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How to cite this article: Giuliani J, Bonetti A. Cost-effectiveness of Osimertinib in activating epidermal growth factor receptor gene (EGFR)-mutations in first-line for advanced non-small cell lung cancer. Cancer Drug Resist 2021;4:[Online First].

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Table 1. Cost of drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pharmacy cost (€) (dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>9.90 (1000 mg)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>6.19 (100 mg)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>9.84 (80 mg)</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>7.18 (150 mg)</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>8.80 (50 mg)</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>6.54 (10 mg)</td>
</tr>
<tr>
<td>Nab-paclitaxel</td>
<td>214.48 (100 mg)</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>2004.61 (1 administration at 7.5 mg pro Kg)</td>
</tr>
<tr>
<td></td>
<td>2672.28 (1 administration at 15.0 mg pro Kg)</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>226.65 (100 mg)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>2056.08 (100 mg)</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>45.80 (150 mg tablet)</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>72.06 (250 mg tablet)</td>
</tr>
<tr>
<td>Afatinib</td>
<td>65.85 (20 mg tablet)</td>
</tr>
<tr>
<td>Osimertinib</td>
<td>145.28 (80 mg tablet)</td>
</tr>
</tbody>
</table>

The aim of our study was to assess the pharmacological costs of TKIs (erlotinib, gefitinib, afatinib and osimertinib) in patients with activating EGFR mutations in first-line treatment for advanced NSCLC. Pivotal phase III randomized controlled trials (RCTs) were considered. The last available update of each trial was considered as the original source. The deadline for trial publication and/or presentation was 30 June 2020. Incremental cost-effectiveness ratio (ICER) was calculated as the ratio between the difference of the costs in the intervention and in the control groups (pharmacy costs) and the difference between the effect in the intervention and in the control groups [overall survival (OS)]. The costs of drugs were based on those at the pharmacy of our hospital and are expressed in euros (€), updated to June 2020. The pharmacy costs of drugs are summarized on Table 1. The dosages of drugs were considered according to those reported in each RCT. The European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) was applied to the pivotal RCTs[4] to derive a relative ranking of clinical benefit[5]. All data were reviewed by two investigators (Giuliani J and Bonetti A) and separately computed by two investigators (Giuliani J and Bonetti A).

Nine phase III RCTs[6-14], including 2291 patients, were considered. The OS of TKIs ranged from 18.8 months for gefitinib in the IPASS trial[8,9] to 38.6 months in the FLAURA trial[14,16]. ESMO-MCBS reached Grade 4 for OPTIMAL trial[6], EURTAC trial[7], IPASS trial[8], LUX-Lung 3 trial[12] and FLAURA trial[14]; Grade 3 for NEJ2002 trial[6], WJTOG3405 trial[10] and LUX-Lung 6 trial[13]; and Grade 1 for First-SIGNAL trial[11]. The lowest cost for 1 month of OS gain was associated with osimertinib, at €9740 per month OS gained [Table 2].

Two main variables influence pharmacy costs: the efficacy of treatment and the price of drugs. The first variable is related to the patient’s inclusions criteria, and we know that results from RCTs might not be representative of daily clinical practice (i.e., of patients treated outside such trials). The price of drugs is the second strong variable. In fact, there may be a cost standardization problem within different European countries (in Italy, there are no significant pharmacy cost differences among the different regions), due to the use of local pharmacy cost. Another limit is related to the consideration of only direct costs (which account for about 55% of total medical expenses). In Europe, expenditure for cancer drugs amounted to €10 billion in 2005, increasing more than three times to €32 billion in 2018[17]. In this scenario, European countries negotiate the price of new drugs with the manufacturers with the aim to obtain a discount, so as to
allow more patients to be treated. This results in “confidential rebates” (i.e., not publicly available), which may hamper access to drugs with a consequent overpayment without improving the value of drugs. The extraordinary costs of novel treatments may form a new type of resistance, costs resistance. In several countries, this may preclude treatments with these compounds.

There are several published articles, mostly in China, regarding this topic. However, to our knowledge, this is the first cost-effectiveness analysis of TKIs in patients with activating EGFR-mutations in first-line treatment for advanced NSCLC in Europe.
In addition, the annual cost of drugs treatment (€116,880 for osimertinib, €118,840 for gefitinib and €165,528 for erlotinib) are not in line with those reported in the literature, which indicate implementing intervention for thresholds of less than $61,500 (€57,138) per life-year gained\textsuperscript{[18]}. 

We also compared the pharmacy costs of TKIs (osimertinib, erlotinib, gefitinib and afatinib) with the pharmacy costs of other immune check-point inhibitors (ICIs), such as nivolumab, pembrolizumab and atezolizumab, registered in other tumors (e.g., NSCLC, head and neck carcinoma and urological malignancies) and known as the most expensive new drugs in medical oncology\textsuperscript{[19-24]}, as well as the costs of the reference elements in international markets, 18 karat (K) gold and platinum. All TKIs have the highest cost per gram, with €305.33 for erlotinib, €288.24 for gefitinib, €3292.50 for afatinib and €1816.00 for osimertinib, with a Δ toward 18 K gold and platinum per gram of €258.43 and €283.88 for erlotinib, respectively; €241.34 and €266.79 for gefitinib, respectively; €3245.60 and €3271.05 for afatinib, respectively; and €1769.10 and €1794.55 for osimertinib, respectively. This leads us to think that ICIs are not the most expensive targeted agents, but there are other more expensive ones. Thus, there is no doubt that data on osimertinib are good in daily clinical practice\textsuperscript{[11,13]}, but a reduction in pharmacological costs is mandatory if we want to consider TKIs (in particular, osimertinib) more advantageous in terms of cost-effectiveness.

In conclusion, based on ICER, osimertinib is more cost-effective than the other TKIs (erlotinib, gefitinib and afatinib) in patients with activating \textit{EGFR} mutations in first-line treatment for advanced NSCLC. The data on osimertinib are good in daily clinical practice (also confirmed by the high grade of clinical benefit on ESMO scale\textsuperscript{[3]}), but a reduction in pharmacological costs is mandatory if we want to consider osimertinib more cost-effective in first-line treatment for \textit{EGFR}-mutated advanced NSCLC.

**DECLARATIONS**

**Authors’ contributions**

Conception and design, acquisition of data, or analysis and interpretation of data: Giuliani J, Bonetti A

Drafting the article and revising it critically for important intellectual content: Giuliani J, Bonetti A

Final approval of the version to be published: Giuliani J, Bonetti A

Each author contributed equally.

**Availability of data and materials**

Not applicable.

**Financial support and sponsorship**

None.

**Conflicts of interest**

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

**Ethical approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.
REFERENCES


