Editorial

Adjuvant TKI treatment of EGFR-mutant lung cancer—already ripe for decision?

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Worldwide, lung cancer is the leading cause of cancer-related deaths (1). Still, most patients are diagnosed with advanced disease and only few patients are eligible for curative treatment. Nevertheless, prognosis after "curative" surgery remains limited due to common relapse. After 5 years a third of stage I and up to 50 % of stage II patients relapse (2). Better staging and new surgical techniques led to only a slight improvement of these historic data. Most of operated NSCLC patients relapse with distant metastases rather than local (3). Thus, common theory is, that undetectable micro-metastases were already present at the time of surgery and lead to tumor relapse during the course of follow-up.

Adjuvant chemotherapy is thought to fight these micro-metastases to improve patients' outcome. Four cycles of adjuvant platinum-based chemotherapy had shown to expand survival of lung cancer patients especially with lymph node involvement and large tumors. However, gain of overall survival after 5 years is only 5.4% (4). As EGFR TKIs are highly effective in stage IV EGFR mutant NSCLC patients (5-8), it was quite reasonable to evaluate if EGFR positive patients will also benefit from adjuvant TKI treatment.

All together there are several studies investigating the role adjuvant EGFR TKI treatment: the BR19 study randomized completely resected stage IB–III NSCLC patients to receive gefitinib or placebo for 2 years. The patients were not selected regarding their EGFR mutation status. No benefit of disease-free survival (DFS) and overall survival (OS) was found neither in the total study cohort nor in the 15 patients with EGFR mutation (9).

In the RADIANT trial, Kelly *et al*. randomized 973 patients with surgically resected stage IB-IIIA NSCLC with EGFR expression or amplification and stratified patients with EGFR mutations. Patients received adjuvant treatment with erlotinib or placebo. The investigators found no benefit in DFS in patients with EGFR expression or EGFR mutation (10).

The EVAN study compared resected stage IIIA EGFR positive patients treated either with erlotinib for 1 year or vinorelbine plus cisplatin. DFS at 2 years was significantly expanded in the erlotinib group (81.4% *vs.* 44.6%) (11).

In the ADJUVANT trial, patients with stage II-IIIA EGFR-mutant NSCLC were treated after surgery with gefitinib over 2 years and compared with a cohort treated with 4 cycles of classic adjuvant chemotherapy. The median DFS was significantly longer in the gefitinib group (28.7 *vs.* 18 months) and the risk of relapse decrease by 40% (12).

Beside these randomized trials, there are some other non-randomized studies focusing on this topic. D'Angelo *et al*. examined a cohort of resected stage I–III EGFR-mutant patients treated either with gefitinib or erlotinib after surgery. They found clues for improvement of DFS (13). Similar results have been reported by Janjigian and

colleagues. The found a 2-year DFS benefit (89% *vs.* 72%) in stage I to III patients treated with gefitinib or erlotinib after complete resection (14). The SELCET trial matched 100 patients with EGFR mutant NSCLC and resected stage IA to IIIA with a historic cohort and treated them with erlotinib for 2 years. DFS after 2 and 5 years was 88% and 56% respectively which was better than in the historic non treated cohort (15).

Recently, a consensus paper on postoperative management of EGFR-mutant lung cancer was published in *Translational Lung Cancer Research* by an Chinese committee of surgeons and oncologists (16). The authors proposed 8 consensuses as follows:

(I) EGFR testing is routinely recommended in all resected non-squamous NSCLC.

(II) Comprehensive predictive and prognostic markers an scores should be used to predict the risk of recurrence.

(III) Adjuvant EGFR-TKI treatment can prolong DFS compared with standard chemotherapy and can serve as one adjuvant therapy for patients with stage II-IIIA EGFR-mutant NSCLC.

(IV) Adjuvant chemotherapy, EGFR-TKI treatment and combination of both approaches can offered to EGFR positive NSCLC patients.

(V) The adjuvant TKI therapy should last at least 2 years.

(VI) Patients with activating EGFR mutation show higher risk of recurrence with brain and bone metastases compared to wild-type patients. Brain MRI and bone scans are recommended annually in addition to regular chest CT.

(VII) The result of genetic testing from initial tumor material could serve as reference in relapsed patients; alternatively, re-biopsy may confirm the gene mutation status and guide further therapy. Liquid biopsy, if available, is also a possible method for detection of EGFR mutation.

(VIII) EGFR-positive NSCLC patients relapsing after surgery, can be treated with EGFR-TKI (preferably osimertinib). In patients, who received adjuvant TKI treatment, re-challenge with EGFR -TKIs is possible. Presence of T790M mutations should be evaluated in re-biopsy specimens.

Despite the promising results of the ADJUVANT study, the data situation is currently not conclusive enough to recommend an adjuvant TKI treatment for EGFR-mutant NSCLC patients. Given the above-mentioned recommendations there are several important points to consider: first of all, the ADJUVANT trial and the EVAN study could demonstrate a DFS advantage for TKI treated patients, but data on overall survival are still missing and the results were not confirmed by the RADIANT trial. Furthermore, the study population comprises only Asian patients of whom we know that they harbour a different EGFR biology than Caucasian patients. Thus, randomized studies also including Caucasian patients and data on overall survival are needed to give a general recommendation for adjuvant TKI treatment. Moreover, EGFR positive NSCLC patients are usually very sensitive to chemotherapy and irradiation, so that studies combining chemotherapy, radiotherapy and TKIs are necessary to evaluate the optimal adjuvant treatment for this cohort.

Regarding the duration of adjuvant TKI therapy: as we know from stage IV patients, TKI treatment dose not cure EGFR positive lung cancer, stopping the adjuvant treatment after 2 years might lead to just postpone the problem. Therefore, it will be crucial to see OS data. Nevertheless, EGFR testing should be performed in all resected non-squamous NSCLC, not to guide an adjuvant treatment at present, but not to lose time in the case of relapse and to establish a risk adapted follow-up with special attention to brain and bone metastases.

There are no data for treatment recommendations in patients how relapse after adjuvant TKI treatment. Renewed EGFR testing would be indispensable in this condition to guide treatment decision. There are no data preferring a distinct TKI in this situation.

In summary, there are promising data that EGFR-mutant NSCLC patients might benefit from adjuvant TKI treatment. Nevertheless, at present data are too weak to give a recommendation for this treatment option, especially in Caucasian patients. However, many open questions raised from the current studies. Accordingly, we need more conclusive data, especially on OS to elucidate the role of adjuvant TKI treatment in EGFR positive NSCLC.

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Footnote

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