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Submitted by:

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RE: NCCN Guidelines Panel: Non-Small Cell Lung Cancer (NSCLC)

On behalf of Biodesix, I respectfully request the NCCN NSCLC Guidelines Panel to consider the referenced prospective, biomarker-stratified, randomized phase 3 trial (PROSE) in thoracic oncology as Level 1 evidence supporting the inclusion of VeriStrat® (VS), a serum proteomic test that is both prognostic and predictive, as a recommendation to help guide decisions regarding 2nd line treatment for advanced NSCLC.

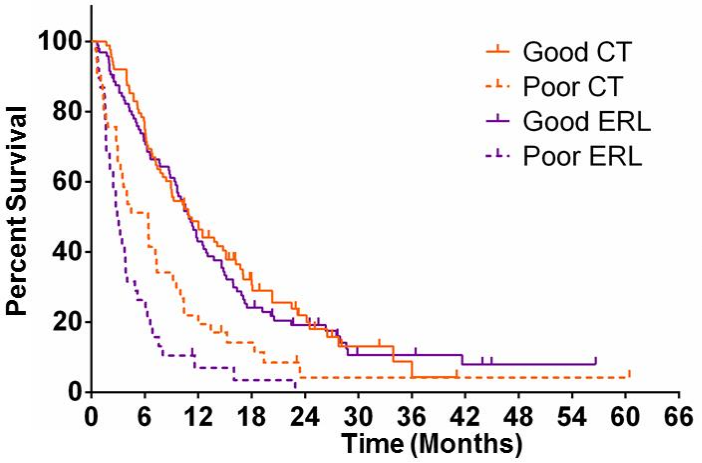
Specific Changes: Recommend VS as a routine test to help guide decisions for 2nd line treatment (erlotinib vs single-agent chemotherapy) of NSCLC patients with wild-type (WT) *EGFR* or with unknown *EGFR* status.

Regulatory Clearance: The VS test is a laboratory developed test performed in a central laboratory that has both a CLIA-certification and a New York State Wadsworth Center Clinical Laboratory Evaluation Program permit.

Rationale: Prior to VS, there were no available clinically validated tests to predict differential survival benefit when considering erlotinib as a 2nd line option for advanced NSCLC following progression after 1st line chemotherapy. Currently, the choice of agent for 2nd line therapy proceeds from a number of factors including patient comorbidities, toxicity from previous treatments, risk of neutropenia, smoking history, histology, and patient preference.[1] Erlotinib is an FDA approved therapy that has become standard of care in patients with *EGFR*-activating mutations; however, it is also approved for advanced 2nd line NSCLC regardless of *EGFR* mutation status and, therefore, is an option in addition to single-agent chemotherapy.[2] In an unselected population who progressed on 1st line platinum-based chemotherapy, erlotinib demonstrated similar survival benefit as chemotherapy while in another trial, docetaxel was borderline superior to erlotinib for survival in patients with *EGFR* WT status.[3,4] A predictive test for erlotinib versus chemotherapy in 2nd line advanced NSCLC (with *EGFR* WT or unknown *EGFR* status) would provide important clinical information to assist with choice of approved therapy in a manner that improves overall survival (OS). The PROSE trial was designed to prospectively evaluate the utility of the VS test as a predictive biomarker regarding overall survival for erlotinib versus chemotherapy in 2nd line NSCLC in patients with *EGFR* WT or with unknown *EGFR* status.[5]

The study reached its primary endpoint, demonstrating significant interaction between VS classification and treatment in terms of OS (**Fig. 1** and **Table 1**). These results demonstrate that the VS test is prognostic and predictive of differential survival benefit between chemotherapy and erlotinib independently of other clinical factors. Furthermore, the prospective randomized PROSE trial confirms the findings of previously published retrospective analyses.[1,6-8]

Figure 1. *Kaplan-Meyer Curves of Overall Survival and Treatment Interaction Analyses*[5]



Treatment Interaction	*P* Value
Unadjusted	.031
Adjusted[a]	.017

[a] Adjusted for smoking history, ECOG performance status, and center

Table 1. *Adjusted Interaction Analysis of Overall Survival*[5]

Covariate	Hazard Ratio (95% CI)	*P* Value
VS classification (Poor vs Good)	1.88 (1.25-2.84)	.003
Treatment (ERL vs CT)	1.15 (0.83-1.59)	.405
VS treatment interaction	1.98 (1.10-3.57)	.022
ECOG PS (2 vs 0-1)	2.67 (1.57-4.53)	.0003
Smoking history (ever vs never)	1.25 (0.79-1.98)	.337
Histology (squamous vs non-squamous)	1.08 (0.75-1.57)	.672
Gender (female vs male)	0.90 (0.64-1.27)	.557
Age (years)	0.99 (0.97-1.01)	.155
EGFR status (mutation vs WT/squamous)	0.66 (0.34-1.27)	.212
EGFR status (not available vs WT/squamous)	1.25 (0.90-1.73)	.180

The practical consequence of these findings is that patients with advanced NSCLC who have *EGFR* WT or unknown *EGFR* mutation status and a VS classification of "Poor" should not be offered 2nd line erlotinib due to inferior survival outcome as compared to chemotherapy, and patients with a VS classification of "Good" may derive similar survival benefit from 2nd line erlotinib or single-agent chemotherapy. In those cases where patients desire the convenience of oral therapy, VeriStrat enables the physician to prescribe erlotinib to VS Good patients in this setting.

The following articles and presentation are submitted in support of this proposed change.

1. Stinchcombe TE, Socinski M. Considerations for 2nd line therapy of non-small cell lung cancer. *The Oncologist.* 2008;13:28-36.
2. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Non-Small Cell Lung Cancer (v3.2014). National Comprehensive Cancer Network. http://www.nccn.org/professionals/physician_gls/PDF/nsclc.pdf. Accessed May 23, 2014.
3. Ciuleanu T, Stelmakh L, Cicenas S, et al. Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study. *Lancet Oncol.* 2012;13(3):300-308.
4. Garassino MC, Martelli O, Broggini M, et al on behalf of the TAILOR trialists. Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. *Lancet Oncol.* 2013;14:981-988.
5. Gregorc V, Novello S, Lazzari C, et al. Predictive value of a proteomic signature in patients with non-small-cell lung cancer treated with second-line erlotinib or chemotherapy (PROSE): a biomarker-stratified, randomized phase 3 trial. *Lancet Oncol.* 2014;15(7):713-721.
6. Taguchi F, Solomon B, Gregorc V, et al. Mass spectrometry to classify non-small cell lung cancer patients for clinical outcome after tyrosine kinase inhibitors: a multicohort cross-institutional study. *JNCI.* 2007;99:838-846.
7. Milan E, Lazzari C, Anand S. SAA1 is over-expressed in plasma of non-small-cell lung cancer patients with poor outcome after treatment with epidermal growth factor receptor tyrosine-kinase inhibitors. *J Proteomics.* 2012;76:Spec No.:91-101.
8. Carbone DP, Ding K, Roder H, 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;7:1653-1660.

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