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 P applications had to be postponed due to toxicity in 2 pts and withdrawn due to allergic reactions in 4 pts.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.

54 ORAL

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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55 ORAL

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.

56 ORAL

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

Japan. According to the report from AstraZeneca, 358 (about 1.9%) patients developed interstitial lung disease (ILD), and of 114 (about 0.6%) had died at the time of December 13, 2002. High incidence and severity of this toxicity was unpredictable in the previous clinical trials. Therefore, we conducted a retrospective survey of ILD in patients, whom received gefitinib practically from August 30, 2002 to January 6, 2003, at the affiliate institutions of WJTOG to clarify the frequency of ILD induced by gefitinib in practical setting and to identify pretreatment risk factors. This study is performed independently from AstraZeneca and the regulatory.

Questionnaires were mailed to 113 of the affiliate institutions of WJTOG with an individual report of patient's characteristics and their clinical courses with treatment of gefitinib in detail. Eighty-six institutions returned questionnaires (response rate, 76.1%). A total of 1,983 patients with advanced NSCLC had been treated with gefitinib during the periods. Ninety-two (4.6%) patients had developed ILD, and 30 (1.5%) had died due to ILD by gefitinib, on the basis of the reports from institutional investigators. Roentgenogram and/or computed tomography of all patients developed ILD will be extramurally reviewed by five experts for chest radiology. Final frequency and mortality rate of ILD will be presented in the meeting. We are also analyzing pretreatment patient's characteristics to determine risk factors for ILD in our constructing database. Furthermore, we will investigate what is correlating with severity of ILD, and what is appropriate treatment for IDL induced by gefitinib.

57 ORAL

Pemetrexed vs docetaxel: a phase III study in patients with advanced non-small cell lung cancer (NSCLC) who were previously treated with chemotherapy

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Docetaxel is currently the standard second-line treatment for non-small cell lung cancer (NSCLC)for patients with a good performance status based on improved outcome compared to ifosfamide or vinorelbine or best supportive care in 2 randomized phase III studies. Pemetrexed a novel multitargeted antifolate that inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyltransferase (GARFT) has shown relevant clinical activity against NSCLC in phase II studies, as initial or second-line therapy. We report results of a multi-center, randomized, phase III comparison of pemetrexed vs docetaxel in previously treated patients with advanced NSCLC. 571 patients were randomized from 3/01 to 2/02, to receive either pemetrexed (500 mg/m^2 IV 10 minute infusion), supplemented with vitamin B injections, folic acid and dexamethasone or docetaxel (75 mg/m^2 IV 1 hour infusion) with dexamethasone on day 1 of 21-day cycles. The primary objective compared overall survival and secondary endpoints included time to event measures, response rate and toxicity (based on randomized and treated patients). There were 411 males, 160 females, median age 58 years (range 22-87), ECOG PS 0-1 (88%), recurrent stage IV disease (75%). 94% had 1 prior chemotherapy regimen and 6% had 2 regimens. 91% had prior platinum therapy and 27% had prior taxanes.

Efficacy	Pemetrexed (N=283)	Docetaxel (N=288)
Median Survival HR (95% CI)	8.3 months (7, 9.4) 0.99 (0.8,1.2)	7.9 months (6.3, 9.2)
Time to Progressive Disease HR (95% CI)	2.9 months (2.4, 3.1) 0.97 (0.8,1.2)	2.9 months (2.7, 3.4)
Response Rate (CR/PR/PRNM)	9.1%	8.8%

Grade 3/4 Toxicities (CTC V.2)	Pemetrexed (N=265)	Docetaxel (N=276)	*P* value
Neutropenia	5%	40%	<.001
Neutropenic fever (F/N)	2%	13%	<.001
Thrombocytopenia	2%	<1%	.116
Infection w/Gr3/4 neutropenia	0	3%	.004
ALT	2%	0	.028
Diarrhea	<1%	3%	.069
Neuropathy Gr2-4	3%	8%	.014
Fatigue	5%	5%	1.00
Hypersenitivity reaction	0	1%	–
Hospitalizations due to F/N Incidence	29 days 4 (2%)	192 days 43 (16%)	– <.001

Patient and disease characteristics were evenly distributed between the two arms. Total cycles delivered were 1164 cycles (median 4, range 1-20) for pemetrexed and 1085 cycles (median 4, range 1-14) of docetaxel. Fewer on-study drug-related deaths occurred with pemetrexed therapy (2) relative to docetaxel (5), and drug-related Serious Adverse Events (SAE) were significantly lower for pemetrexed therapy (10%) compared to docetaxel (24%).

Survival, TTPD and response rates were similar in both treatment arms, but pemetrexed therapy produced a significantly more favorable toxicity profile with less bone marrow suppression and fewer hospitalizations due to neutropenic fever. In conclusion, pemetrexed demonstrated a significantly better risk/benefit profile relative to docetaxel.

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GLOB 2: a randomised phase III study comparing doublets including navelbineâ (NVB) with either gemcitabine (GEM) or carboplatin (C) in inoperable non-small-cell lung cancer (NSCLC) patients

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Background: The pivotal place of cisplatin was questioned due to its toxicity leading to the development of carboplatin combinations. NVB has been widely used in combination with CBDCA with good efficacy/tolerance profile. On the other hand, non-platinum doublets have been developed as NVB-GEM, with a good efficacy/tolerance ratio. This phase III study was set up to compare a non-platinum based regimen (NVB-GEM) to a platinum based regimen (NVB-CBDCA).

Material and methods: Inoperable NSCLC patients (pts) were randomly assigned to Arm A: NVB 30 mg/m2 at D1 and 8+CBDCA AUC 5 at D1 or Arm B: NVB 25 mg/m2+GEM 1000 mg/m2 both given at D1 and 8, both arms given q3weeks. Objective response (OR) was the primary endpoint, median survival (MS), progression free survival (PFS) and tolerance as secondary endpoints.

Results: 316 pts were recruited in 16 countries/31 centres from June 2000 to June 2002. Both groups were well balanced with same median age: 60y, KPS: 90-100% in 63%/69%, stage IV at diagnosis in 71%/72% in Arms A/B respectively. In both arms patients were metastatic at inclusion in 80%; 90%/91% respectively had * 2 metastatic sites with lung/liver in 96%. In both arms a median number of 4 cycles was given. Median RDI for NVB was 91% (Arm A) and 94% (Arm B) with median RDI for CBDCA and GEM at 93%. OR in intent-to-treat-population (ITT) was 22% (1 CR/34 PR/77NC, disease control/DC=70.4%) in Arm A vs 28.7% (3CR/42 PR/75NC, DC=76.4%) in arm B (ns) and in the evaluable population 23.5% in Arm A (DC=75.2%) vs 30.6% in Arm B (DC=81.6%). MS in ITT was 8.5 months (m) for Arm A vs 11 m for Arm B whereas PFS was respectively 3.9 and 4.5 m. Main AEs by pts/cy in Arms A and B, were gr3-4 haematological: neutropenia in 44.8%/19.5% and 23.7%/10.6%, leukopenia in 21.4%/8.1% and 7.8%/2.0%, haemoglobin in 20.8%/7.9% and 5.3%/1.4% and thrombopenia in 4.6%/1.2% and 1.4%/0.4% respectively. In addition there were significantly more febrile neutropenia (16pts/18cy) in Arm A compared to Arm B (1pt/1cy), more gr3-4 infections (14pts/16cy and 4pts/4cy respectively) and more gr3-4 asthenia (17pts/19cy and 6pts/6cy respectively).

Conclusion: NVB-GEM given as non-platinum doublet in this phase III has demonstrated OR and PFS comparable to platinum doublet (NVB–CBDCA) with a favourable MS and tolerance profile. Therefore, the non-platinum based doublet NVB-GEM is a suitable alternative combination whereas CBDCA as an alternative to cisplatin remains questionable.