BACKGROUND

Regorafenib is a multi-kinase inhibitor that targets the activity of multiple tyrosine kinases involved in tumor growth, angiogenesis, and invasion. It is approved for the treatment of metastatic colorectal cancer (mCRC) in the setting of disease progression following at least one prior anti-VEGF and one prior anti-EGFR regimen.

The CORRECT study (ClinicalTrials.gov identifier: NCT01103323) compared regorafenib to placebo in subjects with mCRC who had progressed on one or more lines of prior therapy. The primary endpoint was overall survival (OS). The rate of mortality in the regorafenib group was lower than in the placebo group (30-month OS rate: 32.6% vs. 25.2%; hazard ratio [HR] = 0.774; 95% confidence interval [CI] = 0.60–0.98; p = 0.039; p = 0.035 for the log-rank test and the ROC curves respectively; Figure 3A). Regorafenib also improved progression-free survival (PFS) compared with placebo, with a hazard ratio (HR) of 0.774 (95% CI 0.60–0.98; p = 0.039; Figure 3B). The results were consistent across all predefined subgroups, including patients with previous anti-EGFR therapy, those with BRAF mutations, and those with ≥3 comorbidities.

OBJECTIVES

The correlation of each biomarker with the efficacy of regorafenib was assessed as a secondary objective. A panel of 19 plasma protein biomarkers that may predict response in patients with CRC were selected.

METHODS

Baseline plasma samples were available for 611 of the 760 patients (80%) included in the CORRECT study, and baseline levels of each biomarker were assessed. The biomarker panel included vascular endothelial growth factor A isoform 121 (VEGF-A-121), tissue inhibitor of metalloproteinase 2 (TIMP-2), stromal cell-derived factor-1 (SDF-1), vascular endothelial growth factor C (VEGF-C), von Willebrand Factor (VWF), cell survival 377, 0.035, and LLOQ, lower limit of quantitation

RESULTS

Baseline plasma samples were available for 611 of the 760 patients (80%). The HR for PFS in regorafenib versus placebo in the biomarker patient subgroup was 0.48 (95% CI 0.40–0.58), while the median, best-fit, and ROC cutoff methods failed to reach significance.

Conclusions

Baseline plasma levels of potential biomarkers in the CORRECT study correlated with OS and PFS to varying degrees. The potential biomarkers were further classified into two categories: biomarkers that showed a significant interaction with regorafenib on OS in all regorafenib-treated patients when analyzed using the best fit and ROC curve methods.

Predictive biomarkers

Logistic regression analyses were performed using the best fit and ROC curve cutoff methods. Interleukin-6 (IL-6) and VEGF-A-121 showed significant interaction with OS and PFS, while interleukin-8 appeared to have prognostic value for PFS and OS (Table 3). Vascular remodelling, which may play a role in resistance to anti-VEGF therapy, was identified as a potential biomarker for predicting response to regorafenib.

PROGNOSTIC FACTORS

Table 3: Protein Cutoff method HR (95% CI) Log rank p-value HR (95% CI) Log rank p-value

<table>
<thead>
<tr>
<th>Protein</th>
<th>Baseline</th>
<th>High</th>
<th>Low</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukin-6 (IL-6)</td>
<td>1.10 (0.95–1.28)</td>
<td>0.052</td>
<td>2.46 (1.82–3.35)</td>
<td>&lt;0.001</td>
<td>1.22 (0.91–1.63)</td>
</tr>
<tr>
<td>Vascular endothelial growth factor A isoform 121 (VEGF-A-121)</td>
<td>1.63 (1.29–2.05)</td>
<td>&lt;0.001</td>
<td>1.34 (0.97–1.85)</td>
<td>0.063</td>
<td></td>
</tr>
<tr>
<td>Vascular endothelial growth factor C (VEGF-C)</td>
<td>1.63 (1.29–2.05)</td>
<td>&lt;0.001</td>
<td>1.34 (0.97–1.85)</td>
<td>0.063</td>
<td></td>
</tr>
<tr>
<td>Tissue Inhibitor of Metalloproteinase 2 (TIMP-2)</td>
<td>1.63 (1.29–2.05)</td>
<td>&lt;0.001</td>
<td>1.34 (0.97–1.85)</td>
<td>0.063</td>
<td></td>
</tr>
<tr>
<td>Stromal Cell Derived Factor-1 (SDF-1)</td>
<td>1.63 (1.29–2.05)</td>
<td>&lt;0.001</td>
<td>1.34 (0.97–1.85)</td>
<td>0.063</td>
<td></td>
</tr>
<tr>
<td>Von Willebrand Factor (VWF)</td>
<td>1.63 (1.29–2.05)</td>
<td>&lt;0.001</td>
<td>1.34 (0.97–1.85)</td>
<td>0.063</td>
<td></td>
</tr>
</tbody>
</table>

CONCLUSION

Baseline plasma levels of potential biomarkers in the CORRECT study were associated with OS and PFS. Interleukin-6, VEGF-A-121, and VEGF-C showed significant interaction with OS and PFS, while interleukin-8 appeared to have prognostic value for PFS and OS. These findings may contribute to the development of personalized treatment strategies for patients with mCRC.

REFERENCES


ACKNOWLEDGMENTS

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