Ad(aura): a fresh breeze for patients with resected EGFR-mutant non-small cell lung cancer

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After 2 years of additional follow-up, Herbst and colleagues recently published the updated results from the ADAURA trial, including the final analyses of disease-free survival (DFS), the pattern of recurrence and the long-term safety (1).

ADAURA trial is a randomized, double-blind, placebo-controlled phase III trial that enrolled 682 patients with early-stage [IB–IIIA, according to the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) 7th edition] non-small cell lung cancer (NSCLC) who underwent complete resection and carrying common mutation (*EGFR*) mutations (exon 19 deletions or L858R mutation of exon 21). Enrolled patients were randomized in a 1:1 fashion to receive osimertinib 80 mg daily, an irreversible third-generation *EGFR* tyrosine kinase inhibitor (TKI), or placebo for 3 years. As per study protocol, post-operative chemotherapy was also allowed to be administered before randomization. Osimertinib is strongly selective for activating *EGFR* mutations as well as for *EGFR* T790M through the formation of a covalent bond to the C797 residue in the adenosine triphosphate (ATP)-binding site of mutant *EGFR*. This binding inhibits several downstream pathways, including RAS-RAF-MAPK and PI3K-Akt, which regulate various cellular processes, such as DNA synthesis and proliferation. The study met its primary endpoint and demonstrated a significant prolonged DFS in favor of osimertinib when compared with placebo [hazard ratio (HR) =0.20, 99.12% confidence interval (CI): 0.14–0.30, P<0.001] (2). These data allowed osimertinib to become the new standard of care in the adjuvant setting for *EGFR*-mutated NSCLC patients.

Before the results of the ADAURA study were published, adjuvant chemotherapy was the only treatment option for these patients. However, elderly patients with severe comorbidities or platinum-ineligible could not benefit from adjuvant chemotherapy. In addition, the advantage of platinum-based chemotherapy is limited (3,4) and the presence of *EGFR* mutation could be either a negative prognostic factor or predictive of poor response to adjuvant platinum-based chemotherapy (5).

In advanced NSCLC, first-, second- and third-generation EGFR-TKIs were evaluated and recommended as first-line treatment in patients with common and uncommon *EGFR* mutation (except for exon 20 insertion). Following the results from the FLAURA trial (6), osimertinib was approved as first-line treatment in *EGFR*-mutated (exon 19 deletion or L858R exon 21 mutation) NSCLC patients, as well as being the treatment of choice for patients with acquired T790M mutation on first- or second-generation

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EGFR-TKIs.

Moving to the early-stage disease, some previous studies (7-11) had shown the efficacy of first-generation EGFR-TKIs as adjuvant therapy, although they have not been approved in this setting (*Table 1*). Most of these studies did not meet the primary endpoint or the initial benefit dropped at a longer follow-up. In the phase III CTONG1104 study, 222 resected patients with stage II–IIIA *EGFR*-mutant NSCLC were randomly assigned (1:1) to adjuvant gefitinib for 2 years or vinorelbine plus cisplatin for four cycles. The study met its primary endpoint. Median DFS was significantly longer with gefitinib [28.7 months (95% CI: 24.9–32.5)] when compared with standard chemotherapy [18.0 months (95% CI: 13.6–22.3); HR =0.60 (95% CI: 0.42–0.87), P=0.0054]. Unfortunately, at a longer follow-up, no significant benefit was seen in terms of both 3- and 5-year DFS rates (P=0.316 and 0.928, respectively) and median overall survival (OS) [HR =0.92 (95% CI: 0.62–1.36), P=0.674] (11). Other EGFR-TKIs are being investigated in the adjuvant setting, including erlotinib, gefitinib, icotinib, furmonertinib and almonertinib (*Table 2*).

Updated 3-year results from ADAURA study demonstrated both significant DFS improvement [HR =0.23 (95% CI: 0.18–0.30)] and reduced risk of central nervous system (CNS) relapse [HR =0.24 (95% CI: 0.14–0.42)] in favor of osimertinib, as well as a reduced risk of local (12% *vs.* 23%) and distant recurrence (13% *vs.* 31%) and an acceptable safety profile (1). According to the primary report, osimertinib demonstrated a significant DFS benefit with an HR of 0.23 in stage II–IIIA (95% CI: 0.18–0.30) and 0.27 in the overall population (95% CI: 0.21–0.34) (1). The DFS benefit was observed across all patient subgroups, regardless of sex, age, smoking history, race, stage, type of *EGFR* mutation (exon 19 deletion or L858R mutation of exon 21), or prior adjuvant treatment with chemotherapy, confirming the remarkable efficacy of adjuvant osimertinib (1).

Among patients receiving adjuvant chemotherapy, 89% were alive and disease-free at 24 months if treated with osimertinib and 49% with placebo. In the group of patients who did not receive adjuvant chemotherapy, 89% were alive and disease-free at 24 months if treated with osimertinib and 58% with placebo.

As per protocol, resected patients with pathologic stage IB–IIIA according to AJCC/UICC, 7th edition, were allowed to be enrolled. Herbst and colleagues updated survival outcomes considering the current (8th edition) AJCC/UICC classification. Changes in the T parameter according to the 8th edition allowed a better discrimination of the early stages and improved the prediction of NSCLC patients compared to the 7th edition (12). Following the restaging, the majority of patients (656 of 682) remained in IB–IIIA disease stage. Of the remaining 26 patients, 3 were re-classified as stage IA, 18 were re-classified as stage IIIB, 1 was re-classified as stage IV and 4 were missing while the proportion in each stage group remains comparable: 29% staged IB, 34% staged II and 33% staged IIIA.

However, following the adaptation to the 8th edition, the significant DFS improvement was maintained, probably due to the absence of imbalance in disease stages of the enrolled patients, confirming the robustness of the ADAURA results and their viability in clinical practice.

The pattern of recurrence showed a lower relapse rate in patients treated with osimertinib (27% *vs.* 60%), regardless of metastatic site (local or distant recurrence, including CNS). In the osimertinib group, the loco-regional and distant recurrence rates were comparable, 12% (42/339) and 13% (45/339), respectively, while in the placebo arm, the rate of distant and loco-regional recurrences was 31% (107/343) and 23% (78/343).

In *EGFR*-mutated NSCLC, CNS involvement is common because of a high cerebral tropism, even at diagnosis (13). The FLAURA trial had already highlighted the elevated CNS activity of osimertinib, with higher intracranial response compared with first-generation EGFR-TKIs (66% *vs.* 43%, respectively) and a significantly reduced risk of CNS progression [HR =0.48 (95% CI: 0.26–0.86), P=0.014] (6). In the ADAURA study, CNS relapse rate was markedly lower in patients receiving osimertinib than in placebo group (6% *vs.* 11%, respectively) associated with a reduced risk of CNS progression [HR =0.24 (95% CI: 0.14–0.42) in stage II–IIIA]. Furthermore, most of the CNS relapses in the osimertinib arm occurred after the completion of treatment. This data confirms the high efficacy of osimertinib in preventing CNS relapse and warrants further studies aiming to evaluate whether the continuation of adjuvant osimertinib beyond 3 years can further reduce the risk of disease recurrence (TARGET trial, ClinicalTrials.gov identifier: NCT05526755). Nevertheless, the benefit of osimertinib treatment is clearly maintained after the 3-year treatment period. One year after osimertinib completion, the likelihood of being alive and disease-free is practically more than double in stage II–IIIA patients.

More recently, ADAURA results were updated and also included OS data. The updated results demonstrated a significant OS improvement, with a reduced risk of death

Table 1 Trials evaluating EGFR-TKIs in patients with completely resected NSCLC carrying *EGFR* molecular alterations

Trial, year	No. of patients	Study phase, design	Stage	Type of *EGFR* mutation	Treatment, randomization	Prior chemotherapy (yes/no)	Primary endpoint	Secondary endpoint	Follow-up (months)	Results			
										Median DFS (months)	DFS HR (95% CI)	DFS rate (%)	OS HR (95% CI)
BR19, 2013	503	Phase 3, RCT	IB–IIIA	Exon 19 deletion or exon 21 L858R mutation	2-y gefitinib *vs.* placebo (1:1)	Yes	OS	Toxicity, DFS, establishment of a tumor bank for biomarker analysis	56.4	50	1.84 (0.44–7.73)	NE	3.16 (0.61–16.45)
RADIANT, 2015	973	Phase 3, RCT	IB–IIIA	Exon 19 deletion or exon 21 L858R mutation	2-y erlotinib *vs.* placebo (2:1)	Yes	DFS	OS, DFS, OS in the EGFRm-positive subgroup, safety	47	46.4	0.61 (0.38–0.98)	67.2	1.13 (0.88–1.49)
CTONG1104, 2021	222	Phase 3, RCT	II–IIIA	Exon 19 deletion or exon 21 L858R mutation	2-y gefitinib *vs.* 4 cycles CDDP-VNR (1:1)	No	DFS	3-y OS, 5-y OS, DFS rates, 5-y OS rate	80	30.8	0.56 (0.40–0.79)	39.6	0.92 (0.62–1.36)
ADAURA, 2018	682	Phase 3, RCT	IB–IIIA	Exon 19 deletion or exon 21 L858R mutation	3-y osimertinib *vs.* placebo (1:1)	Yes	DFS in patients with stage II–IIIA	DFS in patients with stage IB–IIIA, OS, safety	44.2 *vs.* 19.6	65.8	0.27 (0.21–0.34)	90.0	0.49 (0.34–0.70)
EVIDENCE, 2021	322	Phase 3, RCT	II–IIIA	Exon 19 deletion or exon 21 L858R mutation	2-y icotinib *vs.* 4 cycles platinum doublet (1:1)	No	DFS	OS, safety	24.9	47	0.36 (0.24–0.55)	63.9	0.91 (0.42–1.94)
IMPACT, 2021	232	Phase 3, RCT	II–IIIA	Exon 19 deletion or exon 21 L858R mutation	2-y gefitinib *vs.* 4 cycles CDDP-VNR (1:1)	No	DFS	OS, safety, recurrence types, AE	70	35.9	0.92 (0.67–1.28)	31.8	1.03 (0.65–1.65)

EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; NSCLC, non-small cell lung cancer; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; CI, confidence interval; y, years; RCT, randomized controlled trial; NE, not evaluated; EGFRm, *EGFR* mutation; CDDP, cisplatin; VNR, vinorelbine; AE, adverse event.

Table 2 Ongoing trials evaluating EGFR-TKIs in patients with completely resected NSCLC carrying *EGFR* molecular alterations

Trial	No. of patients	Stage	Type of *EGFR* mutation	Intervention model, phase	Treatment	Primary endpoint	Secondary endpoint
NCT05546866	50	IB–IIIB	G719X/L861Q/S768I/de novo T790M without Ex19del, L858R, exon 20 insertion	Single group, assignment, phase 2	3-y osimertinib	3-y DFS	2-y DFS rate, 5-y DFS rate, 2-y OS rate 3-y OS rate, 3-y OS rate, 5-y OS rate, median DSF, 4-y DFS rate
NCT05536505	180	IB–IIIB	Ex19del, L858R, L861Q mutation, G719X mutation	Non-randomized, phase 2	Icotinib until MRD turned negativity	DFS, 3-y DFS rate	OS
NCT05526755/ TARGET	180	II–IIIB	Ex19del, L858R, either alone or in combination with other *EGFR* mutations including T790M or G719X, S768I, and L861Q, either alone, in combination with each other, or in combination with other uncommon *EGFR* mutations (excluding all exon 20 insertions)	Non-randomized, phase 2	5-y osimertinib	DFS	3-y DFS rate, 4-y DFS rate, 5-y DFS rate, OS, safety, tolerability, recurrence
NCT05120349/ ADAURA2	380	IA2–IA3	Ex19del, L858R	Randomized, phase 3	3-y osimertinib *vs.* placebo	DFS	DFS in overall population, OS, PK of osimertinib and of metabolite AZ5104 in overall population, impact of osimertinib *vs.* placebo on physical functioning, CNS DFS, safety, tolerability
NCT04762459/ APEX	606	II–IIIA	Ex19del, L858R, either alone or in combination with other *EGFR* mutations including T790M	Randomized, phase 3	3-y almonertinib with or without chemotherapy *vs.* chemotherapy alone (pemetrexed, cisplatin)	DFS	2-y DFS, 3-y DFS, 4-y DFS, 5-y DFS, OS, patient HRQoL and symptoms by SF-36v2 Health Survey
NCT04687241	192	II–IIIB	Ex19del, L858R, either alone or in combination with other *EGFR* mutations including T790M	Randomized, phase 3	Almonertinib *vs.* placebo	DFS assessed by IRC	DFS assessed by INVs, 2-y DFS rate, 3-y DFS rate, 5-y DFS rate, OS, 5-y OS rate, AE, plasma concentrations of almonertinib and HAS-719 metabolite
NCT02264210/ CORIN	128	II–IIIA	Ex19del, L858R	Randomized, phase 2	1-y icotinib *vs.* observation	DFS	OS, number of participants with AE

EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; NSCLC, non-small cell lung cancer; y, years; DFS, disease-free survival; OS, overall survival; MRD, minimal residual disease; PK, plasma concentration; CNS, central nervous system; HRQoL, health-related quality of life; IRC, Independent Review Committee; INVs, investigators; HAS-719, N-desmethylated almonertinib; AE, adverse event.

in about half of the treated patients [HR =0.49 (95.03% CI: 0.34–0.70)]. The OS benefit was consistent in all patient subgroups, regardless of disease stage or prior adjuvant chemotherapy. The 5-year OS was 85% and 73% in stage II–IIIA NSCLC patients treated with osimertinib and placebo, respectively, while in stage IB–IIIA population it was 88% and 78% respectively (14). The ADAURA trial is the only published study demonstrating an OS benefit from an EGFR-TKI in this setting.

Regarding the safety profile, no new signals were reported in the adjuvant setting compared to the primary analysis after the updated follow-up. In the osimertinib group, adverse events (AEs) of all grades were reported in 330 (98%) patients compared with 90% in the placebo group. Most of the AEs associated with osimertinib were mild or moderate in severity. The most common AEs were diarrhea (47% *vs.* 20%), paronychia (27% *vs.* 1%), and dry skin (25% *vs.* 7%), in the osimertinib and placebo groups, respectively. Dose interruptions, dose reductions, and discontinuations in the osimertinib arm were 27%, 12%, and 13% compared to 13%, 1%, and 3% in the placebo arm, respectively. Serious AEs occurred in 68 patients (20%) in the experimental arm and interstitial lung disease, pneumonitis and cardiac diseases represented the most common treatment-related serious AEs. Therefore, the safety profile is comparable to that of the first publication of ADAURA and other Osimertinib studies, such as the FLAURA study, considering the different treatment setting (adjuvant *vs.* first-line treatment in advanced disease). In fact, in the FLAURA trial, the most commonly reported AEs were rash or acne (58%), diarrhea (58%), and dry skin (36%) and the majority of them were of grade 1 or 2. Serious AEs were reported in 60 patients (22%) and fatal AEs occurred in 6 patients (2%). The frequency of dose interruption, dose reduction and treatment discontinuation were 25%, 4% and 13%, respectively. Although osimertinib is generally considered a well-tolerated treatment, it may cause adverse effects that may even lead to permanent discontinuation of the drug. In this case, the clinician must make patients aware of the potential side effects of the drug and manage them properly avoiding the permanent discontinuation of the drug. Updated health-related quality of life (HRQoL) outcomes evaluated by the SF-36 health survey (week 156) showed a maintained quality of life over prolonged exposure to osimertinib. These results align with the aim of an adjuvant treatment, which is to treat with curative intent while maintaining patients' HRQoL (15,16).

Future perspectives

In the adjuvant setting, osimertinib is currently the only EGFR-TKI to show a statistically significant improvement in both DFS and OS, reducing the risk of local or distant recurrences (CNS included), confirming the drug's manageability, and supporting osimertinib as the new standard of care for these patients.

Despite the impressive results from ADAURA study, some doubts and concerns remain to be elucidated. Osimertinib is an expensive drug that, based on the results of ADAURA, needs to be continued for up to 3 years. Some studies have analyzed the financial impact of this drug compared to chemotherapy. Verhoek *et al.* (17) performed an economic evaluation, assessing the cost-effectiveness of osimertinib by including the costs associated with any subsequent treatment in case of progression or relapse compared to active clinical surveillance. They found that the use of adjuvant osimertinib is cost-effective compared with active surveillance. The model of Lemmon *et al.* (18) demonstrated that osimertinib would only be cost-effective if willing to pay $317,119 per quality-adjusted life years-gained (QALY), above the established threshold of $195,000. The cost-effective threshold was arbitrarily set at $195,000 because it represents the three times gross domestic product per capita of USA. The authors used a sensitivity analysis in OS as input to predict the cost-effectiveness. Their analysis was performed when the results of the ADAURA trial were not yet mature in terms of DFS or OS. They assumed that the OS improvement of the experimental arm could be 5% over placebo. They concluded that a considerable OS benefit over placebo or other economic interventions were necessary to reach the cost-effectiveness, and a hypothetical OS benefit of 25–30% would meet the prespecified threshold of $195,000. Further economic analyses with updated OS data are needed to establish the cost-effectiveness of osimertinib compared to other standard adjuvant treatments. Nevertheless, the high costs of osimertinib could be overcome with the implementation of other less expensive drugs. In countries with reduced access to high-cost drugs, a viable alternative could be almonertinib, which is currently being studied in the APEX trial (NCT04762459) in resected patients with *EGFR*-mutated NSCLC. On the other hand, the encouraging OS data, although not conclusive, show that a non-negligible proportion of patients could be cured with adjuvant osimertinib compared to standard post-operative platinum-based chemotherapy or surgery alone, and this, in addition to being an outstanding finding, could reduce

future costs incurred in case of disease recurrence such as new treatments, hospitalizations, interventional procedures, as well as social and psychological impacts. In fact, previous studies have shown that osimertinib is not cost-effective in the metastatic setting (19,20). Additional follow-up is needed to understand the real survival benefit and long-term outcomes.

Other unsolved questions include the duration of adjuvant treatment and the stage of patients to whom osimertinib should be prescribed. While some ongoing studies are evaluating the efficacy and safety of osimertinib in the earliest stages (IA2–IA3) (ClinicalTrials.gov identifier: NCT05120349/ADAURA2) and for a longer time (5 years) (ClinicalTrials.gov identifier: NCT05526755/TARGET), there are also trials evaluating the efficacy of EGFR-TKI as neoadjuvant therapy (Clinical-Trials.gov identifier: NCT04351555/NeoADAURA) or in combination with other therapies. Considering the financial toxicity of this treatment, biomarkers predicting which patients do benefit from adjuvant osimertinib and which patients can be safely spared 3 years of adjuvant treatment are needed.

The monitoring of circulating tumor DNA (ctDNA) as a marker of minimal residual disease (MRD) has already been evaluated in different settings and diseases (21). The detection of ctDNA could identify patients at high risk of disease recurrence, those to whom adjuvant treatment should be proposed, even with a prolonged timeline and not without possible side effects. Indeed, as previously reported, the presence of ctDNA after radical surgery is associated with an increased risk of disease recurrence (22). In their study, Jung and colleagues demonstrated how preoperative ctDNA absence and postoperative ctDNA clearance are associated with increased DFS times (23). In fact, the 3-year DFS was 84% for patients with negative ctDNA at baseline, 78% for patients with positive ctDNA at baseline and associated with a postoperative ctDNA, and 50% for patients with positive ctDNA at baseline and no postoperative clearance. In addition, the authors also observed that MRD detection preceded radiological detection of relapse in 54% of cases in patients with exon 19 deletion and 11% of patients with the L858R mutation, showing how longitudinal ctDNA monitoring allows earlier detection of disease recurrence than other methods used to date. Further analyses from ADAURA are ongoing, including the evaluation of ctDNA. An ongoing trial (ClinicalTrials.gov identifier: NCT05536505) is exploring the efficacy of adjuvant icotinib based on molecular MRD status in patients with stage IB–IIIB *EGFR*-mutated NSCLC.

Although the study met its endpoints, ADAURA has attracted some criticism from the scientific community. Firstly, the duration of adjuvant treatment (3 years) was chosen arbitrarily. The authors analyzed data from previous studies of adjuvant EGFR-TKIs (7-11). These had shown how many of the relapses (CNS included) among treated patients occurred during the third year of surgery. Herbst and colleagues, in the ADAURA study, extended adjuvant treatment to 3 years, using a drug known for its excellent brain penetrance. Another critical aspect of the study is the absence of a correct staging of the locally advanced disease. Patients with stage III–N2 disease did not undergo adequate mediastinal staging nor a correct brain radiological assessment by using magnetic resonance imaging (MRI), risking under-staging the patients with a consequent distortion of the results. Another controversy concerns the crossover of the control arm. Indeed, at the time of study design, osimertinib was not yet approved as the treatment of choice for metastatic disease. After its approval as standard of care, the ADAURA protocol was amended so that patients randomized to control arm were allowed to receive osimertinib at the time of relapse. Among patients randomized to placebo arm, only 79/205 (38.5%) of relapsed patients received osimertinib, while the majority was treated with other EGFR-TKIs (56%), chemotherapy (22%) or other treatments (24). The possibility of crossover could risk compromising OS results but should nevertheless be pursued in a high-quality clinical trial. In this way, the benefit of treatment could be properly assessed: does survival improve when osimertinib is offered in the adjuvant phase or does it not change the prognosis if it is administered at relapse?

Nevertheless, with the confirmation of the OS results, the ADAURA study provided strong evidence for the use of osimertinib as a new standard of care for resected (stage IB–IIIA) patients with *EGFR*-mutated NSCLC.

In this context, testing all patients with early-stage NSCLC for *EGFR* mutations and discussing the optimal management within a multidisciplinary team to define the correct therapy strategy became mandatory. Remarkably, ADAURA trial is the first to demonstrate that using a TKI can also improve survival outcomes in early-stage disease. In this scenario, the way is open towards other oncogene-addicted early-stage NSCLC populations, including ALK, ROS1, RET, and BRAF. Recently, adjuvant alectinib compared with platinum-based chemotherapy in resected stage IB–IIIA ALK-positive patients demonstrated to significantly prolong DFS (ALINA trial). Other studies

of adjuvant and neo-adjuvant treatment with TKIs are ongoing, such as NCT04819100/Libretto-432, NCT04926831/Geometry-N, NCT04302025/Nautika-1. The importance of assessing these treatments, as well as combining them with chemotherapy and loco-regional therapies, in the earliest stages, could increase the number of patients who achieve definitive cure.

While the role of adjuvant osimertinib is clearly established, the efficacy of other adjuvant treatment with TKIs remain to be elucidated. The next steps of ADAURA could be aimed at analyzing the long-term safety and survivorship. Optimal treatment duration, relapse management and follow-up therapies are still unresolved topics that will require further efforts by the scientific community. Future analyses on identifying additional predictive/prognostic biomarkers, including ctDNA for improving patients' selection may provide more data to increase survival rates.

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