Conclusions: Pulmonary resection for metastases from colorectal cancer does produce longer survival, even in patients with multiple lesions and recurrent metastases.

Oral presentations (Thu, 27 Sep, 09.00−11.00)
Gastrointestinal malignancies – non colorectal cancer

3500 ORAL

Preliminary results from a phase II, randomized, double-blind study of sorafenib plus doxorubicin versus placebo plus doxorubicin in patients with advanced hepatocellular carcinoma

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Background: Sorafenib, a tyrosine kinase inhibitor with multiple targets, including Raf kinase and the vascular endothelial growth factor receptor (VEGFr), has demonstrated modest single agent activity in hepatocellular carcinoma (HCC) (Abou-Alfa et al: JCO 2006:24; 4293–4300) Here we report the findings of an unplanned interim analysis, requested by the external data safety monitoring board, of a phase II, randomized, double–blind study, conducted to assess sorafenib plus doxorubicin (dox) versus placebo plus dox in patients with advanced HCC.
Material and Methods: Patients with advanced HCC, ECOG Performance Status (PS) of
0–2, Child–Pugh A only and no prior systemic therapy, received dox 60 mg/m^2 i.v. every 21 days plus either sorafenib 400 mg orally twice daily or placebo, for a maximum of six cycles (18 weeks) of dox. Patients could continue on single-agent sorafenib or placebo beyond 18 weeks until disease progression. The primary efficacy endpoint was time to progression (TTP) by external review. Secondary endpoints included overall survival (OS), response rate according to RECIST criteria, and toxicity. Twenty-six progression events have occurred at this analysis.
Results: A total of 96 patients were randomized (sorafenib plus dox, n = 47; placebo plus dox, n = 49); 76% were male, 91% had an ECOG PS of 0–1, and the median patient age was 65 years. Baseline patient characteristics were balanced between treatment arms. Data are presented in the table. The TTP and OS of the placebo/dox control arm fall within the range of the historically reported data for dox alone.
Conclusions: In this preliminary analysis, TTP and OS in the sorafenib/dox arm appear to be encouraging, and toxicity appears tolerable. Per the external DSMB recommendation, the trial has been unblinded and remaining patients on the control arm have been crossed over to sorafenib. Updated analyses will be presented at the meeting.

	Time to progression	Overall survival	Response rate (CR+PR) %	Grade 3/4 fatigue	Grade 3/4 neutropenia
Sorafanib/dox	8.5 mo	14.0 mo	4.3	10.6%	36.2%
Placebo/dox	2.8 mo	5.6 mo	2.0	6.3%	41.7%

3501 ORAL

Capecitabine/cisplatin vs. continuous infusion of 5-FU/cisplatin as first-line therapy in patients (pts) with advanced gastric cancer (AGC): a randomised phase III trial

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Background: Capecitabine has proven efficacy and safety in a number of tumours, particularly colorectal, breast and gastric cancers. A phase II study in AGC suggested that capecitabine plus cisplatin (XP) has comparable efficacy to the standard 5-fluorouracil/cisplatin (FP) regimen, with potential safety and convenience advantages. We compared XP and FP as first-line treatment for AGC.
Materials and Methods: In this randomised, open-label, multicentre study, pts with previously untreated AGC received either oral capecitabine (1000 mg/m^2 bid days 1–14) plus cisplatin (80 mg/m^2 i.v. day 1) every 3 weeks (XP arm) or 5-FU (800 mg/m^2/day continuous infusion, days 1–5) plus cisplatin (80 mg/m^2 i.v. day 1) every 3 weeks (FP arm). Pts were treated until disease progression or unacceptable toxicity. Primary endpoint: non-inferiority in progression-free survival (PFS), defined as upper limit for 95% CI of the hazard ratio (HR) of
Results: 316 pts were randomised. Median number of treatment cycles per arm was 5. Median follow-up was 21.2 months (range 13–34) for XP, and 21.0 (14–33) for FP. In the per protocol population, median PFS for XP was 5.6 months (95% CI 4.9–7.3) vs. 5.0 months for FP (95% CI 4.2–6.3). Primary endpoint was met with HR of 0.81 (95% CI 0.63–1.05, p < 0.001 vs. non-inferiority margin of 1.25); non-inferiority was highly significant. Median overall survival (OS) for XP was 10.7 months (95% CI 9.5–11.5) vs. 9.5 months for FP (95% CI 7.5–11.4). For OS, XP was significantly non-inferior vs. FP (HR = 0.89, 95% CI 0.68–1.17, p = 0.0146 vs. non-inferiority margin of 1.25 in per protocol population). XP was significantly superior to FP in terms of objective response rate (ORR, RECIST: 41% vs. 29%; p = 0.0295 in ITT population). Both treatments were well tolerated and had similar safety. Most common treatment-related grade 3/4 adverse events: neutropenia (occurring in 16% of XP vs. 19% of FP pts), vomiting (7% vs. 8%), stomatitis (2% vs. 6%), diarrhoea (5% vs. 5%), anaemia (3% vs. 2%). Rate of hand–foot syndrome was low (22% vs. 4%) relative to other studies.
Conclusions: XP showed highly significant non-inferiority for PFS and OS vs. FP and had similar safety. XP was also significantly superior to FP in terms of ORR.

3502 ORAL

Final results of a randomized phase III trial in patients with advanced adenocarcinoma of the stomach receiving first-line chemotherapy with fluorouracil, leucovorin and oxaliplatin (FLO) versus fluorouracil, leucovorin and cisplatin (FLP)

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Background: Cisplatin-based chemotherapy is a standard option in advanced gastric cancer. However, treatment results have been unsatisfactory so far, with a progression-free survival (PFS) of 3 to 4 months and an overall survival (OS) of 6 to 9 months. In addition, treatment regimens are too intense and toxicity is considerable. The aim of this trial was to determine whether FLO prolongs PFS and reduces toxicity as compared to FLP.

Methods: Patients (pts) were randomized to receive FLO: F 2600 mg/m^2 24h infusion, L 200 mg/m^2, and oxaliplatin 85 mg/m^2, every two weeks or FLP: F 2000 mg/m^2 24h infusion, L 200 mg/m^2, weekly, and cisplatin 50 mg/m^2, every two weeks. The primary end point was PFS (power, 80%; 1-sided log-rank test; significance level 0.05).
Results: 220 pts were randomized (FLO, 112; FLP, 108) between Aug 2003 and Jan 2006. Median age was 64 years and median ECOG was 1. Median treatment duration was 4.3 months with FLO and 3 months with FLP. FLO was associated with significantly less NCI-CTC grade 1−4 anemia (54% v 82%), nausea (57% v 71%), vomiting (37% v 52%), alopecia (22% v 39%), fatigue (20% v 36%), renal toxicity (11% v 34%), and serious adverse events related to the treatment (9% v 19%), and FLP was associated with significantly less peripheral neuropathy (25% v 60%). There was a trend toward increased median PFS with FLO versus FLP (5.7 months v 3.8 months, respectively), which did not reach the statistical significance (P=.0725). OS was 10.8 months for FLO and 8.7 months for FLP (NS). However, in pts aged >65 years (n = 94), treatment with FLO resulted in a significantly superior response rate (34.9% v 16.7%), time to treatment failure (5.4 v 2.1 months, p = 0.0001), and PFS (6.0 v 3.1 months, p = 0.021). These differences seemed also to result in an improved OS in elderly pts treated with FLO (13.8 v 7.3 months, p = 0.081). In contrast, there were no significant differences in young pts between arms concerning all efficacy parameter.
Conclusions: FLO reduced toxicity and, in elderly pts, improved efficacy as compared to FLP. This leads us to consider FLO for future studies in combination with targeted drugs to further improve the outcome of pts with gastric cancer.

3503 ORAL

Adding external beam to HDR-intraluminal brachytherapy, improves palliation of oesophageal cancer: a prospective randomized, multicentre trial of the International Atomic Energy Agency

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Background: While the addition of oesophageal high dose-rate intraluminal brachytherapy (HDR-ILBT) has shown improved palliation compared with external beam radiation therapy (EBRT) alone, it is not known whether the addition of EBRT adds to the benefits of ILBT alone. This study aims at identifying resource-sparing treatment strategies to be adopted in low-income developing countries.
Methods: Patients were recruited in 6 countries where oesophageal cancer is common. Patients had localized non-metastatic, squamous-cell carcinoma, not amenable to curative therapy. They were managed with two ILBT of 8 Gy each, at 1 cm of the sources centres, and were randomized to EBRT of 30 Gy in 10 fractions vs. no EBRT. Worsening of dysphagia and the occurrence of a fistula were combined into a "dysphagia-free experience" (DFE) plot. Study endpoints were DFE, dysphagia score, ECOG performance status, quality of life and weight. Patient survival was not an endpoint in this study.
Results: 219 patients were randomized: 110 received EBRT and 109 did not. Patient characteristics, disease stage, symptoms and quality of life in both groups were similar. The main outcome of DFE was significantly improved with EBRT, by an absolute 18% (a sustained difference from 50 to 350 days of follow-up from randomization), with p = 0.019 by log-rank. Mean dysphagia scores were 0.79 with combined therapy and 1.23 with brachytherapy alone, a difference of 0.44 in favour of EBRT. Mean regurgitation scores were 0.36 and 0.72, respectively, a difference in favour of combined therapy. Adverse events were not different between the two study groups (e.g. perforations, ulcers). In particular, occurrences of strictures were in 5 cases with EBRT, and 1 without EBRT (p = 0.21), while occurrences of fistulae were in 12 cases with EBRT, and 7 without EBRT (p = 0.34); and the combined risks of either stricture or fistula at one-year were approximately 25% in both study groups. Overall median survival was 188 days; with no difference between study arms (p = 0.35). Performance status (an ECOG score difference of −0.40), and some quality of life measures ("activity level" and "feeling of well-being") were significantly improved with EBRT. Hierarchical multivariate analyses confirmed the findings regarding the benefits of combined therapy relative to brachytherapy alone.
Conclusions: The addition of EBRT to HDR-ILBT improves palliation in patients with squamous cell carcinoma of the oesophagus.

3504 ORAL

A randomized phase III study comparing gemcitabine monotherapy with observation in patients with resected pancreatic cancer

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Background: Gemcitabine (Gem) is considered to be a standard chemotherapy for unresectable advanced pancreatic cancer. However, the role of Gem in patients (pts) with resectable pancreatic cancer is uncertain. This study was designed to determine whether adjuvant chemotherapy with Gem improves the outcome of pts with resected pancreatic cancer.
Materials and Methods: This randomized phase III study was conducted at 10 centers in Japan. Eligibility criteria included gross complete resection of invasive ductal carcinoma of the pancreas and no prior radiation or chemotherapy. Pts were randomized to receive Gem monotherapy or observation using the minimization method stratified by pathological stage (UICC 5th edition stage I, II vs. III, IV), resection status (R0 vs. R1) and centers. Gem was administered at a dose of 1,000 mg/m^2 over 30 min on days 1, 8, and 15 every 4 weeks for 3 cycles. The primary end point was overall survival (OS), and secondary end points were disease-free survival (DFS) and adverse events.
Results: Between April 2002 and March 2005, 119 pts were entered into the study. Among them, 118 pts were eligible and analyzable (58 in the Gem arm, 60 in the observation arm). Both arms were well balanced in terms of baseline characteristics. Although hematologic toxicity was frequently observed in the Gem arm (grade 3 or 4 leukopenia 24.6%, grade 3 or 4 neutropenia 70.2%), most toxicities were transient, and grade 3 or 4 non-hematologic toxicity rarely occurred. During a mean follow-up period of 21.2 months, 42 pts (72.4%) in the Gem arm and 51 (85.0%) in the observation arm developed recurrent disease. Pts in the Gem arm demonstrated significantly longer DFS than those in the observation arm (median DFS, 11.44 months vs. 4.97 months; hazard ratio = 0.59 [95% confidence interval: 0.39−0.89]; P = 0.01). Also, the median OS of pts in the Gem arm was better than that of pts in the observation arm (median OS, 22.31 months vs. 18.36 months), although not to a significant degree (hazard ratio = 0.79 [95% confidence interval: 0.51−1.22]; P = 0.29).
Conclusions: Adjuvant chemotherapy with Gem significantly improved DFS compared with observation in pts with resected pancreatic cancer. OS was also more favorable in the Gem arm, although the difference did not attain statistical significance. We conclude that adjuvant chemotherapy with Gem may be considered as an optimal treatment in pts scheduled for resection of pancreatic cancer.

3505 ORAL

Glufosfamide (GLU) in metastatic pancreatic adenocarcinoma previously treated with gemcitabine: Results of a Phase III trial

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Background: Glufosfamide is glucose linked to isophosphoramide mustard, the active metabolite of ifosfamide. Cancer cells use glucose at a higher rate than normal cells, which may lead to preferential metabolic targeting by GLU.
Methods: Patients (pts) with metastatic pancreatic adenocarcinoma previously treated with gemcitabine and with adequate KPS and renal (CrCL $\geqslant$ 60 mL/min), hepatic and hematologic function were randomized