# Osimertinib in *EGFR*-Mutated Lung Cancer

**TO THE EDITOR:** With regard to the results of the ADAURA trial reported by Wu et al. (Oct. 29 issue),[1] it is of interest to know whether chemotherapy is necessary when osimertinib is used as adjuvant therapy in patients with epidermal growth factor receptor (*EGFR*) mutation–positive resected stage IB, II, or IIIA non–small-cell lung cancer (NSCLC). Some previous studies involving Asian patients with NSCLC — half of whom had *EGFR* mutation–positive NSCLC — suggested that survival was shorter among patients who received adjuvant chemotherapy than among those who did not. These findings resemble the results in Figure S4 of the article by Wu et al. (available with the full text of the article at NEJM.org) that showed a disease-free survival of 22.1 months in the chemotherapy group, as compared with 33.1 months in the group that did not receive chemotherapy.[1,2]

Can the authors present the comparison of osimertinib with placebo in patients who received chemotherapy and those who did not receive chemotherapy, stratified according to disease stage? If no benefit of chemotherapy is noted in the osimertinib group, an osimertinib-based, chemotherapy-free adjuvant regimen may be indicated. Three phase 3, randomized, controlled trials — the ADJUVANT/CTONG1104 trial,[3] the EVAN trial,[4] and the EVIDENCE study[5] — all suggested that EGFR tyrosine kinase inhibitors outperformed chemotherapy with respect to disease-free survival.

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No potential conflict of interest relevant to this letter was reported.

1. Wu Y-L, Tsuboi M, He J, et al. Osimertinib in resected *EGFR*-mutated non-small-cell lung cancer. N Engl J Med 2020;383:1711-23.
2. Wu Y, Chu X, Wang J, et al. EGFR mutation and survival outcomes in patients with completely resected lung adenocarcinoma — a multiple centers, non-interventional study (Ican Trial). Ann Oncol 2014;25:Suppl 4:iv410. abstract.
3. Wu Y-L, Zhong W, Wang Q, et al. CTONG1104: adjuvant gefitinib versus chemotherapy for resected N1-N2 NSCLC with EGFR mutation — final overall survival analysis of the randomized phase III trial 1 analysis of the randomized phase III trial. J Clin Oncol 2020;38: Suppl 15:9005. abstract.
4. Yue D, Xu S, Wang Q, et al. Erlotinib versus vinorelbine plus cisplatin as adjuvant therapy in Chinese patients with stage IIIA EGFR mutation-positive non-small-cell lung cancer (EVAN): a randomised, open-label, phase 2 trial. Lancet Respir Med 2018;6:863-73.
5. He J, Liang W, Xu S, et al. Icotinib versus vinorelbine/platinum as adjuvant therapy in stage II-IIIA non-small cell lung cancer with EGFR-mutations: a multicenter, randomized, positive-controlled, phase 3, indication-expanding study (EVIDENCE, CCTC-1501). ASCO 2016 (https://meetinglibrary.asco.org/record/122821/abstract).

DOI: 10.1056/NEJMc2033951

**THE AUTHORS REPLY:** Adjuvant chemotherapy, which has been associated with a 16% reduction in the risk of disease recurrence or death (hazard ratio, 0.84) among unselected patients,[1] is recommended in patients with resected stage II to IIIA NSCLC and high-risk stage IB NSCLC.[2] In the ADAURA trial, the use of adjuvant chemotherapy was determined according to physician and patient choice before randomization. This use was consistent with that in previous studies,[3-5] increased with a higher disease stage (as expected),[3,4] and was balanced across the trial groups.

A benefit of osimertinib with respect to disease-free survival was observed with or without the previous use of chemotherapy (hazard ratio for disease recurrence or death, 0.16 and 0.23, respectively). In the placebo group, the shorter median disease-free survival among patients who had received chemotherapy than among those who had not received chemotherapy (22.1 months vs. 33.1 months, respectively) was largely because of the percentages of patients with stage II to IIIA disease in those two subgroups. An analysis of disease-free survival stratified according to disease stage and previous use of chemotherapy is under way.

With the introduction of adjuvant osimertinib as a highly effective targeted therapy in resected *EGFR* mutation–positive NSCLC, the role of chemotherapy is an important question. The ADAURA trial was not designed to answer this question, since previous chemotherapy use reflected standard clinical practice at that time. Any nonrandomized comparisons of efficacy outcomes in patients who received chemotherapy, as compared with those who did not receive chemotherapy, in the osimertinib and placebo groups would be hypothesis-generating only. Future studies are



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warranted to understand the role of chemotherapy for patients with *EGFR* mutation–positive NSCLC.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Pignon J-P, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26:3552-9.
2. Kris MG, Gaspar LE, Chaft JE, et al. Adjuvant systemic therapy and adjuvant radiation therapy for stage I to IIIA completely resected non-small-cell lung cancers: American Society of Clinical Oncology/Cancer Care Ontario Clinical Practice Guideline update. J Clin Oncol 2017;35:2960-74.
3. Chouaid C, Danson S, Andreas S, et al. Adjuvant treatment patterns and outcomes in patients with stage IB-IIIA non-small cell lung cancer in France, Germany, and the United Kingdom based on the LuCaBIS burden of illness study. Lung Cancer 2018;124:310-6.
4. Buck PO, Saverno KR, Miller PJE, Arondekar B, Walker MS. Treatment patterns and health resource utilization among patients diagnosed with early stage resected non-small cell lung cancer at US community oncology practices. Clin Lung Cancer 2015;16:486-95.
5. Kelly K, Altorki NK, Eberhardt WEE, et al. Adjuvant erlotinib versus placebo in patients with stage IB-IIIA non-small-cell lung cancer (RADIANT): a randomized, double-blind, phase III trial. J Clin Oncol 2015;33:4007-14.

DOI: 10.1056/NEJMc2033951

## Subcutaneous or Transvenous Defibrillator Therapy

**TO THE EDITOR:** We inquire about the adjudication of shocks in the Prospective Randomized Comparison of Subcutaneous and Transvenous Implantable Cardioverter Defibrillator Therapy (PRAETORIAN) trial conducted by Knops and colleagues (Aug. 6 issue).[1] Of the 83 patients in the subcutaneous implantable cardioverter–defibrillator (ICD) group who had shocks labeled as "appropriate," 11 had shocks for ventricular tachycardia below the cutoff of 180 beats per minute solely because of oversensing of cardiac signals. For example, ventricular tachycardia at a rate of 150 beats per minute could be sensed as 300 beats per minute. Although the device ultimately terminated an arrhythmia in these 11 patients, oversensing can lead to the highly undesirable outcome of shocks while the patient is awake.

The authors acknowledge that these shocks may have been occasionally clinically desirable but they also could be considered to be unnecessary. They cite a post hoc analysis of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)[2] that showed a strong association between any shocks and higher mortality, and the Multicenter Automatic Defibrillator Implantation Trial (MADIT)–Reduce Inappropriate Therapy (MADIT-RIT),[3] which showed that permissive high-rate programming markedly reduced shocks and decreased mortality. These analyses cited by Knops et al. indicate that shocks for slower ventricular tachycardias are inappropriate because they are both painful and associated with increased mortality.

In the original trial protocol (available with the full text of the article at NEJM.org), Knops et al. defined appropriate shocks as those for ventricular tachycardia at a rate of more than 180 beats per minute. We estimate that if approximately half of these oversensed ventricular tachycardias had been labeled as inappropriate, noninferiority would not have been met.

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No potential conflict of interest relevant to this letter was reported.

1. Knops RE, Olde Nordkamp LRA, Delnoy P-PHM, et al. Subcutaneous or transvenous defibrillator therapy. N Engl J Med 2020;383:526-36.
2. Poole JE, Johnson GW, Hellkamp AS, et al. Prognostic importance of defibrillator shocks in patients with heart failure. N Engl J Med 2008;359:1009-17.



The New England Journal of Medicine

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