Background and importance

Regorafenib, ramucirumab and cabozantinib are used as a second-line therapy in patients with hepatocarcinoma and alpha-fetoprotein value ≥400 ng/mL (HCC-AP≥400). There are no direct comparisons among them.

MATERIAL AND METHODS

A search was conducted to identify phase III clinical trials with similar populations (second line of treatment of HCC-AP≥400), duration and endpoints.

If more than one study of the same drug were found, the results were combined through a meta-analysis (Joaquim Primo calculator). ITC was made according to Bucher’s method.

Delta value (Δ), maximum acceptable difference as a clinical criterion of no-inferiority

The variable selected to determine clinical equivalence was overall survival (OS)

To establish the positioning, the criteria of the ATE Guide were applied. If the 95%CI deviated from the delta margin, this probability was calculated using Shakespeare method.

RESULTS

Four clinical trials were found, ramucirumab (N=2), regorafenib (N=1) and cabozantinib (N=1). Ramucirumab trials were pooled, resulting in HR 0.71 (95%CI 0.58-0.86). The results of the ITC were as follows:

<table>
<thead>
<tr>
<th>Reference</th>
<th>OS: HR (95% IC)</th>
<th>Limitation founds: included population</th>
</tr>
</thead>
<tbody>
<tr>
<td>cabozantinib-regorafenib</td>
<td>1.044 (0.692-1.576)</td>
<td>(only patients with alpha-fetoprotein≥400 ng/mL vs. all patients, then subgroup data were used for ITC), and previous therapy as first line</td>
</tr>
<tr>
<td>ramucirumab-regorafenib</td>
<td>1.044 (0.726-1.501)</td>
<td></td>
</tr>
<tr>
<td>ramucirumab-cabozantinib</td>
<td>1 (0.712-1.405)</td>
<td>(only sorafenib vs. other treatments allowed, in small percentages)</td>
</tr>
</tbody>
</table>

According to the ATE Guide, there was a likely clinical equivalence

The probability that the result exceeded the delta margin above and below was, respectively, 12.45% and 5.76% for cabozantinib-regorafenib, 9.57% and 3.71% for ramucirumab-regorafenib, and 5% and 4.86% for ramucirumab-cabozantinib

CONCLUSION

The ITC showed no statistically differences in OS among the drugs. The 95%CI showed a certain grade of uncertainty, exceeding the equivalence margin. According to the ATE Guide, we could consider that there was clinical equivalence among the drugs due to the small percentage of the 95%CI that is outside the equivalence margin.