with SD. There were no differences across treatment arms for OS or PFS-1 when stratified for best response at induction.

Patients with wild-type tumors treated with BEV had a PFS-1 of 6.8 versus 3.9 months for no therapy ($P < .001$). For any mutation with a poorer prognosis, there was no significant difference for BEV versus no treatment (4.2 vs 3.6 months, $P = .17$). Subgroup analysis of OS did not identify patient groups with more or less benefit from FPs + BEV. Results of QOL studies indicated that active treatment did not reduce QOL, and a lack of therapy did not cause fear of progression.

This study confirms the use of active maintenance treatment as standard of care for most patients to improve PFS-1. The lack of a clear OS benefit suggests that an individualized approach to active maintenance therapy may be appropriate.

Maintenance Therapy With ERL and BEV Prolongs Survival in Unresectable mCRC

Written by Lynne Lederman

Cross-talk between vascular endothelial growth factor (VEGF) and the epidermal growth factor receptor (EGFR) are involved in tumor growth and survival; inhibition of either may increase survival in patients with metastatic colorectal cancer (mCRC). However, combining monoclonal antibodies (mAb) targeting VEGF or EGFR in mCRC has not been effective [Hecht JR et al. J Clin Oncol. 2009; Tol J et al. *N Engl J Med*. 2009]. Benoit Chibaudel, MD, Saint-Antoine Hospital, Paris, France, reported the final results of the Optimized Chemotherapy Followed by Maintenance With Bevacizumab With or Without Erlotinib in Treating Patients With Metastatic Colorectal Cancer That Cannot Be Removed by Surgery study [DREAM; NCT00265824].

DREAM was a randomized, phase 3 trial in patients with unresectable mCRC testing the combination of bevacizumab (BEV), a mAb that targets VEGF, with erlotinib (ERL), a tyrosine kinase inhibitor targeting EGFR, as maintenance therapy in mCRC.

All patients (n = 694) received 1 of 3 induction regimens, all of which contained BEV, and only those patients whose disease did not progress (n = 452 or 65% of the registered population) were randomly assigned to maintenance therapy with BEV (n = 228) or BEV + ERL (n = 224). The primary end point was progression-free survival (PFS) from randomization. Secondary end points included overall survival (OS), PFS from registration, response according to KRAS status, and adverse events.

Table 1. Results from the DREAM Trial

	BEV	BEV + ERL	HR (95% CI)	*P* Value
Patients, n	228	224		
Median PFS, mo				
From randomization	4.9	5.9	0.77 (0.62 to 0.94)	.012
From registration	9.3	10.2	0.76 (0.63 to 0.93)	.007
Median OS, mo				
From randomization	22.1	24.9	0.79 (0.64 to 0.98)	.035
From registration	26.9	30.5	0.80 (0.64 to 0.99)	.040
ORR for maintenance therapy, %				
All patients	11.5	22.5		.003
Wild-type KRAS	15.4	24.0		.133
Mutant KRAS	8.3	19.7		.041

BEV, bevacizumab; ERL, erlotinib; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Baseline characteristics were similar between treatment arms at registration and at randomization. The induction response rate was 55% complete or partial response for patients randomized to BEV vs 58% for those randomized to BEV + ERL; stable disease was 46% vs 42%, respectively. The treatment delivery was similar for both arms, but the BEV + ERL arm received 12% more BEV cycles and 30% of the ERL doses given were a reduced dose. Results at a median follow-up of 50 months of maintenance therapy are shown in Table 1. BEV + ERL was generally favored for maintenance PFS and OS in a subgroup analysis. Maintenance response rates were significantly higher with BEV + ERL, including among the subgroup of patients with mutant KRAS.

There was increased toxicity of any grade in the BEV + ERL arm for nausea, mucositis, diarrhea, and skin rash. Grade 3/4 toxicities were increased for diarrhea, skin rash, and nausea in the BEV + ERL arm.

The same proportion of patients in both arms received the same postprogression therapy, including oxaliplatin reintroduction, irinotecan-based second-line therapy, or anti-EGFR mAb. Survival in patients who received postprogression therapy, including anti-EGFR mAb, is similar in both arms.

In patients with mCRC, induction therapy followed by maintenance therapy with BEV + ERL significantly

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.