

Colorectal Cancer Highlights from the 2009 Joint ECCO/ESMO Multidisciplinary Congress

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O-6010 A three-arm phase III randomized trial of FOLFOX-4 vs. FOLFOX-4 plus bevacizumab vs. XELOX plus bevacizumab in the adjuvant treatment of patients with stage III or high-risk stage II colon cancer: results of the interim safety analysis of the AVANT trial

P Hoff, S Clarke, D Cunningham, E Van Cutsem, M Moore, HJ Schmoll, J Tabernero, B Mueller, A De Gramont

The AVANT trial is a phase III study evaluating the efficacy and safety of bevacizumab in combination with intermittent capecitabine and oxaliplatin (XELOX) or fluorouracil, leucovorin, and oxaliplatin (FOLFOX-4) versus FOLFOX-4 alone in the adjuvant treatment of patients with stage III or high-risk stage II colon cancer. The study randomized 3,451 patients (2,867 stage III, 573 high-risk stage II) to receive 12 cycles of FOLFOX-4 every 2 weeks (arm A), 12 cycles of FOLFOX-4 plus bevacizumab every 2 weeks (arm B), or 8 cycles of XELOX plus bevacizumab every 3 weeks (arm C), followed by an additional 8 cycles of bevacizumab every 3 weeks in arms B and C (1 year of bevacizumab therapy). The main objective was to demonstrate the superiority of arm B or C over arm A, with a primary endpoint of disease-free survival (DFS). The treatment arms were similar in regard to disease stage, age, Eastern Cooperative Oncology Group (ECOG) status, and ethnicity. The median duration of oxaliplatin-based chemotherapy was 5.3 months for arm A, 5.2 months for arm B, and 4.9 months for arm C, and bevacizumab treatment duration was 10.6 months (arm B) and 10.4 months (arm C). The main adverse events (grade 3–5) related to bevacizumab were venous thrombotic events, hypertension, and arterial thrombotic events. Within 60 days of commencing treatment, 2 patients died in arm A, 4 in arm B, and 6 in arm C. In the 3 arms, 8, 4, and 10 patients, respectively, died of reasons unrelated to colon cancer 28 days after the last drug administration. The investigators concluded that bevacizumab plus the XELOX/FOLFOX combination is safe in the adjuvant treatment of colon cancer.

P-6029 Randomized phase III trial comparing preoperative versus postoperative radiotherapy with capecitabine in locally advanced rectal cancer

J Park, S Yoon, E Choi, Y Kim, J Kim, C Yu, T Kim, H Chang, S Jang, J Kim

This phase III, prospective, single-institution trial compared pre-operative versus postoperative chemoradiotherapy using oral capecitabine. Patients enrolled in the study had locally advanced rectal cancer (cT3 or N+). They were randomized to receive either pre-operative (arm 1) or postoperative (arm 2) chemoradiotherapy, which was administered to the pelvis at a dose of 46 Gy in 23 fractions, followed by a boost of 4 Gy in 2 fractions (preoperative) and at a dose of 50 Gy in 25 fractions without boost (postoperative). Capecitabine was administered concurrently with radiotherapy at a dose of 1,650 mg/m² per day. A total of 117 and 123 patients were randomly assigned to arm 1 and arm 2, respectively. The 2 arms were well balanced in regard to clinical characteristics, with the exception of more low-lying tumors in arm 1 (60% vs 42%). In the patients who had low-lying tumors, a higher rate of sphincter sparing surgery was observed in arm 1 compared to arm 2 (68% vs 42%; $P=.008$). The 5-year cumulative incidence of local recurrence at a median follow-up of 47 months was somewhat higher in arm 2 compared to arm 1 (6% vs 3%; $P=.335$). The 5-year overall survival (OS) and DFS rates were similar in the 2 arms. Of all patients, 99 (92.5%) in arm 1 and 84 (74.3%) in arm 2 completed chemoradiotherapy as planned. The safety analysis found a similar incidence of grade 3 or higher toxicities in both arms (15% in arm 1 and 16% in arm 2), along with similar postoperative complications. The researchers concluded that there was no significant benefit seen with pre-operative chemoradiation, and that both pre- and postoperative chemoradiotherapy with capecitabine were safe and well tolerated.

P-6083 Final results from PRECEPT: efficacy and safety of second-line treatment with panitumumab and FOLFIRI in patients with metastatic colorectal cancer (mCRC)

A Cohn, DA Smith, MA Neubauer, D Richards, DL Watkins, K Zhang, M Yassine

This phase III, open-label, single-arm study enrolled patients with unresectable, measurable mCRC (ECOG status 0/1) who failed first-line treatment with oxaliplatin-based chemotherapy plus bevacizumab. Patients were given 6 mg/kg of panitumumab plus FOLFIRI every 2 weeks until disease progression or intolerability. Tumors were evaluated at weeks 8, 16, 24, 32, and every 12 weeks thereafter. Study endpoints for efficacy analyses, which were evaluated by KRAS status, were objective response, progression-free survival (PFS), and OS; incidence of adverse events was the endpoint for safety. The study enrolled 109 patients who received 1 or more doses of panitumumab. Of all patients, 59% had wild-type KRAS tumors and 41% had mutated KRAS tumors. Study findings showed an ORR of 23% in wild-type KRAS patients (3% complete response [CR], 20% partial response [PR], and 41% stable disease [SD]) compared to 16% in mutated KRAS patients (2% CR, 14% PR, 42% SD). Median PFS in wild-type KRAS patients was 26 weeks versus 19 weeks in mutated KRAS patients, and median OS was 50 and 31 weeks, respectively. Adverse events related to panitumumab therapy were observed in 93% of patients, with the 3 most common toxicities being diarrhea, nausea, and fatigue. The most frequently observed serious adverse events were dehydration, pyrexia, and deep vein thrombosis. It was concluded that panitumumab had a toxicity profile that was similar to that reported in similar trials in the same patient population.

10-LBA Randomized phase 3 study of panitumumab with FOLFOX4 compared to FOLFOX4 alone as 1st-line treatment (tx) for metastatic colorectal cancer (mCRC): the PRIME trial

J Douillard, S Siena, J Cassidy, J Tabernero, R Burkes, ME Barugel, Y Humblet, D Cunningham, M Wolf, JL Gansert

This randomized, multicenter, phase III study analyzed the safety and efficacy of first-line treatment with panitumumab plus FOLFOX versus FOLFOX alone in mCRC according to KRAS status. Patients were randomized 1:1 to receive 6 mg/kg of panitumumab plus FOLFOX every 2 weeks (arm 1) versus FOLFOX alone (arm 2). Enrolled patients had metastatic adenocarcinoma of the colon or rectum, no prior chemotherapy and oxaliplatin therapy for mCRC, ECOG of 0–2, and available tumor tissue. Randomization was arranged by

ECOG 0–1 versus 2 and region. The primary endpoint was PFS. The study randomized a total of 1,183 patients, with 593 in arm 1 and 590 in arm 2. The median age was 62 years (range, 24–85), the majority of patients were male (63%), and 95% of patients were ECOG 0–1. KRAS results were obtained for 93% of patients: 60% were KRAS wild-type and 40% were mutant. Wild-type KRAS patients had a median PFS and response rate of 9.6 months and 55% in arm 1, and 8 months and 48% in arm 2. Patients with mutated KRAS had a median PFS of 7.3 months in arm 1 and 8.8 months in arm 2. Adverse events were similar across arms except for those that were associated with anti-EGFR therapy. Study results confirmed the importance of KRAS as a predictive biomarker in the setting of first-line mCRC treatment with EGFR inhibitors.

14-LBA Randomized phase 3 study of panitumumab with FOLFIRI vs FOLFIRI alone as second-line treatment (tx) in patients (pts) with metastatic colorectal cancer (mCRC)

M Peeters, T Price, Y Hotko, A Cervantes, M Ducreux, T Andre, E Chan, F Lordick, A Rong, J Gansert

This randomized, multicenter, phase III study evaluated the efficacy and safety of panitumumab, a fully human anti-epidermal growth factor receptor monoclonal antibody, with fluorouracil, leucovorin, and irinotecan (FOLFIRI) versus FOLFIRI alone as second-line treatment for mCRC. Patients enrolled in the study were randomized to receive panitumumab 6 mg/kg every 2 weeks plus FOLFIRI (arm 1) versus FOLFIRI alone (arm 2). Patients had metastatic adenocarcinoma of the colon or rectum; documented disease progression 6 months or less after 1 prior therapy with fluoropyrimidine for mCRC, and ECOG score of 0–2. Patients were stratified by ECOG 0–1 versus 2, prior oxaliplatin and prior bevacizumab exposure. The evaluation of PFS and OS by KRAS mutational status were the primary endpoints in the study. A total of 1,186 patients were randomized (panitumumab + FOLFIRI, 591; FOLFIRI alone, 595) from May 2006 to March 2008. Of the study population, 61% were men, and the median age was 61 years (range, 28–86 years); 48% of patients were ECOG 0, and 45% were ECOG 1. Of all patients, 1,803 (91%) were evaluable for KRAS, with 598 (55%) being wild-type and 485 (45%) mutated. PFS was longer in wild-type KRAS patients who were in arm 1 versus arm 2 (5.9 vs 3.9 months), but was similar in KRAS mutated patients (5.0 vs 4.9 months). A similar trend was seen with OS in wild-type and mutated patients when arm 1 was compared to arm 2 (wild-type, 14.5 vs 12.5 months; mutated, 11.8 vs 11.1 months). In regard to safety, panitumumab was well-tolerated with a manageable toxicity profile.