requiring study drug discontinuation, protocol noncompliance, or withdrawal of consent. Overall survival (OS) was the primary end point. Progression-free survival (PFS), objective response rate (ORR), time to progression (TTP), and safety were the secondary end points. A stratified log-rank test was used to compare OS and PFS between treatment groups. The ORR was calculated with a Cochran-Mantel-Haenszel test.

A total of 665 patients were randomized worldwide from December 2010 to September 2012 [Wilke H et al. *Ann Oncol.* 2014 (abstr O-0006); *J Clin Oncol.* 2014 (abstr LBA7)]. Of these, 398 were from region 1: 198 in the RAM + PTX group and 200 receiving PTX alone. The baseline characteristics of the patients were considered well balanced between the 2 treatment groups. The median OS was 8.57 months for patients in the RAM + PTX group and 5.91 months for patients receiving PTX alone (HR, 0.726; 95% CI, 0.580 to 0.909; p = .0050). Median PFS was 4.24 months for RAM + PTX versus 2.83 months for PTX alone (HR, 0.631; 95% CI, 0.506 to 0.786; p < .0001). The median TTP was 5.36 months for the RAM + PTX group, compared with 3.15 months for PTX alone (p = .0002). The ORR was 26.8% for patients receiving RAM + PTX and 13.0% in the PTX arm (p = .0004). The significant benefits observed in the Western population were consistent with those observed in the overall intent-to-treat population.

The adverse event profile of the region 1 subgroup was also considered similar to that of the overall patient population. Adverse events grade 3 or higher that occurred in >5% of patients receiving RAM + PTX were neutropenia (32.1% [RAM + PTX] vs 14.7% [PTX]), hypertension (17.9% vs 2.0%), leukopenia (9.7% vs 4.1%), fatigue (10.2% vs 5.1%), asthenia (7.7% vs 2.0%), anemia (6.6% vs 6.1%), abdominal pain (6.6% vs 4.6%), and general physical health deterioration (5.6% in both treatment arms).

These results demonstrate that in the Western population, just as in the overall study population, the combination of RAM and PTX resulted in better survival parameters at the expense of significantly increased risk for neutropenia.

No Benefit to Adding Oxaliplatin to Capecitabine in Locally Advanced Rectal Adenocarcinoma

Written by Lynne Lederman

Treatment options for locally advanced rectal cancer include chemotherapy, surgery, and radiation therapy. It is not known if adding oxaliplatin to capecitabine would increase the efficacy of chemotherapy for patients with locally advanced rectal cancer. Hans-Joachim Schmoll, MD, PhD, Martin Luther University Halle-Wittenberg, Halle, Germany, reported the disease-free survival (DFS) results from the interim analysis of Chemotherapy and Radiation Therapy Before Surgery Followed by Capecitabine With or Without Oxaliplatin in Treating Patients With Locally Advanced Rectal Cancer [PETACC-6; NCT00766155].

PETACC-6 is a randomized, Phase 3 trial to determine if the addition of oxaliplatin to preoperative oral fluoropyrimidine-based chemoradiation (CRT) followed by postoperative adjuvant fluoropyrimidine-based chemotherapy (CT) improves DFS in patients with locally advanced rectal adenocarcinoma [Schmoll HJ et al. *Ann Oncol* 2014 (abstr O-0017)]. PETACC-6 enrolled 1094 patients with rectal adenocarcinoma within 12 cm from the anal verge that was T3 or T4 and/or node-positive, nonmetastatic, and either resectable at the time of enrollment or expected to become resectable. Patients were randomly assigned 1:1 to receive 5 weeks of preoperative CRT with capecitabine, followed by 6 cycles of adjuvant CT with capecitabine (arm 1) or capecitabine plus oxaliplatin (arm 2) before and after surgery.

DFS was defined as the time from random assignment to the first event of loco-regional failure, distant failure, the appearance of a secondary cancer, or death. Unresectable tumors or distant metastases that were discovered at surgery were deemed failures at the time of surgery. To detect an increase in 3-year DFS with 80% power from 65% with capecitabine alone to 72% with capecitabine plus oxaliplatin (HR, .763) using a 2-sided alpha of 5%, 440 events were required; an interim analysis for early efficacy required 200 events.

Of the 547 patients in each arm, 543 in arm 1 and 528 in arm 2 began preoperative treatment (3 patients in arm 2 did not receive oxaliplatin); of these patients, 420 (77.3%) in arm 1 and 381 (72.6%) in arm 2 began postoperative chemotherapy per protocol. In arm 2, 45 patients (11.8%) did not receive postoperative oxaliplatin. Reasons for treatment discontinuation included progressive disease (3.9% in arm 1 vs 3.8% in arm 2), toxicity (7.7% vs 16.5%), complications of surgery (8.7% vs 9.1%), and patient refusal (5.9% vs 10.8%).

At the planned interim analysis, with a median follow-up of 31 months, there were 124 DFS events in arm 1 and 121 DFS events in arm 2 (adjusted HR, 1.036; 95% CI, 0.806 to 1.331; p = .781). The 3-year DFS in arm 1 was 74.5% (95% CI, 70.1% to 78.3%), which was higher than anticipated. The 3-year DFS in arm 2 was 73.9% (95% CI, 69.5% to 77.8%). The conditional power for the HR of 0.763 was only 7%. With 245 DFS events at 31 months of

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