EDITORIALS

# Adjuvant Osimertinib in *EGFR*-Mutated Non–Small-Cell Lung Cancer

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Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have completely reinvented therapeutic care for patients with metastatic non–small-cell lung cancer (NSCLC) harboring an activating *EGFR* mutation (*Ex19del* or *L858R*). The survival benefit with the third-generation EGFR-TKI osimertinib as compared with the first-generation agents gefitinib and erlotinib[1] has cemented its role in the current therapeutic landscape in patients with metastatic disease. However, no such advances have been seen over the past two decades for localized resectable disease. After complete resection, a small but significant survival benefit (5% at 5 years, corresponding to an 11% reduction in the risk of death) has been seen with platinum-based adjuvant chemotherapy for patients with stage II to IIIA disease.[2] The addition of bevacizumab to adjuvant chemotherapy has not been shown to improve overall survival.[3]

As adjuvant therapy, first-generation EGFR-TKIs are not associated with a survival benefit among patients with NSCLC who have *EGFR* wild-type or amplified tumors.[4,5] However, two randomized trials showed a benefit with first-generation EGFR-TKIs in *EGFR*-mutated tumors. The EVAN trial showed a longer disease-free survival at 2 years with adjuvant erlotinib than with chemotherapy among patients with *EGFR* mutation–positive stage IIIA tumors (81.4% vs. 44.6%; hazard ratio for disease recurrence or death, 0.27).[6] In the ADJUVANT/CTONG1104 trial involving patients with stage II to IIIA (N1 and N2 tumors) *EGFR* mutation–positive NSCLC, the median disease-free survival among patients in the intention-to-treat population who received adjuvant gefitinib was significantly longer than that among patients who received chemotherapy (30.8 months vs. 19.8 months; hazard ratio for disease recurrence or death, 0.56) and disease-free survival was higher at 3 years (39.6% vs. 32.5%), although this benefit did not translate to an overall survival advantage (hazard ratio, 0.92; P=0.67).[7]

Wu and colleagues now report in the *Journal* the results of the phase 3, double-blind, randomized ADAURA trial of osimertinib as adjuvant therapy administered for 3 years after complete resection in patients with stage IB to IIIA *EGFR* mutation–positive NSCLC.[8] The trial was powered to show a 30% disease-free survival benefit in patients with stage II to IIIA disease. After a review of data by the independent data monitoring committee, the trial was unblinded 2 years earlier than planned. The resulting interim analysis showed an unprecedented 83% reduction in the risk of disease recurrence or death (overall hazard ratio, 0.17). The benefit was greater at more advanced stages of disease (among patients with stage IIIA disease, the overall hazard ratio was 0.12; among those with stage II disease, it was 0.17; and among those with stage IB disease, it was 0.39). The prognosis in patients who received placebo was poor, with a probability of disease-free survival of 28% at 3 years among patients with stage II to IIIA disease — similar to the 27% reported in the ADJUVANT/CTONG1104 trial. The percentage of patients who underwent exhaustive staging with positron-emission tomography and

computed tomography (PET-CT) or brain magnetic resonance imaging (MRI) was not reported in the ADAURA trial; however, the percentage of patients who undergo rigorous staging is typically low (e.g., of the patients assigned to gefitinib in the ADJUVANT/CTONG1104 trial, 24% underwent PET-CT and fewer than 16% underwent MRI). Furthermore, the variable quality of this challenging surgery in the multicenter ADAURA trial was not evaluated, and the percentage of patients who underwent pneumonectomy was particularly low (<3% in both the osimertinib group and the placebo group), as compared with the percentage in historical studies (approximately 30%).[2]

In the ADAURA trial, the natural history of NSCLC appeared to be significantly altered by osimertinib that was administered as adjuvant therapy, with reductions in both locoregional recurrence (7% in the osimertinib group vs. 18% in the placebo group) and distant recurrence (4% vs. 28%). A particularly impressive effect was seen with respect to the recurrence of central nervous system (CNS) disease (2% in the osimertinib group vs. 11% in the placebo group); this finding clearly differentiated osimertinib from first-generation inhibitors that have been associated with a distant recurrence of 27% (with gefitinib) as compared with a recurrence of 24% with chemotherapy.[9] This result is consistent with those in patients with advanced disease, in whom first-line osimertinib has been shown to result in a 52% decrease in the risk of CNS progression or death.[10]

The benefit of osimertinib, irrespective of the use or nonuse of adjuvant chemotherapy (overall hazard ratio for disease recurrence or death, 0.16 and 0.23, respectively), unfortunately does not shed light on whether patients should be exposed to standard-of-care chemotherapy. Although the jury is still out on this issue, in vitro and clinical data suggest that EGFR-TKIs combined with chemotherapy may act synergistically,[11] limiting acquired resistance. EGFR-TKIs plus chemotherapy are currently being studied as neoadjuvant therapy in patients with *EGFR* mutation–positive stage II to IIIB disease (NeoADAURA trial; ClinicalTrials.gov number, NCT04351555) and as first-line therapy in patients with *EGFR* mutation–positive metastatic disease (FLAURA2 trial; NCT04035486). Evaluation of their use as adjuvant therapy would be the next logical step.

Whether 3 years is the most appropriate duration for the use of osimertinib as adjuvant therapy remains to be determined. Despite the favorable side-effect profile of osimertinib, extending treatment may be challenging; the median duration of osimertinib therapy in the current trial was 22.5 months (although at the data cutoff date, 61% of the patients were still receiving this agent), and two thirds of the discontinuations were attributable to adverse events or patient decision. Since only 11% of the patients in the osimertinib group had disease recurrence or died, quality-of-life evaluations and longer follow-up are needed and should also shed light on the benefit after discontinuation of the trial regimen (in the ADJUVANT/CTONG1104 trial, the small benefit with respect to disease-free survival seen with gefitinib administered for 2 years was lost at 5 years).[7] Thus, a key question is whether osimertinib can cure more patients when administered as adjuvant therapy than it can in patients with metastatic disease, rather than "simply" holding residual disease progression at bay. The question as to whether the effect is the same in patients with different stages of disease also warrants investigation. Circulating tumor DNA might be useful to guide the use of osimertinib by identifying both postoperative minimal residual disease and resistance mechanisms in patients who are receiving this drug as adjuvant therapy.

Mature survival data for osimertinib as adjuvant therapy are eagerly awaited as a critical end point in the context of curative surgery and adjuvant treatments; however, the wait is likely to be long, with only 9 deaths reported in the osimertinib group and 20 in the placebo group. Lifting the blind on this trial (which currently remains blinded for both patients and their physicians) will probably bias the results against osimertinib, with an anticipated high incidence of crossover from the placebo group on disease progression. In the meantime, these extremely impressive results — with reductions of 80% in the risk of disease recurrence or death and 82% in the risk of CNS progression or death among patients with resected stage IB to IIIA disease — provide resounding justification for the rapid

implementation of this approach into clinical practice, combined with routine testing for the presence of *EGFR* mutations, irrespective of the tumor stage.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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# The Power of Antibody-Based Surveillance

Galit Alter, Ph.D., and Robert Seder, M.D.

Antibodies are immune proteins that mark the evolution of the host immune response to infection. Antibodies can be measured in a sensitive and specific manner, providing an archive that reflects recent or previous infection. If maintained at sufficiently high levels, antibodies can rapidly block infection on reexposure, conferring long-lived protection.

Unlike pathogen detection, which is detectable only transiently, at the time of pathogen shedding at sites where diagnostic material is collected, antibodies represent durable markers of infection, providing critical information on infection rates at a population level. Contrary to recent reports suggesting that SARS-CoV-2 RNA testing alone, in the absence of antibodies, will be sufficient to track and contain the pandemic, the cost, complexity, and transient nature of RNA testing for pathogen detection render it an incomplete metric of viral spread at a population level. Instead, the accurate assessment of antibodies during a pandemic can provide important population-based data on pathogen exposure, facilitate an understanding of the role of antibodies in protective immunity, and guide vaccine development.

In midsummer 2020, studies emerged pointing to rapid waning of antibody immunity,[1,2] with reports across the globe suggesting that antibody responses were inversely correlated to disease severity,[4] even suggesting that asymptomatic infection could occur without seroconversion.[5] Consistently, in a month-long study, antibody titers were noted to wane both in patients with mild infection and in those with severe infection,[2] which raised the possibility that humoral immunity to this coronavirus may be very short-lived.

Stefansson and colleagues now report in the *Journal* their findings on the impact and implications of antibody testing at a population level, capturing insights on prevalence, fatality risk,