6006 ORAL

Intermittent Chemotherapy (CT) Plus Continuous or Intermittent Cetuximab (C) in the First-line Treatment of Advanced Colorectal Cancer (aCRC): Results of the Two-arm Phase II Randomised MRC COIN-B Trial

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Background: COIN-B (ISRCTN38375681) is a MRC sponsored, open-label, multi-centre, randomised, 2-arm, phase II trial of intermittent chemotherapy (ICT) plus intermittent cetuximab (C) versus ICT plus maintenance continuous C in the first-line treatment of aCRC. It complements the aims of the COIN trial (Arm A to C, ECCO/ESMO 2009), to investigate how C might safely and effectively be added to an ICT strategy.
Methods: Patients (pts) had measurable, inoperable aCRC; no prior CT for metastases; WHO PS 0−2 and good organ function. Randomisation was: Arm D − continuous OxFU + weekly C for 12 weeks then a planned break from all therapy; Arm E − OxFU + weekly C for 12 weeks then weekly C. Upon RECIST progression on either strategy, OxFU (or FU alone if neurotoxicity) plus C was restarted and continued until a second RECIST progression on maximal tolerated therapy. In 2008 the trial was revised such that only *KRAS* wild-type (wt) pts were eligible for randomisation. The primary outcome measure was Failure-Free Survival (FFS) at 10 months (mo) in *KRAS*-wt pts who had not progressed, died or failed the treatment strategy within 3 mo of randomisation. The trial was powered to differentiate between a desired 10-mo FFS rate of 50% and a minimum of 35%, needing 136 pts (168 pts allowing early drop-outs). Secondary outcome measures included safety of cetuximab reintroduction, overall survival (OS) and toxicity.
Results: 169 *KRAS*-wt pts were randomised between 07/07 and 06/10, 77 arm D/92 arm E. Median age 64 years (IQR 55−70); 92% PS 0−1. In Arms D and E respectively, 65 (84%) and 67 (73%) pts were eligible for the primary analysis; 10-mo FFS rates were 48% vs 54% (one-sided 95% confidence limit 37% and 43% respectively). Median FFS was 12.0 vs 13.7 mo respectively (IQR 6.1–20.3 and 8.6–23.2). Median OS was 20.1 vs 18.4 mo. Length of first CFI was 3.7 mo vs 5.1 mo (IQR 2.5−6.2 and 2.5−8.9). In a pre-planned exploratory analysis, median time to progression/death after CT break was 3.1 mo (IQR 2.1−8.1) in Arm D and 6.0 mo (IQR 2.9–10.9) in Arm E. Toxicity in both arms was similar. Only 1 pt experienced Grade 3 hypersensitivity following reintroduction of C in Arm D.
Conclusions: In COIN-B, C was safely incorporated in two ICT strategies. The use of continuous C maintenance in first line was associated with a longer CFI and longer time to progression/death. The incorporation of this encouraging strategy of biological maintenance therapy into practice needs validation in phase III trials.

6007 ORAL

Panitumumab 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 (ISRCTN93248876) is a 1198-patient (pt) randomised trial evaluating the addition of panitumumab (Pan) or ciclosporin (Cs) to single-agent irinotecan (Ir) in advanced colorectal cancer (aCRC). It 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/IrPan randomisation according to molecular subtype.
Material and Methods: Eligible pts had measurable aCRC progressing after $\geqslant$1 prior regimen with fluoropyrimidines $\pm$ oxaliplatin; no prior Ir; PS0−2. Mutations were assessed by DNA pyrosequencing. Ir was 350 mg/m^2 q3w (300 mg/m^2 if age >70 yrs or PS2). IrPan was the same Ir plus Pan 9 mg/kg q3w. The primary endpoint was overall survival (OS), secondary endpoints PFS and RR. The primary efficacy population was pts with no prior anti-EGFR therapy and KRAS-wt at c.12−13 and 61. Secondary populations were prior anti-EGFR, KRAS/BRAF-wt, BRAF-mut, and KRAS-mut (pts recruited before June 08).
Results: 696 pts were randomised to Ir/IrPan, 460 in the primary efficacy population. Both regimens were well tolerated, though higher rates of diarrhoea, skin and haematological toxicity were seen with IrPan than Ir. OS improvement with IrPan did not reach statistical significance (HR = 0.91, p = 0.44). PFS and RR were however markedly improved with IrPan, and especially so in the KRAS/BRAF-wt population. Exploratory analyses showed no benefit from IrPan in KRAS-mut and potential disbenefit in BRAF-mut tumours.

	KRAS-wt	KRAS/BRAF-wt	KRAS-mut	BRAF-mut
number	460	348	96	63
OS: HR (p-value)	0.91 (0.44)	0.87 (0.30)	0.89 (0.62)	2.03 (0.02)
PFS: HR (p-value)	0.78 (0.01)	0.73 (<0.01)	1.10 (0.66)	1.47 (0.17)
RR: % Ir v. IrPan (p)	12 v. 34 (<0.0001)	13 v. 39 (<0.0001)	16 v. 11 (0.45)	7 v. 9 (0.82)

Conclusions: PICCOLO did not meet its primary endpoint of demonstrating statistically improved OS in KRAS-wt aCRC. Major improvements in PFS and RR were seen in patients with KRAS/BRAF-wt tumours who received Pan. Conversely no benefit from Pan was seen in patients with KRAS or BRAF mutated tumours. Analysis of KRAS c.146, NRAS and PIK3CA mutations will be presented at the meeting.
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6011 ORAL

Unresectable Colorectal Liver Metastases Treated by Intraoperative Radiofrequency Ablation With or Without Resection: the ARF2003 Study

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Background: Despite aggressive combined medical and surgical strategy, only 15% to 25% of patients with colorectal liver metastases (CRLM) are able to undergo curative surgery. Intraoperative use of radiofrequency ablation (IRFA) may enable a greater number of patients to be eligible for surgical treatment.
Material and Methods: Patients with previous resection of the primary colorectal adenocarcinoma and unresectable liver metastases were eligible for this prospective, multicentre, phase II study across 7 centres (Optimal two-stage Simon's design, NTC 00210106). They received IRFA treatment with or without parenchymal resection and underwent clinical and pathological examinations and a Quality of Life (QoL) evaluation. The primary endpoint was complete hepatic response (CHR) at 3 months. Overall survival (OS), event-free survival (EFS), local progression-free survival (LPFS), morbidity and QoL were also examined.
Results: Fifty-two patients were included. They had a median of 5 [1−13] metastases. Most of them were bilateral or recurrent. CHRs were observed for 39 patients in the ITT population (75%, 95% CI [61.0; 86.0]) supporting the primary hypothesis. One-year LPFS was 46.1% (95% CI [32.3%; 58.9%]. Of the 10 patients exhibiting hepatic recurrences at 3 months, 2 (4% overall) relapsed at the site of ablation. The median follow-up was 2.9 years (95% CI [2.5; 3.6]). Five-year OS was 43.4% (95% CI [21.2; 63.7]), but 3-year EFS was 10.3% (95% CI [3.6–20.9]). Post-operative complications were observed for 40.8% of patients but only with 6 (28.7%) stage IIIa or above complications observed. One patient died from septic shock. QoL increased over time for non-progressive patients.
Conclusions: IRFA combined with or without resection is an efficient treatment for patients with unresectable CRLM. This study brings prospective data to confirm that long-term survival can be achieved in a larger group of patients than those previously defined as potentially curable by resection alone, validating the role of IRFA in the surgeon's armamentarium.