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.