improves maintenance PFS, PFS from registration, OS from maintenance, and OS from registration compared with the same induction therapy followed by BEV monotherapy. This effect is independent of the KRAS mutational status; a significant difference in response rate is observed during the chemotherapy-free maintenance therapy in KRAS mutated tumors.

The safety of BEV + ERL is acceptable despite increased incidence of severe skin rash and diarrhea. The survival benefit for BEV + ERL is independent of the subsequent therapy. Anti-EGFR mAb remains active in patients who received prior erlotinib. BEV and a short period of ERL therapy may provide a new treatment option in first-line therapy following induction chemotherapy with BEV for patients with unresectable mCRC.

No Benefit to Adding BEV to Adjuvant CAP in CRC

Written by Lynne Lederman

Although bevacizumab (BEV) has a role in the treatment of colorectal cancer (CRC), it has not been shown to increase the efficacy of doublet chemotherapy in the adjuvant setting. The final results from the Multicentre International Study of Capecitabine ± Bevacizumab as Adjuvant Treatment of Colorectal Cancer [QUASAR 2; ISRCTN45133151], a randomized phase 3 trial that tested capecitabine (CAP) with and without BEV in the adjuvant setting of stage II/III CRC, were presented by Rachel Midgley Kerr, PhD, University of Oxford, Oxford, United Kingdom.

Eligibility criteria included stage III and high-risk stage II CRC after complete resection. The primary end point was 3-year disease-free survival (DFS). Secondary end points included DFS in stage III disease, overall survival (OS), toxicity, and translational analyses. Of 1941 patients recruited, 968 were assigned to CAP and 973 were assigned to CAP + BEV. The demographics appeared balanced across treatment arms, although overall there were more patients with stage II disease (40%) and fewer patients with rectal cancers (12%) than expected.

Toxicities that were significantly higher in the CAP + BEV arm included all grades of hypertension, proteinuria, and epistaxis ($P < .001$ for all), all grades of poor wound healing ($P = .05$), and grade 3/4 hand-foot syndrome ($P = .002$). An excess of possibly treatment-related deaths occurred in the CAP + BEV arm (RR, 2.3; 95% CI, 1.0 to 5.2; $P = .05$), although Prof Kerr suggested that this could be related to the definition of "treatment-related" used in the trial.

There was no difference in 3-year DFS between CAP and CAP + BEV (78.4% vs 75.4%; HR, 1.06; $P = .5$). This was not due to a difference in CAP dose intensity, which was the same in both arms. No DFS advantage for either arm was detected in the analysis of subgroups, including age, disease site, stage, country, and sex. There was no difference in 3-year OS for CAP (89.4%) vs CAP + BEV (87.5%; HR, 1.11; $P = .3$).

A high tumor stroma ratio (TSR) in CRC is predictive of poorer prognosis [Huijbers A et al. *Ann Oncol.* 2013]. The mechanism is not known, but it could be related to upregulated proangiogenic pathways; if so, patients with a high TSR might benefit from therapy with BEV. Tumor DNA was extracted from 1028 formalin-fixed, paraffin-embedded tissue blocks and tested for biomarkers, including chromosomal instability positivity, and KRAS, BRAF, and POLE mutations. None of these were prognostic or predictive. TSR by immunohistochemistry was high at 33%, as previously reported.

Microsatellite instability (MSI) positivity was 14% (n = 135). MSI status had no effect on DFS for treatment arms combined. For patients with microsatellite stability (MSS; n = 840), CAP was associated with significantly longer DFS vs CAP + BEV (HR, 1.43; 95% CI, 1.12 to 1.84; $P = .005$). For patients with MSI, there was no difference in DFS between treatment arms.

Patients with low TSR had a significantly longer 3-year DFS (HR, 1.58; 95% CI, 1.22 to 2.05; $P = .001$ for treatment groups combined). However, there were no differences in DFS between treatment arms when analyzed by TSR.

The results of this study indicated that there is no role for BEV in combination with CAP in the adjuvant treatment of CRC in the general patient population or in any identifiable patient subgroup. In fact, the addition of BEV to CAP monotherapy worsens prognosis for patients with MSS. Although the study confirmed that TSR has prognostic value, it is not related to response to BEV.

Neoadjuvant B and N Safe and Effective With D and H in HER2-Positive Breast Cancer

Written by Nicola Parry

Günther Steger, MD, Medical University of Vienna, Vienna, Austria, presented data from a study demonstrating that neoadjuvant docetaxel (D) plus trastuzumab (H), DH plus bevacizumab (B; DHB), DH plus nonpegylated liposomal doxorubicin (N; DHN), and DHNB treatment regimens are feasible and can be safely administered to patients with early HER2-positive breast cancer.