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Randomized, Open-label, Phase 3 Study of Panitumumab (Pmab) With FOLFOX4 Vs FOLFOX4 Alone as 1st-line Treatment for Metastatic Colorectal Cancer (mCRC) − the Role of Hypomagnesemia (Hypomag) on Efficacy

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Background: Pmab is a fully human anti-epidermal growth factor receptor (EGFR) monoclonal antibody approved as monotherapy for chemorefractory wild-type (WT) *KRAS* mCRC in the EU. The primary analysis of PRIME demonstrated that pmab + FOLFOX4 significantly improved progression-free survival (PFS) vs FOLFOX4 alone for 1st-line mCRC in patients (pts) with WT *KRAS*. In this exploratory subset analysis, the role of the development of hypomag, an adverse event associated with EGFR inhibition, on the efficacy of pmab + FOLFOX4 was evaluated for pts with WT and mutant (MT) *KRAS* mCRC.
Methods: Pts with metastatic adenocarcinoma of the colon or rectum, no prior chemotherapy for mCRC, no prior oxaliplatin, ECOG 0−2 and magnesium (Mg) $\geqslant$ lower limit of normal were randomized 1:1 to pmab 6.0 mg/kg Q2W + FOLFOX4 vs FOLFOX4 alone. The primary endpoint was progression-free survival (PFS); overall survival (OS) was secondary. Serum Mg levels were collected biweekly, and hypomag was defined by CTCAE v3.0 grade (gr).
Results: 1183 pts were randomized, and 593 pts received pmab. For pts with either WT or MT *KRAS* mCRC receiving pmab, respectively, 168 (52%) and 110 (51%) pts developed hypomag, 154 (48%) and 107 (49%) pts had no hypomag, and median time to the onset of hypomag was 11.4 and 8.9 weeks. In the WT *KRAS* pmab group, 29% had gr 1, 11% had gr 2, 7% had gr 3, and 5% had gr 4 hypomag. In the MT *KRAS* pmab group, 24% had gr 1, 16% had gr 2, 6% had gr 3, and 4% had gr 4 hypomag. Baseline characteristics were generally balanced within the WT/MT *KRAS* hypomag CTCAE gr 0 vs gr 1−4 groups. Results are shown in the table.
Conclusions: In pts with WT *KRAS* mCRC who received pmab and developed hypomag, PFS, OS, and ORR were increased. The results presented here did not include any analysis of Mg supplementation in pts receiving pmab. The biological mechanism for the development of hypomag after pmab administration may reflect an interaction between EGFR and Mg homeostasis; further investigation is needed to fully understand this correlation.

	Hypomag-Yes	Hypomag-No	HR (95% CI)	p-value[a]
WT *KRAS*	**n = 168**	**n = 154**		
Median PFS, mos (95% CI)	10.8 (9.4–12.9)	8.9 (7.3–11.3)	0.80 (0.62–1.02)	0.07
Median OS, mos (95% CI)	27.5 (23.5–32.8)	21.2 (17.9–27.1)	0.68 (0.52–0.90)	0.006
Objective response rate[b], % (95% CI)	64 (56−71)	51 (42−59)	–	–
Odds Ratio (95% CI)	1.67 (1.05–2.77)	–	0.03	
MT *KRAS*	**n = 110**	**n = 107**		
Median PFS, mos (95% CI)	7.4 (6.4−8.9)	7.4 (5.7−8.9)	0.89 (0.67–1.18)	0.42
Median OS, mos (95% CI)	16.9 (13.8–21.5)	13.5 (11.4–17.0)	0.86 (0.63–1.16)	0.32
Objective response rate[b], % (95% CI)	44 (35−54)	37 (27−47)	–	–
Odds Ratio (95% CI)	1.41 (0.78–2.57)	–	0.28	

[a]Descriptive; [b]Restricted to pts with baseline measurable disease per modified RECIST

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FOLFOXIRI (Irinotecan, Oxaliplatin, and Infusional 5FU/LV) in Combination With Panitumumab (P) in the First-line Treatment of Metastatic Colorectal Cancer (mCRC) Patients (pts) Selected for KRAS, BRAF, NRas and HRas Mutational Status − a Phase II Study by the G.O.N.O. Group

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Background: The GONO-FOLFOXIRI regimen demonstrated significantly higher activity and efficacy compared to FOLFIRI. The combination of P with oxaliplatin- or irinotecan-based doublets is feasible and associated with improved activity in *KRAS* codon 12−13 wild-type pts. *BRAF*, *NRAS* and *HRAS* mutations have been suggested as additional potential biomarkers to predict benefit from anti-EGFR agents.
Material and Methods: We are conducting a phase II trial to evaluate the combination of P 6 mg/kg on d1 with a modified GONO-FOLFOXIRI regimen in pts with previously untreated unresectable mCRC and wild-type status for *KRAS*, *BRAF*, *NRAS* and *HRAS*. The trial started with the following schedule: irinotecan 150 mg/sqm d1, oxaliplatin 85 mg/sqm d1, l-LV 200 mg/sqm d1 and 5FU 3000 mg/sqm 48-h flat continuous infusion starting on d1 every 2 weeks. Protocol has been amended because of serious adverse events (SAEs) occurred in 2 out of 3 pts enrolled and 5FU dose has been reduced to 2400 mg/sqm.
Results: Up today 46 pts have been screened and 20 pts enrolled. Reasons for exclusion were: *KRAS* mutations (41%), *BRAF* mutations (2%), *NRAS-HRAS* mutations (0%), other (13%). Main pts characteristics are: M/F, 50%/50%; median age (range), 61 (33−72) years; ECOG PS 0/1, 75%/25%; primary colon/rectum, 65%/35%; primary on site, 60%; sites of disease single/multiple, 35%/65%; liver only mts, 30%.16 pts have received $\geqslant$4 cycles of chemotherapy and are assessable for toxicity so far. Among the first 3 pts treated with 5FU 3000 mg/sqm, 2 experienced SAEs (1 G4 diarrhea and febrile neutropenia and 1 G3 diarrhea). After amendment, maximum G3−4 per patient toxicities were: neutropenia, 38% (1 episode of febrile neutropenia); diarrhea, 23%; stomatitis, 15%; neurotoxicity, 8%; asthenia, 8%; cutaneous rash, 15%. 16 out of 81 cycles were delayed, mainly (9/56%) because of toxicity. 1 SAE (febrile neutropenia and sepsis) resulting in pt death occurred after amendment. Up today 14 pts have been evaluated for response and we observed 11 PR (ORR: 79%) and 3 SD (disease control rate: 100%). After a median follow up of 2.6 months, median PFS has not yet been reached.
Conclusions: The addiction of P to the GONO-FOLFOXIRI regimen appears feasible, but requires a modest reduction in irinotecan and 5FU doses to improve gastrointestinal tolerability. After amendment, incidence of hematological and non-hematological toxicities is acceptable and preliminary results in terms of activity are promising. The study is still ongoing and updated results will be presented at the meeting.

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Ciclosporin in Combination With Irinotecan for Chemoresistant Advanced Colorectal Cancer − Results of PICCOLO, a Large Randomised Trial With Prospective Molecular Stratification

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Background: PICCOLO (ISCTRN93248876) is a 1198-patient (pt) randomised trial evaluating the addition of ciclosporin (Cs) or panitumumab (Pan) to single-agent irinotecan (Ir) in advanced colorectal cancer (aCRC). Cs profoundly reduces the hepatobiliary clearance of Ir and its active metabolite SN38. We hypothesised that Cs plus a 40%-standard dose of Ir would have at least the same systemic activity as standard Ir, but would avoid the risk of severe diarrhoea. PICCOLO opened as a 3-arm study in 2007; but from June 08 prospective KRAS testing was introduced and KRAS-wt pts were randomised to Ir/IrPan, KRAS-mut patients to Ir/IrCs. We present here the results of the Ir/IrCs randomisation.
Material and Methods: Eligible pts had measurable aCRC progressing after $\geqslant$1 prior regimen with fluoropyrimidines $\pm$ oxaliplatin; no prior Ir; PS0−2. Pts allocated Ir received irinotecan 350 mg/m^2 (300 mg/m^2 if age >70 yrs or PS2) d1, q3w. IrCs comprised irinotecan 140 mg/m^2 (120 mg/m^2 if age >70 yrs or PS2) d1, ciclosporin 3 mg/kg tds d0−2, q3w. A non-inferiority design was used, with primary endpoint % pts alive and progression-free at 12 wks, lower noninferiority boundary of −10.6%, α 0.025, β 0.80. Secondary endpoints included grade $\geqslant$3 diarrhoea during the first 12 weeks of therapy, loperamide use and overall survival (OS).
Results: 672 pts were randomised to Ir/IrCs. Median age was 64 yrs; 92% were PS0−1; 95% had received prior oxaliplatin; KRAS was wt in 25% (randomised before June 2008), mut in 60%, unknown in 15%. Both regimens were well tolerated, with notably low but similar rates of gr $\geqslant$3 diarrhoea in both arms (Ir 12%, IrCs 10%; $p = 0.38$); however fewer IrCs patients required loperamide (68%, 52%; $p < 0.001$). Non-inferior efficacy of

IrCs was not however confirmed: ITT analysis showed 179/335 (53.4%) pts progression-free at 12 wks with Ir, 159/337 (47.2%) with IrCs, Δ −6.3%, with the 95% CI crossing the prespecified efficacy boundary (−13.8%, +1.3%). OS was not impaired (HR 1.07 [95% CI 0.90, 1.28]).
Conclusions: IrCs was associated with less diarrhoea as assessed by lopermide use, but severe diarrhoea was uncommon in both arms. However, we failed to prove non-inferiority of IrCs compared with Ir, so cannot recommend it as a standard treatment option for aCRC based on the PICCOLO trial data.
Sponsor − University of Leeds. Status − Closed to recruitment.

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CRAFT Trial-Result From Multicenter Phase II Study of Modified FOLFOX7 (Combination Chemotherapy of Infusional 5-FU/l-Leucovorin and Intermittent Oxaliplatin) With Bevacizumab in the First-line Therapy of Colorectal Cancer

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Background: A combination of LV+FU with oxaliplatin (FOLFOX) has been established as a standard first-line therapy for metastatic colorectal cancer (mCRC).
Therefore, prior clinical trial showed that additional bevacizumab (monoclonal antibody for vascular endothelial growth factor) to FOLFOX improved survival in patients(pts) with mCRC (NO16966 study, Saltz et al JCO2008). OPTIMOX1 study suggested that stop and go strategy for oxaliplatin reduced peripheral sensory neuropathy. However OPTIMOX study was not included Bevacizumab. Thus we conducted to confirm stop and go strategy of Bevacizumab containing FOLFOX in this trial.
Materials and Methods: Eligibility criteria included ECOG PS: 0−1, No Peripheral neuropathy (<Grade 1). Patients received mFOLFOX7 (oxaliplatin 85 mg/m^2, LV200 mg/m^2, 5FU 2400 mg/m^2 + bevacizumab 5 mg/kg q2 weeks for 8 cycles, maintenance without oxaliplatin for 8 cycles, and reintroduction mFOLFOX7 + bevacizumab for 8 cycles until progression. Primary endpoint was Progression Free Survival (PFS).
Results: Between March 2009 and June 2010, 52pts were enrolled. Baseline characteristics were median age of 64 years (range, 36−74); PS 0/1 (43/9 pts);male/female(32/20 pts), colon/rectum (25/27pts) and metastatic lesion liver/lung/lymph nodes (34/21/12 pts). A total of 48 pts were evaluated as Par Protocol Set population. 32pts moved from initial FOLFOX7 to maintenance mLV5FU2. 25pts moved to mFOLFOX7 reintroduction. Median PFS was 12.3months (95% CI, 8.6–18.2) and Median TTF was 9.9 months (95% CI, 5.3–11.4). Best overall response rate was 45%. Median mLV5FU2 courses were 7.2 cycles (range 2−8). Oxaliplatin reintroduction rate was 52%. The causes of reintroduction failure were disease progression (4 pts), successfully-liver resection (1pt), withdrawal consent (1pt), peripheral sensory neuropathy Grade 2 (1pt). Main grade 3/4 toxicity were: neutropenia (3pts), peripheral neuropathy (2pts), hypertension (2pts).
Conclusions: This study met its primary endpoint PFS. It was longer than NO16966. mFOLFOX7 without FU bolus and intermittent oxaliplatin indicated to reduce incidence of severe neutropenia and peripheral sensory neuropathy. The results suggested that our treatment strategy was well tolerate and effective for first line therapy in mCRC, and maintenance duration for 8 cycles, was reasonable.

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The Value of Thymidine Kinase 1 (TK1) and Thymidine Phosphorylase (TP) Expression as Predictive Factors With the Treatment Efficacy of TAS-102, a Novel Antitumour Agent, in Patients (pts) With Metastatic Colorectal Cancer (mCRC)

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Background: TAS-102 is a novel oral nucleoside antitumour agent, consisting of trifluorothymidine (FTD) and thymidine phosphorylase inhibitor which prevents degradation of FTD. We will report promising results at the congress that TAS-102 (A) significantly improved overall survival (OS) compared with placebo (P) (A, n = 112; P, n = 57; median OS, 9.0 vs. 6.6 months; HR, 0.56; p = 0.001). FTD has 2 mechanisms of action: it inhibits thymidylate synthase (TS) and is incorporated into DNA molecule after phosphorylation by TK1, leading to antitumour effects that differ from TS inhibitors such as fluoropyrimidine. Therefore, TK1 and TP seem to play key roles in eliciting the potent antitumour effects of TAS-102 in cancer pts. In this clinical study we have investigated whether TK1 and TP expression levels could be useful predictive factors.
Material and Methods: Patients with mCRC who had refractory or intolerable to standard chemotherapy regimens, including fluoropyrimidine, irinotecan and oxaliplatin; had ECOG PS of 0 to 2; and had adequate organ functions were randomly assigned to TAS-102 and placebo, in a ratio of 2:1. TAS-102 or placebo was orally administered twice daily at a dose of 70 mg/m^2/day from d 1 to 5 and from d 8 to 12 every 4 weeks. The H-scores for the cytoplasmic expression of TK1 and TP were blindly scored from immunohistochemical staining. The study primary endpoint was OS, and the correlation between TK1, TP expression and efficacy was analyzed.
Results: The expression data of TK1 and TP before treatment were available for 150 and 149 of pts treated, respectively. The median H-score for TK1 expression was 115.00 vs. 115.00 (mean; A/P, 116.06/113.53) and 115.00 of two pooled groups, and the median H-score for TP expression was 12.50 vs. 15.00 (mean; A/P, 21.58/27.35). Table 1 shows multivariate analysis by Cox proportional hazard model, which included interactions between treatment and TK1 (>115 vs. ⩽115), TP (>15 vs. ⩽15) categorized according to median pooled groups.
Conclusions: TAS-102 treatment significantly improved OS in pts with mCRC. TK1 and TP expression levels were not correlated with OS in pts treated TAS-102. Additional analyses will be reported at the congress.

Table 1

Variable	OS (N = 149)		
	HR	95% CI	*p*
Treatment (A/P)	0.61	0.41 to 0.91	0.015
PS (1 or 2/0)	1.58	1.07 to 2.33	0.022
TP (>15/⩽15)	1.17	0.79 to 1.74	0.433
TK1 (>115/⩽115)	1.20	0.81 to 1.78	0.367
Treatment × TP	0.89	0.60 to 1.32	0.566
Treatment × TK1	0.90	0.61 to 1.34	0.610

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Prolonged Survival of Patients With Metastatic Colorectal Cancer Who Underwent First-line Oxaliplatin Based Chemotherapy With the Introduction of Molecular Targeting Agents and Curative Surgery

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Background: Recently, two types of molecular targeting agents were introduced for treatment of metastatic colorectal cancer (MCRC). However, it remains controversial whether these agents are associated with improved overall survival (OS) in oxaliplatin based chemotherapy.