Gastro-intestinal malignancies

Oral presentations (Wed, 23 Sep, 09:00−10:45)

Gastro-intestinal malignancies − Non-colorectal cancer

6500 ORAL

Gemcitabine with or without cisplatin in patients (pts) with advanced or metastatic biliary tract cancer (ABC): final results of the UK ABC-02 trial

J. Bridgewater[1], J. Valle[2], D. Palmer[3], D. Cunningham[4], D. Anthoney[5], A. Maraveyas[6], S. Hughes[7], M. Roughton[7], H. Wasan[8]. [1]*University College London Medical School, Oncology, London, United Kingdom;* [2]*Christie Hospital NHS Trust, Oncology, Manchester, United Kingdom;* [3]*University of Birmingham, Oncology, Birmingham, United Kingdom;* [4]*Royal Marsden Hospital, Oncology, London, United Kingdom;* [5]*St James' University Hospital, Oncology, Leeds, United Kingdom;* [6]*Castle Hill Hospital, Oncology, Hull, United Kingdom;* [7]*University College London, Clinical Trials Centre, London, United Kingdom;* [8]*Imperial College Healthcare Trust, Oncology, London, United Kingdom*

Background: There is no established standard chemotherapy for pts with inoperable ABC. We previously reported an improvement in progression-free survival (PFS) in a randomised phase II trial of 86 pts (ABC-01) using gemcitabine/cisplatin (GemCis) *vs.* gemcitabine (Gem) (Valle ASCO-GI 2006, abstr. 98). This study was extended into ABC-02, a phase III trial, to recruit a further 314 pts with overall survival (OS) as the primary end-point.
Methods: Consenting pts with histologically/cytologically-confirmed ABC, aged ⩾18 years, ECOG performance status 0−2, and adequate haemato-logical, hepatic and renal function were randomised to receive either Cis (25 mg/m^2) followed by Gem (1000 mg/m^2 D1, 8 q21 d) for 8 cycles, or Gem alone (1000 mg/m^2 on D1, 8, 15 q28 d) for 6 cycles, stratified by extent of disease, site of primary tumour, ECOG score and centre. The trial had an 80% power to detect an OS hazard ratio of 0.73.
Results: From May 2005 to October 2008, 324 pts were randomised to ABC-02 from 34 UK centres. We report the pre-planned combined analysis of ABC-01 and ABC-02 based on 410 pts (GemCis = 206/Gem = 204). Patient characteristics: median age 64 yrs (range 23−85); male (47%); metastatic disease (75%), locally advanced (25%); gallbladder (36%), bile duct (59%), ampulla (5%); and ECOG 0−1 (87%), 2 (12%). With a median follow-up of 6.1 months and 263 deaths, the median OS was greater with GemCis than Gem, 11.7 vs. 8.2 months (log rank p = 0.002), with hazard ratio 0.68 (95%-CI 0.53, 0.86). The median PFS was greater with GemCis than Gem, 8.5 vs. 6.5 months (log rank p = 0.003), with hazard ratio 0.70 (95%-CI 0.56, 0.88). Toxicity was similar between the arms (by week 12, 57% had a grade 3/4 toxicity in each arm), though there was a slight excess of neutropenia using GemCis. We will present CA19.9 and Quality of life data.
Conclusions: This study demonstrates a clear survival advantage for GemCis in ABC without added clinically significant toxicity. We will present updated and final survival, CA19.9 and QL data.

6501 ORAL

Sunitinib (SU) vs placebo for treatment of progressive, well-differentiated pancreatic islet cell tumours: results of a phase III, randomised, double-blind trial

J.L. Raoul[1], P. Niccoli[2], Y.J. Bang[3], I. Borbath[4], C. Lombard-Bohas[5], P. Metrakos[6], A. Vinik[7], D.R. Lu[8], C. Blanckmeister[9], E. Raymond[10]. [1]*Centre Eugene Marquis, Department of Medical Oncology, Rennes, France;* [2]*CHU La Timone, Service d'Oncologie Medicale, Marseille, France;* [3]*Seoul National University Hospital, Department of Internal Medicine, Seoul, Korea;* [4]*Cliniques Universitaires Saint-Luc, Gastroenterology Department, Brussels, Belgium;* [5]*Hopital Edouard Herriot, Service d'Oncologie Digestive, Lyon, France;* [6]*McGill University, Department of Oncology, Montreal, Canada;* [7]*EVMS Strelitz Diabetes Research Center and Neuroendocrine Unit, Department of Internal Medicine, Norfolk, USA;* [8]*Pfizer Oncology, Development, La Jolla, USA;* [9]*Pfizer Oncology, Medical Affairs, New York, USA;* [10]*Service Inter Hospitalier de Cancerologie Bichat-Beaujon, Department of Medical Oncology, Clichy, France*

Background: Limited treatment options exist for advanced pancreatic islet cell tumours (neuroendocrine carcinoma of the pancreas) and most have not been tested in rigorous randomised controlled trials. SU has shown activity in patients with pancreatic islet cell tumours in a phase II study. This multinational phase III trial (NCT00428597, sponsored by Pfizer Inc) assessed SU efficacy and safety in patients with progressive growth of pancreatic islet cell tumours.
Methods: Patients enrolled had local, locally advanced or metastatic, well-differentiated pancreatic islet cell tumours not amenable to curative therapy, and disease progression in the past 12 months. Patients were randomised to placebo or SU 37.5 mg/day continuous daily dosing, with best supportive care. Progression-free survival (PFS) was the primary endpoint; the study was powered to detect a 50% improvement in PFS with a target sample size of 340 patients. Safety and tolerability were assessed.
Results: From Jun 2007 to Feb 2009, patients were randomised to SU (n = 75) or placebo (n = 79). Median age was 56 years (range 25−78); 27% ⩾65 years old; 53% female. Further demographic and treatment history data are being analysed. The most frequently reported all-cause, all-grade adverse events (AEs) with SU were diarrhoea (63%), nausea (53%), vomiting (39%), asthenia (35%) and fatigue (35%). The most frequent Grade 3/4 AEs included neutropenia (SU vs placebo, 12.3% vs 0%), hypertension (8.8% vs 0%), abdominal pain (7.0% vs 10.4%), diarrhoea (7.0% vs 1.5%), hypoglycaemia (7.0% vs 3.0%), and palmar–plantar erythrodysaesthesia (7.0% vs 0%). At interim analysis (73 events evaluated, including 63 due to disease progression), median PFS was 11.1 months in the SU arm vs 5.5 months with placebo (hazard ratio for progression, 0.397 in favour of SU; 95% CI 0.243, 0.649; 2-sided p value <0.001). The study was stopped early as recommended by an independent Data Monitoring Committee; patients in the placebo arm were able to cross over to SU. Analysis of survival is ongoing; 5 deaths occurred in the SU arm and 15 in the placebo arm.
Conclusions: SU prolonged PFS compared with placebo in patients with progressive well-differentiated pancreatic islet cell tumours, with an acceptable safety profile. Analysis of data is ongoing; additional data will be presented as available. These data contribute to a growing body of evidence indicating SU activity in patients with advanced pancreatic islet cell tumours.

6502 ORAL

A double-blinded, placebo-controlled, randomized, phase III study of axitinib (AG-013736; A) plus gemcitabine (G) vs. G plus placebo (P) in advanced pancreatic cancer (PC) patients (pts)

H.L. Kindler[1], T. Ioka[2], D.J. Richel[3], J. Bennouna[4], R. Létourneau[5], T. Okusaka[6], P. Bycott[7], A.D. Ricart[7], S. Kim[7], E. Van Cutsem[8]. [1]*University of Chicago, Medicine, Chicago, USA;* [2]*Osaka Medical Center for Cancer and Cardiovascular Diseases, Department of Hepatobiliary and Pancreatic Oncology, Osaka, Japan;* [3]*University of Amsterdam, Academic Medical Centre, Amsterdam, The Netherlands;* [4]*Centre René Gauducheau, Medical Oncology Services, Saint-Herblain, France;* [5]*Centre Hospitalier Université de Montréal, Hôpital Saint-Luc, Montréal, Canada;* [6]*National Cancer Center, General Inpatient Division, Tokyo, Japan;* [7]*Pfizer Oncology, Development, San Diego, USA;* [8]*Department of Digestive Oncology, University Hospital Gasthuisberg/Leuven, Leuven, Belgium*

Background: A is an oral, potent, selective inhibitor of vascular endothelial growth factor receptors 1, 2, 3. In a randomized, phase II trial of G +/− A in PC pts, there was a non-statistically significant gain in overall survival (OS) in pts treated with A+G compared with G (6.9 vs. 5.6 months; Spano et al. *Lancet* 2008). These data led to an international, double-blind, placebo-controlled, randomized, phase III trial of A+G vs. P+G in advanced PC pts (NCT00219557; Sponsor: Pfizer Oncology).
Material and Methods: Eligible pts had no prior chemotherapy, ECOG performance status (PS) 0/1, no tumor invasion of adjacent organs, no recent thrombosis, and no bleeding risk. Primary endpoint: OS. Stratification: disease extent (locally advanced vs. metastatic). Statistics: 90% power to detect a death hazard ratio of ⩽0.73 for G+A with a 1-sided 0.025 false-positive error rate. Pts were randomized in a 1:1 ratio to receive G 1,000 mg/m^2 over 30 minutes on days 1, 8, 15, Q28 days, and either A 5 mg or P orally BID. CT scans were obtained Q8 weeks.
Results: 632 pts were enrolled from 7/07 to 10/08. At the time of the pre-specified interim analysis, data from 630 pts were available. Based on the interim analysis after 223 deaths had occurred, the Independent Data Monitoring Committee in 1/09 determined that the futility boundary had been crossed. Pts on treatment were notified and unblinded, and discontinuation of A was recommended. Pt characteristics (314 A+G/316 P+G): male 61%/60%; median age 61/62 years; PS 1 52%/49%; stage IV disease 80%/79%. Median time on treatment: 2.7/2.8 months (mo). Median follow-up: 5.6/5.6 mo. Median OS: intent-to-treat population 7.4/8.2 mo (95% CI: 6.2−9.5/6.9−10.4 mo); locally advanced disease 9.0/10.6 mo (95% CI: 7.3−10.1/9.9–not available); metastatic disease 6.9/6.9 (95% CI: 5.6−10.2/6.2−8.2). Overall death hazard ratio: 1.06 (95% CI: 0.82−1.38). Deaths as of 1/09: 112/111 pts. Of the 613 pts evaluable for toxicity, grade 3/4 toxicity included (% pts A+G/P+G): neutropenia 13%/12%; thrombocytopenia 12%/7%; anemia 3%/8%; fatigue 8%/7%; anorexia 6%/4%; hypertension 7%/2%; asthenia 6%/2%; gastrointestinal bleeding

2%/2%; gastrointestinal perforation 1%/1%; pulmonary embolism 2%/2%; deep vein thrombosis 1%/2%; cerebrovascular accident 0.3%/0.3%; proteinuria 1%/0%. Thyroid-stimulating hormone levels were obtained in 217 pts; of 197 pts with normal baseline values, elevations $\geqslant 5\,\mu U/mL$ occurred in 36%/8% of pts.
Conclusion: The addition of A to G does not increase survival in pts with advanced PC.

6503 ORAL

Gemcitabine with or without prophylactic weight-adjusted dalteparin in patients with advanced or metastatic pancreatic cancer (APC): a multicentre, randomised phase IIB trial (the UK FRAGEM study)

A. Maraveyas[1], J. Waters[2], R. Roy[3], D. Propper[4], D. Fyfe[5], F. Lofts[6], E. Gardiner[7], J. Sgouros[8], K. Wedgwood[9]. [1]*Hull and East Yorkshire NHS Trust, Academic Oncology, Hull East Yorkshire, United Kingdom;* [2]*Kent Oncology Centre, Medical Oncology, Maidstone, United Kingdom;* [3]*Diana Princess of Wales, Oncology, Grimsby, United Kingdom;* [4]*St Bartholomew's & London Hospitals, Medical Oncology, London, United Kingdom;* [5]*Royal Lancaster Infirmary, Medical Oncology, Lancaster, United Kingdom;* [6]*St. George's University, Medical Oncology, London, United Kingdom;* [7]*Freelance, Statistics, Hull, United Kingdom;* [8]*Hull and East Yorkshire NHS Trust, Medical Oncology, Hull, United Kingdom;* [9]*Hull and East Yorkshire NHS Trust, Gastrointestinal Surgery, Hull, United Kingdom*

Background: The incidence of vascular thromboembolism (VTE) in advanced pancreatic cancer (APC) is high (17−30%) and has been shown to confer a worse prognosis. Direct mortality and morbidity related to VTE may be an underlying cause. Nullifying VTE therefore could have beneficial effects for APC patients. The study hypothesis is that the use of weight-adjusted dalteparin dosing (WAD) in a primary prophylaxis setting may eliminate VTE to an extent that survival benefit may be seen.
Methods: Patients, aged 18 years or older, with histologically/cytologically-confirmed APC, Karnofsky performance status KPS 60–100, with adequate haematological, hepatic and renal function, no baseline VTE, no hemorrhagic risk, no recent VTE (<6 months) and not on anticoagulants were randomised to either gemcitabine 1000 mg/m^2 (Burris schedule) (Arm A) or same with WAD (CLOT schedule) for 3 months (Arm B) stratified by extent of disease (LA vs. M), and KPS (90–100 vs. 80−60). Primary end point was the reduction of all-type VTE and lethal VTE during study period (<100 days). ('FRAGEM', EUDRACT No:111–111111−11, Sponsored by Hull and East Yorkshire NHS Trust-University of Hull).
Results: From April 2003 to January 2009, 123 (A/B 64/59) pts were randomised from 6 institutions in the UK. Pre-planned analysis of the primary endpoint of overall reduction of VTE and reduction of VTE during WAD treatment period <100 days) is presented. Overall VTE was 31% (A) Vs 12% (B) ($p = 0.019$) with RR = 0.38 (95% CI = 0.17, 0.84). VTE during treatment period (<100 days from randomization): 25% (A) vs. 3.5% (B) ($p = 0.002$) with RR = 0.14 (95% CI 0.03, 0.58). Secondary endpoints, lethal VTE and sudden death were seen only in (A) 9%Vs 0% (B) ($p = 0.028$) RR = 0.08 (95% CI = 0.005, 1.45) and Early Death Burden was 11% (A) vs. 7% (B) ($p = 0.62$). Analysis of VTE profile and results of other secondary endpoints (toxicity, OS and TTF) will be presented at the meeting.
Conclusions: This is the only study to have looked at WAD-dosing in this setting and one of the largest studies of Low molecular weight anticoagulant prophylaxis in APC. It demonstrates a significant reduction in overall VTE and a highly significant reduction of VTE during WAD-prophylaxis with a reduction of lethal VTEs/sudden death. This trial suggests that prophylaxis with WAD over 3 months at least, is beneficial for APC patients receiving gemcitabine and should be considered a new standard of care.

6504 ORAL

Survial advantage for irinotecan versus best supportive care (BSC) as 2nd-line chemotherapy in gastric cancer – a randomized phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO)

P. Thuss-Patience[1], A. Kretzschmar[2], T. Deist[3], A. Hinke[4], D. Bichev[1], B. Lebedinzew[1], B. Gebauer[5], G. Schumacher[6], P. Reichardt[7]. [1]*Charité Campus Virchow-Klinikum, Med. Klinik m.S. Hämatologie u. Onkologie, Berlin, Germany;* [2]*HELIOS-Klinikum Berlin Buch, Robert-Rössle-Klinik, Berlin, Germany;* [3]*Kreiskrankenhaus Aschersleben Staßfurt, Innere Medizin II m.S. Gastroenterologie u. Nephrologie, Aschersleben, Germany;* [4]*WiSP Research Institute, Statistics, Langenfeld, Germany;* [5]*Charité Campus Virchow-Klinikum, Institut f. Radiologie, Berlin, Germany;* [6]*Charité Campus Virchow-Klinikum, Klinik f. Chirurgie, Berlin, Germany;* [7]*HELIOS-Klinikum Bad Saarow, Hämatologie Onkologie u. Palliativmedizin, Bad Saarow, Germany*

Background: Up to now the value of 2nd-line therapy for metastatic gastric cancer is unclear. So far there are no randomized phase III data comparing 2nd-line chemotherapy to BSC. Irinotecan has proven activity in 1st-line therapy. In this randomized phase III study we compared irinotecan to BSC to evaluate the value of 2nd-line chemotherapy for gastric cancer.
Methods: Prospective multicenter randomized phase III study, open label. *Eligibility:* Metastatic or locally advanced gastro-esophageal junction or gastric adenocarcinoma. Objective tumor progession (PD) within 6 months after 1st-line chemotherapy. ECOG PS 0−2. *Statistics:* Primary endpoint: Overall survival (OS). Hypothesis: H1: OS (Irinotecan) >OS (BSC). Calculated number of pts needed (power 80%, alpha error 5%): 60 pts per arm. Stratification for (a) PD less versus (vs) more than 3 months after 1st line chemotherapy, (b) ECOG PS 0/1 vs 2. *Treatment*: Arm A: Irinotecan 250 mg/m^2 q3w (1st cycle) to be increased to 350 mg/m^2, depending on toxicity. Arm B: BSC.
Results: Between Oct 2002 and Dec 2006 40 pts were randomized. The study was closed prematurely due to poor accrual. Arm A:21 pts, arm B 19 pts. Median age A: 58 yrs (43−73), B: 55 yrs (35−72); PD less vs more than 3 months after 1st-line chemotherapy: A: 18/3, B: 17/2 pts. ECOG PS 0/1 vs 2: A: 17/4, B: 14/5 pts. Pre-treatment with cisplatin: A: 21, B:19 pts. *Arm A:* 68 cycles administered in 21 pts. *Toxicity*: (main CTC grade 3/4): Nausea 1 pt, vomiting 1 pt, diarrhoea: 5 pts, neutropenic fever: 2 pts, data incomplete 6 pts. In 37% of 19 evaluable pts irinotecan dose was escalated to 350 mg/m^2. *Response* (19 pts evaluable): No objective responses, SD 58%, PD 42%. Improvement of tumor related symptoms: 44% of pts in arm A, 5% in arm B.
Survival: (all 40 pts evaluable): median survival arm A: 123 days (95%CI 95–216), arm B 73 days (95%CI 53–149); OS: HR = 0.48 (95%CI 0.25−0.92), Logrank test (two-sided): $p = 0.023$. In univariate analyses for potential prognostic markers treatment with irinotecan had the most significant impact on survival.
Conclusion: To our knowledge this is the first randomized phase III study investigating 2nd-line chemotherapy in gastric cancer. Irinotecan as 2nd-line chemotherapy significantly prolongs overall survival compared to BSC. 2nd-line chemotherapy can now be considered as a proven option in gastric cancer.

6505 ORAL

A randomised phase II trial of a drug eluting bead in the treatment of hepatocellular carcinoma by transcatheter arterial chemoembolization

T. Vogl[1], N. Naguib[1], R. Lencioni[2], K. Malagari[3], F. Pilleul[4], A. Denys[5], A. Watkinson[6], J. Lammer[7]. [1]*Universitatsklinikum, Institute for Diagnostic and Interventional Radiology, Frankfurt am Main, Germany;* [2]*University of Pisa, Diagnostic Imaging and Intervention in the Department of Liver Transplantation Hepatology and Infectious Diseases, Pisa, Italy;* [3]*University of Athens, Radiology, Athens, Greece;* [4]*Centre Hospitalier Universitaire, Département d'imagerie digestive, Lyon, France;* [5]*Centre Hospitalier Universitaire, Département de Radiologie, Lausanne, France;* [6]*Royal Devon and Exeter Hospital, Radiology, Exeter, United Kingdom;* [7]*University of Vienna, Radiology, Vienna, Austria*

Background: A widely accepted transarterial chemoembolization (TACE) regimen includes administration of doxorubicin-in-oil emulsion followed by gelatine sponge particles. Recently, a drug eluting bead (DEB) has been developed to enhance drug delivery to the tumor and reduce systemic availability. Purpose of this randomized trial was to compare conventional TACE with DEB-TACE for the treatment of intermediate-stage HCC.
Methods: 212 patients (185 males, 27 females; mean age, 67 years) with Child-Pugh A-B cirrhosis and large and/or multinodular HCC were randomized to receive DEB (DC Bead; Biocompatibles, UK) loaded with doxorubicin or conventional TACE. Randomization was stratified according to Child-Pugh class, performance status, bilobar disease (yes or no) and prior curative treatment (yes or no). Tumor response at 6 months was the primary endpoint.
Results: DEB-TACE showed a higher rate of complete response, objective response and disease control compared with conventional TACE (27% vs 22%; 52% vs 44%; and 63% vs 52% respectively, $P > 0.05$). Patients with Child-Pugh B, ECOG 1, bilobar disease and recurrence following curative treatment showed a significant increase in objective response ($p = 0.038$) compared to the control. There was a marked reduction in serious liver toxicity in patients treated with DEB-TACE. The rate of doxorubicin-related side effects was significantly lower ($p = 0.0001$) in the DEB-TACE group compared with conventional TACE group.
Conclusion: DEB-TACE with doxorubicin is safe and effective in the treatment of intermediate-stage HCC and offers a significant benefit to patients with more advanced disease.