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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)

occurred among the first 3 pts. Treatment response was assessed after every second cycle. In case of disease progression, treatment was stopped. EGFR expression was determined by immunohistochemistry.

Results: All 29 pts screened thus far were found to be positive for EGFR expression. Seventeen pts with metastatic NSCLC (4x squamous cell, 12x adenocarcinoma, 1x mixed) and a median age of 61 [29-73] years were included in the study. Sixteen pts have received at least two cycles [range 2-11] of P/EMD72000 and are eligible. Seven pts had been pretreated [median number of 2 prior chemotherapy regimens (range 1-3)]. A total of 71 cycles have been applied. EMD 72000 related skin toxicity did not exceed NCI-CTC grade 2. Flush (grade 1) and bronchospasm (grade 2) were observed in one pt after the 3rd EMD 72000 application, which did not recur after premedication upon re-exposure. P applications had to be postponed due to toxicity in 2 pts and withdrawn due to allergic reactions in 4 pts. Recruitment at the highest dose level (800mg) is completed and the MTD has not been reached. One complete and 6 partial responses (3 pts pretreated) as well as 4 disease stabilizations (>12 weeks) have been thus far achieved in 16 eligible pts.

Conclusions: The monoclonal EGFR-antibody EMD 72000 given in combination with P appears to be well tolerated. Final results and pharmacokinetic data will be presented.

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The epidermal growth factor receptor tyrosine kinase inhibitor, erlotinib (TarcevaTM, OSI-774), is an active agent in bronchioloalveolar carcinoma (BAC) and its variants: interim results of a Phase II Trial

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Background: Erlotinib has shown promising activity in the treatment of advanced non-small cell lung cancer. Anecdotally, some of the most dramatic results have occurred in patients with BAC. BAC is an increasingly common subtype of non-small cell lung cancer [Read, Proc Am Soc Clin Oncol, 2002], and has been felt to be chemoresistant by most clinicians. We chose to conduct a Phase II trial of erlotinib in BAC to define the activity of this agent in this patient population.

Methods: Patients with clinical presentations or pathologic findings consistent with BAC were screened for trial entry. Those who tumors' consist of pure BAC, BAC with focal invasion, or adenocarcinoma with BAC features [Ebright, Ann Thor Surg, 2002;74:1640-6] were deemed eligible and were then screened for treatment.

Results: Between 6/02 and 4/03, 95 patients underwent pathologic review. Of these, 64 were felt to have BAC or a variant and were eligible for treatment. 54 patients have been treated to date. Patient characteristics: Men-17/Women-37; KPS: 100-1, 90-16, 80-34, 70-3; Prior chemotherapy regimens: None-42; One-12; Smoking history: Never-14; Former or current-40. 47 patients have completed at least 4 weeks of therapy and are therefore assessable for response; 12 patients have achieved a partial response, major response rate 25% (95% CI 14-41). Of the responding patients: Men-2/Women-10; KPS: 100-1, 90-2, 80-9; Prior chemotherapy regimens: None-11; One-1; Smoking history: Never-7; Former or current-5.

Conclusions: Erlotinib is an active agent in BAC. Given this level of activity, a Phase III trial of erlotinib in BAC and its variants is warranted. We are prospectively constructing a tissue microarray to evaluate differences in the EGFR and related signaling pathways in sensitive and resistant tumors.

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Randomized phase II clinical trial of cetuximab in combination with cisplatin (C) and vinorelbine (V) or CV alone in patients with advanced Epidermal Growth Factor Receptor (EGFR)-expressing non-small-cell lung cancer (NSCLC)

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Background: Cetuximab (Erbitux) is a chimeric monoclonal antibody targeting the EGFR, which is highly expressed in patients with NSCLC. Combinations of cetuximab and chemotherapy have shown to be safe and active in combination in several EGFR-expressing tumor types including NSCLC. CV is a standard treatment for advanced NSCLC.

Objective: The primary objective was to determine the response rates for the combination of cetuximab and CV and for CV alone in chemotherapy-naïve patients with EGFR-expressing stage IIIb/IV NSCLC.

Regimens: All patients received C 80 mg/m^2 d1 and V 25 mg/m^2 d1 and 8, q3 weeks. Patients in arm A also received cetuximab 400 mg/m^2 week 1 and 250 mg/m^2 weekly thereafter.

Results: 84/93 (90,3%) of patients screened had EGFR-expressing tumors. 68 patients (63: stage IV, 5: IIIb) have been enrolled to date. Of these 34 patients (9 female (F), 25 male (M), median age 58 years) were randomized to arm A and 34 to arm B (10 F, 24 M, median age 58.5 years). 45 serious adverse events were observed so far, 27 in arm A (including 2 considered related to cetuximab), and 18 in arm B. 55 patients (27 in arm A and 28 in arm B) are currently evaluable for response. The overall response rates to date are 59% [16 PR (13 confirmed), 10 SD, 1 PD] in arm A and 36% [10 PR (8 confirmed), 12 SD, 6 PD] in arm B. The trial is ongoing with a target recruitment of 40 patients per arm.

Conclusion: Cetuximab can safely be added to the regimen of cisplatin and vinorelbine, with preliminary evidence suggesting enhancement of activity.

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An epidemiological survey for interstitial lung disease induced by gefitinib in patients with advanced non-small cell lung cancer. West Japan Thoracic Oncology Group (WJTOG)

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Gefitinib is an orally active, selective epidermal growth factor receptor tyrosine kinase inhibitor, which blocks signal transduction pathways implicated in the proliferation and survival of cancers. IDEAL 1 and 2 were both randomized, double-blind, phase II trials designed to evaluated gefitinib at two dose levels (250 and 500 mg/day) for the treatment of patients in whom advanced non-small cell lung cancer (NSCLC) had not responded to platinum-based and docetaxel-based combination chemotherapy regimens. Gefinitib has been proven to have activity in heavily pretreated and very sick patients. It has clearly shown a clinical benefit to patients, many of whom had improvement in symptoms within two weeks after the start of treatment gefitinib at 250 mg/day had results equivalent to those of the higher dose, with less toxicity.

Gefitinib was approved by the regulatory at July 5, 2002, which was the world's first, in Japan. From August 2002 to December 2002, 19,000 and over patients with advanced NSCLC had received gefitinib in all of