3010 ORAL

Final overall survival (OS) results of CONFIRM 1 (CF1), a randomized, double-blind, placebo-controlled phase III trial in patients with metastatic adenocarcinoma of the colon or rectum (mCRC) receiving first line chemotherapy with oxaliplatin/5-fluorouracil/Leucovorin (FOLFOX 4) and PTK787/ZK 222584 (PTK/ZK) or placebo (PBO)

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Background: PTK/ZK is an oral, small molecule, anti-angiogenesis compound that blocks tyrosine kinase signaling from all known vascular endothelial growth factor receptors (VEGF-R). Progression–free survival (PFS) results have been presented at ASCO 2005 showing a modest but not statistically significant PFS benefit for the PTK/ZK treatment group. High serum LDH at baseline, a factor for poor prognosis in mCRC, appeared to predict a greater treatment effect for patients treated with PTK/ZK.
Methods: Between Feb 2003 and May 2004, 1168 patients were randomized in the CF1 trial. The trial was powered to show a difference in PFS (early primary endpoint, HR: 0.75) and OS (late primary endpoint, HR: 0.80) in favor of PTK/ZK. Patients received FOLFOX-4 every 2 weeks with either PTK/ZK (1250 mg daily, q.d.) or PBO. Patients were stratified by performance status (0 vs. 1 or 2) and baseline LDH ($\leqslant$1.5 ULN vs. >1.5 ULN); 316 patients (27.1%) had high LDH or LDH > 1.5 ULN.
Results: Final key safety and efficacy results, including OS are summarized in the table.

	FOLFOX + PTK/ZK (95% CI)	FOLFOX + PBO (95% CI)	HR	p-value
Randomized (N)	585	583		
OS				
Overall patient population	21.4 mo	20.5 mo	1.08	0.260
High LDH population (>1.5 ULN)	14.8 mo	14.6 mo	1.04	0.751
PFS (central review)				
Overall patient population	9.1 mo	7.7 mo	0.89	0.108
High LDH population (>1.5 ULN)	9.1 mo	5.8 mo	0.79	0.069
Gr 3 or 4 Hypertension	23.0%	6.8%		
Gr 3 or 4 Diarrhea	15.4%	11.1%		
Gr 3 or 4 Dizziness	7.4%	2.3%		
Gr 3 or 4 Deep vein thrombosis	5.2%	3.5%		
Pulmonary embolism	5.7%	1.7%		
Arterial thromboembolism	9.0%	3.1%		
Bowel obstruction/perforation	0.5%	0.7%		
Bleeding	16.4%	16.4%		

Conclusion: The improved PFS observed in the overall and high LDH patient population during the previous analysis was maintained as a trend in the final analysis but this did not translate into an overall survival advantage for either population. The safety profile is consistent with the profile observed during the final PFS analysis.

3011 ORAL

Role of Thymidylate synthase −6bp/1494 deletion polymorphism in capecitabine or 5-fluorouracil (5FU) selection in first line oxaliplatin-based chemotherapy in advanced colorectal cancer

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Background: The replacement of 5FU by capecitabine in combination chemotherapy for metastatic colorectal cancer does not affect negatively either overall toxicity or treatment outcome. Furthermore, capecitabine is well accepted by patients because it is an oral drug and may reduce overall costs compared with i.v. treatments. The use of a molecular marker to select oral or i.v. fluoropyrimidine could be of clinical interest. We studied several genetic polymorphisms affecting fluoropyrimidines and oxaliplatin mechanism of action and their possible usefulness in selecting oxaliplatin plus capecitabine (XELOX) or 5FU (FOLFOX) treatment in metastatic colorectal cancer patients.
Patients and Methods: 96 out of 348 patients enrolled in the 03/TTD/01 randomized clinical trial comparing efficacy and safety of XELOX or FOLFOX combinations in first line chemotherapy from the Spanish group for the Treatment of Digestive Tumours (TTD group), were selected prospectively for a genetic assessment. TS 5'TRP, 5'SNP and −6bp/1494 deletion polymorphisms as well as XRCC1 Arg399Gln, XPD Lys751Gln, ERCC1 Asn118Asn and XRCC3 Met241Thr polymorphisms were studied by PCR, allelic discrimination, RFLP and genescan techniques. Clinical endpoints were time to tumor progression (TTP) and survival. Contingency tables, Fisher's exact test, logrank test and cox regression analysis were used.
Results: Patients homozygous for the 6bp insertion (+6bp/+6bp) in the 3' end of TS gene who had received FOLFOX combination had a worse TTP than patients heterozygous or homozygous for the deletion (X/-6bp) (6.1 vs. 10.76 months log rank p = 0.005). In the XELOX group, +6bp/+6bp patients had similar TTP than X/-6bp. Moreover, in the FOLFOX group, patients whose haplotypes contained −6bp/2R alleles had a TTP of 25.76 months (Log rank p = 0.03). In the multivariate analysis only TS −6bp/1494 was an independent prognostic factor for TTP in the FOLFOX group [p = 0.005; HR for +6bp/+6bp = 2.8, 95% CI 1.36−5.63).
Conclusion: Taking into account these results, colorectal cancer patients carrying the +6bp/+6bp genotype should receive preferably capecitabine plus oxaliplatin instead of 5FU plus oxaliplatin combination in first line chemotherapy. Patients carrying the −6bp/2R haplotype should receive 5FU plus oxaliplatin combination.

3012 ORAL

Capecitabine + oxaliplatin (XELOX) vs. 5-FU/LV + oxaliplatin (FOLFOX4) as second-line treatment for patients with metastatic colorectal cancer (MCRC): Phase III trial results

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Background: The oral fluoropyrimidine capecitabine has demonstrated similar efficacy to bolus 5-FU/LV as first-line treatment for MCRC. However, combination of irinotecan or oxaliplatin with 5-FU/LV has shown improved efficacy vs. 5-FU/LV alone and is widely used as first- or second-line treatment for MCRC. We conducted a phase III study comparing XELOX with FOLFOX4 in patients who had received prior treatment with irinotecan in combination with bolus and/or infusional 5-FU/LV for MCRC.
Materials and Methods: Patients were treated with XELOX (capecitabine 1000 mg/m^2 bid orally days 1–14 + oxaliplatin 130 mg/m^2 i.v. day 1) q3w or FOLFOX4 (LV 200 mg/m^2 2-h i.v. infusion followed by 5-FU 400 mg/m^2 bolus i.v. and 600 mg/m^2 22-h infusion on days 1–2 + oxaliplatin 85 mg/m^2 i.v. on day 1) q2w. Primary endpoint was time-to-tumour progression or death (progression-free survival; PFS). The study had 80% power to detect non-inferiority of XELOX vs. FOLFOX defined by a progression hazard ratio (HR) of
Results: 627 patients were recruited (intent-to-treat, ITT). Baseline characteristics were well balanced. The primary objective was met: XELOX was non-inferior to FOLFOX4 in terms of PFS (Table). PFS and overall survival (OS) were similar between groups in both ITT and per-protocol (PP) populations (Table). An updated analysis (data cut off April 2007) on OS was performed and will be presented at the meeting. Response rates (PP) were similar in the XELOX and FOLFOX4 groups as assessed by investigators (23% vs. 20%) and by independent review (18% vs. 14%). Grade 3/4 toxicities occurred in 60% of XELOX- and 72% of FOLFOX4-treated patients. The most common treatment-related grade 3/4 adverse events were balanced between the XELOX and FOLFOX4 arms. 60-day all-cause mortality was 3.9% in XELOX- and 4.2% in FOLFOX4-treated patients.

Efficacy results

	XELOX	FOLFOX4	HR [95% CI]
PFS (PPP), months	5.1	5.5	1.03 [0.87–1.24]
PFS (ITT), months	4.7	4.8	0.97 [0.83–1.14]
OS (PPP), months	12.7	13.2	1.07 [0.88–1.31]
OS (ITT), months	11.9	12.6	1.03 [0.87–1.23]

Conclusions: Second-line treatment of MCRC with XELOX is non-inferior to FOLFOX4 in terms of PFS, OS and ORR. This study supports the results of another large phase III study in first-line MCRC reported recently [Cassidy et al. ASCO GI 2007], which compared XELOX +/− bevacizumab vs. FOLFOX4 +/− bevacizumab and also showed similar efficacy in PFS and OS. The safety profile was similar to previous studies, with no unexpected toxicities.

3013 ORAL

Tissue biomarkers in colon cancer (COC): Early results of the translational study on a phase III trial comparing infused irinotecan/ 5-fluorouracil (5-FU)/folinic acid (FA) to 5-FU/FA in stage II−III COC patients (PETACC 3–EORTC 40993–SAKK 60/00)

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Background and Aims: PETACC 3 is a large adjuvant trial with 3005 COC pts. The value of biomarkers (BIOM) in COC in adjuvant setting is still a matter of debate because of lack of large data sets. We took advantage of PETACC 3 to assess P53, SMAD4, thymidylate synthetase (TS), telomerase (HTERT) expressions, UGT1A1 genotype, KRAS and BRAF mutations, microsatellite instability (MSI), 18q and 8p LOH with regard to their prognostic and predictive values and their interactions on a very large homogeneous cohort of COC pts.
Methods: 1564 formalin fixed paraffin embedded (FFPE) tissue blocks of PETACC 3 pts were prospectively collected and 5−20μ sections cut. DNA from normal (Nor) and tumoral (Tu) tissues was extracted after section microdissection. P53, SMAD4, TS and HTERT were assessed by immunohistochemistry (IHC); MSI was typed with 10 markers, KRAS exon 2 and BRAF exon 15 mutations by allele specific real time PCR on Tu DNA; 18q and 8p LOH by typing multiple SNPs by pyrosequencing on Nor/Tu DNA; UGT1A1 genotypes by PCR and fragment sizing on Nor DNA. Prognostic/predictive value of each BIOM is analysed by Cox regression for disease free survival and by logistic regression for specific toxicity. Associations between any 2 categorized BIOM and between each BIOM and each known prognostic variable are tested by chi-square tests.
Results: DNA of 1405 pts was extracted and successfully analysed in 97.1% for KRAS, 98.6% for BRAF, 94% for 18q LOH, 93.6% for MSI, 95% for UGT1A1, 8p LOH is still ongoing. Of 1530 pts slides IHC analysis was successful in 94.5% for P53, 94.2% for SMAD4, 82.9% for TS, 53.9% for HTERT. Early results show significant improvement of prognosis with high SMAD4 expression ($p < 0.001$), lack of p53 overexpression ($p = 0.04$), high MSI ($p = 0.04$) and a trend for better prognosis with high TS expression ($p = 0.07$) and lack of BRAF mutation ($p = 0.11$). None of the 4 KRAS mutations tested had any impact on prognosis.
Conclusion: This is the largest multicenter centrally coordinated tissue BIOM study performed in COC to date. The high success rate of analysis shows that large prospective BIOM studies can be performed on routine decentrally processed FFPE material. These early data obtained on a large patient population confirm (MSI, SMAD4, KRAS) or challenge (p53, TS) published results coming from smaller patient cohorts.Further analysis of these data is ongoing.

3014 (Presidential session, Tue 25 Sep 12.30–14.30) ORAL

Association of somatic KRAS gene mutations and clinical outcome in patients (pts) with metastatic colorectal cancer (mCRC) receiving panitumumab monotherapy

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Background: Panitumumab, a fully human monoclonal antibody directed against the epidermal growth factor receptor has demonstrated efficacy as monotherapy in pts with mCRC. Identifying markers of responsiveness would allow physicians to target therapy to those pts most likely to benefit. In this analysis, pt samples from 4 mCRC monotherapy studies of safety and efficacy with panitumumab were used to test the hypothesis that KRAS mutations are associated with resistance to panitumumab.
Methods: Tumor sections from 59/709 treated pts (57/533 pts from three phase 2 studies, and 2/176 pts from a phase 3 extension study) were consented, had response data, and were available for analysis of KRAS gene mutations. Genomic DNA was isolated from FFPE tumor sections (pretreatment). PCR was performed on KRAS (exons 2 & 3) to determine the prevalence of activating mutations. More than 30 colonies per exon were sequenced and resolved on a Genetic Analyzer. Subsequent PCR and genomic DNA sequencing confirmed the existence of mutations. In all 4 studies, best objective response (OR) was assessed using RECIST criteria at prespecified weeks; the phase 2 studies were assessed by blinded central review; the extension study was assessed by local review.
Results: Of the 59 pts, 6 (10%) had a partial response (PR), 22 (37%) had stable disease (SD), and 31 (53%) had progressive disease (PD) as their best OR. 21 of the 59 pts harbored a KRAS mutation: 5 pts had SD (24%) and 16 pts had PD (76%) as their best OR. All of these mutations were located in exon 2 (amino acids 12 and 13). No responders had a KRAS mutation. In the wild-type KRAS population, the PR rate was 16% (95% CI: 4, 27), the SD rate was 45% (95% CI: 29, 61), and the PD rate was 39% (95% CI: 24, 55). There was a statistically significant association between KRAS mutation status and response to panitumumab (Fisher's exact test, $p = 0.013$). From a Cox PH model for KRAS mutation as a predictor of PFS, the HR was 1.7 (95% CI: 1.0−2.9); for OS the HR was 1.73 (95% CI: 1.0−3.1).
Conclusion: Although the sample size is limited, these data suggest that CRC pts with activating KRAS mutations may be less likely to respond to treatment with panitumumab monotherapy. These findings warrant further investigation, including sequencing a larger set of samples to correlate KRAS mutations with pt responsiveness to panitumumab. A prospective trial to evaluate KRAS as a predictive biomarker of response is currently ongoing.

3015 ORAL

Sequential vs. combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (ACC). A Dutch Colorectal Cancer Group (DCCG) phase III study

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Background: Imbalances in salvage treatments may affect overall survival (OS) in phase III studies with 1st line combination therapy in ACC. This is the first trial that prospectively evaluates the sequential versus the combined use of all available effective cytotoxic drugs.
Methods: Previously untreated patients (pts) with ACC, WHO PS 0−2 were randomized between 1st line capecitabine (Cap), 2nd line irinotecan (Iri), and 3rd line Cap + oxaliplatin (CapOx) (Arm A, sequential) vs 1st