**TRIAL SUMMARY: OS advantage with both cetuximab and bevacizumab**

Venook A, Niedzwiecki D, Lenz HJ, et al. CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab or cetuximab for patients with KRAS wild-type untreated metastatic adenocarcinoma of the colon or rectum. 2014 ASCO Annual Meeting, Abstract LBA3.

Patients with metastatic colorectal cancer (mCRC) KRAS wild-type (WT) (codon 12 and 13) were randomly assigned to cetuximab (Cet) 400 mg/m<sup>2</sup> every 2 weeks or bevacizumab (Bev) 5 mg/kg every 2 weeks combined with 5-fluorouracil (5-FU)/leucovorin/irinotecan (FOLFIRI) or 5-FU/leucovorin/oxaliplatin (FOLFOX) chemotherapy in the first-line setting. A total of 1140 patients (pts) with Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 and adequate organ function were included. Patients were treated until progression, death, unacceptable toxicities or curative surgery. The primary endpoint was overall survival (OS), intent-to-treat; secondary endpoints were progression-free survival (PFS) and chemotherapy/biologics interaction.

Patients were stratified based on type of chemotherapy received and previous adjuvant chemotherapy and radiation therapy. Patient characteristics were well balanced between treatment groups (559 pts in the Bev group, 578 pts in the Cet group). There was male predominance in both groups (62.3% in chemotherapy plus Bev and 60.4% in chemotherapy plus Cet); primary in place was present in 28% and 27% respectively; the FOLFOX/FOLFIRI ratio was 73%/27% and 74%/26% respectively.

Results: Median OS was 29.9 months (95% CI, 27.0–32.9) for chemotherapy plus Cet vs 29.0 months (95% CI, 25.7–31.2) for chemotherapy plus Bev; HR 0.92 (0.78, 1.09, p=0.34). In pts treated with FOLFOX, OS was 30.1 months in the Cet arm vs. 26.9 in the Bev arm with p=0.09, HR 0.9 (0.7–1.0). In the FOLFIRI group, OS was 33.4 months in the Bev arm vs 28.9 months in Cet arm with p=0.28, HR 1.2 (0.9–1.6). PFS was 10.4 (95% CI, 9.6–11.3) in the chemotherapy plus Cet arm vs 10.8 months (95% CI, 9.7–11.4) in the chemotherapy plus Bev arm, p=0.55. Following surgery, 94 patients were disease free after a median follow-up of 40 months. The toxicity profile was as expected.

The authors concluded that both regimens (chemotherapy plus either Cet or Bev) are equivalent in OS in patients with KRAS WT (codons 12 and 13) mCRC and may be used as first-line treatment. An OS of 29 months and 8% long-term survivors confirm that progress is being made in treating mCRC.

**TRIAL SUMMARY: Adding cetuximab to FOLFIRI benefits all RAS wild type mCRC**


The addition of cetuximab (Cet) to first-line FOLFOX chemotherapy significantly improves PFS and response rate (RR) in patients (pts) with mCRC KRAS wild-type (WT) (exon 2). In patients with mutant exon 2 KRAS, the addition of Cet resulted in a trend to worse outcome. KRAS exon 2 WT tumour samples from the OPUS study were screened for 26 mutations in 4 additional KRAS codons and 6 NRAS codons (118/179 evaluable samples). New RAS mutation was detected in 31/118 exon 2 WT tumours (26%). In mCRC, RAS WT response was significantly improved by the addition of Cet to chemotherapy. The treatment effect in new RAS mutant mCRC could not be definitely assessed due to low patient numbers. In patients with KRAS exon 2 plus any new RAS mutation, the addition of Cet resulted in worse outcome. Response in FOLFOX plus Cet vs FOLFIRI4 alone was 57.9 vs 28.6 in all loci WT, 53.3 vs 43.8 in the new mutation group, and 37.0 vs 50.0 in any mutation group, respectively. Median OS in FOLFOX plus Cet vs FOLFIRI4 arms was 19.8 vs 17.8 months in the all WT group, 18.4 vs 17.8 months in the new mutation group, and 13.5 vs 17.8 months in the any mutation group, respectively. The authors conclude that Cet administration should be limited to patients with all RAS WT mCRC.

**TRIAL SUMMARY: Adding cetuximab to FOLFIRI benefits all RAS wild type mCRC**


In patients with wild-type (WT) KRAS (exon 2), the addition of cetuximab (Cet) to FOLFIRI chemotherapy resulted in improved progression-free survival (PFS), overall survival (OS), and response rate (RR) in the first-line setting; no such benefit was observed in KRAS mutant mCRC. Available tumour samples from the CRYSTAL study (430/666) were screened for 26 new mutations in 4 additional KRAS codons and 6 NRAS codons. New mutations were identified in 63/430 (15%) patients (pts). In mCRC all mutations WT, the addition of Cet was associated with a significant benefit.
across all endpoints; in those with new RAS mutations, no clear difference in outcome was observed between treatment arms; in pts with KRAS exon 2 mutation with new RAS, no benefit appeared from the addition of Cet. The RR in FOLFIRI plus Cet vs FOLFIRI arm was 66.3 vs 38.6 in all loci WT mCRC respectively; 34.4 vs 35.5 in new mutations mCRC respectively; and 1.7 vs 5.0 in any mutation group, respectively. Comparing FOLFIRI plus Cet vs FOLFIRI in terms of months of OS found 68.4 vs 20.2 in all loci WT mCRC, respectively; 18.2 vs 20.7 in new mutations mCRC respectively; and 16.4 vs 17.7 in any mutation group respectively. The authors conclude that in first-line treatment of mCRC, pts with all RAS WT benefit from the addition of Cet; pts with mutant RAS do not benefit.

**COMMENTARY:** The treatment of metastatic colorectal cancer (mCRC) has changed a lot over the last decade. Overall survival (OS) has improved from 10–12 months with single-agent 5-FU to almost 30 months with current treatment modalities.12

The CRYSTAL phase III study assessed the use of Cet in combination with FOLFIRI in the first-line treatment setting for mCRC.4 It found a significant improvement in PFS, the primary endpoint, with the addition of Cet to FOLFIRI. Secondary endpoints such as RR and OS were also improved in the Cet arm. The benefit of Cet was achieved exclusively in pts with KRAS WT mCRC. As new mutations were identified, further analysis was performed. This concluded that the greatest benefit was in all RAS WT mCRC and that there was no clear benefit from the addition of Cet in pts with KRAS exon 2 WT mCRC with new RAS mutations.

The OPUS study randomized patients to FOLFOX with or without Cet.6 Reported data clearly show an improvement in RR and PFS in pts with KRAS WT. Further analysis to include new mutations confirmed that benefit was limited to all RAS WT mCRC pts. Due to the small number of pts with KRAS exon 2 and any new mutation, the effect of adding Cet could not be definitely assessed. Cet appeared to have a detrimental effect in pts with KRAS exon 2 and any new mutation mCRC.

The CALGB 80405 Phase III trial compared Cet and Bev head-to-head in combination with FOLFOX or FOLFIRI in pts with KRAS exon 2 WT mCRC. The primary endpoint was OS, and secondary endpoints were PFS and chemotherapy/biologics interactions. Stratification was performed based on the type of chemotherapy received and previous adjuvant chemotherapy and radiation therapy. Median OS was equal for both treatment arms (29.9 months for Cet and 29.0 for Bev, HR 0.92 (0.78, 1.09, p=0.34). In the FOLFOX group, OS was 30.1 months in the Cet arm vs 26.9 in the Bev arm with p=0.09, HR 0.9 (0.7–1.0). In the FOLFIRI group, OS was 33.4 months in the Bev arm vs 28.9 months in the Cet arm with p=0.28, HR 1.2 (0.9–1.6). PFS was 10.4 months (95% CI, 9.6–11.3) in the chemotherapy plus Cet arm vs 10.8 months (95% CI, 9.7–11.4) in the chemotherapy plus Bev arm, p=0.55. With regards to toxicity, more rash and diarrhea grade ≥3 was reported in pts treated with Cet vs Bev (7% vs 0% for rash, respectively; 11% vs 8% for diarrhea, respectively); more grade ≥3 hypertension and venous thromboembolism (VTE) was seen with Bev than Cet (7% vs 1% for hypertension, respectively; 6% vs 4% for VTE, respectively). Occurrence of other toxicities such as neuropathy, cytokine release, and hematologic toxicities was comparable in both arms. The authors concluded that both regimens (chemotherapy plus either Cet or Bev) provide equivalent OS benefit in pts with KRAS WT mCRC (codons 12 and 13) mCRC and may be used as a first-line treatment.

In contrast to other trials, CALGB 80405 reports a better OS in pts treated with an addition of Cet (OPUS, OS=22.8 months; COIN, OS=17 months; CRYSTAL, OS=23.5 months). This may be explained by more favourable patient selection in the CALGB 80405 trial, secondary liver resections (11% NED after surgery), and post-progression treatment options (88% with 2 and more lines) for chemotherapy and biologics. As well, it was shown that expanded RAS analysis could change outcome. While KRAS exon 2 mutation accounts for about 40% of mCRC, expanded analysis could bring this number to approximately to 55%.

Patients with mCRC RAS WT may be treated with a combination of chemotherapy and either Cet or Bev, depending on patient preference, medical indications and concerns for potential side effects. About 10% of patients will live for more than 5 years.

**References:**

6. Venook A. Bevacizumab or Cetuximab with FOLFOX or FOLFIRI Offer Similar, Extended Survival in Metastatic Colorectal Cancer. On-line: http://am.ascopubs.org/ bevacizumab-or-cetuximab-folfox-or-folfiri-offer-similar-extended-survival-metastatic-colorectal