9169 POSTER

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

J.C. Lee[1], S.H. Yang[1], H.S. Nam[1], J.S. Koh[2], H.J. Yoo[3], D.H. Choe[4], H.J. Baek[1]. *[1]Korea Cancer Center Hospital, Internal Medicine, Seoul, South Korea; [2]Korea Cancer Center Hospital, Pathology, Seoul, South Korea; [3]Korea Cancer Center Hospital, Radiation Oncology, Seoul, South Korea; [4]Korea Cancer Center Hospital, Radiology, Seoul, South Korea*

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.

9170 POSTER

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)

P. Garrido[1], N. Thatcher[2], L. Crino[3], E. Dansin[4], J. Laskin[5], N. Pavlakis[6], C.M. Tsai[7], M. Reck[8], C.P. Schneider[9], F. Griesinger[10], on behalf of the SAil study group. *[1]Hospital Ramón y Cajal, Medical Oncology, Madrid, Spain; [2]Christie Hospital NHS Trust, Medical Oncology, Manchester, United Kingdom; [3]Perugia General Hospital, Oncology, Perugia, Italy; [4]Centre Oscar Lambret, Oncology, Lille, France; [5]British Columbia Cancer Agency, Medical Oncology, Vancouver, Canada; [6]Royal North Shore Hospital, Medical Oncology, Sydney, Australia; [7]Taipei Veterans General Hospital, Medical Oncology, Taipei, Taiwan; [8]Krankenhaus Grosshansdorf, Thoracic Oncology, Grosshansdorf, Germany; [9]Central Clinic Bad Berka, Oncological Pneumology, Bad Berka, Germany; [10]Pius Hospital, Medical Oncology, Oldenburg, Germany*

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

9171 POSTER

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

C. Tsai[1], F. Griesinger[2], J. Laskin[3], L. Crinó[4], N. Pavlakis[5], E. Dansin[6], N. Thatcher[7], Y.D. Ko[8], J. Metzger[9], P. Garrido[10]. *[1]Veterans General Hospital - Taipei, Chest Department, Taipei, Taiwan; [2]Pius Hospital, Internal Oncology, Oldenburg, Germany; [3]British Columbia Cancer Agency, Medical Oncology, Vancouver, Canada; [4]Perugia Hospital, Oncology, Perugia, Italy; [5]Royal North Shore Hospital, Medical Oncology, Sydney, Australia; [6]Centre Oscar Lambret, Oncology, Lille, France; [7]Christie Hospital NHS Trust, Oncology, Manchester, United Kingdom; [8]Evangelische Kliniken, Oncology, Bonn, Germany; [9]St. Vincentius-Kliniken, Oncology, Karlsruhe, Germany; [10]Hospital Ramón y Cajal, Oncology, Madrid, Spain*

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