**TRIAL SUMMARY:** RAS status predicts response in FIRE-3

Mutations within the EGFR signaling pathway: Influence on efficacy in FIRE-3—A randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) patients. J Clin Oncol 32, 2014 (suppl 3; abstr 445)

FIRE-3 is a randomized multicentre trial comparing the efficacy of FOLFIRI (leucovorin/fluorouracil/irinotecan) plus cetuximab (Cet) to FOLFIRI plus bevacizumab (Bev) as first-line treatment in KRAS WT mCRC patients. Overall response rates (ORR) and progression-free survival (PFS) were comparable between the 2 groups, but overall survival (OS) was significantly longer in the FOLFIRI plus Cet arm.

This preplanned analysis, presented at ASCO-GI 2014, looked at the effect of mutations within the epidermal growth factor receptor (EGFR)-dependent pathway on response to the 2 regimens. Along with mutations within KRAS (exon 2, 3, 4), NRAS (exon 2, 3, 4) and BRAF (V600E), mutations within PIK3CA (exon 9 and 20) and AKT were investigated, and their impact on ORR, PFS and OS within the FIRE-3 population was evaluated. The analysis of all mutations was carried out employing pyrosequencing.

**ORR and OS were increased in patients with Cet plus FOLFIRI as compared to Bev plus FOLFIRI in patients without RAS mutations. The authors concluded that excluding patients with RAS mutations would enable identification of a population more likely to benefit from cetuximab.**

**COMMENTARY:** The EGFR antibodies such as cetuximab (Cet) and panitumumab (Pan) have been recommended for the treatment of KRAS wild-type (WT) metastatic colorectal cancer (mCRC) as monotherapy or in combination with chemotherapy. However, not all patients respond to this treatment.

A number of phase II–III trials that investigated EGFR antibodies in the treatment of mCRC reported a lack of benefit in patients with additional RAS or BRAF mutations (Table 1).2,3

The PRIME study that assessed the efficacy and safety of Pan with 5-fluorouracil, oxaliplatin and leucovorin (FOLFOX4) reported superior OS in the Pan arm vs FOLFOX4 arm (26.0 months vs 20.0 months respectively).1 An updated analysis of OS showed that results of interaction testing between subgroups of patients with WT KRAS exon 2 but other RAS mutations, and patients with WT RAS was significant (p=0.01). Importantly, in the subgroup of patients with mutated RAS tumours, PFS and OS were significantly shorter in the combination arm.

The PEAK trial was the first phase II study to compare Pan and bevacizumab (bev) head-to-head in combination with 5-fluorouracil, oxaliplatin, and leucovorin (mFOLFEX6) as first line treatment of WT KRAS mCRC.1 In the WT KRAS exon 2 subgroup, PFS was similar between the 2 arms, with better OS in the Pan arm than with Bev (34.2 vs 24.3 months; HR, 0.62; 95% CI, 0.44–0.89; p=0.009). On further analysis of the WT all RAS subgroup, PFS was better in the Pan arm (HR, 0.65; 95%CI, 0.39–1.02; p=0.058).

**TABLE 1. RAS/BRAF status in KRAS exon 2 wild-type tumours**

<table>
<thead>
<tr>
<th>STATUS</th>
<th>FIRE-3 (total number, %)</th>
<th>PEAK (cetuximab/FOLFIRI vs bevacizumab/FOLFIRI, %)</th>
<th>PRIME (panitumumab/FOLFOX vs FOLFOX alone, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>treatment arm</td>
<td>control arm</td>
<td>treatment arm</td>
</tr>
<tr>
<td>KRAS exon 3</td>
<td>4.3</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>KRAS exon 4</td>
<td>4.9</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>NRAS exon 2</td>
<td>3.8</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>NRAS exon 3</td>
<td>2</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>NRAS exon 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BRAF exon 15</td>
<td>10</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>BRAF exon 11</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

FIRE-3 is a randomized multicentre phase III trial comparing the efficacy of Cet or Bev in combination with 5-fluorouracil, irinotecan and leucovorin (FOLFIRI) as first-line therapy of mCRC.7 No difference was seen between the 2 arms in ORR or PFS. However, OS was significantly prolonged in the Cet arm.
Further preplanned analysis looked at the effect of other mutations within the EGFR-dependent pathway. In patients with WT RAS tumours, improved ORR (76.0% vs 65.2%, respectively; p=0.044) and OS (33.1 months vs 25.9 months, p=0.010, respectively) were observed in the Cet arm. In patients with mutated BRAF and WT KRAS (exon 2), ORR was 63.2% in the Cet arm versus 42.9% in Bev arm. The same trend was reported for PFS (10.5 vs 10.4 months in patients with WT RAS tumours and 6.3 months vs 5.7 months in mutant BRAF tumours, respectively in favour of the Cet arm).

In summary, the use of EGFR antibodies with or without standard chemotherapy in mCRC is associated with significant clinical and statistical benefit in selected patient populations. The phase III FIRE-3 trial demonstrated the impact of KRAS exon 3,4 and NRAS exon 2,3,4 mutations in a population with KRAS exon 2 WT on the efficacy of first-line chemotherapy with FOLFIRI plus Cet vs FOLFIRI plus Bev. Available data from other trials strongly support the recommendation to include not only exon 2 KRAS testing, but also testing for less common mutations, to identify patients who may benefit from this treatment regimen. Currently, patients with mCRC in Canada are tested only for KRAS exon 2 mutation.

References:

IN BRIEF

Already known
- Cetuximab and panitumumab are recommended for KRAS WT mCRC but not all patients respond.
- Patients with additional RAS or BRAF mutations have been found to benefit less from these EGFR antibodies.

What this study showed
- In the first-line setting, cetuximab prolonged OS over panitumumab.
- Subgroup analysis showed that patients with WT RAS had much better OS, ORR on cetuximab than on panitumumab.

Next steps
- Include testing of less common mutations alongside exon 2 KRAS mutations to determine the best treatment for patients with mCRC.