being statistically significant. When toxicity of all grades was considered, hypertension occurred in 25% vs 17% (p = 0.06), hypomagnesemia 10% vs 32% (p < 0.001), infections 32% vs 28% (p = 0.36) and hypersensitivity reactions 11% vs 19% (p = 0.03). Grade 2 or higher proteinuria was observed in 5% vs 3% (p = 0.86). In arm B, the incidence of all grade and grade 3−4 acneiform skin reactions was 80% and 20%, and all grade and grade 3−4 nail changes 27% and 4%, respectively. These toxicities did not occur in arm A (p < 0.001). The overall 60-day all-cause mortality was 3% (10 pts), 5 pts in each arm. A total of 17 patients died within 30 days after the last administration of study drugs (8 arm A and 9 arm B), of which a drug-related cause was evident in 3 pts in arm A.
Conclusions: Toxicity was acceptable in both treatment arms. Except for skin toxicity due to cetuximab no difference in the incidence of other grade 3−4 toxicities was observed between the two treatment arms. Updated results will be presented at the meeting.

3001 ORAL

CRYSTAL, a randomized phase III trial of cetuximab plus FOLFIRI vs. FOLFIRI in first-line metastatic colorectal cancer (mCRC)

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Background: Cetuximab (Erbitux®), an IgG1 monoclonal antibody targeting the epidermal growth factor receptor (EGFR), is active in combination with irinotecan in previously-treated mCRC patients (pts). FOLFIRI is a standard first-line treatment for mCRC. The CRYSTAL trial investigated the effectiveness of cetuximab in combination with FOLFIRI as compared to FOLFIRI alone in first-line treatment of pts with EGFR-expressing mCRC.
Material and Methods: Pts were randomized 1:1 to Group A: cetuximab (400 mg/m^2 initial dose then 250 mg/m^2/week [w]) plus FOLFIRI q 2 w (irinotecan 180 mg/m^2, FA 400 mg/m^2, 5-FU bolus 400 mg/m^2, 5-FU infusion 2400 mg/m^2 over 46 hours) or Group B: FOLFIRI alone. The primary endpoint was progression-free survival (PFS). Secondary endpoints included: overall survival, response rate (RR), disease control rate and safety. PFS and RR were assessed by an Independent Review Committee. 633 events were required to statistically differentiate PFS between groups with 80% power.
Results: 1217 pts were randomized from August 2004 to October 2005: 608 to Group A and 609 to Group B. In the Intent to treat population: 60% were male, median age 61 [19−84], ECOG performance status <2 = 96.5%. The addition of cetuximab significantly prolonged progression free survival HR = 0.85, 95% CI [0.726, 0.998], p < 0.05). In a subgroup analysis of Group A pts, PFS was correlated to the grade of acne-like rash. RR was significantly increased by cetuximab (46.9% vs. 38.7%, p < 0.005). Significantly more pts underwent complete (R0) resection of metastases in Group A (4.3%) than in Group B (1.5%) p = 0.0034. Treatment was generally well tolerated with neutropenia (26.7% Group A, 23.3% Group B), diarrhea (15.2% and 10.5% respectively) and skin reactions (18.7% and 0.2% respectively) as the most common grade 3/4 adverse events.
Conclusions: Cetuximab in combination with FOLFIRI significantly prolongs PFS in previously untreated patients with mCRC, reducing the relative risk of progression by approximately 15%, and significantly increases response and resection rates. Treatment-related side effects of cetuximab in combination with FOLFIRI were as expected, with diarrhea moderately, and skin reactions significantly, more frequent as compared to FOLFIRI alone.

3002 ORAL

Comprehensive assessment of molecular markers predicting response to cetuximab therapy in colorectal cancer

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Background: In colorectal cancer, biological mechanisms underlying response or resistance to cetuximab, a monoclonal antibody against the extracellular domain of the Epidermal Growth Factor Receptor (EGFR) are not defined. Small retrospective studies suggested that EGFR increased gene copy number measured by fluorescence in situ hybridization (FISH) or presence of KRAS mutations were associated with cetuximab response or resistance, respectively. This study aimed to identify biological predictors for sensitivity/resistance to cetuximab treatment in colorectal cancer. We also compared biomarker results in primary tumors and corresponding metastases.
Methods: We analyzed EGFR (IHC, FISH), HER2 (FISH), and KRAS (mutation) in paraffin embedded tumor blocks from 85 colorectal cancer patients treated with cetuximab.
Results: EGFR FISH positive patients (48.2%), defined as ratio EGFR/nucleus $\geqslant$3, had a significantly higher RR (p = 0.007) and TTP (p = 0.056) than EGFR FISH negative (51.8%). EGFR expression assessed by IHC was no associated with any clinical end-point. HER2 amplification (4.9%) and high polysomy (14.6%) were not associated with response but were significantly associated with a shorter time to progression (p = 0.01) and survival (p = 0.03). KRAS mutation carriers (39.5%) had a significantly lower response rate (p = 0.02) and shorter time to progression (p = 0.07) compared to patients with wild type KRAS. Combination of EGFR FISH and KRAS identified the group of patients deriving respectively the highest response rate (40.0%: EGFR FISH+/KRAS wild type) and the lowest response rate (0%: EGFR FISH-/KRAS mutated) from the treatment.
In 22 patients with available primary and metastatic tumor tissue, there was no difference between these sites for EGFR FISH, HER2 FISH and KRAS results.
Conclusions: Combination of EGFR FISH and KRAS mutation should improve the detection of responder and refractory patients candidate for cetuximab therapy. HER2 genomic gain predicts early escape from cetuximab therapy. Prospective validation of these results is warranted.

3003 ORAL

Cetuximab plus irinotecan in patients (pts) with metastatic colorectal cancer (mCRC) failing prior oxaliplatin-based therapy: the EPIC trial

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Background: Cetuximab, an IgG1 MAb targeting the EGFR, is active in irinotecan-refractory mCRC in combination with irinotecan. The multinational, randomized, phase III trial, EPIC, was designed to demonstrate the impact of cetuximab on survival in pts with EGFR-expressing mCRC failing prior oxaliplatin and fluoropyrimidine therapy. The primary objective was overall survival (OS). Secondary objectives included progression-free survival (PFS), overall response rate (RR), safety and quality of life (QoL).
Methods: Pts with ECOG PS $\leqslant$ 2, were randomized to Arm A (cetuximab 400 mg/m^2 initial dose, then 250 mg/m^2 weekly and irinotecan 350 mg/m^{2}q 3 weeks) or Arm B (irinotecan 350 mg/m^2 q 3 weeks). Health Related Quality of Life (HRQoL) was assessed using the EORTC QLQ-C30 questionnaire.
Results: 1298 pts were randomized (648 to Arm A and 650 to Arm B): 62.9% pts male, median age 62 years, and 94% had an ECOG PS of 0−1. Efficacy (OS, PFS, RR) is shown in the table. 47% pts in Arm B received post-study cetuximab (87% of these in combination with irinotecan). Median OS in Arm A was found to be correlated to the presence of acne-like rash: gr 0: 5.8 mo, gr 1/2: 11.7 mo, gr 3/4: 15.6 mo. The most common grade 3/4 adverse events (AEs) were neutropenia (31.8% Arm A, 25.4% Arm B) and

diarrhea (28.4% Arm A, 15.7% Arm B); acneiform rash was significantly more common in Arm A (8.0% vs 0.2%). Baseline HRQoL scores for social functioning, fatigue, dyspnea, and appetite loss, showed significant differences in favor of Arm A. Pts in Arm A had significantly improved Global Health Status ($p = 0.047$), and 10/15 HRQoL scales, including pain ($p = 0.006$), nausea/vomiting ($p < 0.001$), insomnia ($p < 0.001$), and physical ($p = 0.023$) and cognitive functioning ($p = 0.008$).
Conclusions: Cetuximab plus irinotecan in mCRC pts who failed on oxaliplatin resulted in a significantly longer PFS, higher RR and improved QoL than irinotecan alone. The observed safety profile was as anticipated. Overall survival was similar between the two arms but this may result from the substantial post-study use of cetuximab.

Efficacy results[a]

	Arm A (cetuximab + irinotecan) (N = 648)	Arm B (irinotecan alone) (N = 650)	p	HR	OR
OS, mo [95% CI]	10.7 [9.6, 11.3]	10.0 [9.1, 11.3]	0.712	0.975	
PFS, mo [95% CI]	4.0 [3.2, 4.1]	2.6 [2.1, 2.7]		0.692	
RR, % [95% CI]	16.4 [13.6, 19.4]	4.2 [2.8, 6.0]			4.460

[a]HR, hazard ratio; OR, odds ratio.

3004 ORAL

Cetuximab plus 5-FU/FA/oxaliplatin (FOLFOX-4) in the first-line treatment of metastastic colorectal cancer (mCRC): a large-scale phase II study, OPUS

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Background: FOLFOX-4 is a standard first-line treatment for patients (pts) with mCRC. The IgG1 monoclonal antibody cetuximab (Erbitux®) has proven activity in combination with cytotoxic chemotherapy. Excellent response rates (RRs) have been reported with first-line cetuximab plus FOLFOX-4. This randomized, controlled study compared the RRs of FOLFOX-4 +/− cetuximab first-line in mCRC.
Methods: Pts with previously untreated, epidermal growth factor receptor (EGFR)-expressing mCRC, which was not resectable with curative intent, were eligible for entry in to the study. Randomization was 1:1; pts stratified by ECOG performance status (PS) (0−1 vs 2), to either Group A (cetuximab 400 mg/m^2 initial dose, then 250 mg/m^2/week plus FOLFOX-4 every 2 weeks [oxaliplatin 85 mg/m^2 day 1; FA 200 mg/m^2 day 1 and day 2; 5-FU 400 mg/m^2 bolus + 600 mg/m^2 infusion over 22 hours, day 1 and day 2]) or Group B (FOLFOX-4 only). The primary endpoint was best overall confirmed response as assessed by independent review. Secondary variables were progression-free survival time (PFS), overall survival time (OS), status of resection for subsequent metastatic surgery with curative intent, and safety.
Results: Between July 2005 and March 2006, 337 pts were randomized and treated in >70 centers in Europe. 181 (53.7%) pts were male; median age of all pts was 61.0 years [24–82]; 305 (90.5%) pts had an ECOG PS of 0 or 1 at the time of randomization, and 32 (9.5%) of 2. The best overall confirmed RR was 45.6% in Group A and 35.7% in Group B. The RR for pts with ECOG PS 0−1 was 49.0% in Group A and 36.8% in Group B (Odds Ratio 1.648, 95% CI [1.043−2.604]). OS data are not yet available. The most common reported grade 3/4 adverse event (AE) was neutropenia, experienced by 31.5% pts in Group B and 27.6% pts in Group A. The other most common grade 3/4 AEs were diarrhea (7.1% Group A, 6.0% Group B), leucopenia (7.1% Group A, 5.4% Group B) and rash (9.4%, Group A only).
Conclusions: RRs achieved with the addition of cetuximab to FOLFOX-4 in the first-line treatment of mCRC were higher than those achieved with FOLFOX-4 alone (45.6% in Group A vs 35.7% in Group B). For the ECOG 0−1 group, the RR was significantly higher in cetuximab arm. Of the grade 3/4 AEs reported, only skin rash was significantly more frequent in the cetuximab arm. PFS results will be available at the meeting.

3005 ORAL

Can we predict the nodal status in primary rectal cancer accurately with USPIO MRI?

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Background: Rectal cancer is notorious for its local recurrence. An important risk factor is nodal disease. So far this cannot be accurately predicted with non-invasive imaging. The purpose of this prospective study was to determine the accuracy of Ultrasmall Superparamagnetic Iron Oxide (USPIO) MRI for predicting of the nodal status in rectal cancer patients.
Material and Methods: From February 2003 to July 2007 53 patients with primary rectal cancer underwent 1.5-T high-resolution MRI 24 hr. after administration of USPIO (Sinerem®) contrast agent. Sequences used were axial 2DT2WFSE, 3DT1WGRE & 3DT2*. All patients were treated with Total Mesorectal Excision (TME) surgery, after pre-operative radiotherapy (5×5 Gy). A MR radiologist recorded the amount, localization and signal-intensity of (extra)mesorectal lymph nodes, depicted by MR images. Lesion by lesion analysis was performed with histology as the reference standard.
Results: In 53 patients MR Imaging depicted 531 lymph nodes, which could be recovered in the TME-specimen. Thirty-three patients were predicted as node-positive due to the MRI results. After histopathologic evaluation 21 of these 33 patients were staged as node-positive. The patient-based sensitivity, specificity, PPV and NPV were 100%, 63%, 64% and 100%, respectively. The lesion by lesion analysis results in sensitivity, specificity, PPV and NPV were 97%, 94%, 66% and 99%, respectively.
Striking finding is the high NPV, suggesting that N0 patients can be identified accurately.
Conclusion: This prospective study suggests that USPIO-MRI is highly accurate in identifying N0 patients, stratifying rectal cancer into different risks, allowing individual tailored treatment according to risks.

3006 ORAL

Preoperative evaluation with virtual colonoscopy (VC) in colorectal cancer (CRC) patients candidates to laparoscopic colon resection (LCR)

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Background: Aim of our study was the preoperative evaluation with virtual colonoscopy in patients affected by colorectal cancer, candidates to laparoscopic colectomy.
Patients and Methods: We prospectively evaluated with virtula colonoscopy 55 patients affected by CRC, candidates to laparoscopic resection. We compared virtual colonoscopy data with surgical specimens and follow up data. 45 patients had a prior conventional colonoscopy diagnosis of colorectal cancer. 40 patients had incomplete colonoscopy caused by stenosing lesions. All studies were conducted with 16 slices MSCT after colonic cathartic cleansing and colonic gas distension. We evaluated the presence and site of the lesions, metastases, colon synchronous lesions and polyps.
Results: Virtual colonoscopy detected the presence and site of the lesions in all cases, with an accuracy of 100%; Colonoscopy, incorrectly diagnosed the neoplasm site in 8 patients (18%). In our study Virtual colonoscopy allowed complete evaluation of the colon in 87.2% (n = 48) of the patients with stenosing lesions, versus 15% of Colonoscopy. Synchronous polyps were detected in 13 of these patients (27%), and 1 patient had 3 synchronous lesions. All patients were initially scheduled for laparoscopic surgery. In 16 pts (29%) Virtual colonoscopy data caused changes in therapeutic approach that lead to a more extensive laparoscopic resection in 2 cases (4%), to laparotomic resection in 8 patients (14%), to neoadjuvant therapy in 6 patient (11%).
Conclusionis: Virtual colonoscopy contributes greatly to the treatment planning in patients with Colorectal cancer, especially in those with incomplete endoscopy. We think that Virtual colonoscopy should be the first choice diagnostic modality in the preoperative evaluation of patients affected by stenosing colorectal cancer.