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)

J.R. Hecht[1], T. Trarbach[2], E. Jaeger[3], J. Hainsworth[4], R.A. Wolff[5], K. Lloyd[6], G. Bodoky[7], M. Borner[8], D. Laurent[9], C. Jacques[10]. *[1]UCLA, Jonsson Comprehensive Center, Los Angeles, USA; [2]University of Essen, Medical Center, Essen, Germany; [3]Krankenhaus, Nordwest, Frankfurt, Germany; [4]Sarah Cannon, Cancer Center, Nashville TN, USA; [5]MD Anderson, Cancer Center, Houston TX, USA; [6]Virginia Cancer Institute, Oncology, Richmond VA, USA; [7]Szent Laszlo Hospital, Oncology, Budapest, Hungary; [8]Institute for Medical Oncology, Medical Oncology, Bern, Switzerland; [9]Clinical Affairs, Bayer Schering Pharma, Berlin, Germany; [10]Clinical Affairs, Novartis Pharmaceuticals, Berlin, Germany*

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.

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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

E. Martinez-Balibrea[1], E. Aranda[2], J.L. Manzano[1], J. Sastre[3], J. Aparicio[4], T. García[5], I. Maestu[6], A. Martinez-Cardús[1], A. Ginés[1], A. Abad[1]. *[1]Hospital Universitari Germans Trias i Pujol, Medical oncology service, Badalona (Barcelona), Spain; [2]Hospital universitario Reina Sofía, Medical oncology service, Córdoba, Spain; [3]Hospital Universitario Clínico San Carlos, Medical oncology service, Madrid, Spain; [4]Hospital Universitari La Fe, Medical oncology service, Valencia, Spain; [5]Hospital Morales Meseguer, Medical oncology service, Murcia, Spain; [6]Hospital Virgen de los Lírios, Medical oncology service, Alicante, Spain*

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.

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

M. Rothenberg[1], M. Navarro[2], C. Butts[3], Y. Bang[4], J. Cox[5], R. Goel[6], S. Gollins[7], L. Siu[8], D. Cunningham[9]. *[1]Vanderbilt-Ingram Cancer Center, Medical Oncology, Nashville, USA; [2]Hospital Duran I Reynals, Cancer Prevention, Barcelona, Spain; [3]Cross Cancer Institute, Oncology, Edmonton, Canada; [4]Seoul National University Hospital, Internal Medicine, Seoul, Korea; [5]Texas Oncology PA & US Oncology Research, Oncology, Dallas, USA; [6]The Ottawa Hospital, Pharmacology and Drug Development, Ottawa, Canada; [7]North Wales Cancer Treatment Centre Glan Clwyd Hospital, Oncology, Rhyl, United Kingdom; [8]Princess Margaret Hospital, Oncology, Toronto, Canada; [9]The Royal Marsden Hospital, Oncology, Sutton, United Kingdom*

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.