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.

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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.