, 3.8 mo; 95% CI, 3.1–4.2; HR, 0.254; 95%

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Table 1. Patient characteristics for each trial arm by VeriStrat label

Characteristics	TIV+ERL VS-G (*n* = 351), *n* (%)	TIV+ERL VS-P (*n* = 153), *n* (%)	ERL VS-G (*n* = 367), *n* (%)	ERL VS-P (*n* = 125), *n* (%)
Age				
Mean (standard deviation)	60.84 (10.17)	62.06 (10.14)	61.23 (9.91)	60.69 (9.65)
Median (range)	62.00 (26.00–89.00)	62.00 (31.00–86.00)	62.00 (24.00–87.00)	61.00 (32.00–81.00)
Gender				
Female	152 (43.30)	52 (33.99)	161 (43.87)	40 (32.00)
Male	199 (56.70)	101 (66.01)	206 (56.13)	85 (68.00)
Smoking history				
Current	68 (19.37)	27 (17.65)	64 (17.44)	25 (20.00)
Former	212 (60.40)	101 (66.01)	239 (65.12)	74 (59.20)
Never	71 (20.23)	25 (16.34)	64 (17.44)	26 (20.80)
Performance status				
0	130 (37.04)	30 (19.61)	129 (35.15)	28 (22.40)
1	221 (62.96)	122 (79.74)	238 (64.85)	96 (76.80)
2	0 (0.00)	1 (0.65)	0 (0.00)	1 (0.80)
Disease stage				
IIIB	16 (4.56)	5 (3.27)	11 (3.00)	2 (1.60)
IV	332 (94.59)	146 (95.42)	352 (95.91)	120 (96.00)
Missing	3 (0.85)	2 (1.31)	4 (1.09)	3 (2.40)
Histology				
ADC	326 (92.88)	135 (88.24)	351 (95.64)	116 (92.80)
Large	18 (5.13)	11 (7.19)	13 (3.54)	6 (4.80)
Other	4 (1.14)	4 (2.61)	3 (0.82)	1 (0.80)
Unk	3 (0.85)	3 (1.96)	0 (0.00)	2 (1.60)
Prior treatment regimens				
1	240 (68.38)	91 (59.48)	258 (70.30)	74 (59.20)
2	111 (31.62)	62 (40.52)	109 (29.70)	51 (40.80)
Best response to prior therapy				
CR/PR	101 (28.77)	29 (18.95)	109 (29.70)	30 (24.00)
NE or missing	10 (2.85)	1 (0.65)	7 (1.91)	7 (5.60)
PD	90 (25.64)	71 (46.41)	102 (27.79)	51 (40.80)
SD	150 (42.74)	52 (33.99)	149 (40.60)	37 (29.60)
EGFR status				
Mut	43 (12.25)	9 (5.88)	41 (11.17)	8 (6.40)
NA	0 (0.00)	1 (0.65)	1 (0.27)	0 (0.00)
WT	308 (87.75)	143 (93.46)	325 (88.56)	117 (93.60)
KRAS status				
Mut	92 (26.21)	41 (26.80)	106 (28.88)	32 (25.60)
NA	22 (6.27)	12 (7.84)	22 (5.99)	6 (4.80)
WT	237 (67.52)	100 (65.36)	239 (65.12)	87 (69.60)
MET IHC status				
MET negative	73 (20.80)	31 (20.26)	91 (24.80)	28 (22.40)
MET positive	67 (19.09)	32 (20.92)	69 (18.80)	30 (24.00)
NA	211 (60.11)	90 (58.82)	207 (56.40)	67 (53.60)

VeriStrat labels are distributed among all captured clinical characteristics.

Abbreviations: ADC, adenocarcinoma; CR, complete response; EGFR, epidermal growth factor receptor; ERL, erlotinib; IHC, immunohistochemistry; large, large cell carcinoma; mut, mutation positive; NA, not assessed; NE, not evaluated; PD, progressive disease; PR, partial response; SD, stable disease; TIV, tivantinib; unk, unknown; VS-G, VeriStrat good; VS-P, VeriStrat poor; WT, wild type.

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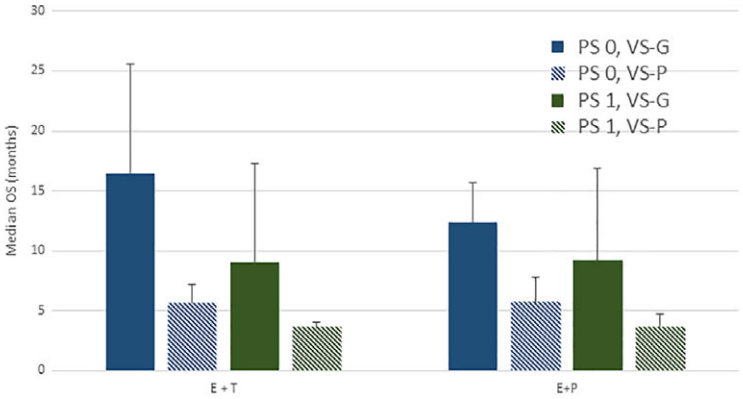

Treatment Group	Performance status	VS	# Subjects	Median OS (95% CI)	HR (95% CI)	*p* value
TIV + ERL	0	good	130	501 (362–779) days 16.5 (11.9–25.6) months	0.275 (0.163–0.463)	<.0001
		Poor	30	170 (105–219) days 5.6 (3.4–7.2) months		
	1	good	221	275 (252–347) days 9.0 (8.3–11.4) months	0.356 (0.270–0.469)	<.0001
		poor	122	110 (87–124) days 3.6 (2.9–4.1) months		
ERL	0	good	129	376 (307–478) days 12.4 (10.1–15.7) months	0.377 (0.215–0.661)	.0007
		poor	28	172 (110–237) days 5.7 (3.6–7.8) months		
	1	good	238	279 (233–322) days 9.2 (7.7–10.6) months	0.419 (0.313–0.559)	<.0001
		poor	96	109 (78–143) days 3.6 (2.6–4.7) months		

Figure 2. VS-G population has higher OS than VS-P within Eastern Cooperative Oncology Group PS categories.

Abbreviations: CI, confidence interval; ERL, erlotinib; HR, hazard ratio; OS, overall survival; PS, performance score; TIV, tivantinib; VS-G, VeriStrat "good" category; VS-P, VeriStrat "poor" category.

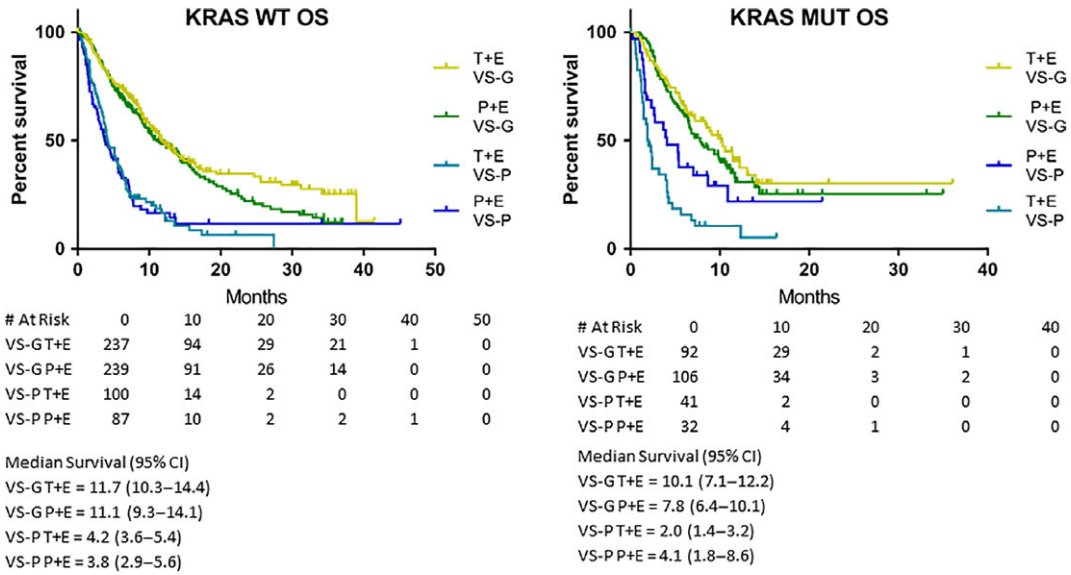

Figure 3. VeriStrat label by treatment group for *KRAS* mutation status.

Abbreviations: CI, confidence interval; MUT, mutation-positive; OS, overall survival; P+E, placebo plus erlotinib; T+E, tivantinib plus erlotinib, VS-G, VeriStrat "good" category; VS-P, VeriStrat "poor" category; WT, wild type.

CI, 0.122–0.529; $p < .0001$) and never smokers (P+E: VS-G OS, 10.1 mo; 95% CI, 6.5–undefined; VS-P OS, 4.5 mo; 95% CI, 2.3–7.8; HR, 0.480; 95% CI, 0.233–0.985; $p \leq .0454$; T+E: VS-G OS, 12.7 mo; 95% CI, 7.9–undefined; VS-P OS, 5.1 mo; 95% CI, 1.5–7.1; HR, 0.339; 95% CI, 0.260–0.442; $p = .00013$; supplemental online Fig. 2).

The original clinical trial included patients with ECOG PS 0–2. For patients who had VeriStrat labels, 317 patients had an ECOG score of 0, 677 patients had an ECOG score of 1, and 2 patients had an ECOG score of 2. VS-G and VS-P patients were found in ECOG categories 0 and 1. However, a higher proportion of ECOG 0 patients were VS-G.

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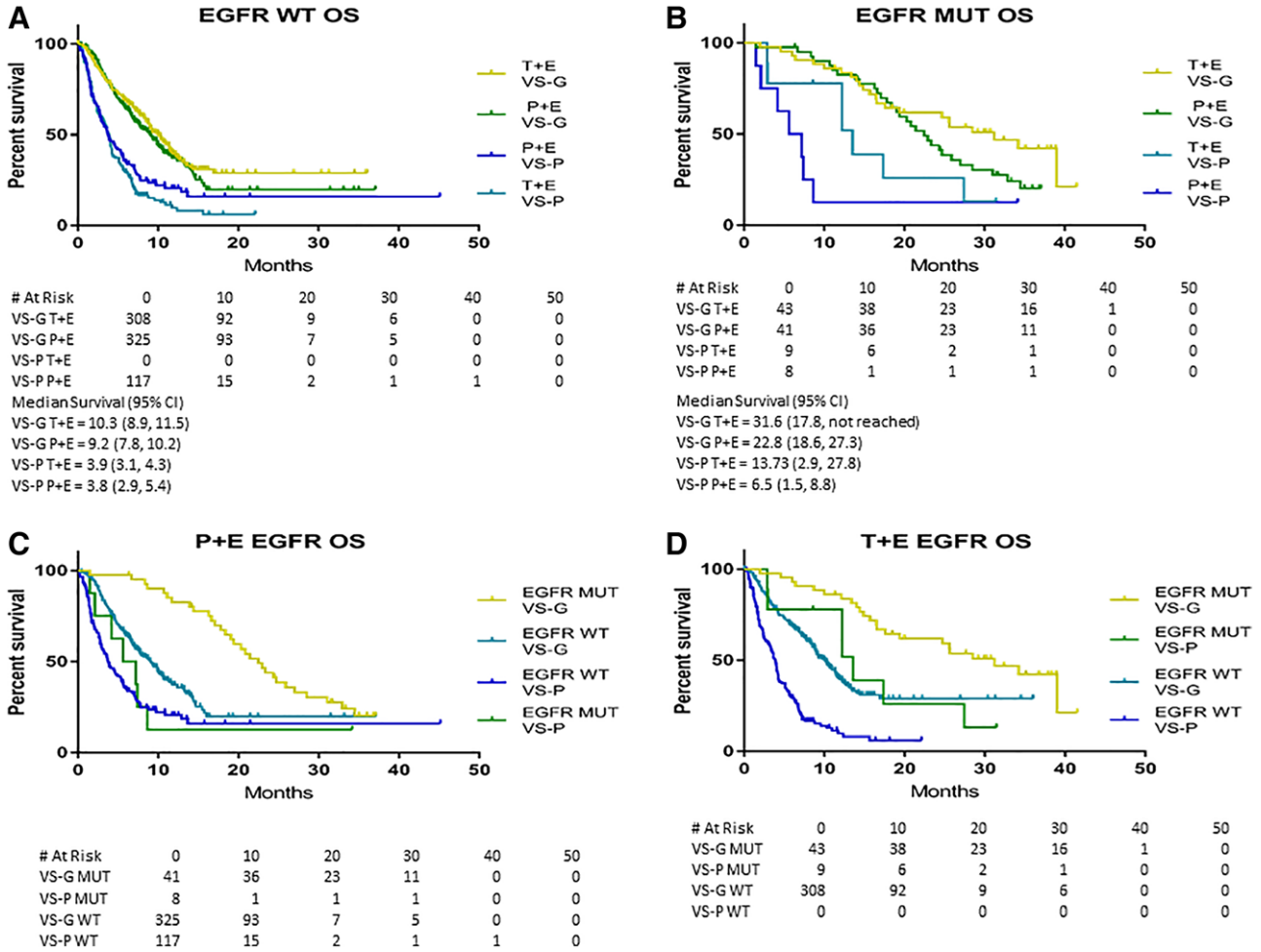

Figure 4. VeriStrat label by treatment group for *EGFR* mutation status. **(A):** Only *EGFR* WT patients by treatment arm and VS status. **(B):** Only *EGFR* MUT patients by treatment arm and VS status. **(C):** Combined *EGFR* WT and MUT patients for P+E arm only. **(D):** Combined *EGFR* WT and MUT patients for T+E arm only.

Abbreviations: CI, confidence interval; MUT, mutation-positive; OS, overall survival; P+E, placebo plus erlotinib; T+E, tivantinib plus erlotinib, VS-G, VeriStrat "good" category; VS-P, VeriStrat "poor" category; WT, wild type.

Overall, patients with a higher ECOG (worse PS) have lower OS, as expected (Fig. 2). However, within ECOG categories, VS-P patients had significantly worse OS than VS-G patients. Patients who had a PS of 0 and were VS-G had a median OS of 16.5 months (T+E) or 12.3 months (P+E), compared with VS-P patients, who had a median OS of 9 months (T+E) or 5.7 months (P+E; $p < .0001$ for T+E; $p = .0007$ for P+E). Similar differences were seen in the PS 1 patient population, with VS-G patients having a median OS of 9 months (T+E) or 9.2 months (P+E) and VS-P patients having a median OS of 3.6 months (T+E) or 3.5 months (P+E; $p < .0001$ for both treatment arms).

VeriStrat Status and *KRAS* Mutation Status

Approximately 27% of all patients in the MARQUEE trial had tumors that were positive for *KRAS* mutations. Twenty-seven percent of *KRAS* MUT and 28% of *KRAS* WT patients were VS-P (Table 1). Regardless of *KRAS* status, VS-G patients had longer OS than VS-P in both treatment arms, and *KRAS* status showed little effect on OS (Fig. 3).

The median OS for the T+E arm was 11.7 months (95% CI, 10.3–14.4) for VS-G, *KRAS* WT patients and 11.1 (95% CI, 9.3–14.1) for VS-G, *KRAS* MUT patients. The P+E arm showed a numerical OS difference between WT and MUT VS-G patients (10.4 mo for T+E and 7.8 mo for P+E; p = .1696; Fig. 3).

Patients that were VS-P and *KRAS* WT had similar OS in each treatment arm (medians: 4.2 mo for T+E and 3.8 mo for P+E; Fig. 3). VS-P *KRAS* MUT patients had significantly lower OS on the T+E arm than on the P+E arm (2.0 vs. 4.1 mo, $p = .05$).

VeriStrat Status and *EGFR* Mutation Status

Within the MARQUEE clinical trial there were 61 patients who were positive for *EGFR* mutations (MUT) patients in total, and 17% of them were VS-P.

EGFR WT patients who were VS-G had significantly better OS (10.3 mo for T+E and 9.2 mo for P+E) than *EGFR* WT patients that were VS-P within the same treatment arm (3.9 mo for T+E and 3.8 mo for P+E; Fig. 4A). Similarly, patients who were VS-G and *EGFR* MUT had significantly better OS (31.6 mo for T+E and 22.8 mo for P+E) than

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EGFR MUT patients in the same treatment arm who were VS-P (13.7 mo for T+E and 6.5 mo for P+E; Fig. 4B).

A comparison of *EGFR* WT and MUT patients within treatment arms showed that *EGFR* mutation-positive patients who were VS-G had the best outcomes on *EGFR*-targeted therapy (Fig. 4C and 4D). VS-G patients who were *EGFR* MUT had an OS more than twice that of any other *EGFR*/VS subgroup. Patients that were VS-P and *EGFR* MUT had similar survival to VS-G, *EGFR* WT patients in either treatment arm. Patients that were *EGFR* WT and VS-P had poorer OS and performed the worst.

Discussion

In this retrospective analysis of serum samples from the MARQUEE trial, adjusting for ECOG PS, EGFR mutation status, smoking status, and *KRAS* mutation status, VeriStrat, PS and EGFR Mutation status were significant predictors of OS. VS-G patients outperformed VS-P patients in both treatment arms, within ECOG PS categories 0 or 1, and in *EGFR* mutation-positive or WT subgroups. Patients who were VS-P had significantly reduced OS compared with VS-G patients with the same PS status. VS-P patients who were *EGFR* MUT did significantly worse than mutation-positive patients that were VS-G. *KRAS* mutation status had little effect on OS, consistent with the original report [19]. An analysis of only the *EGFR* WT group examining the interaction between VeriStrat status and smoking status showed that VS-G groups had improved OS over VS-P within groups of ever smokers and never smokers.

The vast majority of patients included in the MARQUEE trial had ECOG scores of either 0 or 1 [24]. As expected, patients with ECOG scores of 1 had lower OS than patients with ECOG score of 0. A higher percentage of patients with ECOG score of 1 were VS-P, compared with patients with ECOG scores of 0; however, VS-P patients were found in both ECOG categories. Within each ECOG category and treatment arm, VS-P patients had an OS that was less than half that of the VS-G patients.

Analysis of the TOPICAL trial showed that the prognostic role of VS extends to patients with ECOG scores of 2 and 3. In an exploratory analysis [3] of ECOG 2–3 patients in the TOPICAL trial, VS-G patients had longer OS than VS-P patients (median OS for VS-G and VS-P on placebo was 4.9 and 3.5 mo, respectively; HR, 0.51; 95% CI, 0.36–0.73; $p < .001$). MARQUEE and TOPICAL have shown that VS classifications are distributed across ECOG scores 0–3 and that the VS-G subgroup consistently has longer OS than the VS-P subgroup across different treatments. These analyses suggest that including VeriStrat status may enhance the prognostic utility of PS. The combination of patient functional status with an assessment of the patient's circulating proteome allows for a biologically inclusive score and may further refine patient prognosis and tailor treatment plans. Patients with a good PS who are VS-G might derive maximal benefit from standard care, whereas patients with a good PS who are VS-P might benefit from more aggressive treatment.

Current guidelines recommend *EGFR*-targeted therapy only for patients that are positive for *EGFR* mutations in both the first and second line of therapy [25–27]. *EGFR* WT patients do derive some benefit from EGFR-TKIs in the second line [28, 29], regardless of *KRAS* status [30]; however, multiple clinical trials (TAILOR [31], TITAN [32], DELTA [33], and EMPHASIS [8]) have shown that the survival benefit is comparable to chemotherapy. The MARQUEE trial did not select for *EGFR*-activating mutations, and approximately 90% of patients enrolled on the trial had the WT *EGFR* gene. In both treatment arms of the clinical study, *EGFR* MUT patients had improved PFS and OS over WT patients, and a recent report demonstrates that *EGFR* MUT patients did derive some additional benefit from the addition of tivantinib in this trial [34].

Recently, a retrospective analysis of the VeriStrat test was completed for a clinical trial (P06162) that assessed the addition of ficlatuzumab, an anti-c-MET monoclonal antibody, to gefitinib in Asian patients with advanced-stage NSCLC [10]. In the overall population, the addition of the MET inhibitor to gefitinib showed no improvement in overall response rate and no advantage for PFS or OS. However, VS-P patients derived more benefit from combination therapy than gefitinib alone. A significant improvement in both PFS (7.4 vs. 2.3 mo; HR, 0.46; 95% CI, 0.23–0.91; $p = .02$) and OS (23.9 vs. 5.8 mo; HR, 0.41; 95% CI, 0.18–0.90; $p = .04$) was observed in VS-P patients, suggesting that the addition of ficlatuzumab to gefitinib might "rescue" the poor performing group [10].

In both the P06162 [10] and MARQUEE trials [19], VeriStrat status stratified both *EGFR* WT and MUT patients into VS-P and VS-G groups. In both monotherapy arms (erlotinib or gefitinib), VS-P, MUT subgroups did not perform any better than VS-G, WT subgroups of patients. These studies suggest that VeriStrat could identify patients who will not respond well to TKI monotherapy despite the presence of *EGFR* activating mutations. Although *EGFR* MUT, VS-P patients could make up only 1%–3% of the white NSCLC population (in the MARQUEE trial only 1.7% of patients met these criteria), this could be a subgroup of patients to monitor closely while on TKI monotherapy, and perhaps additional therapeutic agents could provide better benefit.

Although VS-P patients have an overall worse prognosis than VS-G, some studies have suggested that certain therapies or combinations may improve outcomes. A small study in elderly patients (LCC0512) showed that VS-G and VS-P groups performed comparably on monotherapy gemcitabine (VS-G median OS, 201 days; VS-P median OS, 197 days; HR, 0.82; 95%CI, 0.35–1.90; $p = .64$) [35]. Although the addition of tivantinib to erlotinib showed no benefit, the addition of ficlatuzumab to gefitinib in the P06162 trial improved OS and PFS in VS-P patients and could potentially act as a "rescue" for these patients, regardless of *EGFR* status. Both ficlatuzumab and tivantinib are MET inhibitors but with different mechanisms of action, and the potential for a "rescue" of VS-P patients treated with ficlatuzumab may be drug specific and not universal to MET inhibitors as a class. However, it should be acknowledged that because of the limited number of considered cases from the specific

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study, the hypothesis may be considered highly speculative and a prospective confirmation is clearly needed.

The data reported in this article justify additional research in the front line combining VeriStrat stratus in combination with *EGFR* mutation status. Given the ability of the VeriStrat test to stratify patient risk, even among *EGFR* mutation-positive patients, further work could support the use of less aggressive first- and second-generation TKI therapy. Furthermore, the ability to risk stratify patients using VeriStrat supports further work on the use of VeriStrat among first-line patients as candidates for third-generation TKI therapy.

Conclusion

A retrospective investigation of the MARQUEE trial with the VeriStrat test confirmed limited benefit of adding tivantinib to erlotinib. More importantly, this analysis suggests that VeriStrat testing could enhance the prognostic of PS and smoking status and replicates findings from other trials that showed that the VeriStrat test identifies *EGFR* MUT patients likely to have a poor response to *EGFR* TKIs. Although these findings should be confirmed in other populations, VeriStrat use could be considered in *EGFR* MUT patients as an additional prognostic tool, and these results suggest that VS-P, *EGFR* MUT patients could benefit from other therapeutic agents given in conjunction with TKI monotherapy.

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Disclosures

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