INTERVIEW

David P Carbone, MD, PhD

Dr Carbone is Professor of Medicine and Director of the James Thoracic Center in Columbus, Ohio.

Tracks 1-11

Track 1 Prognostic and predictive role of the VeriStrat® serum proteomic test in patients with advanced NSCLC treated with erlotinib

Track 2 Impact of EGFR mutation status on the predictive accuracy of VeriStrat

Track 3 Technological foundation of the VeriStrat test

Track 4 Perspective on the Phase III PointBreak trial

Track 5 **Case discussion:** A 60-year-old man with PET-avid bilateral hilar adenopathy and subcentimeter contralateral pulmonary nodules underwent lobectomy and remains disease free 5 years later

Track 6 A physician's personal experience with the diagnosis and treatment of diffuse large B-cell lymphoma

Track 7 **Case discussion:** A 65-year-old never smoker with resected Stage I NSCLC receives repeated stereotactic RT for multiple recurrences of brain metastases and develops multisite EGFR mutation-positive disease 10 years later

Track 8 Approach to systemic treatment for patients with asymptomatic metastatic NSCLC

Track 9 Treatment options for patients with progressive EGFR-mutant NSCLC after sustained response to erlotinib

Track 10 Geographic differences in anaphylactic reactions to cetuximab versus panitumumab

Track 11 **Case discussion:** A 60-year-old smoker who underwent resection of Stage I NSCLC presents with recurrent brain metastasis

Select Excerpts from the Interview

Tracks 1, 3

DR LOVE: Would you discuss the role of the VeriStrat test in identifying patients with advanced NSCLC who may benefit from EGFR TKI therapy?

DR CARBONE: The idea behind the VeriStrat plasma test was to ascertain, using a minimally invasive approach, whether we could identify which patients would benefit from EGFR-targeted therapies. It's clear that patients with EGFR mutations benefit from such targeted therapies, although ultimately they all develop resistant disease.

However, evidence shows that some subsets of patients with NSCLC without detectable EGFR mutations demonstrate several months of minimal responses or progression-free survival with EGFR-targeted therapies. Hence, we set out to determine a protein signature that was able to classify patients as those with good or poor survival outcomes after treatment with erlotinib.

The Canadian Phase III BR.21 study, which evaluated erlotinib versus placebo for previously treated NSCLC, was conducted about a decade ago and reported a survival advantage in an unselected patient population (Shepherd 2005). We performed a retrospective analysis of blood samples from patients enrolled on the BR.21 trial (Carbone 2012; [4.1]).

The median overall survival in the subset of patients receiving erlotinib that we identified with the good-outcome protein signature was 10.5 months. Without that signature, the median overall survival was 3.98 months. So the protein signature seemed to provide prognostic information in patients on the BR.21 trial who received erlotinib by identifying patients with a better chance of survival.

The majority of patients on the BR.21 study were not tested for EGFR mutations, so we don't know how that fits in. Of the blood samples subjected to VeriStrat testing, about 60% were classified as having a good protein signature (4.1). No more than 10% of patients in the Western population harbor EGFR mutations, so clearly the protein signature is not dependent on EGFR mutation status.

In fact, the result of our study was not correlated with EGFR mutations. Out of 19 patients with objective responses, 18 had a good proteomic signature, and that was a statistically significant predictive factor for response (4.1).

We also concluded that in certain circumstances the VeriStrat test might be able to identify subsets of patients with a better chance of survival. Of note, some data suggest that patients with squamous cell carcinomas may have better outcomes than those with adenocarcinomas.

4.1

Prognostic and Predictive Roles of the VeriStrat Plasma Test in Patients with Advanced Non-Small Cell Lung Cancer Treated with Erlotinib or Placebo on the BR.21 Phase III Trial

Outcome	Patients with good protein signature		Patients with poor protein signature	
	Erlotinib (n = 183)	Placebo (n = 83)	Erlotinib (n = 109)	Placebo (n = 61)
Overall survival	10.5 mo	6.6 mo	3.98 mo	3.09 mo
	HR = 0.63; $p = 0.002$		HR = 0.77; $p = 0.1071$	
Progression-free survival	3.68 mo	1.84 mo	1.76 mo	1.71 mo
	HR = 0.54; $p = 0.0000$		HR = 0.73; $p = 0.0495$	
	Erlotinib-treated patients with good protein signature (n = 157*)		Erlotinib-treated patients with poor protein signature (n = 95*)	
PR/CR (ORR)	18 (11%)		1 (1%)	
PD/SD	139 (89%)		94 (99%)	

* Evaluable patients
PR = partial response; CR = complete response; ORR = objective response rate; PD = progressive disease; SD = stable disease

"Of 252 erlotinib-treated patients evaluable for response, 157 (62%) were classified as Good and 95 (38%) as Poor."

Carbone DP et al. *J Thorac Oncol* 2012;7(11):1653-60.

In a set of data yet to be published, we observed a 6-fold difference in median survival for patients with squamous cell carcinoma treated with erlotinib between the patient groups classified as having good and poor proteomic signatures.

If patients with a poor chance of survival after erlotinib therapy are removed, it may be possible to identify a subset of patients with squamous cell carcinoma with excellent progression-free and overall survival with erlotinib. This concept is currently being studied in a prospective European randomized trial (ETOP 3-12 EMPHASIS-lung).

I need to make it clear that I'm not stating that the VeriStrat assay will replace EGFR mutation tests. It would be wrong to say so. All patients with lung cancer should have a mutation analysis performed for EGFR, ALK and other targetable genetic abnormalities. In Western populations, however, most patients with lung cancer don't have clinically validated targets that can be detected by genetic analysis. Therefore, the purpose of our study was to find markers that might correlate with benefit from EGFR TKIs.

DR LOVE: Would you discuss the technology behind the VeriStrat test?

DR CARBONE: The VeriStrat test is a protein-based assay that utilizes the matrix-assisted laser desorption ionization mass spectrometric technique (Taguchi 2007). It is conducted using only a few microliters of plasma or serum. The VeriStrat test can be performed by spotting the plasma onto a paper card and mailing the card for mass spectrometric analysis.

Track 4

DR LOVE: Would you summarize the results of the much-anticipated Phase III PointBreak trial and provide your perspective on it?

DR CARBONE: This study evaluated pemetrexed, carboplatin and bevacizumab followed by maintenance pemetrexed/bevacizumab versus paclitaxel, carboplatin and bevacizumab followed by bevacizumab maintenance for patients with advanced NSCLC (Patel 2012; [4.2]). The paclitaxel, carboplatin and bevacizumab arm of the trial is the same as the positive treatment arm from the ECOG-E4599 study (Sandler 2006).

We have ample data to show that pemetrexed is an extremely active agent in nonsquamous tumors, and many believe that it may be a superior regimen to carboplatin/paclitaxel. Also, the addition of maintenance pemetrexed has demonstrated improvements in progression-free survival. So it was reasonable to compare the ECOG-E4599 regimen to a pemetrexed-based regimen followed by pemetrexed/bevacizumab maintenance.

Many predicted that the pemetrexed/bevacizumab combination would be substantially better than bevacizumab alone as maintenance therapy. However, no difference was observed.

This was disappointing in that it would have been nice to have a documented regimen that was more beneficial than the E4599 regimen. It would have been a costly regimen, however, given that the PointBreak trial used both bevacizumab and pemetrexed as maintenance therapy. Even though the PointBreak trial results validate the E4599 data, it was disappointing that these data didn't point the way toward improving outcomes over the earlier study, which is now almost 10 years old. ■

4.2

PointBreak: A Phase III Trial of Pemetrexed (Pem)/Carboplatin (Cb)/Bevacizumab (B) Followed by Maintenance Pem + B versus Paclitaxel (Pac)/Cb/B Followed by Maintenance B for Patients with Advanced Nonsquamous Non-Small Cell Lung Cancer

All patients	Pem/Cb/B (n = 472)	Pac/Cb/B (n = 467)	HR	*p*-value
Median PFS	6.0 mo	5.6 mo	0.83	0.012
Median OS	12.6 mo	13.4 mo	1.00	0.949
Overall response rate	34.1%	33.0%	NR	NR
Maintenance patients	(n = 292)	(n = 298)		
Median PFS	8.6 mo	6.9 mo	NR	NR
Median OS	17.7 mo	15.7 mo	NR	NR
Adverse events	**Pem/Cb/B** (n = 442)		**Pac/Cb/B** (n = 443)	
	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4
Anemia*	31.0%	14.5%	24.4%	2.7%
Thrombocytopenia*	17.9%	23.3%	17.2%	5.6%
Neutropenia*	14.7%	25.8%	8.4%	40.6%
Hemorrhage – GI/pulmonary†	3.6%	1.8%	3.8%	0.5%
Thromboembolic event	0.5%	3.2%	0.2%	2.0%

* Significant difference between arms for Grade 3 and 4 toxicities
† Grade 5 events: Pac/Cb/B = 0.7%; Pem/Cb/B = 0.5%
PFS = progression-free survival; OS = overall survival; NR = not reported

Conclusion: The primary endpoint of superior OS was not met in this trial, although Pem/Cb/B improved PFS. Toxicity profiles differed and both regimens demonstrated tolerability.

Patel J et al. Chicago Multidisciplinary Symposium in Thoracic Oncology 2012;**Abstract LBPL1**.

SELECT PUBLICATIONS

Carbone DP et al. **Prognostic and predictive role of the VeriStrat plasma test in patients with advanced non-small-cell lung cancer treated with erlotinib or placebo in the NCIC Clinical Trials Group BR.21 trial.** *J Thorac Oncol* 2012;7(11):1653-60.

Gautschi O et al. **VeriStrat® has a prognostic value for patients with advanced non-small cell lung cancer treated with erlotinib and bevacizumab in the first line: Pooled analysis of SAKK19/05 and NTR528.** *Lung Cancer* 2013;79(1):59-64.

Lazzari C et al. **Prospective correlative study of FDG-PET SUV and proteomic profile (VeriStrat) of non-small cell lung cancer patients treated with erlotinib.** *Proc ASCO* 2012;**Abstract e18096**.

Patel J et al. **A randomized, open-label, Phase 3, superiority study of pemetrexed (Pem)+carboplatin (Cb)+bevacizumab (B) followed by maintenance Pem+B versus paclitaxel (Pac)+Cb+B followed by maintenance B in patients (Pts) with stage IIIB or IV non-squamous nonsmall cell lung cancer (Ns-Nsclc).** Chicago Multidisciplinary Symposium in Thoracic Oncology 2012;**Abstract LBPL1**.

Salmon JS et al. **VeriStrat predicts survival in patients with non-small cell lung cancer (NSCLC) treated with erlotinib and bevacizumab.** *Proc ASCO* 2008;**Abstract 8008**.

Sandler A et al. **Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer.** *N Engl J Med* 2006;355(24):2542-50.

Shepherd FA et al. **Erlotinib in previously treated non-small-cell lung cancer.** *N Engl J Med* 2005;353(2):123-32.

Taguchi F et al. **Mass spectrometry to classify non-small-cell lung cancer patients for clinical outcome after treatment with epidermal growth factor receptor tyrosine kinase inhibitors: A multicohort cross-institutional study.** *J Natl Cancer Inst* 2007;99(11):838-46.