Editorial

Writing in PROSE proteomic-based selection for second line treatment in non-small-cell lung cancer

Lorenza Landi, Federico Cappuzzo

Medical Oncology Department, Istituto Toscano Tumori, Ospedale Civile, Livorno, Italy

Correspondence to: Federico Cappuzzo, MD. Medical Oncology Department, Istituto Toscano Tumori, Ospedale Civile, Viale Alfieri 36, 57100 Livorno, Italy. Email: f.cappuzzo@gmail.com.

Submitted Jan 17, 2015. Accepted for publication Jan 30, 2015.
doi: 10.3978/j.issn.2305-5839.2015.02.12
View this article at: http://dx.doi.org/10.3978/j.issn.2305-5839.2015.02.12

Since the identification of epidermal growth factor receptor mutations (*EGFR*$^{mut+}$), biomarker selection of patients for specific targeted agents became the standard of care in advanced non-small-cell lung cancer (NSCLC). Small molecules against the tyrosine kinase domain of EGFR (EGFR TKIs) such as gefitinib, erlotinib or afatinib, induced impressive and durable responses in patients with *EGFR*$^{mut+}$, demonstrating superiority over platinum-based chemotherapy when used in front-line setting (1-3). In addition, previous and recent evidences indicated that in presence of *EGFR*$^{mut+}$ an EGFR TKI is preferable to chemotherapy irrespective of line of treatment (4-7). More recently, crizotinib a potent ALK-MET-ROS1 inhibitor demonstrated superiority *vs*. chemotherapy in chemo-naive and in pretreated NSCLC patients with *ALK* translocations (8,9). Unfortunately, the vast majority of NSCLCs does not harbor any *EGFR* or *ALK* druggable alterations and availability of novel targeted agents is confined to clinical trials. For these patients, platinum-based chemotherapy remains the best front-line treatment, with regimens including pemetrexed and/or bevacizumab for individuals with non-squamous histology (10). Conversely, in second line setting the optimal treatment is not as defined. In 2000, docetaxel was firstly approved for second-line therapy in NSCLC (11) and few years later two other agents, pemetrexed and erlotinib, reached the approval based on the results of phase III trials showing non inferiority in terms of survival *vs*. docetaxel (12) or superiority *vs*. placebo (13). Additional trials, conducted in a general and unselected population of pretreated NSCLC, showed only minimal differences in terms of efficacy among the three drugs, leading to the conclusion that pemetrexed, docetaxel and erlotinib could be reasonably considered an acceptable option (14-16) in both *EGFR* wild type (*EGFR*^{wt}) or EGFR unknown NSCLC. For such reasons, medical oncologists generally based their choice on several factors, including personal experience or familiarity with the drug, toxicity, patient characteristics and preferences, and last but not least, drug costs.

VeriStrat (Biodesix, Boulder, CO, USA) is a serum proteomic test using mass spectrometry, originally developed to identify those NSCLC patients having the best survival outcome with EGFR-TKIs (17). According to the intensity of eight regions in the mass spectra, patients were classified into two categories, good and poor. Previous data have suggested that VeriStrat had a strong prognostic power (18-20) in pretreated NSCLC patients, whereas its predictive role remained controversial (18).

Recently, Grecorc *et al.* published the results of the PROSE trial, a phase III study specifically conducted to assess the predictive value of VeriStrat test in the comparison of erlotinib and chemotherapy (pemetrexed or docetaxel) as second line treatment in NSCLC patients. The primary end point was overall survival (OS) (21). Proteomic tests were obtained before starting therapy and results were blinded for patients and for investigators who administered treatment, whereas treatment was blinded for investigators who generated the proteomic stratification. Among 285 subjects included onto the study, the proportion of patients with good and poor proteomic profile was similar in both chemotherapy and erlotinib arm (68% and 72% and 32% and 28%, respectively). In the whole population, there was no significant difference in OS (9.0 *vs*. 7.7 months, HR 1.14, for chemotherapy and erlotinib, respectively), whereas

by splitting results according to the proteomic stratification patients with good profile had a significant longer survival than those classified as poor (11.0 *vs.* 3.7 months, P<0.001, HR 2.5). Moreover, treatment with erlotinib associated with shorter survival in patients with poor proteomic classification (3.0 *vs.* 6.4 months, P=0.022; HR 1.72); on the contrary, patients with good proteomic test equally benefited from both chemotherapy and erlotinib treatment (OS 10.9 *vs.* 11.0 months, P=0.714, HR 1.06).

Two main conceptual findings emerged from this trial. Authors should be congratulated for their efforts of identifying an alternative and innovative "biomarker" in NSCLC. Actually, PROSE was the first prospective trial in which patient selection was based on proteomic profile of patients rather than on tumor molecular portrait. Second, according to the VeriStrat stratification, they identified a subgroup of patients for which second-line treatment with EGFR TKIs might have a detrimental effect on survival. From this perspective, the PROSE trial seems solving two important medical needs in thoracic oncology. First, VeriStrat stratification could overcome the need of tumor tissue; obviously, in our daily clinical practice, it would be much easier to obtain one microliter of serum suitable for a proteomic test than ten micrometers of tumor slice for molecular analyses. Second, proteomic results could facilitate the choice of a second line treatment in $EGFR^{WT}$ NSCLC, at least in those patients displaying poor proteomic features.

Unfortunately, the reasons why this trial appears so exciting are the same of its weakness. Proteomic stratification suffers of some limitation. Despite the absolute difference in OS observed in PROSE and in other trials (18-21) is numerically and clinically meaningful, it could be mainly driven by the prognostic effect of proteomic signature. VeriStrat poor classification has been identified in a wide range of cancers including NSCLC, colorectal cancer and head and neck squamous cell carcinoma and in almost all studies poor classification correlated with worse survival (18-22). More interestingly, the proportion of patients having a poor test is invariably of around 30%, irrespective of tumor type, disease stage and line of therapy (22), thus suggesting that for a consistent proportion of patients long-term perspectives are inevitably poor. Although the nature and biologic significance of the proteins detected on proteomic peaks remain largely unknown, it is possible that VeriStrat could measure some "tumor-host" response to the presence of cancer, as demonstrated by the fact that poor classification has not been observed in other-than-cancer diseases or in healthy individuals (18). Furthermore, the study failed to clarify the other clinical question that is whether chemotherapy should be preferred as second line treatment in good classified patients. Indeed, VeriStrat has been originally designed to refine selection of NSCLC patients more likely to benefit from EGFRTKIs approximately ten years ago, when the predictive role of EGFR mutations was not yet elucidated (17,18); consequently it performs well for EGFR TKIs but it does not for conventional chemotherapy (17). Results of the ongoing phase II trial exploring the significance of VeriStrat test in predicting benefits from first-line platinum based chemotherapy, are urgently awaited in order to define if the proteomic signature could explained different sensitivity to chemotherapeutic drugs (NCT 02055144, www.clinicaltrials.gov).

Finally, although the aim of the trial was to evaluate the predictive value of a serum test and not to directly compare chemotherapy *vs.* erlotinib in a general population, Grecorc *et al.* results seemed not add substantial changes in current state of the art. In unselect NSCLC second line treatments have only modest efficacy (10). In addition, as suggested by two phase III trials (14,16) and in two meta-analyses (7,23), when *EGFR* status was assessed by using a high sensitive method reducing the risk of including false negative patients, chemotherapy resulted superior to EGFRTKIs in terms of PFS confirming that, once again, *EGFR* status cannot be ignored.

Fortunately, the scenario of NSCLC therapy is rapidly evolving and new therapies potentially more effective are emerging. On January 11th a press-release by Bristol-Myers Squibb announced that the CheckMate-017, a randomized phase 3 study evaluating the checkpoint inhibitor nivolumab *vs.* docetaxel in previously treated squamous lung cancer met its endpoint, demonstrating increased OS in immunotherapy arm (news.BMS.com). It is possible that in coming years, the role of proteomic test should be re-interpreted on the light of the emergent treatment strategies. We hope that in the next future new therapeutic options and more effective predictive tests will be available for our patients offering the concrete possibility to extend their survival.

Acknowledgements

This manuscript is supported by Associazione Italiana per la Ricerca sul Cancro (AIRC) IG 2012-13157, Fondazione Ricerca Traslazionale (FoRT) and Istituto Toscano Tumori

(ITT) Project F13/16.
Disclosure: The authors declare no conflict of interest.

References

1. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.
2. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239-46.
3. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3327-34.
4. Kim ES, Hirsh V, Mok T, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. Lancet 2008;372:1809-18.
5. Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol 2010;11:521-9.
6. Zhang L, Ma S, Song X, et al. Gefitinib versus placebo as maintenance therapy in patients with locally advanced or metastatic non-small-cell lung cancer (INFORM; C-TONG 0804): a multicentre, double-blind randomised phase 3 trial. Lancet Oncol 2012;13:466-75.
7. Li N, Yang L, Ou W, et al. Meta-analysis of EGFR tyrosine kinase inhibitors compared with chemotherapy as second-line treatment in pretreated advanced non-small cell lung cancer. PLoS One 2014;9:e102777.
8. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013;368:2385-94.
9. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 2014;371:2167-77.
10. Reck M, Popat S, Reinmuth N, et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25 Suppl 3:iii27-39.
11. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18:2095-103.
12. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22:1589-97.
13. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123-32.
14. Kawaguchi T, Ando M, Asami K, et al. Randomized phase III trial of erlotinib versus docetaxel as second- or third-line therapy in patients with advanced non-small-cell lung cancer: Docetaxel and Erlotinib Lung Cancer Trial (DELTA). J Clin Oncol 2014;32:1902-8.
15. 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;13:300-8.
16. Garassino MC, Martelli O, Broggini M, et al. 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;14:981-8.
17. Taguchi F, Solomon B, Gregorc V, 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;99:838-46.
18. 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;7:1653-60.
19. Amann JM, Lee JW, Roder H, et al. Genetic and proteomic features associated with survival after treatment with erlotinib in first-line therapy of non-small cell lung cancer in Eastern Cooperative Oncology Group 3503. J Thorac Oncol 2010;5:169-78.
20. Stinchcombe TE, Roder J, Peterman AH, et al. 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. J Thorac Oncol 2013;8:443-51.
21. 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, randomised phase 3 trial. Lancet Oncol 2014;15:713-21.
22. Chung CH, Seeley EH, Roder H, et al. Detection of tumor epidermal growth factor receptor pathway dependence by serum mass spectrometry in cancer patients. Cancer Epidemiol Biomarkers Prev 2010;19:358-65.
23. Lee CK, Brown C, Gralla RJ, et al. Impact of EGFR inhibitor in non-small cell lung cancer on progression-free and overall survival: a meta-analysis. J Natl Cancer Inst 2013;105:595-605.

Cite this article as: Landi L, Cappuzzo F. Writing in PROSE proteomic-based selection for second line treatment in non-small-cell lung cancer. Ann Transl Med 2015;3(3):32. doi: 10.3978/j.issn.2305-5839.2015.02.12

