# 364. Treatment of lung cancer

**3262**

**Bevacizumab (Avastin®) aerosol therapy (AT) inhibits primary and metastatic tumor growth in a murine model with human non-small cell lung cancer (NSCLC)**

Yehuda Schwarz[1], Alex Starr[1], Alexandra Litinsky[1], Lilah Israeli[1], Ofer Merimsky[2]. *[1]Departments of Pulmonary Medicine, [2]Departments of Oncology, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel*

**Rationale:** Avastin is used by systemic delivery only in lung cancer treatment, although the potential AT administration exists. AT of Avastin may increase drug concentration in the tumor and so augment the drug efficacy.
**Objectives:** To evaluate the effect of Avastin AT using mouse models of human (H1299) NSCLC.
**Methods:** An animal model of advanced disseminated NSCLC by orthotopically inoculation of cultivated human NSCLC cells into animal-lung was developed in our lab. AT was performed 5 times a week from day 5 to day 21 after inoculation using a jet nebulizer and a cage specially constructed for the inhalations. The dosages used were 0.05 mg/kg and 0.005 mg/kg of Avastin. The effect of nebulization on Avastin was assessed in terms of in vitro inhibition of tumor cell growth (XTT assay). In vitro growth of H1299 cells was mildly inhibited by AT Avastin (10-20%).
**Results:** 40% reduction of lung/tumor weight and 50% inhibition of regional metastases was seen with Avastin AT. It was well tolerated by the animals without any gross pathological or histological changes in the heart, kidney, liver or spleen. Histological examination of the lungs showed congestion and hemorrhage in the 0.05 mg/kg treated animal, but only minimal findings were seen in the 0.005 mg/kg treated group. Hematological and blood biochemical examination were normal in the treated mice.
**Conclusions:** We demonstrated efficacy of Avastin aerosol treatment in animal model of NSCLC with minimal side effects. The study opens a new therapeutic approach by aerosolizing Avastin to treat patients with advanced disseminated lung cancer.

**3263**

**Definitive radiation therapy for elderly patients with stage III NSCLC not candidates for combined chemoradiation**

Keith Sigel[1], Linda Lurslurchachai[1], Grace Mhango[1], Ethan Halm[2], Marcelo Bonomi[1], Juan Wisniveksy[1]. *[1]Department of Medicine, Mount Sinai School of Medicine, New York, NY, United States; [2]Department of Medicine, University of Texas Southwestern, Dallas, TX, United States*

**Purpose:** Combined chemoradiation is the treatment of choice for locally advanced (stage IIIA-IIIB), unresectable non-small cell lung cancer (NSCLC). However, elderly patients are frequently unable to tolerate this treatment; the benefit of radiation therapy (RT) alone for the management these patients is not well studied. Using population-based cancer data, we evaluated if use of RT alone is associated with improved survival of unresected stage III elderly NSCLC patients.
**Methods:** Using the SEER registry linked to Medicare we identified 13,522 patients >65 years of age with unresected stage IIIA-B NSCLC diagnosed between 1992-2009. We excluded cases receiving chemotherapy as well as patients who could not be candidates for RT because they died within 4 weeks of cancer diagnosis. We determined propensity scores for patients receiving RT alone vs. no therapy based on their pre-treatment characteristics. Survival of patients treated with and without RT was compared using Cox regression adjusting for propensity scores. The odds for toxicity requiring hospitalization among patients treated with RT were also estimated, adjusting for propensity scores.
**Results:** Overall, 7,703 (57%) patients received RT. RT alone was also associated with improved overall survival (HR: 0.76; 95% CI:0.74-0.79) in analyses adjusting for propensity scores. RT treated patients had an increased adjusted risk of hospitalization for pneumonitis (OR: 130; 95% CI:18-928) and esophagitis (OR: 8; 95% CI:4-17).
**Conclusions:** These data suggest that definitive RT alone is associated with improved survival in elderly patients with unresected stage III NSCLC. RT was also associated with risk of severe toxicity.

**3264**

**Histology as a potential clinical predictor of outcome in advanced non-small cell lung cancer (NSCLC) treated with vinorelbine and mitomycin (VM) combination chemotherapy**

Thomas Wibmer[1], Thierry Berghmans[2], Cornelia Kropf[1], Jean-Jacques Lafitte[3], Kathrin M. Stoiber[1], Marianne Paesmans[4], Stefan Ruediger[1], Arnaud Scherpereel[3], Ioanna Blanta[1], Wolfgang Rottbauer[1], Jean-Paul Sculier[2], Christian Schumann[1]. *[1]Department of Internal Medicine II, University of Ulm Medical Center, Ulm, Germany; [2]Department of Intensive Care Unit and Thoracic Oncology, Université libre de Bruxelles, Brussels, Belgium; [3]Department of Pneumology, CHU de Lille, Lille, France; [4]Data Center, Institut Jules Bordet, Université libre de Bruxelles, Brussels, Belgium*

**Introduction:** Histology has emerged has an important clinical predictive factor in patients with advanced NSCLC treated with chemotherapy.
**Aims:** To analyze combined patient level-data from 2 phase II trials on efficacy and safety of VM in advanced or metastatic NSCLC, in order to determine if histology and other patient and disease characteristics including gender, smoking history and TTF-1 immunohistochemistry (IHC) might be potential clinical predictors of outcome.
**Methods:** Response rates, unadjusted survival times and Cox covariate adjusted hazerd ratio estimates (HR) were calculated for each subgroup in each individual trial and in the pooled data set.
**Results:** A total of 175 patients were included in this retrospective analysis. Adjusted HRs for both overall survival (OS) and progression free survival (PFS) consistently favored non-adenocarcinoma (non-AC) histology subgroups, achieving statistical significance for OS in the pooled data (n=175; HR 0.677; 95% CI 0.488-0.938; p=0.019) and within one of those two trials (n=65; HR 0.561; 95% CI 0.318-0.988; p=0.045). TTF-1 negative IHC was associated with non-significant favorable OS compared to TTF1 positive subgroup in the cox-adjusted analysis (n=33; HR 1.232; 95% CI 0.555-2.730; p=0.608) and showed a significantly higher response rate (25% vs. 0%; p=0.040). Gender and smoking history were not strongly related to outcome.
**Conclusions:** These results suggest that non-AC histology and TTF-1 negative IHC may be considered as potential predictors of favorable clinical outcome in the treatment with VM. This approach warrants further investiagtion in a phase III study.

**3265**

**A mRNA signature predicts outcome of patients (pts) with advanced non small cell lung cancer (NSCLC) treated with cisplatin (C) and vinorelbine (V): A ELCWP prospective study**

Thierry Berghmans[1], Luc Willems[2], Marianne Paesmans[3], Lieveke Ameye[3], Jean-Jacques Lafitte[4], Anne-Pascale Meert[1], Arnaud Scherpereel[4], Alexis Cortot[4], Céline Mascaux[1], Ingrid CsToth[1], Tiffany Dernies[1], Nathalie Leclercq[1], Jean-Paul Sculier[1]. *[1]Intensive Care Unit and Thoracic Oncology, Institut Jules Bordet, Brussels, Belgium; [2]Molecular and Cellular Biology Laboratory, Gemboux Agro-Bio Tech, Gembloux, Belgium; [3]Data Centre, Institut Jules Bordet, Brussels, Belgium; [4]Pneumology, CHU Lille, Lille, France*

**Background:** C-based doublets are standard 1st line treatment for advanced NSCLC, without good predictor for response and survival, and important toxicity. Our aim is to identify a predictive mRNA signature for response to 1st line C (60 mg/m$^2$ D1) + V (25 mg/m$^2$, D1+8), by comparing mRNA expression between responders (R) and non responders (NR).
**Methods:** Pts with NSCLC receiving 1st line CV are eligible. A bronchial biopsy was analysed for mRNA expression using whole human microarrays (Agilent Technologies). T-tests were used to compare mRNA expression between R and NR. Survival was measured from the registration date and response by WHO criteria.
**Results:** From 180 pts screened (04/2009 to 11/2011), 34 were assessable; 14 partial responses were observed. Fifty (fold change (FC) > 2) and 19 (FC > 3) mRNA were significantly differentially expressed between R and NR. After a stepwise variable selection, a two-mRNA signature predicted response with 93% sensitivity, 100% specificity, 100% PPV, 95% NPV. By restricting to the 19 mRNA with a FC > 3, a two mRNA signature predicted response with 100% sensitivity, 100% NPV, 70% specificity, 70% PPV. The two models have the same diagnostic performance (p=0.58). A 2 mRNA signature specifically predicting overall survival was designed using mRNA with a FC > 3. It distinguished pts with poor and good survival (HR 22.2; $p < 0.001$).
**Conclusion:** mRNA signatures predict response and are prognostic for survival in pts with NSCLC treated with CV in 1st line. The validation of these results in an independent cohort, taking in consideration conventional prognostic factors, is ongoing.

**3266**

**Combination of erlotinib and bevacizumab in non small cell lung cancer patients**

Efimia Boutsikou, Theodoros Kontakiotis, Pavlos Zarogoulidis, Paraskevi Pataka, Kostas Zarogoulidis. *Pulmonary Department of Aristotle University of Thessaloniki, G. Papanikolaou Hospital, Thessaloniki, Greece*

Bevacizumab and Erlotinib have recently been demonstrated to prolong overall survival in patients with non squamous NSCLC. We present the results of α 4 arm trial we designed to evaluate the efficacy and toxicity of the combination of docitaxel, carboplatin, bevacizumab(B) and erlotinib(E) in the first-line treatment of patients with NSCLC.
229, stage IIIb-IV, non squamous NSCLC patients were treated with 2 cycles of carboplatin (AUC5.5)and docitaxel (100 mg/m$^2$) (CT). After completion of two treatment cycles, pts were evaluated for response and divided into 4 groups: 61/229 continued with 4 more cycles of CT(control group), 52/229 received CT plus E 150mg daily,56/229 received CT plus B 7.5mg/kg and 60/229 were treated with the combination of CT, E and B until disease progression. The primary endpoint was overall survival(OS).
In the 4 years follow up of the study, there was no statistical difference in survival and time to progression among four groups. After division of pts according to their response in responders and non responders after 2 cycles of chemotherapy, non-

responders who received additional therapy with bevacizumab or combination therapy had a survival benefit(657d (349-970)and 681(315-912)retrospectively),which is statistically significant compared with the continuation of treatment with cytotoxic chemotherapy($p<0.001$). The combination therapy had a comparable safety profile with that of B and E taken individually.
Administration of B+E in combination with first-line chemotherapy, followed by bevacizumab and erlotinib monotherapy as maintenance, has shown promising results in pts with NSCLC, with reduced toxicity as compared with chemotherapy alone, but did not translate into a longer OS.

**3267**

**TTF-1 for prediction of response to chemotherapy in patients with locally advanced or metastatic small cell lung cancer (SCLC)**

Daniel Misch[1], Jens Kollmeier[1], Torsten Blum[1], Sergej Griff[2], Christian Boch[1], Timo Weiss[1], Catharina Crolow[1], Wolfram Grüning[3], Thomas Mairinger[2], Torsten Bauer[1]. *[1]Department of Pneumology, HELIOS Klinikum Emil von Behring, Pulmonary Diseases Clinic Heckeshorn, Berlin, Germany; [2]Department of Pathology, HELIOS Klinikum Emil von Behring, Berlin, Germany; [3]Department of Pneumology, HELIOS Kliniken Schwerin, Germany*

**Background:** The thyroid transcription factor-1 (TTF1) plays a crucial role in differentiating primary lung from other cancers, especially in adenocarcinoma (AC). Furthermore, data indicate a possible association between TTF1-status and overall survival (OS) in AC patients. So far, no impact on OS was described in SCLC patients. Besides OS, it is unknown if the TTF1-status influences chemosensitivity of SCLC and might therefore predict response to chemotherapy.
**Aim:** To compare the response to chemotherapy in a population of patients with SCLC stage III/IV according to their TTF1-expression.
**Methods:** We analyzed 294 patients (f, n=110; m, n=184) with SCLC stage III/IV (according to UICC-6, stage IIIA, n=32; IIIB, n=87; IV, n=175) diagnosed in our institution between 01/05 and 12/08. Median age was 65 ($\pm$10) years. TTF1-expression was prospectively determined. Response to treatment was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST Version 1.0). The overall response rate (ORR) and the disease control rate (DCR) were calculated and compared between the group of TTF1-positive and TTF1-negative SCLC.
**Results:** The information on TTF1 and response to treatment was available in 178 (77%) cases. 150 (84%) had TTF1-positive and 28 (16%) TTF1-negative SCLC. Analyzing the DCR, we observed a better response to treatment for patients with TTF1-expression (DCR 90%) as compared to those with TTF1-negative SCLC (DCR 71%; p=0.013). Regarding the ORR, there was no statistically significant difference between both groups (TTF1-pos. 75% vs. TTF1-neg. 71; p=0.642).
**Conclusion:** TTF1-expression may be associated with better response to chemotherapy in SCLC.

**3268**

**Primary lung cancer treated using radiofrequency ablation – One year outcome data**

Faisal Kamal[1], Julie Beeson[1], Sunny Kaul[2], Sarah Stirling[2], Simon Mattison[2], Juliette Tennant[3], Pasha Normahani[4], Paras Dalal[3]. *[1]Respiratory Medicine, Royal Brompton & Harefield Hospitals NHS Foundation Trust, London, United Kingdom; [2]Critical Care, Royal Brompton & Harefield Hospitals NHS Foundation Trust, London, United Kingdom; [3]Radiology, Royal Brompton & Harefield Hospitals NHS Foundation Trust, London, United Kingdom; [4]Medical School, imperial College, London, United Kingdom*

**Background:** Percutaneous image guided radiofrequency ablation (RFA) is increasingly used as an alternative treatment option for patients with inoperable primary non small cell lung cancer (NSLC) but there are little published outcome data. We report safety & efficacy of RFA in patients with NSCLC (stages 1-4) at 1 year.
**Methods:** Thirty-eight patients underwent 50 RFA procedures.
Complications, local progression & survival were evaluated prospectively at 3, 6, 9 & 12 months.
Statistical analysis was performed using log rank test & Cox regression analysis to determine hazard ratios with 95% confidence intervals (CI).
Kaplan-Meier survival curves were plotted to show any differences in the survival pattern using Stata 10.1 (Statacorp, Texas USA).
**Results:** There were no cases of procedure related mortality.
Complications included pneumothorax (61%) of which 10 patients (43%) had an iatrogenically created pneumothorax as part of the procedure, pleural effusion (5%) & respiratory failure (3%).
At 1 year: new (suspicious) nodules observed in 21% (n=8), 88% of patients with tumours <3cm were progression free compared to 76.9% of tumours >3cm (p=0.36).
Mean time to progression for all cases 11.4 months (CI 10.7-12.1).
Tumours <3cm (n=25, 11.6 months, CI 11.1-12.3) versus tumours >3cm (n=13, 10.9 months, CI 9.0-12.7).
Overall & cancer specific 1 year survival were 86.8% & 92.1% respectively.
1 year survival for tumours <stage 4 (n=27) and those at stage 4 (n=11) were 89% (n=24/27) and 63.6% (n= 7/11) respectively which did not reach statistical significance.
**Conclusion:** RFA is a safe, effective & well-tolerated treatment option in patients with inoperable primary lung cancer (stages 1-4).

**3269**

**Prognosis of patients with a lung cancer admitted in intensive care unit**

Gaelle Rousseau-Bussac[1], Dimitri Margetis[2], Anne Lino[1], Arnaud Galbois[2], Sophie Phin-Huynh[1], Eric Maury[2], Christos Chouaid[1]. *[1]Pneumologie, CHU Saint Antoine, APHP, Paris, France; [2]Reanimation, CHU Saint Antoine, APHP, Paris, France*

Admission in ICU (Intensive Care Unit) of patients with lung cancer is still debated. The argument against admission is often their bad prognosis.
We retrospectively included all consecutive patients with a lung cancer histologically proved admitted in ICU for more than 24 hours between January 2003 and December 2010.
104 patients were included with a median SAPS 2 of 54.5; 52% of patients were metastatic. 55 (53%) patients needed invasive mechanical ventilation. Mortality rates in ICU, in hospital and at one year were respectively 31.7%, 48% and 83.7%. Prognostic factors were SAPS 2 score $\geq$ 42 (OR 2,65 IC 95% (1,10-6,36), p=0,03), invasive mechanical ventilation (OR 4,88 IC 95% (1,86- 12,76), p=0,012), vasopressive treatments (OR 6,26 IC95% (2,52- 15,57), p<0,001) and organ dysfunction with need of mechanical invasive ventilation or non-invasive ventilation or vasopressive treatments or dialysis (OR 5,5 IC95% (1,12- 27,2), p=0,0002) in univariate analysis. 75% of survivors of ICU will benefit of specific anticancer treatment after their hospitalisation in ICU. In a Kaplan-Meier survival curve, metastasis group and without metastasis group have a significant difference of median survival whatever the acute complication that conducted to ICU admission (p=0.019).
Prognostic factors in ICU seems to be related to the acute pathology, otherwise long term prognosis is determined by cancer prognosis.