# Targeted adjuvant therapy in non-small cell lung cancer: trick or treat?

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Shareable abstract (@ERSpublications)
**Immuno- and targeted therapy improved survival in metastatic NSCLC, but before their implementation in early disease, several challenges need to be overcome. Adequate staging is important, and molecular testing must be incorporated in early disease.** https://bit.ly/3heLe6W

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Current European and American guidelines strongly recommend adjuvant platinum-based chemotherapy in selected patients with radically resected non-small cell lung cancer (NSCLC), based on a quantitative meta-analysis showing an absolute improvement in survival of 4% at 5 years, which was stage dependent (stage pI: 3%, stage pIII: 13%) [1–3]. The occasional N0-tumour with a diameter >4 cm, which was previously classified IB, is upstaged to at least a IIA (pT2bN0) in the 8th TNM classification [4]. Currently, the selection of patients eligible for adjuvant chemotherapy is based on clinical and tumour characteristics, and is restricted to tumours in stages pII and pIII [5]. Compliance with the preferred three to four cycles of a platinum-based two drug combination regimen is moderate, with about two-thirds of patients receiving the planned dose-intensity at a cost of 2–3% mortality.

Efforts to better characterise the population at risk of relapse and benefiting from adjuvant treatment were based on the expression of somatic biomarkers, and have remained in vain so far. For example, in the Lung Adjuvant Cisplatin Evaluation (LACE)-Bio project, promising predictive immunohistochemistry biomarkers identified in LACE trials, such as β-tubulin, mucin, p27, Cyclin E/p16 and BAX could not be validated [6]. Similarly, tailoring the cytostatic regimen to the pharmacogenetic expression of certain metabolising genes (*e.g.* Excision Repair Cross-Complementary 1 and Thymidylate Synthase genes) has not met its expectations [7]. Adding a vascular endothelial growth factor receptor antibody (with proven efficiency in advanced NSCLC), to the chemotherapy backbone also did not improve the outcome [8].

The subsequent discovery of driver mutations in the epidermal growth factor receptor (*EGFR*) gene and the development of highly active oral tyrosine kinase inhibitors (TKIs) have dramatically changed the fate of patients with *EGFR*-mutated advanced NSCLC [9]. Compared with platinum-doublet chemotherapy, first and second-generation EGFR-TKI (erlotinib, gefitinib, afatinib) significantly improve progression-free survival (hazard ratio (HR) 0.27–0.45) and for *EGFR* exon 19 deletion also overall survival (OS; HR 0.72) [9]. Osimertinib, a third generation EGFR-TKI, was superior to comparator EGFR-TKI (erlotinib or gefitinib) in the FLAURA trial (OS HR 0.80) [10]. Currently, in the metastatic setting, several other oncogenic drivers (*e.g. ALK*, *ROS1*, *BRAF*) have been identified for which targeted therapies with impressive progression-free survival and even OS data have become available. Intuitively, it was hypothesised that the observed benefit could also be extrapolated to earlier disease stages. Therefore, (EGFR-)TKIs were and are being evaluated in the adjuvant setting. This editorial discusses, based on recent evidence, the current limits and implications of this approach. As only for *EGFR*-mutated NSCLC phase III is TKI data available, we focus on this subgroup of patients.

At present, four randomised phase III trials evaluating adjuvant EGFR-TKI solely in patients with completely resected *EGFR*-mutated (exon 19 deletion or exon 21 L858R) NSCLC have reported results. ADJUVANT [11] and IMPACT [12] both evaluated 2 years of gefitinib *versus* chemotherapy, EVIDENCE [13] evaluated 2 years of icotinib (first-generation TKI, only approved in China) *versus* chemotherapy, and ADAURA [14] evaluated 3 years of osimertinib *versus* placebo after standard of care chemotherapy. The trial designs and results are summarised in tables 1 and 2, respectively. All trials had disease-free survival (DFS) as primary endpoint. ADAURA was the only trial allowing stage IB disease (TNM7), while in the others eligibility was limited to stage II–III. Of note, ADAURA was also the only trial in which adjuvant chemotherapy was according to standard of care in both arms (in ADJUVANT, IMPACT and EVIDENCE no chemotherapy was given in the EGFR-TKI arm). The percentage of patients receiving chemotherapy (approximately 25%, 70% and 80% in stage IB, II and III, respectively) was comparable to daily practice [14]. Importantly, none of the trials mandated positron emission tomography–computed tomography (PET-CT), and ADAURA and EVIDENCE also allowed brain computed tomography instead of magnetic resonance imaging (MRI) [11–14]. This contrasts with current guidelines. For example, in the European Society for Medical Oncology (ESMO) guidelines, PET-CT is advised for all non-metastatic disease, and brain MRI is advised in stage III NSCLC and might be considered in other patients eligible for curative intent therapy [1]. As a result, it is likely that patients with occult metastatic disease were enrolled, favouring the DFS results in the TKI arm. In ADJUVANT, EVIDENCE and ADAURA, a benefit for median DFS in favour of the EGFR-TKI was found, with the most impressive hazard ratio observed for osimertinib [11, 13, 14]. It is not clear why IMPACT, with a similar design to ADJUVANT and EVIDENCE, was negative for both DFS and OS. Possible reasons could be differences in baseline staging procedures or imaging follow-up [11–13]. Although ADJUVANT was positive for median DFS, gefitinib never became standard of care in the adjuvant setting and with longer follow-up, 5-year DFS and OS data were not significantly different for gefitinib *versus* chemotherapy [11, 12]. Long-term follow-up data for EVIDENCE is not available yet [13]. In contrast, adjuvant osimertinib for completely resected *EGFR*-mutated stage IB-IIIA NSCLC was recently approved by the European Medicines Agency [15], despite the fact that for ADAURA, OS results are still immature and it is not known whether the impressive DFS benefit translates into an improved OS [14]. An advantage of adjuvant osimertinib is that it prevents or delays recurrence of disease in the brain (at 18 months osimertinib: 1%, placebo: 10%), while this was not clearly found for icotinib (after 24.9 months follow-up, icotinib:7%, chemotherapy: 11%) nor gefitinib (after 36.4 months follow-up, gefitinib: 27%, chemotherapy: 24%) [13, 16, 17]. Efficacy data of subsequent therapy post-osimertinib is awaited [17].

As a result, extensive discussions arose in the scientific literature, with fervent arguments for and against [18–21]. These discussions justify this editorial to focus on the implications that the adjuvant osimertinib approval has for daily practice.

The question is whether we should change our practice based on DFS results only, and whether this differs for TKIs *versus* immune checkpoint inhibitors (ICIs). For the first generation TKIs, while there were conflicting DFS benefits, in both ADJUVANT and IMPACT no improvement in 5-year DFS or OS was observed [11, 12]. Furthermore, in contrast with ICIs, controversy exists whether TKIs induce only a cytostatic or also a cytotoxic effect [22–25]. In both the IMPACT and ADJUVANT trial, the DFS benefit disappeared around 30 months: 6 months after the 24-month administration of gefitinib [11, 12]. This suggests that adjuvant EGFR-TKIs delay disease relapse instead of curing the disease. It also puts into question whether the ESMO magnitude of benefit scale [26] is adequate to evaluate adjuvant TKIs. A grade A rating is given for adjuvant therapies that result in either a >5% survival improvement at ⩾3 years of follow-up, or a DFS HR <0.65 (if survival data is not mature). In ADJUVANT, a HR of 0.56 for median DFS was reported, but no OS benefit was demonstrated [11]. In contrast to TKIs, adjuvant ICIs already resulted in an OS benefit in stage III NSCLC after first showing an improved DFS (HR 0.52) [27, 28]. In ADAURA and EVIDENCE, follow-up time is currently too limited to evaluate whether patients relapse after completion of the EGFR-TKI. For ADAURA, the independent data monitoring committee recommended early unblinding to complete primary reporting, and for EVIDENCE only a preplanned interim analysis has been reported. Furthermore, cross-over was not allowed in both trials, and this will ultimately influence OS data [13, 14].

Before discussing adjuvant EGFR-TKIs, it is important to note that currently also ICIs, mainly programmed death (ligand)1 (PD-(L)1) inhibitors, are gaining more ground in early stage, based on an impressive OS benefit in the metastatic and locally advanced setting [27, 29, 30]. In the phase III IMpower010 trial (n=1280), 16 cycles of 3-weekly adjuvant atezolizumab were compared with observation in molecularly unselected, completely resected stage IB (⩾4 cm)–IIIA (TNM7), after the completion of adjuvant chemotherapy [31]. After a median follow-up of 32.8 months, the observed DFS benefit was most

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**TABLE 1** Study design of randomised phase III adjuvant epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor trials

| Trial | Stage | Required imaging and molecular analysis | Stratification factors | Imaging in follow-up | Treatment | Primary endpoint | Secondary endpoints |
|---|---|---|---|---|---|---|---|
| **ADJUVANT** | II–IIIA (N1–N2)<br>TNM7<br>Histology not specified | Centralised *EGFR* testing (PCR)<br>PET-CT or chest/upper abdomen CT<br>Brain MRI | N1 *versus* N2<br>Ex19del *versus* ex21 L8 58R | Chest CT or chest radiograph + abdominal ultrasound or CT every 12 weeks first 3 years; afterwards brain MRI every 6 months or bone scan only at cycle 7 or 11 and every 12 months | Open label<br>1) Gefitinib 250 mg once daily 24 months<br>2) Vinorelbin 25 mg·m$^{-2}$ day 1, 8 plus cisplatin 75 mg·m$^{-2}$ day 1, every 3 weeks, 4 cycles | Investigator-assessed DFS | OS<br>3-year DFS<br>5-year DFS<br>5-year OS<br>HRQoL<br>Safety/tolerability |
| **IMPACT** | II–III<br>TNM7<br>Histology not specified | Chest/abdomen CT, brain MRI<br>PET/CT or bone scan<br>Testing not specified in abstract or presentation | Institute<br>Stage II *versus* III<br>Gender<br>Age <65 *versus* ⩾65 years | Chest/abdomen CT every 6 months<br>Brain MRI every 12 months<br>PET/CT or bone scan every 12 months | Open label<br>1) Gefitinib 250 mg once daily 24 months<br>2) Vinorelbin 25 mg·m$^{-2}$ day 1, 8 plus cisplatin 80 mg·m$^{-2}$ day 1, every 3 weeks, 4 cycles | Centrally assessed DFS | OS<br>Safety/tolerability<br>Type of recurrence |
| **ADAURA** | IB–IIIA<br>TNM7<br>Non-squamous histology only | Centralised *EGFR* testing (Cobas)<br>Preoperative or baseline brain MRI/CT<br>Chest and abdomen CT | Stage IB *versus* II *versus* III<br>Ex19del *versus* ex21 L8 58R<br>Asian *versus* non-Asian | Chest and abdomen CT 12 weeks, 24 weeks, and then every 24 weeks till 5 years, afterwards yearly | Double blind<br>Completed SoC chemotherapy prior to randomisation<br>Osimertinib 80 mg or placebo once daily for 3 years | Investigator-assessed DFS | OS<br>2-year DFS<br>3-year DFS<br>5-year DFS<br>5-year OS<br>HRQoL<br>Pharmacokinetics<br>Safety and tolerability |
| **EVIDENCE** | II–IIIA<br>TNM7<br>Squamous histology also allowed | Centralised *EGFR* testing (amplification-refractory mutation PCR)<br>Preoperative or baseline brain MRI/CT and bone scan, baseline<br>Chest and abdomen CT | Stage II *versus* IIIA<br>Ex19del *versus* ex21 L8 58R<br>Lobectomy *versus* pneumonectomy | Chest CT and abdominal ultrasonography (±CT) every 12 weeks, till 2 years; afterwards every 24 weeks year 3–5<br>Brain CT/MRI every 48 weeks, bone scan every 48 weeks | Open label<br>1) Icotinib 125 mg thrice daily orally 24 months<br>2) Vinorelbin 25 mg·m$^{-2}$ day 1, 8 plus cisplatin 75 mg·m$^{-2}$ day 1, every 3 weeks, 4 cycles; or pemetrexed 500 mg·m$^{-2}$ day 1 plus cisplatin 75 mg·m$^{-2}$ day 1, every 3 weeks, 4 cycles (non-squamous only) | Investigator-assessed DFS | 3-year DFS<br>OS<br>Safety<br>HRQoL |

TNM: tumour, node, metastases; PET: positron emission tomography; CT: computed tomography; MRI: magnetic resonance imaging; ex: exon; del: deletion; DFS: disease-free survival; OS: overall survival: HRQoL: health-related quality of life; SoC: standard of care.

**TABLE 2** Main outcomes of randomised phase III adjuvant epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) trials

| Trial | N | Performed baseline staging | Median FU (months) | Median DFS (months) | Median OS (months) |
|---|---|---|---|---|---|
| **ADJUVANT** | 222 | 24% PET in both groups<br>All should have had brain MRI | 80.0 | 30.8 (gefitinib) *versus* 19.8 (chemo)<br>HR 0.56, 95% CI 0.40–0.79; p=0.001 | 75.5 (gefitinib) *versus* 62.8 (chemo)<br>HR 0.92, 95% CI 0.62–1.36; p=0.674<br>5-year OS 53.2% (gefitinib) *versus* 51.2% (chemo)<br>p=0.784 |
| **IMPACT** | 234 | PET not specified<br>All should have had brain MRI | 70.1 | 35.9 (gefitinib) *versus* 25.0 (chemo)<br>HR 0.92, 95% CI 0.67–1.28; p=0.63 | NR in both arms<br>5-year OS 78.0% (gefitinib) *versus* 74.6% (chemo)<br>HR 1.03, 95% CI 0.65–1.65; p=0.89 |
| **ADAURA** | 682 | % PET unknown<br>50% brain MRI, 50% brain CT | 22.1 (osi) and 14.9 (placebo) | NR (osi) *versus* 27.5 (placebo)<br>2-year DFS 89% (osi) *versus* 52% (placebo)<br>HR 0.20, 99% CI 0.14–0.20; p<0.001 | Data not mature |
| **EVIDENCE** | 322 | PET not specified<br>% brain MRI *versus* CT not specified | 24.9 | 47.0 (icotinib) *versus* 22.1 (chemo)<br>HR 0.36, 95% CI 0.24–0.55; p<0.001<br>3-year DFS 64% (icotinib) *versus* 33% (chemo)<br>HR not provided | Data not mature<br>HR 0.91, 95% CI 0.42–1.94 |

FU: follow-up; DFS: disease-free survival; OS: overall survival; PET: positron emission tomography; MRI: magnetic resonance imaging; osi: osimertinib; chemo: chemotherapy; HR: hazard ratio; NR: not reached.

pronounced in the PD-L1-positive stage II–IIIA subgroup, with a median DFS not reached *versus* 35.3 months (HR 0.66, 95% CI 0.50–0.88) [31].

Based on the IMpower010 results, PD-L1 status must be evaluated in the near future in resectable stage II–IIIA NSCLC. We argue that besides PD-L1, molecular testing should be performed also, not only because of the opportunity to administer adjuvant osimertinib while waiting for the OS results of ADAURA, but also to avoid giving ICI to patients that will likely not benefit or even will be harmed with ICI. Patients with an oncogenic driver often express PD-L1 due to constitutional activation [32] and it is tempting to select patients for adjuvant ICI based on easily obtained PD-L1 results. However, from the locally advanced and metastatic setting it is known that patients with oncogenic drivers associated with non-smoking, such as *EGFR*, *ALK*, *ROS1* and *RET*, almost never obtain a significant survival benefit with monotherapy ICI [33, 34]. In IMpower010, the subgroups of never smokers or those with an *EGFR* mutation or *ALK* rearrangement did not seem to derive a clear benefit from adjuvant atezolizumab [31]. Furthermore, it is increasingly reported that when TKI are given after (or concurrent with) ICI, an increased risk of toxicity exists, probably due to the long half-life of ICI and the interaction with TKI [35, 36]. Therefore, adjuvant ICI should not be given to patients with an *EGFR* mutation or *ALK* rearrangement.

At present, only adjuvant osimertinib is approved and therefore regarding oncogenic drivers, only *EGFR* testing is currently required. This could be done with a single gene test, such as PCR, resulting in relatively low cost. However, based on the promising adjuvant ICI results, but the disappointing outcomes with single agent ICI for several oncogenic drivers (see above), we argue that an extensive next generation sequencing (NGS) panel makes more sense. In contrast to PCR, NGS can evaluate multiple genes at the same time, including alterations in targetable genes (*e.g. EGFR, BRAF, ALK, ROS1)*, and it can also identify co-mutations in genes that are associated with resistance or decreased TKI benefit. Research incorporating baseline extensive molecular testing will also aid in identifying those patients that will (not) benefit from adjuvant EGFR-TKI or ICI as co-mutations that can influence treatment outcome will be identified. Although these NGS panels are more costly, budget calculations should not only consider the costs of NGS testing, but also the savings regarding adjuvant ICI as well as the probable reduction in healthcare costs for toxicity of TKI after ICI the moment a patient with an oncogenic driver relapses. Furthermore, NGS can also identify rare *EGFR* mutations as well as other oncogenic drivers and, therefore, presents an opportunity to evaluate treatment for these drivers in the adjuvant setting. Examples are NCT02194738 (basket trial) and NCT03456076.

The currently reported phase III trials with adjuvant TKI or ICI only selected patients based on post-operative TNM stage (and presence of a classical activating *EGFR* mutation in the EGFR-TKI trials).

A significant percentage of these patients would have been cured with surgery with or without adjuvant chemotherapy alone. At present, there are no approved methods to identify patients that are either already cured or, in contrast, are at high risk of relapse and are potential candidates for (additional) adjuvant therapy. Research to select patients that will benefit from adjuvant therapy is becoming increasingly relevant with TKI and ICI associated costs. A promising way forward is the determination of minimal residual disease (MRD) post radical therapy using liquid biopsies. In small series in, for example, stage III NSCLC it is suggested that patients who are free from MRD after chemoradiotherapy have a favourable outcome irrespective of the administration of adjuvant durvalumab, while those that are MRD-positive but turn MRD-negative during durvalumab treatment seem to benefit most from adjuvant ICI [37]. These findings need to be validated in randomised clinical trials. For adjuvant ICI, MERMAID-1 (NCT04385368) and -2 (NCT04642469) are examples, and this concept is also of interest for adjuvant TKI trials. Drawbacks of measuring MRD are the associated costs, the low sensitivity (although high specificity) and the fact that there are other, less costly, methods (*e.g.* pathomics, radiomics) to select patients for adjuvant therapy that should be explored.

Moreover, neoadjuvant TKIs (and ICIs) are also being evaluated. However, neoadjuvant gefitinib compared with chemotherapy did not result in an OS benefit in the randomised phase II CTONG1103 trial (HR 0.83, p=0.513) [38]. Other trials, such as NCT04712877, are ongoing. So far, biomarkers to decide whether adjuvant or neoadjuvant therapy would be better for a specific patient are lacking.

In conclusion, although TKIs and ICIs have changed the treatment paradigm in metastatic NSCLC, several tricks and treats exist in their application in the early disease setting. We advocate that adequate staging is of importance, that molecular testing should also be incorporated in this setting and that adjuvant chemotherapy remains the standard of care. Future trials should focus on identifying the subset of patients most likely to benefit from (neo)-adjuvant TKIs or ICIs, to reduce patient-related, as well as financial, toxicity.

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