Methods: Hazard Ratios (HR) with 95% Confidence Intervals (CI) were extracted from prospective, randomized clinical trials (RCTs, either phase II/III) for primary end-points. The log of event-based relative risk ratio (RR) with 95% CI were derived for secondary endpoints through a random-effect model. Primary outcomes were both Progression Free Survival (PFS), and Overall Survival (OS). Secondary end-points were: 1) objective response rate (ORR), 2) partial response rate (PR), 3) grade 3−4 hypertension (HTN) rate, 4) grade 3−4 bleeding rate, and 5) grade 3−4 proteinuria rate. Absolute differences (AD) and the number of patients needed to treat/harm (NNT/NNH) were calculated. Heterogeneity test and a meta-regression analysis with clinical predictors for outcomes were conducted as well. A sensitivity analysis according to the trial phase-design was accomplished. Calculations were accomplished using the SPSS and the CMA v 2.0 software.
Results: Five trials (2,728 pts), 2 phase II (313 pts) and 3 phase III (2,415 pts), were selected.

End-points		Pts (RCTs)	HR/RR 95% CI)	p-value	Het. (p)	AD (%)	NNT/NNH
Primary	PFS	2,624 (4)	0.62 (0.48, 0.69)	*<0.0001*	*0.001*	17.1	6
	OS	2,624 (4)	0.78 (0.66, 0.94)	*0.007*	*0.14*	8.6	12
Secondary	ORR	2,728 (5)	1.16 (0.97, 1.38)	*0.085*	*0.034*	–	–
	PR	1,336 (4)	1.24 (1.06, 1.46)	*0.006*	*0.19*	6.5	15
	HTN	2,728 (5)	4.87 (3.12, 7.61)	*<0.0001*	*0.93*	6.2	16
	Bleeding	2,570 (4)	1.72 (0.96, 3.07)	*0.07*	*0.52*	–	–
	Proteinuria	2,570 (4)	2.10 (0.64, 6.84)	*0.21*	*0.56*	–	–

The benefit in primary outcomes was obtained regardless of the study setting (interaction test: $p = 0.057$ and $p = 0.93$, respectively) between phase II and phase III pooled results. According to the meta-regression analysis, female gender and rectal primary site were significant predictors for PFS benefit ($p = 0.003$, $p = 0.005$).
Conclusions: Notwithstanding all the implications related to costs and the significant HTN risk, the significant outcome improvement provided by BEVA in first-line treatment of unselected MCRC patients, should be considered when choosing the appropriate up-front therapy. Nevertheless, a targeted-based approach would be pursuit as well in order to maximize the efficacy of treatment.

6052 POSTER

Capecitabine single agent or in combination in the routine first-line treatment of a predominantly elderly population with metastatic colorectal cancer (MCRC)

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Background: Most controlled trials on new treatments suffer from a lack of representativity of patients (pts), especially in solid tumor diseases typically prevalent in the senium. The purpose of this ongoing non-interventional observation study is to obtain data on usage, efficacy and safety of capecitabine (Cape) (Xeloda®) in a large unselected patient cohort with specific focus on elderly pts.
Material and Methods: Between February 2005 and February 2009 data on 461 pts with MCRC were recorded in detail on standardized forms until detection of disease progression or up to a maximum of 12 cycles, followed by an additional long-term survey for survival.
Results: The cohort showed a high median age of 73 years (y), with 26% ⩽65 y (stratum A), 34% 66−75 y (B), 36% 76−85 y (C), and 4% >85 y (D). 57% were male, with ECOG performance status 0/1/⩾2 in 23%/50%/27%. 66% suffered from liver and 28% from lung metastases. 34% had previously received adjuvant chemotherapy. The median duration of cape treatment was 5.3 months (mo), with only a slight decrease from 5.6 to 4.7 across the age groups. Half of the pts received cape monotherapy, with a strongly increasing trend by age (A: 29%, B: 51%, C: 61%, D: 70%, $p < 0.0001$). 2-/3-drug combinations were applied in 37%/13%, XELOX in 26%, XELIRI in 6%, bevacizumab was used in 13% and cetuximab in 3% of pts. The median of the overall average daily cape dose per patient was 1803 mg/m^2 and rather constant until the age of 75 y, but lower in older pts. It amounted to 1656 and 1980 mg/m^2 in the groups with or without a concurrent second cytostatic drug, respectively. Dose adaptations were performed in 22%/41% of cycles/pts. Overall best response in an intent-to-treat approach was 8% CR and 33% PR, adding to an overall response rate of 40%, considerably declining with age (A: 51%, B: 41%, C: 34%, D: 25%, $p = 0.0015$), probably at least in part due to the decreasing treatment intensity. Hematoxicity grade 3/4 was observed in less than 10% of pts. Hand-foot skin reaction (HFS) was reported in almost half of the pts, but grade 3 HFS was observed in only 3%. Diarrhea was the predominant gastrointestinal toxicity (grade 2/3/4 in 12%/4%/0%).
Conclusions: Capecitabine, administered either as single agent or part of a combination treatment, proved to be safe and effective in the routine practice of colorectal cancer treatment. Obviously, the oral treatment is a preferred option in elderly patients and/or those unfit for combined cytotoxic treatment.

6053 POSTER

Phase II study of capecitabine, irinotecan (CAPIRI) plus bevacizumab in chemotherapy naive stage IV colorectal cancer, results in 120 patients

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Background: Bevacizumab is an active monoclonal antibody when combined with chemotherapy (Hurwitz. N Engl J Med 2004). Bolus 5FU can be substituted by an infusion increasing the tolerance and probably the efficacy (FOLFIRI), and the infusion of 5FU can be substituted by oral fluoropirimidins (CAPIRI). We chose a reduced dose of irinotecan based in a previously phase I-II study conducted in our hospital (Am J Clin Oncol 2003; 26:107−11) and we employed an empirically reduced dose of capecitabine after the first experience with this combination without monoclonal antibodies (Clin Colorectal Ca 2005; 5(1): 50−6). Irinotecan was chosen instead of oxaliplatin because of the cumulative neurotoxicity of that drug.
Material and Methods: Naive chemotherapy patients (pts) with advanced colorectal cancer were entered into the study with capecitabine (850 mg/m^2/12 hrs po on days 1−14), irinotecan (240 mg/m^2 iv on day 1) and bevacizumab (7.5 mg/Kg on day 1), in a 3-week cycle. The primary end point was overall survival and secundary were time to progression and relation between CEA, karnofsky (KPS), age, number of organ involved (NOI), RAS status and evolution.
Results: From April 2005 to April 2008, 120 pts were enrolled. Median age were 64 years (limits: 40−79 years), KPS 70% (limits: 60−90%). The overall response (OR) rate was 63.3% and the disease stabilization was 30%. The bivariate analyses only found a significant relation between low values of CEA and responses ($p < 0.001$). Time to progression was 18 month (95% CI, 14.3−21.6). but it was different between patients with CEA response (50% reduction), 20 month, and patients without CEA response, 12 month ($p = 0.002$). KPS and NOI were related with survival in bivariate but not in multivariate analyses. The main grade 2−4 toxicities were: diarrhea in 55 pts (grade 3−4 in 16), hand-foot syndrome in 54 pts (grade 3−4 in 2), neutropenia in 40 pts (grade 3−4 in 8), any hypertension in 74 pts (grade 3−4 in 2), any proteinuria in 75 pts (none was grade 3−4), thrombotic events in 7 pts or bleeding in 55 pts (mainly epistaxis); 5 live threatening adverse events: 1 neutropenic toxic death, 2 pulmonary thromboembolism, 2 grade IV diarrhea with secondary renal insufficiency.
Conclusion: There seems to be a relation between the value of CEA at diagnosis and response, and between CEA response and time to progression. Results indicate that the combination of CAPIRI plus bevacizumab has a remarkable anti-tumor activity that is consistent with other combinations published (Schmiegel. J Clin Oncol 2007; 25(20): 4034) and has an acceptable safety profile.

6054 POSTER

Management of isolated non-resectable liver metastases in colorectal cancer patients: a case-control study of isolated hepatic perfusion with melphalan versus systemic chemotherapy

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Purpose: To compare the median overall survival of patients with isolated non-resectable liver metastases in comparable groups of patients treated with either isolated hepatic perfusion (IHP) with melphalan or with systemic chemotherapy.
Patients and Methods: All patients with isolated liver metastases from colorectal cancer origin, who underwent IHP with 200 mg melphalan between August 1994 and December 2004, through both the portal vein and hepatic artery, were included in this study. The control group consisted

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%).