The development of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have revolutionized treatment paradigms in lung cancer. Currently, EGFR TKIs constitute first- and second-line treatment of EGFR-mutant advanced non-small cell lung cancer (NSCLC) patients. The first-generation TKIs (gefitinib, erlotinib and icotinib) have been supplemented by second (afatinib and dacomitinib) and third-generation (osimertinib) molecules. Several other EGFR-TKIs are currently being investigated in clinical trials (1).

Typically, targeted anti-cancer therapies in solid malignancies are first investigated in advanced stages, and subsequently agents with confirmed activity are promptly submitted to studies in early disease. An example of such development includes trastuzumab, a monoclonal antibody used in human type 2 EGFR (HER2) positive breast cancer. The first phase 3 study reporting the high efficacy of this agent in metastatic disease was published in 2001 (2), and just four years later three large randomized trials demonstrated its value in the preoperative and postoperative settings. Several other EGFR-TKIs are currently being investigated in clinical trials (1).

At present, the only standard systemic adjuvant treatment option in operable stage II-III NSCLC, regardless of EGFR mutation status, is cytotoxic chemotherapy, despite its mere five-year overall survival (OS) gain of 5% (10). Until now only five randomized studies have been performed to assess EGFR-TKIs in operable NSCLC (Table 1). Two of these studies compared EGFR TKI vs. placebo (11,12), one chemotherapy followed by EGFR TKI vs. chemotherapy alone (13), and two EGFR TKI vs. chemotherapy (14,15). The results of two early studies including molecularly unselected patients were negative. The prematurely closed NCIC CTG BR19 study did not show disease-free survival (DFS) or OS benefit of gefitinib for two years compared to placebo (11). Similarly, no superiority was found from adjuvant erlotinib vs. placebo in the RADIANT study (12), which included patients with EGFR protein-positive tumors by immunohistochemistry or with EGFR amplification by fluorescence in situ, the biomarkers currently considered ineffective in selection for EGFR TKIs.
As expected, more promising were the results of three completed studies (all performed in China), enrolling selected patients with EGFR-mutant tumors. The first of them, a small phase 2 trial, showed significantly longer DFS of gefitinib for 6 months following pemetrexed-cisplatin combination, compared with chemotherapy alone (13). Another randomized phase 2 study (EVAN) showed significantly higher two-year DFS of erlotinib for two years compared to four cycles of cisplatin-vinorelbine chemotherapy (14). The only phase 3 study (ADJUVANT) showed significantly longer DFS of gefitinib for two years compared to four cycles of a cisplatin-vinorelbine combination, but general results were disappointingly grim, with almost all patients relapsing within four years (15). The meta-analysis of the five above-mentioned randomized studies (including only patients with *EGFR* mutation) showed increased DFS with *EGFR*-TKI-based regimens (HR 0.52; 95% CI: 0.34–0.78, P=0.002), but this was not translated into OS benefit (16).

Most recently presented were the results of an open-label single-arm phase 2 study (SELECT) performed in the USA, that investigated the efficacy of adjuvant erlotinib in patients with *EGFR*-mutant early-stage NSCLC (17). Considering the scarcity of data on adjuvant *EGFR* TKIs in the non-Asian populations, this study has raised great interest. The SELECT study included 100 stage IA–III A patients and was powered to demonstrate a two-year DFS greater than 86%, i.e., 10% more compared with the historic figure of 76%. After a median follow-up of 5.2 years, this primary endpoint was met: two-year DFS was 88%. The median DFS and OS was not reached, the five-year DFS was 56% (95% CI: 45–66%), and the five-year OS was 86% (95% CI: 77–92%). Disease recurred in 40 patients, including four while on adjuvant erlotinib. Treatment adherence was relatively poor, with 40% of patients requiring dose reductions by 50%, and 16% further reduction to 25% of the original dose. Of the 36 patients with recurrence after completing erlotinib treatment, 26 were retreated with this compound, and the majority of them derived clinical benefit from re-exposure. Interestingly, of the 20 patients who had determined *EGFR* mutation status of the recurrent tumor, all but one maintained the original canonical *EGFR* mutation pattern. The only patient with acquired *T790M* resistance mutation was among those four who developed progression while receiving adjuvant erlotinib. This may imply the hypothesis that *EGFR* TKIs inhibit rather than kill cancer cells, and that prolonged anti-*EGFR* treatment is unlikely to induce resistance mechanisms. The SELECT study was properly designed and executed and provides another signal for potential role of *EGFR* TKI in adjuvant setting. However, due to all the limitations of single-arm design, it still does not provide strong evidence.

In view of the relatively high incidence of *EGFR*-mutant NSCLC, the number of studies investigating the role of *EGFR* TKI in an adjuvant setting, and the total number of participating patients is strikingly low. It is really difficult to explain the reluctance to carry out more trials addressing this concept. Additionally, the quality of randomized studies performed so far has been relatively low in terms of patient selection, study design and execution. All three randomized

### Table 1: Completed randomized studies of postoperative therapy with *EGFR* TKIs in NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Selection criteria</th>
<th>Stage</th>
<th>Region</th>
<th>N (total)</th>
<th>N (mEGFR)</th>
<th>Study arms</th>
<th>Primary endpoint</th>
<th>Main results (mEGFR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BR19 (11)</td>
<td>III</td>
<td>All NSCLC</td>
<td>IIBIIA</td>
<td>North America</td>
<td>503</td>
<td>15</td>
<td>G vs. placebo (2 y)</td>
<td>OS</td>
<td>NR</td>
</tr>
<tr>
<td>RADIANT (12)</td>
<td>III</td>
<td>EGFR+ by IHC or FISH</td>
<td>IIBIIA</td>
<td>Global</td>
<td>973</td>
<td>161</td>
<td>E vs. placebo (2 y)</td>
<td>OS</td>
<td>OS NR; median DFS 46.4 vs. 28.5 m (NS)</td>
</tr>
<tr>
<td>Li et al. (13)</td>
<td>II</td>
<td>mEGFR</td>
<td>IIIA (N2)</td>
<td>China</td>
<td>60</td>
<td>60</td>
<td>PC × 4 with vs. without G (6 m)</td>
<td>DFS</td>
<td>Median DFS 39.8 vs. 27.0 (P=0.014)</td>
</tr>
<tr>
<td>EVAN (14)</td>
<td>II</td>
<td>mEGFR</td>
<td>IIIA</td>
<td>China</td>
<td>102</td>
<td>102</td>
<td>E (2 y) vs. 4 × PV</td>
<td>DFS</td>
<td>Two-year DFS rate 81% vs. 54% (P=0.01)</td>
</tr>
<tr>
<td>ADJUVANT (15)</td>
<td>III</td>
<td>mEGFR</td>
<td>II–IIIA (N1–N2)</td>
<td>China</td>
<td>222</td>
<td>222</td>
<td>G (2 y) vs. 4 × PV</td>
<td>DFS</td>
<td>Median DFS 28.7 vs. 18.0 m (P=0.005)</td>
</tr>
</tbody>
</table>

EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer; mEGFR, patients with *EGFR* mutation; G, gefitinib; OS, overall survival; NR, not reported; IHC, immunochemistry; FISH, fluorescence in situ hybridization; E, erlotinib; DFS, disease free survival; NS, not significant; PC, pemetrexed plus cisplatin; PV, cisplatin plus vinorelbine.
studies enrolling exclusively EGFR-mutated patients were small and included the Chinese population. Patients from East Asia comprise a higher proportion of EGFR-mutant cases than those from other geographical regions, and have distinctive clinicopathologic features. Hence, there is the question of whether the results of these studies may be generalized, even though 83% of the SELECT study subjects were of non-Asian ethnicity.

Importantly, none of the completed studies in patients selected by EGFR mutation used OS as the primary endpoint. In consequence there are no robust data on OS impact of adjuvant EGFR TKIs. Further, the available results cannot indicate whether chemotherapy should be replaced or supplemented by an EGFR-TKI. Using EGFR TKIs alone may be viewed as more appealing, as it avoids the burden of chemotherapy toxicity. On the other hand, the combined approach may be potentially more efficient in view of the potential NSCLC heterogeneity. Namely, it may be speculated, that tumors containing both EGFR-mutated and EGFR wild-type clones may derive benefit from complementary mechanisms of action.

An important and unresolved question remains the duration of EGFR TKI treatment. Of the five completed studies, four employed a two-year therapy, but this may be considered a purely empiric approach. Indeed, in advanced NSCLC most responses to EGFR TKIs occur within the first 2–3 months of treatment. This puts in doubt the validity of prolonged treatment, given its toxicity and cost. Although targeted therapy is generally considered less toxic and better tolerated than cytotoxic chemotherapy, it carries prolonged and troublesome skin and gastrointestinal side effects. Two year EGFR TKI treatment instead of three months of chemotherapy may be burdensome and raises the question of patient adherence. Actually, treatment compliance in clinical studies was relatively low, and up to one-third of patients could not receive a two-year medication. EGFR TKIs therapy is also much more costly, and in some insurance systems may create substantial financial problems for patients. An ongoing phase II trial (NCT01746251) compares three months vs. two years of postoperative therapy with afatinib in EGFR-mutated NSCLC.

All completed studies to date used first-generation EGFR TKIs which bind reversibly to EGFR harboring sensitizing mutations (mostly exon 19 deletions and exon 21 substitution), but also to wild-type EGFR, thus increasing treatment toxicity. Additionally, these agents demonstrate marginal inhibition of exon 20 T790M mutant EGFR, constituting a common resistance mechanism. Osimertinib, a third-generation EGFR TKI, has a minimal inhibition of wild-type EGFR, resulting in lower toxicity (18). This compound is also more potent, and has a strong affinity for sensitizing and resistance T790M mutation (19).

The role of EGFR TKIs in an adjuvant setting is the subject of a few ongoing clinical studies. In the ALCHEMIST-EGFR (NCT02193282) trial, initiated in 2014, EGFR-mutant NSCLC patients are randomized to two-year erlotinib or placebo, both preceded by adjuvant chemotherapy. Notably, this trial is being run in parallel with a similar study (ALCHEMIST-ALK, E4512), comparing anaplastic lymphoma kinase (ALK) inhibitor crizotinib vs. placebo in NSCLC patients with identified ALK gene rearrangement. In the WJOG6410L phase III trial, initiated in Japan in 2012, stage II-III NSCLC patients harboring EGFR mutations are randomly assigned to gefitinib for two years, or four cycles of cisplatin-vinorelbine combination. In a similar study (NCT02448797), carried out in China since 2015, patients are randomized to cisplatin in combination with vinorelbine or pemetrexed, or two-year icotinib. Another Chinese phase III study (NCT01996098), initiated in 2013, compares chemotherapy vs. icotinib administered for 6 or 12 months. In the international ADAURA trial (NCT02511106) patients are assigned to three-year osimertinib treatment or placebo. Out of the running studies, only one (ALCHEMIST) uses OS as the primary endpoint, whereas all the others employ DFS.

Do the currently available data justify considering EGFR TKIs as a new paradigm of adjuvant therapy for EGFR-mutant NSCLC patients? On one hand, the results seem encouraging, but the evidence is relatively weak and many questions remain unresolved. Hence, the use of adjuvant EGFR TKIs should still be considered an investigational approach. Ongoing studies can add to the current knowledge and may change the standards of adjuvant treatment in oncogene-addicted early stage NSCLC.

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Footnote

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Ethical statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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