progression and toxicity. Pts were randomized to GEM 1000 mg/m^2 iv d 1+8 and CAP 650 mg/m^2 po q 12 hrs d 1–14 every 3 w or GEM 1000 mg/m^2 weekly x7, 1 w rest and then weekly x3 q4w. Trt continued for 6 mo or until progression. The study was designed to detect an increase of median survival from 5 to 7 months. CB was evaluated based on changes in pain/pain medication, KPS and weight during a period >4 weeks. The trial was independently monitored.
Results: From 7/01 to 6/04 319 pts from 30 institutions in 8 countries were randomized. 79% had metast. disease, 67% required pain medication and 53% had KPS of ⩾90. The median OS was 8.4 mo for GEMCAP and 7.3 mo for GEM (p = 0.314). 89% of all patients have died. Confirmed response rates were 10.1% vs. 7.9%, median duration of response 7.4 vs. 5.9 mo and median TTP 4.8 vs. 4.0 mo for GEMCAP and GEM resp. A multivariate Cox regression of OS on strat. factors and trt revealed that in pts with KPS ⩾90 those treated with GEMCAP had a significantly higher median OS of 10.1 vs 7.5 mo (p = 0.033). 111 pts (73%) with GEMCAP and 121 pts (82%) with GEM were at least 4 weeks on study trt and evaluable for CB.
Conclusions: An update on CBR and other QoL parameters in relation to clinical outcome will be presented.
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718 ORAL

Results of a phase II study with sunitinib malate (SU11248) in patients (pts) with advanced neuroendocrine tumours (NETs)

M. Kulke[1], H. Lenz[2], N. Meropol[3], J. Posey[4], J. Picus[5], D. Ryan[6], E. Bergsland[7], K. Stuart[8], C. Baum[9], C. Fuchs[1]. [1]*Dana-Farber Cancer Institute, Boston, USA;* [2]*USC/Norris Comprehensive Cancer Center, Los Angeles, USA;* [3]*Fox Chase Cancer Center, Philadelphia, USA;* [4]*University of Alabama, Birmingham, USA;* [5]*Washington University, St. Louis, USA;* [6]*Massachusetts General Hospital, Boston, USA;* [7]*UCSF Comprehensive Cancer Center, San Francisco, USA;* [8]*Beth Israel Deaconess Medical Center, Boston, USA;* [9]*Pfizer Inc., La Jolla, USA*

Background: NETs are characterised by an indolent course and are often resistant to standard cytotoxic chemotherapy. These tumours are highly vascular with both carcinoid tumours and pancreatic (islet cell) NETs expressing high levels of VEGF and VEGFR. Sunitinib malate is an oral multitargeted tyrosine kinase inhibitor that specifically inhibits VEGFR, PDGFR, KIT, RET and FLT3, and has shown activity in pts with NETs included in phase I trials.
Patients and methods: Pts (n = 109) with advanced unresectable NETs (43 carcinoid, 66 islet cell) received sunitinib 50 mg/day po for 4 weeks followed by 2 weeks off treatment. Cycles were repeated every 6 weeks. Prior chemotherapy was allowed and pts receiving octreotide could continue with treatment on study. In addition to response, survival and adverse events, quality of life was measured (EQ-5D and FACIT-Fatigue subscale) and correlative safety/efficacy analyses were undertaken using both sunitinib plasma levels and NET biomarkers.
Results: Data are available for 102 pts (median no. of cycles: 5, range 1–14; median dose intensity 93%) with the following characteristics: median age: 57 yrs (range 32–81), M/F (%) 59/41, ECOG PS 0/1 (%) 54/43. The most common (>2%) grade 3/4 treatment-related adverse events (AEs) (%) included fatigue (25/0), neutropenia (12/4), thrombocytopenia (8/0), hypertension (8/0), vomiting (6/0), nausea (60), diarrhoea (5/0), dehydration (4/0), mucosal inflammation (3/0), anorexia (3/0) and glossodynia (3/0). Discontinuations due to AEs were reported for 7% of pts.
Best objective tumour response rates defined by RESIST were (n = 102): partial response (PR) 9 pts (9%); stable disease (SD) 84 (82%) and progressive disease (PD) 4 (4%). Best response according to tumour type is shown. Median time to tumour response was 16 weeks and median time to tumour progression was 40 weeks (carcinoid = 42 weeks; islet cell = 33 weeks). Results from analyses investigating correlation between NET biomarkers and treatment-related outcomes are pending.

	PR**	SD	PD	Not evaluable
Islet cell* (n = 61)	8 (13%) 95% CI 5.8–24.2	46 (75%)	4 (7%)	3 (5%)
Carcinoid* (n = 41)	1 (2%) 95% CI 0.1–12.9	38 (93%)	0 (0%)	2 (5%)

* Patients with baseline and at least 1 subsequent imaging assessment **Confirmed response by investigator (at least two assessments)

Conclusions: Sunitinib shows single-agent clinical activity in pts with advanced unresectable NETs and is associated with acceptable adverse events that result rarely in treatment discontinuation.

719 ORAL

Randomized, multicenter, phase 3 study of 1st-line irinotecan + 5FU/folinic acid vs cisplatin + 5FU in patients with advanced gastric cancer – quality of life analysis

C. Pozzo[1], J. Zaluski[2], M. Dank[3], C. Barone[1], V. Valvere[4], C. Peschel[5], M. Wenczl[6], E. Goker[7], R. Bugat[8]. [1]*Universitá Cattolica del Sacro Cuore, Medical Oncology, Rome, Italy;* [2]*Semmelweis University, Budapest, Hungary;* [3]*Wielkopolskie Centrum Onkologii, Poznan, Poland;* [4]*North-Estonian Regional Hospital Cancer Center, Tallinn, Estonia;* [5]*Klinikum Rechts der Isar, Munich, Germany;* [6]*Markusovsky Hospital, Szombathely, Hungary;* [7]*Ege Uninversity Hospital, Izmir, Turkey;* [8]*Institut Claudius Régaud, Toulouse, France*

Background: An open-label, multicenter study of 1st-line advanced gastric cancer pts was designed to compare the effects of CPT-11 + 5FU/FA with CDDP + 5FU. Primary efficacy variable: time to progression (TTP); secondary endpoints: time to treatment failure (TTF), overall survival (OS), global health status/QOL scale, and safety.
Methods: Male and female pts aged 28–77 y were randomized to receive CPT-11 80 mg/m^2 iv as 30-min infusion, then FA 500 mg/m^2 iv over 2 h, and then 5FU 2000 mg/m^2 iv over 22 h weekly for 6 wk (IF); or CDDP 100 mg/m^2 iv as 1–3 h infusion on day 1, and then 5FU 1000 mg/m^2/d continuous infusion over 5 d every 4 wk (CF). Treatment was administered up to progression, unacceptable toxicity, or consent withdrawal.
Results: Of 337 randomized pts, 333 (170 in IF; 163 in CF) were treated. In the full-analysis population, a trend toward superiority was noted for TTP with IF vs CF (HR 1.23; 95% CI 0.97–1.57, P = 0.088) corresponding to a 19% progression in risk reduction. Median TTP for IF vs CF: 5.0 vs 4.2 mo; median TTF: 4.0 (3.6–4.8) vs 3.4 (2.5–3.8) mo (HR 1.43; 95% CI 1.14–1.78; P = 0.018). There was no difference in OS. Although there were no significant differences between summary measures of postbaseline global health status/QOL, there was a trend toward significance for the maximum and mean measures favoring IF. Mean summary measures for several secondary QOL endpoints showed significantly better results for IF vs CF, eg, physical functioning (P < 0.005), nausea/vomiting (P < 0.05), and Euroqol 5-Dimension thermometer (P < 0.005) and health utility index (P < 0.05). 67 pts (40%) in IF had grade 3/4 drug-related AEs vs 73 (44%) in CF. IF pts had more grade 3/4 drug-related diarrhea (21.6% vs 7.2%); CF pts had more grade 3/4 neutropenia (52% vs 25%), febrile neutropenia or neutropenic infection (10.2% vs 4.8%), stomatitis (16.9% vs 2.4%), and nausea (9.0% vs 4.8%). CF pts had more hematologic and renal toxicities. More pts withdrew from the study due to drug-related AEs with CF than with IF (21.5% vs 10.0%; P = 0.004), including 5 toxic deaths with CF vs 1 with IF.
Conclusions: In advanced gastric cancer pts, IF showed a trend towards TTP superiority vs CF. IF demonstrated significant improvement in several QOL scales vs CF, as well as a better safety profile. Thus, CPT-11 + 5FU/FA is a safe alternative 1st-line treatment option without CDDP for advanced gastric cancer and may be useful in treating pts with poor performance status.

720 ORAL

An intensive weekly chemotherapeutic regimen with 5fluorouracil, leucovorin, cisplatin and epidoxorubicin (PELFw) as adjuvant treatment in high-risk radically resected gastric cancer patients: results of a randomised controlled trial

S. Cascinu[1], R. Labianca[2], C. Barone[3], C. Carnaghi[4], E. Aitini[9], L. Frontini[10], V. Catalano[5], O. Bertetto[6], S. Barni[7], I. Floriani[8]. [1]*Azienda Ospedaliera Ospedali Riuniti-Universita' P, Clinica Di Oncologia Medica, Ancona, Italy;* [2]*Azienda Ospedaliera Ospedali Riuniti Bergamo, Oncologia Medica, Bergamo, Italy;* [3]*Universita' Cattolica-Policlinico Gemelli, Oncologia Medica, Roma, Italy;* [4]*Istituto Humanitas, Oncologia Medica, Milano, Italy;* [5]*Azienda Ospedaliera Santa Croce, Oncologia Medica, Pesaro, Italy;* [6]*Ospedale Molinette, Oncologia Medica, Torino, Italy;* [7]*Ospedale Treviglio, Oncologia Medica, Treviglio, Italy;* [8]*Istituto Mario Negri, Milano, Italy;* [9]*Ospedale Poma, Oncologia Medica, Mantova, Italy;* [10]*Ospedale San Gerardo, Oncologia Medica, Monza, Italy*

PELFw showed significant benefit in metastatic and locally advanced gastric cancer (J Clin Oncol 1997, Br J cancer 2004). This trial was designed to determine whether this effect translates into a survival advantage in high-risk radically resected gastric cancer patients.
From January 1998 to January 2003, 400 patients with stage pT3 N0 and pT2,3 N1,2,3, were randomised to receive PELFw, 8 weekly administration of cisplatin 40 mg/m^2, leucovorin 250 mg/m^2, epidoxorubicin 35 mg/m^2, 5fluorouracil 500 mg/m^2, glutathione 1.500 mg/m^2; lenograstin was administered daily for 6 days every 7at the dose of 6 μg/Kg, or

5fluorouracil 375 mg/m^2 days 1–5 and leucovorin 20 mg/m^2 days 1–5 every 28 days.
The trial was powered ($\alpha = 5\%$, $1\text{-}\beta = 90\%$) to detect a 15% increase in 5-year survival (250 events required).
Of the 400 patients 3 were excluded because of positive margins. About 90% of patients in each arm were node positive (about 30% N3), and about 25% of the tumours were in the cardias. All the known prognostic factors were well balanced in the two arms.
Toxicity were mild in both arms mainly represented in PELFw arm by neutropenia and anaemia, while in the 5FU arm gastrointestinal toxicity was more common. At a median follow up of 3.5 years, the risk of death associated with PELFw was not statistically different (HR 0.89, 95%CI 0.65–1.23), such as the risk for progression (HR, 0.94, 95%CI 0.71–1.24) although it should be remembered that it is a comparison with another treatment arm. Surprisingly, in spite of the poor prognosis of these patients we did not observe a sufficient number of events (150 instead of 250). A final analysis with a median follow up of 54 months will be presented at the meeting.

721 ORAL

Similar safety results of capecitabine/cisplatin (XP) vs. continuous infusion of 5-FU/cisplatin (FP) from a phase III trial in patients (pts) with previously untreated advanced gastric cancer (AGC)

Y.K. Kang[1], W.K. Kang[2], D.B. Shin[3], J. Chen[4], J. Xiong[5], J. Wang[6], M. Lichinitser[7], M.P. Salas[8], T. Suarez[9], J. Santamaria[10]. *[1]Asan Medical Center, Department of Internal Medicine, Seoul, Korea; [2]Samsung Medical Centre, Department of Internal Medicine, Ilwon-Dong, Korea; [3]Gachon Medical school, Gil Medical Center, Department of Internal Medicine, Namdong-Gu Guwal-Dong, Korea; [4]Jiangsu Cancer Hospital, Jiangsu, China; [5]1st Affiliated Hospital of Jianxi Medical College, Jianxi, China; [6]Shanghai Changzheng Hospital, Shanghai, China; [7]Russian Cancer Research Center, Blokhin Cancer Research Center, Moscow, Russia; [8]Hospital Sabogal, Lima, Peru; [9]Centro Medico Pensiones, Yucatan, Mexico; [10]Instituto Oncologico Nacional, Paseo Gorgas with Juan de Arco Galindo, Ancon, Panama*

Background: Combination of continuous infusion of 5-FU and bolus i.v. cisplatin is considered one of the standard chemotherapy regimens in AGC. Capecitabine is an oral fluoropyrimidine with proven efficacy and favourable safety in colorectal cancer, whose administration does not require hospitalisation or placement of central i.v. line. A phase II study of XP in pts with previously untreated AGC suggested that this combination would be comparable to FP in terms of efficacy with the known safety advantages of capecitabine over 5-FU. Efficacy data were as follows: overall response rate 55% (95% CI, 40–70%), median time to progression 5.8 months, and median overall survival 9.7 months [Kim et al. 2002]. A confirmatory phase III non-inferiority study was designed.
Materials and methods: Pts with previously untreated AGC were randomly assigned to: oral capecitabine (1000 mg/m^2 twice daily, days 1–14) and cisplatin (80 mg/m^2 i.v., day 1) every 3 weeks (XP arm), or to 5-FU (800 mg/m^2/day by continuous infusion, days 1–5) and cisplatin (80 mg/m^2 i.v., day 1) every 3 weeks (FP arm). Pts were treated until disease progression or unacceptable toxicities.

	% of pts with adverse events			
	XP (n = 108)		FP (n = 102)	
	All grades	Grade 3/4	All grades	Grade 3/4
Nausea/vomiting	64	5	71	7
Anorexia	25	2	25	0
Fatigue/asthenia	20	<1	25	2
Neutropenia	25	13	16	9
Stomatitis	12	3	29	7
Diarrhoea	14	3	14	3
Leukopenia	12	2	11	0
Hand–foot syndrome	17	<1	4	0
Dizziness	4	0	12	0
Thrombocytopenia	5	3	0	0

Results: From April 2003 to January 2005, 316 pts were enrolled in 46 centres across 13 countries. This is an interim safety analysis of the first 225 pts enrolled. The arms were well balanced for the following: median age (years, range): XP (56, 31–74), FP (56, 23–73); Karnofsky performance status (%, range): XP (80, 70–100), FP (80, 70–100); and male/female (%): XP (68/32) FP (72/28). The median number of cycles was 4 for XP and 4 for FP. Median follow-up was 5.6 months for XP and 5.6 months for FP. The rate of the most common, related, clinical adverse events (>10% all grades) and related grade 3/4 AEs (>2%) are presented in the table. All-cause, 60-day mortality was 3% for XP and 2% for FP; treatment-related deaths were <1% for XP and 0% for FP.
Conclusions: In the AGC setting XP has a similar safety profile to FP. Early efficacy data are expected in 2006 after 220 events and if positive would suggest that XP will be an attractive therapy for AGC, given the patient preference for oral chemotherapy.
Study sponsored by Roche

722 ORAL

Docetaxel when added to cisplatin-5-fluorouracil improves survival and maintains quality-of-life for a longer period in advanced gastric cancer: Final results of a Phase III trial

V. Moiseyenko[1], E. Van Cutsem[2], S. Tjulandin[3], A. Majlis[4], M. Constenla[5], C. Boni[6], A. Anelli[7], A. Blattmann[8], J.A. Ajani[9]. *[1]Cancer Research Institute, Biotherapy and BMT, St. Petersburg, Russian Federation; [2]University Hospital Gasthuisberg, Department of Internal Medicine, Leuven, Belgium; [3]Russian Cancer Research Center, Clinical Pharmacology and Chemotherapy Department, Moscow, Russian Federation; [4]Fundación Arturo López Pérez, Santiago, Chile; [5]C.H. de Pontevedra, Oncology Department, Pontevedra, Spain; [6]Arcispedale Santa Maria Nuova, Medical Oncology Department, Reggio Emilia, Italy; [7]Hospital A.C. Camargo, Oncologia Clínica, São Paulo, Brazil; [8]Sanofi-Aventis, Antony, France; [9]M.D. Anderson Cancer Center, Department of Gastrointestinal Medical Oncology, Houston, USA*

Background: This Phase III portion of a Phase II/III randomized trial compared docetaxel (Taxotere®; T), cisplatin (C), and 5-fluorouracil (F; TCF) with CF in gastric cancer.
Materials and methods: Chemotherapy-na¿ve patients with locally recurrent or metastatic gastric adenocarcinoma (including gastroesophageal junction) received TCF – T 75 mg/m^2 d (day) 1, C 75 mg/m^2 d1, F 750 mg/m^2/d continuous infusion (c.i.) d1–5 every (q) 3 weeks (w) – or CF – C 100 mg/m^2 d1, F 1000 mg/m^2/d c.i. d1–5 q4w. Biased-coin randomization was stratified for center, liver metastases, prior gastrectomy, 5% weight loss, and measurability. Endpoints included time to progression (TTP; primary endpoint), overall survival (OS), overall response rate (ORR), time to treatment failure (TTF) and safety. Quality of life (QoL) was assessed using EORTC QLQ-C30 and EuroQoL EQ-5D instruments. Clinical benefit was assessed by time to definitive worsening of Karnofsky performance status (KPS) by one category.
Results: Of 445 randomized and treated patients (6 patients untreated/arm), median age was 55 years, median KPS was 90 (64% $\geqslant$90), and 97% had metastatic cancer. All efficacy endpoints significantly favored TCF (Table 1). Regardless of relationship to treatment, some grade 3–4 adverse events (AEs) and hematologic abnormalities were increased with TCF (diarrhea, infection, neutropenia and neutropenic infection and/or febrile neutropenia) while others were more frequent with CF (stomatitis, anemia). Treatment discontinuation due to AE was similar between arms (27% TCF, 25% CF) as was nonmalignant death within 30 days of last infusion (7% TCF, 7% CF). Time to 5% definitive deterioration in global health status was longer with TCF (median 6.5 months [mo]) versus CF (median 4.2 mo; log-rank p = 0.0121). Time to definitive deterioration in KPS significantly favored TCF (median 6.1 mo) versus CF (median 4.8 mo; log-rank p = 0.0088).

Table 1: Efficacy Results

	TCF (n = 221)	CF (n = 224)	log-rank P-value
TTP, median (mo)	5.6	3.7	0.0004
Overall survival, median (mo)	9.2	8.6	0.0201
2-year survival (%)	18%	9%	–
Overall response rate (%)	37%	25%	0.0106*
TTF (mo)	4.0	3.4	0.0335**

*chi-square; **Wilcoxon test

Conclusions: Adding docetaxel to CF consistently yielded superior efficacy compared with CF, including longer survival. Although TCF was associated with some increase in toxicity versus CF, this is expected and manageable. In addition, TCF maintained QoL and KPS for a longer period. TCF offers a new option for the treatment of AGC.