of any cause and any grade were reported in 43.4% of pts, including epistaxis (26.1%; Table 1), and either resolved or improved in 33.0% of pts. However, serious (grade ⩾3) bleeding events that were considered to be Bev-related were uncommon, and included epistaxis (0.6%) haemoptysis (0.3%), pulmonary haemorrhage (0.1%) and gastrointestinal haemorrhage (0.3%). Bev was discontinued for bleeding events in 4.3% of pts and interrupted in 1.1% of pts.
Conclusions: In Bev-treated pts, grade ⩾3 bleeding and haemoptysis are rare events, occurring in <1% of patients in this large study. Furthermore, rates for discontinuation or interruption of Bev for bleeding were low. Our results confirm the well-established and manageable safety profile of Bev-based therapy in non-squamous NSCLC pts.

9172 POSTER

Analysis of biomarkers (BMs) in the AVAiL phase III randomised study of first-line Bevacizumab (Bv) with cisplatin-gemcitabine (CG) in patients (pts) with non-small cell lung cancer (NSCLC)

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Background: Addition of Bv to platinum-based chemotherapy in 2 phase III trials, E4599 and AVAiL, improved outcome in pts with untreated advanced NSCLC. The relationship between high levels of certain circulating factors and clinical outcome has been previously described. In study E4599, analysis of several BMs showed that intracellular adhesion molecule-1 (ICAM-1) levels may be predictive of response to therapy and prognostic of survival, whereas pts with high baseline vascular endothelial growth factor (VEGF) levels may have a higher response rate to Bv. This abstract presents the data of an exploratory BM analysis of the AVAiL trial, using the same BMs studied in E4599.
Methods: In AVAiL 1,043 pts with untreated locally advanced, metastatic or recurrent non-squamous NSCLC, ECOG PS 0/1 were randomized to CG q3w for up to 6 cycles plus either Bv 7.5 mg/kg (n = 345), Bv 15 mg/kg (n = 351) or placebo (n = 347). Bv was continued until disease progression or unacceptable toxicity. Primary endpoint was PFS. Plasma samples were collected at baseline and analyzed for VEGF, ICAM-1, vascular cell adhesion molecule-1 (VCAM-1), E-selectin and basic fibroblast growth factor (bFGF) by ELISA. Samples for BM analysis were available for 358 pts. The use of median levels across the samples to categorize them as low and high was pre-specified as a cut-off. Their correlation to PFS and OS was explored using simple and multiple regression approaches as well as subgroup analyses.
Results: Baseline characteristics of pts with available BM samples appeared to be balanced between the 3 treatment arms. However, the treatment effect observed in the 7.5 mg/kg Bv arm of the BM subgroup appeared greater than the effect observed in the 7.5 mg/kg Bv arm of the overall study population. Analysis of ICAM, VCAM, bFGF and VEGF suggested that high baseline levels of these markers were associated with a shorter OS compared to low levels. When comparing PFS between the 15 mg/kg Bv and placebo arms, a trend towards a larger treatment effect was observed in pts with low ICAM-1 levels compared to pts with high ICAM-1 levels. Comparing OS between the 7.5 mg/kg Bv and placebo arms, a trend towards a larger treatment effect was observed in pts with high bFGF levels compared to low bFGF levels.
Conclusions: BMs involved in angiogenic pathways may play a prognostic role in pts with advanced NSCLC. The role of angiogenic BMs in predicting response will be further evaluated in ongoing trials with Bv in NSCLC.

9173 POSTER

Metronomic antiangiogenetic biochemotherapy of non-small cell lung cancer patients with fractioned cisplatinum, oral etoposide and bevacizumab: phase IB/II study

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Background: Platinum-based chemotherapy represents the standard treatment of non-small cell lung cancer (NSCLC) in advanced stage, and its activity is improved when combined with bevacizumab, a moAB to vascular endothelial growth factor (VEGF). Metronomic chemotherapy, an anticancer strategy using conventional cytotoxic drugs at low doses and with very close intervals, shows anti-angiogenetic and epigenetic effects. In the present phase IB-II study in advanced NSCLC patients, we have investigated the toxicity, anti-tumor and biological activity of a newest anti-angiogenetic biochemotherapy (mPEBev) regimen combining metronomic platinum/etoposide (mPE) doublet and escalating bevacizumab doses.
Patients and Methods: Thirty-five patients (31 males and 4 females) with stage IIIB/IV NSCLC (14 adenocarcinoma, 13 spindle-cell carcinoma, 8 poor-differentiated carcinoma), a mean age of 69.2 years, and an ECOG ⩽ 2, were enrolled in the study (registration code: Beva2007). All of them received iv. fractioned cisplatinum (30 mg/sqm) on days 1−3q21 and daily oral etoposide (50 mg/sqm) on day 1−15q21. In order to identify the most effective biological dose of bevacizumab, patients were divided into 5 groups receiving the moAB on the day 3q21 [no antibody (level 0), 2.5 (level 1), 5 (level 2), 7.5 (level 3), and 10 mg/kg (level 4)].
Results: Grade I-II hematological toxicity was the most common adverse event. Moreover, there were: 3 early deaths (two due to cardiovascular accident, level 3; one to lung hemorrhage, level 4); 5 cases of pneumonia, 4 cases of lung cavitation; 7 cases of severe psychic depression. A nuclear magnetic resonance study revealed a significant reduction in blood perfusion in the primary tumor after biochemotherapy, while biological studies demonstrated a significant decline in serum levels of VEGF, angiopoietin and thrombospondin-1 and in VEGF-transporting cells like neutrophils.
Including all the patients, there were an objective response (OR) and stable disease rate (SD) of 74.3% and 14.3% respectively, with a disease control rate (OR + SD) of 88.6%. The treatment resulted very active in those patients receiving bevacizumab, who showed a 92.3% OR rate, with a most active dose at the 5 mg/kg bevacizumab dosage.
Conclusion: The mPEBev regimen resulted moderately safe and very active in NSCLC and this biochemotherapy, at the most efficient and safe bevacizumab dosage of 5 mg/kg, deserves to be investigated in further studies.

9174 POSTER

Phase II study of everolimus plus erlotinib in previously treated patients with advanced non-small cell lung cancer (NSCLC)

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Background: Everolimus (RAD001) is an oral mTOR inhibitor that has been evaluated as monotherapy in a phase II study of NSCLC patients previously treated with platinum-based chemotherapy, with evidence of some activity (ASCO 2007, Abstract 7589). Erlotinib is an oral epidermal growth factor receptor-tyrosine kinase inhibitor that is approved as second-line therapy for advanced/metastatic NSCLC. The present phase I/II study is evaluating the combination of everolimus and erlotinib in patients with advanced NSCLC who had progressed after ⩽2 prior chemotherapy regimens (NCT00456833). Phase I results were promising and establish a feasible dose of everolimus in combination with erlotinib (ASCO 2008, Abstract 8051).
Materials and Methods: This ongoing, randomized phase II study includes patients with advanced NSCLC whose disease progressed following ⩽2 prior chemotherapy regimens. Other inclusion criteria are WHO performance status ⩽1 and adequate liver and bone marrow function. Patients are randomized to receive erlotinib 150 mg/day orally or everolimus 5 mg/day plus erlotinib 150 mg/day orally until disease progression or unacceptable toxicity. Survival data will be collected every 2 months following the end of treatment until all patients discontinue from the study. The primary study endpoint is disease control rate (ie, the proportion of patients with stable disease or response at their 3-month evaluation). Other endpoints include overall response, progression-free survival safety, pharmacokinetics, and molecular markers.
Results: As of April 2009, 133 patients have been randomized, with 60 patients included in the planned interim analysis. Preliminary safety data suggest no new safety concerns with the combination of everolimus plus erlotinib.
Conclusion: The planned interim analysis of this trial is ongoing; full results of the interim analysis will be presented at the meeting. Results of this

study will provide useful data on the efficacy and safety of everolimus in combination with erlotinib in patients with advanced NSCLC who have received prior chemotherapy; there is an urgent need to improve treatment options for these patients.
Acknowledgment: This study is supported by Novartis Pharmaceuticals Corporation.

9175 POSTER

The effectiveness of erlotinib (Tarceva®) treatment in KRAS negative lung adenocarcinomas – preliminary results of an observational cohort study

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Background: In the BR.21 pivotal study, adenocarcinoma histology was significantly associated with responsiveness to erlotinib treatment. KRAS mutations are found in 25−35% of lung adenocarcinomas, and these mutations may be predictive of resistance to treatment with erlotinib. Recent publications have provided support for the hypothesis that KRAS mutational status could be utilized as a diagnostic marker for predicting response to erlotinib-treatment in NSCLC. However, survival data for the KRAS negative cohort are inconclusive.
Materials and Methods: This observational study is conducted in 37 Hungarian sites. Eligible patients have histologically or cytologically verified, advanced, KRAS (codon-12, codon-13) negative lung adenocarcinoma, refractory to at least one prior chemotherapy. Primary endpoint is progression-free survival. Secondary endpoints include tumor response according to RECIST, overall survival, safety and quality of life. KRAS gene mutational status is assessed using real-time PCR. KRAS positive cases are confirmed by DNA sequencing. Planned accrual is 260 patients.
Results: One hundred and sixteen patients were enrolled between February and November 2008. Baseline characteristics: median age: 61 (42−103) years; stage: III/B: 21%, IV: 79%; smoking status: non-smoker: 40%, ex- or current smoker: 60%; prior chemotherapy: erlotinib in the 2nd line: 57%, erlotinib in the 3rd line: 43%. Treatment was discontinued in 33 cases. Treatment length before discontinuation: 80 (8−116) days. Cause of discontinuation: disease progression (15 pts), death of any reason (13 pts), patient decision (1 pt), no reason specified (4 pts).
Conclusions: KRAS mutation screening may influence the clinical practice for erlotinib-treatment of NSCLC. Our study evaluates the effectiveness of erlotinib in a preselected cohort of KRAS negative lung adenocarcinoma patients in the routine clinical practice. Updated survival data will be presented at the meeting.

9176 POSTER

Biomarker analyses from SATURN, a phase III placebo-controlled study of erlotinib as first-line maintenance therapy for advanced NSCLC

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Background: Erlotinib has proven clinical benefit in second-line advanced NSCLC (Shepherd et al, 2005). SATURN (BO18192, Roche, complete) investigated erlotinib maintenance therapy in patients (pts) with advanced NSCLC who did not progress during first-line chemotherapy. To date, no molecular marker to predict outcomes has been identified. This randomised, global, phase III study was the first to include prospective molecular marker analyses for erlotinib, with mandatory sample collection.
Materials and Methods: The following tests were performed in order of priority (tissue was limited; not all analyses could be performed for all samples): EGFR expression (by IHC), EGFR gene copy number (by FISH), and EGFR and KRAS mutation status (by DNA sequencing). EGFR intron 1 CA-repeat polymorphism genotyping was performed using baseline blood samples. Pts were stratified by EGFR IHC status. Co-primary endpoints were PFS in all pts and PFS in EGFR IHC+ pts.
Results: Baseline characteristics, including biomarker status, were similar in both arms. Erlotinib significantly prolonged PFS in all pts (HR 0.71, p = 0.000003), and EGFR IHC+ pts (HR 0.69, p = 0.00002). Molecular subgroup analyses are shown in the table. All biomarker subgroups showed a PFS benefit with erlotinib, including pts whose tumours had wild-type (wt) EGFR. EGFR mut+ status (exon 19 deletions and/or L858R) was associated with a marked improvement in PFS with erlotinib therapy. KRAS mutation status was a prognostic factor but did not affect the clinical benefit seen with erlotinib.
Conclusions: In the SATURN study, although EGFR FISH+ or mut+ pts had longer PFS than those with FISH− or wt tumours, PFS improvement was observed in all patient subgroups, irrespective of biomarker status. In particular, pts receiving erlotinib obtained similar PFS benefit regardless of KRAS mutation status. EGFR mutations appear to be a strong positive predictor of PFS benefit with erlotinib.

Biomarker status	n (% per biomarker)	HR for PFS	interaction p value
EGFR IHC+[a]	618 (84)	0.69	0.6312
EGFR IHC−	121 (16)	0.77	
EGFR FISH+[b]	231 (48)	0.68	0.3515
EGFR FISH−	255 (52)	0.81	
EGFR mut+[c]	49 (11)	0.10	0.0004
EGFR wt	388 (89)	0.78	
KRAS mut+[d]	90 (18)	0.77	0.9480
KRAS wt	403 (82)	0.70	
Long *EGFR* CA-repeat[e]	396 (51)	0.75	0.6104
Short *EGFR* CA-repeat	385 (49)	0.68	

[a]EGFR IHC+: ⩾10% any membranous staining; [b]scoring according to Cappuzzo et al, 2005; [c]L858R and/or exon 19 deletions; [d]codons 12, 13 and/or 61; [e]sum of alleles >35 for Caucasian patients and >37 for Asian patients

9177 POSTER

Lipocalin-2 is an important predictor of susceptibility to therapy with pemetrexed in non-small cell lung cancers

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Background: The pemetrexed disodium (Alimta ®), LY231514 is the first antifolate which is able to inhibit both the synthesis of purines and pyrimidines at the same time. Pemetrexed has been approved for second and first-line treatment in non-small cell lung cancer (NSCLC) patients. However, there is still lacking of clinical biomarkers for predicting the therapeutic response of Alimta. The aim of this study is to establish the correlation between the changing of new biomarker levels and the clinical outcomes.
Material and Methods: Human NSCLC cell lines, with variable expression of the known molecular determinants of Alimta sensitivity, were exposed to Alimta. Antitumor effect was measured by growth inhibition by MTT assay, cell cycle distribution by flow cytometry, and expression of cell cycle mediators by immunoblots. Using Superarray cancer pathway gene array, a total of 482 genes was screened in A549 cell after Alimta treatment.
Results: Significant higher expressions of many genes, especially lipocalin-2 (LCN-2)proteins, were noted in Alimta-sensitive cells (A549) than in resistant cells (H1355) and were confirmed by Western blot and RT-PCR analysis. RNA interference (RNAi)-mediated LCN-2 down-regulation generated susceptibility to Alimta in A549 cells.
Conclusions: From the results in this study, it indicated that LCN-2 could play an important role in resistance to Alimta and LCN-2 could be a potential new drug target.