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2 KRAS status and efficacy in the first-line treatment of patients with metastatic colorectal cancer treated with FOLFIRI with or without cetuximab: the CRYSTAL experience

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Results of the randomized, phase III CRYSTAL study, evaluating first-line treatment of patients with metastatic colorectal cancer, demonstrated a significant improvement in progression-free survival (PFS), overall survival (OS), and curative surgery rate when cetuximab (Erbix, Bristol-Myers Squibb) was added to FOLFIRI (leucovorin, 5-fluorouracil [5-FU], and irinotecan). The CRYSTAL study also found that K-Ras mutation was related to outcome in patients treated with single-agent cetuximab or with a combination of cetuximab and irinotecan. The current study was performed to analyze the influence of K-Ras mutation status on first-line therapy with FOLFIRI with or without cetuximab. The study enrolled 1,198 patients; however, blocks from archived tumor material were available only for 587 patients. Assessment was done by quantitative polymerase chain reaction (qPCR)-based K-Ras mutation analysis of codons 12/13. The evaluable patients (n=540) were analyzed for treatment effect, grouped by K-Ras mutation status (wild-type or mutation) and randomization strata utilizing Cox regression for PFS and Cochran-Mantel-Haenszel test for overall response (OR). The study results found that the K-Ras–available population represented the intent-to-treat (ITT) population. The analysis showed K-Ras mutation in 192 of 540 patients (35.6%). In patients with wild-type K-Ras, a statistically significant difference in PFS and OR rate was seen in patients treated with cetuximab as opposed to without (PFS: $P=.0167$; hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.051–.934; OR rate: 59.3% with cetuximab vs 43.2% without; $P=.0025$). When subgroups by K-Ras mutation status were analyzed, there were no significant differences seen between treatment groups for PFS ($P=.75$; HR, 1.07; 95% CI, 0.71–1.61) or for OR ($P=.46$). Study findings suggested that the treatment effect of cetuximab in patients with wild-type

K-Ras mutation is significantly enhanced compared to chemotherapy alone; however, patients with K-Ras mutation did not benefit from cetuximab treatment.

4000 KRAS status and efficacy of first-line treatment of patients with metastatic colorectal cancer with FOLFOX with or without cetuximab: the OPUS experience

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A previous randomized phase II trial (OPUS) failed to demonstrate significant improvements in PFS and OR in metastatic colorectal cancer patients treated with cetuximab plus FOLFOX (leucovorin, 5-FU, and oxaliplatin [Eloxatin, Sanofi-Aventis]). A considerably better response rate was seen in patients with good performance status (Eastern Cooperative Oncology Group [ECOG] 0/1), along with a higher curative surgery rate, however, when cetuximab was added to FOLFOX versus FOLFOX alone in the first-line setting. The current study was performed to analyze the influence of K-Ras mutation status in first-line therapy with FOLFOX with or without cetuximab. Assessment was done by qPCR-based K-Ras mutation analysis of codons 12/13. Study results found K-Ras mutations in 99 of 233 patients (42%) for whom tissue was available. In patients with wild-type K-Ras, PFS was similar among those patients who received cetuximab compared to those who received only FOLFOX ($P=.02$; HR, 0.57; 7.7 vs 7.2 months, respectively). OR was significantly higher in the group receiving cetuximab compared to the groups without cetuximab ($P=.01$; 61% vs 37%). However, the opposite was seen in patients with K-Ras mutations; PFS was 5.5 months in patients who received cetuximab and 8.6 months in patients who did not receive cetuximab. The overall response in patients receiving cetuximab was 33% ($P=.02$) compared to 49% ($P=.11$) for patients receiving FOLFOX alone. The data demonstrated that the benefit in adding cetuximab to standard chemotherapy was higher in patients with wild-type K-Ras; however, patients with K-Ras mutation did not benefit from cetuximab treatment.

4001 Relationship of efficacy with KRAS status (wild-type versus mutant) in patients with irinotecan-refractory metastatic colorectal cancer treated with irinotecan (q2w) and escalating doses of cetuximab: the EVEREST experience (preliminary data)

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Previous results from the EVEREST trial found that efficacy may be improved in metastatic colorectal patients who fail irinotecan therapy if the dose of cetuximab is increased in combination with standard-regimen irinotecan (180 mg/m²) for patients with grade 0/1 skin reactions. However, it is still uncertain whether dose escalation is able to elicit a response in patients with mutated K-Ras. In the current study, patients with grade 0/1 skin reactions after 22 days of therapy with irinotecan and standard-dose cetuximab were randomly assigned to receive either a standard dose (n=45; 250 mg/m²) or escalated dose (n=44; up to 500 mg/m²) of cetuximab. In 77 of 89 patients, archived tumor tissue was analyzed for K-Ras mutation. In the group receiving standard-dose cetuximab, 19 patients had wild-type K-Ras, 19 had mutated K-Ras, and 7 were not evaluable. In the group receiving the escalated dose of cetuximab, 28 patients had wild-type K-Ras, 11 had mutated K-Ras, and 5 were not evaluable. Analysis of the two groups demonstrated that the response rate was more than doubled in patients with wild-type K-Ras receiving escalated-dose cetuximab (46.4%) compared to standard-dose cetuximab (21.1%). In patients with K-Ras mutation, none experienced a response in either group. Study findings concluded that patients with wild-type K-Ras experienced clinical benefit from irinotecan plus cetuximab, particularly patients in the dose-escalated group. Conversely, patients with K-Ras mutation did not benefit from irinotecan in combination with cetuximab, and dose escalation did not improve response in these patients.

4026 Safety and effectiveness of bevacizumab and chemotherapy in elderly patients with metastatic colorectal cancer: results from the BRiTE observational cohort study

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Bevacizumab (Avastin, Genentech), when added to chemotherapy for first- and second-line treatment of patients with metastatic colorectal cancer, is known to extend OS and PFS. Safety and efficacy analyses from the BRiTE study demonstrated comparable PFS, 1-year survival,

and safety in patients younger than 65 years of age and patients 65 years or older. The current study evaluated clinical outcomes in elderly subgroups: 65–74 years, 75 years or older, and 80 years or older; this patient population represented one that is rarely observed in randomized controlled trials. Cox regression was utilized to assess the independent effect of age on survival after adjusting for other known prognostic factors. Of the 1,953 patients enrolled in the study, 533 were between the ages of 65 and 74 years, 363 were 75 years or older, and 161 were 80 years or older. Univariate analyses demonstrated a worse median OS for elderly subgroups. The HR was 1.1 (95% CI, 0.9–1.3; *P*=.2) for patients 75 years or older versus patients younger than 65 years. Study results showed that bevacizumab-targeted safety was similar in patients less than 65 years of age and in elderly patients. PFS in the three age groups was comparable to PFS seen in patients 65 years or younger (<65 years, 10.2; 65–74 years, 9.7; ≥75 years, 9.8; ≥80 years, 9.2). One-year survival was higher in patients less than 65 years of age (77.3%) compared to patients 65–74 years (72.5%), patients 75 years or older (70.0%), and patients 80 years or older (66.5%). Furthermore, median OS was considerably higher in patients 65 years or younger compared to elderly patients (<65 years, 28.0; 65–74 years, 21.3; ≥75 years, 19.5; ≥80 years, 17.3). Multivariate analyses suggested that the lower OS seen in older patients was partly due to weak performance status and underexposure to active chemotherapy and post-progressive disease therapy. The study findings concluded that age alone should not limit the use of bevacizumab-containing therapy in patients with metastatic colorectal cancer.

4031 FOLFOXIRI in combination with bevacizumab in the first-line treatment of metastatic colorectal cancer: a phase II study by the GONO

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An earlier phase III study has found that the FOLFOXIRI (irinotecan, oxaliplatin, infusional 5-FU, and leucovorin) regimen significantly improved response rate, PFS, OS, and postchemotherapy surgical resection of metastases compared to FOLFIRI (5-FU, leucovorin, irinotecan). The current phase II study was performed to evaluate the combination of bevacizumab (5 mg/kg) with the FOLFOXIRI regimen (165 mg/m² of irinotecan, 85 mg/m² of oxaliplatin, and 200 mg/m² of leucovorin on day 1, and 48-hour continuous infusion of 3,200 mg/m² of 5-FU on day 1) administered every 2 weeks as first-line treatment of patients with unresectable metastatic colorectal cancer. Currently, 40 patients are enrolled in the study,

with a median age of 61 years (range, 41–75). So far, 38 patients have been evaluated for safety; 34% of patients experienced neutropenia, 8% diarrhea, 5% nausea, 3% stomatitis, 3% neurotoxicity, 5% deep vein thrombosis, and 8% hypertension. Twelve patients (32%) developed gastrointestinal bleeding; no deaths have occurred thus far. Of the 40 patients, 29 have been evaluated for response, with 2 patients with CR, 20 patients with PR, and 7 patients with stable disease (OR rate, 76%). To date, 5 patients received secondary surgery for liver metastases; 4 R0 resections have also been performed. Current analyses found that median PFS and OS have not been reached after a median follow-up of 6.5 months. Study results show that the addition of bevacizumab to the FOLFOXIRI regimen has manageable and expected toxicity, and although the OS and PFS have not yet been reached, the preliminary data are encouraging.

4033 Randomized trial comparing cetuximab plus XELIRI versus cetuximab plus XELOX as first line treatment of patients with metastatic colorectal cancer: a study of the German AIO CRC study group

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It has been documented that cetuximab combined with 5-FU, irinotecan, or oxaliplatin is beneficial in the treatment of patients with metastatic colorectal cancer. A German randomized study compared the efficacy of XELIRI (capecitabine [Xeloda, Roche] and irinotecan) plus cetuximab (XELIRI-C) to XELOX (capecitabine and oxaliplatin) plus cetuximab (XELOX-C) in the first-line setting. Patients with measurable lesions, untreated metastatic colorectal cancer, and Karnofsky performance status (KPS) of 70% or higher were randomly assigned to receive either capecitabine ($2 \times 800 \text{ mg/m}^2$ on days 1–14) plus irinotecan (200 mg/m^2 on day 1) or capecitabine ($2 \times 1,000 \text{ mg/m}^2$ on days 1–14) plus oxaliplatin (130 mg/m^2 on day 1) every 3 weeks. The primary objective of the study was OR rate analyzed by response evaluation criteria in solid tumors. Patients in the XELIRI-C ($n=93$) and XELOX-C ($n=92$) groups were well matched in regard to age, KPS, and liver metastases. The patients received a median of six treatment cycles. Analyses of the 142 evaluable patients receiving either XELIRI-C ($n=74$) or XELOX-C ($n=68$) demonstrated a higher OR rate in the XELOX-C arm (52.7% vs 61.8%). Disease control rate (CR+PR+ stable disease) was also considerably higher in the XELOX-C

arm (83.4% vs 97.1%). The median length of remission in the XELIRI-C and XELOX-C groups was 7.7 and 8.2 months and PFS was 8.4 months (95% CI, 6.9–10.7) and 9.2 months (95% CI, 8.1–11.2), respectively. When safety was analyzed in patients in the XELIRI-C and XELOX-C groups, the most frequently reported grade 3/4 adverse events based on chemotherapy toxicity criteria were diarrhea, nausea, skin rash, hand-foot syndrome, and sensory neuropathy. The incidence of these toxicities was similar in both treatment arms. The study findings suggest that cetuximab combined with XELIRI or XELOX is efficacious and tolerable as first-line therapy in patients with metastatic colorectal cancer.

4057 Oxaliplatin in combination with 5-fluorouracil in a 48-hour continuous infusion as first-line chemotherapy for elderly patients with metastatic colorectal cancer: TTD phase II trial

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An earlier study reported a 35% OR rate in elderly patients with metastatic colorectal cancer treated with first-line 5-FU plus irinotecan. The present study was performed in elderly patients to evaluate the efficacy and safety of oxaliplatin in combination with 5-FU. Enrolled in the study were patients older than 72 years of age with histologically confirmed metastatic colorectal cancer, measurable disease, ECOG performance status not more than 0–2, no prior adjuvant oxaliplatin, and no previous treatment for metastatic disease. Patients ($n=129$) received oxaliplatin (85 mg/m^2) plus 5-FU ($3,000 \text{ mg/m}^2$) as a 48-hour continuous infusion every 2 weeks until disease progression, undesirable toxicity, or withdrawal of consent. The analysis of the ITT population found that OR rate was 52% and disease control rate was 80%. PFS and OS at a median follow-up of 14 months were 9 and 16.2 months, respectively. Forty-eight of 129 patients (37%) were administered two or more lines of chemotherapy, whereas 7 patients (5.4%) underwent resection of liver metastasis. An evaluation of safety found that the most commonly reported grade 3/4 toxicities were neurotoxicity (grade 3; 18%), neutropenia (17%), diarrhea (11%), asthenia (9%), nausea/vomiting (4%), febrile neutropenia (2%), and anemia (2%). There was 1 treatment-related death from pneumonia. Study findings concluded that the dosing schedule seemed to be effective in the elderly population and was comparable to other regimens reported in the literature.