objective response rate and secondary endpoints, including disease control rate, time to response and progression-free survival. This abstract will review the correlation between EGFR expression and response rate (⩾17 weeks evaluation) in pts with *KRAS* wild-type or mutant tumours.
Results: Recruitment completed 18 June 08 with 154 pts enrolled. At interim analysis (15 Oct 08), *KRAS* evaluable samples for 92% of pts and EGFR evaluable samples for 84% of pts are available. Of the 85 pts with KRAS wild-type (wt) tumours, and the 57 pts with KRAS mutant (mt) tumours 78%/54% are male; median age is 64 years (range 21−84)/66 years (range 37−80) and 95%/93% of pts had ECOG PS 0−1, respectively. A higher proportion of responders in the wt subset have no EGFR staining versus non-responders (28% vs 5%; Table) with no notable difference seen for pts in the mt subset (13% vs 12%). In the wt subset incidence of moderate and strong maximum staining intensity is lower for responders than non-responders.

	KRAS wt (n = 84)		KRAS mt (n = 56)		All pts (n = 152)	
	Responder (N = 40)	Non-responder (n = 44)	Responder (n = 16)	Non-responder (n = 40)	Responder (n = 63)	Non-responder (n = 89)
Pts with EGFR data	36 (90)	43 (98)	15 (94)	33 (83)	52 (83)	77 (87)
3+ (strong)	3 (8)	11 (26)	2 (13)	1 (3)	5 (10)	12 (16)
2+ (moderate)	6 (17)	14 (33)	7 (47)	11 (33)	13 (25)	26 (34)
1+ (weak)	17 (47)	16 (37)	4 (27)	17 (52)	22 (42)	33 (43)
0	10 (28)	2 (5)	2 (13)	4 (12)	12 (23)	6 (8)

Conclusions: Within the parameters of this small data set, this analysis suggests that EGFR expression unlike *KRAS* status may not be essential for determining response to treatment.

6074 POSTER

Bevacizumab (bev) combined with chemotherapy as 2nd-line treatment for metastatic colorectal cancer (mCRC): results from the phase II BEVACOLOR study

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Background: Bev is approved for treatment of patients (pts) with mCRC in combination with fluoropyrimidine-based chemotherapy. This study assessed efficacy and safety of bev plus chemotherapy regimens commonly used as 2nd-line treatment for mCRC.
Materials and Methods: Prospective, open-label, single-arm, multicentre phase II trial (EUDRACT 2005–000800−14). Pts with mCRC who had progressed or relapsed after 1st-line treatment (oxaliplatin- or irinotecan-based) received bev 2.5 mg/kg/week plus FOLFOX, FOLFIRI, XELIRI, or irinotecan until disease progression. Primary endpoint: disease-control rate (DCR). Secondary endpoints: progression-free survival (PFS), overall survival (OS) measured from 2nd-line treatment and safety. The trial was funded by Roche France.

Table: Response rates, PFS and OS by 2nd-line chemotherapy regimen

Outcome	Bev in combination with:				
	FOLFIRI (n = 30)	FOLFOX (n = 14)	Irinotecan (n = 8)	XELIRI (n = 1)	All (n = 53)
Overall response rate, n (%)	11 (37)	4 (29)	2 (25)	0	17 (32)
Disease control rate, n (%)	27 (90)	11 (79)	7 (88)	1 (100)	46 (87)
Progressive disease, n (%)	2 (7)	2 (14)	1 (13)	0	5 (9)
Median PFS, months (95% CI)	7.8 (6.0−8.7)	5.3 (3.9−6.0)	8.4 (5.9−9.4)	2.6 (NA)	6.5 (5.8−7.8)
Median OS, months (95% CI)	21.7 (17.3−26.4)	13.9 (9.6−27.8)	24.1 (9.7−NR)	14.5 (NA)	19.3 (14.2−25.1)

2 pts were not evaluable. NA=not applicable; NR=not reached.

Results: 53 pts (66% male, median age 62 years, ECOG PS 0−2) received 2nd-line bev plus FOLFIRI (57%), FOLFOX (26%), irinotecan (15%), or XELIRI (2%). DCR was 87% (95% CI 77−97%) and ORR was 32% (95% CI 19−46%). Median PFS and OS were 6.5 (95% CI 5.8−7.8) and 19.3 months (95% CI 14.2−25.1), respectively. The table below provides DCR, PFS and OS by chemotherapy regimen. Median OS for pts receiving 2 lines of chemotherapy was 9.7 months (95% CI 7.8−13.6), and for those receiving 3, 4 and >4 lines was 20.1 (14.2−24.2), 18.7 (13.6−25.7) and 30.9 months (27.8−NR), respectively. Grade 3/4 adverse events included neutropenia (21%), diarrhoea (15%) and asthenia (9%). Grade 3/4 targeted toxicities (known to occur with bev) were reported in 6 pts (11%): hypertension (n = 2), haemorrhage (n = 1) and embolism (n = 3). Serious adverse events (SAE) were reported in 13 pts. One SAE was considered to be related to bev. No toxic deaths were observed.
Conclusions: Bev plus standard 2nd-line chemotherapy is highly active in pts with mCRC and has an acceptable safety profile.

6075 POSTER

A triple combination of Imatinib, Bevacizumab and Cetuximab plus modified FOLFOX-6 in advanced untreated colorectal cancer

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Background: Imatinib inhibits PDGFR interfering with pericytes, the structural support to newly formed tumor blood vessels. It may thus synergize with bevacizumab. Microenvironment and tumor targeted agents along with chemotherapy could be a promising add-on approach.
Methods: Cetuximab 500 mg/m^2, Bevacizumab 5 mg/kg and modified FOLFOX-6 were given i.v. on day 1 and repeated every 2 weeks. Imatinib 400 mg/day per os was given continuously. Due to the cost and potential toxicity of the combination, the endpoint for this phase II study was very ambitious: at least 25% of complete response (medically or surgically achieved), lasting a minimum of 12 months in advanced untreated colorectal cancer patients with clearly unresectable disease.
Results: Of 26 patients (16 with 1 site of disease), 17 completed the first 4 months of treatment according to the protocol, while 9 had to discontinue one biologic drug due to side effects (5 cetuximab, 3 imatinib and 1 bevacizumab). Grade 3−4 toxicity: diarrhea 12%, neutropenia 24%, skin rash 24%, hypersensitivity reactions 16%, asthenia 8%, neuro 8%. All patients were evaluable for response. Eleven responses (1 CR and 10 PR), 13 SD and 2 PD were observed, corresponding to 42% RR (95% CI = 23−61). The minimum follow up is 12 months; median PFS is 10 months. One patient among responders underwent radiofrequency ablation and 17 patients underwent surgery: 8 R-0, 3 R-1, 5 R-2 and 1exploratory laparotomy. Major post surgical complications occurred in 5/17 patients. No evidence of macroscopic disease after the entire treatment plan was obtained in 13/26 patients: 12 surgical and 1 medical CR. 7/13 were disease free at 6 months, but only 3 were still disease free at 12 months. ERCC1, ERCC2/XDP, GSTP1, TS, EGF, COX2, CYCLIN D, FCgR polymorphisms and K-RAS mutations were evaluated on all 26 patients, but no correlations were found with clinical outcome.
Conclusions: The triple combination of biologics with modified FOLFOX-6 is feasible and tolerable as initial aggressive treatment. However, the primary endpoint of the study was not met. In fact the activity (42% RR) was not outstanding. Moreover, the high resectability rate (69%) must be interpreted in the light of the short duration of the surgically induced CR.

6076 POSTER

BOXER: A multicentre phase II trial of capecitabine and oxaliplatin plus bevacizumab as neoadjuvant treatment for patients with liver-only metastases from colorectal cancer unsuitable for upfront resection

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Background: Capecitabine/oxaliplatin+bevacizumab (CAPOX+Bev) is a standard treatment option for metastatic colorectal cancer (CRC). Complete resection of liver metastases (mets) appears to improve long-term survival. Increasingly, patients (pts) with synchronous liver mets are being treated with neoadjuvant therapy. Additionally, neoadjuvant therapy may allow some pts with initially unresectable liver mets to be adequately downsized to achieve resection.
Method: This prospective single arm phase II study assessed response rate (RR) to CAPOX+Bev in pts considered unsuitable for upfront resection of liver-only mets. Eligible pts had unresectable liver-only mets (synchronous: N = 24 or metachronous: N = 4) according to pre-specified

technical criteria or potentially resectable liver-only mets diagnosed synchronously with the primary tumour (N = 17). Resectability was reassessed after every 4 cycles of CAPOX+Bev. Bev was discontinued a minimum 8 weeks prior to surgery. Secondary objectives included complete resection rate, safety and feasibility of the regimen, PFS and OS.
Results: 46/47 pts recruited to the study commenced treatment. 1 pt was ineligible (evaluated for safety only). Based on current best response (table) CAPOX+Bev resulted in an overall response rate of 78% [95%CI 63−89%].

Response (RECIST)	Number = 45	%
CR	3	7
PR	32	71
SD	7	16
PD	3	7

With a median follow-up of 10.2 months, median PFS is 11.5 months.
28/45 pts had unresectable disease at entry. 1/28 has achieved CR; 9/28 have been converted to resectable (4 awaiting surgery); 3/28 are awaiting final assessment regarding resectability.
17/45 pts had potentially resectable synchronous liver mets at entry. 2/17 achieved CR; 10/17 have proceeded to surgery; 3/17 remain resectable and are continuing CAPOX+Bev or awaiting surgery.
15/45 pts have undergone liver resection. With surgery performed a median of 10.9 weeks (range 8.7−24) after Bev, no grade 3/4 perioperative complications have been reported. One grade 2 post-op anastamotic leak has been reported-2%. Specific grade 3/4 Bev-related toxicities were: venous thromboembolism-6.5%, hypertension-2%, duodenal perforation-2%.
Conclusion: In pts with initially unresectable or a synchronous diagnosis of liver-only CRC mets, CAPOX+Bev is associated with a high RR (78%). At least 9/28 (32%) of unresectable pts have been downstaged to potentially resectable. In our study, surgery was safe and feasible as early as 8.7 weeks post Bev. Updated results to be presented.
Supported by Roche: Provision of Bev & unrestricted educational grant.

6077 POSTER

A meta-analysis of the CRYSTAL and OPUS studies combining cetuximab with chemotherapy (CT) as 1st-line treatment for patients (pts) with metastatic colorectal cancer (mCRC): Results according to KRAS and BRAF mutation status

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Background: The CRYSTAL and OPUS studies demonstrated that adding cetuximab to CT (FOLFIRI or FOLFOX4, respectively) as 1st-line treatment for mCRC significantly reduced the risk of disease progression and increased the chance of response, compared with CT alone, in pts with KRAS wild-type (wt) tumors. The objective of the current meta-analysis was to evaluate progression-free survival (PFS) and overall response rate (ORR) in combined CRYSTAL and OPUS pt populations, according to KRAS and BRAF mutation status.
Materials and Methods: The meta-analysis was performed on pooled raw data from the two randomized controlled studies for the primary clinical efficacy endpoints: PFS (CRYSTAL) and ORR (OPUS). Primary definitions were employed, as provided by the individual study protocols. In both studies, the primary analysis of PFS and ORR was based on an independent radiology review committee assessment. Hazard ratios (HRs) for the treatment effect on PFS were obtained by applying a Cox proportional hazards model to pooled raw data adjusted for study and stratified by ECOG performance status, the common stratification factor in both studies. Odds ratios (ORs) for the treatment effect on ORR were obtained by performing a logistic regression on pooled raw data using the same adjustment. Mutations in KRAS (codons 12/13) and BRAF (codon 600) were detected by mutation-specific qPCR.
Results: The meta-analysis of 482 pts with KRAS wt tumors demonstrated that addition of cetuximab to CT provided a significant benefit for the primary study endpoints PFS and ORR. Overall, the addition of cetuximab to CT in pts with KRAS wt tumors significantly reduced the risk of disease progression by 36% (HR 0.64; 95% CI: 0.50−0.83). Furthermore, the likelihood of achieving a response was >2-fold higher among pts with KRAS wt tumors who received cetuximab plus CT, compared with those who received CT alone (OR 2.09; 95% CI: 1.44−3.02). In the adjusted Cox proportional hazards model and the adjusted logistic regression model, tests on heterogeneity did not indicate a difference in the treatment effect across studies. Data on the impact of BRAF mutation status on cetuximab activity will be presented at the meeting.
Conclusions: The meta-analysis results strengthen the findings obtained from the CRYSTAL and OPUS pt populations with KRAS wt tumors. Adding cetuximab to CT significantly reduces the risk of disease progression and increases the chance of response in the 1st-line treatment of mCRC.

6078 POSTER

Cetuximab plus FOLFIRI in 1st-line treatment of metastatic colorectal cancer: Quality of life (QoL) analysis of patients (pts) with KRAS wild-type (wt) tumours in the CRYSTAL trial

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Background: The phase III CRYSTAL study previously showed that adding cetuximab to FOLFIRI as 1st-line treatment for mCRC significantly improves overall response rate and progression-free survival, and extends overall survival by nearly 4 months compared with FOLFIRI alone in pts with KRAS wt tumors. This analysis assessed the impact of treatment on QoL, a secondary endpoint in the CRYSTAL study, in pts with KRAS wt tumors.
Methods: Pts were randomized 1:1 to cetuximab qw (400 mg/m^2 initial dose then 250 mg/m^2/wk) + FOLFIRI q2w (irinotecan 180 mg/m^2, folinic acid 400 mg/m^2, 5-FU bolus 400 mg/m^2, 5-FU infusion 2400 mg/m^2 over 46 h) (n = 599) or FOLFIRI alone (n = 599). QoL was assessed with the EORTC QLQ-C30 (v3.0) questionnaire at baseline, every 8 weeks, and at final tumor assessment. The analysis focused on Global Health Status (GHS) and Social Functioning (SF) scales. A pattern-mixture model that included the drop-out pattern was employed. Analysis of QoL data was performed for the subset of pts with KRAS wt tumors (cetuximab + FOLFIRI, n = 161; FOLFIRI, n = 169).
Results: Pt populations were generally comparable in the two arms, except for fewer pts who had received prior adjuvant chemotherapy (19% vs 24%) and more females (46% vs 37%) in the FOLFIRI arm compared with the cetuximab + FOLFIRI arm. Questionnaire completion rates were similar in the two arms. There were no significant differences between treatment arms in the best and worst scores for the GHS and SF scales. Pts reported less nausea and vomiting in the cetuximab + FOLFIRI arm (p = 0.055), while dyspnoea (p = 0.046) and change from baseline score in physical functioning scale (p = 0.017) were better in the FOLFIRI arm. No between-group difference was observed in the time taken for a 20% decrease in QoL on the GHS (p = 0.46) or SF (p = 0.43) scales. Pattern-mixture analyses showed no significant differences between the two arms for changes from baseline on the GHS (p = 0.63) or SF (p = 0.81) scales. For both treatment arms, a decrease in SF score was seen at week 32 with a subsequent increase at later visits. The proportion of pts maintaining or improving their QoL was consistent across treatment arms over all timepoints.
Conclusions: The addition of cetuximab to chemotherapy did not affect outcomes on either the GHS or SF scales in pts with KRAS wt tumors, despite the skin reactions related to cetuximab treatment that might be expected to contribute to deterioration in social functioning.