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Implication of epithelial to mesenchymal transition and neuroendocrine differentiation in acquired resistance to EGFR-TK inhibitor

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Background: Both epithelial-to-mesenchymal transition (EMT) and neuroendocrine (NE) differentiation have been suggested to be related with therapeutic resistance for cancer. We investigated the implication of these phenomena in acquired resistance to EGFR-TK inhibitor.
Materials and Methods: Resistant sublines to EGFR-TK inhibitor were established in A549 and HCC 827 lung cancer cell lines. Direct sequencing and Scorpion test were used for EGFR mutations. Immuno-stainings and Western blots were done to detect EMT and NE differentiation.
Results: We found that EMT and NE differentiation simultaneously developed in a lung cancer patient with acquired resistance to erlotinib. There were no known resistant mechanisms such as secondary T790M mutation and MET gene amplification while the deletion mutation on exon 19 which was initially present in lung cancer was persistently detected. Morphological and molecular maker changes compatible with EMT and NE differentiation were also found in resistant sublines. NE differentiation induced by treatment with cAMP and IBMX did not affect the sensitivity to gefitinib while EMT induced by TGF-b was related with poor response to gefitinib and increased capability of invasion and migration in both A549 and HCC827 cells.
Conclusions: EMT should be considered as one of possible mechanisms to acquire resistance to EGFR-TK inhibitor in lung cancer.

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Safety and efficacy of first-line bevacizumab (Bv) plus chemotherapy in elderly patients (pts) with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC): SAiL (MO19390)

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Background: SAiL (MO19390, Roche) is an international, open-label, single-arm study of first-line Bv plus chemotherapy in patients (n = 2,166) with advanced NSCLC. Here, we present a subanalysis of safety and efficacy of Bv in elderly (>65 yr) pts.
Methods: Pts with locally advanced, metastatic, or recurrent non-squamous NSCLC received up to six cycles of Bv (7.5 or 15 mg/kg every 3 weeks) plus chemotherapy. Pts continued Bv as single-agent therapy until progression or unacceptable toxicity. Primary endpoint was safety; secondary endpoints included time to disease progression (TTP) and overall survival (OS).
Results: 609 pts >65 yr (median 70 years) and 1,557 ⩽65 yr (median 56 years) were evaluable for this interim safety analysis (data cut-off April 2009). Pts >65 yr were (%): male 62.9; ECOG PS 0/1/2 32/61/7; adenocarcinoma/large cell/other 84/9/7. More pts >65 yr (82.8%) were receiving medication at baseline compared with pts ⩽65 yr (70.3%). Median cycles of Bv and chemotherapy were 6 and 4 for pts >65 yr and 8 and 5 for pts ⩽65 yr. SAEs occurred in 273 (45%) patients >65 yr vs 543 (35%) pts ⩽65 yr. Grade ⩾3 SAEs were related to Bv in 80 (13.1%) patients >65 yr vs 147 (9.4%) pts ⩽65 yr, respectively. Most Bv-related SAEs in pts >65 yr (73%) and pts ⩽65 yr (75%) resolved or improved. Incidence of AEs of special interest was relatively low and comparable between groups (Table 1); in pts >65 yr, these AEs did not frequently lead to interruption (5.3%) or discontinuation (14.1%) of Bv. Overall rate of death due to bleeding was 0.7% (haemoptysis 0.2%, pulmonary haemorrhage 0.1%). Rate of grade ⩾3 neutropenia was similar in pts >65 yr (1.0%) vs those ⩽65 yr (1.6%). Median TTP for pts >65 vs ⩽65 yr was 8.3 vs 7.6 months, respectively, and median OS was 15.3 vs 15.2 months, respectively.
Conclusions: Pts >65 yr are not at increased risk of experiencing AEs of special interest when treated with first-line Bv-based therapy compared with pts ⩽65 yr. TTP and OS data from this interim analysis of SAiL indicate that Bv-based therapy offers a similar level of clinical benefit, irrespective of age.

Table 1. Incidence of AEs of special interest (any grade)

AE, %	>65 yr (N = 533)	⩽65 yr (N = 1,459)
Any bleeding	41.1	44.3
Epistaxis	25.5	26.3
Haemoptysis	7.4	7.6
Pulmonary haemorrhage	0.2	0.3
CNS bleeding*	0.3	0.3
Hypertension	27.9	26.3
Proteinuria	26.1	23.4
Thromboembolic events	12.0	11.9
CHF	5.6	4.4
Gastrointestinal perforation	1.1	1.3
Wound-healing complication	1.1	1.3

*cerebral haemorrhage/haematoma

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Low incidence of grade 3 bleeding events and low discontinuation rates associated with first-line bevacizumab (Bev) in patients with advanced NSCLC: data from the SAiL (MO19390) study

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Background: SAiL (MO19390, Roche) is an international, multicentre, open-label study of first-line Bev in combination with chemotherapy in >2,000 patients with NSCLC. Here, we report interim safety data with a focus on the incidence of serious bleeding events, including pulmonary haemorrhage.
Methods: Pts received Bev (7.5 or 15 mg/kg every 3wks) with chemotherapy for up to six cycles followed by Bev until disease progression. Eligibility criteria included previously untreated advanced non-squamous NSCLC, no uncontrolled hypertension or active cardiovascular disease at baseline, ECOG PS 0−2, no history of grade >2 haemoptysis, and no evidence of tumour abutting or invading major blood vessels. Primary endpoint was safety; secondary endpoints included time to disease progression and overall survival.

Table 1. Bleeding AEs of special interest in SAiL (all reported; N = 2166)

Bleeding AEs	Any grade, %	Grade 3−5, %
Epistaxis	26.1	0.7
Haemoptysis	7.6	0.4
Haematuria	2.8	0
Gingival bleeding	1.9	0
Rectal haemorrhage	1.3	0.1
Petechiae	0.7	0
Gastrointestinal haemorrhage	0.6	0.3
Haemorrhoidal haemorrhage	0.6	0
Red blood cells urine positive	0.5	0
Haematoma	0.4	0
Haematochezia	0.4	0
Vaginal haemorrhage	0.4	0
Anal haemorrhage	0.3	0
Pulmonary haemorrhage	0.3	0.2

Results: Data were available for 2,166 pts at the April 2009 analysis. Baseline characteristics were (%): male 60.2; stage IIIB/IV 19.6/80.4; adenocarcinoma/large cell/other 85.8/7.1/7.1; central tumour yes/no 26.4/73.6; cavitated tumour Y/N 2.4/97.6; ECOG PS 0/1/2 37.4/56.4/6.2. Mean age was 59 years. Overall incidence of grade ⩾3 serious adverse events (SAEs) was 31.0%; grade ⩾3 SAEs were Bev-related in 10.5% of pts. Overall incidence of AEs of special interest was 64.9%. Bleeding events

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.

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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.

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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.

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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