Clinical perspective on PROSE: does VeriStrat testing improve selection of second-line treatment for patients with non-small cell lung cancer?

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Erlotinib is an active agent that triggers dramatic and sustained responses in a subset of patients with non-small cell lung cancer (NSCLC). The vast majority of these patients with miraculous erlotinib responses harbor deletion 19 or L858R activating mutations in the *epidermal growth factor receptor* (*EGFR*) gene (1). However, erlotinib was designed to inhibit the wild-type version of the *EGFR* gene and does have activity for treating EGFR wild-type cancers. The question of whether or not to use erlotinib for EGFR wild-type cancers and in what line of treatment is a matter of ongoing debate. The PROSE investigators have added fuel to the fire of this debate with their recent publication.

Testing for activating mutations in EGFR has become a standard of care and is typically performed at the time of initial diagnosis. Erlotinib is utilized as initial treatment or switch maintenance treatment for patients with del 19 or L858R activating mutations in standard treatment algorithms. For patients with EGFR wild-type cancers, clinical decision making for the use of erlotinib has been a challenge. The results of SATURN and BR21 indicate a survival advantage for use of erlotinib over best supportive care in the maintenance, second-line, and third-line settings (2,3). However, the real-world dilemma is not for the use of erlotinib compared to best supportive care but in comparison to other available treatment options.

Several options exist for the treatment of EGFR wild-type NSCLC in the second-line setting. Among the options are erlotinib and intravenous chemotherapy treatments including docetaxel or gemcitabine (4,5). Studies comparing erlotinib to chemotherapy for EGFR wild-type cancers in this setting have yielded mixed results with some indicating similar clinical outcomes regardless of treatment and others indicating superiority of chemotherapy (6-9). The TAILOR study reported, docetaxel had increased overall survival (OS) (HR 0.73; P=0.05) and progression free survival (PFS) (HR 0.71; P=0.02) as compared to erlotinib (9).

Given that the majority of NSCLC cases do not harbor activating mutations in the EGFR gene, several other molecular diagnostic tests have been evaluated that divide EGFR wild-type cancer into those with a high likelihood of response to erlotinib and those with a low-likelihood of response to erlotinib. These tests include VeriStrat, E-cadherin, TGFα, cyclin D1, and many others (10). While these tests have largely been a matter of research investigation, VeriStrat has made its way into the clinical arena. VeriStrat has several advantages including a more extensive body of clinical research, availability of central laboratory testing, ease of obtaining as a peripheral blood based test, and quick turnaround for results (typically less than 72 hours).

VeriStrat is a serum-based proteomic test designed to predict outcomes of patients with metastatic NSCLC treated with erlotinib. It is a proteomic test that utilizes matrix-assisted laser desorption/ionization mass spectrometry. The test was developed and validated in a study of 460 patients from eight different patient cohorts treated at different institutions (11). In the study by Taguchi *et al.*, patients were treated with gefitnib and were divided into good and poor classifications. This study and others demonstrated that those classified in the poor group had worse outcomes after treatment with an EGFR inhibitor when compared to patients with the good

classification (11-13).

A retrospective study utilizing plasma samples from the BR21 study further supported the ability of VeriStrat to separate patients into good *vs.* poor outcome groups when treated with erlotinib. Those in the good classification group had a median OS of 10.5, while those in the poor group had a median OS of 4.0 months (13). This study also indicated a prognostic role of VeriStrat testing which predicted poorer outcomes in placebo patients with poor test result compared to placebo patients with a good test result.

In PROSE, Gregorc *et al.* performed a prospective phase III, randomized biomarker stratified study where VeriStrat was used to guide the analysis. It sought to test the proteomic signature and treatment effect of erlotinib (14). In the clinical trial, 285 patients with inoperable stage IIIB or IV NSCLC were randomized 1:1 to systemic chemotherapy using chemotherapy (pemetrexed or docetaxel) or erlotinib. Applying the VeriStrat test, 70% of patients were classified as VeriStrat good (VG) and 30% were classified as VeriStrat poor (VP). The patients classified as VP, had a worse OS (HR 2.50; P<0.0001) and PFS (HR 1.75; P<0.0001) than the VG patients. In addition, those classified as VP derived little benefit from erlotinib, and had a better median survival when treated with chemotherapy, 6.38 *vs.* 2.98 months (HR 0.58; P=0.022) (14). For the group as a whole, the median OS and PFS slightly favored chemotherapy over erlotinib, but this was not statistically significant. For the VG patients, the outcomes were similar between chemotherapy and erlotinib.

The VeriStrat test in PROSE confirmed its prognostic ability reporting a dramatically different PFS and OS independent of the treatment given. These results include a 1.4 month difference in median PFS and a 4.5 month difference in median OS between VG and VP patients (14). This magnitude of effect on prognosis indicates that VeriStrat is measuring factors in the blood stream that strongly correlate with the outcomes of patients. Since this is a black-box test, the details of what is being measured have not yet been made available or are not understood. Understanding what these factors are, could potentially lead to identification of new targets and better understanding of resistance to tyrosine kinase inhibitors.

As for the predictive value of VeriStrat, PROSE reports a differential treatment response in VP patients. The VP group derived little benefit from erlotinib with worse OS when compared with to VP patients who received chemotherapy. It is important to note that PROSE was a well-designed clinical trial with a few limitations. A small number of EGFR activating mutations were included in this study which was performed predating EGFR mutation testing as standard of care. In addition, there were a small number of patients with squamous cell histology, and although tumors were evaluated for KRAS status, the role is in predicting response in KRAS positive patients was not reported.

The current clinical question that could be informed by PROSE is whether VeriStrat could be performed on patients with EGFR wild-type tumors to select second-line treatment. The answer to this is largely influenced by the biases of the reader. For some, based on the result of TAILOR, chemotherapy is recommended over erlotinib for as the second line treatment for patients with EGFR wild type cancers. For these readers, PROSE does not impact their clinical practice as the test does not identify a population that benefits from erlotinib over chemotherapy. In third-line treatment, erlotinib could still be considered by clinicians who hold to this approach as the PROSE results do not specifically address that clinical question.

For other clinicians, the multiple second-line studies that have not shown a difference between erlotinib and chemotherapy guide their practice (15). With these data, selection of second-line treatment can be guided largely by the side effect profile and patient preference. While erlotinib certainly has significant side effects, many patients and clinicians may prefer erlotinib over chemotherapy because of its perceived favorable spectrum of toxicity. For clinicians who practice using this approach, VeriStrat offers a new tool to influence therapeutic decision making by identifying patients who should be preferentially be treated with chemotherapy rather than erlotinib. This provides assurance that clinicians are not offering an inferior option of therapy by prescribing erlotinib to the highly resistant population. In recognizing the potential utility for some clinicians, the National Comprehensive Caner Network (NCCN) Clinical Practice Guidelines in Oncology for NSCLC has recently adopted the use of VeriStrat as an option in the treatment algorithm in second-line treatment of NSCLC (16).

In summary, VeriStrat is a test with powerful prognostic utility. For patients with EGFR wild-type cancers who would prefer to take erlotinib rather than chemotherapy in the second-line setting, the results of PROSE support the use of VeriStrat testing to help those patients avoid using an ineffective medication if they fall into a highly resistant group. For patients who prefer intravenous treatment, the

value of VeriStrat testing in the second-line is somewhat more limited. Given that patients may not know what their future preferences may be, it is likely that many clinicians will obtain VeriStrat testing to help their patients make informed decisions using the best technology currently available for weighing risks and benefits.

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