

A new proteomic test could guide treatment decision in second-line therapy for patients with EGFR unselected non-small cell lung cancer?

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Nowadays non-small cell lung cancer (NSCLC) is the first cause of death for tumor worldwide. In the second line setting there are few results upon survival parameters from the various treatment options. European Society of Medical Oncology (ESMO) guidelines say that patients clinically or radiologically progressing after first-line chemotherapy, irrespective of administration of maintenance chemotherapy, and with an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-2, should be offered second-line chemotherapy (1). In this setting, single agents chemotherapy improve disease-related symptoms and overall survival (OS) to nearly 6.7-8.3 months, with 30% of patients alive at 1 year (2,3). Comparable options in the second-line therapy consist of pemetrexed—for non-squamous histology only—or docetaxel. Erlotinib is an additional potential option in patients with PS 0-2 (1). Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are the standard treatment option for advanced NSCLC patients harboring EGFR-activating mutations. Large randomized controlled trials enriching for the patients harboring EGFR-activating mutations showed the superiority of TKI treatment over conventional cytotoxic drugs in terms of progression-free survival (PFS) and objective response rate (ORR) (4). However, the majority of patients with advanced NSCLC worldwide do not have tumors harboring EGFR-activating mutations. Erlotinib was approved as a second or third-line standard treatment based on the results of BR.21 trial, which demonstrated the prolongation of OS compared with the best supportive care in all NSCLC histological subtype patients EGFR-unselected, not eligible for further chemotherapy, including patients

with PS 3 (5). Although the EGFR TKI treatment has been widely used in patients with unknown (UK) or wild-type (WT) EGFR status NSCLC, its benefit is less pronounced and more controversial than in those with EGFR-activating mutations. Three randomized trials (INTEREST, TITAN and HORG study), comparing EGFR TKI with second-line chemotherapy agents (docetaxel or pemetrexed), failed to show greater efficacy of chemotherapy in patients with UK or WT EGFR tumors, with a better toxicity profile and quality of life (QoL) for TKI (6-8). However, the recently reported TAILOR and DELTA trials demonstrated a significant improvement in PFS with second-line chemotherapy compared with erlotinib in patients with WT EGFR NSCLC (9,10). A meta-analysis of these trials demonstrated that for patients with advanced NSCLC harboring WT EGFR tumors conventional chemotherapy was associated with improvement in PFS and with a higher ORR, compared with first-generation EGFR TKIs (11). However, there was no statistically significant difference in terms of OS between the two treatment groups.

In this particular and complicated background, it is becoming increasingly important to identify other markers in order to select patients to treat with an EGFR TKI or with a cytotoxic agent. The PROSE trial aim was trying to indentify one of these markers; this trial was a biomarker-stratified, randomized phase 3 trial, written by Gregorc *et al.* and published in *Lancet Oncology* (12). The biomarker status used to guide analysis but not to assign treatment; the primary aim of this trial was to assess the predictive power of the proteomic test in the comparison of two approved treatments in second line—erlotinib and

chemotherapy—in patients with NSCLC. The proteomic test was developed by Taguchi and colleagues (13); this test, commercially available as VeriStrat (Biodesix, Boulder, CO, USA), was used to assign one of two classifications (good or poor) by comparison of the intensity of eight regions in the mass spectra obtained from patients' pretreatment serum samples with the intensity of those of a reference set; the test was used for the analysis of serum to identify patients likely to have good or poor survival when treated with EGFR TKIs (14,15). The patients enrolled in PROSE study were submitted to the serum test and randomized to receive erlotinib or chemotherapy. The trial enrolled 263 patients: 184 (70%) were classified good and 79 (30%) poor. Patients with a poor proteomic test classification had significantly shorter OS when treated with erlotinib than did those given chemotherapy [median 3.0 months (95% CI: 2.0-3.8) vs. 6.4 months (95% CI: 3.0-7.4); HR 1.72 (95% CI: 1.08-2.74), $P=0.022$]; instead, in the good classification group, there was no significant difference in OS between the treatment groups and median OS was 10.9 months (95% CI: 8.4-15.1) in the chemotherapy group and 11.0 months (95% CI: 9.2-12.9) in the erlotinib group [HR 1.06 (95% CI: 0.77-1.46), $P=0.714$]. In clinical practice, patients considered to have a poor prognosis usually are delivered to TKI therapy, due to its better toxicity profile in comparison with chemotherapy; this trial highlight the fact that this practice is no longer effective, in fact patients with a proteomic test classification of poor (30%) should not receive erlotinib. Conversely, patients classified as good seems to have similar results both with erlotinib therapy and with chemotherapy; but, this study was not originally designed and powered to detect survival benefit of erlotinib versus chemotherapy within the good proteomic classification group, indeed the study was designed to evaluate the interaction test between VeriStrat status and treatment effect. In hindsight, this is a limitation of the trial and the study design could have been improved by enlarging the study to address this additional analysis. In the study no statistical significant differences were detected in terms of PFS and ORR between the two treatment groups, irrespective of the proteomic test. Therefore the trial demonstrate that VeriStrat can be utilized as a predictive factor in order to select which patients are not to be treat with EGFR TKI; in fact poor classified patients exhibit a statistical significant survival advantage when treated with chemotherapy compared to erlotinib; while no significant informations were showed for good classified patients, for whom both treatment options remain effectives. Similar results were showed also for EGFR WT

population.

Furthermore, this was the first prospective study to confirm the prognostic role of VeriStrat test, in fact patients with a classification of good had better OS and PFS than did those with a classification of poor, even when the data is correct considering the other prognostic factors. Median overall survival was 11.0 months (95% CI: 9.3-12.6) and 3.7 months (95% CI: 2.9-5.2) for good and poor classifications, respectively [HR 2.50 (95% CI: 1.88-3.31), $P<0.0001$]. Median PFS was 3.4 months (95% CI: 2.4-4.6) and 2.0 (95% CI: 1.6-2.4) for good and poor classification groups, respectively [HR 1.75 (95% CI: 1.34-2.29), $P<0.0001$]. Finally, the PROSE study is a well conducted and designed trial; anyway open issues remain the evaluation of the costs and the accessibility of the test on a large scale; furthermore it still remains unclear the biological rational of VeriStrat test and its correlation with EGFR.

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