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The value of routine serum carcino-embryonic antigen measurement and computed tomography in the surveillance of patients after adjuvant chemotherapy for colorectal cancer: analysis from a prospective randomised controlled trial

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Background and aim: Two meta-analyses suggest an overall survival advantage for intensifying the follow-up of patients after curative surgery for colorectal cancer (CRC). This analysis aims to evaluate routine carcino-embryonic antigen (CEA) and computed tomography (CT) of thorax, abdomen and pelvis (TAP) as part of protocol specified follow-up policy.

Patients and methods: Patients with resected stage II and III CRC were randomly allocated to bolus 5-FU/leucovorin or protracted venous infusion 5-FU. Following completion of chemotherapy, patients were seen in clinic at regular interval for 5 years. CEA was measured at each clinic visit and CT of TAP was performed at 12 and 24 months after commencement of chemotherapy. Principal detection methods (PDM) of relapse were categorised into symptomatic, CEA, CT and others.

Results: Between 1993 and 1999, 530 patients were randomised. The median follow-up was 5.6 years. Disease relapses were detected in 154 patients by symptoms (n=65), CEA (n=31), CT (n=49) and others (n=9). 34 (22%) relapses occurred beyond 2 years (stage II n=13, stage III n=21). Although there were no significant differences in overall survival (OS) from randomisation among different PDM groups (log rank p=0.352), significant differences in OS were seen from time of relapse (log rank p=0.024) with the CT-detected group having a better survival compared with symptomatic group (log rank p=0.0046). 33 patients (21%) proceeded to potentially curative surgery for relapse and enjoyed a better survival than those who did not (log rank p

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Docetaxel (D), cisplatin (C) 5-fluorouracil (F) compared to cisplatin (C) and 5-fluorouracil (F) for chemotherapy-naïve patients with metastatic or locally recurrent, unresectable gastric carcinoma (MGC): interim results of a randomized phase III trial (V325)

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Background: MGC is incurable with a median survival time ranging 6-9 months. DCF is an active regimen and was selected as the experimental arm based on the phase II randomized portion of study V325.

Methods: Patients with MGC were randomized to either D 75mg/m2 d1, C 75mg/m2 d1, and F 750mg/m2 c.i. d1-5 q3w or C 100mg/m2 d1 and F 1000mg/m2 c.i. d1-5 q4w. Eligibility included histologically-proven metastatic or locally recurrent gastric carcinoma, including esophago-gastric junction, with measurable and/or evaluable disease and chemotherapy-naive. Biased-coin randomization accounted for center, liver metastasis, prior gastrectomy, weight loss ($\leq$ vs. >5%) and measurability. All tumor assessments were independently reviewed, and an IDMC was set up. Time to progression (TTP) was the primary endpoint and overall survival (OS) was the main secondary endpoint.

Results: 463 patients were randomized. Results on 223 patients are presented (111/112 in DCF/CF) based on a planned interim analysis. 88% patients were eligible: median age 54 years, 68% gastric body cancer, 98% metastatic disease. TTP was statistically superior (critical p value of 0.0036) for DCF (5.2 months) compared to CF (3.7 months), hazard ratio 1.704. Median OS was 10.2 months for DCF, and 8.5 months for CF, hazard ratio 1.505 (NS, critical p value of 0.0053). Response rate to DCF (39%) was statistically superior than that to CF (23%), p 0.012. At least 1 related G 3/4 AE was reported in 68% and 65% for DCF and CF, respectively. Death rate of all causes within 30 days of last infusion was 11.7% and 8.0%. The final analysis is planned in the second half of 2003.

Conclusion: DCF resulted in longer TTP and higher response rate than the reference regimen, CF. DCF may emerge as a new standard regimen for advanced gastric carcinoma.

Lung cancer I

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Rapid and durable objective responses in patients with advanced non-small-cell lung cancer in Phase II trials (IDEAL 1 and IDEAL 2) treated with gefitinib

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Background: For patients with advanced non-small-cell lung cancer (NSCLC) there is a high unmet clinical need for effective, well-tolerated treatments. Gefitinib ('Iressa', ZD1839), an orally active EGFR-TKI (epidermal growth factor receptor tyrosine kinase inhibitor) was evaluated in this setting in two large, multi-center Phase II trials (IDEAL 1 and 2).

Methods: In both trials, patients with NSCLC were randomized to receive gefitinib 250 or 500 mg/day, orally. In IDEAL 1, 209 patients had received 1 or 2 prior chemotherapy regimens (at least one platinum based). In IDEAL 2, 216 patients had received $\geq$2 prior chemotherapy regimens, including platinum and docetaxel either concurrently or separately. Objective responses (OR) were measured using UICC/WHO criteria. The 7-item Lung Cancer Subscale of Functional Assessment of Cancer Therapy-Lung (FACT-L) assessed disease-related symptom improvement (SI, defined as an increase of $\geq$2 points for $\geq$4 weeks).

Results: OR rates were similar between the doses: 18% and 19% in IDEAL 1, and 12% and 9% in IDEAL 2 (250 and 500 mg/day, respectively). In IDEAL 1 and 2, respectively, 39 and 22 patients had an OR: 26/39 IDEAL 1 patients had tumors of 10-85 cm^2 and 13/22 IDEAL 2 patients had tumors of 10-60 cm^2, with a mean tumor reduction in both trials $\geq$80%. Responses were rapid: 31/39 IDEAL 1 patients and 16/22 IDEAL 2 patients had achieved an OR by week 4, and at week 16 all patients had achieved an OR. Median durations of OR were 13.0 and 10.1 months in IDEAL 1, and 7.0 and 5.8 months in IDEAL 2 (250 and 500 mg/day, respectively). In evaluable patients with OR, rapid SI (median 8-10 days) was seen in 69% and 86% IDEAL 1 patients, and 100% and 90% IDEAL 2 patients (250 and 500 mg/day, respectively). Improved performance status (PS) was observed in 50% of IDEAL 2 patients with OR and 16% with stable disease. One-year survival rates were 35% and 29% in IDEAL 1, and 29% and 24% in IDEAL 2 (250 and 500 mg/day, respectively). Gefitinib was well-tolerated, especially at the recommended dose of 250 mg/day, with reversible, non-cumulative mild (grade 1/2) skin rash or diarrhea.

Conclusions: In pretreated patients with advanced NSCLC, gefitinib provides unprecedented clinically meaningful and durable antitumor activity. Improvements in disease-related symptoms and PS highlight the clinical benefit of gefitinib in these patients with a high unmet clinical need.

'Iressa' is a trademark of the AstraZeneca group of companies

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A phase I study of epidermal growth factor receptor (EGFR) antibody EMD 72000 in combination with Paclitaxel (P) in patients (pts) with EGFR-positive advanced non-small cell lung cancer (NSCLC)

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Background: The prognosis of patients with advanced NSCLC is still poor. Approximately 50% of all NSCLC pts show an overexpression of EGFR, which makes NSCLC a promising target for antibody-based treatment against this target. EMD 72000 is a humanized monoclonal antibody that binds selectively to the EGFR and inhibits ligand-mediated activation. In order to define the maximally tolerated dose (MTD) and safety of EMD 72000 as well as to gain pharmacokinetic data on EMD 72000 we carried out a phase I study of weekly EMD 72000 in combination with 175 mg/m^2 P given on day 1 of a 21-day cycle.

Patients and methods: EMD 72000 was administered at absolute doses of 100, 200, 400 and 800mg without routine premedication. A sequential dose escalation was performed with three pts being included at each dose level. Three further pts were enrolled if dose limiting toxicity (DLT)