follow-up, another 2 years of follow-up is estimated for accumulation of the required 440 events.

At the interim analysis, adding oxaliplatin to preoperative capecitabine-based CRT and postoperative adjuvant CT did not result in a DFS benefit for patients with locally advanced rectal adenocarcinoma.

Active Maintenance Therapy Prolongs TFS and PFS in CRC

Written by Mary Mosley

One of the current standards of care for the first-line therapy of metastatic colorectal cancer (mCRC) is combination chemotherapy with fluoropyrimidine (FP) and oxaliplatin (OX) plus the angiogenesis inhibitor, bevacizumab (BEV). However, the optimal duration of the initial induction therapy phase (with the combination regime including all compounds) and the optimal maintenance therapy (MT) have not been defined. The Phase 3 AIO KRK 0207 study [NCT00973609] showed that active MT with FP+BEV or BEV alone, compared with no treatment, prolonged the time-to-failure of strategy (TFS) and progression-free survival (PFS) in patients with mCRC after induction treatment, according to Dirk Arnold, MD, Klinik für Tumorbiologie, Freiburg, Germany [Arnold D et al. *Ann Oncol*. 2014 (abstr O-0027); *J Clin Oncol*. 2014 (abstr 3503)].

In the open-label, prospective AIO KRK 0207 study, 473 patients without disease progression after their 24-week standard induction therapy were randomized to any FP (intravenous or oral) plus BEV (n = 159), BEV monotherapy (n = 156), or no treatment (n = 158). The AIO Study Group-sponsored trial was conducted at 106 sites in Germany to determine whether BEV monotherapy or no treatment was noninferior to FP+BEV.

FP+BEV is the widely accepted standard for MT [Chibaudel B et al. *J Clin Oncol.* 2009; Tournigand C et al. *J Clin Oncol.* 2006]. Studies have evaluated whether reducing the intensity of treatment or discontinuing treatment could provide effective MT while improving quality of life for patients through reduced toxicity; however, a clear standard has not been identified [Yalcin S et al. *Oncology.* 2013; Diaz-Rubio E et al. *Oncologist.* 2012].

The primary end point of TFS, comprising MT with planned re-induction therapy, did not differ between the 3 groups. The median TFS was 6.8, 6.5, and 6.1 months in the FP+BEV, BEV monotherapy, and no-treatment groups. The risk of a shorter TFS was slightly higher in the no-treatment group as compared with the FP+BEV group (HR, 1.22; 95% CI, 0.96 to 1.57; log rank p = .11). The TFS risk was similar for the FP + BEV and BEV monotherapy groups (HR, 0.98; 95% CI, 0.76 to 1.26; Log rank p = .85). However, as the TFS definition included the planned re-induction of the initial treatment, the differences in re-induction therapy (21% of the FP+BEV, 43% BEV monotherapy, 45% no-treatment groups) contributed to this result, stated Dr. Arnold. In general, rates of re-induction therapy were surprisingly low, he stated.

The secondary end point of time to first progression (PFS1) of disease from MT initiation was longer with FP+BEV (6.2 months) and BEV monotherapy (4.8 months) as compared with no treatment (3.6 months). Compared with no treatment, the risk of disease progression was lower with FP+Bev (HR, 0.49; 95% CI, 0.38 to 0.63) and with BEV monotherapy (HR, 0.64; 95% CI, 0.50 to 0.82).

There was no significant difference among the 3 treatment groups for the secondary end point of overall survival (OS) from the start of MT (mean, 23.7 months in all patients; log rank p = .70). This OS was surprisingly long after a (not yet added) 6-month induction treatment phase before randomization, based on the current preliminary data with 200 events, stated Dr. Arnold.

The AIO KRK 207 study showed that MT with FP+BEV, BEV monotherapy, or no treatment had a similar effect on the primary end point of TFS in a protocol that included planned re-induction therapy. PFS1 improved with treatment intensity, with FP+BEV yielding better results than BEV alone, and both active MT treatments were better than no treatment. This finding of improved PFS1 confirms the standard of an active MT to exploit the maximum benefit, stated Dr. Arnold.

KRAS Mutations Predictive of Recurrence in Colon Cancer

Written by Emma Hitt Nichols, PhD

Codon 12 *KRAS* mutations are an independent predictor of time to recurrence (TTR) and disease-free survival (DFS) in patients with Stage III colon cancer who received adjuvant treatment. Julien Taieb, Assistance Publique Hôpitaux de Paris, Paris, France, presented data from a post hoc analysis of the Combination Chemotherapy With or Without Cetuximab in Treating Patients With Stage III Colon Cancer That Was Completely Removed by Surgery trial [PETACC8; Taieb J et al. *Ann Oncol* 2014 (abstr O-0024)].

KRAS mutations may be prognostic in colon adenocarcinoma, but the evidence is inconclusive. The purpose of

this post hoc analysis was to determine if *KRAS* mutations are prognostic in patients with Stage III colon adenocarcinoma who received adjuvant leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX4) with or without cetuximab.

The international, open-label, Phase 3 PETACC8 trial randomly assigned patients with resected Stage III colon cancer to receive FOLFOX4 with or without cetuximab for a median follow-up time of 3.3 years [Taieb J et al. *Lancet Oncol* 2014]. A protocol amendment restricted further enrollment to patients with wild-type *KRAS* mutations, and the intention-to-treat population included patients with wild-type *KRAS*. The primary end point of DFS was similar among both arms in the intention-to-treat population and in patients with *KRAS* mutations in exon 2 (including codons 12 and 13). Adverse events such as acne-like rash, diarrhea, mucositis, and infusion reactions occurred more frequently in the cetuximab arm.

In this analysis, 638 out of 1657 tumors harbored *KRAS* mutations [Taieb J et al. *Ann Oncol* 2014 (abstr O-0024)]. TTR was significantly associated with *KRAS* mutations located at codon 12 (HR, 1.67; 95% CI, 1.35 to 2.04; $p < .001$) compared with patients who had tumors with wild-type *KRAS* or BRAF. Similarly, DFS was associated with *KRAS* mutations at codon 12. Mutations at codon 13 were not significantly associated with TTR or DFS. In addition, distal tumors were more likely to relapse in patients with *KRAS* mutations in codon 12 (HR, 1.96; 95% CI, 1.51 to 2.56; $p < .0001$).

In conclusion, Prof. Taieb indicated that, in his opinion, the data from this post hoc analysis of the PETACC8 trial suggest that codon 12 *KRAS* mutations predicted TTR and DFS in patients with Stage III distal colon cancer. He called for future studies to evaluate *KRAS* mutations as well as tumor location.

Impact of First-Line Therapy on Selection of Second-Line Therapy in FIRE-3 Trial

Written by Mary Mosley

The influence of the drug combination used for first-line therapy on the selection and duration of the second-line therapy in patients with metastatic colorectal cancer (mCRC) was the objective of a post hoc analysis in the ongoing 5-FU, Folinic Acid and Irinotecan (FOLFIRI) Plus Cetuximab Versus FOLFIRI Plus Bevacizumab in First Line Treatment Colorectal Cancer trial [FIRE-3]. Dominik Modest, MD, University Hospital, Grosshadern, Munich, Germany, and his team assessed the effect of first-line therapy on overall survival (OS) and the selection of subsequent treatment, and the effect of second-line therapy on OS [Modest D et al. *Ann Oncol*. 2014 (abstr O-0018)].

The multicenter, randomized, FIRE-3 trial is comparing FOLFIRI plus cetuximab (CET; Arm A) and FOLFIRI plus bevacizumab (BEV; Arm B) in 592 patients with *KRAS* exon 12 wild-type mCRC [NCT00433927]. The primary end point of the Phase 3 trial is the objective response rate, whereas secondary end points include progression-free survival (PFS), median OS, safety, and secondary resection rate. Although physicians were free to determine the drugs for the second-line therapy, the study protocol recommended folinic acid (leucovorin calcium), fluorouracil, and oxaliplatin (OX; FOLFOX) plus BEV for Arm A, and irinotecan plus CET for Arm B.

For the *post hoc* analysis, a second-line therapy was defined as any new anticancer drug used after first-line treatment for mCRC and the duration was defined as the time from the first dose to the last dose of the second-line treatment.

After first-line therapy, 260 of 297 patients in Arm A and 250 of 295 were alive. At the time of this analysis, 78.5% of Arm A and 76.4% of Arm B had started second-line therapy.

PFS after first-line therapy was slightly longer in patients whose second-line regimen did not include a monoclonal antibody (mAB) compared with those whose second-line regimen included an antibody against vascular endothelial growth factor (anti-VEGF) or against epidermal growth factor receptor (anti-EGFR). The PFS was 11.3 months in the no-mAB group versus 9.2 months for the anti-VEGF group and 9.7 months for the anti-EGFR ($p = .001$). The OS was 30.8 months, 25.2 months, and 23.7 months, respectively ($p = .02$).

For patients whose second-line regimen included OX, the PFS after first-line therapy was similar to that in patients who did not receive OX (9.9 months for both; $p = .56$). The OS was also similar, at 27.1 months and 29.1 months in the patients who did and did not receive OX in their second-line regimen, respectively ($p = .10$).

The duration of second-line therapy was 17.2 weeks in Arm A and 14.0 weeks in Arm B ($p = .08$). The mean duration of second-line therapy that included an antibody-crossover was 23.9 weeks in Arm A and 16.1 weeks in Arm B ($p = .06$).

This analysis showed that, in patients with a shorter PFS after first-line therapy, the preferred second-line regimen included a mAB. OS was longer in patients whose second-line regimen did not include a mAB as compared with a regimen that did include a mAB. In patients whose first-line regimen included CET, there was a trend towards a longer duration of second-line treatment.