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Letter to the Editor

Treatment for Advanced Non–Small Lung Cancer (NSCLC) with Mutated *EGFR* in Low- and Middle-Income Countries (LMICs)

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In the August issue of the *Journal of Immunotherapy and Precision Oncology*, Mousa et al[1] discussed the economic prospects of first-line treatment for patients with non–small cell lung cancer with epidermal growth factor receptor (*EGFR*) gene mutations. By 2022, Latin America will have more than 660 million inhabitants, of which fewer than 7% have a high- or upper-middle–income level. In addition, almost a fifth of the population fell into the nonpoor-with-low-income stratum. For the same year, more than 95,000 new lung cancer cases were diagnosed; this disease remained the leading cause of cancer death (12%) in the region (Comunidad de Estados Latinoamericanos y Caribeños [CELAC])[2]. In this admixed population with a diverse genomic background, a higher frequency of *EGFR* mutations (26%) was found, with higher figures for Mexico (34%) and Peru (≈40%).[3] Recently, Carrot-Zhang et al[4] explained these figures based on the ancestry analysis of 1153 NSCLC cases, a study that revealed a striking association between Native American ancestry and their somatic landscape, including tumor mutational burden and specific driver mutations in *EGFR*, *KRAS*, and *STK11*. In addition, Arrieta et al[5] demonstrated that approximately 35% of patients with lung adenocarcinoma have a history of wood smoke exposure and that this factor considerably increases the possibility of presenting *EGFR* mutations (≈50%). Considering these data, using osimertinib as the first line for *EGFR*-positive metastatic lung adenocarcinomas and in an adjuvant setting constitutes a real public health problem due to its budgetary impact.

Given the limited access to newer lung cancer therapies in most low- and middle-income countries (LMICs), the effects of targeted therapies and immune checkpoint inhibitors on lung cancer mortality are likely limited. Less than half of all patients globally have access to the molecular testing needed to select patients for targeted therapies, with practice patterns varying substantially depending on geographic location.[6] Barriers to accessing novel lung cancer therapies in LMICs include a lack of access to cancer centers and the unaffordability of therapies and a lack of infrastructure allowing the detection of specific targetable alterations.[5] In Brazil, Aguiar et al[7] found an incremental quality-adjusted life year for osimertinib of 0.594 compared with the first- and second-generation EGFR tyrosine kinase inhibitors (TKIs). In the United States, the osimertinib incremental cost-effectiveness ratios (ICERs) were $226,527 (USD) versus erlotinib, $231,123 versus gefitinib, and $219,874 versus afatinib. In Brazil, the ICERs were $162,329, $180,804, and $175,432 (USD), respectively. The overall survival reported in the FLAURA trial[7] had the strongest association with the ICER, demonstrating that osimertinib price adjustments improved cost-effectiveness. For example, a 10% and 20% discount on osimertinib acquisition cost was associated with a 20% and 40% decreased ICER compared with the base case ICER.[8] In Colombia, Lasalvia et al[9] demonstrated an ICER for osimertinib of $35,062, exceeding the current willingness to pay threshold for the country. This information is like that described by Shu et al[10] for China, where osimertinib had an approximate 46.4% probability of being cost-effective at the willingness to

pay threshold of $37,663.26 per quality-adjusted life year. Consequently, for the largest middle-income country in the world, the first-line osimertinib therapy might not be cost-effective for patients with *EGFR*-mutated advanced NSCLC compared with other EGFR-TKIs based on its current marketed price. For this reason, a significantly more favorable cost-effectiveness could be achieved when the price of osimertinib was reduced by 5%.[10] The controversy becomes more complex considering the results of the ADAURA study. At the American Society of Clinical Oncology 2023 annual meeting, Muthusamy et al[11] demonstrated that using adjuvant osimertinib allowed a gain in disease-free survival of 35.4% at 5 years, but with a high financial cost of about $450,000 per eligible patient. However, the cost-effectiveness modeling of adjuvant osimertinib for the Canadian healthcare system favored the TKI compared with active surveillance.[12]

Given the importance of osimertinib for treating *EGFR*-positive lung cancer, it is urgent to find strategies that allow its widespread use in LMICs. The reduction in drug cost for this scenario and the use of risk-sharing models satisfy drug manufacturers and payers with a decrease in price and effective evaluation of drugs. Alternatively, the rapid adoption of aumolertenib, a third-generation inhibitor that demonstrated better outcomes than gefitinib in the AENEAS trial,[13] could be considered.

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