m for p with L858R in both tumor and serum (P = 0.13). In the multivariate analysis, male gender, L858R and the presence of mEGFR in serum were independent factors for poor prognosis (Table). MS was 31 m for p with mEGFR only in tumor and 28 m for p with mEGFR in tumor and serum (P = 0.21). When only the 97 p with mEGFR in both tumor and serum were analyzed, p with L858R were older than those with del 19 (73 vs 63 years, respectively; P = 0.01). Response rate was higher in p with del 19 (78.3%) than in p with L858R (59.4%) (P = 0.05). TTP for p with del 19 was 13 m vs 11 m for p with L858R (P = 0.07). MS for p with del 19 was 31 m vs 18 m for p with L8585R (P = 0.01).

Conclusions: mEGFR in serum could be an ancillary non-invasive method for genotyping when there is insufficient tumor tissue. The presence of mEGFR in serum is a prognostic marker for shorter TTP.

	HR	95% CI	p
Sex			
Female	1 (ref.)		
Male	2.39	0.39−0.93	0.001
Exon			
19	0.55	0.36−0.85	0.008
21	1 (ref.)		
Serum (EGFR)			
WT	1 (ref.)		
Mutated	1.63	1.05−2.55	0.03

9001 ORAL

Vandetanib plus docetaxel versus docetaxel as second-line treatment for patients with advanced non-small-cell lung cancer (NSCLC): a randomized, double-blind phase III trial

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Background: Vandetanib (ZACTIMA™) is a once-daily oral inhibitor of VEGFR, EGFR and RET signalling. The addition of vandetanib 100 mg/day to docetaxel (doc) prolonged progression-free survival (PFS) in a randomized phase II study in patients with previously treated advanced NSCLC (Heymach *et al*, JCO 2007).

Methods: The primary objective of this phase III study (ZODIAC; D4200C00032) was to determine whether vandetanib 100 mg/day+doc 75 mg/m^2 every 21 days (max 6 cycles) prolonged PFS vs placebo + doc. Secondary endpoints included overall survival (OS), objective response rate (ORR), time to deterioration of symptoms (TDS) and safety. Efficacy and safety in females were assessed as a co-primary analysis population. Eligibility criteria included stage IIIB/IV NSCLC, performance status (PS) 0−1 and previous chemotherapy.

Results: Between May 06−April 08, 1391 patients (mean age, 58 yrs; 30% female; 25% squamous; 10% brain mets; 85% stage IV; 35%/65% PS 0/1) were randomized to vandetanib+doc (n = 694) or placebo+doc (n = 697). Baseline characteristics were similar in both arms. At data cut-off, the median duration of follow-up was 12.8 months, 87% patients had progressed and 59% had died. The addition of vandetanib to doc showed a statistically significant improvement in PFS vs doc (hazard ratio [HR] 0.79, 97.58% CI 0.70−0.90; 2-sided $P < 0.001$), and a similar advantage in females (HR 0.79; 2-sided $P = 0.024$). Significant advantages for vandetanib + doc were also seen for ORR (17% vs 10%, 2-sided $P < 0.001$) and TDS (HR 0.77, 2-sided $P < 0.001$; FACT-L Lung Cancer Subscale). OS showed a positive trend for vandetanib+doc that was not statistically significant (HR 0.91, 97.52% CI 0.78−1.07; 2-sided $P = 0.196$). Exploratory clinical and molecular subgroup analyses for PFS and OS were generally consistent with the results seen in all patients. The adverse event profile was consistent with that previously observed for vandetanib in NSCLC. The vandetanib arm had a higher incidence of diarrhoea (42% vs 33%), rash (42% vs 24%), neutropenia (32% vs 27%) and hypertension (6.0% vs 1.7%). Nausea (23% vs 32%), vomiting (16% vs 21%) and anaemia (10% vs 15%) were less frequent in the vandetanib arm. The incidence of protocol-defined QTc prolongation in the vandetanib arm was 1.9%.

Conclusions: This study met its primary objective of PFS prolongation with vandetanib+doc vs doc alone. Vandetanib is the first and only targeted therapy to show significant clinical benefits when added to chemotherapy in phase III studies in second-line advanced NSCLC. An OS update will be performed in 2009.

9002 ORAL

A phase III, first-line trial of gefitinib versus cisplatin plusdocetaxel for patients with advanced or recurrent non-small cell lungcancer (NSCLC) harboring activating mutation of the epidermal growthfactor receptor (EGFR) gene: a preliminary results of WJTOG 3405

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Background: Patients with non-small cell lung cancer (NSCLC) harboring activating mutations of the EGFR gene respond remarkably well to EGFR specific tyrosine kinase inhibitor, gefitinib. However, its superiority to standard platinum doublet chemotherapy in terms of progression free survival (PFS) or overall survival (OS) is not known.

Material and Methods: Chemo naive patients with stage IIIB/IV or recurrent NSCLC, harboring activating EGFR mutation (either exon 19 deletion or L858R in exon 21) aged 75 years or younger, with PS of 0 or 1 were enrolled. Patients were randomized to receive either gefitinib (250 mg/day) until progression or cisplatin (80 mg/sqm) plus docetaxel (60 mg/sqm) day 1, given every 21 days for three cycles to six cycles. PFS was the primary endpoint. Assuming that PFS for gefitinib was 12.5months and for chemotherapy was 7 month based on the previous reports, hazard ratio would be 0.56. With this HR, 146 patients would be required to have a power of 0.8. However, sample size was set at 200 patients to allow HR up to 0.64.

Results: As of April 25, 164 patients had been randomized. Here, we report the preliminary data for 122 patients of the 164. Of 122, 55 patients were postoperative recurrence and 67 were with stage IIIB/IV diseases. Age, sex, stage, smoking history and absence or presence of postoperative adjuvant chemotherapy were well balanced between two groups. Percentages of the patients with age of 65 or older, female, non-smokers were 49%, 74%, and 75%, respectively. For all patients, median PFS was 8.4 months and one-year PFS rate was 32.4% (95% confidence interval (CI); 22.4−42.9%). Median survival was not reached and one-year OS rate was 94.0% (95% CI; 84.7−97.7%).

Conclusions: The enrollment of this phase III trial is ongoing. NSCLC patients with EGFR mutations had good prognosis irrespective of the treatments confirming the previous reports. Subset analysis of IPASS (Phase III study of gefitinib vs. carboplatin/paclitaxel in Asian, non-/light smokers with adenocarcinoma of the lung) suggested that NSCLC patients with EGFR mutation treated with gefitinib had a significantly longer PFS than those treated with chemotherapy with a HR of 0.48 (~10 months vs. ~6 months). Our study appears to have similar PFS and it would be positive if this HR is reproduced. Data on response rates and safety profile will be available at the presentation. The final analysis is expected in early 2010.

9003 ORAL

Response and progression-free survival in 1006 patients with known EGFR mutation status in phase III randomized trials of gefitinib in individuals with non-small cell lung cancer

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Background: Gefitinib (Iressa®) inhibits tyrosine kinase activity of the epidermal growth factor receptor (EGFR). The EGFR kinase can be constitutively activated by mutations in exon 19 or 21 of the *EGFR* gene. Cells harboring these mutations are “addicted” to EGFR signaling and are exquisitely sensitive to blockade of the kinase. These mutations are often found in the tumors of patients (pts) with marked benefit to gefitinib. We

reviewed results of phase III trials of gefitinib monotherapy, focusing on pts with known *EGFR* mutation status.
Methods: Of the 4864 pts enrolled on the ISEL, INTEREST, IPASS, and V-15−32 trials of gefitinib 250 mg orally daily vs a comparator, we obtained *EGFR* mutation status on 1006 (21%).
Results: Across the different studies, the pooled objective response rate (ORR) with gefitinib in *EGFR* mutation positive pts was 65% [114/176, 95% CI 58% to 71%], range 38% to 71%. In *EGFR* mutation negative pts, it was 3% [11/324, 95% CI 2% to 6%], range 0% to 7%. For active comparators, ORRs in *EGFR* mutation positive pts were 30% [9/30 pooled] for docetaxel alone and 47% [61/129] for carboplatin/paclitaxel. For mutation negative patients, ORRs were 9% [12/132 pooled] with docetaxel alone and 24% [20/85] with carboplatin/paclitaxel. In every study, ORR was numerically better for gefitinib than comparator in *EGFR* mutation positive pts, and similar or poorer than comparator in *EGFR* mutation negative pts. For pts with *EGFR* mutations, the ORR with gefitinib was 71% when used initially and ranged from 38% to 67% in studies where gefitinib was given after chemotherapy. A trend similar to ORR was observed for progression-free survival (PFS) or time to treatment failure, with longest median values in gefitinib-treated *EGFR* mutation positive pts (range 7−11 months). The results of these 4 studies are consistent with the published data in pts with known EGFR mutation status.
Conclusions: For pts with tumors with *EGFR* mutations: 1) ORR with gefitinib was higher in *EGFR* mutation-positive than -negative pts in every study, 2) This ORR was higher on gefitinib than comparator in every study, 3) Median PFS tended to be longer on gefitinib than comparators. 4) ORR was 38% or greater regardless of line of therapy. For pts with tumors without *EGFR* mutations: ORR and median PFS tended to be similar to or poorer for gefitinib than comparators. These results justify pretreatment determination of *EGFR* mutation status at the time of diagnosis to select therapy with higher response and improved PFS.

9004 ORAL

Vandetanib plus pemetrexed vs pemetrexed as 2nd-line therapy in patients with advanced non-small-cell lung cancer (NSCLC): a randomized, double-blind phase III trial

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Background: Vandetanib (ZACTIMA™) is a once-daily oral inhibitor of VEGFR, EGFR and RET signalling. A phase I study of vandetanib + pemetrexed (pem) in advanced NSCLC supported further investigation of this combination in this setting (de Boer *et al,* Ann Oncol 2009).
Materials and Methods: The primary objective of this study (ZEAL; D4200C00036) was to determine whether vandetanib (100 mg/day) + pem (500 mg/m^2 every 21 days; max 6 cycles) prolonged progression-free survival (PFS) vs placebo + pem. Overall survival (OS), objective response rate (ORR), time to deterioration of symptoms (TDS, by Lung Cancer Symptom Scale) and safety were secondary endpoints. Efficacy and safety were assessed in females as a co-primary analysis population. Eligibility criteria included stage IIIB/IV NSCLC, WHO performance status (PS) 0−2, and previous 1st-line therapy.
Results: Between Jan 07−Mar 08, 534 patients (mean age 59 yrs; 38% female; 21% squamous histology; 8% brain metastases; 84% stage IV; PS 0/1/2: 41%/53%/6%) were randomized 1:1 to receive vandetanib + pem (n = 256) or placebo + pem (n = 278). Baseline characteristics were similar in both arms. At data cut-off, the median duration of follow-up was 9.0 months, 83% patients had progressed and 50% had died. Positive trends were observed for vandetanib + pem for both PFS (hazard ratio [HR] 0.86, 97.58% CI 0.69−1.06; $P = 0.108$) and OS (HR 0.86, 97.54% CI 0.65−1.13; $P = 0.219$), which did not reach statistical significance; similar advantages were observed for females. There were statistically significant advantages for ORR (19.1% vs 7.9%, $P < 0.001$) and TDS (HR 0.71; $P = 0.005$). Exploratory analyses showed the effects of vandetanib + pem on PFS and OS were similar among the clinical and molecular subgroups analyzed. The adverse event profile was consistent with that observed in previous vandetanib studies in NSCLC: rash (38% vs 26%), diarrhea (26% vs 18%) and hypertension (12% vs 3%) being more frequent in the vandetanib arm. There was evidence of reduced pem toxicity with the addition of vandetanib: anemia (8% vs 22%), nausea (29% vs 37%), vomiting (15% vs 22%), fatigue (37% vs 45%), and asthenia (11% vs 17%). The incidence of protocol-defined QTc prolongation was <1%. There was no increase in bleeding events in the vandetanib arm.
Conclusions: The combination of vandetanib + pem was well tolerated and demonstrated evidence of clinical benefit in patients with pretreated advanced NSCLC. However, the study did not meet the primary endpoint of statistically significant PFS prolongation vs pem alone. An OS update will be performed in late 2009.

9005 ORAL

Vandetanib versus erlotinib in patients with previously treated advanced non-small-cell lung cancer (NSCLC): a randomized, double-blind phase III trial

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Background: Vandetanib (ZACTIMA™) is a once-daily oral inhibitor of VEGFR, EGFR and RET signalling. A phase II study of vandetanib monotherapy in previously treated advanced NSCLC supported further investigation of vandetanib as a single agent in this setting (Natale *et al*, JCO 2009).
Materials and Methods: The primary objective of this randomized, multicentre, double-blind phase III study (ZEST; D4200C00057) was to show progression-free survival (PFS) superiority for vandetanib vs erlotinib. Patients were randomized 1:1 to receive vandetanib 300 mg/day or erlotinib 150 mg/day. Secondary endpoints included overall survival (OS), objective response rate (ORR), time to deterioration of symptoms (TDS) of pain, dyspnoea and cough (EORTC QoL questionnaire) and safety. Eligibility criteria included stage IIIB/IV NSCLC, WHO performance status (PS) 0−2, and 1−2 prior chemotherapy regimens. Squamous histology was permitted.
Results: Between Oct 06−Nov 07, 1240 patients (mean age 61 yrs; 38% female; 22% squamous) received vandetanib (n = 623) or erlotinib (n = 617); baseline characteristics were similar in both arms. At data cut-off, the median duration of follow-up was 14 months, 88% of patients had progressed and 67% had died. There was no difference in PFS for patients receiving vandetanib vs erlotinib (hazard ratio [HR] 0.98, 95.22% CI 0.87−1.10; $P = 0.721$), and no difference in the secondary endpoints of OS (HR 1.01, 95.08% CI 0.89−1.16; $P = 0.830$), ORR (12% in both arms) and TDS (pain: HR 0.96; $P = 0.582$; dyspnoea: HR 1.08; $P = 0.333$; cough: HR 0.94; $P = 0.402$). A preplanned non-inferiority analysis for PFS and OS demonstrated equivalent efficacy for vandetanib and erlotinib. Exploratory clinical and molecular subgroup analyses for PFS and OS did not demonstrate differential benefits for vandetanib compared to erlotinib. The adverse event (AE) profile for vandetanib was generally consistent with previous NSCLC studies with this agent. There was a higher incidence of some AEs (any grade) in the vandetanib arm, including diarrhoea (50% vs 38%) and hypertension (16% vs 2%), whereas rash was more common in patients receiving erlotinib (38% vs 28%). The overall incidence of CTCAE grade $\geqslant$3 AEs was also higher with vandetanib (50% vs 40%). The incidence of protocol-defined QTc prolongation in the vandetanib arm was 5%.
Conclusions: The study did not meet its primary objective of PFS prolongation with vandetanib vs erlotinib in patients with previously treated advanced NSCLC. However, vandetanib demonstrated clear evidence of antitumour activity and showed equivalent efficacy to erlotinib in a preplanned analysis of PFS and OS. An OS update will be performed in 2009.