Outcomes Similar With BEV or CET Added to Induction CT for mCRC

Written by Mary Mosley

First-line treatment for metastatic colorectal cancer (mCRC) is combination chemotherapy (CT) plus a monoclonal antibody (mAB). The Cetuximab and/or Bevacizumab Combined With Combination Chemotherapy in Treating Patients With Metastatic Colorectal Cancer [CALGB/SWOG 80405; NCT00265850] study examined whether a strategy that blocked endothelial growth factor receptors with the mAB cetuximab (CET) or blocked vascular endothelial growth factors with the mAB bevacizumab (BEV) provided a greater improvement in the effectiveness of CT.

In the CALGB/SWOG 80405 study, patients with *KRAS* wild-type (codons 12 and 13) mCRC and ECOG performance status 0 to 1, at the discretion of the physician and patient at enrollment, received either irinotecan hydrochloride, fluorouracil, and leucovorin calcium (FOLFIRI CT) or modified leucovorin calcium, fluorouracil, and oxaliplatin (mFOLFOX6 CT) [Venook A et al. *Ann Oncol.* 2014 (abstr O-0019)]. The patients were randomized to CET (CT + CET arm; n = 578) or BEV (CT + BEV arm; n = 559).

The study started in November 2005, and 2 changes were made to the study design in June 2009: patients with unselected mCRC (ie, without *KRAS* wild-type tumors) were not eligible, and the third study arm with the combination of CET + BEV was eliminated.

The median follow-up was 24 months. The median age of the patients was 59 years, and 61% were men. Overall survival, the primary end point, was 29.04 months (range, 25.66 to 31.21) with CT + BEV, compared with 29.93 months (range, 27.56 to 31.21) with CT + CET (HR, 0.92; 95% CI, 0.78 to 1.09; p = .34).

Progression-free survival, as assessed by the investigator, was 10.84 months (range, 9.86 to 11.4) and 10.45 months (range, 9.66 to 11.33) in the CT + BEV and CT + CET arms, respectively. No evidence of disease after surgery was identified in 94 patients after a median follow-up of 40 months (range, 8.0 to 86.0). Study outcomes or serious toxicity did not differ in relation to the sex of the patient or the treatment that the patient received.

An analysis of the CT regimens in this study is underway, but it is limited because 73% of patients received mFOLFOX6 and only 27% received FOLFIRI. Other analyses are underway to identify subsets of patients who may have more benefit from a specific regimen compared with another.

In patients with *KRAS* wild-type mCRC, CT + CET or CT + BEV had the same effect on overall survival; thus, either regimen is appropriate for first-line therapy, according to Alan P. Venook, MD, University of California, San Francisco, San Francisco, California. The overall survival of > 29 months achieved in this study was greater than that seen in other studies in this population.

Regorafenib Improves OS in Asian Patients With mCRC After Previous Failure With Standard Therapy

Written by Muriel Cunningham

The oral multikinase inhibitor regorafenib targets multiple pathways involved in tumor development and progression. In the CORRECT study [Grothey A et al. *Lancet.* 2013], treatment with regorafenib improved overall survival (OS) in patients with metastatic colorectal cancer (mCRC) disease progression after standard therapies (HR, 0.77; 95% CI, 0.64 to 0.94; 1-sided p = .0052). The CORRECT study population included 15% Asian patients, primarily from Japan. Jin Li, MD, PhD, Fudan University Cancer Hospital, Shanghai, China, presented the results from the Asian Subjects With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy study [CONCUR; NCT01584830], a trial examining the efficacy and safety of regorafenib in a larger group of Asian patients with mCRC.

Conducted at 25 clinical centers in mainland China, Hong Kong, Taiwan, the Republic of Korea, and Vietnam, the CONCUR study enrolled eligible patients who had stage IV adenocarcinoma of the colon or rectum that had progressed within 3 months after receiving standard therapy and an ECOG Performance Status (PS) ≤ 1. A minimum of 2 prior treatments, including fluoropyrimidine, oxaliplatin, and irinotecan, was a requirement for participation. Previous treatment with anti–vascular endothelial growth factor (VEGF) or anti–epidermal growth factor receptor (EGFR) targeted therapies was permitted.

Patients were randomized in a 2:1 ratio to best supportive care plus regorafenib (160 mg/d) or best supportive care plus placebo for the first 3 weeks of each 4-week cycle [Li J et al. *Ann Oncol.* 2014 (abstr O-0023)]. The randomization was stratified by the number of single versus multiple metastatic sites and time from diagnosis of metastatic disease to randomization (< 18 vs ≥ 18 months). Patients received treatment

until disease progression, unacceptable toxicity, or withdrawal of consent. OS was the primary end point, and progression-free survival (PFS), tumor response, disease control rate (DCR), and safety variables were secondary end points. A stratified log-rank test (1-sided α, 0.2) was used to analyze survival.

A total of 204 patients were randomized in the study between May 2012 and January 2013 to receive regorafenib (n = 136) or placebo (n = 68). The overall median age was 57 years, and the baseline and demographic characteristics were similar between treatment arms. Seventy-five percent of patients had an ECOG PS of 1, and 25% had an ECOG PS of 0. Approximately half of the patients had received ≤ 3 treatment lines for mCRC, and 41% had not received treatment with either an anti-VEGF or anti-EGFR agent.

As of the data analysis cutoff date (November 29, 2013), regorafenib significantly improved OS as compared with placebo (HR, 0.550; 95% CI, 0.395 to 0.765; 1-sided p = .0002). The median OS was 8.8 months for regorafenib-treated patients versus 6.3 months for placebo. The median PFS was 3.2 months for regorafenib and 1.7 months for placebo (HR, 0.311; 95% CI, 0.222 to 0.435; 1-sided p < .0001). The DCR was also greater in regorafenib-treated patients (52% vs 7% for placebo).

Adverse events in the study were consistent with the regorafenib safety profile in Asian patients. In regorafenib-treated patients, the most frequently reported treatment-emergent grade ≥ 3 adverse events were hand-foot skin reaction (16%), hypertension (12%), hyperbilirubinemia (12%), elevated liver enzymes (aspartate aminotransferase 10%, alanine aminotransferase 8%), hypophosphatemia (9%), anemia (7%), and hyperlipasemia (7%). No events of liver failure or pancreatitis were reported.

The editors would like to thank the many members of the 16th World Congress on Gastrointestinal Cancer and the European Society for Medical Oncology presenting faculty who generously gave their time to ensure the accuracy and quality of the articles in this publication.