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Overall survival of patients with KRAS wild-type tumours treated with FOLFOX4 ± cetuximab as 1st-line treatment for metastatic colorectal cancer: The OPUS study

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Background: The addition of cetuximab to FOLFOX4 has previously been reported to increase the overall response rate (ORR) of patients (pts) with metastatic colorectal cancer (mCRC), compared with FOLFOX4 alone, in the randomized phase II OPUS study. In this study, KRAS mutation status was also shown to be predictive for progression-free survival and ORR in pts treated with cetuximab in combination with FOLFOX4. Here we report median overall survival (OS) data from the OPUS study for pts with KRAS wild-type (wt) tumors.
Materials and Methods: Pts with previously untreated EGFR-expressing mCRC, which was not resectable with curative intent, were enrolled in the OPUS study and stratified by Eastern Cooperative Oncology Group performance status (0/1 vs 2). Pts were randomized 1:1 to either cetuximab 400 mg/m^2 initial dose then 250 mg/m^2/week plus FOLFOX4 every 2 weeks, or to FOLFOX4 alone. The primary objective of the randomized phase II OPUS study was to assess best confirmed ORR among pts receiving cetuximab + FOLFOX4, compared with those receiving FOLFOX4 alone. Tumor samples from 238/337 (70.6%) pts were available for survival analysis. KRAS mutation status at codons 12/13 was determined by a quantitative PCR-based assay using isolated genomic DNA. OS was analyzed for pts with KRAS wt tumors treated with FOLFOX4, with or without cetuximab.
Results: Among pts with KRAS wt tumors (136/238; 57.1%), the median OS was 22.8 months (95% confidence interval [CI] 19.3−26.0) in the cetuximab + FOLFOX4 arm, compared with 19.5 months (95% CI 15.5−23.8) in the FOLFOX4-alone arm (hazard ratio 0.89; 95% CI 0.60−1.34; p = 0.58). Further OS results will be presented at the meeting.
Conclusions: The addition of cetuximab to FOLFOX4 in the 1st-line treatment of mCRC resulted in an improvement in median OS of approximately 3 months in pts with KRAS wt tumors; however, this difference was not significant, possibly due to the small number of pts available for this analysis.

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Reintroduction of FOLFOXIRI treatment in metastatic colorectal cancer patients progressed after first-line FOLFOXIRI

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Background: The triple drug combination of irinotecan, oxaliplatin and 5-fluorouracil (FOLFOXIRI) developed by the GONO has demonstrated higher activity and efficacy compared to the doublet FOLFIRI in a phase III trial on 244 metastatic colorectal cancer (mCRC) patients. Several studies demonstrated a positive impact of second-line chemotherapy in mCRC, but the use of all the three active cytotoxics upfront might compromise the activity of second-line chemotherapy. However, recent studies suggested that the reintroduction after progression of disease of drugs received upfront may be associated with response and improved survival. The objective of this retrospective analysis was to evaluate the outcome of mCRC patients treated with first-line FOLFOXIRI who received, at the time of disease progression, retreatment with FOLFOXIRI.
Material and Methods: Overall, a total of 196 initially unresectable mCRC patients were treated with first-line FOLFOXIRI administered for a maximum of 12 cycles in two consecutive phase II and in one phase III studies. Among the 185 patients so far progressed, 137 patients (74%) received a second-line treatment and were evaluable for response; 32 of these patients (23%) received a second-line chemotherapy with FOLFOXIRI.
Results: The main characteristics of these patients were: M/F 26/6 patients, median age 62 years (range 38−74), ECOG performance status 0/1 in 21/11 patients, primary tumor site colon/rectum 20/12. Twenty-nine patients had obtained a partial response and three a stable disease with first-line FOLFOXIRI that was administered for a median of 9 cycles (range 3−12). Median time from the end of first-line FOLFOXIRI to the beginning of second-line was 6.2 months (range 3.3−25.3).
Retreatment with FOLFOXIRI at the time of progression obtained 1 (3.1%) complete and 11 (34.4%) partial responses for an overall response rate of 37.5%; sixteen (50%) patients presented stable disease while 4 (12.5%) progressed. The median progression-free and overall survival from the reintroduction of FOLFOXIRI were 8.2 and 19.3 months, respectively. The median time from the beginning of first-line to definitive failure of FOLFOXIRI treatment was 20.1 months.
Conclusions: Retreatment with FOLFOXIRI in a kind of stop-and-go fashion is an active treatment for selected patients having received the same drugs in first-line and may represent an option for second-line treatment of selected mCRC patients.

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Bevacizumab (BV) in combination with FOLFOXIRI (irinotecan, oxaliplatin and infusional 5FU/LV) in metastatic colorectal cancer (MCRC): updated results of a phase II G.O.N.O. trial

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Background: The combination of BV with fluoropyrimidines and oxaliplatin/irinotecan based doublets is a safe and effective treatment of MCRC. The FOLFOXIRI regimen developed by the GONO group significantly improved response-rate (RR), progression-free survival (PFS), overall survival (OS) and post-CT surgical resection of metastases compared to FOLFIRI in a phase III study.
Methods: This phase II trial evaluates the combination of bevacizumab 5 mg/kg on d1 with the GONO-FOLFOXIRI regimen (irinotecan 165 mg/sqm d1, oxaliplatin 85 mg/sqm d1, l-LV 200 mg/sqm d1 and 5FU 3200 mg/sqm 48-h flat continuous infusion starting on d1) repeated every 2 weeks, as first-line treatment of initially unresectable mCRC patients (pts). After a maximum of 12 cycles of induction treatment a maintenance treatment with bevacizumab +/− 5FU/LV was planned.
Results: A total of 57 pts have been enrolled. Main pts characteristic are: M/F = 60%/40%, median age (range) = 61 (34−75) years, ECOG-PS 0/1/2 = 68%/26%/5%, primary colon/rectum = 72%/28%, primary on site = 23%, sites of disease single/multiple = 58%/42%, liver only mts = 53%. All the 57 pts have been assessed for toxicity. The maximum grade (G) 3−4 observed toxicities per pt during the induction treatment were: neutropenia 50% (febrile neutropenia 2%), diarrhea 14%, nausea 4%, stomatitis 4%, neurotoxicity 2%, deep venous thrombosis 5% and hypertension 11%; G1−2 bleeding occurred in 32% of pts. No toxic deaths have occurred. All pts have been evaluated for response (RECIST) and we observed 7 CR, 37 PR (ORR = 77%) and 13 SD (disease control rate = 100%). So far, 18 pts underwent to secondary surgery on mts and 15 R0 resections (26%) have been performed. In particular among the 30 pts with liver-only mts an R0 surgery was achieved in 13 (43%). After a median follow up of 18.4 months, 39 pts (68%) have progressed with a median PFS of 13.4 months and a 10-months PFS of 72%. Median OS have not yet been reached.
Conclusion: BV can be safely combined with the GONO-FOLFOXIRI regimen with manageable toxicities. Results in term of RR (77%), secondary R0 resection of mts (26%) and PFS (13.4 months) are very promising. On behalf of the GONO group we are conducting a phase III trial comparing this regimen with FOLFIRI+ BV. Partially supported by ARCO Foundation.

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Second-line treatments in patients with metastatic colorectal cancer progressed after first-line FOLFOXIRI

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Background: The GONO-FOLFOXIRI regimen demonstrated significant improvements in response rate (RR), secondary radical resection of metastases, progression-free survival (PFS) and overall survival (OS) compared to FOLFIRI in a phase III study conducted on metastatic

colorectal cancer (mCRC) patients. However, with the use of all the three active cytotoxics upfront, some concerns may arise about the activity of second-line treatments for these patients. In this retrospective analysis, we evaluated the outcome of second-line treatments in patients treated with first-line FOLFOXIRI enrolled in two consecutive phase II and in one phase III studies.

Material and Methods: Overall, a total of 196 initially unresectable mCRC patients were treated with first-line FOLFOXIRI administered for a maximum of 12 cycles. Among the 185 patients so far progressed, 136 (74%) received a second-line treatment and were evaluable for response. Thirty-nine patients (26%) did not receive second line treatments mainly because of deterioration of performance status (PS) or liver function, refusal or death.

Results: Patients' characteristics at the time of second-line treatment included: M/F = 88/48 patients, median age 63 yrs (range 27–76), ECOG PS $\geqslant$ 1 = 52 patients (38%).

Three (2.2%) complete and 28 (20.6%) partial responses were observed for an overall RR of 22.8%; 35.3% of patients obtained a stable disease while 41.9% progressed.

The table reports the regimens used in second-line and the RR obtained.

	Number of patients	RR (%)
Overall	136	22.8
FOLFOXIRI	32	37.5
FOLFIRI	35	31.4
FOLFOX	14	28.6
Mitomycin plus 5-Fluorouracil/Capecitabine	19	5.3
Infusional 5-Fluorouracil/Capecitabine	14	14.3
Cetuximab-containing regimens	7	0
Bevacizumab-containing regimens	3	0
Other regimens (Irinotecan alone, Irinotecan-Oxaliplatin, Irinotecan-Gemcitabine, Raltitrexed, Oxaliplatin plus Raltitrexed or Mytomicin)	12	8.3

After a median follow up of 48 months from the start of salvage treatment, the median PFS and OS were 5.93 and 13.2 months, respectively.

At an explorative analysis, patients treated with second-line FOLFOXIRI, FOLFIRI or FOLFOX had a higher RR (33.3% vs 7.3%, p = 0.0003), PFS (6.9 vs 3.5 months, p = 0.001) and OS (15.2 vs 9.2 months, p = 0.004) compared to patients treated with other regimens.

Conclusions: First-line FOLFOXIRI does not impair the possibility to obtain objective responses and to delay tumour progression with second-line treatments containing the same agents used upfront.

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

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Background: Panitumumab (pmab) is a fully human antibody against the epidermal growth factor receptor (EGFR), a therapeutic target in patients (pts) with mCRC. Response to anti-EGFR therapies can be predicted by mutation status of *KRAS* in tumors. This prospective analysis evaluated the effect of tumor *KRAS* status on efficacy of second-line pmab+FOLFIRI.

Methods: Pts with unresectable, measurable mCRC (ECOG status 0/1) were enrolled in this phase 2, open-label, single-arm study after failure of first-line treatment with oxaliplatin-based chemotherapy+bevacizumab (ClinicalTrials.gov ID: NCT00411450; sponsor: Amgen). Pts received pmab 6 mg/kg + FOLFIRI Q2W until disease progression or intolerability. Tumor assessments were performed at weeks 8, 16, 24, 32, and Q12W thereafter. *KRAS* status was determined by real-time PCR on DNA extracted from fixed tumor sections. Efficacy endpoints included objective response (per investigator), progression-free survival (PFS), and overall survival (OS). Safety endpoints included incidence of adverse events (AEs). Endpoints were evaluated by tumor *KRAS* status.

Results: 109 pts enrolled in the study and received $\geqslant$1 dose of pmab; 59% had tumors with wild-type (WT) *KRAS*, 41% had tumors with mutated (MT) *KRAS*. Efficacy outcomes (excluding 2 pts missing information at baseline) are shown (Table). Hazard ratios (95% CL) by *KRAS* status were 0.8 (0.5, 1.1) for PFS and 0.6 (0.4, 0.9) for OS. Pmab-related AEs were reported in 93% of pts; 94 pts (82%) had grade $\geqslant$3 AEs (related and unrelated). The most common AEs (WT/MT KRAS) were diarrhea (81%/62%), nausea (53%/58%), fatigue (55%/47%), rash (50%/56%), and acneiform dermatitis (41%/36%). The most common serious AEs were dehydration (10% of all pts), pyrexia (5%), and deep vein thrombosis (3%).

Conclusions: Numerical differences in PFS and OS in favor of pts with WT *KRAS* were observed. Pmab had a safety profile consistent with other pmab+FOLFIRI trials in pts of the same study population.

Best Objective Response[a], n (%)	WT *KRAS* (N = 64)	MT *KRAS* (N = 43)
Complete response[b]	2 (3)	1 (2)
Partial response[b]	13 (20)	6 (14)
Stable disease	26 (41)	18 (42)
Disease progression	13 (20)	11 (26)
Unable to evaluate/not done	10 (16)	7 (17)
Objective response rate, n responders	15	7
Response rate, % (95% CL)	23 (13, 34)	16 (5, 27)
PFS, n events	54	43
Median weeks (95% CL)	26 (19, 33)	19 (12, 25)
OS, n deaths	34	36
Median weeks (95% CL)	50 (39, 76)	31 (23, 47)

[a]Primary analysis set (N = 107); [b]Confirmed at next assessment.

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Efficacy and safety of bevacizumab-based combination regimens in patients with metastatic colorectal cancer: final results from a randomised phase II study of bevacizumab + FOLFIRI vs. bevacizumab + XELIRI (FNCLCC ACCORD 13/0503 study)

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Background: The combination of bevacizumab (bev) and chemotherapy improves overall survival and/or progression-free survival (PFS) compared with chemotherapy alone in patients (pts) with metastatic colorectal cancer (mCRC). This randomised non-comparative phase II trial evaluated the efficacy and safety of bev in combination with either XELIRI or FOLFIRI as first-line therapy for mCRC.

Materials and Methods: Pts were eligible for inclusion in this study if they had histologically proven measurable mCRC, were 18–75 years of age, and had an Eastern Cooperative Oncology Group performance status of 0–2. Pts were treated with either 8 cycles of XELIRI (irinotecan 200 mg/m^2 on Day 1 and capecitabine 1000 mg/m^2 bid on Days 1–14) + bev 7.5 mg/kg on Day 1, every 3 weeks or 12 cycles of FOLFIRI (irinotecan 200 mg/m^2 on Day 1 + 5-fluorouracil [5-FU] 400 mg/m^2 + folinic acid 400 mg/m^2 on Day 1 followed by 5-FU 2400 mg/m^2 via 46-h infusion) + bev 5 mg/kg on Day 1, every 2 weeks. Bev was continued until disease progression. Pts $\geqslant$65 years of age received a lower daily dose of capecitabine (800 mg/m^2 bid). The primary endpoint was crude PFS at 6 months.

Table. Efficacy and tolerability of bev + XELIRI and bev + FOLFIRI in pts with mCRC

Outcome	Bev + XELIRI (n = 72)	Bev + FOLFIRI (n = 73)
Efficacy, % (95% CI)		
Objective response rate[a]	58 (47–70)	58 (46–69)
Crude 6-month PFS	79 (70–88)	84 (75–92)
Safety, %		
$\geqslant$1 grade 3/4 AE (grade 4)	58 (8)	59 (12)
Grade 3/4 neutropenia (grade 4)	17 (3)	26 (4)
Grade 3/4 diarrhoea (grade 4)	12 (1)	5 (0)
Grade 3/4 cardiovascular (grade 4)	13 (3)	11 (1)

[a]Evaluated by Response Evaluation Criteria in Solid Tumours. AE, adverse event; CI, confidence interval; PFS, progression-free survival.