In the subset of patients with available growth factor data, the benefit of aflibercept treatment was assessed. Aflibercept is a VEGF trap, which has a wider binding range than other anti-VEGF agents. Aflibercept binds to and blocks VEGF-A, VEGF-B, and placental growth factor (PIGF), preventing them from interacting with their receptors (Figure 1). In the Phase III VELOR trial (NCT00561470), aflibercept improved overall survival (OS) in patients with mCRC who had received prior oxaliplatin, including those treated with prior bevacizumab. Figure 2 shows that patients with mCRC enrolled in the Phase III VELOR trial (NCT00561470) were randomized to receive either 4 mg/kg aflibercept + FOLFIRI (n = 612) or placebo + FOLFIRI (n = 614) every 2 weeks until program end or limiting toxicity. Patients with baseline PIGF and VEGF-A levels (n = 553) were included in the biomarker population. Patients were stratified into four groups according to prior bevacizumab treatment status (yes vs no) and second-line treatment (aflibercept vs placebo). Mean levels of growth factors at baseline, median OS (mOS) and median progression-free survival (mPFS) were calculated for these groups. Median VEGF-A for all patients was 8 mg/mL; median PIGF for all patients was 144 mg/mL. mOS and mPFS were calculated for patients with VEGF-A above median. Hazard ratio (HR) values for PFS and OS were calculated using a stratified Cox procedure with Eastern Cooperative Oncology Group performance status and prior bevacizumab as stratification factors. Note that adjuvant rapid relapse patients were not excluded from this analysis.

VEGF (vascular endothelial growth factor-A), a fusion protein that targets VEGF receptors. VEGFR-2 MAb, monoclonal antibody; PIGF, placental growth factor; VEGF, vascular endothelial growth factor-A. Aflibercept uniquely targets both VEGF-A and PlGF with a higher affinity than bevacizumab or their receptors. The combination of aflibercept with FOLFIRI demonstrated an activity in patient groups with and without baseline PlGF and VEGF-A levels. Aflibercept demonstrated an activity in patients with baseline VEGF-A and PIGF levels above median. Aflibercept plus FOLFIRI improved median OS and mPFS compared with placebo plus FOLFIRI. A retrospective analysis of baseline plasma samples from the VELOR trial investigated the ability of aflibercept to overcome bevacizumab resistance.

Results

OS and PFS: Biomarker population

In the subset of patients with available growth factor data, the benefit of aflibercept treatment compared with placebo was consistent with the overall results of the VELOR study.

OS: HR = 0.81 versus 0.82; PFS: HR = 0.73 versus 0.76 for patients with growth factor data vs all patients, respectively.

OS benefit of aflibercept versus placebo depended on prior bevacizumab treatment:

- for patients with no prior bevacizumab, HR (95% confidence interval [CI]) = 0.80 (0.63–1.01); p-value = 0.06
- for patients with prior bevacizumab HR (95% CI) = 0.84 (0.59–1.19); p-value = 0.33

Patients who had received prior bevacizumab were more likely to have VEGF-A and PIGF levels above median. Mean plasma VEGF-A and PIGF levels were higher for patient groups with prior bevacizumab treatment (Table 1).

Table 1. Baseline VEGF-A and PIGF plasma levels, mPFS and mOS in patients with and without prior bevacizumab treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean VEGF-A, pg/mL</th>
<th>Mean PIGF, pg/mL</th>
<th>mPFS, months (95% CI)</th>
<th>mOS, months (95% CI)</th>
<th>Aflibercept vs placebo</th>
<th>Aflibercept vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 79)</td>
<td>753.1</td>
<td>20.7</td>
<td>9.9 (3.4–1.4)</td>
<td>10.6 (9.1–12.5)</td>
<td>1.5</td>
<td>0.84 (0.59–1.19)</td>
</tr>
<tr>
<td>Aflibercept (n = 90)</td>
<td>762.6</td>
<td>23.1</td>
<td>9.7 (3.6–1.8)</td>
<td>11.2 (10.0–16.9)</td>
<td>1.5</td>
<td>0.80 (0.63–1.01)</td>
</tr>
<tr>
<td>Placebo (n = 186)</td>
<td>148.9</td>
<td>12.0</td>
<td>6.8 (1.0–7.5)</td>
<td>12.9 (11.9–15.7)</td>
<td>1.5</td>
<td>0.80 (0.63–1.01)</td>
</tr>
</tbody>
</table>

OS: Patients with growth factor levels above median

- Patients with baseline VEGF-A plasma levels above median (> 144 mg/mL) had higher OS with aflibercept versus placebo treatment (Figure 3, Figure 4): for patients with no prior bevacizumab, HR (95% CI) = 0.56 (0.38–0.82); p-value = 0.003 for patients with prior bevacizumab, HR (95% CI) = 0.83 (0.55–1.24); p-value = 0.36.

CONCLUSIONS

Prior treatment with first-line bevacizumab induced cytokine changes, including increase of VEGF-A and PIGF, which may impact on patient outcomes.

Aflibercept uniquely targets both VEGF-A and PIGF with a higher affinity than bevacizumab or their receptors. The combination of aflibercept with FOLFIRI demonstrated an activity in patient groups with and without prior bevacizumab treatment and in patients with baseline VEGF-A and PIGF above median. This was a retrospective analysis with limited patient numbers; further studies are warranted to investigate the ability of aflibercept to overcome bevacizumab resistance.

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REFERENCES