Nit-Picking around second line in EGFR<sup>wt</sup> NSCLC: just an academic effort

During the last decade, several new drugs emerged as effective in patients with advanced nonsmall-cell lung cancer (NSCLC). Agents targeting the epidermal growth factor receptor (EGFR), such as gefitinib, erlotinib or afatinib, induced dramatic and durable responses in patients with activating EGFR mutations (EGFR<sup>mut+</sup>), demonstrating superiority versus platinum-based chemotherapy in front-line setting [1–3]. More recently, crizotinib, a potent ALK-MET-ROS1 inhibitor demonstrated superiority versus chemotherapy in chemo-naïve and in pretreated patients with ALK translocations [4, 5]. The striking superiority of targeted agents versus chemotherapy in molecularly selected patients demonstrated that today, in daily clinical practice, identification of biological characteristics of the tumor is crucial for defining the correct therapeutic strategy. Unfortunately, ~85% of all NSCLCs are EGFR and ALK wild type and no targeted therapy is available outside clinical trials. In front-line setting, platinum-based chemotherapy remains the best treatment, with regimens including pemetrexed and/or bevacizumab for individuals with nonsquamous histology [6]. In 2000, docetaxel was the first agent approved for second-line therapy in NSCLC [7] and few years later two other agents, pemetrexed and erlotinib, reached the approval based on the results of phase III trials showing noninferiority in terms of survival versus docetaxel [8] or superiority versus placebo [9]. Additional trials were conducted with the aim of identifying the best second-line therapy [6]. All trials, conducted in a general and unselected population of pretreated NSCLC, showed only minimal differences in terms of efficacy leading to the conclusion that pemetrexed, docetaxel and erlotinib represent an acceptable option as second-line treatment [6]. In second-line setting, gefitinib showed superiority versus docetaxel only in EGFR<sup>mut+</sup> patients [10], with no survival improvement over placebo in unselected NSCLC [11]. For such reason, in the UE, gefitinib use is restricted to individuals harboring EGFR mutations.

In the present issue, Zhou et al. reported the results of a phase II randomized trial comparing pemetrexed versus gefitinib as second-line therapy in patients with nonsquamous EGFR wild-type (EGFR<sup>wt</sup>) advanced NSCLC [12]. The study, conducted in 161 Asiatic patients, showed that pemetrexed is superior to gefitinib in terms of progression-free survival (PFS), with a non-significant difference in terms of overall survival (OS). In addition to the clinical end points, authors also re-analyzed the EGFR status using a highly sensitive method, showing that a consistent percentage of the study population, ~30%, harbored an activating EGFR mutation despite the initial assessment with direct sequencing did not detect any EGFR alteration. Interestingly, in such population of EGFR<sup>mut+</sup> patients, no difference in PFS was observed in the two arms.

This study raises an important clinical question that is whether chemotherapy should be preferred as second-line treatment in EGFR<sup>wt</sup> patients. In such population, the efficacy of standard chemotherapy is modest, with a response rate below 10%, a median PFS of 3–4 months and a median OS of 7–8 months [6]. Even if disappointing, these results seem superior to what achievable with EGFR-TKIs as demonstrated in two phase III trials, the TAILOR and DELTA, and in two meta-analyses [13–16]. In addition, both TAILOR and DELTA trials used a highly sensitive method for EGFR mutation test, reducing the risk of including false-negative patients. Nevertheless, ‘pure’ EGFR<sup>wt</sup> patients did not survive longer with chemotherapy [13, 14] or, in other words, EGFR-TKIs are not detrimental in
pretreated NSCLC irrespective of EGFR status. For such reason, 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. Docetaxel is used in pretreated NSCLC since 2000 when the drug was approved based on the results of a phase III study showing superiority versus placebo only in a small subgroup of patients receiving the dose of 75 mg/m² every 21 days [7]. All studies comparing docetaxel with gefitinib failed to demonstrate any difference between the two arms in the whole population as well as in the EGFRwt [10, 17]. Although the cost of the drug is lower than other agents currently approved for second-line therapy, the standard schedule of docetaxel produces considerable toxicity, particularly neutropenia, resulting not cost-effective from the perspective of a variety of payers and health care systems [18]. That is the reason why many oncologists prefer a weekly schedule that is probably as effective as the three-weekly schedule but not used as reference arm in any randomized study, with the only exception of the TAILOR trial where investigators had the possibility to choose both schedules [13]. Pemetrexed is not inferior to docetaxel in terms of efficacy [8], with better toxicity profile and higher cost. Only two studies, the TITAN and HORG, compared pemetrexed versus EGFR-TKIs in pretreated NSCLC [19, 20] and both showed no difference in survival versus erlotinib even when the analysis was restricted to the EGFRwt population [19]. Therefore, the whole second-line therapy picture includes different drugs with different cost and toxicity profile and with differences in terms of efficacy, thus animating academic debates marginally influencing the most relevant clinical end point that is patient survival.

In such context, it is important to understand how Zhou et al. results compare with previous trials and how they could influence our clinical practice. Comparison with previous studies is difficult for the differences in trial design and patient populations. TITAN and HORG were phase III trials, with TITAN including only chemorfractory patients [19] and the HORG including also patients in third line of treatment [20]. In addition, TITAN and HORG used erlotinib as EGFR-TKI and no study formally demonstrated that erlotinib and gefitinib are equivalent in EGFRwt patients. Previous studies showed that erlotinib has some activity even in the wild-type population [9, 21], while no study demonstrated any survival effect of gefitinib in absence of EGFR mutations [11, 22]. Therefore, the results of the present study are not surprising considering that the comparison is between an agent, pemetrexed, with demonstrated activity in nonsquamous histology and another agent, gefitinib, with no proven efficacy in EGFRwt. In any case, at least in the UE, the study has limited clinical implications since the vast majority of NSCLC with nonsquamous histology are currently treated in front line or in maintenance setting with pemetrexed and gefitinib is not approved in patients without EGFR mutations.

Actually, the heart of the matter remains the choice between erlotinib and docetaxel, also considering that pemetrexed is not indicated for patients with squamous histology [8]. This picture is certainly not exciting because today we are choosing between a cheap but toxic drug and a fancy and expensive targeted agent with modest efficacy in a ‘target-free’ population. Fortunately, the scenario of NSCLC therapy is rapidly evolving and new therapies potentially more effective are emerging. Recent studies showed that adding antiangiogenic agents to chemotherapy modestly but significantly improve survival [23] and new checkpoint inhibitors particularly nivolumab and pembrolizumab, are showing promising results even in heavily pretreated patients. We hope that in the next future new options will be available for our patients offering the concrete possibility to extend survival, making disputes on the best second–line treatment of EGFRwt only the memory of an academic effort.

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references


