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Efficacy and safety findings from a phase II study of capecitabine (X) as first-line therapy in Japanese patients (pts) with metastatic colorectal cancer (MCRC): comparison with published Western data

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Background: The 3-weekly regimen of X (1250 mg/m^2 bid, d1–14, q3w) has demonstrated superior activity and improved safety over bolus 5-FU/LV (Mayo Clinic regimen) as first-line therapy in 2 large randomised phase III trials. We conducted a phase II study to investigate the efficacy and safety of the 3-weekly X regimen in Japanese pts with MCRC and compared our findings with the published pooled efficacy and safety results from the Western phase III trials [Van Cutsem et al. 2004; Cassidy et al. 2002].
Methods: Eligibility criteria were aligned with the randomised phase III studies. Pts received X 1250 mg/m^2 bid on d1–14, q3w. Overall response rate (ORR) and time to progression (TTP) were assessed according to WHO criteria. The most common adverse events (diarrhoea, hand–foot syndrome [HFS], stomatitis, appetite decreased, nausea, hyperpigmentation, vomiting, GOT increased, hyperbilirubinaemia and increased lymphocyte count) were compared across the studies.
Results: 60 chemo-naïve pts were enrolled in the Japanese study. In terms of baseline characteristics, there were minor differences in performance status, cancer type, no. of metastatic sites and previous radiation therapy in the Japanese and phase III studies. The ORR was 32% (95% CI, 20–45%) in the Japanese study compared with 26% (95% CI, 22–30%) in the Western studies. There was no significant difference in median TTP (5.4 months vs. 4.6 months). The following related adverse events (all-grades) occurred more frequently in the Japanese study: HFS (73% vs. 53%), stomatitis (35% vs. 24%), decreased appetite (33% vs. 17%), hyperpigmentation (38% vs. 2%), and hyperbilirubinaemia (67% vs. 48%). However, the rate of diarrhoea was lower (35% vs. 48%), and nausea (35% vs. 38%) and vomiting (15% vs. 23%) were similar. The rate of grade 3/4 related events in the Japanese and Western studies were: HFS (13% vs. 17%), diarrhoea (2% vs. 13%) and hyperbilirubinaemia (33% vs. 23%).
Conclusions: Efficacy and safety data from the Japanese phase II study are similar to published Western data. These findings suggest that the 3-weekly regimen of X is highly effective and well tolerated for Japanese and Western pts with MCRC.

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Cutaneous and non-cutaneous toxicity induced by biologic therapy with cetuximab (erbitux)

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Background: Therapy with monoclonal antibody anti-EGFR (cetuximab) represents an important progress in scenery of medic therapy in advanced colorectal cancer patients. Tolerability and, in particular, cutaneous and non-cutaneous toxicity pattern induced by this new biologic therapy is non yet clearly known. Aim of this study was to analyze and describe cutaneous and non-cutaneous toxicities in a group of advanced colorectal cancer patients treated with cetuximab.
Materials and methods: 44 consecutive metastatic colorectal cancer patients (rectum/colon: 12/32), M/F: 16/28, median age 61 years (27–79), have been treated with cetuximab in monotherapy (5 patients) or combined with irinotecan (39 patients). A total of 762 courses have been administered, with a median of 16 courses for every patient and a range of 3–48 courses.
Results: Cutaneous toxicity: more frequent seats: only face (50%); only trunk (18.2%); face + trunk (27.2%); only limbs (11.4%). Type and grade of cutaneous toxicity are shown in table 1.
Non-cutaneous toxicity: type and grade of non-cutaneous toxicity are shown in table 2:
Conclusions: Toxicity pattern induced by cetuximab is various in terms of type, organ involved and events' severity. In our experience we have registered different types of cutaneous toxicities, generally spontaneously reversible after temporary interruption of therapy. Finally, for the first time in literature, we have reported a characteristic ophthalmic toxicity (blepharitis) caused by cetuximab.

Table 1

Cutaneous toxicity	All grades (%)	Grade 3–4 (%)
Every grade	90.9%	34.1%
Folliculitis	84.9%	27.2%
Erythema	88.6%	22.7%
Peri-ungual toxicity	45.5%	15.9%
Blepharitis	27.2%	18.2%

Table 2

Other toxicities	All grades (%)	Grade 3–4 (%)
Diarrhea	68.2%	27.2%
Stomatitis	59.1%	6.8%
Emesis	54.5%	0%
Hypotension	13.6%	0%
Allergic reactions	0%	0%
Fever	31.8%	0%
Fatigue	27.2%	9.1%

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Phase I/II trial of capecitabine and gefitinib in patients with advanced colorectal cancer after failure of first-line therapy

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Background: Capecitabine is active in advanced colorectal cancer (ACC) and appears to have synergistic activity with gefitinib (IRESSA) *in vitro* (Magne et al, Clin Cancer Res 2003;9:4735–42). The study aimed to evaluate the safety and efficacy of gefitinib in combination with capecitabine in patients (pts) with ACC.
Methods: A multicenter Phase I/II trial (1839/0505) recruited pts aged *18 years with WHO performance status (PS) $\leqslant$2, adequate organ function, and measurable disease. The Phase I study combined gefitinib 250 mg/day with 2 escalating capecitabine doses (1000 and 1250 mg/m^2 twice daily on Days 1–14 of a 21-day cycle). The recommended dose of capecitabine (based on the safety and tolerability results from the Phase I study) was then evaluated in combination with gefitinib in a Phase II trial. Tumor status was assessed every 9 weeks using RECIST. Adverse events were assessed by NCI-CTC (V3).
Results: 10 pts have been enrolled in the Phase I study at doses of 250/1000 (n = 6) and 250/1250 (n = 4): median age, 62 years (range 47–71); male/female, 9/1; PS 0/*1, 7/3; median chemotherapy cycles, 6. The most common adverse drug reactions (NCI-CTC) during the first 2 treatment cycles were: diarrhea (Grade [G] 1, n = 5; G2, n = 1 for 3 weeks [dose-limiting toxicity]), asthenia (G1, n = 2; G2, n = 3), rash (G1, n = 5; G2, n = 1), elevated transaminases (G1, n = 1; G3, n = 1), anemia (G1, n = 3) and leukopenia (G1, n = 1). Two treatment interruptions were required, without associated dose reduction.
Based on these data, a dosage of 250/1250 was carried into the Phase II study, into which 22 pts have been enrolled: median age, 66 years (range 53–81); male/female, 16/6; PS 0/1/2, 11/11/0. The no. of metastatic locations were: 1 site, n = 5 (23%); 2–3 sites, n = 4 (18%); >3 sites, n = 13 (60%). The most frequent metastatic locations were: liver, n = 48 (52%); lung, n = 32 (34%); lymph nodes, n = 7 (7.5%). Twelve pts were evaluable for efficacy: 6 had stable disease and 6 had progressive disease. All pts were evaluable for toxicity. CTC 3–4 Grade AEs were: diarrhea (n = 5, 23%); asthenia (n = 2, 9%); mucositis (n = 1, 5%); febrile neutropenia (n = 1); dysphagia (n = 1); gastrointestinal disorder (n = 1) and dry skin (n = 1).