of a subgroup of colorectal cancer patients with liver metastases only, who were enrolled in the randomized CApecitabine, IRinotecan, Oxaliplatin (CAIRO) phase III study between January 2003 and December 2004.
Results: Ninety-nine patients were treated with IHP, and 111 patients were included in the control group. All patient characteristics were comparable except for age. Median follow up was 78.1 months for IHP versus 54.7 months in the control group. Median overall survival was 25.0 (95% CI 19.4−30.6) months for IHP and 21.7 (95% CI 19.6−23.8) months for systemic treatment (P = 0.29). Overall survival was not influenced by gender, age, LDH, location of primary tumor, timing of liver metastases and adjuvant treatment of the primary tumor and was only influenced by metastasectomy after study treatment (P < 0.001). However, the number of patients in whom metastasectomy was performed did not differ significantly between the two groups. Treatment-related mortality was 2% for the systemic treatment and 6% for IHP (P = 0.11).
Conclusion: Compared to a patient group with comparable characteristics treated with systemic chemotherapy, IHP does not provide a benefit in overall survival in patients with isolated non-resectable colorectal liver metastases. Currently the use of IHP cannot be advocated outside the scope of clinical study protocols.

6055 POSTER

A randomized phase II study of Xeloda with or without oxaliplatin as a first-line treatment in the elderly patients with metastatic colorectal cancer: Korean Cancer Study Group

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Background: More than half of colorectal cancer (CRC) patients (pt) are >70 years old in the western countries and the incidence of CRC in this age group is also increasing. Optimal chemotherapy, however, are not well defined in elderly pts yet. We investigated Xeloda (X) alone and Xeloda plus oxaliplatin (XELOX) as a 1st-line treatment for elderly mCRC pts.
Methods: This is a randomized, open-label, multicenter phase II study. Pts with previously untreated mCRC were randomized stratifying by age, performance status and center; X group (X 2500 mg/m^2/d on D1−14 q 3 wks) and XELOX group (X 2000 mg/m^2/d on D1−14, O 100 mg/m^2/d in 1st cycle only and escalated to 130 mg/m^2/d on D1 in further cycles q 3 wks). Main eligibility criteria were histologically proven adenocarcinoma; measurable lesion; age ⩾70 (PS 0−2) or ⩾65 (PS 2) yr; no prior chemotherapy. Primary endpoint was to investigate response rate (RR) and secondary endpoints were to evaluate toxicity, progression-free survival (PFS), overall survival and quality of life (QoL). QoL was assessed by EORTC QLQ-C30 questionnaire.

	X	XELOX
Confirmed RR	22.5%	32.5%
PFS	5.6 mo	6.0 mo
Toxicity (grade ⩾2)		
Neutropenia	11%	45%
Thrombocytopenia	8%	48%
Diarrhea	5%	20%
Stomatitis	13%	10%
HFS	29%	23%
Sensory neuropathy	8%	3%

Results: Between May 2006 and Apr 2008, 80 pts (X: 40 vs XELOX: 40) were enrolled. Baseline characteristics were balanced between each arm; median age 71 (66−81) vs 72 yo (65−79); M/F 23/17 vs 22/18; PS 0/1/2 12/18/10 vs 9/19/12. The confirmed RR were 22.5% and 32.5% (HR 0.603 [0.22−1.63]) and PFS were 5.6 mo and 6.0 mo (HR 0.762 [0.46−1.26]) in X and XELOX group, respectively. Oxaliplatin dose was escalated to 130 mg/m^2 in 77.5% of pts (31/40) from their 2nd cycle in the XELOX arm. Higher incidences of hematologic toxicities were observed in XELOX group, but significant toxicities were not different except G2−3 diarrhea. Global health status, 5 functional and 4 symptom scales of QoL were deteriorated in XELOX arm.
Conclusions: Combination chemotherapy of reduced dose of XELOX could be a preferable option for elderly patients in terms of efficacy and tolerable toxicity profiles. However, further studies are needed to define optimal dosage and schedule to improve QoL of reduced dose of XELOX regimen in this population.

6056 POSTER

Changing monoclonal antibody keeping unaltered the chemotherapy regimen in metastatic colorectal cancer (mCRC) patients (pts): is efficacy mantained?

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Background: Bevacizumab (B) and Cetuximab (C) both improve overall survival (OS), progression free survival (PFS) and overall response rate (ORR) when combined with irinotecan-containing regimens. The optimal sequence of these monoclonal antibodies in combination with chemotherapy (CT) is controversial. In this study we analysed the efficacy of C associated with irinotecan-based CT (FOLFIRI) after progression with the same regimen plus B in pts with mCRC.
Materials and Methods: Eligibility criteria: progression disease (PD) after chemotherapy with Folfiri-B (FB)->B; ECOG PS 0−1. Primary endpoints: ORR and disease control rate (DCR:ORR plus stable disease >6 months); secondary endpoints: PFS, duration of response, OS and toxicity. ORR and DCR were reported with their confidence interval at 95%, Kaplan-Meier method was used for PFS/OS evaluation.
Results: 41 pts were enrolled to receive Folfiri-C (FC)->C after progression to FB->B. Median age was 67 (44−80), M/F 25/16, ECOG PS 0/1 was 14/27, WT Kras 37 (90%). Median cycles of first line FB->B was 12 (range 4−16)/8 (range 1−23) and median cycles of second line FC->C was 7 (range 1−12)/6 (range 2−12). The ORR was 22% (CI 95% 9.3−34.6), DCR was 36.6% (CI 95% 21.-51.3); 43.8% of pts responders to FB->B obtained a new response to FC->C and 10% of non responders obtained a response. Median duration of response was 4 months (range 1−8) and clinical benefit 6 months (CI 95% 2−13). PFS and OS are shown in table.

Endpoints	6 months (%)	12 months (%)	24 months (%)	Median (CI 95%)
PFS	47.9	19.5	–	6 (3−9)
OS	91.4	54.1	21.2	13 (6−20)

Acne-like rash occurred in 68.3% of pts (34.1% grade⩾2). No grade 4 toxicity was observed.
Conclusions: Efficacy in response and survival is maintained in pts with mCRC treated with the same chemotherapy regimen changing monoclonal antibodies. Data collection is ongoing, and update results will be presented.

6057 POSTER

The final results; bevacizumab (BV) safety post marketing large cohort survey (PMS) in 2712 japanese colorectal cancer patients (PTS)

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Background: BV was approved in Japan in Apr. 2007 with indication for advanced colorectal cancer (CRC). Due to rather limited clinical data on Japanese patients, the Japanese regulatory authorities required Chugai to design a company-initiated PMS on all pts treated with BV as a post-approval commitment in order to evaluate the incidence of adverse drug reactions (ADRs). This study represents a large-scale, well managed, first safety cohort data available in Asian markets as of today.
Objectives: To assess the use of BV in clinical practice and to evaluate ADR incidence in the post-marketing setting.
Material and Methods: All pts treated with BV were registered before initial administration since market launch of BV in Japan in June 2007. The follow-up period was 6 months.
Results: 2712 pts were registered from 574 institutions between Jun. and Nov. 2007. 2696 pts were eligible for analysis. Pts characteristics were colon/rectum/colon and rectum cancer: 1577/1105/14; M/F: 1632/1064; median age: 61 (15−86); ECOG P.S. 0/1/2/3: 2191/474/29/2; combination chemotherapy regimen with BV [FOLFOX/FOLFIRI/5-FU LV/Other (IFL etc.)]: 1711/779/142/64. Of 2696 pts, ADRs were reported in 1668 pts (61.9%) and serious ADRs in 412 pts (15.3%).

Table 1

	Japanese PMS (n = 2696)	First-BEAT (n = 1295)
Hypertension	0.4%	0.5%
Hemorrhage	1.3%	0.8%
Proteinuria	0.1%	–
GI perforation	0.9%	0.7%
Thromboembolism		
Arterial	0.3%	0.6%
Venous	1.3%	1.0%
Wound healing complications	0.4%	0.3%

Onset status by patient background was investigated; however, no new safety signals were detected.
Conclusion: There has been no other large scale, well managed post-marketing safety monitoring data available in Asian countries to date with angiogenesis inhibitor BV for CRC indication. No new ADRs were observed, and no new safety signals were detected, either. Reported number of events was in line with previous clinical experience of First-BEAT international observational study. The data from this surveillance suggest that Avastin is a generally well-tolerated treatment option in Japanese patients.

6058 POSTER

Phase I/II study of weekly intermittent capecitabine with bevacizumab and oxaliplatin on an every-2-week schedule for patients with untreated advanced colorectal cancer (CRC) final results

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Background: Capecitabine and Oxaliplatin (CapOx) with bevacizumab (Bev) is a standard regimen for advanced CRC utilizing Cap on a d 1−14 schedule every 3 wks. Intermittent wkly Cap (3,500 mg/m^2, d 1−7) with Ox (85 mg/m^2) every 2 wks may have advantages compared to the standard CapOx regimen in untreated advanced CRC with superior response and progression free survival (PFS) in a European study (JCO 21, 1307; 2003).
Material and Methods: This phase I/II trial was designed to evaluate weekly intermittent Cap with Ox/Bev in US pts with CRC. The primary endpoint was to detect a 50% improvement in median PFS from 8 to 12 months. Study required 40 patients, with 81% power (1-sided level 0.1 log-rank test). Cap was initially administered at the dose of 2500 mg/m^2 in two divided doses on d 1−7 (n = 11) and was increased to 3000 mg/m^2 dose (n = 29), based on tolerability of the lower dose. The dose of Ox was 85 mg/m^2 and Bev 5 mg/kg. Cycles were repeated every 2 wks. Preliminary results was reported previously (A4061, ASCO 2008).
Results: Patient characteristics: Total accrued 40, with 39 evaluable. Male (n = 25, 40%); ECOG performance status 0 (n = 24), 1 (n = 14); median age 62 (range 38−80 years). Median cycles administered 8 (range 1−25). Dose reduction was required in 21 pts (54%). Pertinent Grade 3/4 toxicities were: Hand Foot syndrome in 10%, diarrhea 18% and peripheral neuropathy in 10% of pts. Bowel perforation in 1 pt (3%) and one death due to a cerebral hemorrhage (3%). Response rate was 36% with one complete response. Downstaging of disease permitted subsequent metastectomy in 10 pts (28%) with R0 resections in 6 pts. PFS is 8.7 mo (5.8−10.7 mo, 95% CI). Median Overall survival is 17 mo. (10.4−24.2 mo, 95% CI). Four of 6 pts with R0 resections are alive with follow up of 12.4 to 42.4 mo.
Conclusions: The first US experience of this regimen shows it to be well tolerated, and Cap (3000 mg/m^2, d 1−7) in combination with Ox and Bev therapy every 2 wks can be safely administered. The incidence of subsequent metastectomy, a marker of activity, is encouraging, and there were no significant surgical complications. The PFS of 8.7 mo is in the range of recently reported studies of CapOX/Bev. (NO16966 study, JCO 12; 2013–2019; 2008.). A phase III trial (n = 430) of this regimen compared to the standard CapOx/Bev regimen has completed accrual in the US.
Study supported by Genentech and Roche Pharmaceuticals, USA.

6059 POSTER

Comorbidities in patients with metastatic colorectal cancer (mCRC)

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Background: Patients with mCRC often have other medical ailments. These comorbidities may impact treatment decisions, prognoses, and quality of care. This study was conducted to describe the prevalence of comorbidities in the newly diagnosed mCRC population.
Material and Methods: This was a retrospective cohort study using a large claims database from a US national, commercially-insured population. Patients aged ⩾18 with newly diagnosed mCRC between 1/2004 and 6/2008 were selected using the ICD-9 diagnosis codes (CRC: 153.x [excluding 153.5], 154.0, 154.1, 154.8; distant metastasis: 196.0, 196.1, 196.3, 196.5, 197.x (excluding 197.5), 198, 199.0). The index date was defined as the date of the initial mCRC diagnosis. One-year continuous medical and drug benefit coverage prior to the index date was required for the selected cohort. Medical diagnoses and medication treatments were examined. All comorbidities were estimated during 1 year prior to the index date except for traumatic conditions (e.g., major surgery, bone fracture and open wound) which were assessed for 30 days prior to the index date.
Results: Based on the selection criteria, 12,648 patients were included with mean (±standard deviation) age of 66.3 (±13.0) years, 54% male, and 70% with colon primary. Distribution of metastases included liver (40%), lung (14%), bone (6%), and brain (3%). The most prevalent comorbidity was cardiovascular disease (CVD) (62% of patients) including hypertension (41%), coronary artery disease (17%), congestive heart failure (7%), dysrhythmias (14%), arterial thromboembolism including ischemic heart disease (18.6%), and venous thromboembolism (6%). Over 10% of patients had a major surgery, bone fracture, or open wound 30 days prior to mCRC diagnosis; 31% had a history of bleeding; and nearly 12% of patients were treated with anticoagulant and 6% with antiplatelet agents. Additionally, 19% of patients had diabetes, 8% had renal failure or insufficiency, and 5% had skin disorders. Fifty-two percent of patients ⩾65 years old had a significantly higher CVD prevalence (73%; $p < 0.001$).
Conclusions: Comorbid medical conditions are common in patients with mCRC. CVD is the most prevalent comorbidity and affects approximately 3/4 of patients over age 65. It is important to assess comorbidities in all patients with mCRC since their presence may impact treatment decision making.

6060 POSTER

KRAS and BRAF mutational analyses in a phase II trial of first-line FOLFOXIRI plus bevacizumab (BV) in metastatic colorectal cancer (mCRC) patients (pts)

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Introduction: *KRAS* codon 12 and 13 mutations have recently acquired a strategic importance for the therapeutic algorithm of mCRC pts, since their presence determines resistance to anti-EGFR antibodies. *BRAF* V600E mutation seems to play a similar role. Moreover, a negative prognostic effect of *KRAS* and *BRAF* mutations has been observed in mCRC pts receiving first-line chemotherapy +/− biologics. On the other hand, benefit from BV seems independent from *BRAF*/*KRAS* alterations.
Materials and Methods: Fifty-seven previously untreated mCRC pts were enrolled in a multicenter phase II single-arm study of FOLFOXIRI+BV. DNA was extracted from formalin-fixed paraffin-embedded samples of primary tumour after microdissection. Mutational analyses of *KRAS* codons 12−13 and *BRAF* codon 600 were conducted by means of PCR and direct sequencing.
Results: Analyses were successfully performed in 54 cases. *KRAS* and *BRAF* were mutated (mut) in 21 (39%) and 10 (18.5%) cases, respectively. One sample beared both *KRAS* and *BRAF* mutations. Examined mutations were not associated with response (RR: 27/33, 82% in *KRAS* wild-type (wt) pts vs 15/21, 71% in *KRAS* mut, p = 0.371; 33/44, 75% in *BRAF* wt pts vs 9/10, 90% in *BRAF* mut, p = 0.426). *KRAS* mutated pts had a PFS similar to that obtained by *KRAS* wt pts, (median PFS 13.1 vs 12.2 months; HR = 1.27, p = 0.474). Similar results were obtained for *BRAF*. Combined analysis showed that *KRAS* and/or *BRAF* mut pts had a PFS comparable to that of wt pts (13.1 vs 12.0 months; HR = 1.26, p = 0.456). OS data are still immature.
Conclusions: The outcome of mCRC pts treated with first-line FOLFOXIRI+BV does not differ on the basis of *KRAS* and/or *BRAF* status. Therefore it could be suggested that the triplet combination may counterbalance the negative prognostic impact of such mutations. These preliminary data need confirmation in larger prospective studies.