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HER2-positive advanced gastric cancer: similar HER2-positivity levels to breast cancer

F. Lordick[1], Y.J. Bang[2], Y.K. Kang[3], D. Otero Reyes[4], G.M. Manikhas[5], L. Shen[6], E. Kulikov[7], O. Stoss[8], B.W.M. Jordan[9], E. Van Cutsem[10]. *[1]Munich University of Technology, Oncology, Munich, Germany; [2]Seoul National University Hospital, Oncology, Seoul, South Korea; [3]Asan Medical Centre, Oncology, Seoul, South Korea; [4]Hospital CIMA, Oncology, San José, Costa Rica; [5]St Petersburg City Oncology Hospital, Department of Oncogynaecology, St Petersburg, Russian Federation; [6]Peking University School of Oncology, Department of Gastrointestinal Oncology, Beijing, China; [7]Ryazan State IP Pavlov Medical University, Oncology, Ryazan, Russian Federation; [8]TARGOS Molecular Pathology GmbH, Oncology, Kassel, Germany; [9]F Hoffmann-La Roche, Oncology, Basel, Switzerland; [10]University Hospital Gasthuisberg, Oncology, Leuven, Belgium*

Background: To date, there has been no consensus on the rate of HER2 positivity in gastric cancer (GC). Previous studies have reported HER2 positivity in 6−35% of GC tumours, although sample sets have been small and different methods of evaluation and scoring have been used. Accurate HER2 testing is important to identify patients eligible for treatment with trastuzumab (Herceptin®). The Phase III ToGA trial was designed to evaluate the combination of trastuzumab with standard fluoropyrimidine plus cisplatin chemotherapy for the treatment of advanced HER2-positive GC. Before initiating this trial, a validated methodology was set up for HER2 testing in advanced GC.
Methods: Following the validation study, standardised HER2 IHC (HercepTest™) and FISH (PharmDx™) protocols and scoring systems were established for GC (Hofmann et al. ASCO Gastrointestinal Cancers Symposium 2006. Abs 24). Tumour samples were collected from patients with GC, and centrally tested using both IHC and FISH to identify patients eligible for enrolment in the ToGA trial.
Results: To date, 1527 tumour samples have been assessed (341 HER2 positive; 1186 HER2 negative), giving an overall HER2-positivity rate of 22.3%. Both IHC and FISH results are available for 1425 patients, with 87% concordance. Differences were largely due to FISH-positive cases that were IHC 0/1+. HER2 positivity differed significantly by histological subtype: 34% in intestinal, 6% in diffuse and 20% in mixed. HER2 positivity also varied according to the site of the tumour: 32% (23/72) in gastro-oesophageal junction tumours and 18% (149/817) in gastric tumours. The HER2-positivity rate was similar in specimens obtained by biopsy (242/1027; 24%) and surgery (95/477; 20%).
Conclusions: Using validated protocols and based on the large sample set from the ongoing ToGA trial, the observed overall HER2-positivity rate in advanced GC is as high as in breast cancer at ~22%. First efficacy data from the ToGA trial are expected in 2009.

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Preliminary results from a phase II study of sunitinib as second-line treatment for advanced gastric cancer

Y. Bang[1], Y. Kang[2], W. Kang[3], N. Boku[4], H. Chung[5], J. Tursi[6], M.J. Lechuga[6], L. Verkh[7], R. Chao[8], A. Sobrero[9]. *[1]Seoul National University, Hospital, Seoul, South Korea; [2]Asan Medical Center, Medical, Seoul, South Korea; [3]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [4]Shizuoka Cancer Center, 1007 Shimonagakubo, Shizuoka, Japan; [5]Cancer Metastasis Research Center, Yonsei Cancer Center, Seoul, South Korea; [6]Pfizer Italy, Clinical Research Oncology, Milan, Italy; [7]Pfizer Inc, Pfizer Clinical Pharmacology, La Jolla, USA; [8]Pfizer Inc, Pfizer Global Research & Development, La Jolla, USA; [9]Department of Medical Oncology, Ospedale San Martino, Genoa, Italy*

Background: Sunitinib malate (SUTENT®; SU), an oral, multitargeted tyrosine kinase inhibitor of VEGFRs, PDGFRs, KIT, RET and FLT3, is approved for the treatment of advanced RCC and imatinib-resistant or -intolerant GIST. Preliminary results from a phase II, open-label, multicenter study investigating the safety and activity of SU monotherapy in patients (pts) with previously treated gastric cancer are reported here.
Patients and Methods: Pts with measurable stage IV disease, 1 prior chemotherapy regimen and ECOG PS < 1 were enrolled. SU 50 mg/day for 4 weeks followed by 2 weeks off treatment was administered in 6-week cycles (4/2 schedule). A Simon 2-stage design (target accrual 38 pts in the first stage) was used and the cohort was expanded to 63 pts if $\geqslant$2 partial responses (PRs) were observed. The primary endpoint is RECIST-defined objective response rate. Secondary endpoints include duration of response, time-to-event rates and safety.
Results: As of April 2007, 42 pts (median age 56 years [range 25–78]; $\geqslant$2 metastatic sites, 74%; prior treatment with 5-FU $\pm$ platinum [P], 40%, capecitabine $\pm$ P, 17%, TS-1 $\pm$ P, 36%, other, 21%) are evaluable and have received a median of 2 SU cycles (range 1–6). PR was confirmed in 2 pts and 15 pts had stable disease (SD; 12 with SD for >3 months and 3 for >6 months) among 33 pts evaluable for efficacy. Median progression-free survival and overall survival were 12.3 weeks (range 10.1–18.4) and 50.7 weeks (range 28.0–not reached), respectively. Enrollment of the second cohort is ongoing. Common adverse events (AEs) were typically grade 1/2 in severity and included stomatitis, skin discoloration, fatigue, anorexia, diarrhea, hand–foot syndrome (HFS), nausea and vomiting. Grade 3/4 toxicities included HFS (9.5%), fatigue (9.5%), anorexia (9.5%) and mucosal inflammation (4.8%). Grade 3/4 hematological toxicities were neutropenia (31.0%), thrombocytopenia (26.2%) and anemia (14.3%). Of 7 pts experiencing serious SU-related AEs, 3 required dose modifications and 1 required treatment discontinuation. Preliminary PK investigations indicate that plasma drug concentrations seen in gastric cancer pts are similar to those in SU-treated pts with other tumor types.
Conclusions: Initial findings indicate that SU is generally well tolerated and shows promising signs of single-agent antitumor activity in gastric cancer pts following failure of chemotherapy. Further studies of SU in combination with standard chemotherapy are planned.

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Phase I trial of capecitabine and gemcitabine with concurrent radical radiotherapy in locally advanced pancreatic cancer: final results

M. Michael[1], T. Price[2], T. Leong[3], V. Ganju[4], A. Strickland[5], M. Jefford[1], S. Ngan[3], A. Milner[6], J. Zalcberg[1]. *[1]Peter MacCallum Cancer Centre, Medical Oncology, Melbourne, Australia; [2]Queen Elizabeth Medical Centre, Medical Oncology, Adelaide, Australia; [3]Peter MacCallum Cancer Centre, Radiation Oncology, Melbourne, Australia; [4]Frankston Hospital, Medical Oncology, Melbourne, Australia; [5]Monash Medical Centre, Medical Oncology, Melbourne, Australia; [6]Peter MacCallum Cancer Centre, Biostatistics, Melbourne, Australia*

Background: Primary chemoradiation with infusional 5FU is widely used for the treatment of patients (pts) with locally advanced, unresectable pancreatic cancer (PaC), but with disappointing results. To improve efficacy and pt convenience novel chemotherapy regimens need to be evaluated in combination with radical radiotherapy (RT). The combination of capecitabine (Cap) (Xeloda®) and gemcitabine (G) has shown activity in advanced PaC and both agents are potent radiosensitisers. The aim of this phase I trial was to determine the MTD of the Cap plus G combination with concurrent RT in pts with localised PaC.
Patients and Methods: Eligible pts had unresectable, locally advanced PaC based on imaging and surgical staging, adequate organ function, ECOG PS 0−1 and no prior therapy. In combination with RT, G was escalated from 20 to 50 mg/m^2/day IV (days 1 and 4 of each week of RT), and Cap was escalated from 800 to 2000 mg/m^2/day (in 2 divided doses, days 1−5 of each week of RT) in 7 planned dose levels. RT consisted of 50.4 Gy/28 fractions/5.5 weeks using conformal techniques. Three pts were entered to each dose level. If 1 of 3 pts had a dose limiting toxicity (DLT) the cohort was expanded to 6 pts. DLTs were defined prospectively and based on treatment related toxicities and treatment interruptions.
Results: 18 pts have been accrued, with complete data on 15. Dose level 1: Cap/G; 800 mg/m^2/day/20 mg/m^2/day (3 pts). Dose level 2: 1,000/20 (10 pts). Dose level 3: 1,300/30 (5 pts). 3 pts (20%) had a PR, 8 pts (53%) had SD and 4 pts (27%) had PD. No DLTs were observed on dose levels 1 and 2, whilst 2 DLTs were observed in dose level 3; grade 3 dehydration (1 pt) and grade 3 diarrhoea (1 pt). Dose level 2 was declared the recommended dose level and was expanded to a total of 10 pts. No grade 3 or 4 haematological toxicities have been observed.
Conclusions: The addition of Cap and G to radical RT was both feasible and generally well tolerated. For future trials, Cap 1000 mg/m^2/day and G 20 mg/m^2/day (twice per week) is the recommended dose when combined with 50.4 Gy of RT. Final results and survival parameters will be presented.

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Phase I study of gemcitabine as a fixed dose rate infusion and S-1 combination therapy in gemcitabine-refractory pancreatic cancer patients.

C. Morizane[1], T. Okusaka[1], J. Furuse[2], H. Ishii[2], H. Ueno[1], M. Ikeda[1], T. Ogura[1], K. Nakachi[2], E. Suzuki[2]. *[1]National Cancer Center Hospital, Hepatobiliary and Pancreatic Oncology Division, Tokyo, Japan; [2]National Cancer Center Hospital East, Hepatobiliary and Pancreatic Oncology Division, Kashiwa, Japan*

Background: Gemcitabine (Gem) monotherapy or Gem-containing chemotherapy is the standard first-line therapy for advanced pancreatic cancer

(PC). After disease progression, there is no standard regimen available. In a previous phase II trial, S-1 has been reported to show marginal efficacy, achieving a response rate of 15%, a median progression-free survival (PFS) of 2.0 months and a median overall survival time (MST) of 4.5 months in Gem-refractory PC patients. The schedule of Gem administration, with fixed dose rate (FDR) infusion of 10 mg/m^2/min, would maximize the intracellular rate of accumulation for Gem triphosphate, and may improve clinical efficacy. The aim of this study was to determine the dose-limiting toxicity (DLT) and maximum-tolerated dose (MTD) of combination therapy with FDR-Gem and S-1 in patients with Gem-refractory PC.
Materials and Methods: Gem-refractory patients with histologically or cytologically proven metastatic PC were enrolled. The patients received Gem intravenously as an FDR (10 mg/m^2/min) on day 1 and S-1 orally twice daily from days 1 to 7. Cycles were repeated every 14 days until disease progression. Patients were scheduled to receive Gem (mg/m^2/week) and S-1 (mg/m^2/day) at four dose levels: 800/80 (level 1), 1,000/80 (level 2), 1,200/80 (level 3) and 1,200/100 (level 4).
Resuls: A total of 15 patients (pts) were enrolled in this study between June 2006 and April 2006. All three pts at the level 4 demonstrated DLT involving grade 4 neutropenia in two pts and grade 3 stomatitis in one. The MTD was Level 3. Fourteen pts are currently evaluable for response in this ongoing trial. There have been 4 confirmed partial responses (27%), 8 pts with stable disease, and only 2 pts with progressive disease. The median PFS was 3.5 months and MST has not been reached. Final results will be presented at the meeting.
Conclusions: This biweekly, outpatient regimen may offer a good compliance and quality of life, and may be a promising treatment for Gem-refractory PC patients. This regimen will be evaluated in Phase II studies on Gem-refractory PC patients.

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Long-term results of the phase II study on radiotherapy combined with nedaplatin and 5-FU for postoperative locoregional recurrent esophageal cancer

K. Jingu[1], K. Nemoto[2], H. Matsushita[3], C. Takahashi[4], Y. Ogawa[1], H. Ariga[1], K. Takeda[1], M. Koto[1], Y. Takai[5], S. Yamada[5]. *[1]Tohoku University, Radio-oncology, Sendai, Japan; [2]Yamagata University, Radio-oncology, Yamagata, Japan; [3]Ishinomaki city hospital, Radio-oncology, Ishinomaki, Japan; [4]Oosaki city hospital, Radio-oncology, Oosaki, Japan; [5]Tohoku University, Radiation technology, Sendai, Japan*

Background: Although the effectiveness of radiotherapy with concurrent administration of several anti-tumor drugs for postoperative recurrent esophageal cancer has been demonstrated, the results are not satisfactory. In June 2000, we started a phase II study on treatment of postoperative locoregional recurrent esophageal cancer with radiotherapy combined with nedaplatin and 5-fluorouracil. We have reported a preliminary result of the present study, however, we show the long-term results of the phase II study on this occasion.
Materials and Methods: From June 2000 to May 2005, 32 patients with locoregionally postoperative recurrent esophageal cancer were treated with radiotherapy (60 Gy/30 fractions/6 weeks) combined with chemotherapy consisting of two cycles of nedaplatin (70 mg/m^2/2 hours) and 5-fluorouracil (500 mg/m^2/24 hours for 5 days). The primary endpoint of the present study was overall survival rate, and the second endpoints were irradiated-field control rate, tumor response and toxicity. The mean follow-up period of survival patients was 41.6 months (range, 24.0 to 80.0 months).
Results: The 3-year and 5-year overall survival rates were 35.7% and 22.3%, respectively, with a median survival period of 22.5 months (95%C.I.= 12.8−32.2), and the 5-year local control rates were 71.4%. Complete response and partial response were observed in 18.8% and 53.1% of the patients, respectively. Grade 3 or higher leukocytopenia and thrombocytopenia were observed in 37.5% and 3.1% of the patients, respectively, but renal toxicity of grade 3 or higher was not observed. The regimen was completed in 84.4% of the patients.
In univariate analysis, the difference between survival rate in preradiotherapy performance status ($p = 0.031$), number of recurrent regions ($p = 0.018$) and recurrent pattern [worse for patients with anastomotic recurrence ($p = 0.036$)] were statistically significant.
Conclusions: Radiotherapy combined with nedaplatin and 5-FU is a safe and effective salvage treatment for postoperative locoregional recurrent esophageal cancer.

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(XELOX)Capecitabine plus Oxaliplatin: clinical efficacy and safety in first-line treatment for metastatic gastric cancer

M. Alu', A. Laudani, V. Leonardi, V. Palmisano, G. Savio, A. Pepe, C. Arcuri, M.P. Cusimano, C. Calabria, B. Agostara. *Ospedale Oncologico Maurizio Ascoli, Oncologia, Palermo, Italy*

Background: Capecitabina is a oral fluoropyrimidine with proven efficacy and favourable safety in colorectal cancer, whose administration does not require hospitalisation or placement of central iv line.
The trial was designed to evalute the efficacy of XELOX in metastatic gastric cancer.
Materials and Methods: To date 22 pts were enrolled in this study and treated with Oxaliplatin 120 mg/mq on day 1 and capecitabine 1.000 mg/mq twice daily from day 2 to day 15 every 3 weeks until disease progression or unaccepted toxicity. The evalutation of efficacy was performed every 3 cycles.
The characteristics of enrolled patients were: M/F = 13/9, Median age 56 yrs; median ECOG status 1 (range 0−2), all patients had adequate haematological, liver and renal function. The sites of disease were liver 10 pts, lymph nodes 7 pts, bone 1 pts and peritoneum 4 pts.
Results: All patients were evalutable for efficacy and toxicity. Were registered 3 RC and 6 RP with an overall Response Rate of 40%, in 8 pts we registreted a SD, 5 patients progressed. Two patients of 3 with RC had a single liver localization. The schedule was well tolerated, the main G 3/4 toxicity (according to NCI-CTC) observed were neutropenia 13% of the pts, diarrhoea 8% of pts. Neuropathy G2 was recorded in 3 pts (13%). No treatment related was reported.
Conclusions: XELOX appears to be effective and well tolerated in first-line and treatment of pts with metastatic gastric cancer. These results are superior to those of historical controls from this institution, but is necessary to confirm these data with a longer follow up and more patients.

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Image-guided intensity modulated radiation therapy (IG-IMRT) for extrahepatic cholangiocarcinoma: Results from a mature case control comparison with conventional radiotherapy (CRT)

C.D. Fuller[1], G.D. Starling[2], A. Wong[3], S.J. Wang[4], C.R. Thomas[4], M. Fuss[5]. *[1]University of Texas Health Science Center, Radiation Oncology/Radiological Sciences, San Antonio, USA; [2]University of Texas Health Science Center, Radiation Oncology, San Antonio, USA; [3]University of Texas Health Science Center, Diagnostic and Interventional Imaging, Houston, USA; [4]Oregon Health & Science University, Radiation Medicine, Portland, USA; [5]Oregon Health & Science University/University of Texas Health Science Center, Radiation Medicine/Radiological Sciences, Portland, USA*

Purpose: Cholangiocarcinomas are comparatively rare neoplasms, and the optimum role of radiotherapy remains to be determined. The specific aim of this study was to report the clinical results of a single-institution cholangiocarcinoma series treated with modern radiotherapeutic techniques, and to ascertain if clinical benefit was observed using ultrasound (US) image-guided intensity-modulated radiation therapy (IG-IMRT).
Methods and Materials: From 2001 to 2005, 11 patients with primary adenocarcinoma of the extrahepatic bile ducts were treated by daily US-guided IG-IMRT to a mean dose of 57 Gy. To compare outcomes, data from a sequential series of 8 patients treated between 1995 and 2005 with conventional radiotherapy techniques (CRT) were collected in a comparator set. Demographic and treatment parameters were collected. Endpoints included treatment-related acute toxicity and survival.
Results: A statistically significant higher mean dose was given to patients receiving IG-IMRT compared to CRT, 57 vs. 45 Gy ($p < 0.01$). At last contact 3 patients were living, with a median follow-up of 32 months or those alive at last contact. Median estimated survival for all 19 patients was 11.1 months (range 2−62 months). 1-and 3-year survival for the IG-IMRT cohort was 64% and 23%, compared to 12.5% and 0% for the CRT patients. A statistically significant survival differential between IG-IMRT and CRT cohorts was observed (median 15.0 vs 6.9 months, $p = 0.01$). Surgical resection was associated with improved survival ($p < 0.01$). One IG-IMRT patient (9%) experienced an RTOG acute toxicity score >2, specifically upper GI grade 3 nausea/vomiting requiring tube or parenteral support; no CRT patients experienced a score >2. The most commonly reported GI toxicity requiring medication (RTOG Grade $\geqslant 2$) was nausea and abdominal pain relieved with oral medication, experienced by 25% of CRT patients and 54% of IG-IMRT patients ($p =$ n.s.).
Conclusion: This hypothesis generating series presents the first mature clinical outcomes of extrahepatic cholangiocarcinomas treated with IG-IMRT. IG-IMRT shows potential for improved survival in biliary tract tumors,