

6095 POSTER
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) $\geq$ 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	

^aDescriptive; ^bRestricted to pts with baseline measurable disease per modified RECIST

6096 POSTER
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, I-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 $\geq$ 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 addition 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.

6097 POSTER
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 $\geq$ 1 prior regimen with fluoropyrimidines $\pm$ oxaliplatin; no prior Ir; PS0–2. Pts allocated Ir received irinotecan 350 mg/m² (300 mg/m² if age >70 yrs or PS2) d1, q3w. IrCs comprised irinotecan 140 mg/m² (120 mg/m² 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 $\sim$ 10.6%, α 0.025, β 0.80. Secondary endpoints included grade $\geq$ 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 $\geq$ 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