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