Patients With mCRC Benefit From Active Maintenance Therapy

Written by Lynne Lederman

The optimal duration of treatment with fluoropyrimidines (FPs), oxaliplatin (OX), and bevacizumab (BEV) for patients with metastatic colorectal cancer (mCRC) is not known. Susanna Hegewisch-Becker, MD, Onkologische Schwerpunktpraxis Eppendorf, Hamburg, Germany, presented results from the phase 3 study Optimal Maintenance Therapy With Bevacizumab After Induction in Metastatic Colorectal Cancer (CRC) [AIO KRK 0207; NCT00973609]. This trial investigated maintenance chemotherapy with FPs + BEV, BEV alone, or no treatment following a 24-week first-line induction with FPs, OX, and BEV for patients with mCRC.

Patients with at least stable disease (SD) after induction therapy were randomly assigned to FPs (any standard regimen that includes an FP, eg, FOLFOX4) plus BEV (n = 158), BEV alone (n = 156), or no therapy (n = 158). At first progression, patients received reinduction therapy with any FP with or without either BEV or OX until second progression occurred. The primary end point was the time to failure of strategy (TFS), including maintenance plus reinduction after first progression. Secondary end points included time to first progression (PFS-1), overall survival (OS), quality of life (QOL), and biomarker studies.

All 3 arms appeared well balanced for baseline characteristics. Median TFS from randomization for all patients was 6.4 months. Median PSF-1 for all patients from randomization was 4.6 months. Updated outcome results are summarized in Table 1.

There was no significant difference in TFS between FPs + BEV and BEV (HR, 1.03; 95% CI, 0.81 to 1.31; $P = .82$) or between FPs + BEV and no therapy (HR, 1.27; 95% CI, 1.0 to 1.62; $P = .054$). There was no significant difference in PFS-1 between FPs + BEV and BEV (HR, 1.26; 95% CI, 0.99 to 1.60; $P = .061$); however, there were significant differences in PFS-1 between FPs + BEV and no therapy (HR, 2.05; 95% CI. 1.61 to 2.63; $P < .00001$) and BEV versus no therapy (HR, 1.53; 95% CI, 1.21 to 1.93; $P = .00039$).

There was no significant difference among groups for OS, which may be because not enough events occurred and because of the use of new further-line therapies at progression that became available during the study. Dose reductions or discontinuations of OX during induction did not appear to affect PFS-1 or OS.

The best response at induction had a prognostic effect on OS. Median OS was 24 months for patients with complete response or partial response, whereas OS was 19.8 months for patients

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Table 1. Updated Outcome Results

	FPs/BEV (n = 158)	BEV (n = 156)	No Therapy (n = 158)
Best response at randomization			
CR/PR, %	59	60	59
SD, %	41	40	41
	FPs/BEV (n = 144)	**BEV (n = 153)**	**No Therapy (n = 153)**
TFS from randomization, median, mo	6.8	6.2	6.4
Reinduction after first progression, %	21	43	45
PFS-1 from start of maintenance, median, mo	6.2	4.6	3.6

BEV, bevacizumab; CR, complete response; FP, fluoropyrimidine; PFS-1, progression-free survival at first progression; PR, partial response; SD, stable disease; TFS, time to failure of strategy.

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