

gastrointestinal tumors

5030 PROGNOSTIC AND PREDICTIVE VALUE OF KRAS AND BRAF MUTATIONS IN PATIENTS ENROLLED IN THE MRC FOCUS TRIAL

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Activating mutation of the KRAS oncogene is now established as a predictive biomarker for resistance to treatment with anti-EGFR antibody therapies in patients with advanced colorectal cancer (aCRC). However it is not known whether KRAS mutation is also predictive for other aCRC treatments. In the UK FOCUS trial, which compared first-line 5FU, 5FU/irinotecan or 5FU/oxaliplatin in aCRC, formalin-fixed, paraffin-embedded (FFPE) tumour blocks were obtained from consenting patients. DNA was extracted from 801 patient samples, and KRAS/BRAF pyrosequencing performed. Firstly we assessed KRAS/BRAF mutation rates in this large population, and investigated whether mutation status is a prognostic marker. Secondly, we determined whether KRAS/BRAF mutation status is predictive of benefit from irinotecan or oxaliplatin. Finally, we looked for a correlation between BRAF mutation status and loss of mismatch repair (MMR) proteins MLH1 or MSH2 by IHC, as a causal link has been suggested between defective MMR and BRAF mutations. Mutation rates: Consistent with previous literature:

	KRAS (codons 12,13, 61)	BRAF (V600E)	Either
Mutation	336 (41.9%)	60 (7.5%)	392 (48.9%)
No mutation	449 (56.1%)	729 (91.0%)	406 (50.7%)
No result	16 (2.0%)	12 (1.5%)	3 (0.4%)

Prognostic analysis: Patients with a KRAS and/or BRAF mutation showed significantly worse overall survival (OS) compared to patients with no mutation [HR 1.34, 95%CI (1.15-1.57) (p<0.0001)]. Predictive analysis: The impact of oxaliplatin and irinotecan on Progression-Free Survival (PFS) and OS were analysed. Patients with wild-type and mutant phenotypes are equally likely to benefit from these drugs (p value for interaction = 0.4-0.8). BRAF/MSI: We demonstrated that of the patients who did not show loss of MLH1 or MSH2, 7% had a BRAF mutation compared with 22% of patients who showed loss of MLH1 or MSH2 (chi-square p=0.002 with 1df). We have shown, in the setting of a large, RCT that KRAS/BRAF mutation confers a poor prognosis but does not preclude benefit from irinotecan or oxaliplatin. We confirmed a strong correlation between MMR status and BRAF mutation status.

5040 CIRCULATING TUMOR CELLS (CTC) IN ADVANCED COLORECTAL CANCER (ACC) PATIENTS UNDERGOING 1ST LINE TREATMENT WITH CHEMOTHERAPY, BEVACIZUMAB AND CETUXIMAB AS AN IMPORTANT AND EARLY PREDICTOR OF SURVIVAL

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Background: CTC have been correlated with clinical outcome in patients (pts) with ACC treated with various regimens in different lines (Meropol; ASCO2007). This study aims to assess the correlation between CTC and progression-free and overall survival in ACC pts undergoing 1st line treatment in a phase III study (CAIRO2) of the Dutch Colorectal Cancer Group with chemotherapy plus bevacizumab with or without cetuximab.

Methods: Pts were treated with a 3-weekly schedule of capecitabine, oxaliplatin, and bevacizumab (arm A) or the same regimen with the addition of weekly cetuximab (arm

B). CTC levels were determined in 467 ACC pts, 235 in arm A and 232 in arm B. CTC/7.5mL of blood were measured at baseline (n=451) and after 1-2 (n=369), 3-5 (n=321), 6-12 (n=346) and 13-20 (n=261) weeks using the CellSearch SystemTM.

Results: At baseline, ≥ 3 CTC were detected in 129 pts (29%). After 1-2 weeks ≥ 3 CTC were detected in 21 pts (6%). The presence of ≥ 3 CTC at baseline and during treatment was similar between arm A and arm B. The median progression-free survival (PFS) was 10.5 months in all pts with <3 CTC and 8.2 months if ≥ 3 CTC were detected at baseline (p=0.0005, HR 1.5). The median overall survival (OS) was significantly lower if ≥ 3 CTC were detected at baseline (22.2 vs 13.7 months; p=0.0000; HR 2.3). Pts with ≥ 3 CTC at any time point had a significantly worse PFS and OS, and this predictive value is already observed at 1-2 wks after start of treatment. In univariate and multivariate analyses, the presence of CTC prior to or at any time during treatment was a better predictor of PFS and OS than the stratification parameters (prior adjuvant therapy, number of affected organs and serum LDH).

Conclusions: The number of CTC is an important early predictor of PFS and OS in ACC pts at any time point. Updated results will be presented at the meeting, including data on KRAS in relation to CTC and outcome of treatment.

5050 GSTP1 ILE105VAL POLYMORPHISM AND IRINOTECAN EFFICACY IN METASTATIC COLORECTAL CANCER (MCRC), A STUDY OF THE DUTCH COLORECTAL CANCER GROUP (DCCG)

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Purpose: The Valine (Val) variant of glutathione-S-transferase Pi (GSTPi) codon 105 results in decreased enzyme activity compared to Isoleucine (Ile). In vitro experiments suggest that nuclear GSTPi activity decreases irinotecan cytotoxicity. Patients with one or more Val alleles may therefore benefit more from irinotecan chemotherapy. Our aim was to investigate possible association of the GSTPi genotype with the efficacy of irinotecan in the treatment of MCRC.

Patients and methods: Patients with MCRC received first-line chemotherapy with either the combination of capecitabine plus irinotecan (CAPIRI), or capecitabine (CAP) single agent therapy as part of a multicenter phase-III study of the DCCG (CAIRO). PFS was evaluated using RECIST criteria for progressive disease. GSTP1 Ile105Val genotype was determined by pyrosequencing. HRs (hazard ratios) for progressive disease were calculated using multivariable Cox regression, with serum LDH as a covariate.

Results: Genotyping was successful in 267 (100%) patients. Genotype frequencies were 40% for Ile/Ile, 48% for Ile/Val and 12% for Val/Val. In total, 126 patients were allocated to receive CAP, and 141 patients to CAPIRI. Patients receiving CAP showed a PFS of 6.6 months (Ile/Ile), 6.0 months (Ile/Val) and 6.5 months (Val/Val); compared to 7.0 (Ile/Ile), 8.8 (Ile/Val) and 9.2 months (Val/Val) with CAPIRI. The risk of progression (HR) for Val-allele carriers using CAPIRI was 0.63 (0.46-0.87) compared to CAP. PFS was significantly longer (mean: 2.6 months) if Val-allele carriers were treated with CAPIRI (p<0.005). However, patients with the Ile/Ile genotype showed similar PFS irrespective of the addition of irinotecan (p=0.972). For the Ile/Ile genotype, the risk of progression did not differ significantly between both regimens (HR=0.99, 0.67-1.48).

Conclusion: The results of this study suggest that in contrast to the Ile/Val and Val/Val genotype, the Ile/Ile genotype does not benefit from the addition of irinotecan to CAP, in terms of PFS. This is the first study reporting an association of the GSTPi codon 105 variants with the clinical efficacy of irinotecan, which clearly deserves to be investigated in more detail.

5060 LONG-TERM OUTCOME OF THE FIRST UKCCCR RANDOMISED TRIAL OF CHEMO-RADIATION FOR THE TREATMENT OF EPIDERMOID ANAL CANCER

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Background: The first UKCCCR Anal Cancer Trial (1996) demonstrated the benefit of chemo-radiation (CRT) over radiation for the primary treatment of squamous carcinoma of the anus. CRT became the standard treatment. There was a 46% reduction in local treatment failure and 29% reduction in anal cancer deaths. These

patients have been followed for an additional 12 years since that report, to determine the long-term effects of treatment.

Methods: 577 eligible patients were recruited; 285 patients received 45Gy radiotherapy in 20/25 fractions over 4 or 5 weeks (RT) and 292 received the same radiotherapy combined with 5-fluorouracil (3750-4000mg/m² over 4 or 5 days) during the first and final weeks of radiotherapy, and mitomycin C (12 mg/m²) on day 1 of CRT. All centres were contacted to obtain information on date and cause of death, relapse and date last seen alive. We examined overall survival (OS), death from anal cancer and relapse-free survival (RFS).

Results: Since recruitment closed in 1994, there have been 405 deaths, 278 local relapses and 217 anal cancer deaths. CRT produced a highly significant reduction in the risk of relapse and anal cancer deaths, similar to those first reported. There were clear benefits several years after randomisation (Table). There was no evidence of a difference in non anal cancer deaths. There was a suggestion that CRT had a greater benefit among patients with T4 stage tumours: HRs 1.05, 0.72, 0.96 and 0.45 for stages T1, T2, T3 and T4 respectively.

	Absolute risk difference % (95%CI)* No. years after randomisation		
	5	10	12
OS	5 (-1 to 11)	6 (-1 to 13)	6 (-1 to 13)
Anal cancer death	11 (4 to 17)	12 (4 to 19)	12 (4 to 19)
RFS	14 (7 to 20)	13 (7 to 20)	13 (6 to 20)

*CRT minus RT (positive value favours CRT)

Conclusions: CRT is associated with a clear and sustained benefit in patients with squamous carcinoma of the anus. The magnitude of the benefit seen in the first few years is maintained as long as 12 years later.

5070 NEOADJUVANT UFT VS SUPPORTIVE CARE IN RECTAL ADENOCARCINOMA TREATED WITH RADIOTHERAPY AND SURGERY: A MULTICENTER PHASE III FRENCH STUDY

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Objective: Does neoadjuvant chemoradiotherapy (CRT) with oral UFT, like i.v. 5FU, improve surgical outcomes compared with radiotherapy (RT) alone in patients (pts) with rectal adenocarcinoma (RAC).

Methods: Pts, age <80 with RAC stage T3 (T4 if anal extension) N<2 M0 were randomized to either (RT Arm) RT 45 Gy/25 fractions (Fc)/5 weeks or (CRT Arm) RT 45 Gy/25 Fc plus daily UFT 300 mg/m² plus Leucovorin 90 mg for 5 weeks. 6-8 weeks after treatment, pts undergo TME surgery. Adjuvant CT permitted at investigator discretion. Primary endpoint is pathological complete response rate (pCR) and secondary endpoints include downstaging, QOL, clear-margin resectability, sphincter conservation and recurrence rates, and disease-free and overall survival.

Results: At interim analysis at 50% of target, 160 pts were randomized. Of these, 79 pts (58M/21F, 66y, range 28.0-79.0) were allocated to RT and 81 pts (57M/24F, 67y, range 46.0-80.0) to CRT. Compliance: RT dose intensity 98.7% (n=78) in RT arm vs 95.2% (n=77) in CRT arm with UFT mean dose 291.1 i, ± 39.6 mg/m². 155 pts underwent surgery and 5 pts did not (4 liver and 1 lung metastases plus 1 CVA.). Both RT and CRT were well tolerated despite 4 deaths: 3 in RT arm (2 post-op, one progression without surgery), 1 in CRT arm, also post-op. After this analysis, 18 pts were still recruited.

	RT (n,%)	CT RT (n, %)	p
pCR rate	3 (3.8)	11 (13.6)	0.03
EUS downstaging T	7 (19.3)	13 (30.3)	
EUS downstaging N	10 (30.3)	13 (39.4)	
Sphincter conservation rate	77 (58.1)	78 (71.7)	
Toxicity SAE	14 (15)	17 (24)	
G III	7 (3.8)	21 (9.2)	
G IV	4 (2.2)	10 (4.4)	
Diarrhea G III	0	1 (2)	
Diarrhea G IV	1 (4.3)	8 (16.4)	
Neutropenia G IV	0	0	

Conclusions: At interim analysis, toxicity is acceptable with a clear difference between the arms in pCR rate, although insufficiently great to normally recommend study stop. Independent data monitoring committee, advised that, provided the results of the 18 additional pts confirm those of the first 160 pts the primary superiority endpoint will be achieved. Since recruitment has slowed, the study is closed and final analysis is underway.

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508PD A PHASE II TRIAL OF DAILY ORAL RAD001 (EVEROLIMUS) IN PATIENTS WITH METASTATIC PANCREATIC NEUROENDOCRINE TUMORS (NET) AFTER FAILURE OF CYTOTOXIC CHEMOTHERAPY

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Background: There are no established treatments for pancreatic NET after chemotherapy failure. Octreotide is used to control symptoms and may affect tumor growth. In patients with progression prior to starting trial therapy, the six months progression free survival (PFS) rate with somatostatin analogues was 28% (Panzuto, Ann Oncol 2006). RAD001 is a novel oral signal transduction inhibitor of mTOR (mammalian target of rapamycin), a key serine-threonine kinase regulating protein synthesis, cell growth, cell proliferation and angiogenesis.

Methods: This phase II study assessed response rate (RR) and PFS in subjects with metastatic pancreatic NET who progressed (RECIST) during or after prior chemotherapy. Subjects were stratified and treated according to prior and ongoing use of depot octreotide therapy. Stratum 1: RAD001 alone, stratum 2: RAD001 and depot octreotide. RAD001 was administered daily at 10 mg orally. Tumor assessments (RECIST) were performed at baseline and every 3 months.

Results: 115 subjects were enrolled in stratum 1 and 45 subjects in stratum 2. The RR by central radiology was 7.8% in stratum 1 and 4.4% in stratum 2. Time to response ranged from 77 days to 181 days in stratum 1 and approx 80 days in stratum 2. Six months PFS rates by central radiology were 65.4% in stratum 1 and 70.6% in stratum 2. Median PFS was 9.3 months in stratum 1 and 12.9 months in stratum 2. Fifteen month survival was 52.6% in stratum 1 and 90.3% in stratum 2. At the time of data cut, 37.4% of subjects in stratum 1 and 46.7% in stratum 2 were still on treatment. Treatment was generally well-tolerated and most adverse events were mild to moderate in severity. The most frequent adverse events were diarrhea (48%) stomatitis (47%) rash (44%) fatigue (42%) nausea (41%) pyrexia (32%) vomiting (30%) headache (27%) asthenia (27%) peripheral edema (28%) and abdominal pain (27%). Only 4% of subjects had a grade 4 adverse event possibly related to trial therapy. Grade 1/2 pneumonitis were reported in 4% of subjects and no Grade 3/4 were reported. There were no major differences in safety between the two strata.

Conclusion: Daily RAD001, with or without concomitant depot octreotide, demonstrates anti-tumor activity and is well-tolerated in patients with low-intermediate grade pancreatic NET after failure of prior systemic chemotherapy.

509PD RADIOPEPTIDE CONTROL OF ENDOCRINE CANCER: A PHASE IIA STUDY OF 177LU-OCTREOTATE/ CAPECITABINE THERAPY OF DISSEMINATED NEUROENDOCRINE TUMOURS

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Introduction: Metastatic neuroendocrine malignancy and hepatic carcinoid syndrome, may respond to radiopeptide therapy. Early trials show stabilization of disease in 47% of patients treated with Lutetium-177 octreotate. Our study investigates the role of capecitabine as a radiosensitizer. Toxicity study of 30 patients receiving 4 cycles of 7.8 GBq ¹⁷⁷Lu octreotate each with 2 weeks of 1650 mg/m² daily capecitabine was also analysed for objective response and symptom relief.

Methods: All patients had unresectable neuroendocrine tumours positive on ¹¹¹In-octreotide scan and measurable progressive disease (PD) on CT/MRI with biopsy-proven diagnosis and abnormal serum Chromogranin A/urine HIAA with normal creatinine and haematopoietic parameters. Whole body and SPECT/CT imaging at 4, 24, 48 hours and 5 days with blood sampling defined dosimetry. Follow-up CT/MRI at the time of referenced comparative ¹⁷⁷Lu-octreotate whole body 24 hour imaging to correlate objective response in tumour dimensions with radiopeptide uptake indicative of metabolic response. Symptomatic response was evaluated by EORTC QOL.

Results: Twenty six patients on study have received 7.8 GBq ¹⁷⁷Lu-octreotate/capecitabine 4 cycles 10, 3; 1, 2; 11, 1; 4 at cycle intervals 6-11 weeks (median 10). All 68

episodes of therapy followed for 8 weeks were assessable for toxicity. Minimal transient myelosuppression at 3–4 weeks resulted in grade I thrombocytopenia in 2 patients and no neutropenia was observed. There was no elevation of serum creatinine in any patient. Critical organ radiation dosimetry mean estimates for each treatment episode were kidneys 2Gy, liver 5–10 Gy and bone marrow 0.5Gy, all below thresholds for toxicity. Response of carcinoid symptoms of flushing and diarrhoea was significant in 15 of 23 assessable patients with complete resolution in 6. ORR on CT/MRI criteria was PR 3, SD 15, MR 3 PD 2. Conclusion: Addition of capecitabine radiosensitizing chemotherapy does not increase the minimal toxicity of ¹⁷⁷Lu-octreotate radiopeptide therapy of disseminated neuroendocrine tumour. Eighteen of 23 patients with progressive disease at entry achieved partial response or stable disease

510PD RANDOMIZED MULTICENTER STUDY OF CETUXIMAB PLUS FOLFOX OR PLUS FOLFIRI IN NEOADJUVANT TREATMENT OF NON-RESECTABLE COLORECTAL LIVER METASTASES (CELIM-STUDY)

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Background: Resectability of colorectal liver metastases (mets) can be induced by an effective chemotherapy regimen. Combinations of cetuximab with FOLFIRI or FOLFOX have been shown to increase response and resection rates.

Methods: Patients (pts) with non-resectable liver mets were randomized to receive FOLFOX6 or FOLFIRI plus cetuximab each in this multicenter, randomized phase II study. Pts were stratified according to the reason for non-resectability (technically non-resectable vs. ≥ 5 liver mets), the use of PET scans at initial staging and EGFR status. Preoperative treatment was planned for 8 cycles. In case of persistent non-resectability, multidisciplinary evaluation was planned every four cycles.

Results: From Dec 2004 to Mar 2008, 124 pts were screened for the study. 111 pts were randomized to receive FOLFOX-Cet. (56 pts) or FOLFIRI-Cet. (55 pts). Median age was 63 years. Out of the 111 pts, 60 pts (54%) were judged as technically non-resectable, 20 pts (18%) were staged with PET, and 81 pts (73%) were EGFR detectable. At the interim analysis in March 2008, response and resection data were available from 81 pts. Best response was 75.3% (61/81 pts, 95%CI 64.5–84.2%, combined analysis for both arms), confirmed response 59.3% (48/81 pts, 95% CI 47.7–70.0%). KRAS status was available for 86 pts, best response rate in KRAS wild type pts was 85.4% (41/48 pts, 95%CI 72.2–93.9%), and 50% (7/14 pts) in KRAS mutant pts. Sixteen resections were performed in pts with ≥ 5 liver mets, 18 resections in technically non-resectable pts. In total, 34/81 pts were resected (42.0%, 95%CI 31.1–53.5%), twenty nine with microscopically free margins (R0). Interim data on toxicity of 98 pts demonstrated acne like rash (32%), neutropenia (20%), diarrhea (15%), allergic reaction (6%), neurologic toxicity (5%) to be the most common preoperative grade ≥3 toxicities in both arms. One patient had a fatal pulmonary embolism (2.9%).

Conclusion: In the interim analysis, the combination of cetuximab with standard chemotherapy has demonstrated high activity and an encouraging rate of liver resection. Mature resection and response data per treatment arm and KRAS status will be reported at the meeting.

511PD COMPARISON OF FOLFOX6 PLUS CETUXIMAB WITH FOLFIRI PLUS CETUXIMAB AS FIRST-LINE THERAPY IN METASTATIC COLORECTAL CANCER (mCRC): A RANDOMIZED OPEN-LABEL PHASE II CECOG STUDY

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Background: Cetuximab (Erbix[®]) has previously shown activity in combination with the standard first-line regimens FOLFOX6 or FOLFIRI in mCRC. This phase II trial evaluated the efficacy and safety of FOLFOX6 + cetuximab (FX+C) versus FOLFIRI + cetuximab (FF+C) as first-line therapy in mCRC.

Methods: Patients with mCRC were randomized to either FOLFOX6 (folinic acid 400 mg/m² plus oxaliplatin 100 mg/m², followed by 5-fluorouracil [5-FU] 400 mg/m² bolus then 5-FU 2400 mg/m² over 46 hours) or FOLFIRI (as for FOLFOX6 with irinotecan 180 mg/m² instead of oxaliplatin) every 2 weeks. All patients also received cetuximab (400 mg/m² initial dose then 250 mg/m² weekly). The primary endpoint was progression-free survival (PFS) at 9 months. Secondary endpoints were: PFS at 3, 6, and 12 months; objective response rate (ORR); overall survival (OS); and safety.

Results: Overall, 151 patients from 25 centers in 13 countries were randomized to FX+C (n=77) or FF+C (n=74) between July 2005 and July 2006. Median age was 62 years (range 23–81), 58% were male, and 56% of patients had an ECOG performance score [PS] of 0. PFS rates were similar in the two groups (Table). Best-confirmed ORRs were 43% (FX+C) and 45% (FF+C), with disease control in 83% (FX+C) and 77% (FF+C) of patients. Higher ORR rates were observed in patients with acne-like rash in the first 6 weeks: 58% ORR for grade 2 and 80% ORR for grade 3/4. Median OS based on 85 events was 17.4 months (FX+C) and 18.9 months (FF+C). Hazard ratio of OS was 0.97 (95%CI: 0.64–1.4). Cox proportional hazard analyses showed that the occurrence and severity of acne-like rash during treatment were the most significant factors for prolonged survival.

Timepoint months	PFS (%)		Difference (95% CI)
	FX+C (n=77)	FF+C (n=74)	
3	92	78	13 (2 to 25)
6	69	69	0 (-16 to 16)
9	45	34	11 (-6 to 28)
12	18	18	0 (-13 to 14)

Conclusions: The combination of cetuximab with either FOLFOX6 or FOLFIRI was active in the first-line treatment of patients with mCRC. Efficacy outcomes, including OS, were similar in the two groups. The occurrence and severity of acne-like rash during treatment were the most important factors associated with higher response rates and prolonged survival.

512PD SORAFENIB IS EFFECTIVE IN HEPATITIS B-POSITIVE PATIENTS WITH HEPATOCELLULAR CARCINOMA (HCC): SUBGROUP ANALYSIS OF A RANDOMIZED, DOUBLE-BLIND, PHASE III TRIAL PERFORMED IN THE ASIA-PACIFIC REGION

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Objective: In the Asia-Pacific (A/P) region, the majority of patients with HCC are HBV positive; hence, it is important to evaluate efficacy and safety of systemic anticancer therapy in this subpopulation. Sorafenib, a potent multikinase inhibitor, has been shown to significantly improve overall survival (OS) in patients with advanced HCC. We evaluated the clinical benefit and safety profile of sorafenib in HBV-positive patients with HCC from the A/P region.

Methods: In the A/P trial, patients with advanced, measurable HCC, ECOG PS 0-2, CP A/B, and no prior systemic therapy for HCC were randomized 2:1 to sorafenib (400 mg bid) or placebo. Endpoints included OS, time to progression, time to symptomatic progression, disease-control rate (DCR; defined as complete/partial response, or stable disease by RECIST, maintained for ≥28 days from first demonstration), and safety. The trial was stopped early by the DMC after an interim analysis revealed a significant survival benefit for the sorafenib group.

Results: Of 226 enrollees, 165 were HBV positive. Baseline characteristics are summarized in the table.

Baseline Characteristic	HBV-Positive Sorafenib (n=106)	HBV-Positive Placebo (n=59)
Age, median (y)	49	51
Male (%)	89	86
Child-Pugh A (%)	97	97
Extrahepatic spread	68	68
Vascular invasion	39	37
ECOG PS		
0	24	27
1	71	71
2	6	2

Among HBV patients, median OS was 5.9 months in the sorafenib group, compared with 4.1 months in the placebo group (hazard ratio: 0.74 [95% CI: 0.51, 1.06]). DCR was greater in the sorafenib group than in the placebo group (30.2% vs 17.0%). The most frequent drug-related grade 3/4 adverse events in the sorafenib and placebo groups, respectively, were hand-foot skin reaction (12.4% vs 0%) and diarrhea (5.7% vs 0%).

Conclusions: Sorafenib treatment was effective in patients with HCC from the A/P region, independent of HBV status. The safety profile of sorafenib in HBV-positive patients was comparable to that in the overall study population. Most adverse events were low-grade and manageable.

513PD

META-ANALYSIS OF THE REAL 2 AND ML17032 TRIALS COMPARING CAPECITABINE WITH 5-FLUOROURACIL (5-FU) IN ADVANCED OESOPHAGO-GASTRIC CANCER

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Background: The REAL 2 trial randomised 1002 patients with untreated advanced oesophago-gastric cancer in a two-by-two design to receive triplet combination chemotherapy with epirubicin and cisplatin plus either infused 5-FU (ECF) or capecitabine (ECX), or epirubicin and oxaliplatin plus either infused 5-FU (EOF) or capecitabine (EOX). The ML17032 trial randomised 316 patients with untreated advanced gastric cancer to receive cisplatin plus either infused 5-FU (CF) or capecitabine (CX). Both trials met their primary endpoints of non-inferiority of capecitabine combinations to 5-FU combinations in overall survival (OS) and progression-free survival (PFS), respectively. Neither trial was powered to detect superiority of capecitabine over infused 5-FU; therefore we have performed a meta-analysis of the combined data.

Methods: Data was collected on all patients randomised within the REAL 2 and ML17032 trials (n=1318). Kaplan Meier survival curves were generated and comparison for OS and PFS between patients receiving 5-FU versus capecitabine combinations, were made using the Log-rank test. Stepwise multivariate Cox regression analysis was used to calculate corrected Hazard ratios (HR) and 95% Confidence Intervals (CI) for OS, PFS and Logistic Regression was used for objective response rate (RR) for known prognostic factors. Forest plots with tests of heterogeneity were used to display the treatment effects for different prognostic groups on OS. The primary endpoint was OS; secondary endpoints were PFS and RR.

Results: OS was superior in the 654 patients treated with capecitabine combinations compared to the 664 patients treated with 5-FU combinations; HR 0.87 (95% CI 0.77-0.98, p=0.02). The difference in PFS was not statistically significant; unadjusted HR 0.91 (95% CI 0.81-1.02, p=0.09). Patients with measurable disease who were treated with capecitabine combinations were more likely to have an objective response than those treated with 5-FU combinations; Odds ratio 1.38 (95% CI 1.10-1.73, p=0.006).

Conclusions: In these two trials, capecitabine combinations were superior to 5-FU combinations for the treatment of advanced oesophago-gastric cancer.

514PD

'LIMITED TREATMENT DURATION AND RE-INDUCTION WITH THE SAME REGIMEN ON PROGRESSION' VS 'TREATMENT UNTIL PROGRESSION' WITH BIWEEKLY CAPECITABINE + OXALIPLATIN ± BEVACIZUMAB IN PATIENTS (PTS) WITH ADVANCED COLORECTAL CANCER (CRC): A RANDOMISED PHASE II STUDY

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Introduction: The efficacy of re-induction therapy, giving an additional potentially effective therapy line, in advanced CRC pts treated for a limited duration and achieving an objective response or stable disease (SD) has been shown previously.

Methods: In this study, 2 different treatment strategies using the same regimen were compared in non-resectable metastatic CRC pts. Arm A: capecitabine 1750mg/m² bid d1-7 + oxaliplatin 85mg/m² d1 (XELOX2) for 8 cycles; thereafter, treatment was withheld until progressive disease (PD) when XELOX2 was re-introduced in pts with prior response or SD for another 8 cycles or until deemed ineffective. Arm B: XELOX2 continuously until PD. This trial started in 2004; the protocol was amended in 2006 and bevacizumab 5mg/kg d1 was added to both arms. Primary objective: demonstrate or exclude that intermittent treatment (arm A) results in improvement in progression-free survival (PFS). Secondary objectives: compare tolerance, quality of life, response rate (RR), overall survival (OS) and costs.

Results: By 31 March 2008, 109 pts (96% of planned) were randomised to arm A (n=57) or arm B (n=52). 63% (arm A) and 58% (arm B) were evaluated for efficacy and 91% and 87% for safety, respectively. Pt characteristics including age, gender, prior adjuvant treatment, localisation of metastases, and tumor load were similar in both arms. RR (44.4% arm A, 43.3% arm B, median duration of 7 mos each) and SD (41.7% vs 36.7%, median duration 6 mos each) were not significantly different between arms. Severe (grade 3+4) diarrhea (13.5% vs 24.4%), vomiting (1.9% vs 4.4%), sensory neuropathy (3.8% vs 11.1%) and fatigue (3.8% vs 9.9%) were more frequent in arm B. To date, 13 pts in arm A have been re-induced after a median drug holiday duration of 4 mos (range 0.5-12.2).

Conclusions: Encouraging preliminary efficacy suggest similar outcomes between arms; treatment tolerance, as anticipated, appears to be in favour of arm A. Mature results, including PFS and OS, will be presented at the meeting.

515P

A PHASE II STUDY OF IMATINIB MESYLATE AS ADJUVANT TREATMENT FOR CURATIVELY RESECTED HIGH-RISK LOCALIZED GASTROINTESTINAL STROMAL TUMORS WITH C-KIT EXON 11 MUTATION

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Background: In our previous study, the presence of c-kit mutation as well as tumor size and mitotic count was an independent poor risk factor for relapse after curative resection of primary localized GIST. The patients with all the 3 poor risk factors had only 30% of 2 year relapse free survival rate (RFSR). (Kim, et al. Clin Cancer Res 2004) It is also well known that c-kit exon 11 mutant GISTs respond better to imatinib treatment than the other mutant or wild type GISTs. Therefore, the patients who have primary localized GISTs with large size, high mitotic count, and c-kit exon 11 mutation may be the best candidate of adjuvant imatinib treatment. In this phase II study, we have evaluated the efficacy and safety of adjuvant imatinib for this patient group.

Patients and methods: Patients who underwent complete resection of a primary GIST with 1) c-kit exon 11 mutation, and 2) 10 mitoses/50 HPF, or tumor size 10 cm, or 5 mitoses/50 HPF and tumor size 5 cm were eligible. Patients received imatinib 400mg p.o. daily until recurrence of disease, intolerable toxicities, or for 2 years. The primary end point was relapse-free survival (RFS).

Results: A total of 47 patients from 4 centers in Korea were enrolled. The median age was 57.0 years. Stomach was the most common primary site (n=31). Median primary tumor size was 7.5cm and median mitoses index was 11/50 HPF. With a median follow-up of 22.6 months, the median RFS and OS have not yet been reached. RFSR was 97.9% at 1-year and 91.9% at 2-years. Only 4 relapses (2.1%) were documented among the 47 patients. The treatments were generally well tolerated. Grade 3-4 toxicities included neutropenia 23.4%, rash 6.4%, anorexia 4.3%, and diarrhea 4.3%. There was no treatment-related death.

Conclusion: Postoperative adjuvant imatinib for 2 years were safe and seemed to prolong the RFS in patients with c-kit exon 11 mutation and high-risk of recurrence following complete surgical resection of the primary GIST.

516P **NEOADJUVANT CHEMORADIOTHERAPY WITH FOLFOX-4 AND CETUXIMAB IN LOCALLY ADVANCED ESOPHAGEAL CANCER: PRELIMINARY DATA FROM B152 TRIAL**

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Background: Primary chemoradiotherapy (CRT) improves significantly the survival of patients with esophageal cancer (EC) over surgery alone, even with modest benefit. In EC, increased EGFR expression is associated with a poor outcome supporting the therapeutic role of anti-EGFR drugs such as Cetuximab.

Methods: We started a phase II trial to investigate the safety and efficacy of Cetuximab plus FOLFOX-4 as induction CT followed by the combination of Cetuximab and RT in pts with locally advanced EC. Staging: EUS plus biopsies, PET and CT scans. Eligibility: EUS stage II-III; surgical candidate; ECOG PS 0-2. All pts received Cetuximab at a starting dose of 400 mg/m² and further weekly infusion at a maintenance dose of 250 mg/m² and 4 cycles of FOLFOX-4 every two weeks. Post-induction EUS and CT scans were performed, while a PET scan was repeated early before second cycle of CT: pts without progression disease (PD) were treated with daily RT (50Gy) and concurrent weekly Cetuximab. Post RT, EUS plus biopsies, CT scan and PET were performed. At wk 18, pts without PD underwent to esophagectomy. The primary end-point was the pathologic complete responses (pCR) rate. According on a two step Simon Minimax design, 31 subjects have to be enrolled at the first step of the study. In case of 4 or more pts with a pCR, the study will be continued and 24 additional subjects will be treated.

Results: Up to march 2008, 33 pts have been enrolled in the study: 23 men, 10 women, median age 59 (21-72), squamous 21, adenocarcinoma 12, stage II (T2N1) 6 pts, stage III (T3-4N1) 27 pts. 17 pts completed induction treatment and the following grade 3-4 toxicities were recorded: neutropenia 7%, thrombocytopenia 4%, skin rash 4%. Among pts who completed RT and Cetuximab, the main grade 3-4 toxicities observed were: esophagitis 6%, skin rash 12%. 16 pts completed the planned treatment (CT plus RT): 3 pts progressed, 10 underwent to esophagectomy and 3 pts are waiting for surgery; 17 pts ended the induction CT. All 10 pts had R0 resections: 9 pts were downstaged with 4 pCR 1 pt had no change.

Conclusions: Preliminary analysis suggests that CRT with Cetuximab is safe and active, suggesting the continuation of the study until the final sample of 55 pts.

517P **PREOPERATIVE CHEMOTHERAPY FOLLOWED BY SURGERY VERSUS SURGERY ALONE IN RESECTABLE ESOPHAGEAL CANCER: A SINGLE INSTITUTE PHASE III TRIAL**

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Introduction: Surgical resection is essential in esophageal cancer management. Unfortunately outcome of patients (pts) with locally advanced disease is still poor with only 15-20% long-term survival. There are conflicting results of previous studies dedicated to preoperative chemotherapy (CT) in esophageal cancer. Therefore the aim of our study was to increase overall survival (OS) of esophageal cancer pts by the use of preoperative chemotherapy.

Methods: Previously untreated pts with stage T₃₋₄N₀₋₁M₀, T₁₋₂N₁M₀ resectable esophageal cancer were eligible for the study. After clinical evaluation they were randomized into CT (two cycles of FLEP: cisplatin 80 mg/m², day 1; etoposide 80 mg/m² d 1-3, leucovorin 20 mg/m² and 5-fluorouracil 425 mg/m², bolus, days 1-3; every 21 days) followed by surgical resection (Ch-S group), or resection alone (S group). Four weeks after completion of CT pts underwent transthoracic subtotal esophageal resection with complete two-field (I. Lewis procedure). Esophageal endosonography was used for staging and objective response evaluation.

Results: 115 pts were enrolled from 2000 to 2006 (Ch-S group, n=57, S group, n=58). Pts' characteristics (tumor stage and histology, coexisting disorders, age and gender) were well balanced between the two treatment groups. Predominant histological type was squamous cell carcinoma (94%). Objective response in Ch-S group was observed in 42%. Main toxicity (grade 3-4) was hematological: 70% of neutropenia and 20% of thrombocytopenia. There were two chemotherapy-related deaths due to ischemic stroke and transmural myocardial infarction. Postoperative mortality was similar in both groups (12%). R0-resection rate did not differ in Ch-S and S groups (85% and 83% respectively). Median OS (3-year OS) were 22 months (45%) in Ch-S group and 20 months (31%) in S group (p=0.24). Pts with objective response to chemotherapy had better OS compared with S group (3-year OS 75% and 31%, p=0.008, respectively).

Conclusions: Preoperative chemotherapy does not prolong OS in most esophageal cancer pts. Pts who achieved objective response after two cycles of chemotherapy have better outcome.

518P **DOCETAXEL AND CISPLATIN CHEMOTHERAPY FOLLOWED BY CHEMORADIOTHERAPY (CRT) IN PATIENTS WITH INOPERABLE, LOCALLY ADVANCED ESOPHAGEAL (E) CANCER A MULTICENTER PHASE II TRIAL (SAKK 76/02)**

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Introduction: Patients (pts) with inoperable locally advanced non-metastatic E cancer are a therapeutically challenging population. Efforts to improve local control by increasing the radiotherapy dose have failed. Improving on the chemotherapy component of CRT may hold greater rewards. We investigated feasibility and efficacy of this approach in a multicenter setting in Switzerland, in parallel to a trial with a similar regimen (5 instead of 7 weeks of RT + surgery) in operable pts (JCO 2007, 18S, 4562).

Methods: Eligibility criteria: histologically confirmed E squamous cell or adenocarcinoma (AC), stage T4 (unresectable) or M1a (tumor encompassable in one RT-field) or inoperable for medical reasons, staged by CT/EUS and (optional) PET. Pts were age 18-70 y, PS ≤ 1, with normal organ functions. Treatment consisted of 2 cycles of docetaxel 75mg/m² and cisplatin 75mg/m² q3w, followed by 5 weeks of docetaxel 15 mg/m² and cisplatin 25mg/m² with concomitant 7 weeks radiotherapy 59.4 Gy in 33 fractions. Primary endpoint was local control 6 months after the end of the CRT, as assessed by CT and endoscopy with multiple biopsies. A two-stage design was adopted with maximum 46 patients.

Results: The trial was stopped early after enrolling 21 pts from 7 institutions due to insufficient efficacy in the stage 1 analysis. Patient characteristics: 18 males, median age 64 y (46 -73 y), 29 % AC, 10 PS 0 and 11 PS 1. 3 pts were ineligible. 19 pts (90 %) finished primary chemotherapy, 16 pts (76 %) completed the entire therapy. Grade 3/4 toxicity during chemotherapy: Neutrophils (N) 9, platelets (plts) 1, infection 2, dizziness 2, dysphagia 2, stomatitis 1, nausea 1. During CRT: dysphagia 3 (G3), N 1, plts 1.

At 6 months, 17 patients did not achieve local control (5 did not have the stipulated evaluation) and 4 patients achieved local control on CT and endoscopy / biopsy and had no evidence of metastatic disease. 15 patients had progressed locally (5 also developed distant metastases). Quality of life data will be presented.

Conclusion: Therapy was feasible and toxicity (esp. dysphagia) was moderate. Local efficacy was however disappointing and led to early trial closure.

519P **SERUM VEGF LEVELS IN PATIENTS WITH ESOPHAGEAL CANCER UNDERGOING PREOPERATIVE CHEMORADIATION CORRELATE WITH PROGNOSIS AND EFFICACY OF TREATMENT**

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Background: Vascular Endothelial Growth Factor (VEGF), known as the most potent direct angiogenic protein, plays an essential role in the growth and progression of several tumors. Serum VEGF levels are regarded as a surrogate marker of tumor angiogenesis and increased serum VEGF concentrations have been correlated with outcome in a variety of solid tumors, including esophageal cancer (EC). The current retrospective study evaluated serum VEGF levels in patients with locally advanced EC to elucidate its association with clinico-pathologic parameters and response to chemoradiotherapy.

Methods: Using enzyme-linked immunosorbent assay, the levels of VEGF were determined in serum of 72 patients with untreated EC (Stage: II 23; III 49; Histology: squamous cell carcinoma, 45; adenocarcinoma, 27).

Results: Pretreatment VEGF serum levels were significantly higher in patients with carcinoma (mean ± SD, 455.2 pg/mL ± 108 pg/mL; range, 234-1235 pg/mL) compared with the levels in the control group (mean ± SD, 85.1 pg/mL ± 21 pg/mL; range, 32-105 pg/mL; P < 0.001). Serum VEGF levels in patients with EUS stage III disease (655.7 ± 87.3 pg/mL; were significantly higher than those in EUS stage II disease (381.2 ± 48.7 pg/mL; P = 0.0025). VEGF levels were affected by neoadjuvant treatment. Serum VEGF levels in the responding group (pCR + PR) were significantly lower than those of the non-responding group (SD + PD) (315.3 ± 95.3 vs 689.58 ± 132.1 pg/mL, respectively; P = 0.001). With a mean follow-up time of 31.2 months (range, 5.1 to 81.3 months), the 3-years OS for all patients was 37%. According to VEGF levels, the patients with

higher VEGF levels had a lower 3-year survival rate than the patients with lower VEGF levels (61% vs 17%, respectively; $P < 0.001$). The 3-years DFS for all patients was 32%. The patients with higher VEGF levels had a lower 3-year DFS rate than the patients with lower VEGF levels (70 % vs 19%, respectively; $P < 0.0014$).

Conclusions: This study supports the role of serum VEGF levels as useful predictor of outcome in EC patients receiving chemoradiation before surgical treatment.

520P

WHOLE BODY 18 F-DG-PET PREDICTS PROGRESSION FREE AND OVERALL SURVIVAL IN PATIENTS WITH SQUAMOUS CELL CARCINOMA OF THE ESOPHAGUS: A PROSPECTIVE TRIAL

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Purpose: A previously published study suggested that measured of therapy induced changes in tumor glucose metabolism by positron emission tomography (PET) with the glucose analog 18 fluorodeoxyglucose (18 FDG) predicts the response, survival and recurrence in adenocarcinoma of esophagogastric junction. The aim of this study was to prospectively validate these findings in squamous cell carcinoma (SCC) of the esophagus.

Patients and methods: Twenty one patients with squamous cell carcinoma of the esophagus who were potentially resectable were included in the study. All patients underwent 18 FDG-PET imaging before 1st cycle of neo-adjuvant chemotherapy and 14 days at least after the 3rd cycle. Patients were classified as metabolic responder when the metabolic activity of the primary tumor had decreased by 50% or more at the time of second 18 FDG-PET.

Results: The median age of the study cohort was 60 (+/-9.7) years, 12 patients were males and 9 were females. 18 FDG-PET demonstrated increase activity in the primary tumor in all patients. Metabolic response was shown in 14 patients (66%), while 7 patients didn't show metabolic response. Metabolic responders showed a high clinical response rate (92 %), median progression free survival (PFS) (16.4 months) and median overall survival (OS) (35.3 months). In contrast, prognosis was poor for metabolic non-responders with clinical response rate of 42% ($p=0.025$), median PFS of 7.13 months ($p=0.032$) and median OS of 12 months ($p=0.038$).

Conclusion: Current results demonstrate that changes in tumor metabolic activity after neo-adjuvant chemotherapy predicts PFS and OS in esophageal SCC patients. These data provide the basis of clinical trials in which early assessment with 18 FDG-PET could change the pre-operative treatment guided by the metabolic response.

521P

THE EFFECT OF P53 PROTEIN OVER-EXPRESSION AND CLINICAL FEATURES ON THE RESPONSE TO PREOPERATIVE CHEMORADIOTHERAPY FOR ESOPHAGEAL SQUAMOUS CELL CARCINOMA

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Background/Objective: P53 is a suppressive gene that plays a key role in DNA repair and apoptosis. The purpose of this study is to investigate the effect of P53 protein over-expression and some clinicopathological factors on the esophageal SCC response to neoadjuvant chemoradiotherapy.

Patients and methods: In this retrospective cohort study, 44 patients with localized esophageal SCC undergoing neoadjuvant chemoradiotherapy (cisplatin + 5FU and 40 Gy in 20 fractions of irradiation) and surgery were evaluated. Pretreatment specimens were assessed immunohistochemically for p53 over-expression and scored according to the frequency of stained cells. The pathologic response in resected specimens was categorized as follows: complete response (CR), no evidence of malignant cell; partial response (PR), small foci of malignant cells and negative lymph nodes and minor response, macroscopic residual tumor or positive lymph nodes.

Results: We found p53 protein over-expression in 29 cases (65.9%). Following chemoradiotherapy, CR and PR were found in 9 (20.5%) and 19 cases (43.2%) respectively. There were no significant association between tumor responses and clinicopathological features such as sex ($p=1$), age ($p=0.82$), dysphagia grade ($p=0.82$) and longitudinal length of the tumor ($p=0.59$). No significant correlation was found between p53 expression and pathological response to preoperative chemoradiotherapy ($p=0.94$).

Conclusion: These results suggest that p53 protein expression is not reliable for predicting the response to neoadjuvant chemoradiotherapy. There were also no

correlations between pathological response to chemoradiotherapy and clinical features such as age, sex, dysphagia grade and longitudinal diameter of the tumor.

522P

IS CHEMOTHERAPY RE-CHALLENGE WORTHWHILE IN PATIENTS WITH RECURRENT GASTROESOPHAGEAL CANCER?

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Background: Recurrence rates after radical surgery or radiotherapy for gastroesophageal cancer remain high. Palliative combination chemotherapy produces a survival advantage over best supportive care in chemo-naïve patients. Patients with advanced gastroesophageal cancer will often have received a prior short course of adjuvant or neoadjuvant chemotherapy with regimens containing cisplatin and a fluoropyrimidine. Second-line chemotherapy is not yet established and the value of re-challenging with the same drugs is unknown. We aim to define response in this setting in a non-trial population by retrospective case analysis.

Patients and methods: We reviewed the electronic medical records of all eligible patients with recurrent gastroesophageal cancer at our centre. Eligible patients had received radical treatment for gastroesophageal cancer including adjuvant or neoadjuvant chemotherapy and following recurrence received palliative chemotherapy.

Results: 38 patients met the eligibility criteria. Clinical benefit (radiological and/or clinical response or stable disease) was seen in 24 (63%) for all regimens. No responses were seen in the cohort of patients receiving non-cisplatin based regimens. Median time to progression was 3.8 months and median overall survival was 6.8 months. 18 patients received adjuvant/neoadjuvant cisplatin combinations and were subsequently re-challenged with cisplatin combinations after cancer recurrence. Of these 18 patients, clinical benefit was seen in 13 (72%). Patients with a time to recurrence of less than 12 months ($n=9$) were compared to those exceeding this time($n=9$). Clinical benefit rates were 89% and 56% respectively.

Conclusion: Re-challenge chemotherapy with cisplatin based combination chemotherapy is active in this setting. Response rates fall short of those reported in trials of palliative chemotherapy in chemo-naïve gastroesophageal cancer patients but compare favorably with phase II trials of second line chemotherapy. A longer time interval prior to recurrence may predict response. Research exploring optimal chemotherapy in this increasing patient population is required.

523P

PHASE II TRIAL OF DOCETAXEL, CISPLATIN, IRINOTECAN, AND BEVACIZUMAB IN METASTATIC ESOPHAGOGASTRIC CANCER

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Background: The combination of weekly docetaxel, cisplatin and irinotecan has demonstrated a response rate of 60% in chemo-naïve patients (pts) with metastatic esophagogastric cancer (Enzinger. ProcASCO '04). The addition of bevacizumab to standard chemotherapy has improved response rates and survival in pts with metastatic colorectal, lung, and breast cancer in randomized trials. Pts with the *28 allele of the UGT1A1 gene have an increased risk of toxicity to irinotecan-containing therapy.

Methods: Pts with measurable, metastatic esophagogastric cancer received bevacizumab 10mg/kg on day 1 every 3 weeks, docetaxel 30mg/m², cisplatin 25mg/m², and irinotecan 50mg/m² on days 1, 8, of each 3-week cycle. Unless contraindicated, pts were urged to take aspirin 81mg daily. Responses were adjudicated by the independent Harvard Tumor Metrics Core. UGT1A1 genotyping was required of all pts entering the study. Additionally, blood samples and endoscopic biopsies of tumor were obtained at baseline and after one cycle of therapy in all consenting pts.

Results: 35 eligible pts have been enrolled: median age = 59 (32-79), male/female = 30/5, ECOG: 0/1 = 14/21, gastric/GE junction/esophageal = 13/8/14, adenocarcinoma/ squamous cell carcinoma = 32/3. Sites of metastatic disease included: lymph nodes (26 pts), liver (19 pts), peritoneum (6 pts), lung (4 pts), bone (4 pts), adrenal gland (4 pts), ovary (1 pt), other (12 pts). Grade III/IV toxicities occurring in > 5% of 35 pts: grade III diarrhea = 12 pts (34%), grade III/IV neutropenia = 10 pts (29%), febrile neutropenia = 5 pts (14%), grade III nausea = 3 pts (9%), grade IV thromboembolic events = 3 pts (9%); none of these pts were taking aspirin. One pt with grade III (upper GI) bleeding. 17 of 34 pts (50%) had the *28 allele present (6/7 or 7/7); of these, 65% had grade III/IV diarrhea and/or neutropenia; 35% of patients without the *28 allele had these toxicities. 32 patients are evaluable for response: partial = 22 (69%), stable = 8 (25%), progression = 2 (6%).

Conclusion: The combination of docetaxel, cisplatin, irinotecan and bevacizumab is well-tolerated and has a promising response rate in chemo-naïve patients with esophagogastric cancer. UGT1A1 testing appears to predict the risk of severe diarrhea/neutropenia in this group of patients. Supported by Genentech.

524P **INTRAOPERATIVE, ADJUVANT TREATMENT OF GASTRIC CANCER WITH THE TRIFUNCTIONAL ANTIBODY CATUMAXOMAB COMPARED TO SURGERY ALONE: A PHASE II STUDY**

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Background: Gastric cancer patients (pts) have a high risk of peritoneal recurrence due to disseminated tumor cells after surgery. The trifunctional antibody catumaxomab (anti-EpCAM x anti-CD3) administered locally into the peritoneal cavity aims at residual tumor cells while activating a complex anti-tumor immune reaction.

Methods: A total of 55 gastric cancer pts (T2b/T3/T4, N+/-, M0) were randomized during surgical D2 procedure to surgery alone or catumaxomab administered as one intraoperative intraperitoneal (ip) and 4 postoperative ip infusions with ascending doses on day 7, 10, 13 and 16. Primary objectives were safety, tolerability and feasibility.

Results: All 55 pts (27 surgery alone, 28 catumaxomab) were included in the safety analysis. The target antigen EpCAM was confirmed in 100% of pts. 78% (22/28) of the patients treated with catumaxomab received all 5 infusions. 40% of the treatment-emergent adverse events (TEAEs) occurred directly after the intraoperative administration. TEAEs (CTC-grade ≥3) occurred in 22 patients (control arm: 10 patients). The most frequently TEAEs in the catumaxomab group were anemia, pyrexia, SIRS and abdominal pain. All related serious TEAEs resolved until end of treatment except for nephropathy (one patient), which resolved with minor sequelae. No trend of an accumulation of severe adverse reactions or complications (e.g. wound healing) occurred compared with the surgery only group. First efficacy data will be demonstrated for early tumor recurrence (1 year follow-up).

Conclusion: Adjuvant treatment of ip administration of catumaxomab is safe and well tolerated in pts after curative resection, the safety results reflecting catumaxomab's mode of action (cytokine release related symptoms). This offers a new chance to avoid intraabdominal tumor recurrence.

525P **ANALYSIS OF THE SAFETY AND EFFICACY OF S-1+ CDDP TREATMENT FOR ELDERLY PATIENTS WITH ADVANCED GASTRIC CANCER : THE SPIRITS TRIAL**

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Background: The oral fluoropyrimidine S-1 is based on the biochemical modulation of 5-fluorouracil, and is widely used not only as a single agent but also in combination therapies for advanced gastric cancer (AGC) in Japan. In the SPIRITS trial (W. Koizumi, et al. Lancet Oncol. 2008 Mar;9(3):215-21), S-1 plus cisplatin (SP) was superior to S-1 monotherapy (S) in terms of median survival time (MST), progression-free survival (PFS) and time to treatment failure (TTF). The effectiveness against the

elderly patients (pts) with AGC is especially important since the life span is prolonged in Japan compared to western countries. Patients and

Methods: 305 pts were randomized and the full analysis set comprised 298 pts (SP/S arm 148/150). The eligibility criteria of age in this trial was 20-74 years old and we defined "Elderly pts" as aged 70 and over and "Young pts" as aged less than 70. In the SP arm of this trial, the safety and efficacy for the elderly pts were analyzed by comparing with those of the young pts.

Results: There were 21 elderly pts and 127 young pts in SP arm. Overall incidence of grade 3/4 adverse events did not differ by age (elderly, young pts: 76.2%, 65.4%; p=0.45). The most common grade 3/4 adverse events were leucopenia (19%, 10%), neutropenia (33%, 41%), Hb decreased (33%, 24%), nausea (14%, 11%) and anorexia (38%, 29%), and there were no remarkable differences between elderly and young pts. For the efficacy analysis, the MST, PFS and TTF of the elderly pts were 424 days (95%CI: 260-525), 224 days (95%CI: 135-279) and 150 days (110-), and those of the young pts were 391 days (95%CI: 323-471), 181 days (95%CI: 153-236) and 145 days (95%CI: 107-162), respectively. The response rates reviewed extramurally according to RECIST criteria were 68.8% (95%CI: 41.3-89.0) in elderly pts and 50.7% (95%CI: 38.6-62.8) in young pts. The relative dose intensities of (S-1, cisplatin) were (98%, 97%) in elderly pts, and (93%, 93%) in young pts. These were nearly equivalent.

Conclusions: The combination of S-1 and cisplatin was also found to be effective and well tolerated in elderly pts with AGC. The further research is expected about feasibility of SP treatment to pts aged 75 and over.

526P **RANDOMIZED PHASE II CLINICAL TRIAL OF TAILORED IRINOTECAN (CPT-11) PLUS S-1 VERSUS S-1 IN PATIENTS WITH ADVANCED OR RECURRENT GASTRIC CARCINOMA AS THE FIRST-LINE CHEMOTHERAPY (THE JAPANESE FOUNDATION FOR MULTIDISCIPLINARY TREATMENT OF CANCER, JFMC31-0301)**

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Objective: Tailored CPT-11+S-1 therapy with a personalized CPT-11 dose using toxicity-based grading as an index was compared with S-1 monotherapy to evaluate the effect of the tailored regimen.

Methods: Patients (pts) with advanced /recurrent gastric cancer were randomized to tailored CPT-11+S-1 (Group A) or S-1 alone (Group B). In Group A, S-1 (80 to 120 mg/m²/day) was given for 14 days, combined with CPT-11 on day 1 and 15, every 4 weeks. The initial CPT-11 dose was 75 mg/m² (Level 0), and it was adjusted to Level -2 (25 mg/m²), Level -1 (50 mg/m²), Level +1 (100 mg/m²), or Level +2 (125 mg/m²) based on toxicity in the previous course (Gr 0/1=increase; Gr 2=no change; Gr 3/4=decrease). For diarrhea, the dose was decreased after ≥ Gr 2. In Group B, S-1 (80 to 120 mg/m²) was given for 28 days, every 4 weeks. The primary endpoint was the response rate (RR). Pharmacokinetics were also assessed in Group A.

Results: Pts were enrolled from August 2003 to March 2005: 95 pts were randomized (48 in Group A and 47 in Group B). The RR with the primary tumor was 25.0% in Group A (12/48) and 14.9% in Group B (7/47), while the RR by RECIST was 27.8% (10/36) versus 21.9% (7/32). The TTF was 82 days in Group A (95% CI: 60 – 105 days) vs. 73 days in Group B (59 – 113 days), and TTP was 148 days (97 – 210 days) vs. 115 days (59 – 168 days), respectively. Hematological toxicity, anorexia, and diarrhea were significantly more common in Group A, but both groups had similar Gr 3 or 4 toxicities. In Group A, the CPT-11 dose level at the third course was Level +2 in 4 patients, Level +1 in 3, Level 0 in 15, Level -1 in 4, and Level -2 in 3. A response was seen in 1/4 at Level +2, 3/3 at Level +1, 5/15 at Level 0, 1/4 at Level -1, and 2/3 at Level -2. In Group A, 11 pts had pharmacokinetic assessment. The CPT-11 dose was decreased at the 2nd course in 6 pts. The mean AUC of SN-38 at dose Level 0 was 114 ng·h/mL in patients requiring dose reduction and 34 ng·h/mL in those without it.

Conclusions: This study revealed the usefulness of tailored CPT-11+S-1 therapy, in which the CPT-11 dose is adjusted for toxicity.

527P

A PHASE II CLINICAL TRIAL OF PACLITAXEL/CISPLATIN/S-1 TRIPLET COMBINATION CHEMOTHERAPY IN PATIENTS WITH ADVANCED GASTRIC CANCER AS FIRST-LINE THERAPY

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Background: The studies on the efficacy and safety of taxol, cisplatin and S-1 in advanced stage stomach cancer with adenocarcinoma in histology are limited. This study were planned to evaluate efficacy and toxicity in patients with metastatic stomach cancer with triple regimen chemotherapy.

Methods: Eligible patients had untreated metastatic or recurrent stomach cancer with measurable lesion(s), histologic proof of adenocarcinoma, ECOG PS 0-2, adequate organ function, and signed informed consent. Treatment consisted of taxol 80mg/m² i.v. on day 1, 8, cisplatin 30mg/m² on day 1, 8 and S-1 35mg/m² bid p.o. on day 1-14 of 21-day cycle. Measurable and/or unmeasurable lesions were assessed every 2 courses by RECIST.

Results: From June 2007 to February 2008, total 42 patients (M/F=29/13) were enrolled. The median age was 52 years. The common metastatic lesions were abdominal lymph nodes (49%), liver (27%), peritoneum (10%), pancreas (4.3%) and lung (2.9%). There were 1 (3.4%) CR, 15 (51.7%) PRs, 11 (37.9%) SDs, and 2 (6.9%) PDs among 29 evaluable patients [13 patients were early to evaluate]. Objective response rate was 55.2%, median PFS was 7.4 months (95% C.I.: 5.1-9.6), and median survival was not reached. All 42 patients were assessed for safety. This treatment was relatively tolerable with grade 3/4 neutropenia in 11.9%/9.9%, grade 2/3 anemia in 12.6%/5.3%, febrile neutropenia in 6.0% of cycles. Non-hematologic toxicities were grade 2/3 nausea in 21.4%/2.4%, grade 2/3 vomiting 7.1%/2.4%, grade 2 general weakness in 7.1%, grade 2 general ache in 11.9% and grade 2 anorexia in 7.1% of patients.

Conclusion: Taxol, cisplatin and S-1 combination chemotherapy showed significant antitumor effect with manageable and tolerable toxicities in patients with metastatic stomach cancer.

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A PHASE II STUDY OF S-1 COMBINED WITH IRINOTECAN AND OXALIPLATIN IN PATIENTS WITH METASTATIC GASTRIC CARCINOMA

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Background: We conducted a phase II study of S-1 combined with irinotecan and oxaliplatin to evaluate the efficacy and toxicity in pts with metastatic gastric cancer (MGC).

Methods: Pts with MGC, age ≥18 yrs, ECOG PS 0-2, measurable lesion, adequate organ function, and no prior chemotherapy were eligible. S-1 40 mg/m² was given twice daily, p.o. on D1-14, irinotecan 150 mg/m² and oxaliplatin 85 mg/m² i.v. on D1 every 3 weeks. Treatment was continued for a maximum of 12 cycles until disease progression or unacceptable toxicity.

Results: From Jun. 2007 to Dec. 2007, planned 44 pts have been enrolled. Clinical characteristics were as follows: median age=54 yrs (range, 27-66); M/F=34/10; PS 0/1/2=0/41/3; recurrent/initial metastatic disease=5/39; and the number of metastatic organ site 1/2/≥3=14/19/11. A total of 324 cycles were administered up to now, with a median of 8 cycles per pt (range, 1-12). Among 42 efficacy-evaluable pts, 4 pts had a complete response (9.5%), 28 pts (66.7%) a partial response, 7 pts (16.7%) stable disease, and 3 pts (7.1%) progressive disease; the overall response rate was 76.2% (95% CI, 63.3-89.1%). 6 pts (14.3%) had a biopsy-proven complete regression in primary gastric tumor. At a median follow-up of 6.7 months (range, 3.0-9.3+), the median TTP and OS were not reached. Updated survival data will be provided at presentation. Among 44 toxicity-evaluable pts, the most common G3/4 toxicity was neutropenia (61.4% of pts) and 6 pts (13.6%) had G3 febrile neutropenia. Grade 3 non-hematological toxicities included abdominal pain (13.6%), diarrhea (11.4%), anorexia (9.1%), nausea (4.5%), vomiting (4.5%), and fatigue (4.5%).

Conclusion: Triple combination of S-1, irinotecan, and oxaliplatin is a highly active regimen with a tolerable toxicity profile as a first-line chemotherapy in MGC. (Irinotecan, oxaliplatin, and S-1 were provided by Pfizer Inc., sanofi-aventis Korea, and Boryung Inc., respectively)

529P

FOLLOW UP OF A MULTICENTER PHASE II STUDY OF SEQUENTIAL PACLITAXEL AND S-1 (TXL/S1) AS POSTOPERATIVE ADJUVANT CHEMOTHERAPY FOR GASTRIC CANCER (GC)

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Background: Of patients who undergo R0 resection for GC with serosal invasion (T3-4), more than half recur mainly in the peritoneum, while TXL and S1 exhibited efficacy for diffuse type and peritoneal metastases in the phase II studies. Primary analysis of the sequential chemotherapy with TXL/S1 had shown its safety and tolerability, its survival benefit is being tested in a large phase III study (the SAMIT trial) with oral fluoropyrimidines as controls. The analysis for survival of this preceding phase II study is performed.

Methods: Eligibility criteria included histologically proven GC; sT3-4; sN0-2; M0 (except peritoneal cytology: CY); post D2-3 gastrectomy and R0-1; ECOG PS 0-1; and 20-80 years old. On postoperative day 14 to 56, patients received 3 courses of weekly TXL (80mg/m² on day 1, 8 for the 1st course and on day 1, 8, 15 for the 2nd and 3rd courses, repeated every 3 or 4 weeks) followed by 4 courses of S1 (80mg/m² daily for 2 weeks, repeated every 3 weeks). The primary endpoints were % of patients who completed all 7 courses (compliance) to see whether the lower 95% confidence limit of compliance was greater than 69% and incidence of severe toxicities and the secondary endpoints were 3-year survival and toxicities.

Results: 50 patients were accrued from May 2003 to March 2004. The median age was 63 (range 34-74); male/female: 34/16; pT2/T3/T4: 1/44/5; CY0/CY1: 4/46; stage2/3a/3b/4: 12/15/16/7. The overall compliance was 84%. Median follow up time was 1279 days for survivors (1212-1605). Three-year DFS were 68% for all; stage 2/3a/3b/4: 83.3/86.7/43.8/57.1 (%). Three-year OS were 74% for all; stage 2/3a/3b/4: 83.3/86.7/62.5/57.1 (%).

Conclusions: Sequential TXL/S1 may serve as an active adjuvant for gastric cancer patients especially who are at high risk for peritoneal spread.

530P

RANDOMIZED PHASE II STUDY OF CISPLATIN AND HIGH-DOSE 5-FLUOROURACIL/LEUCOVORIN OR PACLITAXEL AND HIGH-DOSE 5-FLUOROURACIL/LEUCOVORIN IN LOCALLY ADVANCED OR METASTATIC GASTRIC CANCER AND ADENOCARCINOMAS OF THE GASTRO-OESOPHAGEAL JUNCTION

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Background: First-line treatment of advanced or metastatic gastro-oesophageal adenocarcinoma with high-dose 5-fluorouracil plus leucovorin (HDFU/LV) in combination with cisplatin (CDDP) has previously shown response rates (RR) of approximately 40%. This randomised phase II trial compared this regimen with HDFU/LV and paclitaxel.

Methods: Patients (pts) with measurable histologically confirmed adenocarcinoma were randomized into 2 groups. Arm A (n=50): weekly 5FU (2.0 g/m² d 1,15,22,29,36) plus LV (500 mg/m²) and biweekly CDDP (50 mg/m² day 1,15,29) with cycles repeated every 7 weeks. Arm B (n=45): weekly 5FU (2.0 g/m² d1,8,15) plus LV (500 mg/m²) and weekly paclitaxel (80 mg/m² d1,8,15) with cycles repeated every 4 weeks. Treatment was continued until disease progression or up to 24 weeks of treatment. The primary endpoint was RR.

Results: So far of all 95 pts, 87 are evaluable for response of whom 28 pts still on treatment. Results are presented of the first 59 pts and 94 pts for toxicity. The best overall RR (ORR) was 47% (95% CI, 28-66%) for arm A (5FU/LV/CDDP), and 45% (95% CI, 26-64%) for arm B (5FU/LV/paclitaxel). The median time to progression (TTP) was 3.9 months (mo) (0.3-18.5) for arm A vs. 4.2 mo (0.1-16.4) for arm B. The median overall survival time (OS) was 4.9 mo (1.0-19.1) for arm A vs. 5.4 mo (0.7-26.2) for arm B. Haematological toxicity was common, although WHO grade 3-4 toxicity only occurred in 2 patients in group A. Neutropenic fever occurred in 3 resp. 4

pts of whom 1 pt died (group A). Non-hematological adverse reactions were usually mild to moderate; WHO grade 3-4 toxicities included emesis in 5 pts, fatigue in 7 pts, stomatitis in 2 pts, with a majority of pts in group A, diarrhoea in 6 pts, with a majority in group B and thromboembolism in 3 pts (all in group A).

Conclusions: These results suggest that both treatment arms have comparable overall response rates, TTP and OS. Paclitaxel in combination with HD 5FU/LV however had a slightly better toxicity profile.

531P PHASE II STUDY OF CETUXIMAB PLUS WEEKLY CISPLATIN AND 24-HOUR INFUSION OF HIGH-DOSE 5-FLUOROURACIL AND LEUCOVORIN FOR THE FIRST-LINE TREATMENT OF ADVANCED GASTRIC CANCER

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Introduction: Cisplatin-HDFL regimen, using weekly 24-hour infusions of cisplatin and high-dose 5-fluorouracil (5-FU) and leucovorin, is commonly used in Taiwan for patients with advanced gastric cancer (GC), producing an overall response rate of around 60% (95% CI: 45%-76%) [J Clin Oncol (Suppl) 2006; 24(18S): A14063]. We have demonstrated that cetuximab is cytotoxic to human GC cells, and has a chemosensitizing effect for cisplatin and 5-FU in GC cells [Proc AACR 2006; 47: A1233].

Methods: All patients had pathologically confirmed recurrent/metastatic chemo-naïve GC, at least 1 measurable lesion, a fasting serum triglyceride level > 70 mg/dl, WHO PS 0/1/2, adequate hepatic, renal, and marrow functions. Cetuximab 400 mg/m² was given as 2h infusion, initially (i.e., D1 of cycle 1); and followed by weekly 1h infusion of 250 mg/m² (i.e., D8, D15, D22 of cycle 1, and D1, D8, D15, D22 of cycle 2). Cisplatin 35 mg/m² was given as a 24h infusion, admixing with 5-FU 2,000 mg/m² and leucovorin 300 mg/m² (HDFL), D1, D8. A 24h infusion of HDFL was given on D15. Cycles were repeated every 28 days, and response evaluation was performed every 2 cycles & at the end of protocol treatment. The primary end-point was confirmed objective response rate (RR) by RECIST.

Results: Between Dec. 2005 and Mar. 2008, 31 patients (M:17, F:14) with a median age of 58 (40-74) were enrolled and evaluable for response. The overall RR was 67.7% (48-83%, 95% C.I.) with 1 CR and 20 PRs. Among total 177 cycles (median: 5, range: 2 to 14+ cycles) given, Gr3/4 neutropenia, infection, and hepatic toxicity developed in 7.3%, 5.1%, and 1.1% of 177 cycles, respectively. Two patients have developed acute hepatitis B flare-up among nine HBsAg (+) carriers, and were well controlled by oral lamivudine. Gr1, Gr2, and Gr3 acne-like rashes have developed in 54.8%, 35.5%, and 6.5%; Gr1, Gr2, and Gr3 paronychia have developed in 38.7%, 9.7%, and 3.2% of 31 patients, respectively. Both median PFS (range: 2+ to 14+ months) and median OS (range: 2+ to 28+ months) have not been reached yet.

Conclusions: Cetuximab plus cisplatin-HDFL is an effective regimen with low toxicities in the first-line treatment of advanced GC.

532P A PROSPECTIVE PHASE II STUDY OF CETUXIMAB IN COMBINATION WITH XELOX (CAPECITABINE AND OXALIPLATIN) IN PATIENTS WITH METASTATIC AND/OR RECURRENT ADVANCED GASTRIC CANCER

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Objective: We evaluated the efficacy and safety of cetuximab in combination with XELOX chemotherapy in previously untreated patients with advanced gastric cancer (AGC). The objectives were to evaluate the overall response rate (RR), progression-free survival (PFS), overall survival (OS), safety and tolerability of cetuximab plus XELOX.

Patients and methods: Previously untreated metastatic and/or recurrent AGC patients received intravenous infusion of cetuximab 400mg/m² on day 1 (starting dose) followed by weekly infusion of 250mg/m². Oxaliplatin 130mg/m² was administered intravenously on day 1 and capecitabine 1,000mg/m² bid was administered orally for 14 days of a 3-week cycle. Patients were treated until disease progression or intolerable toxicities for a maximum of 8 cycles. On completing 8 cycles of chemotherapy, non-progressing patients were allowed to receive weekly cetuximab until progression. Response evaluations were done every two cycles, and toxicities were collected at each visit.

Results: Forty-four patients (29 male) were enrolled; median age was 57.5 years (range 36-70). In total, 250 cycles of XELOX chemotherapy (median 6.5 cycles) and 843 cetuximab infusions (range 1-54, median 19.0) were delivered. Overall RR was 52.3%

(all partial responses). Median PFS was 6.6 months (95% CI, 4.9-8.3), and estimated median OS was 15.9 months with 29 patients (66%) alive at a median follow up of 7.2 months. The most common hematologic toxicities of all grades were anemia (81.8% of patients). Grade 3-4 hematologic toxicities were uncommon (anemia, 6.8%; thrombocytopenia, 2.3%). Common non-hematologic toxicities of all grades included asthenia (81.8%), anorexia (79.6%), hand-foot syndrome (79.6%), acneiform skin eruption (77.2%), and sensory neuropathy (75.0%), and were mostly grade 1 or 2. Reported SAEs included two CVAs, one tumor bleeding, one E coli sepsis, one grade 3 infusion reaction to cetuximab, and one interstitial lung disease. There was no treatment-related death.

Conclusions: Cetuximab in combination with XELOX chemotherapy was active and safe as first-line treatment of metastatic and/or recurrent AGC patients.

533P BIWEEKLY COMBINATION CHEMOTHERAPY OF DOCETAXEL, IRINOTECAN AND CISPLATIN AS SECOND-LINE TREATMENT FOR ADVANCED GASTRIC CANCER

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Background: Insufficient data is available on the efficacy or safety of new drug combination regimens after the progression following first-line chemotherapy for treating advanced gastric cancer. Docetaxel (DOC), irinotecan (CPT-11), and cisplatin (CDDP) are active cytotoxic agents currently used for treating gastric cancer. The synergic effects of CPT-11 and CDDP are already known, and recently those of DOC and CDDP have been reported. **OBJECTIVE:** We conducted a retrospective investigation to evaluate the antitumor effects and toxicity of a biweekly combination regimen of DOC, CPT-11, and CDDP for patients with metastatic or recurrent gastric cancer.

Patients and methods: Sixty-eight patients with histologically confirmed metastatic or recurrent gastric cancer and a history of at least one prior chemotherapy regimen were included. Entry criteria included histological diagnosis of gastric adenocarcinoma, Eastern Cooperative Oncology Group performance status of 0 to 2, and preserved bone marrow, liver, and renal function. In a previously conducted phase 1 study, patients received DOC, CPT-11, and CDDP at the dosage of 25 mg/m², 40 mg/m², 20 mg/m², respectively, on days 1 and 15 every 4 weeks. Disease evaluation was performed after every 2 cycles.

Results: First-line treatment was the fluoropyrimidine anticancer drug S-1 in 77.9%, CDDP and infusional 5-fluorouracil (5-FU) in 11.8%, and infusional 5-FU in 2.9% of the patients. The median number of courses in the present regimen was 8.5 (range, 1-19). The overall response rate was 34.5% (20/58) in measurable lesions. Median survival time was 11.1 months from the commencement of this treatment. All patients were evaluated for toxicity. Grades 3-4 toxicities were observed for leukopenia (13.2%), neutropenia (20.6%), and anemia (2.9%), anorexia (7.4%), vomiting (2.9%), fatigue (2.9%), diarrhea (4.4%), and allergic reaction (1.5%).

Conclusions: The combination of DOC, CPT-11, and CDDP is active and well tolerated as second-line chemotherapy for gastric cancer patients. Further studies are needed to test the effectiveness and role of this combination therapy as a second-line treatment for advanced gastric cancer.

534P THE ROLE OF OXALIPLATIN-CONTAINING REGIMENS IN THE TREATMENT OF ADVANCED GASTRIC CANCER: A META- ANALYSIS OF THE PHASE III RANDOMIZED TRIALS

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Objective: Gastric cancer is one of the most common malignancies in China. The prognosis of advanced gastric cancer remains poor. For these patients, systemic chemotherapy is the main treatment option. Although many chemotherapeutic regimens have been tested, there is no standard care. In recent years, many hospitals in China have carried out clinical studies of oxaliplatin-containing regimens for gastric cancer. The main objective of this meta-analysis was to determine the role of oxaliplatin-containing regimens in the treatment of advanced gastric cancer.

Patients and Methods: Using a prospective meta-analysis protocol, two independent investigators reviewed the publications and extracted the data. Fully published randomized controlled trials (RCTs) done in China were included, which compared oxaliplatin/fluorouracil/leucovorin regimen with cisplatin/fluorouracil/leucovorin regimen in the management of advanced gastric cancer. The censor data were up to October 2007. Efficacy and tolerability were the primary outcome measure.

Results: Twelve RCTs which included 734 patients (369 in oxaliplatin/ fluorouracil/ leucovorin arm, 365 in cisplatin/fluorouracil/leucovorin arm) were eligible. The overall response rates of two arms were 50.9% and 41.5% respectively with rate difference (RD) 0.089 (95%CI 0.015 to 0.163; P=0.018). The one-year overall survival rate were 53.4% and 43.5% respectively with RD 0.108 (95%CI 0.007 to 0.209; P=0.036). Grade 3/4 toxicities such as neutropenia, thrombocytopenia, diarrhea, stomatitis and peripheral neuropathy were similar between two arms, but oxaliplatin-containing

regimen was associated with lower incidence of grade 3/4 nausea/vomiting (6.7% vs. 28.7%, $P=0.000$).

Conclusion: This is the first meta-analysis of oxaliplatin/fluorouracil/ leucovorin regimen vs cisplatin/ fluorouracil/leucovorin regimen in the treatment of advanced gastric cancer, which included RCTs only done in China. The result confirmed that oxaliplatin-containing regimen was associated with higher response rate, improved overall survival and a favorable toxicity profile compared with cisplatin-containing regimen.

535P CAPECITABINE AS FLUOROPYRIMIDINE OF CHOICE IN COMBINATION CHEMOTHERAPY FOR ADVANCED AND/OR METASTATIC GASTRIC CANCER

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Background: Fluoropyrimidine-based chemotherapy remains basic in Advanced Gastric Cancer (AGC) treatment. Recently several new drugs have shown to be active in this disease (f.i. docetaxel and oxaliplatin). Oral fluoropyrimidine Capecitabine (Xeloda®) has proved non-inferiority to i.v. 5-FU in gastric cancer, avoiding central venous devices associated risks. This trial evaluate the efficacy and safety of Capecitabine (Xeloda®) in combination with different chemotherapy agents in AGC.

Methods: Patients (p) with histologically confirmed AGC, CCR >60 ml/min, ECOG < 2 and normal LFT were included. P were treated at investigators discretion with any of the following: Cisplatin, Capecitabine (CX) (80 mg/m² d1/21d and 1.000 mg/m² bid for 14 days/3 weeks); Epirubicine, Cisplatin and Capecitabine (ECX) (50 mg/m² d1/21d, 60 mg/m² d1/21d and 625 mg/m² bid continuously); Docetaxel, Cisplatin, Capecitabine (DCX) (60 mg/m² d1/ 21d, 60 mg/m² d1/21d and 825 mg/m² bid for 14 days/ 3 weeks), and Epirubicine, Oxaliplatin, Capecitabine (EOX) (50 mg/m² d1/21d, 130 mg/m² d1/21d and 625 mg/m² bid continuously). Primary objective was safety profile and secondary was efficacy in terms of overall response rate and overall survival.

Results: 158 p were recruited from 03/07 to 02/08. Data from 152 pats are available. Median age: 61 years (20-79) Most p were male (71%) and Caucasic (98%) with Adenocarcinoma histology (91%). ECOG 0/1/2 was (%) 40.9/49.6/9.4. The DCX combination was used in 35% of p, followed by CX (27%), ECX (20%) and EOX (18%). There was a clear correlation between PS, age and chemotherapy election. Thus, 92% of p treated with DCX had PS<1. Although 1 every 4 p were older than 70 years, DCX was rarely used in that population (only 7.4% vs 40%CX, 29.0%ECX or 29.6%EOX). Preliminary data from 65 p show overall response rate (RR) 53%. Per treatment group RR was: ECX 46%, CX 37.5%, DCX 75%, EOX 45%. 41% of the p had an Adverse Event. (AE). Most frequent AE were emesis (48%) and diarrhea (33.8%). Hand-foot syndrome was present in 10 p, with only 1p with grade 3.

Conclusions: Capecitabine (Xeloda®) can be used as fluoropyrimidine of choice in combination with cisplatin, epirubicine, docetaxel and/or oxaliplatin, showing a similar efficacy and safety profile as i.v. 5-FU. Analysis is ongoing and updated results will be presented

536P SECOND-LINE THERAPY WITH BIWEEKLY PACLITAXEL AFTER FAILURE OF FLUOROPYRIMIDINE BASED TREATMENT IN PATIENTS WITH ADVANCED OR RECURRENT GASTRIC CANCER: RESULTS OF A MULTICENTER PHASE II TRIAL

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Background: There is no established treatment regimen for advanced or recurrent gastric cancer failure of standard fluoropyrimidine based first-line chemotherapy. Paclitaxel (PTX) has shown promising clinical activity and most common schedule in the gastric cancer is weekly administration. Thus weekly schedule is feasible, the patient should be squandered much time, we planned to establish biweekly PTX. Dosage of biweekly PTX was decided on the bases of phase I study (Koizumi, W. et al. Anticancer Res: 3797-802, 2006.).

Methods: Eligibility criteria: age 20-80 years, failure of first-line fluoropyrimidine single-agent or combination therapies with measurable and unresectable histopathologically confirmed gastric cancer, ECOG performance status 0-2. PTX was administrated at 140 mg/m² q2w (1 hour infusion) and pre-medication with H1, H2

blocker and steroid. Primary endpoint was response rate, secondary endpoints were progression free-survival and overall survival and safety.

Results: 41 pts were recruited between November 2004 and April 2007 and 40 pts were evaluated (one pt. was not treated). The median age was 63 (range: 48-77) years and male:female ratio was 31:9. 32 pts has received S-1 alone, 5 pts has received S-1 combination therapy, PS 0/1/2 was 22/13/5. Median of treatment cycle was 7 (range: 1-28) cycles. Seven partial responses, 21SD, 10PD, 2NE were confirmed, giving an overall response rate of 17.5% (95% CI: 7.3% to 27.7%). Disease control rate (PR+SD) was 70.0%. At median follow-up of 255 days, the median progression-free survival was 111 days, whereas median overall survival was 254 days. Grade 3/4 neutropenia occurred in 11 pts (28%), while febrile neutropenia was not observed. Most common non-hematologic toxicity was sensory neuropathy (grad 1/2/3: 16/9/1 65.0%). There were no treatment-related deaths.

Conclusion: Biweekly paclitaxel was found to be well tolerated and effective in patients with advanced or recurrent gastric cancer after failure of fluoropyrimidine based treatment.

537P COMPARISON OF TOXICITY, TOLERABILITY AND OUTCOME BETWEEN ASHKENAZI AND SEPHARDIC JEWS IN ISRAEL RECEIVING POSTOPERATIVE CHEMORADIATION FOR LOCALLY ADVANCED GASTRIC CANCER

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Background: The Israeli Jewish population is heterogenic. Its two main ethnic subgroups are the Ashkenazi and Sephardic Jews, differing in some genetic and life style features. Data on differences in toxicity and tolerability of chemotherapy or radiotherapy among different ethnic groups is very limited; such data on the Jewish subpopulations in Israel is essentially absent. The aim of this study was to evaluate possible differences in toxicity and tolerability between Ashkenazi and Sephardic Jews using postoperative chemoradiation for locally advanced gastric cancer (LAGC) as a model.

Patients and methods: Between 6/2000 and 12/2007, 84 Ashkenazi patients (pts) and 60 Sephardic pts underwent postoperative chemoradiation after R0 or R1 resection of LAGC. The treatment regimen was the one used in the INT-116 trial (Macdonald, NEJM, 2001). Parameters of treatment related toxicity and administration were compared using standard statistical methods.

Results: Pts and tumor characteristics in both groups were comparable. Ashkenazi Jews experienced significantly higher rates of all grade fatigue (58% vs. 32% $p=0.001$) and anorexia (49% vs. 30% $p=0.02$) compared to Sephardic Jews. Ashkenazi pts also showed a trend toward a higher rate of diarrhea of any grade (39% vs. 25% $p=0.052$). The incidence of other toxicities (hematological, gastrointestinal and dermal) was similar between the groups. Administration of chemotherapy and radiotherapy, as measured by dose intensities of 5-fluorouracil and leucovorin and the rates of dose reductions, irradiation delays, and completion of each treatment modality, did not differ between the two groups. The Ashkenazi and Sephardic Jews had comparable rates of progression free and overall survival.

Conclusions: Ashkenazi Jews receiving postoperative chemoradiation for LAGC seem to experience more toxicity compared with Sephardic Jews. Their lower tolerability of treatment, however, was not found to affect the actual administration of treatment or patients' outcome. To our knowledge, this is the first trial comparing treatment toxicity, tolerability and outcome between these two ethnic groups.

538P CHARACTERISTICS OF PATIENTS WITH EARLY GASTRIC CANCER WHO HAD UNDERGONE SURGERY IN SINGLE INSTITUTE

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Background: The incidence of early gastric cancer (EGC) has been increasing worldwide owing to advances with diagnostic techniques and screening programs. Radical gastrectomy with lymph node dissection is still the gold-standard treatment for EGC. The present study was designed to investigate the characteristics of EGC patients who had undergone surgery.

Methods: According to the Japanese classification of gastric carcinoma, EGC is defined as a lesion confined to the mucosa or submucosa, regardless of the presence of regional lymph node metastasis. We reviewed 529 patients with gastric cancer who had undergone gastrectomy at Ulsan University Hospital, Ulsan, Korea, from December 2002 to December 2005.

Results: Two hundred sixty-one patients (49%) were diagnosed as EGC (155 intramucosal EGC (mEGC), 106 intrasubmucosal EGC (smEGC), 123 differentiated EGC, and 138 undifferentiated EGC). One hundred sixty-one patients (61.7%) were male and median age was 55. The mean diameter of tumor was 2.49 ± 1.55 cm (2.18 ± 1.45 cm in mEGC and 2.94 ± 1.60 cm in smEGC, $p=0.000$). The incidence of lymph node metastasis was 11.5% (30 out of 261 patients). Univariate analysis revealed that a tumor larger than 2 cm (17.6% vs. 6.3%), submucosal invasion (20.8% vs. 5.2%), and the presence of lymphovascular invasion (LVI) (33.3% vs. 6.6%) were significantly associated with a higher lymph node metastasis rate. There were no significant associations between lymph node metastasis and differentiation, age, gender, tumor location, macroscopic type, CEA level, or CA19-9 level. In multivariate analysis, LVI was independent predictive factor for lymph node metastasis ($p=0.005$), while submucosal invasion was marginally predictive ($p=0.069$) and tumor size was not ($p=0.208$). At a median follow-up of 1023 days, only 2 patients relapsed and 1 patient died due to disease progression.

Conclusions: LVI was independent predictive factor for lymph node metastasis. In cases that LVI was present after endoscopic resection, radical gastrectomy should be recommended. Endoscopic resection data will be analyzed and compared with surgery data.

539P COMPARISON OF TWO ADJUVANT CHEMOTHERAPY REGIMENS FOR LOCALLY ADVANCED GASTRIC CANCER WITH LONG TERM FOLLOW-UP

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Background: Although adjuvant chemotherapy (CTX) has demonstrated small but significant survival benefit in locally advanced gastric cancer in several meta-analyses, optimal chemotherapy regimen remains to be determined.

Methods: We retrospectively analyzed the survival of 313 locally advanced gastric cancer patients (pts) (stage IB: 28, II: 95, IIIA: 89, IIIB: 46, IV: 55) who underwent adjuvant CTX after curative resection (³D2 dissection). One hundred and six pts received 5-FU, doxorubicin (DOX) CTX (5-FU 500 mg/m² weekly for 36 wks, DOX 40 mg/m² q 3 weeks x 12) with or without OK432 (FA group), while 207 pts underwent 5-FU, mitomycin-C (MMC), and polysaccharide-K (PSK) CTX (5-FU 500 mg/m² weekly for 24 wks, MMC 8 mg/m² q 6 wks x 4, PSK 3 g/day for 16 wks) (FM group).

Results: The median follow-up durations of survivors in the two groups were 149 (134-163) months (FA group) and 113 (93-136) months (FM group), respectively. The stage distribution and mean age in the two groups were almost identical. There was no significant difference in 8-year overall survival (OS) between FA and FM groups (52.8% vs. 55.6%, $p=0.755$). FM group showed superior 8-year OS (80.0% vs. 64.1%, $p=0.034$) compared with FA group in stage IB or II patients, while there was no statistically significant difference in 8-year OS (39.0% vs. 46.3%, $p=0.175$) in stage IIIA to IV patients.

Conclusions: 5-FU, MMC, and PSK CTX for 24 wks is as effective as 5-FU and DOX-based CTX with longer treatment duration and even superior in stage IB and II pts.

540P A RETROSPECTIVE ANALYSIS OF SECOND-LINE CHEMOTHERAPY VERSUS BEST SUPPORTIVE CARE (BSC) IN PATIENTS WITH ADVANCED GASTRIC CANCER (AGC)

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Purpose: Because treatment of AGC patients after failure with first-line chemotherapy remains controversial, we performed this retrospective analysis based on the data obtained from 254 patients enrolled in 3 consecutive prospective randomized trials with respect to receiving or not receiving subsequent chemotherapy.

Methods: The decision for administering second-line chemotherapy was, in all cases, at the discretion of the physician. One-hundred sixty (63%) received second-line chemotherapy (second-line group) in the context of second-line clinical trials, and 94 (37%) received BSC (BSC group). There were significant differences between second-line and BSC groups in terms of age, response to first-line chemotherapy, and performance status after first-line treatment.

Results: Three (1%) complete and 48 (19%) partial responses to second-line chemotherapy were observed for an overall response rate of 20% (95% confidence interval, 15 to 25%). The median survival was 7 and 3 months ($P < 0.001$) for the second-line and BSC groups, respectively. Multivariate analysis revealed that only performance status was significantly associated with longer survival. The administration of second-line chemotherapy was also independently correlated with improved survival.

Conclusion: Performance status could be used to identify the subgroup of patients most likely to benefit from second-line chemotherapy for AGC.

541P WHICH IS BETTER IN PATIENTS WITH RADICALLY RESECTED EXTRAHEPATIC BILIARY TRACT CANCER?: ADJUVANT CONCURRENT CHEMORADIATION (CCRT) ALONE VERSUS CCRT FOLLOWED BY MAINTENANCE CHEMOTHERAPY

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Background: There is currently no standard adjuvant therapy for patients (pts) with curatively resected extrahepatic biliary tract cancer (EHBTC). The role of adjuvant concurrent chemoradiation (CCRT) alone or CCRT followed by maintenance chemotherapy (MC) is not yet established.

Patients and methods: We enrolled pts with EHBTC who received radical resection and then received adjuvant CCRT with or without MC between 2000 and 2006 at Seoul National University Hospital. 5-fluorouracil (5-FU) was administered at a dose of 500mg/m² on D1,2,3 and D28, 29, 30 along with 40-50 Gy of external beam radiation. MC was delivered with 5-FU based regimen for 6-12 months. We retrospectively analyzed the clinical features, disease free survival (DFS) and overall survival (OS) between adjuvant CCRT alone and CCRT followed by MC.

Results: Total 122 pts were enrolled. The median age was 62 years (range 24-87) and male was 91. Eighty one pts received R0 resection (pathologically negative margins) and 41 pts R1 resection (microscopically positive margins). The median follow-up duration for all pts was 20 months. 3-year DFS and 3-year OS rate were 40.9% and 63.7%, respectively. Out of 122 pts, 30 received CCRT alone and 92 received CCRT followed by MC. Baseline characteristics were comparable between the two groups. 3-year DFS rates for the CCRT alone and CCRT followed by MC were 26.6 and 45.3% ($p=0.04$) and 3-year OS rates were 36.2% and 71.9% ($p=0.003$) respectively. There was no statistical difference between both groups in the pattern of treatment failure such as local and systemic recurrence ($p=0.463$). For subgroups with R1 resection, CCRT followed by MC led to longer OS and DFS than CCRT alone. Also, CCRT followed by MC showed more prolonged OS and DFS than CCRT alone in negative nodal state, but not in positive nodal state.

Conclusions: In patients with curatively resected EHBTC, adjuvant CCRT followed by MC had significant prognostic impact on DFS and OS compared with CCRT alone.

542P TEMOPORFIN IMPROVES TUMORICIDAL EFFICACY OF PHOTODYNAMIC THERAPY (PDT) FOR BILE DUCT CANCER

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Aim: Local ablation of hilar bile duct cancer (BDC) using porfimer and laser irradiation (632nm) of tumour stenoses improves obstructive cholestasis and survival time, although the tumoricidal effect is confined to inner 4mm of the tumour wall (6-9 mm) resulting in TTP >6 months. We have studied (EUDRA CT Nr. 2005-004866-17), whether temoporfin-based PDT (T-PDT, 652 nm) shows twice as deep tumoricidal tissue penetration and similar adverse events.

Methods: Eleven patients (7:4 f / m; age 71 [55 - 88] yrs) with hilar BDC (Bismuth III and IV) were treated with T-PDT and analysed according to the two-stage Simon optimal design for the tumoricidal depth of T-PDT and additional parameters. When tumoricidal penetration of 7.5 mm in >2 of 11 patients, another 24 patients will be studied in the 2nd stage of the trial to validate T-PDT.

Results: From 11 patients followed for median 9.3 [range 2.3- 27] months after T-PDT, two had died after 5 months (due to liver abscess, or peritoneal carcinosis, resp.), and one (lost to endoscopic follow-up) after 18.5 months (from undrained liver abscess). Cholestasis improved in all, palliation in 8. BDC ablation with T-PDT showed a local partial response in 8, local complete response in 1, and residual

tumour (biopsy after 6 weeks) in another one of 10 patients (tumoricidal efficacy 90%). At least 4 patients exhibited tumoricidal depth >7-8 mm, i.e. two had a complete necrosis of a 24 mm and a 15mm thick polypoid tumour, resp., one the widening by 14 mm of a scirrhous tumour stenosis, and one the complete necrosis of a BDC (>6-7 mm thick). As adverse events, we observed 4 cases with phototoxic skin reactions (2x grade I, 1x grade II; 1x grade III [the temoporfin-injected vein]), 3 cases with cholangitis (cured with antibiotics), and 3 liver abscesses (one fatal; two cured with a Yamakawa-type drainage).

Conclusion: Temoporfin-PDT, as compared with porfimer-PDT, shows doubling of the tumoricidal depth (to >7-8 mm), tumoricidal efficacy of ~90%, a similar rate of infectious complications and grade I and II skin phototoxicity. Stage 2 of the trial needs to confirm the superior tumoricidal efficacy and minimize infectious complications.

This study is partly supported (for temoporfin and light source) by biolitec pharma Ltd.

543P **A PHASE II STUDY OF COMBINATION CHEMOTHERAPY WITH S-1 AND OXALIPLATIN IN PATIENTS WITH RECURRENT UNRESECTABLE OR METASTATIC BILIARY CANCER**

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Objectives: Although there is currently no established palliative standard of treatment for biliary cancer, 5-fluorouracil-based chemotherapy has been considered the mainstay of palliative chemotherapy. Oxaliplatin has also shown antitumor activity with a favorable toxicity profile for this tumor. We conducted a phase II study of combination chemotherapy with substituting S-1 for 5-fluorouracil and oxaliplatin in patients with advanced biliary cancer and evaluated the efficacy and toxicities of this regimen.

Methods: Patients with metastatic or recurrent biliary adenocarcinoma were enrolled for this study. They received oral S-1 40 mg/m² twice daily on days 1-14, and intravenous oxaliplatin 130 mg/m² on day 1. This cycle was repeated every 21 days. Patients who benefited from the treatment were continued on treatment for a maximum of nine cycles of treatment.

Results: Forty-nine patients were enrolled from September 2006 through January 2008. Ten patients (20%) had gallbladder cancer, 9 patients (18%) had intrahepatic cholangiocarcinoma, and 30 patients (61%) had extrahepatic cholangiocarcinoma. A total of 206 cycles of treatment was done to 49 patients (median 3 cycles, range 1-9 cycles). Of these, 45 patients were evaluable for response and all 49 patients were assessable for safety. The overall objective response rate was 25% (12 partial response and 0 complete response), with 35% of patients with stable disease in the intention-to-treat population. The median progression-free survival and overall survival were 3.7 months (95% confidence interval, 2.0 to 5.4) and 9.5 months (95% confidence interval, 6.9 to 12.0), respectively. The most common grade 3/4 toxicity was vomiting (22%) and other common grade 3/4 toxicities were neutropenia (14%), anorexia (14%) and asthenia (10%).

Conclusions: The combination chemotherapy of S-1 and oxaliplatin has effective antitumor activity and is well tolerated in patients with advanced biliary cancer.

544P **BEVACIZUMAB IN PATIENTS (PTS) WITH ADVANCED HEPATOCELLULAR CARCINOMA (HCC): RESULTS OF A PHASE II STUDY WITH CIRCULATING ENDOTHELIAL CELL (CEC) MONITORING**

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Objective: The primary objective of this phase II trial was assess the 16 weeks disease control rate (DCR) in pts with advanced HCC treated with bevacizumab.

Material and methods: Pts with unresectable HCC received bevacizumab at 5-10 mg/kg bimonthly. Prior treatment for HCC was allowed. Main ineligibility criteria included Child-Pugh score > 7; CLIP score > 3; recent (< 6 months) thromboembolic event; and anticoagulation or anti-platelet therapy. Propranolol had to be prescribed in case of large esogastric varices. CEC, identified by a CD45 CD31⁺CD146⁺7AAD⁻ phenotype by four-color flow cytometry, were measured at day (D) 1,3,15 and 46 after start of treatment.

Results: Overall, 43 pts (34 men; median age, 66 years [range, 23-84]; histologically proven cirrhosis, 32 pts; Child-Pugh A5/A6/B7/B8: 17/21/3/2; CLIP 0/1/2/3/4/5: 4/9/14/13/2/1) received a median of 8 injections (range, 2-39; total, 462). A progressive disease (PD) was observed within 16 weeks in 12 pts after inclusion of the first 23 pts treated at 5mg/kg, subsequent pts (n=20) were treated at 10 mg/kg as planned by the protocol design. Out of the 40 pts who stopped treatment, 29 (73%) discontinued bevacizumab because of progression, 4 (10%) because of decompensated cirrhosis, 4 (10%) because of potential treatment related toxicity (lower limb ulcer (n=1), grade 2 (n=1) and grade 3 (n=1) proteinuria, grade 2 gastrointestinal bleeding (n=1)), and 3 (8%) others causes. Among the 38 pts evaluable for efficacy, 5 (13%) had confirmed partial response (PR), and 20 (53%) had stable disease (SD) (> 16 weeks in 13 pts (34%) resulting in a 16 weeks DCR of 47% (95% confidence interval:31-64). Median baseline CEC level (n=33) was 15/ml (range, 2-62), as compared to 5.5/ml (range, 0-15) in healthy subjects (n=20) and 16/ml (range, 0-179) in pts with various metastatic cancers (n=80).

Conclusion: Bevacizumab is relatively safe and provides an encouraging DCR in patients with HCC and compensated cirrhosis. The predictive value of CEC will be presented at the meeting.

545P **SORAFENIB IS EFFECTIVE IN PATIENTS FROM THE ASIA-PACIFIC REGION WITH HEPATOCELLULAR CARCINOMA (HCC): SUBGROUP ANALYSIS OF MACROSCOPIC VASCULAR INVASION (MVI), EXTRAHEPATIC SPREAD (EHS), AND ECOG PERFORMANCE STATUS**

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Objective: We performed a subanalysis of the Phase III randomized, placebo-controlled, double-blind Asia-Pacific (A/P) study of single-agent sorafenib for unresectable HCC to evaluate the efficacy and safety of sorafenib in patients with known baseline predictors of poor prognosis.

Methods: Patients with advanced, unresectable, measurable HCC, ECOG PS 0-2, CP A/B, and no prior systemic therapy for HCC were randomized 2:1 to sorafenib 400 mg BID or placebo. End points included overall survival (OS), disease-control rate (DCR; defined as complete/partial response, or stable disease by RECIST, maintained for ≥28 days from first demonstration), and safety. Stratification factors for the subanalysis included ECOG PS (0 vs 1/2) and tumor burden (defined as presence or absence of MVI and/or EHS).

Results: Median OS and DCR for each stratification category are shown in the table.

Stratification Category	OS (Sorafenib/Placebo)		DCR (%) (Sorafenib/Placebo)	
	Median HR (mo)	(95% CI)		
Overall study population: sorafenib (n=150) vs placebo (n=76)	6.5/4.2	0.68 (0.50, 0.93)*	53.3	29.0
Pts with MVI and/or EHS: sorafenib (n=118) vs placebo (n=61)	5.6/4.1	0.75 (0.54, 1.05)	30.5	11.5
Pts without MVI and/or EHS: sorafenib (n=32) vs placebo (n=15)	14.3/8.0	0.45 (0.19, 1.06)	53.1	33.3
Pts with PS 0: sorafenib (n=38) vs placebo (n=21)	7.1/8.1	0.77 (0.42, 1.44)	39.5	23.8
Pts with PS 1/2: sorafenib (n=112) vs placebo (n=55)	6.1/3.9	0.61 (0.42, 0.88)	33.9	12.7

*P=0.014 The incidence of grade 3/4 drug-related adverse events (AEs) across these subgroups was consistent with that reported for the overall population. The most common grade 3/4 AEs in the sorafenib and placebo groups, respectively, were hand-foot skin reaction (7-12% vs 0%), diarrhea (3-16% vs 0%), and fatigue (0-5% vs 0-2%).

Conclusions: Sorafenib is effective for the treatment of HCC in patients from the A/P region, independent of ECOG PS or MVI/EHS. The safety profile of sorafenib in the subpopulation described was comparable with that for the overall population. Further studies with a larger sample size are warranted.

546P **SAFETY AND ANTITUMOR ACTIVITY OF NGR-HTNF, A SELECTIVE VASCULAR TARGETING AGENT (VTA), ADMINISTERED AT LOW DOSE IN PRE-TREATED PATIENTS (PTS) WITH HEPATOCELLULAR CARCINOMA (HCC): PRELIMINARY RESULTS OF A PHASE II TRIAL**

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Background: NGR-hTNF is a VTA exploiting a tumour homing peptide (NGR) selectively binding angiogenic vessels in solid tumours, where NGR-hTNF specific binding relies on dynamic interactions with TNF-receptors and aminopeptidase N/CD13. NGR-hTNF combines activity on tumour vascular permeability and direct anticancer activity, both at low doses and at high doses.

Methods: Pts with unresectable, recurrent or metastatic HCC were treated with a low dose of NGR-hTNF given at 0.8 µg/m² as 1-hour intravenous infusion every 3 weeks (q3w). This phase II trial had a 2-stage design with 16 and 27 pts to be enrolled in first and second stage, respectively. Progression-free survival (PFS) was the primary endpoint and tumour reassessment was performed q6w.

Results: To date, 22 pts with progressive disease following prior loco-regional treatment (59%), systemic therapy (41%), or both (18%), have been recruited. Pts characteristics were: M/F 17/5; median age 67 years (range, 53 to 79); PS 0/1 17/5; Child-Pugh score A/B: 18/4. Globally, 63 cycles (median, 2; range, 1 to 8) were administered and 6 pts (27%) have received ≥4 doses. Neither grade 3-4 treatment-related adverse events nor toxicity-related death were observed. Main grade 1-2 toxicities per patient were infusion-related constitutional symptoms, including chills (59%), and transient blood pressure increase (14%). A confirmed partial response lasting 3.3+ months was observed in one patient with lung and node metastases. Stabilization of disease occurred in an additional 5 pts with a median duration of 4.3 months (range, 2.6 to 5.9 months). The median and 3-month PFS were 2.5 months (95% CI, 1.8 to 3.1 months) and 42% (95% CI, 18 to 63%), respectively. Currently, the study is completing recruitment into the second stage.

Conclusion: NGR-hTNF given at 0.8 µg/m² q3w is well tolerated and appears to induce promising disease control in pre-treated patients with advanced HCC. The drug will be further developed as single agent exploring a weekly schedule of administration in this setting.

547P **TUMOR NECROSIS AS A CORRELATE FOR RESPONSE IN SUBGROUP OF PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA (HCC) TREATED WITH SORAFENIB**

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Objective: In a phase II trial of sorafenib in patients with advanced HCC (Abou-Alfa, et al, 2006), sorafenib-treated patients exhibited a partial response rate of 29%; however, 33.6% of patients had stable disease (SD) for ≥16 weeks, and central tumor necrosis in response to sorafenib was common. We performed a sub-analysis to evaluate the correlation between tumor necrosis and response.

Methods: Using baseline and follow-up triphasic CT scans; liver lesions were manually delineated by an experienced radiologist. A k-means method was used to initialize the necrosis segmentation. To refine the result of necrosis, a maximum a priori (MAP) method was applied, which jointly considered density distributions of necrosis and tumor and a priori knowledge of piece-wise contiguity. Wilcoxon rank sum test was used to test for differences in changes from baseline in the ratio of necrosis and tumor volume (N/T) and AFP between responding (SD or SD with necrosis) and non-responding (progression of disease) patients. A landmark analysis was performed, in which overall survival (OS) was computed from the date of the last CT scan to the date of death or last follow-up. Univariate Cox-models were employed to evaluate the association between OS and changes from baseline in N/T and in AFP.

Results: CT scans of 12 patients (median age, 73 years; 8 male) were evaluated. 5 patients had SD or SD with necrosis; 7 progressed on therapy. Median survival (from landmark analysis) was 3.1 months (4.8 months and 3.1 months in responders and non-responders, respectively). N/T was significantly associated with response, with

responders having greater increases in the ratio between necrosis and tumor volume relative to baseline, as compared to non-responders (P=0.02), N/T was not significantly associated with OS. Change from baseline in AFP levels was not associated with response or OS.

Conclusions: Sorafenib, like other systemic anti-angiogenic therapies, can exert its therapeutic effect as "tumor necrosis". The data presented show an association between response and N/T. N/T as a surrogate of response needs to be further evaluated as part of a large clinical study.

548P **A PHASE II TRIAL OF HEPATIC ARTERIAL INFUSION CHEMOTHERAPY WITH CISPLATIN FOR ADVANCED HEPATOCELLULAR CARCINOMA WITH PORTAL VEIN TUMOR THROMBOSIS**

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Background: The objective of this study was to evaluate the antitumor, survival, and adverse effects of hepatic arterial infusion chemotherapy using cisplatin in patients with advanced hepatocellular carcinoma (HCC) and portal vein tumor thrombosis (PVTT).

Methods: Twenty-five patients with advanced HCC with PVTT in the main or first branch who had no prior chemotherapy, with measurable lesions, adequate liver and renal function, and adequate bone marrow reserve, were enrolled. A dose of 65 mg/m² cisplatin was administered from the proper hepatic artery. Treatment was repeated every 4 to 6 weeks for a maximum of six courses, if there was no evidence of tumor progression or unacceptable toxicity. The primary end-point was the tumor response to this regimen, and the secondary end-point was toxicity, survival and progression-free survival.

Results: The median number of treatments was 3 (range: 1-6). Among the 25 enrolled patients, 1 (4%) achieved a complete response, 6 (24%) had a partial response, and the response rate was 28% (95% confidence interval: 12-49%). The serum AFP and PIVKA II levels were reduced by more than 50% in 44% and 68% of the patients who had shown a pretreatment level of 100 U/ml or greater and 100 mAU/ml or greater, respectively. The median survival time, 1-year survival rate and median progression-free survival for the patients as a whole were 10.3 months, 40.3%, and 4.4 months, respectively. The main grade 3 and 4 non-hematological toxicities of this treatment were elevation of the aspartate aminotransferase (44%) and alanine aminotransferase (24%) levels, but no grade 4 hematological toxicity was seen. These toxicities were generally brief and well tolerated.

Conclusion: Hepatic arterial infusion chemotherapy with cisplatin has moderate activity with mild toxicity in HCC patients with PVTT, and this is expected to be confirmed in a prospective randomized controlled study.

549P **ROLE OF CONCURRENT TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION (TACE) DURING FLUOROPYRIMIDINE AND CISPLATIN-BASED SYSTEMIC CHEMOTHERAPY IN PATIENTS WITH METASTATIC HEPATOCELLULAR CARCINOMA**

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Background: The role of local intrahepatic tumor control by TACE during systemic chemotherapy in patients with metastatic HCC is uncertain

Patients and methods: We analyzed advanced HCC patients with more than one measurable metastatic lesion, no prior systemic chemotherapy and good liver function (Child-Pugh A,B) who received fluoropyrimidine derivative (5-FU or capecitabine) and cisplatin combination chemotherapy between October 2001 and June 2007 at Seoul National University Hospital and Seoul National University Bundang Hospital.

Results: A total 89 patients (5-FU+cisplatin ;57, capecitabine+cisplatin ;32) were enrolled. Male was 76 (85.4%) and the median age was 53 years (range 25-70). The overall response rate was 10.2% and disease control rate was 38.6%. The median TTP was 2.3 months (95% CI 1.7-2.9) and median OS 9.5 months (95% CI 5.3-13.7).

Patients with intrahepatic viable tumor (n = 60) had shorter TTP (HR 2.25, p = 0.006) and OS (HR=1.72, p=0.08) than did patients without intrahepatic viable tumor in multivariate analysis. 11 patients of 60 received the concurrent TACE during systemic chemotherapy. The clinical and demographic characteristics including age, etiology, PS, portal vein thrombosis, AFP and chemotherapy regimen were not different between concurrent TACE group (n = 11) and systemic chemotherapy only group (n = 49). The concurrent TACE group showed longer TTP (6.5 vs 1.9 months, p=0.00) and OS (17.4 vs 5.8 months, p=0.03) than did systemic chemotherapy only group. The frequency of hematologic and non-hematologic toxicity including liver transaminase showed no significant difference between two groups.

Conclusions: In patients with metastatic HCC, the presence of intrahepatic viable tumor is poor prognostic factor during systemic chemotherapy and in that case, the concurrent TACE for local tumor control during systemic chemotherapy is beneficial in terms of TTP and OS.

550P ASSESSMENT OF THE THERAPEUTIC RESPONSE OF HEPATOCELLULAR CARCINOMA TREATED WITH RADIOFREQUENCY ABLATION : COMPARISON OF CONTRAST-ENHANCED ULTRASONOGRAPHY AND COMPUTED TOMOGRAPHY

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Purpose: The purpose of this study was to assess the efficacy of contrast-enhanced ultrasonography (CEUS) with perflubutane microbubbles (Sonazoid[®] / DD723 / NC100100) to evaluate the therapeutic response to radiofrequency ablation (RFA) of hepatocellular carcinoma (HCC) in comparison with contrast-enhanced computed tomography (CECT).

Material and method: From April 2007 to January 2008, 25 patients with 30 HCCs within 3cm were included. CECT and CEUS were performed in all patients after RFA treatment in the following 2-7 days later. Total 39 assessments of therapeutic response were performed. Absence of contrast enhancement and presence of ablative margin in the treated HCCs were statistically analyzed. CECT was used as gold standard in analyzing the accuracy of CEUS.

Results: Follow-up CECT detected residual lesions in 2 of 39 assessments and incomplete ablative margins in 18 of 39 assessments. CEUS detected residual lesions in 2 of 39 assessments and incomplete ablative margins in 18 of 39 assessments. CEUS predicted the CECT results 90% (sensitivity 90%, specificity 89%, positive predictive value 90%, negative predictive value 89%).

Conclusion: Contrast-enhanced ultrasonography with perflubutane microbubbles has high diagnostic accuracy compared with CECT in assessment of RFA treatment response.

551P SORAFENIB IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA: EXPERIENCE IN SINGLE INSTITUTE

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Background: Sorafenib is the first drug which showed survival benefit in advanced hepatocellular carcinoma (HCC) by randomized clinical trial. In the trial, however, only patients with good liver function, Child-Pugh (CP) class A were enrolled. In this retrospective study, the efficacy and feasibility of sorafenib in practice setting were evaluated including patients with CP B.

Methods: Clinical data from 97 unresectable or metastatic HCC patients who were treated with sorafenib in Asan Medical Center were reviewed. Tumor response was assessed using RECIST criteria.

Results: Between May 2006 and December 2007, 97 patients enrolled. Ninety percent of the patients was male and median age, 53 years. Ninety one percent of the patients had HBsAg (+) and CP A and B were 70% and 30%, respectively. Median duration of treatment with sorafenib was 48 days (range, 1-451 days). Only five (5.2%) patients achieved a partial response and 43 (45%) patients had stable disease. Disease control rate (PR+SD) is higher in CP A than CP B (57.4% vs 32.1%, p=0.04). After a median follow-up of 189 days, the median progression free survival (PFS) of all patients was 68 days and the median overall survival (OS) was 214 days. According to the CP class, PFS was 72 and 48 days (p=0.12) in CP A and B. Median OS was not reached in CP A and 111 days in CP B (p=0.009). Hematologic toxicities of grade 3/4 were rare. Fatigue of grade 1/2 was developed in 12.4% of patients and grade 1/2 diarrhea in 14.6%. Fatigue or diarrhea of grade 3/4 was not observed. Hand-foot syndrome was developed in 56.2%, including grade 3 in 9%.

Conclusion: The results of this study showed that the efficacy and safety of sorafenib in practice setting is compatible with the results of clinical trial in advanced HCC. However, in patients with Child-Pugh class B, disease control rate and OS was lower than in Child-Pugh class A.

552P EFFECT OF SORAFENIB TREATMENT ON LEFT VENTRICULAR EJECTION FRACTION IN CANCER PATIENTS: AN OPEN-LABEL, PHASE I STUDY

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Background: Hypertension (HTN) is a recognized class effect of anti-VEGF therapy. Reduction in left ventricular ejection fraction (LVEF) and clinical congestive heart failure (CHF) recently associated with these compounds suggests a potential anti-VEGF effect. LVEF was evaluated in cancer patients (pts) following 2 and 4 cycles (C, 28 d) of sorafenib monotherapy.

Methods: This open-label, 2-center study enrolled 53 pts with solid tumors or lymphomas. 35 pts were expected to complete ≥4 sorafenib (400 mg bid) C. LVEF was evaluated using multiple gated acquisition (MUGA) scanning. Scans were performed at baseline (BL), on day 1 of cycles 3 and 5, and within 2 weeks after the last dose of sorafenib. Other coprimary endpoints measured were QT/QTc interval on ECG, heart rate, and blood pressure.

Results: Preliminary data from all treated pts showed a slight decrease from BL in mean LVEF at the start of C3, and a further slight decrease at the start of C5. There was no clinically significant change in mean LVEF from BL to that observed at the start of C5. Similar results were observed in the subgroup of pts who received ≥75% of all scheduled sorafenib doses, including just prior to MUGA scans. On day 1, C5, 2 pts showed changes from BL in LVEF >10 EF%, 1 pt had an increase in LVEF of 17 EF% (BL: 63%) and 1 pt had a decrease in LVEF of 23 EF% (BL: 73%). CHF occurred in 1 pt, concurrently with pulmonary embolism; both Adverse Events resolved simultaneously. Results from all 4 coprimary endpoints will be presented when available.

LVEF Data: Treated Pts*						
Time of LVEF Assessment	Ejection Fraction (%)			Change from Baseline in Ejection Fraction (%)†		
	n	Mean	SD	n	Mean	SD
BL	32	64.93	±7.04	—		
Cycle 3	31	63.93	±8.27	31	-0.83	±8.58
Cycle 5	24	62.94	±8.32	24	-1.22	±7.75

*preliminary data

†from each pt with a BL & post-BL MUGA scan.

Conclusions: These preliminary data do not suggest any notable effect of sorafenib on LVEF following 4 cycles of therapy. The effect of long-term sorafenib use on LVEF is currently unknown. Unlike HTN, reduction in LVEF and clinical CHF may not be categorized as class effects based on available data. Additional research is warranted to compare the cardiac safety profile of sorafenib with that of other multitargeted TKIs and anti-angiogenics.

553P SORAFENIB IS NOT ASSOCIATED WITH A HIGH INCIDENCE OF CARDIOVASCULAR EVENTS IN MANY TUMOR TYPES

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Objective: Sorafenib has been shown to be effective in improving overall survival (OS) in patients (pts) with hepatocellular carcinoma (HCC) (SHARP Study; Llovet JM, ASCO 2007; median OS vs placebo, 10.7 vs 7.9 mo; P=0.0006). In a preplanned secondary analysis (censoring placebo pts at crossover) of a pivotal Phase III trial (TARGET; Escudier B, NEJM 2007; median progression-free survival [PFS] vs placebo, 5.5 vs 2.8 mo; P<0.01), sorafenib doubled PFS and demonstrated an OS advantage in pts with clear-cell renal-cell carcinoma (RCC). Adverse cardiovascular (CV) events,

including myocardial infarction (MI), hypertension (HTN), congestive heart failure (CHF), and arrhythmia, have been associated with anti-angiogenic tyrosine kinase inhibitors (TKIs) as a class effect (Force T, Nat Rev Cancer, 2007). We performed a pooled analysis of clinical-trial data to determine the incidence rates of CV events during sorafenib monotherapy.

Methods: Data from 18 completed Phase I-III sorafenib monotherapy trials across multiple tumor types (breast, colorectal, HCC, RCC, non-small cell lung cancer) were combined to form the clinical data pool. A total of 2127 sorafenib-treated pts were evaluated for incidence of CV events (of any CTC grade).

Results: CHF was reported in 34 pts (1.6%), and was a SAE in 21 pts (1.0%). One pt experienced a decrease in left-ventricular ejection fraction, and one pt sustained left-ventricular failure. MI was reported in 32 pts (1.5%), and was a serious adverse event (SAE) in 29 pts (1.4%). Treatment-emergent HTN, which is frequently associated with anti-angiogenic TKIs, occurred in 395 pts (18.6%), and was a SAE in 11 pts (0.5%). Most cases of HTN were grade 2 or 3 (6.4% and 8.1%, respectively). Severe HTN occurred in 5 pts (0.2%), and was a SAE in 4 pts (0.2%). Additional CV safety data will be presented.

Conclusions: Overall, the incidence of CV events reported for pts receiving sorafenib in a large clinical data pool was low, and most events were clinically manageable. HTN was the most common event; the majority of cases were mild-to-moderate in severity and were manageable with standard antihypertensive therapy. These results suggest that except for HTN, adverse CV outcomes are not a class effect of sorafenib.

554P COMBINATION CHEMOTHERAPY (CHT) FOLLOWED BY CHEMORADIATION FOR STAGE III PANCREATIC ADENOCARCINOMA (PA)

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Objectives: Role and timing of CHT and radiation for treating stage III PA remains controversial, yielding a median survival of 8 to 12 months. We evaluated the outcome of a strategy consisting of sequential combination CHT and chemoradiation.

Methods: Treatment-naïve patients (pts) with 18-75y, performance status (PS) >50 and stage III PA not resectable, who were enrolled in trials assessing 4-drug combinations in advanced disease, were considered for this analysis. CHT was PEFG/PEXG (cisplatin, epirubicin, 5fluorouracil (F)/capecitabine (X), gemcitabine) or PDXG (same as above with docetaxel substituting epirubicin). Pts without progression (PD) after a maximum of 6 months of induction CHT received radiation (50-60 Gy) with concurrent F or X.

Results: Between October 97 and December 2006, 79 pts (44 males, median age 63y, median PS 1) were registered. Best response to CHT was partial remission in 38 pts (48%) and stable disease in 32 (41%). Eleven patients (14%) were radically resected yielding 2 pathologic complete remissions; 56 pts (71%) received planned chemoradiation, while 23 did not due to: refusal (N=6; 8%); clinical deterioration (N=4; 5%); systemic (N=5; 6%) local and systemic (N=3; 4%) or isolated local PD (N=4; 5%); pathologic complete remission (N=1; 1%). Median survival (OS) was 16.5 months; 2y and 5y OS was 19% and 5%. Among 38 partial responders, 11 pts submitted to surgery lived longer than 27 pts who remained not amenable to resection (median OS 21+ versus 17; 2y OS 72% versus 12%; p=.003). Median progression-free (PF) survival was 10.5 months. Pattern of failure was known in 61 of 71 failing patients and consisted of isolated local failure (N=21; 34%); both local and systemic failure (N=12; 20%); isolated systemic failure (N=28; 46%). Noteworthy, among pts with known pattern of failure, local failure was reported in 19 of 50 pts (38%) receiving radiotherapy and in 5 of 6 pts (83%) refusing radiotherapy.

Conclusion: Combination CHT with 4-drug regimens followed by chemoradiation was a feasible strategy showing relevant results in this large series of stage III PA. Isolated local failure during induction CHT was rare and radiotherapy seems to improve local control. Systemic failure remains the main issue.

555P AN ITALIAN SURVEY OF METASTATIC PANCREATIC ADENOCARCINOMA (PA) TREATMENT OVER THE LAST DECADE

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Background: Since Gemcitabine (G) became the standard treatment for patients (pts) with metastatic PA, combination chemotherapy (CHT) obtained conflicting results on survival (OS) improvement. A series of 767 pts treated between Jan 97 and Dec 2006 in 10 Italian centers was analyzed.

Methods: Data on pts characteristics, diagnosis, treatment and outcome were provided. Inclusion criteria were: histological or cytological diagnosis of metastatic PA; age >18 y, performance status (PS) > 3, no prior CHT.

Results: Median age was 62y, median PS 1. G was included in upfront treatment in 675 pts (88%). Single agent CHT was used in 425 pts (55%; G 416); doublets in 116 pts (15%; G-based 109); G-free triplets in 76 pts (10%); G-based 4-drug regimens in 150 pts (20%). With respect to treatment trends (1997-2001 versus 2002-2006), G alone was the most used therapy in both periods (49%; 57%); G-fluoropyrimidine doublets were administered in 8% and 2% of cases; G-platinating agent doublets in 1% and 14%; G-free triplets in 17% and 7%; G-based 4-drug regimens in 21% and 19%. Median and 1y survival for all patients was 6.7 months and 22%, respectively. Patients' characteristics, outcome and results of univariate analyses are reported in the table. Multivariate analysis confirmed that PS, basal CA19.9 and 4-drug regimens use are independent predictors for OS.

Conclusions: This survey confirms the prognostic value of PS and CA 19.9 in metastatic PA. Data suggest that OS may be improved by G-platinum doublets when compared to G alone and that 4-drug regimens may be superior in terms of response rate and OS to both G alone and G-platinum doublets

Variable	Subgroup	Number	Response (CR +PR)	mOS (months)	p- value
Age	<65y >65y	428 339		6.6 8.7	.5
Gender	male female	432 335		6.8 6.5	.5
PS	0 1 2	306 293 77		7.6 6.0 3.1	<.001 (0 vs 1) <.001 (1 vs 2)
CA 19-9	normal >normal and <5xULN >5xULN	94 92 512		9.0 7.5 6.4	.14 (normal vs <5xULN) <.001 (<5xULN vs >5xULN)
Period	97-2001 2002-06	231 536		6.8 6.6	.23
Regimen	1. G 2. G-free triplets 3. G + platinum compound 4. 4-drug G-based	416 76 150	11% 8% 16% 48%	5.8 5.8 6.9 9.0	.29 (2 vs 1) .01 (3 vs 1) <.00001 (4 vs 1) .06 (4 vs 3)

556P FERMENTED MISTLETOE (VISCUM ALBUM L.) EXTRACT AS LONG-TERM SUPPORTIVE CARE IN PANCREATIC CARCINOMA OF UICC STAGES I-IV

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Objectives: To evaluate efficacy and safety of a mistletoe extract (Iscador®, ISC) in supportive care of patients with pancreatic carcinoma of any UICC stage as compared with a parallel control group without ISC.

Methods: In a retrospective multicenter observational cohort study, ISC was given in addition to conventional adjuvant chemo- and radiotherapy (ConT) or passive aftercare. The control received ConT or passive aftercare only. Unselected, anonymized data from medical records of patients, that satisfied the eligibility criteria, were followed until last visit or death. All endpoints were adjusted to baseline imbalances, therapy regimen and other confounders.

Results: 396 (201 ISC, 195 control) patients from 17 centers were evaluable. Median follow up was 15 vs. 10 months, median ISC therapy duration 15 months. Significantly fewer ISC (13.7%) than control patients (48.9%) had ConT-related ADR (p<0.001), had fewer persistent symptoms during the therapy (p=0.006), had an on average 17 days shorter hospitalization (p<0.001), and showed a 42% hazard reduction in overall survival (OS-HR=0.58, p=0.001). No severe ISC-related ADRs or tumor enhancement were observed.

Subgroup analysis: In a subgroup analysis the survival results (OS) were calculated separately for the four UICC stages I-IV.

UICC I (N=49): The multivariable-adjusted OS analysis in this subgroup revealed a HR=0.76 (95%-CI: 0.33-1.77), p=0.522, suggesting a non-significant trend in relative mortality hazard reduction (by 24%) in favor of the ISC group during therapy and follow-up.

UICC II (198): HR=0.49 (0.30-0.82), p=0.006, significant hazard reduction by 51%.

UICC III (61): HR=0.81 (0.33-1.99), p=0.651, non-significant trend to hazard reduction by 19%.

UICC IV (88): HR=0.56 (0.30-1.02), p=0.058, distinct non-significant trend to hazard reduction by 44%.

Conclusion: As compared to control, the ISC-treated group showed significantly fewer ConT-related ADR, fewer disease- and therapy-related symptoms and longer overall survival. The OS results suggest a possibly independent, beneficial effect of supportive ISC treatment in any stage (UICC I-IV) of pancreatic carcinoma patients, in the attempt to extend survival.

557P GEMCITABINE, OXALIPLATIN AND CAPECITABINE (GEMOXEL) FOR PATIENTS WITH ADVANCED PANCREATIC ADENOCARCINOMA (APC). PRELIMINARY RESULTS OF AN ONGOING PHASE I/II TRIAL

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Introduction: Gemcitabine (GEM) is the mainstay of palliative chemotherapy for patients with advanced pancreatic cancer (APC). Recent randomized trials have shown increased clinical benefit with the addition of oxaliplatin (OXA) and prolonged median survival with the addition of capecitabine (CAP) to GEM. Primary objective of the first part of this ongoing phase I/II study was to find the recommended dose of OXA and CAP in the triple combination.

Methods: Chemotherapy-naïve patients with histologically proven, locally advanced or metastatic adenocarcinoma of the pancreas were treated with a total of 6 3-week cycles of GEM (1000mg/m² iv, d 1, 8), CAP (650mg/m² po, bid, d 1-14) and escalating doses of OXA iv, d 1. The OXA dose was escalated in cohorts of 3-6 patients (no inpatient dose escalation). After OXA escalation up to the dose level of 130mg/m², CAP was escalated.

Results: 40 patients were included. The first 20 patients analyzed here received a total of 93 cycles (median 6, range 1-6). Median age was 63 years (range 43-74), 8 patients were female. Median baseline Karnofsky Performance Score was 90% (range 80-100). 4 patients had locally advanced disease. The liver was the primary site of metastases in 14 out of the 16 patients with distant metastases. DLTs were observed at the OXA dose level of 130mg/m² and CAP dose of 800mg/m² bid, d1-14. Grade 3 or 4 toxicities according to NCICTC v3.0 possibly related to chemotherapy were reported in 28 of 93 cycles: thrombocytopenia in 11, neutropenia in 11, SIRS in 1, diarrhea in 4, nausea in 1 cycle. Of 18 patients assessable for response (RECIST criteria), 4 had a partial remission, 9 a disease stabilization and 5 showed progression.

Conclusions: The recommended dose -currently studied in the ongoing phase II trial- is OXA 130mg/m² on d 1, CAP 650mg/m² bid, d 1-14, combined with GEM. This combination is safe for first-line treatment of APC patients with mild, mainly hematological, toxicity.

558P SECOND-LINE CHEMOTHERAPY IN GEMCITABINE PRETREATED ADVANCED PANCREATIC CANCER: ANALYSES ON PROGNOSTIC AND PREDICTIVE FACTORS

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Background: Many advanced pancreatic cancer (APC) patients are eligible for second-line chemotherapy (SLCT) after progression on gemcitabine (GEM) based chemotherapy (CT). However, the clinical outcomes as well as prognostic and predictive factors in this setting have been poorly studied.

Methods: We enrolled APC patients who received SLCT after progression on GEM based CT from 2001 through 2006 at Seoul National University Hospital. Twenty four clinical variables at the time of SLCT were retrospectively analyzed, with objective tumor response, CA 19-9 response and other clinical outcomes.

Results: A total of 105 patients were enrolled. Median age was 60 years and 67% were male. Performance status was ECOG 0/1 in 64%. Chemotherapy regimens were as follows: fluoropyrimidines based CT in 62%; GEM based CT in 32%; other CT in 6%. Median follow-up was 22 weeks. Overall response rate was 6.7% (95% CI 1.9~11%) and disease control rate was 30% (95% CI 22~39%). Time to progression (TTP) and overall survival (OS) from the day of SLCT were 9.1 weeks (95% CI 6.7~12 weeks) and 23 weeks (95% CI 20~25 weeks), respectively. In multivariate analyses, performance status (HR 0.591), baseline CA 19-9 level (HR 0.577) and GEM sensitivity (HR 0.591), as defined by relapse > 1 month, at the time of SLCT were significant independent prognostic factors for OS. Also, objective tumor response and/or early (after 1 or 2 cycles of treatment) CA19-9 response of more than 20% were associated with prolonged OS and TTP. Chemotherapy regimens used did not affect the treatment outcome.

Conclusions: In GEM pretreated APC patients under SLCT, good performance status, low baseline CA 19-9 level, and GEM sensitivity are prognostic factors for OS. Response to SLCT (RECIST and/or CA19-9) is predictive for prolonged OS and TTP.

559P A CLINICAL PRACTICE SURVEY OF STAGE III PANCREATIC CARCINOMA (PC) TREATMENT

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Background: To assess treatment trends and efficacy in stage III PC, a series of 623 patients (pts) treated between 1997 and 2006 in 10 Italian centers was analyzed.

Methods: Data on pts characteristics, treatment and outcome were collected. Inclusion criteria were: histological or cytological diagnosis of stage III PC; age >18 y, performance status (PS) > 3, no prior chemotherapy or radiotherapy.

Results: Median age was 63y, median PS 1. Upfront chemoradiation was rarely used (6%). Most of pts (94%) received upfront chemotherapy with 19 different regimens including gemcitabine (G) in 508 cases (81.5%). Treatment consisted of: G (N= 325; 52%), G-platinum compound doublets (N=75; 12%), G-fluoropyrimidine doublets (N=18; 3%); G-based 4-drug combinations (N=90; 14.5%), fluorouracil (N=18; 3%) and intra-arterial G-free triplets (N=57; 9%). The use of G-platinum compound doublets and of 4-drug regimens increased over time (1997-2001: 2% and 9%; 2002-2006: 19% and 18%) while the inverse trend was observed for G-fluoropyrimidine doublets (5% and 1%), chemoradiation (9% and 4%) and intra-arterial treatment (14% and 6%). G alone was extensively used in both periods (56%; 49%). Median, 1y and 2y survival (OS) for all patients was 10.9 months, 43% and 11%. Results of univariate analyses are reported in the table. Multivariate analysis stratified by center and year of diagnosis showed that CA19.9 (HR 1.27; 95CI 1.03-1.58; p=0.03) and 4-drug regimens use (HR 0.66; 95CI 0.46-0.94; p=0.02) independently predict OS.

Conclusions: This very large survey shows that upfront chemotherapy is a widely used therapeutic strategy for stage III PC. No standard treatment exists. However, the addition of a platinum compound to G seems to improve OS over G alone. Further OS prolongation may be yielded with 4-drug regimens

Variable	Subgroup	Number	Median OS (months)	OS (%)	OS (%)	1y	2y	p-value
Age	< 65y > 65y	339 284	11.0 10.8	42 13	44 10			.15
Gender	male female	338 285	10.5 11.2	40 11	46 11			.26
PS	0 1 2	220 292 77	13.0 9.5 9.0	55 14	37 10			<.001 (0 vs 1)
						34	8	.19 (1 vs 2)
CA 19.9	normal > normal and <5xULN >5xULN	130 124 336	11.0 13.5 10.0	43 12	56 7			.09 (normal vs <5xULN) <.001 (<5xULN vs >5xULN)
Period	1997-2001 2002-2006	260 363	10.5 11.3	40 10	44 13			.09
Regimen 1.	G 2. G-free triplets 3. G + platinum compound 4. 4-drug G-based	325 57 75 90	9.7 8.3 13.5 15.6	36 8	36 8 60 21			.38 (2 vs 1) .0005 (3 vs 1) <.00001 (4 vs 1) .11 (4 vs 3)

560P PLASMAIC VEGF AND KRAS STATUS: PROGNOSTIC VALUE IN PANCREAS CANCER

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Background: In several tumours, micro-vascular density (MVD) and expression of vascular endothelial growth factor (VEGF), have been associated with prognosis. Recently, a significant correlation of elevated VEGF levels with poor prognosis and K-RAS status has been shown in gastrointestinal cancers.

Methods: We aim to evaluate the clinical and prognostic significance of plasmaic VEGF (pVEGF) levels, MVD and K-RAS status in patients with pancreatic cancer (PC). We examined pVEGF levels in samples from 39 patients with resected PC and we correlated the results with the clinico-pathological features of PC, MVD and K-RAS. The Mann-Whitney and Chi-square tests were used to evaluate differences between groups. Survival curves were calculated using the Kaplan-Meier method and compared by the log rank test. The Cox regression model was used for multivariate analyses. Significance was presumed at P<0.05. Tumour specimens were

immunohistochemically stained for CD31 (endothelial marker). The concentrations of pre-surgical pVEGF were measured by an enzyme linked immunosorbent assay. DNAs from human PC were analysed for the presence of K-RAS gene mutations by polymerase chain reaction followed by direct sequencing.

Results: A pVEGF cut-off level of 230 pg/ml, was determined based on a graphic operating curve. The survival for patients with high pVEGF levels was shorter compared with that for patients with low pVEGF levels ($P=0.012$). Multivariate analysis indicated that only the VEGF status was a significant factor for prognosis (HR =9,651; CI 95% 1.113-83.69; $P=0.040$). The median follow-up time was 9 months (range 0.7- 37.7 meses). The median pVEGF level in patients with tumor recurrence was 269.09 (range 98.6-1201.71 pg/ml), versus 109.01 (range 0-965.83 pg/ml) in patients with no recurrence tumor ($P=0.025$). By now, we have examined the K-RAS status in 15 pancreatic tumors. We are increasing this number to verify the preliminary results concerning K-RAS status.

Conclusions: The results of this study show that patients with pancreatic carcinoma who have high pre-surgical pVEGF levels are associated with a poor prognosis and we hypothesize that K-RAS oncogene mutation may be associated with these pVEGF levels and the outcome of these patients.

561P **DETECTION OF METHYLATION IN THE CPG ISLANDS OF THE P16INK4A, RASSF1A AND METHYL-GUANINE METHYL-TRANSFERASE (MGMT) GENE PROMOTERS IN PANCREATIC ADENOCARCINOMA (PC)**

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Pancreatic cancer consists of an accumulation of genetic and epigenetic alterations. Methylation is an important epigenetic mechanism of transcriptional regulation during tumor development. We examined the methylation status of p16^{INK4A}, RASSF1A (tumor suppressor) and MGMT (DNA repair) genes considered to be inactivated by promoter methylation in several tumours. The p16^{INK4A} is an important G1/S cell cycle regulator gene. RASSF1A gene is involved in apoptotic signalling, microtubule stabilization and cell cycle progression. MGMT gene removes mutagenic adducts from the O6-position of guanine in DNA. Little is known about the exact role of hypermethylation of these genes in PC, as the molecular mechanisms underlying these neoplasms remain poorly understood.

Patients and methods: Tumor specimens from 13 PC patients (M/F: 8/5, mean age 67.2 years, range 54 -79) were evaluated for epigenetic alterations of p16^{INK4A}, RASSF1A and MGMT genes. Genomic DNA was extracted from formalin-fixed paraffin-embedded tumor tissues. DNA methylation was determined by chemical modification of genomic DNA with sodium bisulfite and subsequent double "hot start" Methylation-Specific PCR (MSP). All double MSPs were performed with controls for unmethylated and methylated alleles followed by detection on agarose gel. The results on promoter methylation of all genes were correlated with known clinicopathological parameters.

Results: The p16^{INK4A} gene was methylated in all 13 pts. RASSF1A was methylated in 2pts while the MGMT gene was methylated in the only patient with poorly differentiated PC. The same patient has also methylated and the RASSF1A gene. Lymph node status did not correlate with methylation of gene promoters in PC pts.

Conclusions: Our findings suggest that p16^{INK4A} gene is commonly down regulated in PC through a promoter hypermethylation of CpG islands. Further studies of promoter hypermethylation within RASSF1A and MGMT genes, with more pts, are now carried out in order to assess if the methylation status may afford an accurate diagnostic molecular marker and predictor of neoplastic behaviour of PC.

562 **EFFICACY OF DOCETAXEL, OXALIPLATIN AND CAPECITABINE COMBINATION REGIMEN IN ADVANCED GASTROESOPHAGEAL CANCERS**

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Background: Cisplatin based chemotherapy remains the treatment of choice for metastatic gastroesophageal cancers. Docetaxel, Cisplatin & 5-FU (DCF) is an effective treatment, however quite toxic. With this background, we conducted a pilot study combining Docetaxel, Oxaliplatin & Capecitabine in such patients. Docetaxel and capecitabine have synergistic action, as docetaxel upregulates thymidine phosphorylase enzyme in tumor cells. This enzyme converts capecitabine to its active metabolite, 5-FU that kills tumor cells. Oxaliplatin was used instead of cisplatin due to the equivalent efficacy and better side effect profile of the former.

Methods: Patients with advanced gastroesophageal cancer received oxaliplatin 50 mg/m² and docetaxel 40 mg (fixed dose) on day 1 and day 8, with capecitabine 625 mg/m² BID from day 1 to 14, in 21-day cycles.

Results: 21 chemo-naïve patients were enrolled; 16 males & 5 females; median age was 57 yrs. 18 patients had adenocarcinoma & 3 had squamous cell carcinoma. 13 patients had LN mets, 6 had liver mets, 5 had omental mets, 5 had ascites, 2 had peritoneum mets, 2 had lung mets & 1 had CNS mets. 19 patients took a minimum of 3 cycles. Of 19 evaluable patients, 1 achieved complete response (CR) (5%), 5 partial response (PR) (26%), 4 stable disease (SD) (21%) and 9 progressive disease (PD) (47%), resulting in a response rate (RR) of 31%, after 3 cycles. Of the 11 patients who continued further therapy, 2 CR (18%), 2 PR (18%), 3 SD (27%) and 4 PD (36%), with a RR of 36% was seen. A maximum of 6 cycles of chemotherapy were given. The median survival for 19 patients was 9 months. The protocol was well tolerated in 57 % patients. Severe side effects of diarrhoea and pain abdomen due to Capecitabine were seen in 9 (43%) patients. This was managed by reducing its dose by 25-50 %. 2 patients developed hand-foot syndrome & grade I-II neuropathy. Hematological toxicity was noted in 5 (24%) patients, which was managed with blood transfusions, EPO & G-CSF.

Conclusions: This is a simple and effective, day care based chemotherapy regimen for advanced gastroesophageal cancers; however, considerable challenges exist to select the optimal therapy for an individual patient. Enrollment continues at this dose regime.

563 **A PHASE II STUDY OF S-1 AND OXALIPLATIN AS FIRST-LINE THERAPY FOR PATIENTS WITH RECURRENT OR METASTATIC GASTRIC CANCER**

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Background: Palliative chemotherapy for patients with recurrent or metastatic gastric cancer has been shown to have a survival benefit. 5-fluorouracil (5-FU), adriamycin, cisplatin have been widely used in different combinations. We performed a phase II study of combination chemotherapy with new agents, S-1 and oxaliplatin (SOx) in patients with recurrent or metastatic gastric cancer to evaluate efficacy and toxicity of this regimen.

Patients and methods: Histologically confirmed recurrent or metastatic gastric cancer were treated with S-1 80 mg/m²/day given as orally on days 1-28, and oxaliplatin 85 mg/m² given as a 90-min intravenous infusion on days 1, 15, and 29. Treatment courses were repeated every 6 weeks. Patients received a maximum of four cycles.

Results: Thirty-three patients were enrolled (22 male, 11 female) and the median age was 59 years (range, 36-74). The overall response rate was 64% (95% confidence interval (CI), 47-80%) with no complete response. With a median follow-up of 13.1 months, the median time to progression was 5.7 months (95% CI, 3.9-7.6 months) and median overall survival was 7.9 months (95% CI, 6.2-9.6 months). A total of 83 cycles of chemotherapy was delivered. The grade 3 hematologic toxicities included neutropenia (2.4% of all cycles) and anemia (3.6% of all cycles) and no grade 4 hematologic toxicities were observed. The grade 3 non-hematologic toxicities included nausea (3.6% of all cycles) and diarrhea (1.2% of all cycles). There was no treatment-related death.

Conclusion: S-1 and oxaliplatin (SOx) combination chemotherapy showed relatively high response rate and was well tolerated as first-line therapy for recurrent or metastatic gastric cancer.

564 **PHARMACOKINETIC STUDY OF S-1 FOR ELDERLY PATIENTS WITH GASTRIC CANCER**

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Background: S-1 is a novel oral antitumor agent of fluorinated pyrimidines, in which tegafur (FT) is combined with two classes of modulator, 5-chloro-2,4-dihydropyridine (CDHP) and potassium oxonate (Oxo) at a molar ratio of FT:CDHP:Oxo = 1:0.4:1. It is one of the key drug for gastric cancer in Japan. On the basis of the results of phase I and II studying Japan, 80mg/m²/day is recommended. As 50% of CDHP is excreted in urine, renal dysfunction may directly affect the DPD inhibitory effect and lead to increased 5-FU concentration. But we have no prospective data of elderly patients(pts). So we conducted pharmacokinetic study of S-1 for elderly patients with gastric cancer.

Methods: Elderly pts (>70 y.o.) with gastric cancer who planed to receive S-1 containing treatment entered this study. The initial dose of S-1 for each pts was determined according to his/her body surface area (BSA) as follows: for BSA < 1.25 m², 80 mg/body/day; for 1.25 m² < or = BSA < 1.5 m², 100 mg/day; and for 1.5 m² < or = BSA, 120 mg/day. The dose was given daily in two divided doses. We investigated the pharmacokinetics of 5FU, intact FT and CDHP after administration of S-1.

Results: Between 10/07 and 2/08 1 male and 4 female pts were enrolled: Ages were between 71 and 78 years (median, 77 years) and median performance status was 1 (range 0-1). Ccr (Cockcroft & Gault Equation) were between 51.7 mL/min and 87.5 mL/min. All had no prior chemotherapy. No severe toxicity was observed except grade 3 anemia in one patient. Pharmacokinetic parameters of plasma 5FU were as follows: C_{max} , 121.8±47.9 ng/ml; T_{max} , 2.8±1.8 h; AUC_{0-10} , 755±204.5 ng h/ml; and $T_{1/2}$, 4.5±3.0 h. And those of CDHP were 176.2±89.3 ng/ml; T_{max} , 2.0±0.0 h; AUC_{0-10} , 1029.3±389.7 ng h/ml; and $T_{1/2}$, 5.7±3.5 h. AUC_{0-10} of 5FU and CDHP were increased in one pts with Ccr 51.7 mL/min (958.8 ng h/ml and 1368.6 ng h/ml, respectively)

Conclusion: Pharmacokinetic parameters of elderly pts were comparable to previous phase I study. However, pts with renal dysfunction may need individualized dosing based on pharmacokinetic monitoring. Now we are investigating further pharmacokinetic study for elderly pts with impaired renal function.

565 IRINOTECAN WITH BIWEEKLY, LOW DOSE LEUCOVORIN AND BOLUS AND CONTINUOUS INFUSION 5-FLUOROURACIL (MODIFIED FOLFIRI) AS FIRST LINE THERAPY FOR PATIENTS WITH RECURRENT OR METASTATIC GASTRIC CANCER

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Purpose: To determine the activity and toxicities of low dose leucovorin (LV) plus 5-fluorouracil (5-FU) regimen, combined with irinotecan every two weeks (modified FOLFIRI), as a first-line therapy for patients with recurrent or metastatic gastric cancer.

Methods: Patients were treated with irinotecan 150 mg/m² as a 90-minute infusion on days 1 plus LV 50 mg bolus, followed by 5-FU a 400 mg/m² bolus and 22 hour continuous infusion of 600 mg/m² 5-FU on day 1 and 2. This treatment was repeated in 2 week intervals.

Results: Between February 2005 and February 2008, a total of 42 patients were assigned to treatment. The median patient age was 55 years (range, 29-74), and 76.2% (32/42) of the patients had performance status (ECOG) of 0 or 1. Of the 38 patients evaluated for their tumor response, 5 patients (13.2%) and 9 patients (23.7%) achieved a complete and partial response, respectively, with an overall response rate of 36.9% (95% CI: 21-53%). 13 patients (34.2%) showed a stable disease, and eleven patients (28.9%) progressed during the course of the treatment. The median time to progression and overall survival time were 5.0 months (95% CI: 3.8-6.2 months) and 8.7 months (95% CI: 4.0-13.4 months) from the start of the chemotherapy, respectively. A total of 248 cycles were analyzed for toxicity. Major hematologic toxicities included grade 1-2 anemia (59.6%), neutropenia (37.1%), and grade 3-4 neutropenia (15.2%). There were 6 cycles of neutropenic fever. The common grade 3 non-hematologic toxicities were nausea/vomiting (21.4%), diarrhea (4.8%), and mucositis (2.3%). There was no treatment related death.

Conclusion: The modified FOLFIRI regimen is safe and feasible regimen as a first-line therapy for recurrent or metastatic gastric cancer patients.

566 EPIRUBICIN (E), CISPLATIN (C) AND CAPECITABINE (X) IN CHEMOTHERAPY NAÏVE PATIENTS WITH LOCALLY ADVANCED (LA) OR METASTATIC GASTRIC CANCER (MGC)

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Background: Continuous infusion of 5-fluorouracil (F) in combination with epirubicin and cisplatin is known as an effective regimen in advanced and metastatic gastric cancer. Continuous infusion of F is not always feasible or widely acceptable and may be replaced by oral fluoropyrimidines. Here we evaluate the antitumor activity and toxicity of combined ECX regimen including capecitabine instead of continuous F infusion for untreated patients (pts) with LA or MGC.

Methods: Eligibility included: (a) histologically proven gastric adenocarcinoma, (b) LA or MGC, (c) measurable disease, (d) no previous chemotherapy, (e) PS ECOG 0-2, (f) age 18 years or older, and (g) no contraindication to chemotherapy. Pts received E (50 mg/m² IV on D1), C (60 mg/m² IV on D1) and X (2000 mg/m²/day PO on D1-14) every 3 weeks.

Results: Between March 2003 and January 2008, 36 pts were enrolled in this study; median age was 63.5 years (range, 38 to 79) with 22 male and 14 female pts; 28 metastatic diseases and 8 LA diseases. A total of 139 cycles were administered with a median of 4 cycles per patient (range, 1-6). All pts were assessable for toxicity and 33 for responses. The most common grade 3/4 hematological adverse events were: neutropenia in 29 cycles (21%), leukopenia in 23 cycles (16%), and thrombocytopenia in 14 cycles (10%). Febrile neutropenia occurred in 6 cycles (4%). One patient died of neutropenic sepsis. Grade 3/4 non-hematological toxicity was: nausea/vomiting, stomatitis and diarrhea in 7%, 14%, and 15% of the patients, respectively. Grade 2/3

hand-foot skin reaction developed in 8% of patients. The overall best response rate by intent-to-treat analysis was 33% (95%CI, 17-50%) including 25% of PR and 8% of CR. Median follow-up was 7.5 months (range, 1-40 months). Median time to progression was 6 months (95%CI, 3.0-9.0) and median survival for all patients was 10 months (95%CI, 4.0-12.0).

Conclusions: Capecitabine in combination with epirubicin and cisplatin is an effective and safe alternative to ECF avoiding risks and costs of a continuous venous access.

567 COMBINATION CHEMOTHERAPY (CT) WITH DOCETAXEL (D), OXALIPLATIN (O), CAPECITABINE (C) IN PATIENTS (PTS) WITH ADVANCED GASTRIC CANCER (AGC): RESULTS ON TOXICITY OF A PILOT STUDY

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Introduction: The outcome among pts with gastric or lower oesophageal adenocarcinoma (LEA) is determined by the stage of the disease at presentation. Overall, at diagnosis, approximately 84% of pts have AGC. In this setting of pts, palliative CT induces a significant increase in median survival and quality of life in comparison with best supportive care only (7-10 months vs. 3-4 months). The recent evolution of CT allows an increase in response rate, but also in toxicity. **RATIONALE:** Identify a program to be introduced in the clinic employing drugs characterized by less toxic effects and a schedule adapted to compromised patients (weight loss, gastrointestinal dysfunction). Ways to reach the goal: 1) fractionation of doses (Days 1 and 8) instead of the classic/toxic 3-week schedule; 2) Introduction of more convenient agents (oxaliplatin instead of cisplatin); 3) Oral way avoiding continuous infusion with catheters and pumps (capecitabine instead of 5-FU continuous infusion).

Aims and methods: To explore in a limited group of pts the feasibility of a combination of three modern CT agents and to define the schedule to be tested in a formal study. CT consisted of: D 20-30 mg/m² iv, day 1, 8; O 45-70 mg/m² iv, day 1, 8; C 600-800 mg/m², po, day 2-15; cycles repeated every 3 weeks.

Results: from May 2007 to March 2008, 20 pts (15 males and 5 females) with a median age of 55 years (range 44-72), PS 0/1/>1 = 9/10/1, were enrolled. Previous treatment was: adjuvant CT in 4, 1st line CT in 8, no previous treatment in 8 pts, respectively. A total of 71 cycles were administered. Non-hematological toxicity > grade (G) 1: Diarrhoea G3 = 3, Nausea/vomiting G2 = 6, neurotoxicity G2 = 6, G3 = 2. Hematological toxicities > G1: neutropenia G3 = 2, thrombocytopenia G2 = 1, anaemia G2 = 2. Febrile neutropenia = 0. Admission for serious adverse events = 1 (diarrhoea), Death during CT = 0.

Conclusions: This approach was feasible and useful for pts with AGC and allowed to start a formal phase I trial, in untreated pts, of increasing doses of all three drugs where 5 pts have been enrolled in the first two levels, up to now.

568 PHASE II STUDY OF OXALIPLATIN COMBINED WITH LEUCOVORIN AND 5-FLUOROURACIL AS FIRST-LINE CHEMOTHERAPY IN PATIENTS WITH ADVANCED GASTRIC CANCER

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Background: This study was to evaluate the efficacy and safety of oxaliplatin combined with leucovorin and infusional 5-FU in advanced gastric cancer.

Methods: Patients with previously untreated and measurable advanced gastric cancer received oxaliplatin (100 mg/m², day 1) followed by leucovorin (100 mg/m², day 1) and 5-FU (1000 mg/m², day 1, 2) every 2 weeks. Responses were assessed every 3 cycles of chemotherapy.

Results: Out of 48 patients, 45 were evaluable for efficacy and 47 for toxicity. A total of 322 cycles of chemotherapy were administered, with a median of 6 cycles (range 1-27) per patient. One complete response (2.1%) and 19 partial responses (39.6%) were noted, with a response rate of 41.7% (95% CI: 27.7-55.6) according to RECIST. The median follow-up duration was 22 months (range 5.7-41.5). The median TTP was 5.3 months (95% CI 2.8-7.8), and the median overall survival was 13.6 months (95% CI 9.3-17.9). The most common grade 3/4 toxicity was neutropenia which occurred in 36.1% of patients. Grade 2/3 nausea occurred frequently (40.4%) but was manageable. There was one treatment related death and three patients discontinued treatment because of serum creatinine elevation.

Conclusion: The oxaliplatin, leucovorin and infusional 5-FU regimen was effective and tolerable, except a rare nephrotoxicity, as a first-line chemotherapy for patients with advanced gastric cancer.

569 **ECONOMIC ASSESSMENT OF CAPECITABINE/CISPLATIN VERSUS 5-FU/CISPLATIN REGIMENS IN ADJUVANT TREATMENT OF ADVANCED GASTRIC CANCER IN SPAIN**

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Background: A randomized phase III trial of Capecitabine/Cisplatin (XP) versus continuous infusion of 5-FU/Cisplatin (FP) as first-line therapy in patients with advanced gastric cancer (AGC) met its primary endpoint of non-inferior progression-free survival (PFS). There was a trend toward superior efficacy with XP in terms of both PFS (median 5.6 months for XP versus 5.0 for FP) and response rates. An economic assessment was conducted in Spain to compare the costs of the two therapies taking into account unit costs and medical resource consumption for year 2007.

Methods: Direct medical costs during the study period were estimated from the perspective of the Spanish National healthcare system. The costs of the two alternative therapies were estimated based on the trial

Results: on actual dose and the number of administrations, and unit costs in different hospitals in Spain. The adverse event (AE) profiles were used to estimate the costs of treating AEs. An expert panel estimated typical treatment patterns and costs of treating major AEs. Indirect costs for time and travel for study drug administration were also estimated.

Results: Annual pharmacologic cost in the XP arm were estimated to be €1,333 greater than in the FP arm, but drug administration costs and AE costs were lower in the XP arm (€2,575 and €27, respectively). Overall, direct an indirect medical cost were estimated at €2,688 in the XP arm and at €4,014 in the FP arm. According to budget impact results, 1.58 patients are likely to be treated with XP for each patient treated with FP.

Conclusion: In Spain, oral capecitabine benefits AGC patients by reducing the number and time spent in infusion visits, and would produce significant direct medical cost savings. Given the trend to superior efficacy, the projected direct and indirect cost savings, and the convenience of oral treatment, XP treatment would be considered less costly than FP treatment for AGC from both a healthcare system and a societal perspective.

570 **ANALYSIS OF CHARACTERISTICS IN CURATIVELY RESECTED STAGE IV GASTRIC CANCER PATIENTS**

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Patients with stage IV gastric cancer usually have poor prognoses, but in AJCC TNM staging system, stage IV contains both resectable and unresectable cases and these prognoses may be different. In this study, we investigated some subgrouping of stage IV gastric cancers to elucidate prognosis and prognostic variables affecting survival in the curatively resected stage IV gastric cancer patients. A retrospective analysis was performed in curatively resected stage IV gastric cancer patients who had no macroscopic residual lesion on postoperative imaging study from January 2001 to December 2007 at Ewha Womans University Hospital. Characteristics including histology, TNM staging, extent of resection, adjuvant therapy and other clinical factors were reviewed. Sixty seven patients (M:F=40:27) who diagnosed as T₂₋₄N_{any}M₀ or T_{any}N_{any}M₁ gastric cancers according to AJCC staging system and underwent curative surgery were evaluated. The median age of these patients was 56 years old (34-75). The median number of retrieved lymph nodes (LNs) was 48 (9-119) and the median positive rate of retrieved LNs was 39.3 % (4.0-88.0). Thirty five patients (52.2%) received adjuvant therapy and among them 27 patients (77.1%) had platinum-containing chemotherapy. With the median follow up duration of 42.3 months (4.0-88.7), 45 patients (67.2%) experienced the recurrence and peritoneal seeding (24 patients, 53.3%) was the most frequent pattern of failure. The median time to

recurrence (TTR) and median overall survival (OS) were 10.8 months (2.4-39.3) and 30.4 months (3.0-72.6), respectively. In univariate analysis, higher nodal status at diagnosis (N₁₋₂ vs. N₃, 39.4 vs. 23.4 months, P=0.007) and positive LN ratio (<0.5 vs. ≥ 0.5, 41.0 vs. 17.9 months, P=0.000) affected the overall survival significantly. In Cox regression analysis, total gastrectomy affected on TTR (HR 2.39, P=0.007, CI:1.269-4.498) and ratio of positive LN counts more than 0.5 on OS (HR 3.66, P=0.000, CI:1.819-7.358). Resectable stage IV gastric cancers have relatively superior survival than historical stage IV gastric cancer data. In these cases, we need to apply the different prognostic variables and we need a proper prospective postoperative management study.

571 **P53 CAN BE EFFECTIVE IN EARLY DETECTION OF GASTRIC CARDIA CANCER**

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The incidence of adenocarcinoma of gastric cardia is increasing rapidly. Upper gastrointestinal tumors develop from a premalignant lesions, particularly Barrett disease. p53 plays a crucial role in cellular proliferation and apoptosis and as the guardian of genomic integrity. Molecular analysis of p53 might help to identify patients from high risk population at early stage of malignant transformation.

Patients and methods: Immunohistochemical staining was performed on routinely processed paraffin primary tumour sections from 23 adenocarcinoma of gastroesophageal junction (Siewert 1-2-3)(S1, S2, S3). 5 esophageal squamous cell carcinoma, and 13 patients with non-cancer lesion or normal tissue of upper digestive tract was choose as control group. P53 was evaluated by 2 categories: intensity (grade of staining - 0, 1, 2, 3) and diffusion (part of cell with involved in reaction - 0, 1 less 30% of cell, 2 - 30- 70%; 3 - more than 70% of cell). None of the patient received preoperative chemo and/or-radiotherapy. Complete resection was performed for all cancer patients.

Results: Median survival was higher in cardial than esophageal cancer (p=0,004): Siewert-2 (20 months)(m) > S-1 (18 m) > Siewert-3 (15 m)>esophageal cancer (3,3 m). P53 was significantly higher in the cancer tissue than in normal (p=0,014623 for diffusion, p=0,003382 for intensity). p53 was significantly lower (p <0.001) in the S3 group than in S2. But no significant difference was observed in p53 expression between S1 and S2 cancers (both for diffusion and intensity). We found no association between p53 expression and median survival of esophageal and cardia cancer patients.

Conclusions: P53 was significantly higher in the cancer tissue than in normal for all patients with upper digestive tract cancers. P53 examination in specimens taken during endoscopies in patients with precancerous lesions may be helpful for early detection of upper digestive tract tumors.

572 **UNRESECTABLE INTRAHEPATIC CHOLANGIOCARCINOMA: A THERAPEUTIC APPROACH BASED ON OEM-CHEMOEMBOLIZATION**

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Background: Unresectable cholangiocarcinoma is a malignancy with a poor prognosis, ranging from 6 to 12 months from time of diagnosis. Newer chemotherapy regimen with gemcitabine and oxaliplatin have shown increased response rate, but didn't show improve in survival. Transcatheter arterial chemoembolization (TACE) prolong survival in hepatocellular carcinoma, but experience in cholangiocarcinoma treatment is limited. The purpose of this study was to determine the safety and efficacy of TACE with microsphere eluted with oxaliplatin in unresectable cholangiocarcinoma.

Materials and methods: Ten patients with unresectable cholangiocarcinoma were treated with one or more OEM-TACE in our institution. Age range from 55 to 74 years, with a mean of 64.5 years, with five men and five women; mean tumor size was 6 +/- 3.2 cm (range, 1.5 – 10.4 cm). Seven patient had a multifocal disease (five pts > 3 lesions), while three had unifocal disease. Each patients received a median of 3.5 OEM-TACE (range, 2 – 7), with a mean time between each treatment of three months (range, 1 – 6). Follow-up imaging was performed in all patients 4-8 weeks after each treatment to determine tumor response.

Results: According to RECIST criteria stable disease was observed in three patients (30%), a partial response in 5 (50%), and extrahepatic tumor progression in one (10%). One patient (10%) with previously unresectable disease underwent successful resection after OEM-TACE. No severe adverse events (AEs G3/4) occurred.

Conclusion: Our results suggest that OEM-TACE is a safe and effective loco-regional therapy in patient with unresectable cholangiocarcinoma.

573 IS THE PLATELET COUNT A PROGNOSTIC FACTOR IN PANCREAS CANCER AND CHOLANGIOCARCINOMA?

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Background: Locally advanced or metastatic pancreatic cancer and unresectable cholangiocarcinoma are associated to a short median survival, and few prognostic factors have been identified. In our patient cohort, we have observed that some patients have a thrombocytosis at presentation. HYPOTHESIS: We hypothesize that patients with thrombocytosis at presentation have a shorter survival than those with normal platelet count.

Methods: A retrospective review of the data of 64 consecutive patients with advanced pancreatic cancer or cholangiocarcinoma and assessed at the McGill University Health Center between December 2004 and December 2007 was performed. All patients had given informed consent and permission was obtained from the Research Ethics Board of McGill University. Clinical data and outcomes were recorded and analyzed.

Results: There were 30 males and 34 females, with age ranging between 42 and 92 (median 67 years). The diagnosis was pancreatic cancer in 84% of cases, and cholangiocarcinoma in 16%. Metastatic disease was identified in 66% of patients, and locally advanced disease in 34%. The ECOG performance status was 0 or 1 in 34% of patients, 2 or higher in 66%. A high platelet count was defined as $\geq 440 \times 10^3/L$. There was no evidence of iron deficiency. The 11 patients with a high platelet count had a median survival of 5 weeks (CI 5.5-6.5), in comparison to 22 weeks (CI: 12-31) in the remaining patients with a normal platelet count. This difference was statistically significant (p value 0.02 by log rank test).

Conclusion: Among different causes of thrombocytosis in this population, cancer-induced chronic inflammation is of particular importance. We are presently studying thrombocytosis as both a marker for inflammation and an adverse prognostic factor for advanced pancreatic cancer and cholangiocarcinoma.

574 PERCUTANEOUS RADIOFREQUENCY ABLATION FOR RECURRENT HEPATOCELLULAR CARCINOMA AFTER CURATIVE TREATMENT: LONG-TERM RESULTS AND PROGNOSTIC FACTORS

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Background: We evaluated the survival results and safety of RFA for recurrent HCC retrospectively.

Method: One hundred sixty tree patients, who had recurrent HCC in their liver, were analyzed. All the patients had a history of hepatic resection (HR) or percutaneous ethanol injection therapy (PEIT) or RFA as a first-line treatment modality for HCC. First line treatments were: HR 20% (34 of 163), PEIT 34% (55 of 163), RFA 45% (73 of 163). The treatment modalities for recurrent HCC, prognosis and recurrence rate were analyzed. The chi square test, t-test, Kaplan-Meier method, log-rank test and Cox proposal hazard method were used for statistical analysis.

Result: Median disease free survival after a first-line treatment was 14.0 months. Mean number of tumors was 2.8. Maximal diameters of the recurrent tumors were: 2cm > 65.6%, 2-3cm 20.2%, 3-5cm 9.8%, and 5cm < 4.3%. Second-line treatment for recurrent HCC was HR 4.3%, Percutaneous tumor ablation (PTA, RFA+PEIT) 73.0%, TAE 15.3%, Chemotherapy 5.5%, and Best supportive care 1.8%. The cumulative survival rates at 1, 2, and 3 years after 2nd-line treatment were 92.6, 67.6, 67.6% for HR; 93.3, 69.4, 65.5% for RFA; 90.9, 55.9, 32.6% for PEIT; 84.4, 46.3, 19.8% for TAE, respectively. The recurrence free survival rates at 1, 2, and 3 years after RFA were 56.7, 21.4, 14.1%, respectively. Median disease free survival after RFA was 14.5 months. Patients with a lower serum alpha-fetoprotein (AFP) level (Vor=70%) or with better JIS score (<or=1) demonstrated better survival results (P <0.05, univariable analysis). There was no major complication during follow-up period.

Conclusion: RFA is an effective and safe treatment modality for intrahepatic recurrent HCC after curative treatment. Several possible prognostic predictors of long-term survival were demonstrated.

575 S-1 IN COMBINATION WITH GEMCITABINE FOR ADVANCED PANCREATIC CANCER

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Background: We recently reported a phase I/II study of gemcitabine with S-1, oral fluorouracil prodrug tegafur combined with two modulators, 5-chloro-2, 4-dihydropyridine and potassium oxonate, in patients with metastatic pancreatic cancer (Br J Cancer, 2005 and 2006). Because the efficacy results were very promising, we expanded the cohort and evaluated the long-term outcome.

Methods: From January 2003 to December 2007, 85 patients with advanced pancreatic cancer (median age: 63 years, range 40 - 82) were treated with S-1 combined with gemcitabine. S-1 was given orally (30 mg/m²) b.i.d. for 14 consecutive days and gemcitabine (800 - 1000 mg/m²) was given on days 8 and 15. The cycle was repeated every 21 days.

Results: A total of 908 courses were administered to the 85 patients (median 8, range 0 - 63). 2 patients (2%) had complete response, and 32 (38%) had partial response. The median survival time was 10 months with a one-year survival rate of 45% and a two-year survival rate of 20%. Grade 3 and 4 toxicities included neutropenia in 61% of the patients, thrombocytopenia in 21%, anemia in 13%, anorexia in 8%, rash in 5%, interstitial pneumonia in 2%, febrile neutropenia in 2%.

Conclusion: S-1 in combination with gemcitabine showed a promising activity in patients with advanced pancreatic cancer. Further clinical investigation is warranted.

576 PHASE II TRIAL OF GEMCITABINE AND S-1 COMBINATION FOR PATIENTS WITH ADVANCED PANCREAS AND BILIARY TRACT CANCER

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Background: Gemcitabine and S-1 as a single agent have shown efficacy in pancreas and biliary tract cancer. We performed a phase II study of combination gemcitabine and S-1 (GS) to evaluate the efficacy and safety in unresectable pancreas and biliary tract cancer.

Methods: Eligible patients were those who had locally advanced or metastatic adenocarcinoma arising from the pancreas or biliary tract. The patients of age 18 to 70 with ECOG PS 0-2 were enrolled to this study. Gemcitabine 1,000mg/m² was administered intravenously on day 1 and day 8. S-1 60mg/m² was administered orally on days 1-14. Cycles were repeated every 21 days. Patients were treated until disease progression or unacceptable toxicity.

Results: Twenty-one patients (male/female 15/6; median age 59, range 37-69; ECOG PS 0/1 9/12) have been enrolled to this study. Seven patients had recurrent cancer after surgery with/without adjuvant chemo-radiotherapy and 14 patients were diagnosed as metastatic disease. Twelve patients had pancreas cancer and 9 patients had biliary duct cancer. A total of 105 cycles were administered (median 4, range 1-12+). Twenty patients were evaluated for toxicity and response. The grade 3/4 toxicities were leucopenia (5.8% of whole cycles), neutropenia (8.7% of whole cycles), anemia (1.0% of whole cycles) and jaundice (1.0% of whole cycles). There were 2 PR, 13 SD and 5 PD. The response rate was 10.0 (95% CI: -3.1-23.1%) and the disease control rate was 75.0 (95% CI: 58.0-94.0%). The median time to progression was 7.3 (95% CI, 2.8-11.9) months and median survival time was 10.2 (95% CI, 6.2-14.2) months.

Conclusion: These preliminary data suggest that GS regimen is well tolerated, but has relatively low activity in patients with advanced pancreas and biliary tract cancer. Based on these results, we will increase the dose of gemcitabine and S-1 in the second stage of this study.

577 SALVAGE THERAPY WITH MITOMYCIN AND IFOSFAMIDE (MI) IN PATIENTS WITH GEMCITABINE-RESISTANT METASTATIC PANCREATIC CANCER

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Objectives: At time of upfront treatment failure, over half of the patients with advanced pancreatic cancer (PC) are candidate for further treatment. This study assessed activity and safety of MI regimen in patients with progressive disease (PD) after gemcitabine-based chemotherapy.

Methods: Patients with stage IV PC, Karnofsky performance status (PS) >50 were treated with mitomycin 8 mg/m² day 1, ifosfamide 2500 mg/m² day 1 to 3 and mesna 3000 mg/m² day 1 to 3 every 28 days; until PD or a maximum of 6 cycles. A positive responder was defined to be a patient who was progression-free at 6 months from trial enrolment (PFS-6). According to Fleming design, a sample size of 34 patients was estimated assuming P0=0.05; P1=0.20; alpha=0.05; beta=0.10. MI would be considered an active regimen in this patient population if at least 5 patients PFS-6 were noted.

Results: Between May 2006 and December 2007, 21 patients (median age 56; median KPS 80) were enrolled. One patient did not receive any treatment due to death of brain hemorrhage immediately after enrolment and was excluded from further analysis. CA19.9 was elevated in 17 patients (85%); 4 patients had prior surgery and 7 prior

radiotherapy; median previous PFS was 5.7 months (range 1.6-11.7). Previous treatment was combination chemotherapy with doublets (N=3) or four-drug (N=17); 7 patients received a second-line chemotherapy as well. Forty-eight cycles of MI were administered (median 2, range 1-6). Only 2 patients completed 6 cycles of chemotherapy; 18 patients interrupted chemotherapy due to PD (15), toxicity (2) or refusal (1). Dose intensity was 93% for mitomycin and 91% for ifosfamide. Grade > 2 toxicity consisted of neutropenia in 80% of patients, thrombocytopenia in 20%, anemia in 10%, fatigue in 20%, and vomiting in 5%. Only one patient was PFS-6 (5%).

One patient had partial response (5%) and 2 patients had stable disease (10%). CA19.9 was reduced by >50% in 2/17 (12%). Median and 1-yr survival (OS) was 3.7 months and 10%.

Conclusions: Based on the poor outcome observed and on the high level of G3-4 toxicity observed in the first 20 patients, the trial was prematurely stopped and MI regimen was considered insufficiently active in gemcitabine pre-treated advanced PC.