TUMOUR BIOLOGY AND PATHOLOGY

1O
DETECTION OF ALK REARRANGED NON-SMALL CELL LUNG CARCINOMAS BY IMMUNOHISTOCHEMISTRY: COMPARISON OF DIFFERENT ANTIBODIES (D5F3 AND 5A4), DETECTION SYSTEMS AND AUTOMATED IMMUNOSTAINERS

S. Savic[1], J. Diebold[2], A. Zimmermann[3], W. Jochum[4], B. Baschiera[1], R. Epper[1], S. Grieshaber[1], L. Tornillo[1], K. Kerr[5], L. Bubendorf[1] [1]Pathology, University Hospital Basel, Basel, SWITZERLAND, [2]Institute of Pathology, Cantonal Hospital Lucerne, Luzern, SWITZERLAND, [3]Institute of Surgical Pathology, University Hospital Zurich, Zürich, SWITZERLAND, [4]Institute of Pathology, Cantonal Hospital St.Gallen, St. Gallen, SWITZERLAND, [5]Department of Pathology, Aberdeen Royal Infirmary Anchor Unit, Aberdeen, UNITED KINGDOM

Aim: Immunohistochemistry (IHC) has become a promising method for prescreening predictive ALK-rearrangements in non-small cell lung carcinomas (NSCLC). Various ALK antibodies, enhanced detection systems and automated immunostainers are available. We therefore aimed to compare the performance of: 1. the D5F3 (Cell Signaling, Ventana) and the 5A4 (Novocastra, Leica) monoclonal antibodies (mAb) and 2. the 5A4 mAb on two different automated immunostainers (BenchMark, Ventana and BOND-MAX, Leica).

Methods: Sixty-five formalin-fixed and paraffin-embedded non-squamous NSCLC with available ALK FISH results were retrospectively analysed. The specimens were enriched for ALK FISH-positive NSCLC (24/65, 36.9%). IHC was performed with the OptiView Amplification Kit (Ventana) on BenchMark using the D5F3 and the 5A4 mAb, respectively. Additionally IHC with the 5A4 mAb and the Bond Polymer Refine Detection Kit (Leica) on Bond-MAX was performed. For D5F3 any strong IHC-staining (3+) was regarded as a positive result, as suggested by the manufacturer. For 5A4 any IHC-staining (1+, 2+, 3+) was regarded as a positive result. The IHC results of all three protocols were compared to the FISH results. In case of a discrepancy the IHC-stained slide and the FISH signals were reviewed.

Results: Fifty-seven out of 65 NSCLC (87.7%) were evaluable and all showed congruent results for all three IHC protocols used. Twenty-three out of 24 ALK FISH positive NSCLC (95.8%) were ALK IHC-positive. Only one ALK FISH positive NSCLC (3.2%) was false negative by IHC. The sensitivity, specificity and positive and negative predictive values for ALK IHC compared to ALK FISH were 96%, 100%, 100% and 97%, respectively, irrespective of antibody, detection system and immunostainer used.

Conclusions: D5F3 and 5A4 are equally well suited and BenchMark and BNOND-MAX immunostainers can both be used for prescreening ALK-rearrangements in NSCLC.

Disclosure: All authors have declared no conflicts of interest.

2O
SIGNIFICANCE OF LEPIDIC GROWTH COMPONENT IN THE DISCRIMINATION OF MULTIPLE PRIMARY LUNG CANCERS FROM INTRAPULMONARY METASTASES

D. Lin[1], W. Sun[1], Y. Liu[2], X. Liu[2], L. Shan[2], X. Yang[2] [1]Department of Pathology, Cancer Institute and Hospital of the Chinese Academy of Medical Sciences, Beijing, CHINA, [2]Department of Etiology and Carcinogensis, Peking Union Medical College, Cancer Institute and Hospital of the Chinese Academy of Medical Sciences, Beijing, CHINA

Aim: The distinction of intrapulmonary metastases from multiple primaru tumors is of great clinical importance as it influences staging, prognosis and therapeutic strategy. Although Comprehensive Assessment (CHA) was recommended by IASLC/ATS/ERS to differentiate multiple lung primary non-small cell carcinoma from metastases, the limitaitons of CHA have been addressed. Lung adeocarcinoma in situ is characteried by noninasive lepidic growth. Whether this histological characterized by noninvasive lepidic growth. Whether this histological characteristic could be served for assessing primary lung cancer has not been well determined. In this study, we evaluated the applicaion value of CHA and lepidic growth component (LGC) in ditinguishing multiple primary lung cancers from intrapulmonary metastass.

Methods: We retropectively analyzed a cohort of 31 patients with 68 multiple lung tumors. All of the patients have follow up data. The histological evaluation was performed according to 2011 IASLC/ATS/ERS Classification of Lung Adenocarcinoma. The percentage of each tumor subtype in each case was recorded. The inrapulmonary metastases and multiple primary tumors were differentiated based on CHA and LGC (if applicable).

Results: According to CHA alone, there were 13 and 18 cases diagnosd as multiple primary tumors and intrapulmonary metastases, respecively. Disease-free interval (DFI) of the 13 patients with multiple tumors was ranged from 11 to 110 months and DFI of the 18 patients with intrapulmonary metastases was range from 1 to 93 months. There was no statistically difference between these two types of patients (p=0.240). According to CHA with inclusion of LGC, 20 and 11 cases were diagnosed as multiple primary tumors and intraplumonary metastases, respectvely. DFI of the 20 and 11 cases were ranged from 11 to 110 months and from 1 to 34 months, respectvely. Statistical signifcance was detected (P=0.003). These results suggested that CHA combining with LGC might have assesssment advantage to distinguish multiple primary tumors from intrapulmonary metasases compared to use CHA alone.

Conclusions: The apperence of adenocarcima with LGC might indicate lung primaries. Combining with CHA, LGC could potentially improve diagnosis to differentiate multiple primary tumors and intrapulmonary metastases.

Disclosure: All authors have declared no conflicts of interest.

3PD
ALK AND MET ARE SYNERGISTIC CO-ACTIVATORS OF DOWNSTREAM SIGNALS BY AMPLIFICATION IN PULMONARY SARCOMATOID CARCINOMA: A POTENTIAL FOR TARGETED THERAPY?

G. Pelosi[1], P. Gasparini[2], G. Sozzi[3], V. Ciravolo[3], S. Pupa[3], E. Tamborini[1], P. Scanagatta[4], F. De Braud[5], U. Pastorino[4] [1]Department of Pathology, Fondazione IRCCS Istituto Tumori Milano, Milano, ITALY, [2]Department of Pathology and Experimental Oncology, Fondazione IRCCS Istituto tumori Milano, Milano, ITALY, [3]Department of Experimental Oncology, Fondazione IRCCS Istituto tumori Milano, Milano, ITALY, [4]Department of Thoracic Surgery, Fondazione IRCCS Istituto tumori Milano, Milano, ITALY, [5]Department of Medical Oncology, Fondazione IRCCS Istituto tumori Milano, Milano, ITALY

Aim: Genetic alterations suitable for targeted therapy are poorly known issues in pulmonary sarcomatoid carcinoma (PSC), an uncommon and life-threatening family of non-small cell lung cancer (NSCLC). We here investigate the role of ALK and MET in this subtype of aggressive NSCLC.

Methods: Eighty-six cases of PSC, all formalin-fixed and paraffin-embedded, were assessed for ALK and MET gene status by FISH and relevant protein expression by immunohistochemistry (IHC) also taking advantage of phosphorylated antibodies for MET. Moreover, ALK and MET mRNA evaluation by real-time PCR (qPCR) and biochemistry assay by Western Blotting (WB) for downstream activation pathways involving p-MAPK, p-AKT, p-SRC and p-FAK were also carried out.

Results: ALK amplification was found in 15/86 (17%) and MET amplification in 21/86 (24%) PSC, with ALK-amplified tumors also showing MET amplification. A few PSC, however, showed MET amplification without any ALK gene alteration. Fifty metastatic lung adenocarcinomas used as controls showed ALK or MET amplification in 1 and 1 cases, respectively (p=0.1). ALK protein expression was always lacking in PSC, while p-MET

was limited to the relevant amplified tumors. Increased levels of ALK and MET mRNA were instead detected in tumors, especially amplified cases. WB assays showed complete activation of downstream signal pathways up to p-SRC and p-FAK recruitment in ALK/MET co-amplified tumors, whereas isolated MET amplification or coexisting increased gene copy gain of ALK/MET was limited to activate p-MET, p-MAPK and p-AKT.

Conclusions: ALK and MET genes acted as synergistic, non-random co-activators of downstream signal when co-amplified in a subset of PSC patients, so indicating an oncogene addiction mechanism. These alterations could have a potential for targeted therapy by specific inhibitors.

Disclosure: All authors have declared no conflicts of interest.

4PD
THE PROGNOSTIC EFFECT OF IASLC/ ATS/ERS CLASSIFICATION OF LUNG ADENOCARCINOMA ON POSTRECURRENCE SURVIVAL IN RESECTED ADENOCARCINOMA

J. Hung[1], T. Chou[2], Y. Wu[1], W. Hsu[1] [1]Department of Surgery, Taipei Veterans General Hospital, Taipei, TAIWAN, [2]Department of Pathology, Taipei Veterans General Hospital, Taipei, TAIWAN

Aim: Factors predicting post-recurrence survival (PRS) in resected lung adenocarcinoma after recurrence have not been reported. This study aimed to investigate the prognostic factors of PRS, including the new classification of lung adenocarcinoma proposed by the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS), in resected lung adenocarcinoma after recurrence.

Methods: The clinicopathological characteristics of 140 patients with recurrence after complete resection of lung adenocarcinoma at Taipei Veterans General Hospital were retrospectively reviewed. The prognostic factors of PRS were analyzed.

Results: The pattern of recurrence included local only in 22 (17.1%), distant only in 40 (31.0%), and both local and distant in 84 (51.9%) of patients. The 2- and 4-year PRS were 67.2% and 39.1%, respectively. The most common organ sites of metastasis were the contralateral lung (40.7%), followed by the brain (37.1%) and bone (30.7%). Univariate analysis showed that N2 status (vs. N0 and N1) ($P = 0.007$), stage III (vs. stage I and II) ($P = 0.043$), micropapillary/solid predominant pattern group ($P = 0.012$), liver metastasis ($P = 0.033$), and no treatment for recurrence ($P < 0.001$) were significant predictors of worse PRS. Multivariate analysis revealed that N2 status ($P = 0.036$), micropapillary/solid predominant pattern group ($P = 0.018$), and no treatment for recurrence ($P < 0.001$) were still significant predictors of worse PRS.

Conclusions: N2 status, micropapillary/solid predominant pattern group, and no treatment for recurrence predict worse PRS in patients with resected lung adenocarcinoma. The new classification of lung adenocarcinoma had significant impact on PRS.

Disclosure: All authors have declared no conflicts of interest.

6P
ESTROGEN RECEPTOR BETA OVER EXPRESSION IN WOMEN WITH LUNG ADENOCARCINOMA IS ASSOCIATED WITH BETTER SURVIVAL

N.J. Lalic Invasive Diagnostic Procedures, Institute of Oncology Vojvodina, Sremska Kamenica, SERBIA

Aim: Adenocarcinoma of lung is becoming the most common histologic type of lung cancer in both sexes. It is more frequent in females than in males and developes more frequently than other histologic types in individuals who have never smoked. This evidence suggests that other etilogic factors of lung cancer need to be ivestigated, such as sex hormones. Recent studies have shown that estrogens promote the growth of lung cancer cells and may potentially be responsible for incresed susceptibility to lung cancer in woman. The aim of this study was to elucidate the correlation between expression of beta estrogen receptor and clinicopathologic factors and prognosis in adenocarcinoma of the lung.

Methods: This study evaluated paraffin embedded, histological material wich were collected from 200 patients (100 men and 100 women). Histological materials collected as specimens wich were taken during bronchoscpy procedures or from operated adenocarcinoma specimens in the period 2006–2008. Estrogen receptor beta (ERβ) was immunohistochemically analised. Kaplan-Meier survival curves were generated to evaluate the significance of ERβ expression for the prognosis.

Results: ERβ positivity was demonstrated in 78 (39,0%) of the tumour specimens. There was no statisticaly significant correlation between ERβ expression and age, gender, stage, smoking status, comorbidity, fertility among women, therapeutic aproaches. In multivariate analyses, females were more likely to have ERβ-positive tumors but not statistically significant. Hoewer females with ERβ-positive tumors had significant reduction in mortality compared with men and ERβ-negative tumors women (Breslow: p= 0,037; Mantel-Cox: p= 0,112). Females with ERβ-positive tumors had statistically significant longer disease free period (n= 42) 23,8±6,8% during two years period and 7,1±4,0% during five years period (Mantel-Cox, p= 0,049).

Conclusions: The presence of ERβ in a tumor seems to be a positive prognostic factor for women with lung adenocarcinoma. The finding confirms another recent study and suggest that the relations between estrogens and lung cancer be investigeted futher especially with evaluation of EGFR mutation because cross-talk mechanism between an EGFR mutation and expression or function of ERβ.

Disclosure: All authors have declared no conflicts of interest.

7P
EXPLORING TUMOR-STROMA INTERACTION IN LUNG ADENOCARCINOMAS: A GENOME WIDE ANALYSIS OF THE RESPONSE TO BMP SIGNALING IN HUMAN LUNG FIBROBLASTS

M. Buess[1], M. Rajski[2] [1]Medical Oncology, St. Claraspital, Basel, SWITZERLAND, [2]Institute of Physiology, University of Zürich, Zürich, SWITZERLAND

Aim: The BMP signaling system plays a key role in development, morphogenesis and cancer. As observed for development, heterotypic cellular interactions also play an essential role in carcinogenesis. The aim of this study was to characterize the response of lung stromal fibroblasts to BMPs and their antagonists and investigate its potential role in human lung adenocarcinomas.

Methods: We used an ex vivo culture model and measured changes in gene expression in human lung fibroblasts after stimulation with BMP2, BMP4, or BMP7, as well as their antagonists, gremlin and noggin, using HEEBO microarrays. The in vitro data were correlated with in vivo observations by comparing the results with published expression datasets of human lung adenocarcinoma biopsies.

Results: In addition to differential expression of several genes that play direct roles in the BMP signaling pathway, we observed a fundamental reprogramming of gene expression patterns typical for carcinoma-associated fibroblasts and deregulation of genes involved in several other processes such as development and angiogenesis. We have systematically analyzed the cellular response to BMP2, BMP4 and BMP7, as well as their antagonists, gremlin and noggin, to define common and specific gene expression patterns. A BMP2 induced gene expression signature was defined, which is specific for the response of the stromal fibroblasts. The gene expression data from lung adenocarcinoma biopsy specimens were analyzed to determine the prognostic significance of the "Fibroblast specific BMP2 induced gene list". The expression of the genes in the "Fibroblast specific BMP2 induced gene list" provided a basis for segregating the patients of different published gene expression datasets. In two small datasets (Garber et al. and Lee et al.) there was a strong trend for a worse prognosis of patients with adenocarcinomas of all stages over-expressing the "Fibroblast speciic BMP2 induced gene list". In a larger dataset with stage I adenocarcinomas (Bhattacharjee et al.) we observed a significantly worse recurrence-free (p=0.002) and overall survival (p=0.0002).

Conclusions: The effects of BMPs and their antagonists are very heterogeneous depending on the target cell type. The expression patterns of genes induced by BMP2 in primary lung fibroblasts may predict outcomes of patients with lung adenocarcinomas.

Disclosure: All authors have declared no conflicts of interest.

8P
PLASMA CELL-FREE DNA CONCENTRATION AND INTEGRITY ANALYSIS IN PATIENTS WITH CHEST RADIOLOGICAL FINDINGS: NSCLC VERSUS NON-MALIGNANT PATHOLOGIES

A. Szpechcinski[1], W. Kupis[2], R. Langfort[3], J. Zaleska[4], K. Maszkowska-Kopij[5], R. Struniawski[1], M. Skronski[1], T. Orlowski[2], K. Roszkowski-Sliz[4], J. Chorostowska-Wynimko[1] [1]Department of Genetics and Clinical Immunology, National Institute of Tuberculosis and Lung Diseases, Warsaw, POLAND, [2]Department of Thoracic Surgery, National Institute of Tuberculosis and Lung Diseases, Warsaw, POLAND, [3]Department of Pathomorphology, National Institute of Tuberculosis and Lung Diseases, Warsaw, POLAND, [4]III Department of Lung Diseases, National Institute of Tuberculosis and Lung Diseases, Warsaw, POLAND, [5]Outpatient Clinic, National Institute of Tuberculosis and Lung Diseases, Warsaw, POLAND

Aim: The quantification of cell-free DNA in plasma (cfDNA) has been repeatedly shown to accurately differentiate NSCLC patients from healthy individuals and indicate the increased cancer risk. However, to be of clinical value, such quantitative assay should also discriminate between lung cancer and non-malignant pathologies presenting similar radiological image. Recently, we demonstrated that increased cfDNA levels in NSCLC patients result from complicated tumor-host interactions, but not from chronic respiratory inflammation itself. In present study we determine cfDNA levels in resectable NSCLC versus non-malignant lung tumors to evaluate the factual clinical utility of cfDNA quantification for early NSCLC detection.

Methods: We measured cfDNA levels and integrity index (DII) using real-time PCR in 66 NSCLC patients (ADC, SQC, NOS, stage I-IIIA), 28 patients with benign lung nodules and tumors (hamartoma, granuloma, tuberculoma and other) and 40 healthy controls.

Results: Mean cfDNA level of 21,5 ng/ml in NSCLC group was significantly higher than 4,5 ng/ml in healthy controls (p=0.000). There were no significant associations between cfDNA levels and TNM stages or histological types in NSCLC. The cfDNA levels in NSCLC did not differ significantly from values observed in patients with non-malignant tumors (23,4 ng/ml; p=0,45). Similarly, the mean DII in NSCLC (4,0) significantly differed from control values (1.0; p=0.000), but not from DII observed in non-malignant group (4,0).

Conclusions: Our data suggest that while massive cell death is common for benign and malignant lung tumors, more complex mechanisms regulate massive cfDNA release into the blood circulation of NSCLC patients. The presence of a solitary pulmonary nodule or lung tumor, irrespectively to its malignancy status, significantly increased the mean cfDNA integrity index with respect to healthy controls, thus reflecting the intensified cell death processes.

Disclosure: All authors have declared no conflicts of interest.

9P
SYSTEMATIC DETERMINATION OF EGFR MUTATION (M) AND IMMUNOHISTOCHEMISTRY (IHC) OF ALK TRANSLOCATION (T) STATUS IN PATIENTS (P) WITH NEWLY NON SMALL CELL LUNG CANCER (NSCLC)

S. Ponce Aix[1], J. Zugazagoitia[2], M. Blazquez Arroyo[1], G. Ruiz Ares[1], J.A. Nuñez Sobrino[1], L.C. Iglesias Docampo[1], R.A. Manneh Kopp[1], R.M. García Martín[3], J.L. Rodriguez Peralto[3], A.B. Enguita Valls[3] [1]Servicio de Oncologia Medica, University Hospital 12 de Octubre Medical oncology, Madrid, SPAIN, [2]Medical Oncology, Hospital 12 Octubre. Universidad Complutense, Madrid, SPAIN, [3]Servicio Anatomia Patológica, University Hospital 12 de Octubre Medical oncology, Madrid, SPAIN

Aim: Detection of EGFR m. p. is done in a routine way. Also detection of ALK t. has become an important issue for therapeutic decision making in NSCLC. Which is the best technic to broad test of ALK t. remain unclear. We implemented a systematic determination of EGFR m. and ALK t. status to asses feasibility and accuracy in a clinical setting.

Methods: We have selected all p. with newly diagnosed NSCLC non squamous or squamous never smokers between May 2013 to November 2013. The objective was to evaluate the accuracy of EGFR m. testing, using TheraScreen or Cobas EGFR mutation test, and ALK t. testing, using IHC Ventana (D5F3) and positive patients checked by FISH (Abbot Vysis Break Apart)

Results: One hundred and one p. were analyzed. Median age was 64.6. 27 (26.73%) women and 74 (73.26%) men; 100 (99%) caucasians and 1 (1%) asiatic; 100 (99%) non squamous (including adenocarcinoma, large cell carcinoma and others) and 1 (1%) squamous; Current smokers 38 (37.62%), former smokers 51 (50.49%), never smokers 6 (5.94%) and unknown 6 (5.94%). The tumor sample was paraffin embedded (91.1%) and cytology (8.9%). We performed successfully both determination in 97.02% of the samples, and only in 3 p. ALK was not done (2.98%). The median time to results was 5.8 days. Only 8 patients with EGFR m. were found (7.92%): del 19 (62.5%), 21 L858R (25%) and exon 18 (12.5%). IHC for ALK t. positive for 9 patients (8.9%) and confirmation by FISH in 8 p. (88.8%). T. rate in women was 11.11% and men 88.88%. Median age was 59.7 (48- 67); 7 adenocarcinoma (77.77%), 1 squamous (11.11%) and 1 neuroendocrine (11.11%). The only discordance between the results of IHC and FISH was in a p. with neuroendocrine subtype.

Conclusions: Systematic determination of EGFR m. and ALK t. in a public center is feasible offering an acceptable time to result and with good performance. Rate of EGFR m. was minor than reported previously in our center due to the small number of patients tested in this series. In other hand ALK t. is higher than reported in literature may be due to the same reason. ALK t. testing can be done by IHC as screening method in all non squamous NSCLC patients and in those squamous never smokers. Special consideration must be made in p. with NSCLC with neuroendocrine differentiation.

Disclosure: All authors have declared no conflicts of interest.

10P
DOWN-REGULATION OF ERCC1 BY EGFR-TKI IMPROVES PLATINUM-BASED CHEMOTHERAPY EFFICACY FOR NON-SMALL CELL LUNG CANCER (NSCLC)

H.T. Cheong[1], C.W.C. Hui[1], F. Xu[2], T.S.K. Mok[1], C.H. Wong[1] [1]Clinical Oncology, State Key Laboratory In Oncology In South China, The Chinese University of Hong Kong, Hong Kong, CHINA, [2]Medical Oncology, Sun-Yat Sen University Cancer Center, Guangzhou, CHINA

Aim: Platinum-based chemotherapy (Chemo) is the standard first line treatment for patients with EGFR wild type while EGFR TKI is the standard for patients with the mutation. FASTACT-2 (Wu et al Lancet Oncology 2013) compared intercalated Chemo and EGFR-TKI with Chemo, and subgroup biomarker studies showed that patients with EGFR wild type and positive ERCC1 attained longer progression free survival and overall survival. We postulate that EGFR TKI down-regulates ERCC1 expression in wild type EGFR NSCLC cells, thus enhances the chemotherapy efficacy.

Methods: *In vitro* and *in vivo* studies were designed to study the impact of EGFR TKI on ERCC1 expression. H358 and H1993 cells were treated with EGFR-TKI for 72 hours and transient siRNA transfection was performed for ERCC1 suppression. The cisplatin sensitivity of the transfected cells was tested by cell viability assay. H358 and H1993 xenograft tumor model were established and animals were treated with 2 weeks of oral erlotinib. ERCC1 expression was studied by western blot and IHC by Mab clone 8F1.

Results: ERCC1 expression is not directly related to EGFR-TKI sensitivity. However, ERCC1 expression progressively reduced over 72-hours of EGFR-TKI exposure. ERCC1 knock-down increased cells' sensitivity towards cisplatin, the IC_{50s} for H358 and H1993 were reduced from 11.94μM to 0.31μM and 14.67μM to 0.16μM respectively. On the other hand, TKI showed no effect on

tumor volume of these EGFR wild type xenografts but displayed a significant reduction in ERCC1 level by IHC staining after treatment with TKI.

Conclusions: These data suggested that EGFR-TKI may reduce ERCC1 expression and potentially enhance sensitivity to platinum-based chemotherapy.

Disclosure: All authors have declared no conflicts of interest.

11P
GENE EXPRESSION OF EPIDERMAL GROWTH FACTOR RECEPTOR, MYC-INDUCED NUCLEAR ANTIGEN, 53KDA AND MECHANISTIC TARGET OF RAPAMYCIN IN PULMONARY NEUROENDOCRINE TUMORS

D.M. Marinova[1], Y. Slavova[2], G. Stancheva[3], D. Kachakova[3], A. Mitkova[3], R. Kaneva[3] [1]Pneumology, University Hospital for Pulmonary Diseases, Sofia, BULGARIA, [2]Pathology, University Hospital for Pulmonary Diseases, Sofia, BULGARIA, [3]Medical Chemistry and Biochemistry, Medical University - Sofia, Sofia, BULGARIA

Aim: To study the gene expression of Epidermal growth factor receptor (EGFR), MYC-induced nuclear antigen, 53kDa (MINA53) and Mechanistic target of rapamycin (MTOR) in pulmonary neuroendocrine tumors (pNET), and their correlations and prognostic significance.

Methods: Surgically resected specimens from 42 patients with pNET were studied: 23 carcinoid tumors (CT), 13 small cell lung carcinomas (SCLC), 6 large cell neuroendocrine carcinomas (LCNEC). The histological subtype, pTNM stage, survival and gene expression of EGFR, MINA53 and MTOR were evaluated.

Results: Overexpression of EGFR was found in 17% (3 CT, 13%; 4 SCLC/LCNEC, 21%), of MINA53 – in 38% (5 CT, 22%; 11 SCLC/LCNEC, 58%) and of MTOR – in 69% (17 CT, 74%; 12 SCLC/LCNEC, 63%). Decreased expression of EGFR was found in 38% (5 CT, 22%; 11 SCLC/LCNEC, 58%) and of MTOR – in one CT (4.3%). CT were more often with normal expression of EGFR (65%), while SCLC/LCNEC were more often with decreased expression (58%) (p=0.015), confirmed by regression analysis (Odds ratio 8.25; p=0.007). There were no difference in the expression of MINA53 (p=1.000) and MTOR (p=0.400) between CT and SCLC/LCNEC. The median survival time was significantly longer in cases with normal EGFR and MINA53 expression compared to cases with overexpression (p=0.003; p=0.042 respectively). Patients with normal MTOR expression survive insignificantly longer (p=0.50). The Cox regression analysis showed survival advantage for cases with normal EGFR expression compared to those with overexpression (Hazard ratio [HR] 13.31; p=0.021) and a prognostic potential for MINA53 (HR 4.5; p=0.063). No prognostic significance of MTOR expression was found (p=0.505). Positive correlations between EGFR and MINA53 (r=0.45, p=0.003), EGFR and MTOR (r=0.48, p=0.001) and MINA53 and MTOR (r=0.46, p=0.002) were observed.

Conclusions: EGFR and MINA53 overexpressions are negative prognostic factors in pNETs. EGFR, MTOR and MINA53 are potential targets for combined therapy – there are positive correlations between their expression levels. As EGFR and MTOR are often overexpressed in pNETs and are therapeutic targets in lung cancer so in future the patients with tumors that overexpress them can be considered for treatment with these drugs.

Disclosure: All authors have declared no conflicts of interest.

12P
EGFR GENE MUTATION IN ADVANCED NON-SMALL CELL LUNG CANCER - A CASE SERIES

T. Mehmood Radiation Oncology, Shaukat Khanum Memorial Cancer Hospital and Reserch Centre (SKM), Lahore, PAKISTAN

Aim: Molecular targeted therapy based on TKIs, directed at the Epidural growth factor receptor (EGFR) is one of the recent options for the management of advanced Non-Small Cell Lung Cancer (NSCLCs). EGFR gene mutations, exon 19 deletions (LREA deletions) and exon 21 (L858R) are most common and good predictions of response to EGFR-TKI treatment. EGFR gene mutations are found in approximately 10% of Caucasian patients and up to 50% of Asian populations. Recent studies have endorsed these incidences in European and Asian populations. The frequency of EGFR mutation is higher in non-smokers and in women. To objective of this study was to determine the frequency of EGFR gene mutations in non–small-cell lung cancer patient presenting at our institute.

Methods: Between September 2011 and September 2013, we sent EGFR mutation testing for 39 patients with proven histology of TTF-1 positive adenocarcinoma lung. EGFR gene mutations in exons 18, 19, 20 and 21 were carried out by National University Hospital Singapore and and at Shaukat Khanum Memorial Cancer Hospital Lahore, Pakistan.

Results: 72% of the patients were males and 28% were females. 49% were smokers, 41% were non-smokers and this information was missing in 10% of the patients. 18.5% of the patients were found to have EGFR gene mutation positive; 28.5% on exon 18, 28.5% on exon 19, 14.5% on exon 20 and 28.5% on exon 21. Among patients having EGFR gene mutation positive, 57% were smokers while 43% were non-smokers.

Conclusions: The frequency of EGFR mutation in our institution was 18.5% and all these patients were male, with almost half of the patients being smokers. This trend is not in accordance with published literature. This merits similar study with a larger number of patients to find out the real trend of EGFR gene mutation in our population.

Disclosure: All authors have declared no conflicts of interest.

13P
LEPDIC AND MICROPAPILLARY GROWTH PATTERN AND EXPRESSION OF NAPSIN A CAN STRATIFY PATIENTS OF STAGE I LUNG ADENOCARCINOMA INTO DIFFERENT PROGNOSTIC SUBGROUP

D. Lin[1], Y. Xin[2] [1]Department of Pathology, Cancer Institute and Hospital of the Chinese Academy of Medical Sciences, Beijing, CHINA, [2]Department of Pathology, Cancer Institute, Beijing, CHINA

Aim: Aim of this study was to investigate contribution of histologic categories and relative growth pattern proposed by IASLC/ATS/ERS classification to patients' clinical outcome in stage I lung adenocarcinoma, and whether expression of thyroid transcription factor-1 (TTF1) and napsin A can further stratify patients of specific histologic subgroup with respect to prognosis.

Methods: A total of 211 cases were available for histologic analysis. Histological subtypes and percentage of lepidic and micropapillary growth patterns according to the IASLC/ATS/ERS classification were estimated with slight modifications. Tissue microarrays were constructed and expression levels of TTF1 and napsin A were evaluated by immunohistochemistry. Kaplan-Meier curves were used to calculate survival rate for each separate histopathologic features and immunohistochemistry variant. Univariate and multivariate analyses were undertaken to control for validated prognostic factors.

Results: In univariate analyses, female sex (p=0.009), lepidic growth pattern (P=0.011) and lack of micropapillary pattern (P=0.048) were favorable predictor significantly associated with disease-free survival (DFS). Lack of mitosis (P=0.044) and napsin A expression (P=0.031) were favorable predictors for overall survival (OS). Tumors with a maximum diameter ≤2cm had both longer DFS (P=0.008) and OS (P=0.020). Negative TTF1 expression indicated increased risk of death, but failure in statistical significance (P=0.215). After multivariate analysis, histologic subtype, tumor size and gender were identified as independent predictor for DFS (RR: 0.343, 3.697, 0.494; P=0.006, 0.029, 0.019), no feature was found as an independent predictor for overall survival (P>0.05).

Conclusions: In early-stage lung adenocarcinoma, lepidic growth pattern, female sex and tumor size ≤2cm were independent favorable predictors for tumor recurrence. Tumors with any percentage of lepidic growth pattern will have a better prognosis than absence.

Disclosure: All authors have declared no conflicts of interest.

14P
CASE-CONTROL STUDY: SMOKING HISTORY AFFECTS THE PRODUCTION OF TUMOR ANTIGEN SPECIFIC ANTIBODIES IN PATIENTS WITH NSCLC IN COMPARISON WITH CANCER DISEASE FREE GROUP

D. Myšíková[1], J. Šimonek[1], J. Pozniak[1], J. Kolařík[1], R. Špíšek[2], R. Lischke[1]
[1]Thoracic and Lung Transplantation Division, 3rd Department of Surgery, First Faculty of Medicine, Charles University in Prague and University Hospital Motol, Prague, CZECH REPUBLIC, [2]Department of Immunology, Second Faculty of Medicine, Charles University in Prague and University Hospital Motol, Prague, CZECH REPUBLIC

Aim: We focused on an impact of active smoking in a prospective case-control study comparing differences in the frequency of tumor antigen specific antibodies (TAA) in the serum in the group of NSCLC patients versus benign diagnosis group.

Methods: Serum from two comparable groups of patients was analyzed for the presence of TAA against 3 tumor antigens HER2 neu, NY-ESO-1 and MAGE A4 by ELISA: 57 patients with NSCLC were compared with 57 benign controls. Serum from 32 healthy volunteers was used for cut-off point calculation. Seropositivity was evaluated in three subgroups (smokers, ex-smokers, non-smokers) of NSCLC patients and similarly in 3 subgroups of benign patients.

Results: TAA were detected in NSCLC group - NY-ESO-1 in 28,1 % (16/57), HER 2 neu in 10,5% (6/57) and MAGE A4 in 19,3% (11/57) as well as in group of benign controls - NY-ESO-1 in 17,5 % (10/57), HER 2 neu in 8,8 % (5/57) and MAGE A4 in 7,7 % (4/57).However, the highest frequency of TAA was observed in NSCLC smokers and declined in the groups of ex- and non-smokers. This trend was the most prominent in NY- ESO 1 detection, 40% (12/30) NSCLC smokers were NY-ESO 1 positive, only 22,2% (4/18) ex-smokers were positive and all of 9 non-smokers were NY-ESO 1 negative. Results were not significant probably due to an uneven distribution of patients in subgroups, p=0,052. Similarly, higher not significant frequency of HER 2 neu and MAGE A4 was observed in NSCLC smokers.There was a significant difference in NY ESO 1 production between group of NSCLC patients in comparison with benign controls according to smoking history p=0,002. The difference was most evident in subgroup of smokers, 12/30 NSCLC smokers versus only 4/30 benign controls were positive for NY-ESO 1.There was no similar significant difference in Her 2 neu and MAGE A4 frequency.

Conclusions: We show that an active smoking has a profound impact on the frequency of TAA in the serum of NSCLC patients in comparison with benign controls. Antibody production in smokers might indicate the chronic inflammatory state that potentiates the development of tumor specific immune response.

Disclosure: All authors have declared no conflicts of interest.

15P
THE TARGETING OF MTOR PATHWAY BY SPORE-FORMING BACILLUS FROM CHEONGGUKJANG, KOREAN FERMENTED SOYBEAN PASTE TO OVERCOME DRUG RESISTANCE IN NON-SMALL CELL LUNG CANCER

J.K. Park, M. Yang Department of Microbiology, Chungnam National University, School of Medicine, Cancer Research Institute, Daejeon, KOREA

Aim: Drug resistance is one of the main problems associated with non-small cell lung cancer (NSCLC) treatment. Targeting of mTOR pathway is an attractive strategy in the development of therapeutic agents against resistant NSCLC cells. Recently, we have isolated the Bacillus subtilis (BS) as a gram-positive, spore forming, non-pathogenic bacterium isolated from Cheonggukjang, Korean traditional fermented food that might have an apoptotic effects on NSCLC cells through the inhibition of mTOR pathway. In this study, we investigated the growth inhibition effects of BS in NSCLC cell lines via molecular mechanism studies of BS induced apoptosis signaling pathway.

Methods: NSCLC cell lines (TKI-sensitive PC9, TKI-resistant H1975), HepG2, HCT116, and human dermal fibroblast cell line were exposed with BS with MOI of 0.1 or 1 and its cytotoxic effect was evaluated by MTT. For further explore of in vitro protein level changes made by the apoptotic reagent, western blotting analysis was conducted.

Results: We isolated five Bacillus species from Cheonggukjang. Among them, the only strain BS showed 90% of cytotoxicity on all NSCLC cell lines (less than 60% by rapamycin). However, the cell viability of BS treated HepG2, HCT116, and fibroblast cell were not affected. Treatment of NSCLC cell lines with BS activated caspase-9, -3 and increased cleavage form of poly (ADP-ribose) polymerase (PARP). However, caspase-8 activity was not increased by BS. BS-activated intrinsic pathway via increase of pro-apoptotic (Bax) and decrease of anti-apoptotic (Bcl-2) proteins on mitochondria, disruption of mitochondrial membrane potential, release of cytochrome c from mitochondria.

Conclusions: Findings in this study direct us that BS can become a promising specific tumor targeting therapeutic agent in NSCLC via intrinsic cell death pathways. These results suggest that the combination of molecular targeted agents and BS has the potential to be a therapeutic strategy for drug resistant NSCLCs.

Disclosure: All authors have declared no conflicts of interest.

16P
PROGNOSTIC VALUE OF CYCLOOXYGENASE 2, ENHANCER OF ZESTE HOMOLOG 2 AND P53 EVALUATED BY QUANTITATIVE IMAGE ANALYSIS IN MALIGNANT NSCLC

K. Hainis[1], A.M. Athanasiadou[2], E. Haini[1], A. Tsipis[2], M. Gonidi[3], P. Athanassiadou[2] [1]Pulmonary, Corfu General Hospital, Corfu, GREECE, [2]Pathology Laboratory, Medical School, University of Athens, Athens, GREECE, [3]Cytology Lab, Corfu General Hospital, Corfu, GREECE

Aim: Cyclooxygenase 2 (COX-2), Enhancer of Zeste Homolog 2 (EZH-2) and p53 overexpression is seen in many malignancies including lung cancer. The aim of this study was to investigate the usefulness of the expression of COX-2, p53 and EZH-2 in NSCLC using an image analysis system on immunostained specimens with regard to biological behavior of the tumor.

Methods: The samples consisted of FNA material from 80 NSCLC lung carcinomas. Twenty specimens with hyperplastic lesion were using as control group. FNA specimens were collected in Cytolyt solution and Thin Prep slides were prepared. Image analysis of the smears stained immunocytochemically with the use of COX-2, p53 and EZH-2 antibodies was performed.

Results: The intensity and extent for COX-2 correlated with staining extent (p<0,001). Extent of staining for COX-2 correlated with percentage of positive for EZH-2 (0,001) and p53 nuclei (p<0,001). The intensity of COX-2 was lower in the carcinoma group (118,57 ± 12,43) than in the hyperplastic (127,16 ± 11,71) group. On the contrary the mean value of staining extent was greater in the carcinoma cases (15,96 ± 13,03) than in hyperplastic cases (4,04 ± 1,94). The percentage of EZH-2 and p53 positive cells correlated with histological type of the lesions (p=0,001 and p=0,011 respectivelly). There was also a statistic correlation between the histological type of the lesions with the expression of COX-2 (p=0,001), EZH-2 (P=0,010) and p53 (p=0,010).

Conclusions: In conclusion our results provide a basis for the concept that high expression of EZH-2, COX-2 and p53 as detected by IHC at quantitative level may be a predictor for distinguishing histologically benign lesions at high risk for malignant progression.

Disclosure: All authors have declared no conflicts of interest.

17P
CAN SUBTYPING DIAGNOSIS HELP IN OPTIMIZING THE MANAGEMENT OF LUNG ADENOCARCINOMA PATIENTS?

T.T. Kondratieva[1], N. Velizheva[2], M.V. Dardyk[3], A. Pavlovskaya[4], N. Mazurenko[5], I. Tsyganova[5], S. Subramanian[6] [1]Clinical Cytology Laboratory, Clinical Oncology Research Institute, FSBI N. N. Blokhin RCRC RAMS, Moscow, RUSSIAN FEDERATION, [2]Laboratory of Cell Imunity, Research Institute of Experimental Diagnostics and Tumor Therapy, FSBI N. N. Blokhin RCRC RAMS, Moscow, RUSSIAN FEDERATION, [3]Department of Oncology, Moscow State University of Medicine and Dentistry, Moscow, RUSSIAN FEDERATION, [4]Human Tumor Pathologic Anatomy Department, Clinical Oncology Research Institute, FSBI N. N. Blokhin RCRC RAMS, Moscow, RUSSIAN FEDERATION, [5]Laboratory of Oncogenomics, Research Institute of Carcinogenesis, FSBI N. N. Blokhin RCRC RAMS, Moscow, RUSSIAN FEDERATION, [6]Eurasian Federation of Oncology, Moscow, RUSSIAN FEDERATION

Aim: In the era of targeted therapy of metastatic and locally advanced lung cancer (LC) the final verdict already often belongs to genetists. Is it reasonable to do molecular screening for 80% of LC that are NSCLC? Are the advantages worth the price of research? Are there any correlations between molecular changes, morphological features of different histological subtypes, clinical implications and prognosis of disease? 1. To evaluate the need and clinical significance of subtyping lung cancer adenocarcinomas (AC) on small biopsies and cytological samples in daily practice 2. To analyze the correlation between histologic subtypes of Lung AC, EGFR/KRAS-status and efficiency of the treatment in LC patients.

Methods: Cytological and histological samples of 271 (100%) bronchoscopies conducted in 2012 were analyzed. Simultaneous histological and cytological examinations were performed in 162 (60%) cases. In 78 (29%) patients EGFR/KRAS-status was analyzed.

Results: 78 (100%) Lung AC was confirmed. Among them: AC with papillary patterns – 26 (33%), with the predominance of solid and acinar patterns and presence of mucus – 23 (29,5%), large cell low differentiated – 16 (21%), AC with micropapillary patterns – 9 (11,5%) and mucoepidermoid cancer – 4 (5%). Poor clinical course of disease was observed in patients with AC with the presence of large, middle and small cells with the severe anaplasia of nuclei. The differential feature is presence of multiple metastasis, especially in bones. EGFR-mutations were observed in 14 (18%) patients. In this subgroup the following subtypes were observed: AC with solid and acinar patterns with clear cells, AC with papillary and micropapillary patterns and production of mucus and combined subtypes. Presence of mutated KRAS was associated with prominent adenous differentiation of the tumor and the evident presence of mucus production

Conclusions: 1. Accurate subtyping of lung AC within the International Classification is essential stage in diagnosis and treating patients. Simultaneous usage of histologic and cytological examination helps to solve the problem. 2. No evident correlation between genetic mutations and morphological features of adenocarcinomas were found. Further data collection and analysis on morphogenetic changes with its clinical implications are needed.

Disclosure: All authors have declared no conflicts of interest.

18P
PROTEIN TYROSINE KINASE 7 PLAYS A TUMOR SUPPRESSOR ROLE BY INHIBITING ERK AND AKT PHOSPHORYLATION IN LUNG CANCER

H.W. Lee[1], M.C. Kang[1], J.H. Kwon[1], D.W. Choe[2], C.H. Kim[3], H.J. Yoo[4], J.S. Koh[5], J.H. Park[1] [1]Thoracic Surgery, Korea Cancer Center Hospital, Seoul, KOREA, [2]Radiology, Korea Cancer Center Hospital, Seoul, KOREA, [3]Pulmonology, Korea Cancer Center Hospital, Seoul, KOREA, [4]Radiation Oncology, Korea Cancer Center Hospital, Seoul, KOREA, [5]Pathology, Korea Cancer Center Hospital, Seoul, KOREA

Aim: Protein tyrosine kinase 7 (PTK7) is a catalytically inactive receptor tyrosine kinase that is also known as colon carcinoma kinase-4 (CCK-4). Recent reports have shown that PTK7 plays an important role in carcinogenesis, and it is known to be up-regulated in gastric cancer, colon cancer, esophageal cancer, and liposarcoma. However, we found that PTK7 expression was down-regulated at the mRNA as well as protein levels in human lung squamous cell carcinoma (LSCC), unlike in other tumors. In this study, we attempted to explore the role of PTK7 in lung cancer.

Methods: We analyzed expression of PTK7 by RT-PCR and western blot analysis using tumor and normal lung tissue from 10 LSCC patients. To explore the functional role of PTK7, the expression of PTK7 in LSCC cells was examined using empty vector and PTK7 gene inserted vector.

Results: We found that PTK7 expression was down-regulated at the mRNA as well as protein levels in human lung squamous cell carcinoma (LSCC). Upon investigating the functional role of PTK7 in LSCC, we found that overexpression of PTK7 in LSCC cells resulted in inhibition of cell proliferation, invasion, and migration. Further, we confirmed that these phenotypic changes are associated with the activation of Akt and ERK.

Conclusions: These observations may indicate a role for PTK7 in cell proliferation, wound healing and invasion via regulating Akt and Erk activation. Our findings suggest that PTK7 has different oncogenic roles in organs and target tumors.

Disclosure: All authors have declared no conflicts of interest.

19P
CYTOTOXIC EFFECT OF VENOM FROM SEA ANEMONES ON HUMAN NON-SMALL-CELL LUNG CANCER CELL LINE

M. Ramezanpour[1], B. Sanderson[1], K. Burke da Silva[2] [1]Medical Biotechnology, Flinders University, Adelaide, SA, AUSTRALIA, [2]School of Biological Sciences, Flinders University, Adelaide, SA, AUSTRALIA

Aim: Nature has been instrumental as a source of therapeutics. The major anti-infective, anticancer, analgesics and immunosuppressive compounds are of natural origin. Sea anemones are well known for being rich sources of toxins. The goal of this study was to determine the susceptibility of human non-small-cell lung cancer cell line (A549) to killing by four different sea anemone venoms.

Methods: In this study, the nematocyst venom of four sea anemones (Heteractis malu, Heteractis Crispa, Cryptodendrum adhaesivum and Entacmaea quadricolor) were obtained by the milking technique, and the potential of these venoms to kill cancer cells was tested on human non-small-cell lung cancer (NSCLC) A549 cells. The total protein level in the crude extract was determined by the bicinchoninic acid (BCA) protein assay. The cytotoxicity on the cell line was assayed using the 3-(4, 5-dimethylthiazol-2- yl)-2, 5-diphenyltetrazolium bromide (MTT) assay which measures survival based on the detection of mitochondrial activity and by the crystal violet assay, which measures survival based on the ability of cells to remain adherent to microplates.

Results: In the MTT assay, C. adhaesivum and H. malu had significant inhibitory effect on A549 cells, although E. quadricolor and H, Crispa showed less inhibitory effect on A549 cells. In the crystal violet assay, the toxic effects of the extracts were evident for C. adhaesivum and H. malu and E. quadricolor at 24 and 72 hours however, H, Crispa did not show any significant effect.

Conclusions: Venom from H. malu, C. adhaesivum and E. quadricolor show promising results against human non-small-cell lung cancer (NSCLC) cell line.

Disclosure: All authors have declared no conflicts of interest.

20P – LINGUISTIC CORRECTION
EVALUATION OF 1H-NMR SPECTROSCOPY IN PREDICTING PLATINE-RELATED TOXICITIES IN LUNG CANCER PATIENTS

K. Vanhove[1], L. Mesotten[2], M. Thomeer[3], E. Louis[1], P. Adriaensens[4] [1]Faculty of Life Sciences, University of Hasselt, Diepenbeek, BELGIUM, [2]Nuclear Medicine, ZOL, Genk, BELGIUM, [3]Respiratory Division, ZOL, Genk, BELGIUM, [4]Institute for Material Research, University of Hasselt, Diepenbeek, BELGIUM

Aim: Lung cancer is the leading cause of cancer mortality worldwide. Despite progress in treatment of lung cancer we experience unacceptable toxicities without a significant increase in overall survival (OS) and progression free

survival (PFS). The goal of this study was to find out whether the metabolic profile derived from blood plasma can differentiate between subject groups who do and do not develop toxicities.

Methods: This project investigated subjects with a new diagnosis of lung cancer (n = 76) independent of stage (IB 1.3 %, IIA, 7.9%, IIB 5.3%, IIIA 31.6%, IIIB 18.4% and stage IV 35.5%) and who received chemotherapy. All patients received a platinum-based cytotoxic treatment.Participants were asked to provide a fasted sample of blood. Samples were analysed by 1H-NMR spectroscopy using a 400 MHz spectrometer. Slightly T2-weighted spectra were acquired and the chemical shifts were referred to TSP at 0.015 ppm. The integration values of 110 spectral integration regions (IRs) were analyzed appropriate statistical methods followed by an orthogonal partial least squares discriminant analysis (OPLS-DA) to investigate whether a discriminating classifier can be constructed.

Results: There were severe adverse events (grade 3 and 4) in both groups: thrombopenia (9%), neutropenia (38%), leukopenia (17%) and anemia (8 %). There were no cases of severe renal failure. According to the ECOG criteria of toxicity subgroups were created. Normal probability plots were constructed and a Kolmogorov-Smirnov test was carried out. Analysis of variance (ANOVA) was performed if the null hypothesis of the Kolmogorov Smirnov test was accepted. In the case of rejection of the null hypothesis Kruskall-Wallis was performed. No significant difference was found between the groups with and without toxicities. This was true for all the toxicities of interest in this study. Multivariate analysis (OPLS-DA) was not able to construct a discriminating classifier.

Conclusions: Lung cancer patients experiencing toxicities could not be differentiated from those without toxic effects based on the metabolic profiles obtained by 1H-NMR spectroscopy. However, this might be due to the treatment schedule, number of cycles administered, and the rather small and heterogeneous group of subjects.

Disclosure: All authors have declared no conflicts of interest

21P
ALTERATION OF TUMOR SUPPRESSOR GENES IN MALIGNANT PLEURAL EFFUSION

J. Chang Respiratory Center, Ewha Womans University, Seoul, KOREA

Aim: Pleural fluid is one of the most important materials for cancer diagnosis. Although cytologic examination has been used as a standard method to diagnose malignant effusion, its sensitivity is still insufficient. To determine whether the genetic analysis of pleural fluid can be used for the diagnosis of malignant effusion, mutations of p53 and FHIT, loss of heterozygosity (LOH), and microsatellite instability (MA) were investigated in malignant pleural effusion.

Methods: To determine whether gene analysis of pleural fluid can be used for the diagnosis of malignant effusion, malignancy-associated pleurisy (ME) were enrolled in 40 subjects and tuberculous pleurisy (TB) enrolled in 17 subjects as controls. From DNA of Pleural fluid and Blood, mutations of p53 and FHIT gene and microsatellite alteration were evaluated. As markers of microsatellite alteration, D3S1234, D3S1285, D9S171, and TP53 were applied for the analysis.

Results: Among 40 malignant associated effusion subjects, 5 subjects (12.5%) of p53 mutation and 7 subjects (17.5%) of FHIT mutation were detected. Using 4 microsatellite markers, 25 subjects (63%) exhibited LOH and/or MI in at least one marker. In 4 of 5 effusion with negative cytopathology and negative CEA in pleural fluid, microsatellite alterations were identified.

Positivity of cytopathology, CEA, and microsatellite alteration (MA) in malignancy pleural effusion

Pathology	Cytopathology (%)	CEA [a](%)	MA [b](%)
Overall	58	68	63
NSCLC	81	73	58
Squamous cell	80	60	80
Adenocarcinoma	81	76	52
SCLC	29	57	71

a: > 12ng/ml. b: LOH and/or MI

Conclusions: Diagnostic yield of pleural fluid cytopathology was 58% and positivity of analysis using 4 microsatellite markers was 63%. Gene analysis of pleural fluid could be used as a diagnostic tool to compromise conventional methods.

Disclosure: All authors have declared no conflicts of interest.

22P
PEGYLATED γ-FE2O3-NANOCRYSTAL FROM GOAT RED BLOOD CELLS ENHANCES THE NUCLEAR-TARGETED DELIVERY OF DOXORUBICIN IN LUNG CANCER THERAPY

V. Sreevani[1], K. Shanthi[1], S. Kannan[2] [1]Zoology, Bharathiar University, Coimbatore, INDIA, [2]Zoology, Periyar University, Salem, INDIA

Aim: • To synthesis DOX loaded PEGylated γ-Fe_2O_3-NC using goat blood as a bio-precursor (Molecular approach).

• To exhibit potent cytotoxicity against A549 and iron detection by Prussian blue stain.

• To detect apoptosis by Ao/EtBr and nuclear fragmentation by DAPI.

• To study DOX signal detection implies nuclear targeting.

• To observe cellular internalization of nanocrystals.

Methods: Synthesized DOX loaded PEGylated γ-Fe_2O_3-NC was characterized using UV spectroscopy, XRD (X-ray diffraction), HR-TEM (High Resolution Transmission Electron Microscope), DLS (Dynamic Light Scattering), EDS (Energy Dispersive Spectrometric analysis) techniques, and FTIR (Fourier transform infrared). MTT assay determines A549 cell viability, intracellular iron detection by Prussian blue stain, morphological assessment by AO/EtBr and DAPI staining techniques with the confocal studies for DOX detection and internalization of nanocrystals by TEM.

Results: The results have shown that the particle size of the DOX loaded PEGylated γ-Fe_2O_3-NC was found to be highly crystalline with 60–70 nm and confirmed the presence of DOX and PEG. The dose dependent cytotoxicity and morphological changes was observed. Intracellular iron detection was also confirmed. Strong DOX signals in the nucleus clearly implies the nuclear-targeted chemotherapy and cellular internalization of DOX loaded PEGylated γ-Fe_2O_3-NC was also observed.

Conclusions: Synthesis was very effective as the protocol developed here avoid the use of harsh reaction conditions such as high temperature, corrosive reagents, etc., and could be used as promising nanotherapeutic for nuclear-targeted chemotherapy for non-small cell lung cancer.

Disclosure: All authors have declared no conflicts of interest.

23P
ESTABLISHMENT OF LUNG CANCER MOUSE MODEL INDUCED BY BENZO (A) PYRENE

H.S. Moon[1], H.Y. Lee[2], I.K. Kim[1], C.D. Yeo[2], C.H. Kim[2], S.H. Lee[1] [1]Department of Internal Medicine, St. Paul's Hospital, The Catholic University of Korea, Seoul, KOREA, [2]Department of Internal Medicine, The Catholic University of Korea, Seoul, KOREA

Aim: Several novel animal models for lung cancer have been developed in recent years. Cancer mouse models by exposure to various carcinogens are still commonly used tumor mouse models. Benzo(a)pyrene (B[a]P) is one of the major environmental pollutants and induces carcinogenesis specifically targeting the lung. The aim of this study is to establish a standard design of mouse models for lung cancer following B[a]P exposure method.

Methods: A lung cancer mouse model was developed through repeated oral gavage or intratracheal (i.p.) injection of B[a]P, and then the incidence of lung tumor in B[a]P treated mice was measured following time course

from 20 weeks to 32 weeks. To make precise pathological diagnoses, lung tissue sections were hematoxylin and eosin stained and observed under a microscope.

Results: B[a]P administration by oral gavage induced slight reductions in body weight, while significant reductions in body weight were found in B[a]P i.p. injection group steadily through 32 weeks compared with the control group ($p < 0.001$). The tumor multiplicity following treatment with B[a]P (oral gavage or i.p) was similar by 28 weeks, while the size of lung tumors was significantly increased at 28 weeks. At 32 weeks, the size of lung tumors as well as tumor multiplicity significantly increased compared to 28 weeks, especially showing greater increase following treatment with IP injection. In addition, the adenomas and adenocarcinomas in B[a]P-treated mice significantly appeared to increase from 20 weeks to 32 weeks.

Conclusions: This study presented a standard period and method of carcinogen exposure to establish an effective spontaneous lung cancer model. Treatment of B(a)P by oral gavage or IP injection showed similar tumor multiplicity, however the IP method showed slight more increase in tumor formation and is more convenient as the injection is single dose. From 32 weeks onwards, there is a significant increase in tumor multiplicity and size. Therefore we suggest that the results of the B(a)P induced lung cancer mouse model should be investigated after 32 weeks to yield effective outcomes.

Disclosure: All authors have declared no conflicts of interest.

PREVENTION, EARLY DETECTION, EPIDEMIOLOGY, TOBACCO CONTROL

24O
CLINICAL UTILITY OF A PLASMA-BASED MICRORNA SIGNATURE CLASSIFIER WITHIN COMPUTED TOMOGRAPHY LUNG CANCER SCREENING

U. Pastorino[1], M. Boeri[2], G. Sozzi[2] [1]Thoracic Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, ITALY, [2]Experimental Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, ITALY

Aim: Recent screening trial results indicate that low-dose computed tomography (LDCT) reduces lung-cancer mortality in high risk subjects. However, high false positive rates, costs and potential harms highlight the need for complementary biomarkers. MicroRNAs (miRNAs) are tissue and disease specific molecules, actively released by cells in the circulatory system, which are associated with protein complexes and/or packaged in exosomes and microvesicles. Circulating miRNAs are rather stable and easily detectable in body fluids suggesting the possibility of using miRNAs as a new promising class of biomarkers. We previously reported that miRNA profiling in plasma samples of disease-free smokers enrolled in two independent spiral-CT screening trials, resulted in the generation of miRNA signatures with strong predictive, diagnostic, and prognostic potential (Boeri et al. PNAS 2011).

Methods: The diagnostic performance of a non-invasive plasma microRNA signature classifier (MSC) was retrospectively evaluated in samples prospectively collected from smokers within the randomized Multicentre Italian Lung Detection (MILD) trial. Plasma samples from 939 subjects including 69 lung cancer patients and 870 disease-free individuals (652 LDCT arm; 287 observation arm) were analyzed using a qRT-PCR based assay for MSC. Diagnostic performance of MSC was evaluated in a blinded validation study using prespecified risk groups.

Results: The diagnostic performance of MSC for lung cancer detection was 87% for sensitivity and 81% for specificity across both arms, and 88% and 80% respectively in the LDCT arm. For all subjects, MSC had a negative predictive value of 99% and 99.86% for detection and death-by-disease respectively. LDCT had sensitivity of 79% and specificity of 81% with a false positive rate of 19.4%. Diagnostic performance of MSC was confirmed by time dependency analysis. Combination of both MSC and LDCT resulted in a 5-fold reduction of LDCT false positive rate to 3.7%. MSC risk groups were significantly associated with survival (=49.53, $p<0.0001$).

Conclusions: This large validation study indicates that MSC has predictive, diagnostic and prognostic value and could reduce the false positive rate of LDCT improving the efficacy of lung cancer screening.

Disclosure: All authors have declared no conflicts of interest.

25O
INTERNATIONAL COMPARISON OF TREATMENT AND SURVIVAL FOR PLEURAL MESOTHELIOMA, COMBINED ANALYSIS OF 9.014 PATIENTS FROM BELGIUM, THE NETHERLANDS AND ENGLAND

J.P. van Meerbeeck[1], R.A. Damhuis[2], A. Khakwani[3], H. De Schutter[4], A. Rich[3], S.A. Burgers[5] [1]Thoracic Oncology, U.Z.A. University Hospital Antwerp, Edegem, BELGIUM, [2]Comprehensive Cancer Centre, Utrecht, NETHERLANDS, [3]Division of Epidemiology & Public Health, University of Nottingham, Nottingham, UNITED KINGDOM, [4]None, Belgian Cancer Registry, Brussels, BELGIUM, [5]Thoracic Oncology, Netherlands Cancer Institute, Amsterdam, NETHERLANDS

Aim: Pleural mesothelioma is refractory to treatment and has a poor prognosis. Only chemotherapy was proven effective in randomized trials. Novel chemotherapy may increase median survival by several months and was gradually introduced in the period 2003–2006. Little is known about contemporary treatment practice in Europe. To determine patterns of care and current survival rates, three large population-based registries were queried in a uniform manner.

Methods: Data from the Belgian Cancer Registry, the Netherlands Cancer Registry and the UK National Lung Cancer Audit were analyzed for patients diagnosed with pleural mesothelioma as of 2007. Treatment patterns and survival rates were compared between countries.

Results: The study comprised 900, 2.306 and 5.808 patients from Belgium, Netherlands and England, respectively. Fifty-nine percent of patients were 70 years or older and 84% were men. Surgery and radiotherapy patterns varied between countries but comparisons were hampered due to variation in coding practice. Chemotherapy rates decreased with advancing age and chemotherapy was more often applied in Belgium (53%) than in the Netherlands (41%) and England (37%). Median survival was 10,6 months in Belgium versus 9,5 months for England and 9,2 months for the Netherlands. Survival rates decreased with advancing age. After stratification for age and chemotherapy, survival was comparable for the three countries.

Conclusions: Combined analysis of data from three countries with high mesothelioma rates demonstrates that chemotherapy has become standard treatment for younger patients. Less toxic treatment options will be required to improve the prospects for elderly mesothelioma patients.

Disclosure: All authors have declared no conflicts of interest.

26PD
AN INNOVATIVE TECHNOLOGY FOR IN VIVO ISOLATION OF CIRCULATING TUMOR CELLS IN NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS AND IMMUNOFLUORESCENT DETECTION OF ALK PROTEIN

B. Dlugaszewska[1], L. Gasiorowski[2], S. Herold[1], B. Nowack[3], G. Dworacki[4], K. Luecke[5], W. Dyszkiewicz[2] [1]KS, GILUPI GmbH, Potsdam, GERMANY, [2]Department of Thoracic Surgery, University of Medical Sciences, Poznan, POLAND, [3]R&D, GILUPI GmbH, Potsdam, GERMANY, [4]Department of Clinical Immunology, University of Medical Sciences, Poznan, POLAND, [5]GM, GILUPI GmbH, Potsdam, GERMANY

Aim: Circulating tumor cells (CTCs) in lung cancer patients can provide additional information on patient prognosis and treatment efficacy. Currently, CTCs are isolated in vitro from limited volumes of patient blood samples. To overcome this limitation, an innovative device, Detektor CANCER01 (DC01), was used to isolate CTCs in vivo, directly from the bloodstream of lung cancer patients.

Methods: 48 NSCLC patients (stages I-IIIB) and 12 non-cancer patients were enrolled in this study. The DC01 was inserted into a cubital vein through a standard cannula for 30 minutes. The interaction of target CTCs with the device was mediated by an antibody directed against the epithelial cell adhesion molecule (EpCAM). CTC binding was confirmed by immunocytochemistry (ICC) with EpCAM and/or cytokeratines as positive markers, and CD45 for negative cell selection. Enumeration data were available for 34 NSCLC patients and 8 non cancer patients. For 34 patients, blood samples were tested with a reference method (CellSearch).

Results: Using the DC01, we successfully isolated EpCAM-positive tumor cells from the peripheral blood of NSCLC patients. DC01 sensitivity for in vivo CTC isolation was 94% (similar for early and late stage NSCLC patients) compared to the in vitro detection rate of 5.8% (CellSearch). In all matched pairs, the DC01 detected the same number or more CTCs then the CellSearch method. In non-cancer patients, no CTCs were detected (100% specificity of the DC01). Furthermore, the anaplastic lymphoma kinase protein (ALK) was identified by ICC in cell lines captured on DC01.

Conclusions: Due to a high CTC detection rate (>90%), the DC01 may overcome present limitations in the enrichment of CTCs. Its implementation into clinical practice may improve early detection, prognosis and therapy monitoring in NSCLC patients. Tumor cells captured by the DC01 can be subsequently analyzed by immunofluorescence or molecular techniques. This opens the possibility of establishing personalized therapies, e.g. based on the identification of ALK rearrangements or EGFR mutations.

Disclosure: B. Dlugaszewska: GILUPI employee S. Herold: Stock-ownership in GILUPI B. Nowack: GILUPI employee K. Luecke: Stock ownership in GILUPI All other authors have declared no conflicts of interest.

27PD
LUNG CANCER DETECTION WITH CHEST DIGITAL TOMOSYNTHESIS: RESULTS FROM THE SOS OBSERVATIONAL STUDY

L. Bertolaccini[1], A. Viti[1], C. Tavella[2], R. Priotto[2], D. Ghirardo[2], G. Giovinazzo[2], C. Vinay[2], M. Grosso[2], A. Terzi[1] [1]Division of Thoracic Surgery, Azienda Ospedaliera St. Croce e Carle, Cuneo, ITALY, [2]Radiology, Azienda Ospedaliera St. Croce e Carle, Cuneo, ITALY

Aim: Low-Dose Computed Tomography (LDCT) screening for Lung Cancer (LC) is currently suggested (grade of recommendation = 2B); nevertheless, radiation exposure and costs are still a problem. In Baseline results of SOS study, single-arm observational study of chest Digital Tomosynthesis (DT) in a LC at-risk population, we have shown a LC detection rate comparable to LDCT (0.98%), low effective radiation dose (0.13 mSv), and 1/6 cost of LDCT. DT is limited angle tomography that allows reconstruction of multiple image planes and provides high-resolution images in coronal planes. We present the results of the SOS study.

Methods: Sample size of 2,000 subjects (current or former smoker >20 pack-years; age 45 – 75 years; no previous cancer in 5 years before study) was planned on basis of incidence and mortality data reported in Piedmont Cancer Registry. DT was performed one-year later in negative Baseline subjects. In subjects with uncertain nodule >5 mm or with multiple nodules, first-line LDCT was warranted.

Results: 1,703 candidates (mean age = 60 years, range = 49 – 73) underwent First Round DT (92% of baseline, drop out = 0.4%). Lung nodules >5 mm were detected in 13 (0.7%) subjects; none had any nodules at Baseline DT. There was one false positive at CT; 2 subjects had follow-up schedule. Surgery was performed in 10. Histology revealed organizing pneumonia = 2, tuberculosis nodule = 1, intrapulmonary lymph node increased in size = 1, and lung metastasis from biliary tree adenocarcinoma (operated more than 10 years before) = 1. LC was diagnosed and resected by VATS lobectomy in 5 subjects (Table). LC detection rate at First Round was 0.3% (5/1703).

Table. Tumor stage and histology in LC diagnosed by chest DT at Baseline and First Round.

	No. of Subjects	
TUMOR STAGE	**Baseline**	**First Round**
IA	6	4
IB	2	
IIA	2	1
IIB	1	
IIIA	1	
IIIB	1	
IV	5	
HISTOLOGY	**Baseline**	**First Round**
Adenocarcinoma	10	1
Squamous cell carcinoma	7	4
Carcinoid	1	

Conclusions: First Round results on DT in early detection of LC are as good as for baseline. LC detection rate is comparable to LDCT and achieved at far lower costs and radiation dose. DT is a possible first-line LC screening tool and is effective in high-risk subjects follow-up. Nevertheless, studies on larger number of subjects are needed to confirm these results.

Disclosure: All authors have declared no conflicts of interest.

28PD
MEASURING THE POPULATION IMPACT OF INTRODUCING STEREOTACTIC ABLATIVE RADIOTHERAPY (SABR) FOR STAGE I NSCLC IN CANADA

A.V. Louie[1], G.B. Rodrigues[2], D.A. Palma[2], S. Senan[1] [1]Radiation Oncology, VU University Medical Center, Amsterdam, NETHERLANDS, [2]Radiation Oncology, London Regional Cancer Program, London, CANADA

Aim: SABR achieves long-term local control rates of up to 90% in stage I NSCLC. We used the Cancer Risk Management Model (CRMM) to estimate the health and economic impact of introducing SABR for stage I NSCLC in Canada.

Methods: The CRMM employs Monte Carlo microsimulation of all Canadians from birth to death. The lung cancer module outputs were previously validated internally using Health Canada census data, and externally with Canadian Cancer Registry data. We updated costs using the Ontario schedule of fees and benefits, or consumer price index (Bank of Canada) to calculate 2013 Canadian dollars, discounted at a 3% rate. Our baseline model assumed that for stage I NSCLC, 75% of patients undergo surgery (lobectomy, sublobar resection, or pneumonectomy), 12.5% radiotherapy (RT), and 12.5% best supportive care (BSC). SABR was introduced in 2008 as an alternative to sublobar resection, RT, and BSC at rates reflective of the current literature. Incremental cost effectiveness ratios (ICER) were calculated; a willingness to pay threshold of $100,000 per QALY was used from the healthcare payer perspective.

Results: The total cost for 25,085 new cases of lung cancer in 2013 was calculated to be $608,002,599. Median upfront costs for the 4,318 stage I cases were: RT ($7,646.98), SABR ($8815.55), sublobar resection ($12,161.17), lobectomy ($16,266.12), pneumonectomy ($22,940.59), and BSC ($14.582.87). SABR dominated (higher QALY, lower cost) RT, sublobar resection, and BSC (Table 1). RT had lower initial costs than SABR, which were offset by subsequent costs associated with recurrence. Lobectomy was cost-effective when compared to SABR, with an ICER of $55,909.

Table: Cost-effectiveness of SABR

Scenario when SABR is introduced	Incremental Cost ($)	Incremental QALYs	ICER ($/QALY)
RT	-5,187,816	1693	Dominated
BSC	-9,951,612	660	Dominated
Sublobar resection	-3,288,656	2353	Dominated
Lobectomy	-164,370,264	-294	55909

Conclusions: The use of SABR for stage I NSCLC is projected to result in significant cost savings and survival gains in Canada. In this model, SABR dominated most alternative treatments, but lobectomy was the most cost-effective treatment option and should be employed where appropriate.

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29P
ASSOCIATION OF POLYMORPHISMS IN THE MICRORNA TARGET SITES AND SURVIVAL OF PATIENTS IN EARLY-STAGE NON-SMALL-CELL LUNG CANCER

J.E. Choi[1], M.J. Hong[1], J. Jang[1], H. Jeon[1], Y.Y. Choi[1], J.Y. Park[2] [1]Department of Biochemistry and Cell Biology, School of Medicine, Kyungpook National University, Daegu, KOREA, [2]Internal Medicine, Kyungpook National University School of Medicine, Daegu, KOREA

Aim: MicroRNAs (miRNAs) have a key role in carcinogenesis through the negative regulation of their target genes. This study was conducted to investigate the associations between single-nucleotide polymorphisms (SNP) located in the microRNA target sites (poly-miRTSs) and survival of patients with early-stage non–small cell lung cancer (NSCLC), and to identify the lung cancer prognosis-specific poly-miRTS.

Methods: In the discovery cohort, 392 poly-miRTSs were investigated in 357 patients using a Sequenom mass spectrometry-based genotype assay. A replication study was performed on an independent patient population (n = 479). Luciferase assays were conducted to examine functional relevance of a potentially functional poly-miRTSs.

Results: Of the 392 SNPs, 289 poly-miRTSs were excluded (failed genotype, genotype call rate < 90%, minor allele frequency (MAF) < 10% or Hardy-Weinberg equilibrium Equation P value < 0.05) from further analysis. 14 SNPs were significantly associated with survival outcomes in a discovery study. Among the fourteen miRTSs, one miRTS (KRT81 rs3660) were found to be associated with survival outcomes in a validation cohort. In combined analysis, Patients with the rs3660 CC genotype had a significantly decreased overall survival (OS) compared with patients with GG+GC genotype (adjusted hazard ratio [aHR] for OS, 0.65; 95% Confidence Interval [CI] 0.50–0.85; P= .001). An increased expression of the reporter gene for the C allele of rs3660 was observed then compared with the common G allele by luciferase assay.

Conclusions: The rs3660G>C affects KRT81 expression and thus influences survival in early-stage NSCLC. The analysis of the rs3660G>C polymorphism can be useful to identify patients at high risk of a poor disease outcome.

Disclosure: All authors have declared no conflicts of interest.

30P
EVALUATION OF EPIDERMAL GROWTH FACTOR RECEPTOR MUTATIONS IN BULGARIAN PATIENTS WITH NON-SMALL CELL LUNG CANCER

S. Bichev[1], D.M. Marinova[2], Y. Slavova[2], A. Savov[1] [1]National Genetic Laboratory, University Hospital of Obstetrics and Gynecology "Maichin Dom", Sofia, BULGARIA, [2]Pulmonology, University Hospital for Pulmonary Diseases "St. Sofia", Sofia, BULGARIA

Aim: The aim of the present study is to determine the prevalence of EGFR mutations in non-small cell lung carcinomas (NSCLCs) in the East European Bulgarian population in different histological subtypes, in cytological vs. histological samples and in primary lung carcinomas vs. metastatic locations.

Methods: Our cohort consisted of 1427 tissue specimens from patients with NSCLC. DNA was extracted from eighter paraffin embedded tissues or cytology slides and analyzed for TKI activating mutations in EGFR gene by real-time PCR technique.

Results: EGFR mutations were significantly more often in: female (n=355,69 positive) than in male (n=1072,58 positive) patients (19.4% vs. 5.4%, p<0.001); adenocarcinomas (n=576,72 positive) than in squamous cell carcinomas (n=676,42 positive) or other types (n=118,9 positive) (12.5%, 6.2%, and 7.6% respectively, p=0.009); in never smokers (n=192,44 positive) compared to ex-smokers (n=434,37 positive) and current smokers (n=662,28 positive) (22.9% vs. 8.5% vs. 4.9% respectively, p<0.001). There wasn't any significant difference between the frequency of EGFR mutations in primary tumors (n=1083) compared to metastases (n=269) (7.9% vs. 11.2%,p=0.092); or in histological samples (n=1365, 95.7%) compared to cytological samples (62,4.3%) (8.9% vs. 8.1%, p=0.813). From patients with TKI activating mutations 66 had deletions in 19th exon (52%), 54 - L858R point mutation in 21st exon (42.5%), 3 - L861Q point mutation in 21st exon (2.4%), 3 - S768I point mutation in 21st exon (2.4%), and 1 - G719X point mutation in 18th exon (0.8%). Also, 26 (TKI resistant) T790M point mutations in exon 20 were detected, none in combination with another (activating) EGFR mutation – 1.8% of all cases.

Conclusions: Overall frequency of EGFR mutations in lung adenocarcinomas in the studied East European cohort is within the frequency range of North American and West European populations, whereas EGFR mutation frequency in SCC is higher than in any population described to date. All materials are suitable for EGFR molecular testing, even cytological samples, regardless of origin – primary or metastatic.

Disclosure: All authors have declared no conflicts of interest.

31P
SERUM TUMOR MARKERS CEA, CYFRA 21-1 AND ANTI-P53 IN PATIENTS WITH LUNG CANCER

F. Lumachi[1], F. Mazza[2], A. Del Conte[3], G.B. Chiara[4], S.M.M. Basso[4] [1]Department of Surgery, Oncology & Gastroenterology, University of Padua, School of Medicine, Padova, ITALY, [2]Pneumology, S. Maria degli Angeli Hospital, Pordenone, ITALY, [3]Medical Oncology, S. Maria degli Angeli Hospital, Pordenone, ITALY, [4]Surgery 1, S. Maria degli Angeli Hospital, Pordenone, ITALY

Aim: Lung cancer is one of the most common neoplasms throughout the world, and the most devasting cause of cancer-related death. The 5-year survival rate is very low, accounting for approximately 15%, and it has changed minimally over the past 25 years (1). The poor survival is attrubutable to the fact that the majority of cases are diagnosed when the disease is already metastatic. At this stage, the therapeutic options are restricted to palliative systemic chemotherapy or radiation therapy. Only for patients diagnosed and treated at early stage (Stage I) the 5-year survival is relatively good, ranging between 50% and 80% (2). Several serum tumor markers have been tested in patients with lung cancer, including carcinoembryonic antigen (CEA), cytokeratin 19 fragments (CYFRA 21-1), squamous cell carcinoma antigen, neuron-specific enolase (NSE), and more recently anti-p53 antibody circulating

markers. The aim of this study was to evaluate the usefulness of serum CEA, CYFRA 21-1, and anti-p53 assay in patents with lung cancer.

Methods: Data regarding a group of 42 patients (27 men, 15 women, median age 62 years, range 51–78 years) with confirmed Stage I lung cancer, and a group of 45 sex- and age-matched smokers patients with benign chronic pulmunary diseases underwent serum CEA, CYFRA 21-1, and anti p53 measement.

Results: The sensitivity, specificity, positive predicting vaule, negative predicting value, and accuracy were the followings: 47.6%, 80.0%, 68.9%, 62.1%, and 64.0% for CEA (chi-squared 0.0006); 40.5%, 92.8%, 85.0%, 60.9%, 67.0% for CYFRA 21-1 (chi squared 0.00031); 30.9%, 95.2%, 86.7%, 57.9%, 63.0% for anti-p53 (chi squared 0.00017), respectively.

Conclusions: All the tested serum markers had low sensitivity (from 30.9% to 47.6%) in detectiing cancer, but good specificity, ranging between 95.2% and 80.0%. However, the accuracy ranged from 63% to 67%, and thus they were not useful for early diagnosis of lung cancer. References: 1. Kumar S et al. Plasma nucleosome leves might predict response to therapy in patients with advanced non-small.cll lung cancer. Clin Lung Cancer 2010; 11 36-40. 2. Park Y et al. Usefulness of serum anti-53 antibody assay for lung cancer diagnosis. Ach Patol Lab Med 201; 135: 1570–1575.

Disclosure: All authors have declared no conflicts of interest.

33P
RADIOGRAPHIC SCREENING FOR LUNG CANCER IN VARESE, ITALY: COST-EFFECTIVENESS ANALYSIS

A. Imperatori[1], P. Pertile[2], A. Poli[3], N. Rotolo[1], M. Castiglioni[1], D. Di Natale[1], W. Mantovani[3], M. Paolucci[4], A. Paddeu[5], L. Dominioni[1] [1]Center for Thoracic Surgery, University of Insubria, Varese, ITALY, [2]Department of Economics, University of Verona, Verona, ITALY, [3]Department of Public Health, University of Verona, Verona, ITALY, [4]Department of Radiology, Ospedale S. Antonio Abate, Gallarate, ITALY, [5]Respiratory Care Unit, Ospedale S. Anna, San Fermo della Battaglia, Como, ITALY

Aim: Screening for lung cancer (LC) has recently been shown to reduce LC mortality, however the cost-effectiveness of LC screening in the community is uncertain. In the PREDICA project (ISRCTN90639073), an observational population-based chest X-ray (CXR) screening that compared the screening invitees (PREDICA Cohort) to the local reference population receiving National Health Service (NHS) usual care (Control Group), we showed that screening reduced LC mortality by 18%. The present study analyzes in the PREDICA Cohort the cost-effectiveness of CXR screening for LC.

Methods: In the PREDICA project, all smokers of >10 pack-years, 45–75 years old, resident in 50 communities of the Varese Province, screening-eligible, in 1997 were invited by their general practitioner to a programme of five annual CXR screenings. The entire invitation-to-screen cohort (n=5,815 subjects) received NHS usual care, with the addition of CXR exams in volunteer participants (1,244 subjects, 21% of invitees). All invitees (participants and nonparticipants) were followed up through December 2006. For each of the 245 LCs diagnosed in the invitees during the 9.5-year follow-up, and for all 156 Control Group LCs, survival was divided into 5 periods with specific quality of life (QoL) indexes obtained from the literature. Cost of all LC-related events and interventions was obtained from NHS tariff (year 2012) whenever possible, or analytically estimated. Costs and utilities were discounted on a monthly basis. Correction for censoring of individuals alive at the end of follow-up was based on the median of non-censored individuals, conditioning on the length of survival. Correction for lead time bias was included.

Results: The cost-effectiveness of CXR screening was respectively: 21,588 € per Quality-Adjusted Life Year (QALY) for participants vs. controls; 23,865 € per QALY for all invitees (participants and nonparticipants) vs. controls. These estimates were robust to various assumptions on QoL indexes available. A probabilistic sensitivity analysis based on Monte-Carlo simulations is under way.

Conclusions: The results show that a programme of CXR screening for LC should be seriously considered as a potentially cost-effective strategy.

Disclosure: All authors have declared no conflicts of interest.

34P
THE DESCRIPTIVE EPIDEMIOLOGY OF LUNG CANCER: AN INTERNATIONAL COMPARISON OF INCIDENCE AND MORTALITY

Z. Zaidi, A. Mahnane, S. Laouamri, M. Hamdicherif Epidemiology, University hospital of Setif, Setif, ALGERIA

Aim: The global burden of cancer continues to increase largely because of the aging and growth of the world population alongside an increasing adoption of cancer-causing behaviors, particularly smoking, in economically developing countries. Lung cancer is the leading cancer site in males, comprising 17% of the total new cancer cases and 23% of the total cancer deaths. The link between tobacco and lung cancer was established more than sixty years ago, smoking prevalence is higher in men than women in most countries worldwide. This communication presents the latest international descriptive epidemiological data for lung cancer, including incidence and mortality in the worldwide.

Methods: Incidence and mortality rates (number of cases or deaths per 100,000 persons per year) were estimated in GLOBOCAN database (version 1.2), which presents estimates by country, using the most recently available data collected at the International Agency for Research on Cancer IARC for 2008 and presented on may 2011.

Results: Lung cancer was the most commonly diagnosed cancer as well as the leading cause of cancer death in males in 2008 globally. Among females, it was the fourth most commonly diagnosed cancer and the second leading cause of cancer death.It accounts for 13% (1.6 million) of the total cases and 18% (1.4 million) of the deaths in 2008. *In males, the highest lung cancer incidence rates are in Eastern and Southern Europe, North America, Micronesia and Polynesia, and Eastern Asia, while rates are low in sub-Saharan Africa. *In females, the highest incidence rates are found in North America, Northern Europe, and Australia/New Zealand. Despite their lower prevalence of smoking (less than 4% adult smokers), Chinese females have higher lung cancer rates (21.3 cases per 100,000 females) than those in certain European countries such as Germany (16.4) and Italy (11.4), with an adult smoking prevalence of about 20%. Very low rates are still estimated in Middle and Western Africa (2.8 and 3.1 per 100,000 respectively).

Conclusions: Most lung cancers could be prevented by reducing smoking initiation among adolescents and increasing smoking cessation among adults. This requires a comprehensive tobacco control program includes raising the price of tobacco products through excise taxes, banning smoking in public places, restricting tobacco advertising and promotion.

Disclosure: All authors have declared no conflicts of interest.

35P
THE RISK LEVEL OF CANCER AMONGST MEN WHO WERE EXPOSED TO SECOND-HAND SMOKE AT CHILDHOOD

M.O. Tagbarha Epidemiology, University of Abuja, Abuja, NIGERIA

Aim: To ascertain the level of risk of cancer amongst men severely exposed to environmental tobacco smoke at child hood.

Methods: We conducted this study among 1,520 men who were diagnosed for lung cancer for a period of 6 years from 2006–2012. We checked hospital records at childhood for frequent hospitalization related to tobacco effects like middle ear infections, pneumonia, bronchitis and worsened asthma conditions.

Results: We were able to show the relationship between exposure to environmental tobacco smoke during childhood and cancer risk. Out of the total number of participants, 2.5% percent (31 men) had been exposed to environmental tobacco smoke (ETS) at childhood. We found that the overall cancer risk was greater for individuals with exposures to environmental tobacco smoke during both childhood and adulthood than for individuals with exposure during only one period. When specific cancer sites or types were considered, it was found that leukemia and lymphoma among these men were significantly related to exposure to maternal passive smoke before 10 years of age.

Conclusions: Results of epidemiologic studies including this one provide evidence that exposure of children to environmental tobacco smoke is associated with increased rates of lower respiratory illness and increased rates of middle ear effusion, asthma, and sudden infant death syndrome. Exposure during childhood to environmental tobacco smoke may also be associated with development of cancer during adulthood.

Disclosure: All authors have declared no conflicts of interest.

36P
EVALUATION OF A TOBACCO CESSATION CLINIC IN SOUTH INDIA - WHERE DO WE STAND?

B. Sivanesan[1], P. Alagappan[2], T. Balaji[3] [1]Medical Oncology, G Kuppuswamy Naidu Memorial Hospital, Coimbatore, INDIA, [2]Counselling, Coimbatore Cancer Foundation, Coimbatore, INDIA, [3]Oncology, G Kuppuswamy Naidu Memorial Hospital, Coimbatore, INDIA

Aim: India is the second largest consumer of tobacco in the world with an estimated 120 million smokers and 75 million smokeless tobacco users. In India, the annual deaths from smoking are expected to rise from the present 930,000 to 1 million during 2010's. In the west, the effectiveness of smoking cessation programmes are well established. Smoking cessation programmes are few and far in India. We evaluated a pilot tobacco cessation clinic at a tertiary Cancer Care Centre in South India.

Methods: The Tobacco Cessation Clinic was started in November 2009 and functions 5 days a week from 9.00AM to 4.00PM. A trained counselor provided individual counseling and the medical management was done by a Thoracic Medical Oncologist. The programme was evaluated in terms of outcome.

Results: From November 2009 to November 2012, 2906 tobacco users attended the Clinic. Out of these, 84% were Cardiac patients, 8% were Cardio-thoracic patients, 3% were Pulmonology patients, 2% were Oncology patients and 3% were from general population. The Average Fagerstrom Addiction Score was 7.5/11. Majority of the tobacco users (93%) were managed by counselling. 5% were treated with Nicotine Chewing gum. Another 1% with Nicotine patch. 2% were treated with Vermicline. 1960 tobacco users were followed up for 6 months. The 7 day point prevalence quit rate was 33%. 40% had reduced their level of tobacco use. 26% had relapsed or had no change in their habit. The quit rate among the general population was only 11%.

Conclusions: Tobacco Cessation Clinic definitely was successful in reducing or quitting the tobacco usage. The high quit rates is essentially due to the fact that majority of these tobacco users were hospital based and suffered some form of morbidity due to tobacco use and were more willing to quit tobacco. The quit rate among the general population tobacco users was only11%. We plan to increase our coverage of general population by low cost advertisements and improve Quit rates in the general population by more aggressive follow up.

Disclosure: All authors have declared no conflicts of interest.

37P
LEVEL OF AWARENESS OF LUNG CANCER RISK FACTORS, SIGNS, SYMPTOMS AND SAFE PRACTICES AMONG COLLEGE TEACHERS OF DIFFERENT STATES IN INDIA: DO AWARENESS PROGRAMMES HAVE AN IMPACT ON ADOPTION OF SAFE PRACTICES?

A. Shankar, G.K. Rath, R. Bhandari, P.K. Julka, K. Kishor Radiation Oncology, All India Institute of Medical Sciences, New Delhi, INDIA

Aim: The aim of this study was to determine the impact of awareness programmes on change in adoption of safe practices in prevention and early detection.

Methods: This assessment was part of pink chain campaign on cancer awareness. During the events in 2011- 2013 at various womens colleges in various states in India, Pre test was followed by awareness program consisting of lectures on preventive aspects of lung cancer with special note of tobacco and smoking and an interactive session. Post test using the same questionnaire was conducted at the end of the interactive session. Literatures related to cancer awareness were sent regularly for one year to email ids provided. After 6 months and 1 year, the same questionnaires were mailed to the participants to see the changes in practice. Data were collected and analyzed by using statistical software STATA 10.1. *P* values less than 0.05 were taken as significant.

Results: A total of 1257 out of 1346 teachers participated in the study (93.38%). The same questionnaire was answered by 1109 and 795 teachers at the end of 6 and 12 months, respectively. Mean age was 42.46 years (28–59 yrs). Among teachers, 31.42% were smokers and 35.73% were alcoholic. Correct risk factors mostly indicated by teachers were smoking (89%), Secondhand smoke (37%), and tuberculosis (36%). Lung cancer symptoms known to teachers were Persistent cough (24%), hemoptysis (36%), chest pain (12%), and voice change (12%). Magazines and newspapers were sources for knowledge in 60%, and 30% of teachers were educated by doctors. There was a significant increase in knowledge regarding lung cancer at 6 months and this was sustained at 1 year with significant changes in smoking and alcohol habits. Major reasons not going for checkup were ignorance (50%), lethargic attitude (44.87%) and lack of time (34.61%). 3.81% teachers contacted us within 1 year for chest complaints. Three teachers (0.23%) were found to be positive for cancer, and one for lung cancer.

Conclusions: Knowledge of lung cancer was very low among teachers. Though there was significant change in addiction habits, there was not much improvement in people undergoing regular check ups. To inculcate safe practices in the lifestyle of people, awareness programmes such as the pink chain campaign should be conducted more widely and frequently. Further, creating awareness among health care providers is another issue which has to be looked into.

Disclosure: All authors have declared no conflicts of interest.

TRANSLATIONAL RESEARCH

38O
PD-L1 AND PD-1 EXPRESSION IN MOLECULARLY SELECTED NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS

A. D'Incecco[1], M. Andreozzi[2], V. Ludovini[3], E. Rossi[4], L. Landi[1], G. Minuti[1], G. Fontanini[5], L. Crinò[3], L. Terracciano[2], F. Cappuzzo[1] [1]Istituto Toscano Tumori, Oncologia Medica, Ospedale Civile, Livorno, ITALY, [2]Department of Pathology, Basel Hospital University, Basel, SWITZERLAND, [3]S.C. Oncologia Medica, Ospedale S. Maria della Misericordia, Perugia, ITALY, [4]Oncologia Medica, Istituto Toscano Tumori, Ospedale Civile, Livorno, Italy, Livorno, ITALY, [5]Anatomia Patologica, Azienda Ospedaliera Universitaria Pisana, Pisa, ITALY

Aim: The programmed death 1 (PD-1) receptor is an inhibitory T-cell receptor with two known ligands, PD-L1 and PD-L2 (programmed death-ligand 1 and 2). Aim of the present study was to evaluate PD-L1 and PD-1 expression in a cohort of molecularly selected NSCLC patients.

Methods: The study was conducted in a cohort of 125 NSCLC patients, including 56 (44.8%) EGFR mutated, 29 (23.2%) KRAS mutated, 10 (8.0%) ALK translocated and 30 (24.0%) EGFR/KRAS/ALK wild-type (wt), defined as triple negative. PD-L1 and PD-1 expression was assessed by immunohistochemistry (IHC), considering as positive a staining intensity ≥ 2 in more than 5% of cells.

Results: PD-L1 was successfully evaluated in 123 specimens and PD-L1 positive expression was observed in 68 (54.4%) cases. PD-L1 positivity was significantly associated with presence of EGFR mutations ($p<0.0001$), while no association was observed with other biomarkers. PD-1 was assessed in 122 specimens and PD-1 expression was demonstrated in 43 (34.4%) cases. PD-1 positive expression was significantly associated with KRAS mutated status ($p=0.005$), while no association was observed with other biomarkers. Among the 95 patients treated with gefitinib or erlotinib and evaluable for

response, PD-L1 positive (N=49, 51.6%) patients had significantly higher RR (61.2% versus 34.8%, p=0.010), significant longer TTP (11.7 months versus 5.7 months, p<0.0001) and longer OS (21.9 months versus 12.5 months, p=0.087) than PD-L1 negative (N=46, 48.4%) patients. In the subset of EGFR mutated patients treated with EGFR-TKIs and evaluable for response (N=55), PD-L1 positive (N=39, 70.9%) cases showed a longer TTP (13.0 months versus 8.5 months, p=0.011) and a trend of better OS (29.5 months versus 21.0 months, p=0.752) than PD-L1 negative (N=16, 29.1%) patients. No differences in terms of RR, TTP and OS were identified in PD-1 positive versus PD-1 negative patients.

Conclusions: Our results suggest a strong correlation between PD-L1 expression and EGFR mutation and between PD-1 expression and KRAS mutations, supporting further investigation of anti-PD-L1 or anti-PD-1 agents in combination with targeted therapies.

Disclosure: All authors have declared no conflicts of interest.

39PD
ULTRA-DEEP SEQUENCING OF CIRCULATING FREE DNA TO IDENTIFY PREDICTIVE, MUTATED HSP90 CLIENTS IN GALAXY-1 (NCT01348126), A RANDOMIZED PHASE 2B STUDY OF GANETESPIB PLUS DOCETAXEL VERSUS DOCETAXEL ALONE IN 2ND LINE ADVANCED NSCLC

D. Fennell[1], J. Shaw[2], I. El-Hariry[3], V.M. Vukovic[3], V. Reichert[4], L.M. Martins[5] [1]Thoracic Medical Oncology, University Hospitals of Leicester Leicester Royal Infirmary, Leicester, UNITED KINGDOM, [2]Cancer Studies and Molecular Medicine, University of Leicester, Leicester, UNITED KINGDOM, [3]Clinical, Synta Pharmaceuticals, Lexington, UNITED STATES OF AMERICA, [4]Translational Research, Synta Pharmaceuticals, Lexington, UNITED STATES OF AMERICA, [5]Cell Death Regulation Laboratory, MRC Toxicology Unit, Leicester, UNITED KINGDOM

Aim: Inhibition of Hsp90, a key molecular chaperone required for activation of many oncoproteins critical to NSCLC growth and aggressiveness, can lead to cancer cell death. Ganetespib (G) is a 2nd generation Hsp90 inhibitor (Hsp90i) that has shown single agent clinical activity in patients with tumors harboring ALK, KRAS, HER2, and BRAF mutations. Circulating free DNA (cfDNA) is present at low levels in plasma of healthy individuals allowing detection of somatic mutations by deep sequencing. The aim of this work was to determine the mutational spectrum of patients enrolled into the GALAXY-1 trial using this liquid biopsy strategy.

Methods: Prospective exploratory analysis was performed to identify plasma-borne somatic mutations as predictors of clinical outcome with G in GALAXY-1. Plasma samples were collected from approximately 318 patients with adenocarcinoma at baseline prior to initiation of treatment, during cycles 1 and 2, and end of treatment. cfDNA samples were evaluated using the Ion AmpliSeq™ Cancer Panel on the Ion Torrent |PGM platform to survey 739 amplicons in 46 cancer genes at up to 6000x depth.

Results: CfDNA targeted sequence analysis reached the quality control (QC) threshold in 94% of samples. Analysis of the first 105 patients revealed multiple concurrent mutations in HSP90 client proteins. Sequencing of DNA from a larger cohort is underway. Longitudinal sampling of plasma has been conducted to monitor temporal evolution of the penetrance of mutations.

Conclusions: Ultra-deep re-sequencing of multiple somatic mutations in circulating cfDNA is feasible, and can be used to identify biomarkers of response to G. This represents a new approach to biomarker discovery in the context of phase 2 trials. Results of analysis of cfDNA from the large cohort enrolled in GALAXY-1 will be presented.

Disclosure: I. El-Hariry: Full-time employee of Synta Pharmaceuticals and stock ownership in this company V.M. Vukovic: Synta pharmaceuticals: stock ownership and full-time employee V. Reichert: Synta Pharmaceuticals: full-time employee, stock ownership All other authors have declared no conflicts of interest.

40P
CLINICAL IMPLICATIONS OF RE-BIOPSY IN PATIENTS WITH NSCLC HARBOURING EGFR MUTATIONS WITH ACQUIRED RESISTANCE TO EGFR TYROSINE KINASE INHIBITORS

A. Passaro[1], B. Gori[2], A. Leone[3], P. Graziano[3], F. de Marinis[1] [1]Division of Thoracic Oncology, European Institute of Oncology, Milan, ITALY, [2]1st Pneumo-oncological Unit, Azienda Ospedaliera S.Camillo Forlanini, Rome, ITALY, [3]Pathology Unit, Azienda Ospedaliera S.Camillo Forlanini, Rome, ITALY

Aim: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are the gold standard for the treatment of patients with advanced or metastatic NSCLC harbouring EGFR mutations. Since aquired resistance occurs at disease progression (PD), increasing efforts have led to the discovery of counter mutations in EGFR exon 20 and C-MET amplification related to molecular resistance. We evaluated the incidence of these mutations in an Italian cohort of EGFR mutated NSCLC patients who had a progression disease after an oral EGFR TKI treatment.

Methods: We evaluated 17 pts, 12 women and 5 men, 15 with adenocarcinoma and 2 with squamous cell carcinoma. 12 pts had an EGFR exon 19 deletion and 5 pts a L858R mutation in exon 21. At first progression disease, after a TKI therapy, after previous written informed consent, a second biopsy was performed on the PD site to reassess the EGFR mutational status and c-MET amplification. Exon 20 T790M mutation analysis was performed on 14 pre-treatment and all post-treatment specimens by direct sequencing while c-MET was studied by FISH on 13 rebiopsies. 10 pts received oral TKIs as first line treatment, while the other 7 pts in second line.

Results: In the second biopsy specimen the T790M mutation was detected in 8 pts (47%), while a c-MET specific amplification was identified in 4 of 13 evaluated pts (31%). In one patient, T790M mutation and c-MET amplification were present in a concomitant fashion while 3 pts exhibited a c-MET amplification without any T790M alteration. Therefore clinical resistance was explained in the present cohort by novel EGFR T790M and/or c-MET molecular alterations in 11 assessed patients (65%). In 2 cases the original EGFR TKI-sensitive mutation found in the first diagnostic specimen evaluated was not detected on the site of disease progression. We had 1/5 pre-treatment EGFR T790M mutations defined by Real Time PCR and one of the others by direct sequencing. We did not observe any change in histotype.

Conclusions: EGFR T790M mutations and c-MET amplifications are common in Italian patients treated with oral TKIs that eventually develop drug resistance. Since new generation drugs are currently being developed against EGFR (irreversible TKIs) or c-MET, a "molecular follow-up" will allow the identification of pts eligible for future treatment options.

Disclosure: All authors have declared no conflicts of interest.

41P
CIRCULATING TUMOR CELLS AS PREDICTOR OF RESPONSE TO PLATINUM AND PEMETREXED CHEMOTHERAPY IN PATIENTS WITH ADVANCED ADENOCARCINOMA OF THE LUNG – AN UPDATE ON AN ONGOING STUDY

F. Grossi[1], E. Rijavec[1], G. Barletta[1], C. Sini[1], A. Truini[1], A. Alama[1], M.G. Dal Bello[1], S. Coco[1], M. Truini[2], C. Genova[1] [1]Lung Cancer Unit, IRCCS AOU San Martino IST - Istituto Nazionale per la Ricerca sul Cancro, Genova, ITALY, [2]Department of Pathology, IRCCS AOU San Martino IST - Istituto Nazionale per la Ricerca sul Cancro, Genova, ITALY

Background: Circulating Tumor Cells (CTC) are cells spread from the primary tumor into the bloodstream; CTC are involved in the development of distant metastases and are associated with aggressive disease.The aim of this study is to evaluate the correlation between the numeric variation of CTC in the blood of patients (pts) with advanced adenocarcinoma (ADK) of the lung during chemotherapy (CHT) and the radiological response to explore their potential role as early predictor of treatment response.

Methods: Blood samples and CT-scans were obtained at baseline from pts with ADK candidate for first-line CHT with carboplatin or cisplatin and pemetrexed. Blood samples and CT-scans were repeated after 2 cycles. Radiologic responses were assessed with RECIST 1.1. CTC were collected from blood through a filtration-based device (ScreenCell®, Sarcelles France) able to isolate and sort CTC by size. CTC were enumerated and characterized through H&E stain and immunofluorescence (IF). Radiological variations in tumor size were compared with variations in CTC count.

Results: Baseline CTC and CT-scans were obtained from 45 pts; male/female:28/17, median age:67 years (range:45–81); to date, 20 pts underwent evaluation after 2 cycles, while 6 pts died before assessment, and 1 retired consent; 18 pts are expected to be assessed within the following weeks. H&E revealed that CTC were morphologically compatible with tumor cells and they were present in all pts at baseline (range 1–67 CTC/ml); IF showed CK7 positivity. Two pts achieved partial response (PR), 5 pts showed progressive disease (PD), and 13 pts achieved stable disease (SD) as best response. Variation of CTC count was concordant with variation of tumor size in 14/20 (70%); in particular, reduction in CTC count was observed in 8 pts out of 11 (73%) with reduced tumor size, while increase in CTC count was observed in 6 pts out of 9 (67%) with increased tumor size.

Conclusions: This study demonstrates the feasibility of isolating CTC in all advanced ADK pts using a size-based low cost technique. The concordance between CTC counts and CT-scans suggests that CTC may represent a predictive factor of treatment outcome.

Disclosure: All authors have declared no conflicts of interest.

42P
GEMCITABINE (GEM) SENSITIVITY-RELATED GENE MRNA EXPRESSION AND CLINICAL OUTCOME IN ADVANCED NON-SMALL CELL LUNG CANCER (ANSCLC)

G. Ioannidis[1], C. Papadaki[2], E. Lagoudaki[3], E. Tsakalaki[2], M. Trypaki[2], E. Stathopoulos[3], D. Mavroudis[4], V. Georgoulias[4], J. Souglakos[4] [1]Department of Oncology, Nicosia General Hospital of Cyprus and Laboratory of Tumor Cell Biology, School of Medicine, University of Crete, Heraklion, GREECE, [2]Laboratory of Tumor Cell Biology, School of Medicine, University of Crete, Heraklion, GREECE, [3]Department of Pathology, University General Hospital of Heraklion, Heraklion, GREECE, [4]Department of Medical Oncology, University General Hospital of Heraklion and Laboratory of Tumor Cell Biology, School of Medicine, University of Crete, Heraklion, GREECE

Aim: Gem remains a viable first-line treatment option for aNSCLC, either as monotherapy or within combination regimens. We report the updated total results of an exploratory study on the potential predictive value of tumor mRNA levels of six chemosensitivity-related genes for clinical outcome in this setting.

Methods: By real-time quantitative polymerase-chain reaction, we retrospectively analyzed mRNA expression of the human equilibrative nucleoside transporter-1, deoxycytidine kinase, cytidine deaminase (CDA), breast cancer 1, early-onset, ribonucleotide reductase M1 (*RRM1*) and M2 (*RRM2*) genes in microdissected, formalin-fixed, paraffin-embedded primary tumor specimens from 152 chemonaïve, stage wet-IIIB and IV (UICC 6th TNM edition) NSCLC patients treated with Gem, either as monotherapy (G) or combined with platinums (GC/Cb), taxanes (GD/P), or vinorelbine (GV) in the context of Hellenic Oncology Research Group clinical trials. Relative gene expression was quantified by the $2^{-\Delta\Delta Ct}$ method and normalised to β-actin. Individual and combined gene-transcription patterns were statistically evaluated for association with clinicopathological features and outcome endpoints.

Results: Patient, tumour, and therapy characteristics were as follows: median age, 64 years; males, 87%; ECOG performance status 0–1, 89%; stage IV, 71%; adenocarcinomas, 56% and squamous-cell carcinomas, 30%; GC/Cb: 20%, GD/P and GV: 71%. Patients with samples successfully amplified for the potentially unfavorable genes *RRM1, RRM2* and *CDA* were classified into high- (17%), low- (20%) and mixed- (62%) coexpression groups defined by the corresponding median mRNA levels. Overall response and disease control rates (DCR) were significantly higher for the low- compared to the high coexpression group [48% *versus (vs)* 13%, *P*=0.003; and 59% *vs* 33%, *P*=0.04, respectively]. Likewise, median time to progression (TTP) and overall survival (OS) were significantly longer for patients in the low coexpression group [6 *vs* 2.5 months, *P*=0.03; and 14.5 vs 5 months, *P*=0.01, respectively]. mRNA coexpression of the three unfavorable genes was a multivariate independent predictor for DCR, TTP and OS.

Conclusions: Tumor mRNA coexpression profile of *RRM1, RRM2* and *CDA* is a potential biomarker for guiding first-line Gem-based therapy in aNSCLC. Independent validation is pending.

Disclosure: All authors have declared no conflicts of interest.

43P
ARE TUMOURAL MICRORNA (MIR) A RELIABLE TOOL IN PREDICTING CHEMOSENSITIVITY AND PROGNOSIS IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)? A PROSPECTIVE STUDY FROM THE EUROPEAN LUNG CANCER WORKING PARTY (ELCWP)

T. Berghmans[1], L. Ameye[2], M. Paesmans[2], J. Lafitte[3], A. Meert[1], A. Scherpereel[3], I. CsToth[1], T. Dernies[1], N. Leclercq[1], J. Sculier[1] [1]Intensive Care and Oncological Emergencies & Thoracic Oncology, Institut Jules Bordet, Brussels, BELGIUM, [2]Data Centre, Institut Jules Bordet, Brussels, BELGIUM, [3]Pneumology, CHU Calmette, Lille, FRANCE

Aim: The activity of cisplatin chemotherapy for NSCLC is not individually predictable. In a prospective study (Berghmans et al, Lung Cancer 2013), we found two signatures predicting either chemosensitivity (predictive, 2 miR) either survival (prognostic, 4 miR), in a group of 38 patients treated with cisplatin-vinorelbine. We are presenting the results of a validation study.

Methods: We used the same methodology than in the derivation set. The biopsy from the primary tumour was lysed into Tripure Isolation Reagent (Roche Diagnostics) on ice, snap frozen and stored at -80°C. The expression of the 6 miR was individually assessed using the same probes and the same protocol than with the TaqMan Low Density Arrays (Life Technologies, Applied Biosystems) and normalized using the delta delta CT method to RNU48 (SNORD48) CT value for every sample. Survival was measured from registration date and response by WHO criteria.

Results: Biopsies for miR analysis were obtained from 22 consecutive patients: median age 62 years, male/female 17/5, 80–100 Karnofsky PS 17, stage IV 15, adenocarcinoma 8. When comparing derivation and validation sets, no statistically significant differences were observed according to these clinical characteristics and for response rate (43% vs 41%) or survival (median 25 vs 29 months). The difference between responders and non-responders, in mean expression of the two-miR from the predictive signature, was not statistically significant (miR-149, p=0.07 and miR-375, p=0.11). Sensitivity, specificity, positive and negative predictive values of the signature were 33%, 77%, 50% and 63%. Among the 4 miR included in the prognostic signature, only miR424 retained a borderline statistical significance for survival (HR 0.66, p=0.05). The 4-miR signature did not anymore distinguish patients with poor and good prognosis.

Conclusions: In this prospective study with advanced NSCLC treated with cisplatin-vinorelbine, we were not able to reproduce our results in an independent validation set. The role of miR as predictive or prognostic factor remains questionable.

Disclosure: All authors have declared no conflicts of interest.

44P
THE IDENTIFICATION OF CIRCULATING MICRO-RNAS (MIRNA) TO MONITOR TUMOUR BURDEN (TB) IN SMALL CELL LUNG CANCER (SCLC)

A. Greystoke[1], M. Ayub[1], N. Smith[1], C. Hodgkinson[1], D. Morris[1], R. Metcalf[1], L. Carter[1], F. Blackhall[2], C. Dive[1], G. Brady[1] [1]Clinical and Experimental Pharmacology, CRUK Manchester Institute, Manchester, UNITED KINGDOM, [2]Medical Oncology, Christie NHS Trust, Manchester, UNITED KINGDOM

Aim: SCLC is characterized by high metastatic burden, poor prognosis and emergence of treatment resistance. Sensitive circulating biomarkers

of TB have potential to inform on progression prior to onset of symptoms, to aid in identifying novel treatment targets and as pharmacodynamic biomarkers in early clinical trials. We evaluated miRNA profiling of plasma from SCLC patients in order to identify potential biomarkers of TB. Using explants derived from patient circulating tumour cells (CTCs) we evaluated the relationship between levels of identified miRNA in the circulation and TB.

Methods: miRNAs were extracted from 200µl of plasma from SCLC patients (n=16) and healthy volunteers (n=11) and from 10µl of plasma from mice bearing xenografts (4 derived from CTCs from SCLC patients and 3 SCLC cell-lines (H526, H1048, COR-L103)). 754 miRNAs were assessed using Taqman Low Density Arrays. Significant miRNAs were identified by LIMMA analysis using MEVsoftware.

Results: 43 miRNAs were significantly elevated in patients with SCLC cf to healthy controls (28 in a stage specific manner; with extensive stage patients having significantly higher levels that patients with limited disease). 30 of these miRNAs had not previously been identified as potential biomarkers in SCLC. The identified miRNAs were significantly elevated in the circulation of mice bearing xenografts compared to non-tumour bearing mice ($P<0.0001$). Serial sampling showed that exemplar miRNAs were detectable in the circulation of mice at an estimated implant size of only 10mm3 and levels mirrored the subsequent implant growth curves.

Conclusions: The combination of miRNA profiling of plasma from patients and xenograft-bearing mice can identify novel sensitive biomarkers of tumour burden in SCLC.

Disclosure: All authors have declared no conflicts of interest.

45P
DEBIO 1143, AN ORAL ANTAGONIST OF INHIBITOR OF APOPTOSIS PROTEINS, ACTIVATES APOPTOSIS AND ENHANCES RADIOSENSITISATION OF NON-SMALL CELL LUNG CANCER CELLS IN VITRO

B. Lu Rad Onc, Thomas Jefferson University, Philadelphia, PA, UNITED STATES OF AMERICA

Aim: Resistance to radiotherapy-induced apoptosis is a hallmark of cancer. Inhibitors of apoptosis proteins (IAPs) limit the effectiveness of radiation in non-small cell lung cancer (NSCLC). Debio 1143 (a.k.a AT-406) is an oral antagonist of multiple IAPs (cIAP1/2 and XIAP) currently in early clinical development. The purpose of this study was to investigate the potential of Debio 1143 as a radiosensitiser in NSCLC.

Methods: HCC193 and H460 NSCLC cell lines were treated with Debio 1143 to determine the effects of the compound on cell proliferation, apoptosis, drug target inhibition, and radiosensitivity. The extent of apoptotic cell death was characterised by Western blot for cleaved caspase 3 and 8. TNF-α release was determined by ELISA.

Results: HCC193 cells were more sensitive to Debio 1143-induced apoptosis than H460 cells with an IC50 of 1 µM and > 20 µM, respectively. HCC193 and H460 cells both demonstrated noticeable time-dependent cleavage of caspase-3 and -8, and a decrease in IAP levels, the former at 2.5 µM Debio 1143 and the latter at 10 µM. In HCC193 cells, but not in H460 cells, apoptosis occurred via the extrinsic apoptotic pathway, as evidenced by dose-dependent TNF-α release. Combining infliximab, an anti-TNF-α antibody, with 10 µM Debio 1143 increased HCC193 cell viability by nearly 3-fold (23% vs. 64% viability). Finally, Debio 1143 significantly sensitised both cell lines to radiation, but a higher concentration was necessary for H460 cells.

Conclusions: Debio 1143 significantly enhanced the radiosensitisation of HCC193 and H460 cells in vitro. The sensitisation was mediated by TNF-α. More research is warranted to understand the mechanism of action of Debio 1143 and assess its potential in the clinical setting.

Disclosure: B. Lu: This study was supported by Debiopharm.

46P
ACTIVITY OF IAP ANTAGONIST DEBIO 1143 AS A MONOTHERAPY AND IN COMBINATION WITH STANDARD OF CARE AGENTS IN MODELS OF HUMAN LUNG CANCER OF DIFFERENT HISTOTYPES

N. Wiedemann[1], C.G. Langdon[2], M.A. Held[2], J.T. Platt[2], C. Zanna[3], M. Sorensen[4], S. Wang[5], M.W. Bosenberg[2], D.F. Stern[2], G. Vuagniaux[1] [1]Pharmacology & Screening, Debiopharm International S.A., Lausanne, SWITZERLAND, [2]School of Medicine, Yale University, New Haven, UNITED STATES OF AMERICA, [3]Medical Affairs, Debiopharm International S.A., Lausanne, SWITZERLAND, [4]R&D, Ascenta Therapeutics, Malvern, UNITED STATES OF AMERICA, [5]Internal Medicine and Pharmacology, Medicinal Chemistry, Michigan University, Ann Arbor, UNITED STATES OF AMERICA

Aim: Drug resistance is a major problem in cancer therapy and response to therapy varies between histotypes and within the same histotype. Resistance may be overcome by the combination of drugs simultaneously targeting multiple critical nodes of the signalling networks controlling growth and survival of cancer cells. The members of the Inhibitor of apoptosis protein (IAP) family are frequently overexpressed in most cancer types contributing to tumour cell survival and resistance to cancer therapy. The oral monovalent IAP inhibitor Debio 1143/AT-406 is currently in clinical development for cancer treatment. The aim of the study was to evaluate the activity of Debio 1143 as a single agent and in drug combinations in *in vitro* and *in vivo* lung cancer models of different histotypes.

Methods: Drug sensitivity was assessed on 3-D cultures of lung cancer patient-derived xenografts (PDX) in clonogenic assays and on human lung adenocarcinoma cell lines in cell viability assays. Synergy of drug combinations was assessed using AUC-based analysis or the Chou-Talalay method and selected combinations were studied in tumor xenograft mouse models.

Results: As a single agent Debio 1143 showed selective anti-proliferative activity *in vitro* in a majority of PDX of small, large and squamous histology, whereas adenocarcinoma-derived PDX and cell lines were less responsive. Furthermore, when combined with NSCLC standard of care (SOC) compounds Debio 1143 displayed synergy on human lung adenocarcinoma cell lines. Synergy of Debio 1143 combined with docetaxel was further confirmed *in vivo* on mouse xenografts of human adenocarcinoma cell lines where a marked anti-tumor activity was observed.

Conclusions: The IAP inhibitor Debio 1143 displays a differential antiproliferative activity across 3-D PDX lung cancer models, as well as strong anti-tumor activity on NSCLC tumor xenografts in mice. These findings provide a rationale for the combination of the IAP inhibitor Debio 1143 with SOC compounds in different lung cancer histotypes and are the basis for ongoing clinical trials in several cancer types.

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47P
ETHNIC DIFFERENCES IN COPPER TRANSPORTER CTR1 EXPRESSION AND TISSUE PLATINUM CONCENTRATION IN NSCLC

E.S. Kim[1], X. Tang[2], C. Chow[3], J. Fujimoto[4], N. Kalhor[3], S.G. Swisher[5], D.J. Stewart[6], I. Wistuba[2], Z.H. Siddik[7] [1]Wilmot Cancer Center, University of Rochester, NY, UNITED STATES OF AMERICA, [2]Translational Molecular Pathology, MD Anderson Cancer Center, Houston, TX, UNITED STATES OF AMERICA, [3]Pathology, MD Anderson Cancer Center, Houston, TX, UNITED STATES OF AMERICA, [4]Thoracic and HN Oncology, MD

Anderson Cancer Center, Houston, TX, UNITED STATES OF AMERICA, [5]Thoracic Surgery, MD Anderson Cancer Center, Houston, TX, UNITED STATES OF AMERICA, [6]The Ottawa Hospital Cancer Center, The University of Ottawa, Ottawa, CANADA, [7]Experimental Therapeutics, MD Anderson Cancer Center, Houston, TX, UNITED STATES OF AMERICA

Aim: African Americans (AAs) have lower lung cancer survival rates compared to Caucasian Americans (CAs). A recent study using ethnically-defined lymphoblastoid cell lines demonstrated that CAs were significantly more sensitive to cisplatin compared with AAs. Furthermore, African-American ethnicity was independently prognostic of poor tumor response to cisplatin in patients with advanced cervical cancer. We previously demonstrated that low tissue platinum (Pt) concentration and undetectable CTR1 (a Pt uptake transporter) level in NSCLC tumor specimens were significantly associated with reduced tumor response following Pt-based therapy. We hypothesized that NSCLC specimens from CAs would have higher CTR1 expression level and intratumoral Pt concentrations.

Methods: We identified paraffin-embedded NSCLC tissue blocks of known intratumoral tissue Pt concentrations from 30 patients who underwent neoadjuvant Pt-based chemotherapy at MD Anderson Cancer Center. There were 23 CAs, 6 AAs and 1 Hispanic patient. Expression of CTR1 was determined by immunohistochemistry with adequate controls; 0 = undetectable; 1+ = barely detectable staining; 2+ = readily appreciable staining; and 3+ = dark brown staining. Tissue Pt concentration, CTR1 expression scores and tumor response were compared between AAs and CAs.

Results: Intratumoral Pt concentration significantly correlated with tumor response in 30 patients who received neoadjuvant Pt-based chemotherapy ($P<0.0001$). CAs had significantly higher CTR1 expression scores ($P=0.0002$) and intratumoral tissue Pt concentrations ($P=0.004$) compared to AAs. Furthermore, CAs had a significantly greater tumor shrinkage compared to AAs following neoadjuvant Pt-based chemotherapy ($P=0.021$).

Conclusions: We report a novel finding that CAs had a significantly higher level of CTR1 expression compared to AAs which corresponded with higher tumor Pt concentrations and greater tumor response in CAs. Differential CTR1 expression may be a contributing factor to ethnic differences in response to Pt therapy. A larger study is warranted.

Disclosure: All authors have declared no conflicts of interest.

48P
CURCUMIN INDUCES CELL CYCLE ARREST AND APOPTOSIS BY UPREGULATING P53-INDUCIBLE MIR-192-5P/215 IN HUMAN LUNG CANCER

J. Zhang, M. Ye Department of Pulmonary Medicine, Xijing Hospital, Fourth Military Medical University, Xian, CHINA

Aim: Non-small cell lung cancer is one of the leading causes of cancer-related mortality world wide. The overall survival of lung cancer is far from satisfactory and it is urgent to explore more efficient and well-tolerated regimens. The medical herb Curcuma longa derived phytomedicine, curcumin, has attracted increasing interest as an anti-cancer drug. The mechanisms of action for curcumin involve multiple signaling associated with cancer. The present study highlighted curcumin can act as an epigenetic agent for miRNAs in human lung cancers.

Methods: miRNAs microarray, qPCR, RT-PCR, luciferase reporter gene assay, siRNA, transient transfection, flow cytometry, bioinformatics approach and Western blot were applied to investigate expressions and functions of indicated miRNAs.

Results: Curcumin exerts cytotoxic effects on H460 and H661 lung cancer cells in vitro and in vivo. miRNAs microarray and qPCR indicated miR-192-5p and miR-215 were the most upregulated miRNAs upon curcumin treatment. miR-192-5p/215 exerted anti-cancer effects in terms of cell cycle arrest and apoptosis. Antagonizing miR-192-5p/215 abrogated curcumin's efficiency. Curcumin promoted p53 accumulation in H460 and H661 cells. p53 knockdown in both cell lines attenuated miR-192-5p/215 upregulation by curcumin treatment. Similarly, in the p53 proficient A549 cells, curcumin was able to upregulate miR-192-5p/215 expressions. While in H1299 cells, a p53 deficient lung cancer cell line, curcumin failed to modulate miR-192-5p/215 expressions. By bioinformatics methods, luciferase reporter assay, RT-PCR and Western blot, XIAP was proved to be a target for miR-192-5p/215. Curcumin upregulated XIAP in p53-expressing H460, H661 and A549 cells, rather than in p53-nonexpressing H1299 cells.

Conclusions: The p53-inducible miR-192-5p/215 acts as crucial mediators of curcumin efficiency. The p53-miR-192-5p/215-XIAP axis is an important pathway that contributes to curcumin's anti-cancer activities in lung cancer.

Disclosure: All authors have declared no conflicts of interest.

49P
SRC INHIBITORS ACT THROUGH DIFFERENT MECHANISMS TO COOPERATE WITH EGFR OR MEK INHIBITORS IN NSCLC MODELS SENSITIVE OR RESISTANT TO ERLOTINIB

L. Raimondo, L. Formisano, R. Rosa, L. Nappi, A. Servetto, R. Marciano, V. D'Amato, C. D'Amato, C. Di Mauro, R. Bianco Medicina Clinica e Chirurgia, Università degli studi di Napoli Federico II, Naples, ITALY

Aim: The EGFR TKIs gefitinib and erlotinib are the first-line therapy for NSCLCs with EGFR-activating mutations. The intrinsic resistance to these agents and the onset of acquired resistance in the responders is a relevant clinical issue. Although Src TK has been involved in such resistance in preclinical models, clinical development of these agents has been so far limited

Methods: We used human NSCLC cell lines with these characteristics: PC9 and HCC827 (EGFR-activating mutation; highly sensitive to erlotinib), Calu3 (EGFR/Ras wild-type, wt; moderately sensitive), Calu3-ER (acquired resistant), H1299 and A549 (Ras mutant; resistant), H1975 (EGFR T790M mutant; resistant). In these cells, we tested three different Src inhibitors (saracatinib, dasatinib and bosutinib), both in vitro and in vivo.

Results: NSCLC cell lines showed different activation of EGFR- and Src-dependent pathways and variable sensitivity to Src inhibitors. A kinase assay demonstrated that all the compounds are able to directly inhibit not only Src, but also EGFR TK variants. However, in cell lysates only saracatinib and bosutinib efficiently reduced EGFR activation, while dasatinib was the more effective agent in inhibiting Src TK. Consistently, in EGFR-activating mutant, erlotinib sensitive cells, saracatinib and bosutinib showed anti-proliferative effects related to simultaneous EGFR/Src inhibition. In EGFR wt/Ras mutant cells Src inhibition by dasatinib interfered with cell proliferation and signal transduction. Since Src inhibitors had only moderate effects as single agents, both in vitro and in vivo, we tested the combination of saracatinib with EGFR inhibitors (erlotinib or cetuximab) in EGFR-addicted cells, and of dasatanib with MEK inhibitors (selumetinib) in Ras mutant, erlotinib resistant models. These combinations were effective both in vitro and in nude mice, inhibiting tumor growth, prolonging mice survival and interfering with signal transduction. Importantly, the combination of saracatanib and cetuximab was effective also in the erlotinib resistant, EGFR T790M mutant model.

Conclusions: Src inhibitors may act with different mechanisms in NSCLC cell lines, depending on EGFR/Ras mutational profile. Integration of anti-Src agents with EGFR or MEK inhibitors could represent effective therapeutic options for different cohorts of NSCLC patients.

Disclosure: All authors have declared no conflicts of interest.

50P
UTILITY OF THE FOLATE RECEPTOR-SPECIFIC IMAGING AGENT 99MTC-ETARFOLATIDE IN PREDICTING VINTAFOLIDE THERAPY RESPONSE IN VITRO AND IN VIVO

C. Leamon[1], J. Reddy[2], P. Klein[3], I. Vlahov[4], M. Vetzel[2], A. Bloomfield[2], R. Dorton[2], M. Nelson[2] [1]Research & Development, Endocyte Inc., West Lafayette, IN, UNITED STATES OF AMERICA, [2]Biology, Endocyte Inc., West Lafayette, IN, UNITED STATES OF AMERICA, [3]Discovery Biology, Endocyte Inc., West Lafayette, IN, UNITED STATES OF AMERICA, [4]Discovery Chemistry, Endocyte Inc., West Lafayette, IN, UNITED STATES OF AMERICA

Aim: Many epithelial cancers express the folate receptor (FR) – a biomarker target for drug development. Vintafolide, a potent folate-targeted vinca

alkaloid conjugate, is currently being evaluated in a phase 3 trial in platinum-resistant ovarian cancer patients and in a phase 2 study for advanced non-small-cell lung cancer patients. ^{99m}Tc-etarfolatide is a folate-based companion imaging agent which can non-invasively identify the location of functionally active and anatomically accessible FRs in real-time. (Pre)clinical studies have demonstrated that response to vintafolide is associated with FR expression; therefore real-time screening for FR-positive disease is of high value. The aim of these studies was to determine if ^{99m}Tc-etarfolatide could predict response to vintafolide therapy.

Methods: The pharmacological properties of ^{99m}Tc-etarfolatide were evaluated *in vitro* (cell lines) and *in vivo* (mouse xenograft models). ^{99m}Tc-etarfolatide's relative FR binding affinity in tumor cells was determined using increasing competitor concentrations of folic acid or vintafolide. BALB/c mice bearing subcutaneously inoculated tumor cells were used to examine ^{99m}Tcetarfolatide's ability to target tumors.

Results: ^{99m}Tc-etarfolatide and vintafolide bind the FR with high affinity (K_d ~3 nM) in an FR expression-dependent, cell type-independent saturable manner. ^{99m}Tc-etarfolatide's in vivo specificity was demonstrated by i) correlation of ^{99m}Tc-etarfolatide's binding to cells and its accumulation within solid tumors to FR expression, and ii) competitively blocking ^{99m}Tc-etarfolatide's cell/tissue binding with excess folic acid or vintafolide. Cellular ^{99m}Tc-etarfolatide uptake correlated to the cytotoxic effect of vintafolide, which could also be blocked by excess un-labeled etarfolatide.

Conclusions: These data suggest vintafolide and ^{99m}Tc-etarfolatide are distributed similarly *in vivo*, FR mediates ^{99m}Tc-etarfolatide tissue binding, and ^{99m}Tc-etarfolatide can identify tumors that may respond to vintafolide. This novel predictive medicine approach may enable the identification of patients likely to benefit from FR-targeted treatment.

Disclosure: C. Leamon: Dr. Leamon owns Endocyte Inc. stock J. Reddy: Dr. Reddy owns Endocyte Inc. stock I. Vlahov: Dr. Vlahov owns Endocyte Inc. stock M. Vetzel: Dr Vetzel owns Endocyte Inc. stock All other authors have declared no conflicts of interest.

51P
GENERATION OF IMMUNOGENIC KILLED TUMOR CELLS FOR DENDRITIC CELL-BASED LUNG CANCER IMMUNOTHERAPY

I. Adkins, N. Hradilova, L. Sadilkova, I. Truxova, I. Vancurova, L. Sojka, J. Palich Fucikova, R. Spisek Research Department, Sotio a.s., Prague, CZECH REPUBLIC

Aim: High hydrostatic pressure (HHP) was shown to induce immunogenic tumor cell death, which is now believed to be crucial for an effective anti-tumor response. HHP as a physical cell-inducing modality can be suitable for the preparation of immunotherapeutic cancer vaccines

Methods: We tested if HHP induces immunogenic cell death in NSCLC cell lines H520 and H522 by measuring cell surface levels of HSP70, HSP90 and calreticulin as well as by detecting the release of HMGB1 and ATP from the dying cells. Monocyte-derived DCs were generated in vitro for 3 days in cGMP-compliant media X-VIVO 15. DCs were incubated with a mixture of HHP- or UVB light-killed tumor cells for 4h and subsequently with or without poly(I:C) for 24h and their capacity to mature, migrate and stimulate T cell responses in vitro was compared.

Results: DCs incubated with a mixture of HHP- or UVB light-killed tumor cells displayed similar capacity to migrate and express co-stimulatory molecules. However, HHP-treated cancer cells were phagocytosed more efficiently and induced higher levels of pro-inflammatory cytokine production in DCs than UVB light-treated cells. Even though the low number of T regulatory cells in DC-T cell co-cultures was similar, DC+HHP-treated cells induced a higher number of IFN-γ-producing T cells than DC+UVB-treated cells suggesting a higher immunogenicity of HHP-treated cells. The immunogenic cell death induced by HHP was confirmed by the surface exposure of immunogenic markers, HMGB1 and ATP release.

Conclusions: These results showed that HHP, but not UVB light induces immunogenic cell death in tested NSCLC cell lines. Furthermore, DC generated short-term in serum free media are capable of processing HHP-killed tumor cells and stimulate T cell responses. This optimized protocol might be used for the development of a DC-based immunotherapy for NSCLC.

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52P
GENETIC VARIATION OF BCL3 IS ASSOCIATED WITH FIVE-YEAR SURVIVAL OF NSCLC PATIENTS

F.D. Dimitrakopoulos[1], A.G. Antonacopoulou[1], A.E. Kottorou[1], D. Dougenis[2], C. Scopa[3], H. Papadaki[4], H. Kalofonos[1] [1]Molecular Oncology Laboratory, Division of Oncology, Department of Internal Medicine, Medical School, University of Patras, Patras, GREECE, [2]Department of Cardiothoracic Surgery, Medical School, University of Patras, Patras, GREECE, [3]Department of Pathology, Medical School, University of Patras, Patras, GREECE, [4]Department of Anatomy, Medical School, University of Patras, Patras, GREECE

Aim: BCL3 is an atypical member of the IκB family and it has been found to be overexpressed in hematological malignancies and in some solid tumors, playing a pivotal role in tumor initiation and progression. A tag single nucleotide polymorphism of BCL3 (SNP; rs8100239, T>A) has been identified recently but there are no data relating to its role in non-small cell lung cancer (NSCLC) development.

Methods: To investigate the role of BCL3 in NSCLC, we genotyped the rs8100239 in 281 patients and 279 controls and we retrospectively assessed BCL3 expression in 112 NSCLC specimens by immunohistochemistry.

Results: NSCLC patients with AA genotype were observed to have significantly worse prognosis compared with T allele carriers ($p<0.001$) and to have higher nuclear BCL3 protein levels ($p=0.042$). In addition, BCL3 was found to be overexpressed in tumour tissue compared with normal tissue ($p<0.001$). Furthermore, BCL3 expression was associated with the grade ($p=0.013$), the relapse rate ($p=0.05$) and tumor's primary location ($p=0.045$) and maximum diameter ($p=0.012$).

Conclusions: The present study represents the first quantitative evaluation of BCL3 expression in NSCLC and the first report which relates genetic variation of BCL3 with survival outcome in cancer patients. Our data suggest rs8100239 may be a novel prognostic indicator. Also, our results demonstrate the deregulation of BCL3 protein in NSCLC, implicating this central molecule in pathogenesis of NSCLC.

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Disclosure: All authors have declared no conflicts of interest.

53P
TARGETING ER-GOLGI HOMEOSTASIS IS AN ADVANTAGEOUS THERAPEUTIC STRATEGY IN LUNG CANCER: SYNERGISTIC INTERACTION OF HSP90 ANTAGONIST AND PROTEASOME INHIBITOR

M. Gottfried[1], L. Drucker[2], V. Zismanov[3] [1]Oncology, Meir Medical Center, Kfar Saba, ISRAEL, [2]Oncogenetic Laboratory, Meir Medical Center, Kfar Saba, ISRAEL, [3]Lung Cancer Research Laboratory, Meir Medical Center, Kfar Saba, ISRAEL

Aim: Lung cancer remains the most common cause of cancer-related death worldwide. This malignancy is a complex disease, and it is important to identify potential biological targets, the blockade of which would affect multiple downstream signaling cascades. A growing number of reports recognize novel therapeutic targets in the protein homeostasis network. These include the heat shock protein 90 (Hsp90) essential to posttranslational folding and maturation of multiple oncogenic kinases, and the proteasome that

orchestrates the turnover of innumerable cellular proteins. Previous studies demonstrate that targeting Hsp90 or the proteasome separately has anti-non small cell lung cancer (NSCLC) activity. Here, we explored whether combined administration of Hsp90 and proteasome inhibitors promotes the anti-NSCLC activity of the drugs by augmenting disruption of ER-Golgi homeostasis.

Methods: NSCLC cell lines (A549, H1299, H460) were treated with 17-DMAG (Hsp90 inhibitor), Velcade (proteasome inhibitor) and both drugs simultaneously for 24 hours. Cells were harvested and analyzed for ER stress markers (Immunoblot), viability (WST1 assay), motility (Scratch assay), and death (Flow cytometer).

Results: Our results demonstrate that co-administration of 17-DMAG and Velcade induced significantly elevated ER stress (BiP: <160%, CHOP: <900%, pJNK: <125%, ATF-6: <70%). The anti-NSCLC activity of the drug combination was also evident in decreased lung cancer cell lines motility (85–100%, $p<0.05$), viability (20–40%, $p<0.05$), cell count (50–60%, $p<0.05$), and synergistically increased apoptotic cell death (7–28%, $p<0.05$).

Conclusions: Our findings provide proof-of-concept that targeting several facets of ER-Golgi homeostasis concurrently is therapeutically beneficial in lung cancer cell lines.

Disclosure: All authors have declared no conflicts of interest.

54P
TELOMERE LENGTH, TELOMERASE ACTIVITY AND DAPK1 EXPRESSION, NEW MARKERS FOR PROGNOSIS IN NON-SMALL CELL LUNG CANCER

T. Fernández[1], I. Pascua[1], C. de Juan[1], J. Head[1], A. Gómez[2], J.R. Jarabo[2], E. Fernández[3], M. Benito[4], P. Iniesta[1], F. Hernando[2] [1]Biochemistry and Molecular Biology II, Faculty of Pharmacy, Complutense University and Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IDISSC), Madrid, SPAIN, [2]Servicios de Cirugía General y Torácica and Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IDISSC), Hospital Clínico San Carlos, Madrid, SPAIN, [3]Thoracic Surgery, Hospital Clínico San Carlos, Madrid, SPAIN, [4]Biochemistry and Molecular Biology II, Faculty of Pharmacy, Complutense University and Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IDISSC), Madrid, SPAIN

Aim: The essential role that telomeres and telomerase play in cancer makes them an important objective in the field of molecular oncology. Our aim in this work consists of analysing the prognostic role of telomere length and telomerase activity in non-small cell lung cancers (NSCLCs). Moreover, considering previous results[1] and its potential as an important downstream target of Src kinase inhibitors (bosutinib, dasatinib)[2], we evaluated the expression of death-associated protein kinase 1 (DAPK1), in relation to telomere status. [1] Oncology 82, (2012). [2] FEBS Journal 277, (2010).

Methods: We analyzed 203 NSCLCs, and their corresponding control samples, obtained from patients submitted to surgery at San Carlos Hospital, Madrid. Survival analyses were performed by the Kaplan-Meier method and differences were evaluated with the Log-Rank test. The primary outcome used was Disease-Free Survival. Telomerase activity and telomere length were established in cancer tissues and control samples. The ratio of telomere length in cancer to control tissue was defined as T/N ratio. DAPK1 expression was determined by real time quantitative PCR and Western-blot. SPSS 19 was used for statistical analyses, and Cutoff Finder web application to determine optimal cut-off values.

Results: Regarding survival analysis, patients whose tumours showed a telomere length < 7.29 or T/N ratio < 0.97 had a significantly poor clinical evolution ($P = 0.034$ and 0.040, respectively, Log-Rank). In multivariate analysis, both parameters proved to be independent prognostic markers. Kaplan-Meier curves showed that telomerase activity resulted in a predictor of poor clinical outcome ($P = 0.028$, Log-Rank). A significant association was found between telomere status and DAPK1 expression ($P = 0.048$; Mann-Whitney): tumours with the shortest telomeres exhibited a significantly diminished expression of DAPK1 mRNA. DAPK1 protein expression correlated with mRNA levels, as we confirmed by Western-blot.

Conclusions: Telomere length and telomerase activity represent prognostic markers in NSCLC. DAPK1 may be a new target in NSCLC therapy, in relation to telomere status.

Disclosure: All authors have declared no conflicts of interest.

55P
MED12 AND STAT3 INFLUENCE OUTCOME TO PLATINUM-BASED CHEMOTHERAPY IN PATIENTS (P) WITH ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC)

D. Morales-Espinosa[1], N. Karachaliou[2], C. Costa[2], M.Á. Molina[3], A. Gimenez-Capitán[2], J.J. Sánchez[4], B. Massuti[5], L. Bonanno[6], M. Majem[7], R. Rosell[8] [1]Translational Research Laboratory, Institut Catalá d'Oncologia, Badalona, SPAIN, [2]Translational Research, RNA Unit, Pangaea Biotech, Barcelona, SPAIN, [3]Translational Research, Pangaea Biotech, Barcelona, SPAIN, [4]Department of Preventive Medicine, Facultad de Medicina,, Universidad Autónoma de Madrid, Madrid, SPAIN, [5]Departamento de Oncología, Hospital General Universitario de Alicante, Alicante, SPAIN, [6]Second Medical Oncology Unit, Istituto Oncologico Veneto IRCCS, Padova, ITALY, [7]Oncología Médica, Hospital de la Santa Creu i Sant Pau, Barcelona, SPAIN, [8]Medical Oncology Service, Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Badalona, SPAIN

Aim: To examine MED12 – a negative regulator of the TGF-b receptor signaling -, IDO, IL6, RelA (NFkB), BIM and the JAK2/STAT3 pathway and KRAS in NSCLC tumor samples and correlate results with progression-free survival (PFS).

Methods: The mRNA expression of MED12, IDO, JAK2, STAT3, RelA and BIM was examined in microdissected tumor samples from p with stage IV NSCLC. mRNA levels were assessed by RT-PCR and categorized by terciles (high vs low/intermediate). KRAS mutations were assessed by high resolution melting.

Results: A total of 55 p with performance status (PS) 0–1, treated with platinum plus either gemcitabine or pemetrexed: median age, 62 years; 27.6% females; 84.2% smokers; 66% adenocarcinoma; 16% with KRAS mutations. There was no correlation between gene expression levels and KRAS mutation status. In the multivariate analysis, including gene expression levels, histology and PS, only MED12 and STAT3 were associated with PFS (low MED12: HR=11.6, P=0.005; high STAT3: HR=6.5, P=0.01). HR for low BIM expression was 2.4 (P=0.16). None of the markers were associated with overall survival.

Conclusions: To the best of our knowledge, this is the first time that low expression of MED12 with significantly shorter PFS in NSCLC p receiving platinum-based chemotherapy. MED12 could be a new biomarker of chemoresistance and inhibition of TGF-bR signaling can restore chemotherapy response in patients with low MED12.

Disclosure: All authors have declared no conflicts of interest.

56P
ENHANCED EFFECT OF CYTOTOXIC DRUGS IN THE TREATMENT OF LUNG CELLS CANCER

A.R. Rama Ballesteros, P.J. Alvarez, R. Luque, J.R. Delgado, J.C. Prados, C. Melguizo, R. Maddedu, A. Aranega Biomedicine Regenerative, Institute of Biopathology and Regenerative Medicine (IBIMER), Granada, SPAIN

Aim: The potential use of combined gene therapy is under intensive study to improve the effectiveness of these cytotoxic agents and reduce their adverse effects. In this context, the association of the cytotoxic drugs with killer genes could enhance their antiproliferative effect. The gene E from Φ*X174* encodes for a membrane protein with a toxic domain which causes cell lysis. To improve the antitumoral effect of some classical citotoxic agents we investigated a combined suicide gene therapy on A-549 cells (lung cancer).

Methods: The gene E was cloned into the plasmid pcDNA3.1 (pcDNA3.1-E) and the lung carcinoma cell line A-549 were grown in monolayer. Experiments were performed in two groups:

- Gene E alone: A-549 transfected (pcDNA3.1-E).

- Combined gene therapy: A-549 transfected and non-transfected cells were exposed to Paclitaxel (Pac), Carboplatin (Car) and Gemcitabine (Gem), all of them to 100, 50 and 1 μM concentration.

We evaluated the effect of gene E and its combination with the cytotoxic drugs by several techniques.

Results: Our results showed that the E expression in A-549 cells carried to ultrastructural changes, including dilated mitochondria. These findings were corroborated with a significant decrease in mitochondrial transmembrane potential ($p<0.05$).

On the other hand, assays with combined therapy showed that effect of the drugs at all different concentration was enhanced by gene E expression. Pac induces the greater inhibition of the proliferation, showing at the average concentration and transfecting 3 times 85% of growth inhibition, just as the therapy only with Pac to the maximum concentration. Parental and cancer cells treated with combined therapy or with citotoxic or gene E separately were analysed by FACscan after anexin-PI staining. The results indicated the ability of gene E to stimulate apoptosis in A-549 treated with their respective drugs.

Conclusions: In conclusion, gene E has a killer effect in A-549 lung cancer cells which enhances growth inhibition cell when used with citotoxic drugs. That suggests a possibility to reduce the dose of cytotoxic agents applied in the tumours. These results indicate that this combined therapy may be of potential therapeutic value in lung cancer.

57P
MUCIN 1 (MUC1) EXPRESSION IN PATIENTS (PTS) WITH EARLY STAGE NON-SMALL CELL LUNG CANCER (NSCLC): RELATIONSHIP BETWEEN IMMUNOHISTOCHEMISTRY (IHC) IN PRIMARY TUMOUR AND PLASMA SOLUBLE MUC1 (SMUC1) LEVEL

P.L.R. Mitchell[1], K. Asadi[2], T. John[1], C. Murone[3], S. Knight[4] [1]Ludwig Medical Oncology Unit, Olivia Newton-John Cancer and Wellness Centre, Austin Health, Melbourne, AUSTRALIA, [2]Anatomical Pathology, Austin Health, Melbourne, AUSTRALIA, [3]Anatomical Pathology, Austin Health and Ludwig Institute for Cancer Research, Melbourne, AUSTRALIA, [4]Thoracic Surgery, Austin Health, Melbourne, AUSTRALIA

Aim: MUC1, a glycoprotein highly expressed in many malignancies, is being explored as an antigen for immunotherapy. Although MUC1 expression on IHC is very frequent In NSCLC (Mitchell et al. Proc ASCO 2013, abs 3011) and circulating sMUC1 may be elevated, the relationship has been poorly studied. This study explored the relationship between MUC1 IHC and plasma sMUC1 in patients undergoing lobectomy or pneumonectomy for NSCLC.

Methods: Tissue Micro Arrays (TMAs) were constructed using triplicate 1mm cores of FFPE primary tumour and stained with 214D4 (recognises protein core) anti-MUC1 antibody. TMAs were assessed for polarisation, both cytoplasmic and membranous staining intensity (scored 0–3) and proportion cells +ve (0–100%; scored 0 – 5), averaged for multiple cores. A composite score (intensity x cells +ve) was derived, ranging from 0 – 15 (3+ in >75% cells). Plasma obtained prior to surgery was analysed for sMUC1 (CA15-3) using the Cobas kit.

Results: Of 39 pts analysed. most were adenocarcinoma (26) with 8 squamous and 5 other. There were 21 stage 1, 10 stage 2, 7 stage 3 and 1 stage 4 (brain metastasis). Tumours from 36 pts (92%) stained with 214D4 with a mean composite score of 9.25 and median 10. Of tumours staining, 20 (56%) were depolarised and 16 (44%) polarised. sMUC1 ranged from 5.9 – 60.7 KU/L, with 9 cases (23%) elevated (> 25 KU/L). The mean and median IHC scores for those with elevated sMUC1 were 9.3 and 10.0, compared with 9.23 and 10.5 respectively for those without elevated sMUC1. There was no clear relationship between elevated sMUC1 and histology, stage or primary tumour diameter. However 8/9 (89%) of those with elevated sMUC1 had depolarised IHC staining compared with 12/27 (44%) without elevated sMUC1 ($p=0.026$, Fisher's exact test).

Conclusions: Of 39 surgical resection cases, 92% stained for MUC1 while 9 had elevated plasma sMUC1 levels. No relationship was seen between elevated sMUC1 and the presence or degree of MUC1 IHC staining. However cases with depolarised MUC1 IHC were significantly more likely to have elevated sMUC1. A depolarised pattern of expression has been previously shown to be associated with poor survival in adenocarcinoma (Mitchell 2013). In this ongoing study, data on additional cases will be presented along with survival analysis.

Disclosure: All authors have declared no conflicts of interest.

58P
LUNG CANCER ABLATION BY USING LUNG FLOODING AND THERAPEUTIC ULTRASOUND- A NEW PARENCHYMA SPARING APPROACH

F. Wolfram, T. Lesser Thoracic and Vascular Surgery, SRH Waldklinikum Gera, Gera, GERMANY

Aim: For inoperable patients alternative thermal interventions (RF) have been explored. Those require invasive applicator insertion with a considerable complication rate and are applied for palliation only. Treatment of lung cancers and metastases would benefit from minimal-invasive, no-touch ablative principles. Unilateral lung flooding enables intra-operative ultrasound guidance while the non-flooded lung maintain ventilation (TLV). Our work showed it's safety and stability of surfactant levels. Therapeutic Ultrasound (HIFU) as a non invasive ablation technique heat embedded cancer without damaging the overlying parenchyma. Recently our work showed that ultrasound guidance and the physical conditions in flooded lung are superior for HIFU ablation of NSCLC. This data's demonstrate the usability of minimal-invasive NSCLC ablation on human ex vivo and in vivo large animal models.

Methods: Human lung lobes containing NSCLC were flooded with saline following intra-surgical atelectasis. Ex-vivo ultrasound images were acquired. HIFU was applied into centrally located cancer tissue under temperature monitoring. Ablated lung cancer tissue were histological analyzed (HE, NADPH). Unilateral lung flooding was performed on pigs ("Deutsches Landschwein" 28-33Kg) with permission of the federal ethics committee (TLLV). HIFU was applied trans-thoracic into central tissue mimicking targets. Vital parameters (HR, SO2, pCO2) and lesion temperature was monitored. Flooding was maintained for 90 minutes before re-ventilation.

Results: In all animals, lung flooding was performed without remaining gas content. Vital parameters stayed inside physiological range (HR 45–91 bpm / SO2 (85–100%)/ pCO2 (30-63mmHg)). Temperature rose up to 60°C in central lung lesion. NSCLC could be visualized and disciminated from flooded parenchyma by ultrasound. In targeted cancer temperature reached 80–85°C, in parenchyma only 40–45°C. HE stain show areas of thermal necrosis while NADPH stain confirmed loss of vitality in targeted NSCLC.

Conclusions: NSCLC can be radically ablated by therapeutic Ultrasound without applicator insertion and loss of functional parenchyma. HIFU ablation under flooded lung is feasible and could lead to a potential treatment option for inoperable patients and demands further research.

Disclosure: All authors have declared no conflicts of interest.

IMAGING AND STAGING

59O
ALTERNATIVE METHODS OF PET-CT INTERPRETATION: CAN WE IMPROVE MEDIASTINAL NODAL STAGING IN LUNG CANCER PATIENTS?

M. Evison[1], P. Crosbie[2], J. Martin[1], P. Barber[1], R. Booton[2] [1]North West Lung Centre, University Hospital South Manchester, Manchester, UNITED KINGDOM, [2]University of Manchester, Institute of Inflammation and Repair, Manchester, UNITED KINGDOM

Aim: In the absence of distant metastases, lymph node staging becomes the pivotal factor in determining treatment and prognosis for lung cancer patients.

The sensitivity of PET-CT for nodal staging remains sub-optimal. Using a different SUV 'cut-off' value to define a positive lymph node (traditionally 2.5) or using the ratio of the lymph node SUV compared to the primary tumour SUV may provide more clinically relevant information.

Methods: This prospective observational study included all lung cancer patients referred to the University Hospital South Manchester Hospital for EBUS-TBNA nodal staging, whom also underwent PET-CT during their staging work-up. Lymph node SUV (LN-SUV), the ratio of lymph node SUV to primary tumour SUV (LN:PT-SUV) and the final lymph node diagnosis (benign versus malignant) was recorded for every lymph node sampled. ROC curves were produced and used to define the most appropriate 'cut-off' values for LN-SUV and LN:PT-SUV.

Results: 354 patients with primary lung cancer underwent EBUS-TBNA nodal staging and PET-CT imaging in the study period. The mean age was 69.9 (SD +/-9.4). In total, 566 lymph nodes were sampled. 62.5% (354/566) of lymph nodes were ultimately proven to be malignant. The mean LN-SUV for benign lymph nodes was 3.0 (SD +/-1.3) compared to 10.4 (SD +/-6.1) for malignant nodes. The area under the curve was 0.941. Using a LN-SUV 'cut-off value' of >4.0 to indicate nodal metastases, the specificity was 88.2%, sensitivity 90.9%, PPV 92.7% and NPV 84.2%. The mean LN:PT-SUV for benign lymph nodes was 26.4% (SD +/-19.2%) compared to 93.6% (SD +/-54.8%) for malignant nodes. The area under the curve was 0.933. Using a LN:PT-SUV 'cut-off' of >40% to indicate nodal metastases the specificity was 86.3%, sensitivity 91.0%, PPV 91.7% and NPV 85.1%.

Conclusions: In lung cancer patients, LN-SUV and LN:PT-SUV are highly effective at predicting lymph node metastases using a cut-off of >4.0 and >40% respectively to indicate malignancy. This should not, however, replace pathological nodal staging as approximately 10% and 15% of patients would be over-staged and under-staged respectively. The most clinically relevant use of these alternative PET-CT interpretation methods may be in classifying which patients need further surgical nodal staging following a negative EBUS-TBNA.

Disclosure: All authors have declared no conflicts of interest.

60P
EVALUATING THE POTENTIAL OF 99MTC-ETARFOLATIDE TO SELECT NSCLC PATIENTS LIKELY TO BENEFIT FROM VINTAFOLIDE TREATMENT

W. Harb[1], P. Bonomi[2], J. Symanowski[3], B. Nguyen[4], M. Edelman[5] [1]Horizon Oncology Research Inc., Lafayette, IN, UNITED STATES OF AMERICA, [2]Hematology/oncology, Rush University Medical Center, Chicago, IL, UNITED STATES OF AMERICA, [3]Cancer Biostatistics, Levine Cancer Institute, Carolinas Healthcare System, Charlotte, NC, UNITED STATES OF AMERICA, [4]Medical Affairs, Endocyte Inc., West Lafayette, IN, UNITED STATES OF AMERICA, [5]Cancer Center, University of New Mexico Cancer Center, Albuquerque, NM, UNITED STATES OF AMERICA

Aim: Folate receptor (FR) is expressed in non-small cell lung cancer (NSCLC) tumors, making it potentially useful as a biomarker and a therapeutic target. Vintafolide is a potent drug conjugate of folic acid and the vinca alkaloid desacetylvinblastine hydrazide. ^{99m}Tc-etarfolatide, a technetium bound folate molecule, allows for full body, real-time, SPECT imaging of FR. These two companion agents are being co-developed. This study aimed to evaluate the ability of ^{99m}Tc-etarfolatide imaging to identify FR expression in NSCLC patients' tumors and to correlate this with response to vintafolide.

Methods: In a phase 2 study (NCT00511485), FR expression in NSCLC target lesions was assessed by ^{99m}Tc-etarfolatide uptake. Patients were categorized as FR(100%) (all target lesions FR positive, n=14) and FR(10−90%) (≥10%, but ≤90%, target lesions FR positive, n=14). Patients received vintafolide (IV bolus) in an induction phase (1.0 mg, days 1−5/8−12/15−19 of 4-week cycles, 2 cycles), followed by a maintenance phase (2.5 mg, days 1/3/5/15/17/19 of 4-week cycles). Up to 8 cycles of therapy could be received. Patients with tumor shrinkage could continue treatment until clinical benefit ceased (defined as 2 sequential scans with stable disease).

Results: Median progression-free survival was 31.1 weeks in FR(100%) vs 7.3 weeks in FR(10–90%) patients (hazard ratio [HR] = 0.326; p = 0.014). Median overall survival was longer in FR(100%) patients (47.2 vs 14.9 weeks; HR = 0.539; p = 0.101). Tumor response and stabilization were also greater in FR(100%) patients (response rate 7.1% vs 0%; disease control rate 57.1% vs 14.3%). Both agents were generally safe and well tolerated. Drug related adverse events were reported in 3.3% of ^{99m}Tc-etarfolatide-treated patients (all grade 1/2) and 83.7% of vintafolide-treated patients (14.0% grade 3, no grade 4), most commonly fatigue, constipation, nausea, and anorexia.

Conclusions: These data support the potential utility of ^{99m}Tc-etarfolatide in identifying patients most likely to benefit from vintafolide. An ongoing randomized phase 2 study (TARGET) will determine the predictive versus prognostic value of this approach

Disclosure: P. Bonomi: Dr Bonomi has received support from Endocyte Inc to perform the clinical trial. J. Symanowski: Dr Symanowski has been a consultant for Endocyte Inc. B. Nguyen: Dr Nguyen owns Endocyte Inc. stock M. Edelman: Dr Edelman has been a member of an advisory board for Endocyte Inc. and has performed research sponsored by Endocyte Inc. All other authors have declared no conflicts of interest.

61P
THE PROVISION OF EBUS-TBNA SERVICES ACROSS A UK LUNG CANCER NETWORK; A REPORT FROM THE GREATER MANCHESTER AND CHESHIRE LUNG CANCER NETWORK EBUS SUB-GROUP

M. Evison[1], P. Crosbie[1], J. Martin[1], P. Barber[1], R. Booton[2] [1]North West Lung Centre, University Hospital South Manchester, Manchester, UNITED KINGDOM, [2]Institute of Inflammation and Repair, University of Manchester, Manchester, UNITED KINGDOM

Aim: Given the variability in lung cancer outcomes across the UK and the explosion of EBUS-TBNA services in recent years, there is a need to ensure timely and equitable access to quality assured EBUS-TBNA services for lung cancer patients. This report describes how a large cancer network in England is taking steps towards achieving this aim.

Methods: The Greater Manchester and Cheshire Cancer Network (GMCCN) is made up of eleven NHS trusts. In 2012 the number of EBUS-TBNA services increased from one to four. This prompted the formation of a GMCCN EBUS sub-group committee and subsequently an EBUS service specification. This mandated the collection of pre-defined data for every EBUS-TBNA procedure performed. This data collection then allows patient pathways, complications and performance data to be analysed at both a network and individual service level.

Results: From the 1st January 2012 to 30th September 2013 756 patients with lung cancer underwent EBUS-TBNA. 56.2% (425/756) of procedures were for nodal staging with the remainder being performed for pathological diagnosis. The average time from referral to procedure was 7.4 days (SD +/-4.9) and 75.2% of patients wait 9 calendar days or less. There were 6 major complications from EBUS-TBNA (0.7%) and 45 minor complications (5.9%). From 1st January 2012 to 30th April 2013 (to allow 6 months of follow-up) a total of 894 lymph nodes were sampled by EBUS-TBNA, from 406 patients, at three centres. One centre did not submit any lymph node outcome data. Overall, 5.5% (49/894) of lymph nodes were sampled inadequately, 494 lymph nodes were proven malignant and 321 were deemed negative. 47/321 were subsequently proven to be false negatives. The overall sensitivity (when inadequate samples are classified as false negative) and NPV of EBUS-TBNA was 83.7% and 85.4% respectively.

Conclusions: There is clearly work to be done in improving both the completeness of data submission and the outcome measures across this cancer network. Furthermore, the number of patients undergoing pathological nodal staging with EBUS-TBNA appears low and requires more detailed investigation. However, this represents a step in the right direction and ongoing measurement and publication of performance should help to drive improvements in these outcomes.

Disclosure: All authors have declared no conflicts of interest.

62P
PERCUTANEOUS CT-GUIDED BIOPSY FOR DIAGNOSIS OF LUNG AND MEDIASTINAL LESIONS

Y. Ragulin, V. Usachev Thoracic, Medical Radiological Research Center, Obninsk, RUSSIAN FEDERATION

Aim: The aim of study is the determination of the diagnostic value of transthoracic biopsy under the computer tomography. To compare the diagnostic efficacy of percutaneous aspiration and core biopsy intrathoracic lesions.

Methods: From 2007 to 2012 transthoracic needle biopsy under CT control in 107 patients were performed. Lesions size was 10 x 10 mm to 200 x 87 mm (mean 49.6 x 38.7 mm). To fine-needle aspiration biopsy (FNAB) used needle diameter 20G. Core needle biopsy was performed, representing a trocar, which is held inside a stiletto with a split end, allowing you to capture a piece of tissue is sufficient for histological examination (diameter 14G, length 100 mm). This technique allows to obtain material for cytology.

Results: In 4 cases a puncture failed. The diagnosis of malignant lung tumor delivered in 80 pts out of 107. FNAB made 34 pts. Final diagnosis: cancer - in 24 pts, non-neoplastic process - in 10. Of the 24 pts with a diagnosis of lung cancer - in 18 could correctly identify the pathology. In 6 cases received false-negative findings. Sensitivity FNAB for verification of malignancy was 75%. Of the 10 pts with non-tumor formations in 7 verified correctly diagnosed. The sensitivity was 70%. FNAB accuracy is 0.74. Complications in the form of a pneumothorax is not accompanied by clinical symptoms were observed in 5 (14.7%) pts. Core biopsies were performed in 69 pts. Malignant process was in 56 cases, 13 - non-tumor formation. In 56 pts with a cancer - in 53 cases correctly verified pathology (83.9% - histologically, 76.8% - cytology). False-negative results were obtained in 3 cases. The sensitivity was 94.6%. Of the 13 pts with non-tumor formations in 12 verified correctly diagnosed. The sensitivity was 92.3%. Core biopsy accuracy was 0.94. Complications have been observed in 10 cases (14.5%) patients. Pneumothorax - in 8, hemoptysis - in 2. Clinically significant complications were observed in 2 pts (drainage of the pleural cavity, hemostatic therapy). According to histological material obtained in 5 pts we have EGFR mutations.

Conclusions: Core biopsy of intrathoracic nodules has greater diagnostic value in verifying the volume processes in the lung and mediastinum. Method is simple to use and is not accompanied by serious complications. Obtaining the tissue allows the molecular genetic studies and individualized treatment of patients.

Disclosure: All authors have declared no conflicts of interest.

63P
OUTCOMES OF CT-GUIDED LUNG BIOPSIES FOR SUSPECTED LUNG MALIGNANCY - SINGLE CENTRE DISTRICT GENERAL HOSPITAL EXPERIENCE

M.A. Abbasi, J. Bhosle, V. Varney, S. Paramothayan, V. Kahr, M. Lapsley, A. Witwit Radiology, Respiratory Medicine & Histopathology, St Helier University Hospital NHS Trust, Surrey, UNITED KINGDOM

Aim: An audit of CT-guided lung biopsies performed in our institution against standards provided by British Thoracic Society guidelines for radiologically-guided lung biopsy (2003), National Institute for Health and Care Excellence (NICE) Lung Cancer guidance (2011) and QS17 Quality Standards (2012).

Methods: All patients undergoing CT-guided biopsy performed between March 2012 to March 2013, (12 months and 13 days) were included. The complication rate, adequacy of samples as defined by BTS guidelines, false negative and positive rates, sensitivity (lesions >2cm) and the success of tumour sub-typing and analysis of predictive markers were assessed,

Results: Fifty patients (males 22, females 28, mean age= 67 years) were identified. Adequate samples for diagnosis were obtained in 47 patients (94%). Six patients (12%) had pneumothorax, of which 1 patient (2%) required chest drainage. Haemoptysis was observed in 4 patients (8%), of which 1 patient required medical management (2%). There were no fatalities. The false positive rate was 0% and the sensitivity (lesions >2cm) was 94%. Adenocarcinoma was diagnosed in 23 patients (46%), NSCLC NOS - 4 (8%), squamous cell carcinoma - 4 (8%), small cell carcinoma - 1 (2%), carcinoid - 1 (2%), metastases - 1 (2%), tuberculosis - 1 (2%). Three patients (6%) had insufficient samples; 2 (4%) were subsequently diagnosed with adenocarcinoma and no malignancy was seen in 1 patient (2%). Twelve patients (24%) had no malignant disease on the initial sample; 4 (8%) were subsequently diagnosed with adenocarcinoma by alternative methods, giving a false negative rate of 33%. 20/37 (54%) of cases underwent subsequent EGFR-TK analysis. 3 samples (8%) were unsuitable due to inadequate material. 1 sample (3%) was positive for mutant EGFR-TK (exon 19 deletion).

Conclusions: CT –guided biopsies in our institution are largely within standards set by BTS guidelines. However, there is scope for improvement to meet NICE Quality standards for the analysis of predictive molecular markers.

Disclosure: All authors have declared no conflicts of interest.

64P
THE ROLE OF ENDOBRONCHIAL ULTRASOUND IN THE MANAGEMENT OF PATIENTS PREVIOUSLY TREATED FOR LUNG CANCER

M. Evison[1], P. Crosbie[2], R. Califano[3], Y. Summers[3], J. Martin[2], P. Barber[2], R. Booton[4] [1]Institute of Inflammation and Repair, University of Manchester, Manchester, UNITED KINGDOM, [2]North West Lung Centre, University Hospital South Manchester, Manchester, UNITED KINGDOM, [3]Department of Medical Oncology, University Hospital South Manchester, Manchester, UNITED KINGDOM, [4]University of Manchester, Institute of Inflammation and Repair, Manchester, UNITED KINGDOM

Aim: Safe and effective pathological sampling methods are pivotal in the management of lung cancer patients that have previously undergone either curative intent or palliative treatment. Early diagnosis of localised disease recurrence may facilitate further curative treatment and re-biopsy in disease progression after palliative treatment can inform further management. This study assessed the safety and effectiveness of bronchoscopy with radial and linear endobronchial ultrasound (EBUS) in patients with suspected lung cancer recurrence or progression following treatment.

Methods: Prospective data was collected on all patients with suspected recurrence/progression of previously treated primary lung cancer having EBUS at the University Hospital South Manchester from August 2010 to June 2013. Patient characteristics, complications, pathological results from EBUS and 6 months of clinical-radiological follow up were recorded for each patient.

Results: 64 patients (58 with suspected recurrence and 6 with suspected progression) underwent EBUS in the study period. A total of 76 lymph nodes and 14 intra-pulmonary lesions were sampled. The mean age was 67.2 (SD +/-9.4) and 61% (39/64) were male. Of the 58 patients with suspected recurrence, 36 were ultimately confirmed to have recurrence, 20 were proven to have benign pathology, one was diagnosed with metastatic bladder cancer and one with a new small cell lung cancer. EBUS correctly diagnosed 95% (55/58) of patients (sensitivity 92.1%, NPV 87%). Of the 6 patients with suspected progression, 80% (4/6) were confirmed pathologically by EBUS. In 100% (16/16) of patients requiring molecular testing EBUS guided sampling provided adequate tissue. The major and minor complication rate was 0% and 3.1% (2/64) respectively.

Conclusions: Bronchoscopy with endobronchial ultrasound is a safe and highly effective diagnostic procedure in suspected lung cancer recurrence/progression. All physicians, oncologists and surgeons involved in the follow-up and surveillance of lung cancer patients require rapid and reliable access to endobronchial ultrasound services.

Disclosure: All authors have declared no conflicts of interest.

653P
SYNCHRONOUS LUNG AND THYROID TUMORS: A STAGING DILEMMA IN THE PET-CT ERA

M. Moskovitz[1], D. Levy Faber[2], M. Lapidot[2], M. Wollner[1], M. Orlovsky[2], L.A. Best[2], R. Kremer[2] [1]Oncology, Rambam Health Care Campus, Haifa, ISRAEL, [2]General Thoracic Surgery, Rambam, Haifa, ISRAEL

Aim: Lung cancer is the second most common non-skin malignancy. In a PET-CT-based staging of lung cancer, positive metabolic neck avidity may be

considered a metastasis; however, other interpretations may be synchronous tumor or non-malignant avidity. We present nine cases of synchronous lung and thyroid cancer, which do not share common characteristics, and whose concurrent detection affects the patients' treatment and prognosis

Methods: A retrospective analysis of patients admitted to our department of General Thoracic Surgery between January 1, 2004, to January 1, 2013, identified nine patients with synchronous lung and thyroid malignancies. Data collection was of demographics, disease characteristics, diagnosis, surgical and oncological treatment, and clinical outcomes.

Results: Nine patients had synchronous thyroid and lung cancer upon diagnosis, substantiated by FDG-PET scans with pathological SUV uptakes. Lung cancer: All eight operable patients underwent anatomical lobectomies. Thyroid cancer: Six patients had total resection of the thyroid; one patient passed away presurgery; one patient is still recovering from lung malignancy treatment; one thyroidectomy was postponed due to lung cancer associated oncological treatments. One patient passed away due to intestinal perforation before the thyroidectomy. Four patients had typical complications of lung surgery. Three patients had oncological treatment complications. Six patients completed their preplanned treatment course of both malignancies.

Conclusions: A high index of suspicion should be given to a PET-CT scan demonstrating a pathological lung and neck metabolic avidity, presented during the process of lung cancer evaluation; in such case, further evaluation is warranted to accurately conclude the patient's clinical staging.

Disclosure: All authors have declared no conflicts of interest.

SCLC

66O
OUTCOMES OF PLATINUM-SENSITIVE SMALL CELL LUNG CANCER (SCLC) PATIENTS TREATED WITH PLATINUM-BASED CHEMOTHERAPY RECHALLENGE: A MULTI-INSTITUTIONAL RETROSPECTIVE ANALYSIS

G. Genestreti[1], G. Metro[2], H. Kenmotsu[3], F. Carloni[4], M.A. Burgio[5], C. Casanova[6], M. Tiseo[7], E. Scarpi[8], T. Korkmaz[9], R. Califano[10] [1]Department of Medical Oncology, AUSL Rimini, Cervesi Hospital, Cattolica, ITALY, [2]Oncologia Medica, Azienda Ospedaliera di Perugia S. Maria della Misericordia, Perugia, ITALY, [3]Division of Thoracic Oncology, Shizouka Cancer Center, Shizouka, JAPAN, [4]Department of Medical Oncology, AUSL Rimini, "Cervesi" Hospital, Cattolica, ITALY, [5]Department of Medical Oncology, IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (I.R.S.T.), Meldola, ITALY, [6]Oncology Hematology, Ospedale Sta Maria delle Croci, Ravenna, ITALY, [7]Oncologia Medica, Azienda Ospedaliera di Parma, Parma, ITALY, [8]Unit of Biostatistics and Clinical Trials, IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (I.R.S.T.), Meldola, ITALY, [9]Medical Oncology, Dr. Lutfi Kirdar Kartal Education and Research Hospital, Istanbul, TURKEY, [10]Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, UNITED KINGDOM

Aim: Patients with small-cell lung cancer (SCLC) that progress after first-line (FL) chemotherapy have a poor prognosis and second-line (SL) chemotherapy has limited efficacy. Patients relapsing/ progressing > 90 days after completion of FL platinum-based treatment are considered platinum sensitive and could be rechallenged with same treatment. We conducted a multicenter retrospective analysis to evaluate outcomes of SCLC patients who received platinum/etoposide rechallenge as SL.

Methods: The endpoints were: overall survival (OS) from diagnosis and rechallenge chemotherapy, and response rate (RR) and progression-free survival (PFS) after rechallenge. Survival curves were calculated using the Kaplan-Meier method.

Results: We reviewed 2000 SCLC patients treated in 8 institutions between January 2007 and December 2011. Patients with sensitive SCLC treated with SL platinum/etoposide rechallenge were 112 (5.6%). 64% were males with a median age of 64 years (range 40–83). At diagnosis, 49 (44%) patients had limited disease. Eastern Cooperative Oncology Group performance status (ECOG-PS) was 0–1 and 2 in 87% and 13% of patients, respectively. Response to FL chemotherapy: complete response (CR) 14%, partial response (PR) 84% and stable disease (SD) 2%. Median time-to-progression from completion of FL chemotherapy was 240 days (range 90–1200). Mean number of cycles of chemotherapy was 3.6 (range 1–7). Carboplatin and cisplatin were administered in 96 (86%) and 16 (14%) patients, respectively. Median OS from diagnosis and rechallenge chemotherapy was 21.4 months (95% CI 19.8–24.1) and 7.9 months (95% CI 6.9–9.7), respectively. Median PFS from rechallenge was 5.5 months (95% CI 4.4–6.3). Response to rechallenge chemotherapy: CR 3%, PR 42%, SD 19%, progressive disease 27% and not evaluable 9%. Forty patients (36%) received further chemotherapy: CAV (cyclophosphamide, adriamycin and vincristine) (12%), topotecan (9%), platinum/etoposide (6%) and other regimen (9%). There was no difference in OS from diagnosis, OS and PFS from rechallenge according to stage at diagnosis, PS or type of platinum drug administered.

Conclusions: The outcome for SL chemotherapy for SCLC is poor. Platinum sensitive disease may be rechallenged with platinum-based treatment. Stage, PS and platinum drug administered do not seem to be independent prognostic factors.

Disclosure: All authors have declared no conflicts of interest.

67O
CABAZITAXEL (CBZ) VS TOPOTECAN (TPT) IN PATIENTS (PTS) WITH SMALL CELL LUNG CANCER (SCLC) WITH PROGRESSIVE DISEASE DURING/ AFTER FIRST-LINE (1L) TREATMENT WITH PLATINUM-BASED CHEMOTHERAPY (CTX)

T. Evans[1], B.C. Cho[2], K. Udud[3], J.R. Fischer[4], F.A. Shepherd[5], P. Martinez[6], R. Ramlau[7], K.N. Syrigos[8], M. Chadjaa[9], M. Wolf[10] [1]Perelman Center for Advanced Medicine, University of Pennsylvania, Philadelphia, PA, UNITED STATES OF AMERICA, [2]Yonsei Cancer Center, Yonsei University Health System, Seoul, KOREA, [3]Korányi National Institute of Pulmonology, Budapest, HUNGARY, [4]Klinikum Loewenstein, Loewenstein, GERMANY, [5]Princess Margaret Cancer Centre, Toronto, CANADA, [6]Vall d'Hebron University Hospital, Barcelona, SPAIN, [7]Poznan University of Medical Sciences, Poznan, POLAND, [8]Oncology Unit, 3rd Department of Medicine, Athens University School of Medicine, Sotiria General Hospital, Athens, GREECE, [9]Sanofi, Vitry-sur-Seine, FRANCE, [10]Division of Haematology and Oncology, Klinikum Kassel, Kassel, GERMANY

Aim: Platinum-based ctx is the 1L standard of care for SCLC, but despite high response rates, most SCLC pts experience rapid relapse and die from systemic metastases (mets). Therefore, more effective second-line (2L) treatments are needed. Taxanes are active 2L in SCLC, and Cbz is effective in 2L in other solid tumors. We compared Cbz vs Tpt in a randomized open-label Phase II trial in pts with SCLC who had progressed during/after 1L ctx (NCT01500720).

Methods: Pts with locally advanced or metastatic SCLC who had progressed during/after 1L platinum-based ctx, ECOG PS ≤1, ≤1 prior ctx and no prior taxane/Tpt treatment were enrolled. Pts received IV Cbz 25 mg/m^2 (Day 1 Q3W) or IV Tpt 1.5 mg/m^2 (Days 1–5 Q3W) (1:1 ratio). Pts were split into ctx-sensitive and ctx-refractory subgroups and stratified by brain mets (yes vs no) and lactate dehydrogenase (LDH) plasma concentration (≤ vs > upper limit of normal). Endpoints included progression-free survival (PFS; primary endpoint), overall survival (OS), safety and health-related quality of life.

Results: 179 pts (Cbz 90; Tpt 89) were randomized. Median age was 61 yrs. Baseline characteristics were balanced between treatment arms; approximately 50% of pts in each arm were ctx-refractory. Median number of cycles received was 2 (Cbz) and 4 (Tpt). Median PFS was 1.4 months (mo) (Cbz) and 3.0 mo (Tpt). The primary endpoint of improvement in PFS for Cbz vs Tpt was not met (log-rank test, 2-sided p<0.0001; HR=2.169, 95% CI 1.563, 3.010, 90% CI 1.648, 2.856). Similar results were observed in the ctx-sensitive and ctx-refractory subgroups. Cbz was less favorable than Tpt for OS (median: 5.2 mo Cbz, 6.8 mo Tpt; log rank test, 2-sided p=0.0125; HR=1.574, 95% CI 1.099, 2.253, 90% CI 1.165, 2.127). All-grade adverse events (AEs)

were more frequent with Tpt (94.3%) vs Cbz (88.8%), as were grade 3–4 AEs (Tpt 71.6%, Cbz 58.4%). Febrile neutropenia (Tpt 15.9%, Cbz 11.2%), neutropenic infection (Tpt 6.8%, Cbz 4.5%) and neutropenic sepsis (Tpt 1.1%, Cbz 3.4%) were similar across arms.

Conclusions: Cbz failed to meet the primary endpoint of superior PFS and showed less favorable median OS vs Tpt in pts with SCLC who had progressed during/after 1L ctx. No new safety concerns were identified.

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68P
PACLITAXEL PLUS BEVACIZUMAB IN PATIENTS WITH CHEMORESISTANT RELAPSED SMALL CELL LUNG CANCER AS SALVAGE TREATMENT: A PHASE II MULTICENTER STUDY OF THE HELLENIC ONCOLOGY RESEARCH GROUP

G. Mountzios[1], C. Emmanouilidis[2], N. Vardakis[2], E. Kontopodis[2], D. Hatzidaki[2], E. Popis[2], N. Karachaliou[2], A. Kotsakis[2], M. Agelidou[2], V. Georgoulias[2] [1]Medical Oncology, 251 Airforce General Hopsital, Athens, GREECE, [2]Medical Oncology, University of Crete School of Medicine, Herakleion, GREECE

Aim: Therapeutic options for patients with relapsed, chemo-resistant small-cell lung cancer (SCLC) are limited. Since paclitaxel has demonstrated single-agent activity in the second-line setting of SCLC and angiogenesis seems to play an important role in the pathogenesis of the disease, a phase II trial was conducted in order to evaluate the efficacy and the tolerance of their combination in patients with relapsed, chemo-resistant SCLC.

Methods: Patients with an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 2 who experienced relapse within 3 months after completion of 1st line chemotherapy for SCLC were eligible. Patients were treated with paclitaxel (90 mg/m2, days 1, 8 and 15) along with bevacizumab (10 mg per kgr of body weight, days 1 and 15) in cycles of 28 days.

Results: Thirty patients (male/female: 27/3) with a median age of 64 years and ECOG Performance Status 0/1/2: 2/25/3 were enrolled. Nineteen patients (63.3%) had received at least two lines of prior treatment, 17 (56.7%) had undergone prior radiotherapy and nine (30%) had brain metastases at the time of study entry. The overall objective response rate was 20% (95% CI: 5.69%-34.31%), including one complete remission, whereas the disease control rate was 36.7%. The median duration of response was 2.5 months (range, 1.5–5.7), the median progression-free survival 2.7 months (range, 0.5 – 9.2) and the median overall survival 6.3 months (range 0.5 – 17.9). Grade 3 and 4 toxicities were limited in neutropenia, diarrhea and fatigue. There was one case of non-fatal pulmonary embolism.

Conclusions: The combination of paclitaxel with bevacizumab was feasible and active in this poor prognosis and heavily pretreated population of patients with advanced, chemoresistant SCLC, representing a valid therapeutic alternative which merits further evaluation.

Disclosure: All authors have declared no conflicts of interest.

69P
MONOTHERAPY WITH SINGLE-AGENT TOPOTECAN SHOWS SIMILAR EFFICACY AND LESS TOXICITY COMPARED TO A COMBINATION TREATMENT WITH ADRIAMYCIN, CYCLOPHOSPHAMIDE AND VINCRISTINE (ACO) – A SINGLE CENTER EXPERIENCE

R. Hagmann, A. Zippelius, S. Rothschild Medical Oncology, University Hospital Basel, Basel, SWITZERLAND

Aim: Small-cell lung cancer (SCLC) accounts for about 10–15% of all lung cancer cases and has a dismal prognosis. Randomized trials established topotecan and the combination of adriamycin, cyclophosphamide and vincristine (ACO) as options for second-line therapy. In this study we evaluated the outcome of patients with SCLC with a special focus on patients undergoing a second-line chemotherapy at our institution.

Methods: 92 patients (67.4% male, mean age 63 years) with a histopathological diagnosis of SCLC between January 2000 and December 2010 at our institution were identified. Patients' characteristics, treatment delivery, response, outcome, toxicity and established prognostic parameters were evaluated. 85 patients (92.4%) were evaluable for outcome data.

Results: From the 22 patients (23.9%) diagnosed with limited disease (LD) SCLC 16 patients (72.7%) received platinum-based combined radio-chemotherapy (RCT) as first-line treatment. All patients received platinum-based chemotherapy as first treatment. 69 (98.5%) of the 70 patients diagnosed with extensive disease (ED) SCLC received first-line palliative chemotherapy. In the whole cohort, the median overall survival (OS) was 12.7 months (22.7 months for LD-SCLC and 10.2 months for ED-SCLC). 42 patients (46.1%) received a second-line therapy after having relapsed. The most frequently used regimen was ACO in 47.6% of patients. 31.0% of patients received intravenous topotecan. 8 patients (19.1%) were rechallenged with a platinum and etoposide. The treatment decision (ACO vs. topotecan) was not significantly related to any clinical parameter. Compared to topotecan ACO had a higher ORR (44.4% vs. 30.0%). Neither PFS (3.2 month vs. 3.2 month) nor OS (6.3 month vs. 6.6 months) did differ significantly. Patients treated with ACO showed more toxicity leading to inpatient care (51.2 vs. 39.2 days).

Conclusions: In this retrospective analysis including all patients with SCLC treated at our department between 2000 and 2010 we showed similar outcomes as reported in clinical trials. In the second-line setting the combination chemotherapy with ACO did not show superiority to intravenous topotecan but was associated with a clinically relevant longer hospitalization time. Therefore, we recommend intravenous topotecan as preferred option for second-line chemotherapy in patients with SCLC.

Disclosure: All authors have declared no conflicts of interest.

70P
SMALL CELL LUNG CANCER – THERAPEUTIC CHALLENGE. A LONG TIME SINGLE INSTITUTION EXPERIENCE

N. Chilingirova[1], D. Damyanov[1], G. Kurteva[1], S. Tonev[2], N. Dimitrova[2] [1]Medical Oncology Clinic, National Oncology Center, Sofia, BULGARIA, [2]Bulgarian National Cancer Registry, Bulgarian National Cancer Registry, Sofia, BULGARIA

Aim: Despite reported decrease in small cell lung cancer (SCLC) incidence, it still remains a considerable source of mortality. The aim of our study is to present a single institution experience on standard treatment of SCLC during the last 40 years, compare different treatment regiments and evaluate treatment efficiency and survival rates.

Methods: A retrospective study of the medical records of patients with histologically proven SCLC was performed for an interval of 40 years (1970–2010) in the National Oncology Center, Sofia.

Results: To verify the reliability of therapeutic regiments and median survival rates we have studied retrospectively a group of 144 patients (23 women, 121 men), median age by diagnosis – 57 years and median follow up time of 320 months, divided by age into 3 groups – to 55, between 55–65, and over 65 yo with median survival of 9,3 months and no statistically significant difference in survival by age, but statistically significant difference in the median overall survival (OS) by gender 8,9 months for males, and 12,6 for females. 69 of the patients were with LD and 75 with ED SCLC, median survival rates of 10,6 and 9,3 months respectively. Patients were divided in groups based on the induction chemotherapy they had received: Group 1 - Vincristine, Cyclophosphamide, Methotrexate(VCM) followed by radiotherapy(RT), Group 2 – Cyclophosphamide (C) followed by RT, Group 3 – VCM, Group 4 – C only, Group 5 – without treatment, Group 6 – Etoposide, Cisplatinum (EP) followed by RT, Group 7 – EP. Groups 1–4 include therapeutic regiments used before introducing EP as standard treatment for SCLC. According to

the subgroup analysis no statistically significant difference in OS rates was observed between groups 2-1, 2–4, 2–6, 2–7, 3–4, 4-1, 4–7, 6-1, 7-1 and 6–7, which gives no superiority of EP/RT and EP over VCM/RT and C/RT. Old therapeutic regiments showed no statistically significant difference between VCM/RT - C/RT and VCM - C, but pointed the role of RT for some improvement in survival rates. Generall comparison between old and new regiments gives superiority to EP+/-RT.

Conclusions: Although there were some advances after introduction of new therapeutic regiments, changes in OS rates remain relative small, there is no dramatic change in outcomes and treatment of SCLC still remains a challenge, which makes it important to look for new therapeutic options.

Disclosure: All authors have declared no conflicts of interest.

71P
INVESTIGATING MOLECULAR BIOMARKERS IN SCLC

F. Abdelraouf[1], D. Gonzalez de Castro[2], A. Wotherspoon[3], M. Maurya[2], D. Mair[2], J. Bhosle[4], S. Popat[4], M. O'Brien[4] [1]Departments of Medicine and Clinical Pathology, The Royal Marsden NHS Foundation Trust and Cairo University, Surrey, UNITED KINGDOM, [2]Department of Molecular Diagnostics, The Royal Marsden NHS Foundation Trust, The Institute of Cancer Research, Surrey, UNITED KINGDOM, [3]Department of Histopathology, The Royal Marsden Hospital NHS Foundation Trust, Surrey, UNITED KINGDOM, [4]Department of Medicine, The Royal Marsden Hospital NHS Foundation Trust, Surrey, UNITED KINGDOM

Aim: Small cell lung cancer (SCLC) is an aggressive cancer that relapses quickly after conventional treatment. Molecular biomarkers have been investigated in non-small cell lung cancer (NSCLC) and targeted treatments in advanced disease are established. Currently there are no established targeted therapies in SCLC and the aim of this study was to examine for the presence of known molecular targets in patients with SCLC.

Methods: A panel of histopathologically proven formalin fixed paraffin embedded (FFPE) specimens of SCLC diagnosed between 1990 and 2010 were analysed for EGFR, KRAS, NRAS, BRAF mutations, ALK gene rearrangements and MET amplification. EGFR and KRAS testing were done using real time-polymerase chain reaction (RT-PCR cobas®), BRAF and NRAS using capillary electrophoresis-single strand conformation analysis (CE-SSCA) and ALK and MET using fluorescent in situ hybridization (FISH). Any positive results were repeated for confirmation. Any inconsistent results were sequenced using the direct Sanger sequencing. .

Results: A hundred and five cases of SCLC were identified and 75 FFPE blocks retrieved. Sixty samples were suitable for molecular testing, with 25 examined for all 6 molecular targets successfully. No mutations in EGFR were detected in 31 cases suitable for analysis. KRAS and NRAS mutational analysis was successful in 35 and 37 cases respectively; all of which were wild type. Fifty-eight cases were assessed for ALK gene rearrangements and 42 cases for MET gene amplifications; no rearrangements or amplifications were detected. Forty-seven samples were successfully analysed for BRAF gene mutation, with one V600E mutation detected (2.1% of cases). This patient was a 55 years old Caucasian male smoker who was diagnosed as SCLC, limited stage. He had a history of squamous cell carcinoma diagnosed 6 months prior to the SCLC diagnosis (treated by lobectomy). He responded well to his SCLC treatment (radical chemoradiotherapy and prophylactic cranial irradiation). He died nine months after diagnosis.

Conclusions: EGFR, KRAS, NRAS, ALK and MET were not detected in the examined panel of SCLC patients. A BRAF mutation was identified in a single patient with a recent diagnosis of squamous cell carcinoma of the lung, suggesting a mixed pathology tumour rather than a biomarker in SCLC. This panel of biomarkers should no longer be explored in SCLC.

Disclosure: All authors have declared no conflicts of interest.

72P
OVERCOMING MACROPHAGE IMMUNOSUPPRESSION IN SMALL CELL LUNG CANCER WITH HIGH-AFFINITY SIRPA VARIANTS

K. Weiskopf[1], P.J. Schnorr[1], N. Jahchan[1], A. Ring[1], A. Volkmer[1], J. Volkmer[1], K.C. Garcia[2], J. Sage[1], I.L. Weissman[1] [1]Institute for Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine, Stanford, CA, UNITED STATES OF AMERICA, [2]Molecular and Cellular Physiology, Stanford University School of Medicine, Stanford, CA, UNITED STATES OF AMERICA

Aim: CD47 is a cell-surface molecule that allows cancer cells to evade the immune system by signaling through SIRPa, an inhibitory receptor on macrophages. Therapies that block CD47 stimulate macrophage phagocytosis and destruction of cancer cells. Here, we hypothesized that CD47-blocking therapies could be used as effective treatments for small cell lung cancer (SCLC) in preclinical models. We aimed to identify new tumor antigens on SCLC cells and target them in combination with CD47-blocking therapies.

Methods: To examine CD47 expression levels and identify novel SCLC-specific antigens, we screened SCLC samples by high-throughput flow cytometry using LEGENDScreen comprehensive antibody arrays. We evaluated the ability of CD47-blocking therapies to stimulate phagocytosis using primary macrophages and SCLC cells. The therapeutic efficacy of CD47 blockade was evaluated in vivo using mouse xenotransplantation models of SCLC.

Results: We found all SCLC samples tested expressed high levels of CD47 on their surface. Moreover, we identified CD99, CD56, CD166, CD326, and CD164 as antigens highly expressed on the surface of SCLC cells. Using purified macrophages in vitro, we found that CD47-blocking therapies were able to induce macrophage phagocytosis of SCLC cell lines and primary patient samples, especially when combined with antibodies to the identified tumor antigens. In xenotransplantation models, CD47-blocking therapies were able to inhibit tumor growth and significantly prolong survival of mice engrafted with human SCLC.

Conclusions: We found that SCLC cells are susceptible to destruction by macrophages of the innate immune system upon CD47-blockade. Therefore, our study validates CD47 as a therapeutic target for SCLC and provides rationale for translation to the clinic. Comprehensive flow cytometry-based profiling proved valuable for identifying new tumor antigens. Combining SCLC-specific antibodies with CD47-blocking therapies is an optimal approach to maximizing macrophage mediated-destruction of SCLC.

Disclosure: All authors have declared no conflicts of interest.

73P
INVESTIGATING NEUROENDOCRINE MARKERS OF SMALL CELL LUNG CANCER

T. Layton Faculty of Life Sciences, University of Manchester, Oxford, UNITED KINGDOM

Aim: Small cell lung cancer (SCLC) is a widespread and devastating disease. SCLC tumours contain a neuroendocrine cell population that exhibit ectopic hormone production in a minority of patients. The aim of this study was to investigate a panel of neuroendocrine peptides as potential biomarkers fof SCLC, including pro-opiomelanocortin, neuron specific enolase, chromogranin A and neural-cell adhesion molecule. This study validates further investigation into the neuroendocrine phenotype in SCLC, and POMC as a potential biomarker for the disease.

Methods: Immunohistochemistry methods were used to examine neuroendocrine peptides in five human lung cancer cell lines (CORL24, CORL47, DMS79, H526, A549) and a novel murine subcutaneous SCLC xenograft tumour. Liver, lung and brain samples were taken from xenograft mice to identify possible metastasis. ELISA measured POMC secretion and expression in cell lines during incubation and a Western Blot quantified chromogranin A levels in all cell lines and xenograft tumours.

Results: Results confirmed a significant neuroendocrine cell population within SCLC xenograft tumours and cell lines.Results confirmed a

significant neuroendocrine cell population within SCLC xenograft tumours and cell lines. Additionally, POMC secretion proved to be a marker of SCLC growth in vitro in CORL24 and DMS79. H526, CORL47 and A549 did not secrete POMC. Xenograft tumours appeared invasive with infiltration of surrounding connective tissue, but no metastases were present in liver, lung and brain samples.

Conclusions: This study validates further investigation into the neuroendocrine phenotype in SCLC, and POMC as a potential biomarker for the disease.

Disclosure: All authors have declared no conflicts of interest.

EARLY STAGE NSCLC

74PD
WHEN IS A PATHOLOGICAL DIAGNOSIS PREFERRED BEFORE STEREOTACTIC ABLATIVE RADIOTHERAPY (SABR) FOR STAGE I LUNG CANCER? A DECISION ANALYSIS

A.V. Louie[1], M.G. Hunink[2], P. Patel[3], B.S. Ferket[2], F.J. Lagerwaard[1], G.B. Rodrigues[4], J.K. Salama[3], C. Kelsey[3], D.A. Palma[4], S. Senan[5] [1]Radiation Oncology, VU University Medical Center, Amsterdam, NETHERLANDS, [2]Department of Epidemiology, Center for Health Decision Sciences, Harvard School of Public Health, Boston, MA, UNITED STATES OF AMERICA, [3]Radiation Oncology, Duke University, Durham, NC, UNITED STATES OF AMERICA, [4]Radiation Oncology, London Regional Cancer Program, London, CANADA, [5]Radiation Oncology, Vrije University Medical Centre (VUMC), Amsterdam, NETHERLANDS

Aim: In unfit patients who are at increased risk for complications from a biopsy, SABR for a solitary pulmonary nodule (SPN) is acceptable after review by a multidisciplinary tumor board [ESMO recommendations 2013]. We performed a decision analysis that can be employed to inform the appropriate lung cancer prevalence threshold of when this strategy is warranted.

Methods: A decision tree and Markov model were constructed to evaluate the relative merits of 1) observation, 2) performing SABR without pathologic confirmation of malignancy, or 3) performing a transthoracic biopsy prior to SABR, when faced with a SPN at different lung cancer prevalences. Diagnostic test performance characteristics were extracted from the literature. Toxicity and recurrence rates, as well as health utilities (derived via mapping procedures) were abstracted from a prospectively collected database of 382 patients receiving SABR for confirmed or suspected stage I NSCLC. Deterministic and probabilistic sensitivity analyses on all model inputs were performed to assess their effect on predicted prevalence thresholds between 3 treatment strategies. The model was constructed with a 5-year time horizon using a cycle length of one month; quality adjusted life years (QALYs) were discounted at a rate of 3%.

Results: The model was validated internally with source data and externally by predicting for results consistent with published recurrence and survival outcomes. In the base case analysis, the prevalence threshold between strategies 1 (observation) and 2 (SABR without pathology) was 17.0%; and 85.0% between strategies 2 and 3 (performing transthoracic biopsy prior to SABR). The latter finding was confirmed on probabilistic sensitivity analysis (85.2%; 95% confidence interval: 80.0% – 87.2%). The predicted prevalence threshold of 85.0% was most sensitive to the variability in the diagnostic sensitivity of transthoracic biopsy (prevalence range: 77.2 – 94.0%).

Conclusions: SABR appears warranted for a SPN in the absence of pathologic confirmation if the prevalence of lung cancer is above 85%, a finding that is dependent on the diagnostic performance of biopsy within the area of practice.

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75PD
EFFICACY BY T CATEGORIES OF THE POSTOPERATIVE ADJUVANT IMMUNOTHERAPY WITH UBENIMEX (BESTATIN○R) ON SURVIVAL IN PATIENTS WITH STAGE I SQUAMOUS-CELL LUNG CANCER: AN EXPLORATORY ANALYSIS FROM A RANDOMIZED PHASE III STUDY

M. Tsuboi[1], H. Kato[2] [1]Thoracic Surgery & Oncology, Yokohama City University Medical Center, Yokohama, JAPAN, [2]Thoracic Surgery & Oncology, Tokyo Medical University, Tokyo, JAPAN

Aim: The 7th Edition of the TNM Classification of Malignant Tumors in non-small cell lung cancer (NSCLC) has demonstrated a more detailed classification of primary tumor diameter. Stage IA T1 disease is subdivided into two groups: T1a disease (tumor diameter, < or = 2 cm) and T1b disease (tumor diameter, >2 to < or = 3 cm). Ubenimex (BestatinR), which is a competitive protease inhibitor of aminopeptidase N (CD13) and aminopeptidase B, improves survival in patients with stage I squamous-cell lung cancer (JNCI 2003; 98:605–610). However, whether it is effective in patients with each subset of T categories, such as T1b and T2a, remains controversial. The objective of this study was to further explore the effectiveness of Ubenimex.

Methods: Data from a randomized double-blind placebo-controlled trial of Ubenimex in patients with resected stage I squamous-cell lung cancer were reanalyzed to evaluate the effectiveness of Ubenimex according to T1a, T1b and T2a tumors based on UICC7-TNM classification.

Results: Data from 398 patients were analyzed: 108 (27.1%) had T1a tumors, 100 (25.1%) had T1b tumors, and 190 (47.8%) had T2a tumors. In the surgery-alone group, overall survival rates (OS) at 5 years were 80.4% in patients with T1a tumors, 80.9% in those with T1b tumors, 68.0% in those with T2a tumors. On the other hand, in the adjuvant treatment group with Ubenimex, OS at 5 years were 88.2% in patients with T1a tumors, 79.2% in those with T1b tumors, and 77.9% in those with T2a tumors. In patients with T2a tumor, both the overall survival rate and the recurrence free survival were significantly higher in the Ubenimex group than in the surgery-alone group (hazard ratio = 0.63 and 0.67, log-rank p = 0.026 and 0.025, respectively). The hazard ratio for death in the Ubenimex group when compared with the surgery-alone group was 0.75 for those with T1a-b disease (95% confidence interval, 0.42–1.34).

Conclusions: This exploratory analysis demonstrated that postoperative adjuvant therapy with Ubenimex significantly improved survival in patients with stage IB, T2aN0 NSCLC compared with surgery alone. The confirmatory adjuvant phase III study with Ubenimex for stage I squamous-cell lung cancer is warranted.

Disclosure: All authors have declared no conflicts of interest.

76P
ADJUVANT CHEMOTHERAPY IN RESECTED NSCLC: TREATMENT FACTORS THAT IMPACT SURVIVAL OUTCOMES

K. Ramsden, J. Laskin, C. Ho Medical Oncology, British Columbia Cancer Agency, Vancouver, BC, CANADA

Aim: Platinum-based adjuvant chemotherapy is the standard of care for resected stage II non-small cell lung cancer (NSCLC). In practice, the proportion of patients who receive adjuvant treatment is limited and the dose delivered is often reduced compared to the clinical trials. The purpose of this population-based study was to identify factors that predict for receiving adjuvant therapy and assess the impact of delayed administration and dose reduction on survival.

Methods: The British Columbia Cancer Agency (BCCA) provides cancer care to a population of 4.5 million. A retrospective review was conducted

on all patients diagnosed with stage II NSCLC who underwent resection and were referred to the BCCA between 2005 and 2010.

Results: Of 258 stage II NSCLC patients, 158 received adjuvant chemotherapy (61%). No-adjuvant versus adjuvant population: M 52%/57%, median age 67/62, ECOG <=1 55%/75%, Charlson comorbidity index <=1 61%/74%, pneumonectomy 11%/26% respectively. On multivariate analysis (MVA): younger age, better ECOG and pneumonectomy were predictive of adjuvant treatment. In patients who received chemotherapy: cisplatin/carboplatin 81%/19%, maximum cycles received 1/2/3/4 - 10%/9%/9%/72%, number of weeks from surgery to adjuvant chemotherapy <8/8–10/10–12/>12 - 11%/40%/25%/24%, percent of total planned dose received <50%, 50–75%, >75% - 12%/11%/77%. On MVA, patients who received less than 80% of their total planned platinum dose had poorer overall survival (HR 2.06, p=0.014). Time from surgery to adjuvant chemotherapy did not have a significant effect on overall survival (all intervals NS).

Conclusions: Factors associated with better functional status (younger age, good ECOG) and pneumonectomy predicted for adjuvant chemotherapy. For patients who received adjuvant chemotherapy the total platinum dose administered impacted survival. The type of platinum and time from surgery, however, did not. We conclude that achieving a platinum dose delivery of 80% or greater is important in maintaining the efficacy of adjuvant chemotherapy for resected stage II NSCLC in this retrospective population-based study.

Disclosure: All authors have declared no conflicts of interest.

77P
ADJUVANT CHEMOTHERAPY IN RESECTED STAGE IB-III NON SMALL CELL LUNG CANCER

B. Zhang[1], H-L. Wong[1-2], D. Gunawardana[2], P. Parente[1], R. de Boer[2], A. Barling[3], P. Antippa[4], R. Wong[1] [1]Medical Oncology, Eastern Health, Box Hill, AUSTRALIA, [2]Medical Oncology, Royal Melbourne Hospital, Parkville, AUSTRALIA, [3]Cardiothoracic Surgery, Eastern Health, Box Hill, AUSTRALIA, [4]Cardiothoracic Surgery, Royal Melbourne Hospital, Parkville, AUSTRALIA

Aim: A substantial proportion of patients (pts) with resected stage I, II or III non small cell lung cancer (NSCLC) recur and die. Adjuvant chemotherapy (CT) using platinum-based regimens is recommended for pts with stage II and III NSCLC, and may have a role in stage IB disease. The aim was to evaluate the role of adjuvant CT following complete resection of NSCLC in a real life setting.

Methods: A retrospective analysis was conducted on pts who underwent surgical resection of stage IB-III NSCLC at two tertiary institutions in Melbourne, Australia between 1 July 2006 and 30 June 2012. Follow up was to 30 September 2013. Pts who received neo-adjuvant CT or post-operative combined chemoradiation were excluded.

Results: 127 pts were identified with a median age of 68.9 years and a median follow up of 41 months. 45 pts (35%) received adjuvant CT. The proportion of pts receiving CT increased with higher tumour stage; Stage IB – 7%, Stage II – 38%, Stage III – 68%. The median time to commencing CT post-operatively was 6.4 weeks (range 3.4–17.1). The commonest regimens used were cisplatin-vinorelbine, carboplatin-vinorelbine and carboplatin-paclitaxel. The median number of cycles was 4 (range 1–5). 84% of pts completed treatment. CT recipients had a longer median time to relapse (12.3 vs 10.4m). By stage, median time to relapse was 10.4 vs 7.4m (stage II) and 12.6 vs 4.3m (stage III) for pts receiving CT vs no CT. Overall survival (OS) was 59.3m (no CT) vs not reached (CT). When stratified by stage, CT was associated with significantly increased OS in stage II disease (not reached vs 48.5m, p=0.05) and a trend toward increased OS in stage III disease (not reached vs 30.1m). Median relapse free survival (RFS) and OS were worse for those who received <3 vs ≥3 cycles of CT: 12.6 vs 29.2m and 17.1m vs not reached, respectively. Choice of platinum backbone did not impact on RFS or OS. There was no significant difference in RFS or OS for those who commenced CT: ≤6 vs >6 wks, or ≤8 vs >8 wks post-operatively.

Conclusions: Overall survival was superior in patients with resected stage II-III NSCLC who received platinum-based adjuvant chemotherapy. Survival was influenced by the number of chemotherapy cycles received, but not by choice of platinum backbone, or time to starting chemotherapy.

Disclosure: All authors have declared no conflicts of interest.

78P
REPLICATION OF RESULTS OF A GENOME-WIDE ASSOCIATION STUDY ON LUNG CANCER SURVIVAL IN A KOREAN POPULATION

M.J. Hong[1], S.S. Yoo[2], H. Jeon[1], S.Y. Lee[2], E. Lee[3], J.Y. Park[2] [1]Department of Biochemistry and Cell Biology, Kyungpook National University School of Medicine, Daegu, KOREA, [2]Internal Medicine, Kyungpook National University School of Medicine, Daegu, KOREA, [3]Department of Thoracic Surgery, Kyungpook National University School of Medicine, Daegu, KOREA

Aim: Recently, a genome-wide association study (GWAS) has identified single nucleotide polymorphisms (SNPs) which may influence the prognosis of early-stage non-small cell lung cancer (NSCLC) in Caucasians. We attempted to replicate the impact of genetic variants identified in the GWAS for lung cancer survival in a Korean population.

Methods: Three hundred and sixty-three patients with surgically resected NSCLCs were enrolled. Twelve SNPs were genotyped by using SEQUENOM's MassARRAY® iPLEX assay, TaqMan assay, or a polymerase chain reaction-restriction fragment length polymorphism assay. The association between genotypes and overall survival (OS) was analyzed.

Results: Among the 12 SNPs, rs6034368T>C was associated with OS. Patients with the rs6034368C allele showed a better OS than the rs6034368T allele (adjusted hazard ratio = 0.72, confidence interval = 0.56–0.93, P = 0.01). The rs12446308A>G had an effect on OS, with marginal significance (under a codominant model, adjusted hazard ratio = 1.85, confidence interval = 0.98–3.47, P = 0.06). The association of the rs6034368T>C with the survival outcome was further examined after categorizing the patients by clinicopathological factors such as age, gender, smoking status, pack-years, histologic type, pathologic stage, and adjuvant therapy. The effect of the rs6034368T>C on OS was not different according to these factors (P values for homogeneity test > 0.05).

Conclusions: In the present study, we attempted to replicate the association between the 12 genetic variants identified in the GWAS in Caucasians and survival of early-stage NSCLC in a Korean population. Among the 12 SNPs, rs6034368T>C was significantly associated with OS and the rs12446308A>G had an effect on OS, with marginal significance.

Disclosure: All authors have declared no conflicts of interest.

79P
ROLE OF EXPRESSION LEVELS OF FABP3, H19, TFPI2, ARK1B1 CYP3A5, SCGB3A2 GENES IN ADENOCARCINOMA STAGE I PATIENTS.

L. Crinò[1], V. Ludovini[1], A. Siggillino[1], F. Bianconi[2], F.R. Tofanetti[1], L. Pistola[1], G. Metro[1], M. Ragusa[3], A. Sidoni[4], F. Puma[3] [1]Medical Oncology Division, Ospedale S. Maria della Misericordia, Perugia, ITALY, [2]Department of Electronic and Information Engineering, Perugia University, Perugia, ITALY, [3]Department of Thoracic Surgery, University of Perugia, Perugia, ITALY, [4]Institute of Pathological Anatomy and Histology, University of Perugia, Perugia, ITALY

Background: In a previous study, we compared gene expression profiling from adenocarcinoma (ADC) specimens and normal lung (NL) tissue with non relapse (NR) and early relapse (ER), and we selected 5 genes up-regulated and 4 genes down-regulated were predictive for clustering patients (pts) (Siggillino et al. ECCO 2011). Here, we validate our results using an independent cohort of patients with lung ADC stage I

Methods: We selected 58 frozen specimens of lung stage I ADC tissue with corresponding NL from tissue banking of 180 resected NSCLC. Quantification of mRNA expression levels of 9 genes (5 up-regulated:CLCA2, FABP3, H19, TFPI2, ARK1B1 and 4 down-regulated: CYP3A5, ALDH3A1, SCGB3A2, SCGB1A1, were analyzed by real-time one-step RT-PCR using QuantiFast technology.

Results: Fifty-eight ADC stage I pts were evaluable, 17% of which had an ER. Among all genes evaluated, the NR vs ER mean expression levels of two

genes down-regulated (CYP3A5, 1.09 vs 0.30; SCGB3A2, 2.28 vs 0.98) and two genes up-regulated (ARK1B1, 4.53 vs 34.20; FABP3 1.25 vs 1.55) were superimposable respect to the results of previous microarray analysis. The median disease free survival (DFS) and overall survival (OS) were 21 and 23 months, respectively. In the logistic multivariate analysis the mean expression levels of all genes showed a tendency to predict the ER in the overall population (p=0.07). Nevertheless considering only the expression levels of genes (FABP3, H19, TFPI2, ARK1B1 CYP3A5, SCGB3A2) identified as significant with t-test, the covariates in multivariate analysis increased their capacity of ER prediction (p= 0.028).

Conclusions: Our results indicate that it is possible to define, through gene expression, a characteristic gene profiling of early relapse tumor patients with an increased risk of relapse disease. The contemporary expression levels of 6 genes (FABP3, H19, TFPI2, ARK1B1 CYP3A5, SCGB3A2) predicted a worse DFS. Such features may have important implications for future targeted therapies. We thank Italian Association for Cancer Research (AIRC) for supporting the study.

Disclosure: All authors have declared no conflicts of interest.

LOCALLY ADVANCED NSCLC

80O
DETERMINANTS OF SURVIVAL IN 7.214 PATIENTS WITH STAGE III NSCLC TREATED WITH CHEMORADIOTHERAPY IN THE NETHERLANDS

J. Belderbos[1], J. Widder[2], H. Groen[3], R.A. Damhuis[4] [1]Radiation Oncology, The Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Amsterdam, NETHERLANDS, [2]Radiation Oncology, University Medical Center Groningen, Groningen, NETHERLANDS, [3]Pulmonology, University Medical Center Groningen, Groningen, NETHERLANDS, [4]Comprehensive Cancer Centre, Utrecht, NETHERLANDS

Aim: Chemoradiotherapy (CRT) for stage III non-small cell lung cancer (NSCLC) is a curative treatment that involves sequential or concurrent chemotherapy. The landmark meta-analysis by Auperin (2010) reported a five-year survival of 10.6% in sequential setting, as opposed to 15.1% in concurrent setting. However, that analysis comprised only 1205 patients and most of these had been treated before the year 2000. Since then, modern radiation techniques (IMRT, image guided RT) and staging examinations (FDG-PET and brain CTscan or MRI) were introduced. In the Netherlands, a national guideline was introduced in 2004, advocating concurrent CRT, but chemo- and radiotherapy regimes are known to differ between regions. The aim of our study was to assess time trends and regional differences in overall survival (OS) for patients receiving CRT.

Methods: Data from the Netherlands Cancer Registry were queried for patients diagnosed with stage III NSCLC from 2003 to 2011. Evaluation concerned age, gender, histopathology, TNM stage, year of treatment and treatment modality. Information regarding WHO performance score or CRT regimen (concurrent or sequential) was not available. Results were anonymously stratified by region (n=9) and radiotherapy department (n=21). Survival data were calculated from day of diagnosis and analysed using multivariable proportional hazards analysis.

Results: The total study group comprised 20.432 patients and 7.214 (35%) were treated with CRT. CRT use increased from 25% in 2003 to 46% in 2011. Median OS for patients treated with CRT was 19 months and five-year OS was 18%. Median OS improved from 16 months in 2003 to 21 months in 2011. Five-year OS improved from 14% in 2003–2005 to 20% in 2006–2008 (p<0.001). Multivariable analysis designated age, stage, gender and year of diagnosis as prognostic factors. Survival rates remained stationary after 2005. Histopathology type, region and radiotherapy department had no prognostic influence on OS.

Conclusions: Despite regional variation in treatment regimens for stage III NSCLC, the 5-year OS increased for all centers in the Netherlands and compares favorably with the recent meta-analysis. This improvement may be explained by better patient selection and the introduction of modern radiotherapy techniques.

Disclosure: All authors have declared no conflicts of interest.

81O
POTENTIALLY FUNCTIONAL SINGLE NUCLEOTIDE POLYMORPHISMS IN CD133 PREDICT LOCAL RECURRENCE AND DISTANT METASTASIS AFTER RADIOTHERAPY FOR NON-SMALL CELL LUNG CANCER

Q. Wang[1], P. Li[1], H. Liu[2], H. Xiong[2], J. Qian[2], T. Xu[3], Z. Liu[2], Z. Liao[3], Q. Wei[2] [1]Department of Internal Medicine, Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, CHINA, [2]Departments of Epidemiology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, UNITED STATES OF AMERICA, [3]Departments of Radiation Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, UNITED STATES OF AMERICA

Aim: Cancer stem cells are believed to be involved in resistance to radiotherapy and chemotherapy and responsible for local recurrence and distant metastasis. We hypothesized that genetic variations in CD133 (also called PROM1), an important marker gene of cancer stem cells, affect clinical outcomes among patients with non-small cell lung cancer (NSCLC) treated with definitive radiotherapy.

Methods: We identified 393 patients with primary NSCLC who had received definitive radiotherapy at a single institution between March 1998 and February 2009. We genotyped four potentially functional single nucleotide polymorphisms (SNPs) of CD133 (rs2240688A>C, rs10022537A>T, rs7686732G>C, and rs3130T>C) and estimated their associations with local recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), and overall survival (OS) by using Cox proportional hazards models.

Results: The rs2240688 SNP was found to be associated with LRFS and DMFS after adjustment for patient characteristics. Specifically, patients with the rs2240688C variant genotypes (AC/CC) had longer LRFS (log-rank P=0.048, adjusted hazard ratio [HR] =0.74, 95% CI 0.58–0.96, adjusted P=0.023) and DMFS (log-rank P =0.059, adjusted HR=0.76, 95% CI 0.59–0.98, adjusted P=0.032) than did patients with the AA genotype. In stratified analysis, associations of the AC/CC variant genotypes with LRFS, DMFS, and OS were the strongest among patients with stage III-IV disease, or those who received <66 Gy in log-rank test and multivariable Cox models analysis.

Conclusions: Our findings suggest that rs2240688 SNP in CD133 may be marker for prognosis in patients with NSCLC, if confirmed in larger, prospective studies.

Disclosure: All authors have declared no conflicts of interest.

82PD
EUROPEAN HARMONIZATION STUDY FOR THE IMMUNOHISTOCHEMICAL DETECTION OF ALK-REARRANGED NSCLC (ON BEHALF OF ALL 16 PARTICIPATING INSTITUTES ENROLLED IN THE STUDY)

M. von Laffert[1], A. Warth[2], R. Penzel[2], P. Schirmacher[2], D. Lenze[1], M. Hummel[1], M. Dietel[1] [1]Institue of Pathology Charité, Charite Berlin Mitte, Berlin, GERMANY, [2]Pathology, University Hospital, Heidelberg, GERMANY

Aim: The reliable identification of ALK-gene rearranged NSCLC is crucial for the treatment with ALK-inhibitors. Even though fluorescence in-situ hybridization (FISH) is regarded as the diagnostic gold standard, studies based on immunohistochemistry (IHC) seem promising. However, such an approach is only applicable if it is validated and standardized for multi-centre use.

Methods: To test the reliability of an ALK IHC assay in a multi-centre environment (16 European institutes), two tissue microarrays (TMA) consisting of 15 NSCLC cases (3 cores/case; diameter: 1 mm/core) were independently tested for ALK-protein expression (binary interpretation: positive vs. negative) by each laboratory using the Ventana ALK (D5F3) Rabbit Monoclonal Primary Antibody combined with OptiView DAB IHC detection and OptiView Amplification kits. Included cases were unequivocal ALK break-positive (6x), negative (7x) and ALK positive-"borderline" (2x) as demonstrated by FISH. The latter show a low percentage of ALK break-positive

cells (around the cut-off of 15%) and are challenging for unequivocal FISH-diagnosis. ALK breaks were confirmed by EML4-ALK-RT-PCR. To provide a uniform baseline interpretation, a webinar-based training was given to all observers.

Results: All 7 ALK FISH-negative cases were homogenously scored negative after ALK-IHC. All participants scored the 2 ALK positive-"borderline" cases as positive according to their ALK protein expression (RT-PCR: EML4-ALK Variant 1 and 3a/b). Concordant IHC interpretation was also noticed in 4 of 6 unequivocal ALK positive cases. In the remaining 2 ALK-FISH positive cases, a weak and heterogeneous staining was described by some observers, which would have resulted in subsequent testing (FISH/ PCR) in their diagnostic setting.

Conclusions: After harmonization of the staining instruments and training of the observers, ALK IHC using the D5F3 clone in combination with OptiView detection can be regarded as a very reliable technique for the detection of ALK protein expression and is applicable for multi-centre use. So far, this ALK IHC assay might help as an alternative predictive test in cases with reduced FISH interpretability and could lead to broad use of ALK testing. However, further investigation is needed to implement this test as the stand-alone pre-screening tool.

Disclosure: All authors have declared no conflicts of interest.

83P
SURGICAL RESULTS FOR T4 NSCLC INVADING MEDIASTINAL STRUCTURE

H.W. Lee[1], M.C. Kang[1], J.H. Park[1], J.S. Koh[2], H.J. Yoo[3], C.H. Kim[4], D.W. Choe[5] [1]Thoracic Surgery, Korea Cancer Center Hospital, Seoul, KOREA, [2]Pathology, Korea Cancer Center Hospital, Seoul, KOREA, [3]Radiation Oncology, Korea Cancer Center Hospital, Seoul, KOREA, [4]Pulmonology, Korea Cancer Center Hospital, Seoul, KOREA, [5]Radiology, Korea Cancer Center Hospital, Seoul, KOREA

Aim: Non-small cell lung cancer (NSCLC) with invasion of mediastinal structures is now classified as stage IIIA or IIIB according to N stages, and has been considered a surgically unfavorable category. However, in a selected group of these patients, better results have been reported after surgical resection compared with the non-surgical group. The aim of this study is to evaluate the role of surgical resection in treatment of mediastinal T4 NSCLC and risk factors that need to be considered.

Methods: From 1999 to 2012, 407 patients received treatment for non-small cell lung cancer invading mediastinal structures. Among them, 108 patients (Group I) received initially surgery and 297 patients(Group II) received chemotherapy or chemoradiation therapy as initial treatment. Their medical records were reviewed and they were followed up completely until April 2013. We compared the clinilcal outcomes of both groups.

Results: Among group I patients, R0 resection was possible in 83 (77%) and their overall 5 year survival rate was 19%. Operative mortality was 8.4%, and 80.7% was squamous cell carcinoma. Among group II patients, 31 (10.4%) patients underwent surgery after initial chemotherapy or chemoradiation therapy and their overall 5year survival rate was 17%. When nodal stage was N0 or N1, there was a significant survival difference between the two groups. (30.5% vs 19%, p=0.001) In group I, complete resection (p<0.0001) and adjuvant chemotherapy (p=0.013) were significant prognostic factors.

Conclusions: The operative risk of NSCLC invading mediastinal structures was high because of the high rate of pneumonectomy and wider range of resection, however it can be acceptable. Long-term outcome of the surgery group was better than the non-surgery group in selected patients (N0-1). When chemotherapy is executed as an initial therapeutic option, only 10.4% patients could receive complete resection. This study is not a randomized controlled trial study; however, our results imply that an aggressive surgical appraoch can be recommended in selected patients with good performance and N2(-) mediastinal T4 lesions.

Disclosure: All authors have declared no conflicts of interest.

84P
POSTOPERATIVE RADIOTHERAPY IN RESECTED STAGE III-N2 NON-SMALL CELL LUNG CANCER (NSCLC): CAN 3D-CONFORMAL RADIOTHERAPY IMPROVE THE 5-YEAR OVERALL SURVIVAL (OS) IN PATIENTS WITH PERSISTENT N2 DISEASE AFTER INDUCTION CHEMOTHERAPY?

C. Billiet[1], Z. Gouw[1], H. Decaluwé[2], S. Peeters[1], J. Vansteenkiste[3], C. Dooms[4], P. De Leyn[2], D. De Ruysscher[5] [1]Radiaton Oncology, University Hospitals Leuven, Leuven, BELGIUM, [2]Thoracic Surgery and Leuven Lung Cancer Group, University Hospitals Leuven/ KU Leuven, Leuven, BELGIUM, [3]Respiratory Oncology Unit (Pulmonology), University Hospitals Leuven - Campus Gasthuisberg, Leuven, BELGIUM, [4]Department of Pulmonology and Leuven Lung Cancer Group, University Hospitals Leuven - Campus Gasthuisberg, Leuven, BELGIUM, [5]Radiation Oncology, University Hospitals Leuven - Campus Gasthuisberg, Leuven, BELGIUM

Aim: To investigate the effect on 5-year OS of modern postoperative radiotherapy (PORT) in NSCLC patients with persistent N2 disease after induction chemotherapy.

Methods: Patients with pathologically proven N2 NSCLC who received induction chemotherapy followed by surgery were selected from a prospective database. In order to have at least 2 years of follow-up, we selected September 1999 to December 2010 as inclusion period. 103 patients without progressive disease after chemotherapy underwent resection. 95% of patients were staged with FDG PET and 85% underwent brain imaging. In case of incomplete resection or persistent ypN2 status, patients received 3D-PORT (n=53) to a dose of 50–66 Gy in 2 Gy QD fractions. Patients with a complete resection and nodal downstaging to ypN0 or ypN1 did not receive further therapy.

Results: Median follow up time was 46.3 months. For the entire operated group of (n=103), the 5-year outcome were: OS 31.3%, relapse free survival (RFS) 29.8%, 5-year cumulative local recurrence (LR) rate 51.0%. For the ypN2 or R1-2 resection (PORT) patients, the 5-year results were: OS 27.8 %, RFS 28.0 %, LR 52.3%; for the ypN0-1 R0 group OS 35.7 %, RFS 32.0 %, LR 49.3 % (table 1). None of these differences reached statistical significance. In a multivariate analysis for OS, significant parameters for a better survival were PORT, downstaging after chemotherapy and completeness of surgical resection. **Table: % 5-year results (OS, RFS, LR) in different subgroups**

	Whole group	ypN0-1 R0 resection (no PORT)	ypN2 or R1 resection (with PORT)
n	103	50	53
OS	31.3%	35.7%	27.8% (p=0.84)
RFS	29.8%	32.0%	28.0% (p=0.52)
LR	51.0%	49.3%	52.3% (p=0.51)

PORT: post-operative radiotherapy; OS: overall survival; RFS: relapse free survival; LR: local recurrence;p: p-value PORT vs no PORT in univariate aynalysis.

Conclusions: Although patients having received PORT were a group with adverse prognostic factors, their LR and OS were similar to ypN0 or yPN1 patients, suggesting that PORT may improve OS. As LR also remains high in the ypN0 and ypN1 groups, PORT is worth to be investigated (as in the ongoing EORTC Lung- ART trial) or considered in these patients, as well as optimizing local control in all groups.

Disclosure: All authors have declared no conflicts of interest.

85P
CONCURRENT CHEMO-RADIOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED NSCLC: TOXICITY AND CLINICAL ASSESSMENT USING VMAT (RAPID ARC)

A.M. Ascolese[1], F. De Rose[1], P. Navarria[1], M.C. Campisi[1], E. Villa[1], C. Iftode[1], A. Stravato[1], L. Cozzi[2], S. Tomatis[1], M. Scorsetti[1] [1]Radiotherapy and Radiosurgery, Humanitas Research Hospital, Rozzano, ITALY, [2]Physics, IOSI, Bellinzona, SWITZERLAND

Aim: In locally advanced NSCLC (stage IIIA-IIIB) concurrent chemo-radiotherapy improves clinical outcomes compared with sequential treatments. However, patient selection and increased toxicity represent main limitation to the use of combined modalities. In this study we investigated toxicity and clinical outcomes in concurrent chemo-radiotherapy of advanced lung cancer using volumetric modulated arcs therapy (VMAT) by rapid arc (RA).

Methods: Patients with locally advanced NSCLC, age<70 years, good performance status (PS 0-1) and minimal weight loss (< 10% within the 3 months prior to diagnosis) underwent to concurrent chemo-radiotherapy. Total body computed tomography (CT) scan, FDG positron emission tomography (PET) and pathological diagnosis were performed in each patient before treatment and every three months thereafter. Patients received five cycles cisplatin and etoposide (CDDP-VP16) every 21 days. The first cycle was completed prior to the radiotherapy. Total dose prescription was 60-70 Gy/30-35 fractions. Acute and late toxicity were evaluated by RTOG and CTCAE v. 4.0 score respectively. Evaluation of tumour response was defined according to the Response Evaluation Criteria in Solid Tumor (RECIST) v1.1.

Results: Between May 2009 and March 2013 44 patients were treated at our Institution. Patients characteristics: IIIA(N2)/IIIB 25/19; m/f 29/15; adeno/squamous/NOS 29/10/5; age: median 62 (range 37-69). Acute Esophageal toxicity Grade 1- 2 occurred in all patients. No grade 3 toxicity occurred. Only one patient had a symptomatic pneumonia a month after the end of concurrent treatment requiring hospitalization. The median follow up was 24 months (range 4-48). Four patients had only locoregional progression and eight patients had local and systemic disease progression. The overall survival at 1, 2, 3 years was 70%, 45%, 35% respectively.

Conclusions: Concurrent chemo-radiotherapy using VMAT proved to be a safe and advantageous treatment modality for locally advanced NSCLC with good toxicity profile. Clinical outcomes were satisfactory and comparable to the literature data.

Disclosure: All authors have declared no conflicts of interest.

86P
FEASIBILITY AND EFFICACY OF INDUCTION CHEMO OR CHEMORADIATION FOLLOWED BY CURATIVE RESECTION OR RADIOTHERAPY IN ELDERLY PATIENTS WITH LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

D. Marquez-Medina, A. Martin-Marco, A. Gasol-Cudos Medical Oncology, University Hospital Arnau de Vilanova, Lleida, SPAIN

Aim: Half of lung cancers are diagnosed as locally-advanced non-small cell lung cancer (LA_NSCLC) in patients older than 60 years. However, elderly patients are rarely included in multimodal programs of inductive chemotherapy (CT) or chemo-radiation (CRT). We analyzed the feasibility and efficacy of induction CT or CRT followed by surgery or curative RT in elderly patients with LA-NSCLC.

Methods: We retrospectively reviewed the 108 ECOG-0-2 LA-NSCLC diagnosed in our center from October 2005 to June 2012. All of them were treated by combining induction CT or CRT plus surgery or RT. Feasibility, tolerability, and efficacy were compared between patients younger and older than 70 years.

Results: Mean age of the series was 66.7 years. Sixty-four patients were younger (59.2%) and 44 older than 70 years (40.7%). Female patients were 7.4% only. Elderly trended to present worse ECOG score (p= 0.088), but no differences in respiratory function were found. Proportion of squamous cell carcinomas, adenocarcinomas, and non-specified NSCLC was similar between age groups. Stage-IIIB NSCLC were more common among elderly patients (35.9% vs. 50%). Treatment was: 1) Induction CRT plus Surgery in 26.5% and 15.9% of younger and elderly patients, respectively; 2) induction CRT plus RT in 32.8% and 34%; 3) induction CT plus surgery in 26.5% and 31.8%, and; 4) induction CT plus RT in 14% and 18.1%. CT included platinum-doublets with vinorelbine, gemcitabine, and taxanes. Carboplatin- doublets were more commonly used in elderly patients. No differences were found in clinical and methabolic responses by PET/SCAN (p= 0.723 and p= 0.323, respectively). Grade 3-4 toxicity was higher among younger patients (20.3 vs. 6.8%, p= 0.053). No grade 3-4 pneumonitis was detected. Resection was performed in 50 patients: 1) Pneumonectomy in 31.4 vs. 23.5%, respectively; 2) Lobectomy in 54.3 vs. 52.9%, respectively; 3) Sublobar-resections in 8.6 vs. 23.5%, respectively. Medistinal dissection was performed in 90% of cases. Pathologic responses did not differ between age group. No differences in disease free and overall survival were found (p= 0.959 and 0.757, respectively).

Conclusions: Induction treatment including CT or CRT plus surgery or RT are feasible and tolerable in elderly patients. Their tolerance, response, and outcome is at least as well as that found in younger patients.

Disclosure: All authors have declared no conflicts of interest.

87P
THE COMPARATIVE EVALUATION OF RADIOTHERAPY WITH CONCURRENT WEEKLY CISPLATIN VERSUS CONCURRENT 3-WEEKLY CISPLATIN AND ETOPOSIDE IN PATIENTS WITH UNRESECTABLE LOCALLY ADVANCED NON SMALL CELL LUNG CANCER

P.K. Bagri[1], P. Hirapara[1], A. Kapoor[1], M. Singhal[1], D. Singh[1], S.L. Jakhar[1], S.K. Beniwal[2], N. Sharma[1], H. Kumar[1], A. Sharma[1] [1]Radiation Oncology, Acharya Tulsi Regional Cancer Treatment and Research Institute, Bikaner, INDIA, [2]Medical Oncology, Acharya Tulsi Cancer Treatment and Research Institut, Bikaner, INDIA

Aim: In India, lung cancer is currently the fourth most common cancer and accounts for nearly 8% of all cancer related deaths. In our centre, lung cancer contributes approximately 8-10% of all newly diagnosed cases. This is a prospective comparison of weekly cisplatin to 3-weekly cisplatin and etoposide as concurrent chemotherapy with standard radiotherapy (CCRT) for unresectable locally advanced non-small cell lung cancer (LA-NSCLC).

Methods: Between July 2011 and July 2013, 60 patients with histologically confirmed unresectable LA-NSCLC, Eastern Cooperative Oncology Group (ECOG) performance status 0-2, who met inclusion criteria were randomly assigned in two different groups of CCRT. In the first group, cisplatin (40 mg/m^2) was given intravenously (IV) on a weekly basis for a total of six cycles (n=30). In the second group, cisplatin (40 mg/m^2 IV day 1-2) and etoposide (120 mg/m^2 IV day 1-3) were repeated on a 3-weekly basis for a total of three cycles (n=30). The total dose of radiotherapy was 66 Gy. Dose schedule of radiotherapy was 2Gy per fraction and 5 fractions in a week. The primary end point was response rate at 6 weeks post-treatment. Patients were followed for 15 months after completion of treatment for treatment response, toxicities and overall survival.

Results: 6 weeks after completion of treatment, complete response was seen in 13.8% and 10.3% patients (p=0.47); partial response in 17.2% and 34.5% (p=0.016); stable disease in 41.4% and 31% (p=0.22); and progressive disease was seen in 27.6% and 24.1% patients (p=0.62) in first group and second group, respectively. Median overall survival was 8.5 months and 10 months (p=0.72), and survival at 15 months was 30.7% and 39.6% (p=0.4) in the first and second group, respectively. Of acute toxicities, grade I & II haematological, renal toxicities, and pneumonitis were more common in second group; nausea, vomiting, and esophagitis were more common in first group. Of chronic toxicities, grade I & II renal and skin toxicities were more common in the second group, while grade I & II

esophagitis was common in the first group. Differences in toxicities were not statistically significant.

Conclusions: A better response rate was achieved with the 3-weekly cisplatin and etoposide regimen, and overall survival was also improved in 3-weekly cisplatin and etoposide regimen as compared with that seen with weekly cisplatin for CCRT.

Disclosure: All authors have declared no conflicts of interest.

88P
COMPARATIVE EVALUATION OF NON-CONVENTIONAL RADIATION AND CHEMORADIATION IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

Y. Ragulin[1], D. Gogolin[2], Y. Mardynsky[2], I. Gulidov[2], I. Ivanova[2], A. Zolotkov[2] [1]Thoracic, Medical Radiological Research Center, Obninsk, RUSSIAN FEDERATION, [2]Radiology, Medical Radiological Research Center, Obninsk, RUSSIAN FEDERATION

Aim: Results of the treatment of inoperable locally advanced non-small cell lung cancer are unsatisfactory. To improve the results of treatment of patients there is a need for new treatment approaches. Non-traditional modes of radiation therapy and the simultaneous use of chemotherapy can be an alternative to the traditional treatment methods. The aim of this study was to compare the efficiency of a radiotherapy and chemoradiotherapy in the mode accelerated hyperfractionation.

Methods: To improve the results of treatment of inoperable locally advanced non-small cell lung cancer (NSCLC) IIB-IIIB stage a methodology of accelerated hyperfractionated was developed with uneven crushing of the daily dose into two fractions (1 +1.5 Gy with an interval of 5-6 hours) to give a total focal dose of 60-70 Gy. In the period from 2005 to 2012, 123 patients with a verified diagnosis of NSCLC were treated by this method. The patients were divided into two groups. The study group included 55 patients who received concurrent chemoradiotherapy (2 courses with cisplatin and etoposide), and the control group consisted of 68 patients who received only a radical course of radiation therapy.

Results: The overall three-year survival rate in the study group was 37.5%, and in the control group 19%; complete regression of the tumor in the study group was 7.2%, compared with 4.4% in the control. Acute reactions of II-III degree esophagitis were seen in 32.6% in the intervention group and in 29.5% in the control group. Acute reactions from the blood were observed only in the study group and were as follows: grade 2 leukopenia 10.9%, grade 3 leukopenia 5.5%, anemia 7.2%, thrombocytopenia 3.6%.

Conclusions: Thus, we can conclude that simultaneous chemoradiotherapy conducted as described, using hyperfractionated accelerated with uneven crushing daily dose is satisfactorily tolerated and improves long-term outcomes.

Disclosure: All authors have declared no conflicts of interest.

89P
THE IMPACT OF EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATION ON CENTRAL NERVOUS SYSTEM (CNS) INVASION AND SURVIVAL IN PATIENTS WITH SURGICALLY RESECTED LUNG ADENOCARCINOMA

T. Akita, T. Etou, Y. Shishido, S. Morita, K. Asada, M. Hirose, S. Ota, M. Fujii, T. Shirai Pulumonary Division, Shizuoka-General-Hospital, Shizuoka, JAPAN

Aim: CNS invasion is common in patients with non-small cell lung cancer (NSCLC) and associated with a poor outcome. For patients who have developed CNS invasion, those with epidermal growth factor (EGFR) mutation derive clinical benefit from EGFR tyrosine kinase inhibitors (TKIs). The clinical manifestation of CNS invasion, the EGFR mutation, and prognosis are unclear in patients with resected stage I to III lung adenocarcinoma. The aim of this study is to analyze the impact of EGFR gene mutation on CNS-recurrence and prognosis in patients with surgically resected lung adenocarcinoma.

Methods: Between March 2002 and January 2012, 29 patients underwent the complete resection of stage I to III lung adenocarcinoma and developed CNS progression in their clinical course. Pathological records including EGFR mutation testing were reviewed retrospectively. Basic patient demographics, EGFR mutation data, survival data and information on the first treatment for CNS progression were collected. Kaplan Meier curves were used for survival analysis.

Results: Twenty-nine patients were identified, with a median age of 63. The cumulative incidence of CNS progression was significantly higher in those with the EGFR mutation (69%) compared with the EGFR wild-type (38%). Tumor stages I, II, and III numbered 11, 8, and 10, respectively. The time from surgery to CNS invasion was 20 months for those with the EGFR mutation and 9 months for patients with the EGFR wild-type. MST from surgery was 83 and 49 months, respectively. MST from CNS progression was 42 and 6 months, respectively (P=0.002). The rate of the first treatment being gamma knife therapy for CNS lesions was 90% for patients with EGFR mutation and 44% for patients with the EGFR wild-type.

Conclusions: Compared with EGFR wild-type, we observed the late occurrence of CNS invasion and significantly better survival in patients with EGFR mutation showing CNS invasion in their clinical course. The present findings suggest that we need to be aware of the occurrence of CNS invasion, and combined modality treatment including EGFR-TKI and gamma knife therapy is important in CNS recurrence in patients with EGFR mutation with surgically resected lung adenocarcinoma.

Disclosure: All authors have declared no conflicts of interest.

90TiP
A MULTI-CENTER PHASE II RANDOMIZED STUDY OF CUSTOMIZED NEOADJUVANT THERAPY VS. STANDARD CHEMOTHERAPY (CT) IN NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS WITH RESECTABLE STAGE IIIA (N2) DISEASE (CONTEST TRIAL)

F. Grossi[1], E. Rijavec[1], G. Barletta[1], C. Genova[1], C. Sini[1], M.G. Dal Bello[1], G. Burrafato[1], G.B. Ratto[2], M. Truini[3], D.F. Merlo[4] [1]Lung Cancer Unit, IRCCS AOU San Martino IST - Istituto Nazionale per la Ricerca sul Cancro, Genova, ITALY, [2]Department of Thoracic Surgery, IRCCS AOU San Martino IST - Istituto Nazionale per la Ricerca sul Cancro, Genova, ITALY, [3]Department of Pathology, IRCCS AOU San Martino IST - Istituto Nazionale per la Ricerca sul Cancro, Genova, ITALY, [4]Unit of Epidemiology And Biostatistics, IRCCS AOU San Martino IST - Istituto Nazionale per la Ricerca sul Cancro, Genova, ITALY

Background: The most powerful prognostic factor that has been identified in stage IIIA is clearance of mediastinal lymph nodes and pathologic complete response (pCR). A pCR is obtained in 5-15% of pts with a significant survival prolongation. The identification of molecular biomarkers, such as excision repair cross-complementation 1 (ERCC1), ribonucleotide reductase subunit M1 (RRM1), and thymidylate synthase (TS), may predict response to CT. Similarly, EGFR mutations may predict response to EGFR inhibitors.

Trial design: CONTEST, a multicenter (19 Italian centers), randomized (2:1) 2-arm phase II study, recruits pts with resectable stage IIIA (N2) NSCLC. Pts will be randomized to receive before resection either standard CT with Cisplatin (CDDP) + Docetaxel (Doc) or customized therapy using predetermined values for ERCC1, RRM1, TS, and EGFR mutations. Specimens are sent to Response Genetics (Los Angeles, CA, USA) for the evaluation of ERCC1, RRM1 and TS using RT-PCR and EGFR using Sanger sequencing. The choices of customized arms are as follows:

-EGFR+: Gefitinib.

-EGFR-/non-squamous (NS)/TS-/ERCC1-: CDDP + Pemetrexed.

-EGFR-/squamous (S) or NS TS+/ERCC1-/RRM1+: CDDP + Doc.

-EGFR-/S or NS TS+/ERCC1-/RRM1-: CDDP + Gemcitabine (Gem).

-EGFR-/S or NS TS+/ERCC1+/RRM1+: Doc + Vinorelbine.

-EGFR-/S or NS TS+/ERCC1+/RRM1-: Doc + Gem.

The primary end point will be obtained by comparing the pCR in all randomized pts based on treatment arm. Because pCR is a surrogate endpoint and given the expected proportion of pCR's in the control group pc= 5%, the minimal clinically worthwhile effect of this customized treatment is an increase in this proportion to 20%. To detect such an effect at the 0.05 (1-sided) significance level with 80% power, a total of 168 pts (112 in the investigational arm and 56 in the standard arm) will be enrolled. Secondary endpoints are: OS, DFS, OS at 1, 2 and 5 years, Overall Response, safety.

This study is open for accrual; further details can be found on ClinicalTrials.gov (NCT01784549). Funded by the Italian Ministry of Health – RF 2009-1530324.

Disclosure: All authors have declared no conflicts of interest.

ADVANCED NSCLC

91O
QUALITY OF LIFE (QOL) ANALYSIS FROM ENSURE, A PHASE 3, OPEN-LABEL STUDY OF FIRST-LINE ERLOTINIB VERSUS GEMCITABINE/CISPLATIN (GP) IN ASIAN PATIENTS WITH EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATION-POSITIVE (MUT+) NON-SMALL-CELL LUNG CANCER (NSCLC)

Y. Wu[1], C. Zhou[2], G. Wu[3], X. Liu[4], Z. Zhong[5], S. Lu[6], M.C.L. Fernando[7], C. Liam[8], M. Chen[9], Y. Zuo[10] [1]Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, CHINA, [2]Department of Oncology, Affiliated Shanghai Pulmonary Hospital of Tongji University, Shanghai, CHINA, [3]Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, CHINA, [4]Department of Lung Cancer, 307 Hospital of PLA, Beijing, CHINA, [5]Cancer Centre, Research Institute of Surgery, Daping Hospital, Third Military Medical University, Chongqing, CHINA, [6]Shanghai Lung Cancer Center, Shanghai Chest Hospital Affiliated to Shanghai Jiao Tong University, Shanghai, CHINA, [7]Internal Medicine, Manila Doctors Hospital, Manila, PHILIPPINES, [8]Department of Medicine, University of Malaya, Kuala Lumpur, MALAYSIA, [9]Biostatistics, Roche Product Development in Asia Pacific, Shanghai, CHINA, [10]Roche Product Development in Asia Pacific, Shanghai, CHINA

Aim: ENSURE, a randomised, phase 3 study, met its primary endpoint of improved progression-free survival (PFS) with erlotinib vs GP in Asian patients with *EGFR* mut+ NSCLC: interim analysis median PFS 11.0 vs 5.5 months (HR 0.34, 95% CI 0.22–0.51; p<0.0001); updated analysis median PFS 11.0 vs 5.5 months (HR 0.33, 95% CI 0.23–0.47). QoL is important in assessing treatment benefit, as it examines the balance between efficacy and tolerability. Here we present QoL data from ENSURE (updated data cut-off).

Methods: Patients ≥18 years with histologically confirmed stage IIIB/IV *EGFR* mut+ NSCLC were randomised 1:1 to erlotinib (oral; 150mg qd until progression/unacceptable toxicity) or GP (G 1250mg/m^2 iv d1 & 8 q3w; P 75mg/m^2 iv d1 q3w; ≤4 cycles). QoL was assessed every 6 weeks until week 25, then every 12 weeks until progression. The Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire was used, comprising subscales on physical, emotional, social and functional well-being, as well as the lung cancer subscale (LCS). These were used to calculate time to symptomatic progression (≥3-point decline in LCS score from baseline), time to deterioration in Trial Outcome Index (TOI; ≥6-point decline in LCS score plus physical and functional scores from baseline) and time to deterioration in QoL (≥6-point decline in TOI score plus social and emotional scores from baseline). Data cut-off was 19 November 2012.

Results: FACT-L completion rates were 99% for erlotinib and 98% for GP at baseline, and 100% and 78%, respectively, at week 48. QoL results are shown in the Table.

Time to	Symptomatic progression		Deterioration in TOI		Deterioration in QoL	
	E	GP	E	GP	E	GP
Median, mo	13.8	5.5	11.4	4.2	8.2	2.8
HR	0.56		0.51		0.64	
95% CI	0.36–0.87		0.34–0.76		0.44–0.93	
p	0.0076		0.0006		0.0168	

Conclusions: Erlotinib was associated with improved QoL (FACT-L) compared with GP across all assessments, providing further support for the use of first-line erlotinib for Asian patients with *EGFR* mut+ NSCLC.

Disclosure: Y. Wu: Speaker fee from Roche, AstraZeneca, Eli Lilly, Sonofi, Pfizer M. Chen: M. Chen is an employee of Roche Product Development in Asia Pacific, China. Y. Zuo: Y. Zuo is an employee of Roche Product Development in Asia Pacific, China. All other authors have declared no conflicts of interest.

92O
TUMOR BURDEN AND TYROSINE KINASE INHIBITORS (TKI) BENEFIT IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS WITH EGFR SENSITIZING MUTATIONS (EGFRM) AND ALK REARRANGEMENT (ALK+)

C. Leduc[1], N. Moussa[2], L. Faivre[3], P. Biondani[4], J. Pignon[5], C. Caramella[2], B. Besse[4] [1]Pneumologie, Hopitaux Universitaires de Strasbourg, Strasbourg, FRANCE, [2]Radiologie, Institut Gustave Roussy, Villejuif, FRANCE, [3]Biostastistique, Institut Gustave Roussy, Villejuif, FRANCE, [4]Oncologie, Institut Gustave Roussy, Villejuif, FRANCE, [5]Biostatistique, Institut de Cancérologie Gustave Roussy, Villejuif, FRANCE

Aim: EGFRm and ALK+ are eligible to TKI. Predictive factors of response to TKI are poorly known, in particular the impact of the initial tumor burden. The objective of this study is to define if the initial tumor volume impacts TKI benefit in advanced NSCLC with EGFRm or ALK+.

Methods: We retrospectively reviewed all consecutive patients with advanced NSCLC harboring EGFRm or ALK+ in a single center (Gustave Roussy). Baseline clinical characteristics were collected. CT images were centrally reviewed to assess initial tumor volume (volumetry software program lung VCAR, GE Healthcare), number, and type of metastatic lesions. EGFRm patients were treated with gefitinib or erlotinib, and ALK+ patients with crizotinib. Uni and multivariate Cox analyses were used to correlate with progression-free-survival (PFS) and overall survival (OS).

Results: Ninety-seven patients (80 EGFRm, 14 ALK+, 3 both) treated from june 2006 to november 2013 were included: median follow up was 31 months (m), median age 57 years, 70% of females. Median PFS and OS were 8.5 (95% CI: 7.3-11) and 25 (16.2 - 28.7) m. Patients were divided in 3 groups according to their volume (n=33, 31 and 33). A significant decrease in PFS with increasing tumor volume was found (<35 cm3: median 9.0 m 95% CI (5.7-21.2); 35-74 cm3: 8.0 m (7.3-15.3); > 75 cm3: 7.3 m (4.3-10.1); p for trend=0.04). In multivariate analysis, results were similar when number of sites with metastasis and genomic alteration were included (<35 cm3: HR=1; 35-74 cm3: HR=1.54 95% CI [0.87-2.72]; > 75 cm3: HR=1.73 [1.01-2.96], p for trend=0. 04), but they were not significant when sex and presence of liver metastasis were included. Initial tumor volume was not associated to OS. Number of metastatic sites was associated with PFS and OS in multivariate analysis.

Conclusions: In patients with EGFRm and ALK+ advanced NSCLC treated by TKI, PFS, but not OS, decreases with increasing tumor volume. Number of metastatic sites is a stronger survival predictor. Those results suggest that TKI onset should not be delayed after diagnosis or begun after a cytoreductive treatment such as chemotherapy.

Disclosure: All authors have declared no conflicts of interest.

93O
FIRST-IN-HUMAN EVALUATION OF CO-1686, AN IRREVERSIBLE, HIGHLY SELECTIVE TYROSINE KINASE INHIBITOR OF MUTATIONS OF EGFR (ACTIVATING AND T790M)

H. Wakelee[1], J. Soria[2], R. Camidge[3], S. Gadgeel[4], J. Goldman[5], A. Varga[2], B. Solomon[6], V. Papadimitrakopoulou[7], P. Kaur[8], L.V. Sequist[9] [1]Thoracic Oncology, Stanford University, Stanford, CA, UNITED STATES OF AMERICA, [2]Medical, Institut Gustave Roussy, Villejuif, FRANCE, [3]Medical, University of Colorado, Denver, CO, UNITED STATES OF AMERICA, [4]Medical, Karmanos Cancer Institute, Detroit, MI, UNITED STATES OF AMERICA, [5]Medical, UCLA, Santa Monica, CA, UNITED STATES OF AMERICA, [6]Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, AUSTRALIA, [7]Medical Oncology, MD Anderson Cancer Center, Houston, TX, UNITED STATES OF AMERICA, [8]Clinical, Clovis Oncology, Boulder, CO, UNITED STATES OF AMERICA, [9]Medical, Massachusetts General Hospital, Boston, MA, UNITED STATES OF AMERICA

Aim: Efficacy of existing EGFR tyrosine kinase inhibitors (TKIs) in NSCLC is limited by emergence of the T790M mutation in approximately 60% of patients, and significant skin rash and diarrhea, caused by wild-type (WT)-EGFR inhibition. CO-1686 is an oral, covalent TKI that targets common activating EGFR mutations and T790M, while sparing WT-EGFR.

Methods: This is an ongoing first-in-human dose finding study in patients with EGFR mutated recurrent, advanced NSCLC. All patients are previously treated with an EGFR TKI and must undergo tumor tissue biopsy within 28 days before study drug dosing for central EGFR genotyping. Oral CO-1686 is administered continuously in 21-day cycles. Endpoints include safety, pharmacokinetics (PK), and efficacy.

Results: As of 15th November 2013, 66 patients were treated with CO-1686; initially, 57 with CO-1686 free base, up to 900mg BID (N=19 dose expansion at 900 mg BID); then, following formulation optimization, 9 with CO-1686 HBr up to 750 mg BID). Dose escalation continues. 70% of patients are T790M+,14% are T790M unknown/pending, median age is 60 years, 80% are female, 80% are white, and 75% are ECOG 1. The median number of previous therapies was 3 (range: 1- 6); 45% had received > one line of EGFR TKI. Treatment-related AEs (all grades) occurring in ≥20% patients were: nausea (21%) and fatigue (20%). The majority of all events were mild or moderate. Events typical of EGFR WT inhibition, in particular rash combined with diarrhea, have not been observed. Nine T790M+ patients treated with 900 mg BID (free base) were evaluable for response; 6 (67%) achieved PRs, 2 (22%) achieved SD. One patient at a lower dose also achieved a PR. Eight of the 9 patients had progressed on an EGFR TKI immediately before initiating CO-1686. Data for the cohorts receiving the optimized formulation are maturing and current data will be presented at the meeting.

Conclusions: CO-1686 has demonstrated good tolerability and promising efficacy against proven T790M+ EGFR mutant NSCLC. Dose-related WT-driven diarrhea and rash has not been seen. Dose escalation is continuing with CO-1686 HBr which has improved exposure and reduced PK variability.

Disclosure: H. Wakelee: Research funding from Clovis Oncology to Stanford University. R. Camidge: Advisory board member for Clovis Oncology. S. Gadgeel: Research funding from Clovis to Karmanos. J. Goldman: Advisory board member and research funding from Clovis Oncology. B. Solomon: Advisory board member for Clovis Oncology. P. Kaur: Employee and stock owner of Clovis Oncology Ltd L.V. Sequist: Advisory board member for Clovis Oncology. Research funding from Clovis Oncology to Mass General. All other authors have declared no conflicts of interest.

94O
LUNG ADENOCARCINOMA WITH RET FUSION: EARLY EXPERIENCE WITH DIAGNOSIS AND TARGETED THERAPY

O. Gautschi[1], G. Pall[2], A. Schultheis[3], F. Aebersold Keller[4], M. Gardizi[3], J. Heuckmann[5], S. Merkelbach-Bruse[3], J. Diebold[4], J. Wolf[6], L. Heukamp[3] [1]Klinik für Onkologie, Luzerner Kantonsspital, Luzern, SWITZERLAND, [2]Innere Medizin, Universitätskliniken Innsbruck, Innsbruck, AUSTRIA, [3]Institut für Pathologie, Universitätsklinikum Köln, Köln, GERMANY, [4]Institut für Pathologie, Luzerner Kantonsspital, Luzern, SWITZERLAND, [5]Blackfield AG, Köln, GERMANY, [6]Innere Medizin, Universitätsklinikum Köln, Köln, GERMANY

Aim: Lung adenocarcinoma with RET fusion is a new diagnostic entity with potential clinical implications. Experience with diagnosis and targeted therapy is limited.

Methods: In November 2012, we integrated RET break-apart fluorescence in-situ hybridization (FISH) into our diagnostic test algorithms for primary lung adenocarcinoma. Positive cases were recorded in our databases, and clinical outcomes were collected from patients who received RET inhibitors on an individual compassionate use or off-label use basis. Next generation sequencing and PCR were performed on selected diagnostic and repeat biopsy samples, to identify RET kinase mutations and fusion partners. All patients with targeted therapy consented to treatment, translational research and publication.

Results: By November 2013, 529 consecutive tumor samples were analysed by RET-FISH in our diagnostic laboratories. Twelve (2.3%) samples were positive, and none carried a secondary mutation in EGFR, HER2, KRAS, BRAF, ALK, or ROS1. So far, 4 pts with RET fusion and previous chemotherapy received one or more lines of targeted therapy. One pt received sunitinib and had prolonged disease stabilization. Three pts received vandetanib as first targeted therapy and 2 had a response. The same 3 pts received cabozantinib as second targeted therapy after progression on vandetanib. Two pts had a response to cabozantinib and one pt started with ponatinib recently. Three pts had tumor rebiopsy after targeted therapy. Molecular analyses are ongoing and updated results will be presented at the meeting.

Conclusions: The incidence of RET fusion was higher than expected, and preliminary activity of targeted therapy was confirmed. Of note, we observed preliminary activity of cabozantinib in pretreated tumors with primary and secondary resistance to vandetanib. Activation of a global phase II trial with cabozantinib in RET fusion positive lung cancer is planned. Clinicians should be aware of it, and refer eligible patients to participating centers.

Disclosure: J. Heuckmann: Co-founder, shareholder and full time employee of Blackfield AG, Cologne, Germany All other authors have declared no conflicts of interest.

95PD
MOLECULAR HETEROGENEITY AND RESPONSE TO GEFITINIB OF EGFR MUTANT ADVANCED LUNG ADENOCARCINOMA

E. Bria[1], S. Pilotto[1], E. Amato[2], M. Fassan[2], S. Novello[3], T. Vavalà[3], L. Righi[3], I. Sperduti[4], A. Scarpa[5], G. Tortora[1] [1]Medical Oncology, Azienda Ospedaliera Universitaria Integrata Verona-"Borgo Roma", Verona, ITALY, [2]Applied Research on Cancer Center, ARC-NET, Verona, ITALY, [3]Medical Oncology, Azienda Ospedaliero-Universitaria ASOU San Luigi Gonzaga, Orbassano, Turin, ITALY, [4]Biostatistics, Regina Elena National Cancer Institute, Roma, ITALY, [5]Pathology and Diagnostics, University of Verona, Verona, ITALY

Aim: Among EGFR mutant advanced lung adenocarcinoma (ALA) patients treated with Gefitinib, 40% benefit for >12 months, while 1/3 rapidly progress. Assessment of molecular heterogeneity may help identify these clinically relevant subgroups.

Methods: Eighteen EGFR mutant ALA treated with gefitinib in first line were analyzed for mutations in 22 genes using paraffin embedded tissues and next-generation sequencing (NGS) technology (Ion Lung and Colon Cancer Panel, Life Technologies), which also permits the assessment of the Rate of Mutated Cells (RMC). Patients were grouped according to the time to progression:

poor responders (progression at first disease assessment); intermediate and good responders (within or after 12 months).

Results: Patients features: m/f 6/12, and had median age 72 yrs (range 37-83), PS 0/1: 14/4, EGFR deletion-19/L858R: 13/5, progressions/deaths: 13/7. At gefitinib therapy, 6 (33%) were poor, 5 (28%) intermediate, and 7 (39%) good responders. Median progression-free-survival (PFS) was 1.7 (95% CI 0.1-3.2), 6.1 (95% CI 3.0-9.2), and 17.9 months (8.9-25.7) for poor, intermediate and good responders, respectively (p<0.0001). Median RMC for EGFR was 33.5%, 46% and 64% for poor, intermediate and good responders, respectively. A trend towards significance was found between pts with a EGFR-RMC cut-off of 30% (p[Tarone-Ware]=0.17). Mutated genes in addition to EGFR were: TP53 in 7 cases; KRAS and CTNNB1 in 2 cases each; PIK3CA, SMAD4 and MET in 1 patient each, respectively. TP53 mutations with a median RMC of 45% occurred exclusively among poor and intermediate responders (poor/intermediate vs good responders, 66.7% vs 0%, p[Fisher]=0.01). A significant difference in PFS between patients with more than 1 mutation and an EGFR-RMC <30% (10 pts, median PFS 12.3 [95% CI 5.9-18.7]) and those with EGFR mutation alone with a RMC >30% (6 pts, median PFS 3.0 [95% CI 0.1-5.9]), p[Tarone-Ware]=0.05.

Conclusions: Our pilot study shows that NGS technology may reveal of help to characterize EGFR mutant ALA patients into clinically significant prognostic and/or predictive subgroups, according to the proportion of EGFR mutated cells and of the associated molecular lesions. The study is ongoing to a larger series to assess its validity in accurately predicting the individual patient risk

Disclosure: All authors have declared no conflicts of interest.

96PD
CLINICAL ACTIVITY, SAFETY AND SUBPOPULATION RESPONSE ANALYSIS OF NIVOLUMAB (ANTI-PD-1; BMS-936558; ONO-4538) IN PATIENTS (PT) WITH NON-SMALL CELL LUNG CANCER (NSCLC)

J.R. Brahmer[1], L. Horn[2], S.J. Antonia[3], D.R. Spigel[4], L.V. Sequist[5], C.M. Ahlers[6], V. Sankar[6], G. Kollia[6], S. Gettinger[7] [1]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, UNITED STATES OF AMERICA, [2]Department of Medicine, Vanderbilt-Ingram Cancer Center, Nashville, UNITED STATES OF AMERICA, [3]Department of Interdisciplinary Oncology and The Immunology Program, H. Lee Moffitt Cancer Center & Research Institute, Tampa, UNITED STATES OF AMERICA, [4]Hematology/oncology, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, UNITED STATES OF AMERICA, [5]Hematology/oncology, Massachusetts General Hospital, Boston, MA, UNITED STATES OF AMERICA, [6]Bristol-Myers Squibb, Princeton, UNITED STATES OF AMERICA, [7]Medical Oncology, Yale Cancer Center, New Haven, UNITED STATES OF AMERICA

Aim: Treatment with nivolumab, a fully human IgG4, PD-1 immune checkpoint inhibitor antibody resulted in durable objective responses (ORs) and prolonged stable disease in pts with advanced NSCLC in a phase 1 study (CA209-003; NCT00730639) (Topalian S, et al. *N Engl J Med*. 2012;366:2443-54). We report long-term safety, efficacy, updated survival outcomes and clinical activity in subpopulations of the NSCLC cohort.

Methods: NSCLC pts received nivolumab 1, 3, and 10 mg/kg IV Q2Wk with tumor assessment (RECIST 1.0) after each 4-dose cycle. Clinical activity by select pt characteristics (age, gender, ECOG PS, histology, number of prior therapies, prior TKI therapy, *EGFR* and *KRAS* status) was also assessed.

Results: 129 pretreated NSCLC pts (non-squamous [n=74], squamous [n=54], unknown histology [n=1]) were treated as of September 2013. Durable OR occurred in 22 pts (17%); estimated median duration, 74.0 wk (6.1+, 133.9+); with responses ongoing in 45% (10/22) of pts. Responses were rapid; 50% of pts (11/22) demonstrated response at first tumor assessment (8 wk) and in some pts continued following treatment discontinuation. Across doses, 1- and 2-year OS rates were 42% and 24%. Across histologies, median OS was 9.9 months across doses and 14.9 months at 3 mg/kg. Any grade drug-related select adverse events occurred in 41% (53/129) of pts (grade 3/4, 5% [6/129]); most common were skin (16%), gastrointestinal (12%), and pulmonary (7%). Any grade drug-related pneumonitis occurred in 6% (8/129) of pts (grade 3/4, 2% [3/129]), resulting in 2 deaths early in the trial and leading to increased emphasis on management algorithms. Responses were observed across a broad range of NSCLC pt populations regardless of histology, including pts with >3 prior therapies, pts >70 years old and pts with/without tumors driven by *KRAS* or *EFGR* mutations.

Conclusions: In advanced NSCLC pts, nivolumab produced durable responses and survival benefit with a long-term safety profile acceptable for the outpatient setting. Responses were observed in a wide array of NSCLC pt populations. These findings support the ongoing development of nivolumab in phase 3 trials.

Disclosure: J.R. Brahmer: BMS – advisory board member – uncompensated Merck – advisory board member – uncompensated L. Horn: Paid advisory board for BMS, Clovis, Theradex. Paid conference attendance BI. Research funding Astellas. S.J. Antonia: Corporate sponsored research and consultant D.R. Spigel: Consultant for Bristol-Myers Squibb. L.V. Sequist: Non-compensated advising for Clovis Oncology, Boehringer-Ingelheim, Merrimack Pharmaceuticals, and AstraZeneca. Compensated advising for GSK. C.M. Ahlers: Employee of and stock ownership in Brisol-Myers Squibb. V. Sankar: Employee of Brisol-Myers Squibb. G. Kollia: Employee of and stock ownership in Brisol-Myers Squibb. S. Gettinger: Consultant for Bristol-Myers Squibb.

97PD
NINTEDANIB (BIBF 1120) + DOCETAXEL AS 2ND-LINE THERAPY IN PATIENTS WITH STAGE IIIB/IV OR RECURRENT NSCLC: RESULTS OF THE PHASE III, RANDOMISED, DOUBLE-BLIND LUME-LUNG 1 TRIAL. (FOR THE LUME-LUNG 1 STUDY GROUP)

M. Reck[1], A. Mellemgaard[2], J. Douillard[3], S. Orlov[4], M. Krzakowski[5], J. von Pawel[6], M. Gottfried[7], B. Gaschler-Markefski[8], R. Kaiser[8], S. Novello[9] [1]Thoracic Oncology, Lung Clinic Grosshansdorf, Grosshansdorf, GERMANY, [2]Oncology, Herlev University Hospital, Herlev, DENMARK, [3]Medical Oncology, Centre René Gauducheau, Nantes, FRANCE, [4]Thoracic Oncology, St. Petersburg State Medical University, Petersburg, RUSSIAN FEDERATION, [5]Oncology, The Maria Sklodowska-Curie Institute of Oncology, Warsaw, POLAND, [6]Oncology, Pneumology Clinic, Asklepios Fachkliniken, Gauting, GERMANY, [7]Lung Cancer Unit, Meir Medical Center, Kfar Saba, ISRAEL, [8]Oncology, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, GERMANY, [9]Oncology, University of Turin, Turin, ITALY

Background: Nintedanib (N) inhibits VEGFRs, PDGFRs and FGFRs. LUME-Lung 1 was a placebo (P) controlled Phase III trial of N + docetaxel (D) in patients with locally-advanced/metastatic NSCLC progressing after 1st line therapy.

Methods: Stage IIIB/IV or recurrent NSCLC patients (stratified by histology, ECOG PS, prior bevacizumab and brain metastases) were randomised to N 200mg bid + D 75mg/m^2 q21d (n=655) or P+D (n=659). The primary endpoint was centrally reviewed PFS after 713 events. The key secondary endpoint, OS, was analysed hierarchically after 1121 events (1. adenocarcinoma patients <9mo since start of 1st line therapy, 2. all adenocarcinoma patients, 3. all patients). Predefined sensitivity analyses added sum of longest diameters of target lesions (SLD) to stratification factors in the Cox model. Patient-reported quality of life (QoL) was recorded at regular intervals using standard QoL questionnaires.

Results: Patient characteristics were balanced between the arms. N+D prolonged PFS v P+D (HR 0.79; CI 0.68–0.92; p=0.0019; median 3.4 v 2.7mo) regardless of histology (squamous HR 0.77, p=0.0200; adenocarcinoma HR 0.77, p=0.0193). OS was significantly prolonged in adenocarcinoma patients (HR 0.83; p=0.0359; median 12.6 v 10.3mo) and in T<9mo adenocarcinoma patients (HR 0.75; p=0.0073; median 10.9 v 7.9mo). A trend for improved OS was seen for the overall patient population (HR 0.94; p=0.2720; median 10.1 v 9.1mo). Adjusted for SLD, OS benefit was seen in all patients (HR 0.88; CI 0.78–0.99; p=0.0365). Patients with squamous cell histology with a high tumour burden showed a trend towards improved OS (SLD ≥7.5cm; HR 0.82; p=0.0995; median OS 7.7 v 6.1mo). Survival benefits were achieved without substantial alterations in patient-reported QoL. The most common AEs were diarrhoea (any: 42.3 v 21.8%; Gr ≥3: 6.6 v 2.6%) and ALT elevations (any: 28.5 v 8.4%; Gr ≥3: 7.8 v 0.9%).

Conclusions: N+D significantly improved PFS independent of histology, and prolonged OS for adenocarcinoma patients. AEs were generally manageable with dose reductions and symptomatic treatment.

Disclosure: M. Reck: 1. Compensated Member of Advisory Board: Hoffmann-La Roche, Lilly, BMS, AstraZeneca, Daiichi-Sankyo, Pfizer 2. Honoraria for lectures: Hoffmann-La Roche, Lilly, BMS, AstraZeneca, Daiichi-Sankyo, Pfizer J. Douillard: Consultant/Advisory: Boehringer Ingelheim J. von Pawel: Consultant or advisory: Boehringer Ingelheim B. Gaschler-Markefski: Employment: Boehringer Ingelheim Pharma GmbH & Co. KG R. Kaiser: Employment: Boehringer Ingelheim Pharma GmbH & Co. KG All other authors have declared no conflicts of interest.

98PD

EXON 20 MUTATIONS OF THE EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) IN LUNG ADENOCARCINOMAS: CLINICOPATHOLOGIC FACTORS AND RESPONSE TO THERAPY

J. Naidoo[1], C.S. Sima[2], M.D. Hellmann[1], M.E. Arcila[3], N.A. Rizvi[1], H.A. Yu[1] [1]Thoracic Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, UNITED STATES OF AMERICA, [2]Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY, UNITED STATES OF AMERICA, [3]Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, UNITED STATES OF AMERICA

Aim: EGFR exon 20 insertions or point mutations in EGFR S768 or R776 represent 10-15% of mutations in EGFR. It is unclear whether their presence predicts response to EGFR tyrosine kinase inhibitors (TKI).

Methods: Patients with EGFR exon 20 insertions (Ex20ins) or point mutations were identified through molecular pathology testing including a PCR-based fragment length analysis, mass spectrometry-based genotyping (Sequenom) and Sanger sequencing. Age, gender, performance status (PS), smoking history, mutation position and size as well as concurrent mutations were noted. Treatment data including progression free survival (PFS) on cytotoxic chemotherapy and EGFR TKI was collected for patients with stage IV disease. Overall survival (OS) of these patients was compared to a cohort of patients with either sensitizing EGFR mutations (Exon 19 del or L858R) or EGFR/KRAS wild-type (WT).

Results: From 2009-2013, 77 patients were identified, 55 (71%) had Ex20ins, 18 (23%) had S768I, and 4 (5%) had R776H. Nineteen patients (24%) had concurrent mutations in EGFR (74%, n=14), KRAS (16%, n=3) or PI3K (11%, n=2). Among the patients with Ex20ins 66% were female, 57% were never smokers and the median age was 69 years. 61% (n=34) had a 9bp insertion (range 3-26 bp). Compared to patients with sensitizing EGFR mutations, patients with Ex20ins were older (p=0.04) and more likely to have PS≥80 (p<0.001). There was no difference in OS between patients with Ex20ins and those with sensitizing EGFR mutations (1yr OS 86% vs 90%, p=0.45). Both groups had better OS compared to stage-matched EGFR/KRAS WT patients (Ex20ins vs WT, p=0.028). Twelve patients received erlotinib: 8 Ex20ins, 3 S768I and 1 R776H. The best radiologic response was a partial response, with a median PFS of 3 months on erlotinib (range <1 mo to 8 years).

Conclusions: OS in stage IV patients with EGFR Ex20ins is similar to those with classically sensitizing mutations, and superior to EGFR/KRAS WT patients. Patients with EGFR Ex20ins and point mutations exhibited a range of responses to EGFR TKI, suggesting that the decision to treat with EGFR TKI should be individualized based on the specific genetic alterations within EGFR exon 20.

Disclosure: All authors have declared no conflicts of interest.

99PD

HIGH PROPORTION OF COMPLETE RADIOLOGIC AND METABOLIC RESPONSE AND PROLONGED PROGRESSION-FREE SURVIVAL AFTER INTERCALATED CHEMOTHERAPY AND ERLOTINIB FOR ADVANCED NSCLC WITH ACTIVATING EGFR MUTATIONS

M. Zwitter, V. Kovac Department of Radiotherapy, Institute of Oncology, Ljubljana, SLOVENIA

Aim: NSCLC with activating EGFR mutations is a tumor sensitive to both tyrosine kinase inhibitors (TKIs) and to cytotoxic drugs. To avoid their mutual antagonistic effect and still derive benefit from the combination, pharmacodynamic separation of the two classes of drugs has been proposed. Here we present experience from a Phase 2 trial on patients with advanced NSCLC without prior systemic treatment and with confirmed activating EGFR mutations.

Methods: Eligible patients had stage IIIB or IV NSCLC with activating EGFR mutations; had not received any prior systemic therapy; fulfilled the standard criteria for platin-based chemotherapy; and provided written informed consent. Patients received gemcitabine (1250 mg/m2 on days 1 and 4), cisplatin (75 mg/m2 on day 2) and erlotinib (150 mg on days 5 to 15) every 3 weeks for 4 – 6 cycles, followed by uninterrupted erlotinib maintenance. The primary objective was progression-free survival (PFS); secondary objectives were toxicity, response to treatment, metabolic response and overall survival (OS).

Results: Among 35 patients (19 female; mean age 61 years), 34 had stage IV disease, 8 were in performance status (PS) 2-3 and 13 had brain metastases (1 untreated and 12 after whole-brain radiotherapy). Grade 4 toxicity included 1 case of neutropenia and 4 thrombo-embolic events. Among 31 patients with measurable disease, complete response (CR) or partial response (PR) according to RECIST was seen in 13 (41.9%) and 13 (41.9%) patients, respectively, for an overall response rate of 83.9%. PET-CT scanning was performed in 27 patients and confirmed CR and PR in 13 (48.1%) and 11 (40.7%) cases, respectively (objective metabolic response 88.9%). Median PFS was 24.3 months (95% CI 17.7 – 30.8). Median OS was 32.5 months (25.5 – 39.5). After median follow-up of 29 months, 20 patients are alive, of whom 9 continue the treatment and are still in CR.

Conclusions: High response rate and long PFS obtained in our trial of intercalated therapy are most promising, especially after considering a relatively unfavourable population of patients. A randomized trial with comparison to monotherapy with TKI is clearly warranted.

Disclosure: All authors have declared no conflicts of interest.

100PD

PGG β-GLUCAN WITH CARBOPLATIN, PACLITAXEL AND CETUXIMAB FOR CHEMOIMMUNOTHERAPY OF ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

F. Schneller[1], M. Thomas[2], P. Sadjadian[3], J. Kollmeier[4], N. Bose[5], M. Antonysamy[5], M. Patchen[6], J. Lowe[6], R.D. Huhn[7], P. Mattson[6] [1]Technical University of Munich, Klinikum Rechts der Isar, Munich, GERMANY, [2]Thoraxklinik, University of Heidelberg, Heidelberg, GERMANY, [3]Klinik Hamatoloie/onkologie, Johannes Wesling Klinikum Minden, Minden, GERMANY, [4]Lung Clinic Heckeshorn, Helios Clinic von Behring, Berlin, GERMANY, [5]Immunology R&D, Biothera, Inc., Eagan, UNITED STATES OF AMERICA, [6]Clinical, Biothera, Eagan, UNITED STATES OF AMERICA, [7]Pharma Clinical Development, Biothera, Inc., Eagan, UNITED STATES OF AMERICA

Aim: PGG β-glucan (Imprime PGG®, Imprime) primes innate immune cells to kill monoclonal antibody-targeted cancer cells via complement receptor 3 (CR3). In humans, naturally occurring anti-beta glucan antibodies (ABA) are required for binding of Imprime to CR3. Subjects with ABA levels conducive to binding are considered "biomarker positive" (BM+).

Methods: In a Phase 2 study, stage IIIb/IV NSCLC subjects received cetuximab (CET) 250 mg/m2 following initial 400 mg/m2 loading dose) without (Control, N=30) or with Imprime 4mg/kg (Imprime, N=60) on Days 1, 8 and 15 of each 3-week treatment cycle of carboplatin (AUC 6) + paclitaxel (200 mg/m2) on Day 2 for the first 4 to 6 cycles. After completion, subjects achieving radiographic stable disease or tumor response (RECIST 1.0) received CET or CET/Imprime maintenance treatment.

Results: Among all RECIST-evaluable treated subjects, median overall survival (mOS) was 11.2 mo in the control group (N=26), 10.2 mo in the entire Imprime group (N=46) (HR 1.06, p=0.85 vs. control), 16.5 mo in the BM+ Imprime group (N=15) (HR 0.63, p=0.26) and 9.1 mo in the BM- Imprime group (N=31) (HR 1.35, p=0.35). Three-year survival was 0% in the control group, 7% in the entire Imprime group, 17% in the BM+ Imprime group and 0% in the BM- Imprime group. The objective response rate (ORR,

primary endpoint for the study) was 23% in the control group, 48% in the entire Imprime group (p= 0.048 vs. control), 67% in the BM+ Imprime group (p=0.009) and 39% in the BM- Imprime group (p=0.26). Among subjects with squamous cell histology (SqCC), 6 of 6 BM+ Imprime subjects had responses compared with 3 of 10 control subjects (p=0.01). In SqCC subjects, mOS was 15.6 vs. 12.2 mo in BM+ Imprime subjects (N=6) vs. control (N=10), respectively (HR 0.62, p=0.47). Demographic factors of age, gender and ECOG performance status were balanced across analysis populations. Adverse events were consistent with toxicities attributable to the cytotoxic drugs or CET.

Conclusions: In summary, the addition of Imprime PGG to the chemoimmunotherapy regimen of carboplatin, paclitaxel and CET resulted in improved outcomes in BM+ subjects with respect to increased ORR and extended survival compared to control subjects and had a good safety profile.

Disclosure: N. Bose: Employee of Biothera, Inc. M. Antonysamy: Employee of Biothera, Inc. M. Patchen: Employee of Biothera, Inc. J. Lowe: Employee of Biothera, Inc. P. Mattson: Employee of Biothera, Inc. All other authors have declared no conflicts of interest.

101P
THYMIDYLATE SYNTHETASE (TYMS) EXPRESSION IS NOT PREDICTIVE IN PATIENTS WITH METASTATIC NSCLC TREATED WITH PEMETREXED, CISPLATIN AND BEVACIZUMAB IN THE SAKK19/09 TRIAL

O. Gautschi[1], S. Rothschild[2], Q. Li[3], S. Savic[4], L. Bubendorf[4], M. Brutsche[5], L. Stalder[3], N. Mach[6], A. Ochsenbein[7], R. Jaggi[8] [1]Klinik für Onkologie, Luzerner Kantonsspital, Luzern, SWITZERLAND, [2]Medical Oncology, University Hospital Basel, Basel, SWITZERLAND, [3]Coordinating Center, SAKK, Bern, SWITZERLAND, [4]Pathology, University Hospital Basel, Basel, SWITZERLAND, [5]Pulmonology, Kantonsspital St. Gallen, St. Gallen, SWITZERLAND, [6]Oncology, Geneva University Hospital, Geneva, SWITZERLAND, [7]Medical Oncology, Bern University Hospital, Bern, SWITZERLAND, [8]Department of Clinical Research, Bern University, Bern, SWITZERLAND

Aim: Retrospective data suggest thymidylate synthetase (TYMS) expression as a predictive marker for pemetrexed activity in patients (pts) with advanced nonsquamous NSCLC. We prospectively measured TYMS by quantitative PCR (qPCR) in the phase II trial SAKK19/09 (NCT01116219).

Methods: The clinical results of SAKK19/09 were reported recently (Gautschi et al, WCLC 2013). This trial enrolled 77 pts with advanced nonsquamous NSCLC and EGFR wild type. Pts received 4 cycles of cisplatin (or carboplatin), pemetrexed and bevacizumab, followed by pemetrexed and bevacizumab maintenance. All tumor samples were tested for KRAS mutations. RNA isolation and qPCR for TYMS were performed from tissue sections or core biopsies (AmpTec, Hamburg, Germany). Two independent sets of control genes were used for normalization, one internal set (GAPDH, RPLP0, TFRC, UBB) and one external set (GUSB, HMBS, SDHA, TOP1) published recently (Nicholson et al, JTO 2013). TYMS expression was calculated using TYMS quantification cycle (Cq) value minus mean Cq value of control genes. The exact Wilcoxon Mann-Whitney rank sum test was used to assess the association between progression free survival (PFS) at 6 months/objective response (OR) and TYMS expression, while Cox regression was used to assess the association between PFS/overall survival (OS) and TYMS expression.

Results: Sufficient high-quality RNA was available for qPCR in 57 out of 77 pts (74%). Large variation was observed for normalized TYMS expression (range 1.8-37.6). We found no statistically significant associations between TYMS expression based on the internal control set with PFS at 6 months (primary endpoint, P=0.56), PFS (P=0.97), OS (P=0.68), or OR (P=0.47). Using the external control set, all results stayed insignificant. KRAS mutation associated with poor OS (P=0.03), but not with TYMS expression (P=0.8).

Conclusions: This study showed significant intertumor heterogeneity and no predictive value for TYMS expression in pts with NSCLC and pemetrexed therapy. Until the results of other prospective trials are available, we do not recommend the use of TYMS expression for clinical decision-making outside of a controlled trial.

Disclosure: All authors have declared no conflicts of interest.

102P
CHARACTERIZATION OF PD-L1 EXPRESSION AND ASSESSMENT OF ASSOCIATION WITH TUMOR HISTOLOGY AND GENE EXPRESSION STATUS IN PRETREATMENT NON-SMALL CELL LUNG CANCER (NSCLC) TUMOR SPECIMENS

C.T. Harbison, J.F. Kurland, C.E. Horak, J.P. Cogswell, H.D. Inzunza, X. Hu, X. Han, J.F. Novotny, J.S. Simon, M.N. Jure-Kunkel Oncology, Bristol-Myers Squibb, Princeton, UNITED STATES OF AMERICA

Aim: Immunohistochemistry (IHC) analysis suggested an association between pretreatment tumor programmed death ligand 1 (PD-L1) expression and response to the human IgG4 PD-1 immune checkpoint inhibitor antibody nivolumab (Nivo) (Grosso ASCO 2013 abstract 3016). Associating PD-L1 expression with gene profiles, mutational status, or patient (pt) characteristics may inform which pts may be more likely to benefit from Nivo therapy.

Methods: 60 NSCLC tumor samples (Asterand) were analyzed. PD-L1 expression was evaluated by IHC using an automated assay with the sensitive and specific PD-L1 monoclonal antibody clone 28-8. PD-L1 positivity (PD-L1+) was defined as ≥5% tumor cell membrane staining at any intensity. DNA mutations were analyzed on the AmpliSeq™ cancer panel. Gene expression was conducted on the Affymetrix platform and association with PD-L1 status analyzed by ANOVA.

Results: 25/59 (42%) tumor samples were PD-L1+. No association between PD-L1 protein expression and NSCLC histology was apparent: 38% squamous and 47% non-squamous tumors were PD-L1+. PD-L1+ tumors showed higher expression of several immune-related genes (eg, interferon-gamma) and other genes involved in immune-cell regulation. The PD-L1 gene was differentially expressed in PD-L1+ and PD-L1-negative samples, with no continuous relationship noted. Genes for tumor progression and signaling pathways (eg, proto-oncogene tyrosine kinase [MET]) were over-expressed in PD-L1+ tumors. PD-L1 positivity was observed amongst KRAS mutation positive (8/10) and wild-type tumors (15/43). PD-L1 positivity was not associated with PTEN or EGFR protein expression.

Conclusions: PD-L1 expression on NSCLC tumors may associate with factors, including expression of immune genes, tumor progression markers, and driver mutations. Ongoing analyses of this tumor panel and ongoing Phase III studies are exploring putative associations of PD-L1 expression with pt characteristics and outcomes to help define other factors that may influence the likelihood of response to Nivo.

Disclosure: C.T. Harbison, J.F. Kurland, C.E. Horak, J.P. Cogswell, X. Hu, X. Han, J.F. Novotny, J.S. Simon, and M.N. Jure-Kunkel: Employed by and has stock ownership in Bristol-Myers Squibb. All other authors have declared no conflicts of interest.

103P
COMPARATIVE ANALYSIS OF INCIDENCE AND TREND OF NON-HEMATOLOGIC TOXICITIES IN ADVANCED NON-SMALL-CELL LUNG CANCER PATIENTS TREATED WITH EGFR TKIS

A. Passaro, E. Del Signore, F. de Marinis Division of Thoracic Oncology, European Institute of Oncology, Milan, ITALY

Aim: Rash and diarrhoea are frequently observed in patients receiving epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy in advanced non-small-cell lung cancer (NSCLC). Nowadays, three different EGFR TKIs are approved for the treatment of patients harbouring EGFR mutations, though these drugs showed different safety profile. Among patients treated with afatinib, erlotinib and

gefitinib, we performed a retrospective comparative analysis evaluating the incidence and trend of rash and diarrhoea, before and after correct management.

Methods: Patients and methods: From 2010 to 2013, we evaluated 158 patients with advanced NSCLC treated in first-, second- or third-line with the EGFR TKIs: afatinib, erlotinib or gefitinib. We assessed the incidence of rash and diarrhoea by grade (G) at initial assessment (< 30 days) compared to last assessment after correct management.

Results: The incidence of toxicities (rash, diarrhoea) classified by grade at the initial assessment, and the re-evaluation after management demonstrated an approximate reduction of 95% from the starting toxicity grade for diarrhoea and approximately 65% for cutaneous rashes. The time course for skin rash appearance from the time of starting TKIs was 7 days (95% CI: 5 to 12 days) for afatinib, 9 days (95% CI: 7 to 18 days) for erlotinib, and 14 days (95% CI: 9 to 19 days) for gefitinib. The time course for diarrhoea onset was 13 days (95% CI: 7-18 days) for erlotinib, 18 days (95% CI: 10 to 19 days) for gefitinib 5 days (95% CI: 4 to 11 days) for patients receiving afatinib. About 82% of all AE were grade 1/2 in severity and 10% were grade ≥3. However, the results collected after reparative management were similar and did not demonstrate any significant differences among the three different drug. Most patients had lower grades of AEs at their last assessment compared with their initial assessment. The last evaluation for the toxicity profile was similar for the three EGFR TKIs used.

Conclusions: This analysis suggests that immediate therapeutic approaches and continuous management are required to ensure patient treatments without severe adverse events (SAEs) that could adversely affect survival and the quality of life (QoL). No significant differences were detected among the three different drug, when evaluated after management.

Disclosure: All authors have declared no conflicts of interest.

104P
SURGICAL MANAGEMENT IN OLIGOMETASTATIC NON–SMALL CELL LUNG CANCER: A CRITICAL ANALYSIS FROM A SINGLE CENTER MULTIDISCIPLINARY TEAM

L. Bertolaccini[1], A. Viti[1], M. Merlano[2], I. Colantonio[2], E. Russi[3], A. Terzi[1]
[1]Division of Thoracic Surgery, Azienda Ospedaliera St. Croce e Carle, Cuneo, ITALY, [2]Division of Medical Oncology, Azienda Ospedaliera St. Croce e Carle, Cuneo, ITALY, [3]Division of Radiation Oncology, Azienda Ospedaliera St. Croce e Carle, Cuneo, ITALY

Aim: Does oligometastatic (OMTS) state in NSCLC justify aggressive approach? Clinical study: radical surgery in OMTS NSCLC.

Methods: Observational study on prospectively collected data. Minimum follow-up >12 months. We defined surgically resectable OMTS NSCLC, primary tumor with 1 eradicable MTS in patients aged <75 years fit for surgery. Data of 27 OMTS NSCLC were collected. Survivals were calculated by Kaplan-Meier. Univariate (Wilcoxon and Log–Rank) and multivariate (Cox) analysis identified independent prognostic factors.

Results: Characteristics and postoperative features were reported in Table. MTS sites were brain (18), adrenal gland (6), and vertebrae (3). For brain MTS, 11 patients underwent surgical radical excision, and 7 radiosurgery. Adrenal MTS underwent surgery, vertebral MTS radiation therapy. Therapeutic sequences were MTS treatment/neoadjuvant therapy/lung surgery in 6 (22.2%); MTS treatment/lung surgery in 9 (33.3%); neoadjuvant therapy/lung surgery/MTS treatment in 7 (25.9%); and lung surgery/MTS treatment in 5 (18.6%). Lung resection was complete in all cases. There was no 30-day mortality. Major complications occurred in 3 (11.1%): 1 pneumonia, and 2 bleeding with reoperation. Minor complications occurred in 14 (51.9%): 5 arrhythmias, 8 persistent air leak, 1 atelectasia. Adjuvant therapy was administered in 8 (29.6%). Median follow-up was 53 months (minimum: 12 months). At last follow-up, 10 (37.1%) had died of disease, 5 (18.5%) alive with disease, and 12 (44.4%) alive with no evidence of disease. At multivariate analysis, pN was correlated with overall survival (p = 0.005). Mediastinal involvement influenced control of disease (p = 0.017). Control of MTS (surgery or radiation therapy) has seem to impact on disease-free survival (p < 0.001). Disease-free survival was 38 months.

Age	61 (56 – 74)
ECOG - 0 - 1	21 6
Stage cTN - IA - IB - IIA - IIB	16 11
Histology - Adenocarcinoma - Squamous	20 7
Lung surgery - Lobectomies - Bilobectomies - Pneumonectomies	24 1 2
Stage pTN - IA - IB - IIA - IIB - IIIA	9 14 4
First recurrence - Local - Distant	5 1 4

Conclusions: Surgery in selected OMTS NSCLC represents feasible and effective option. Completeness of resection and pN0 status emerged as predictive factors for long-term survival. Further prospective investigations are needed for this highly debated cohort of patients.

Disclosure: All authors have declared no conflicts of interest.

105P
A LITERATURE-BASED META-ANALYSIS ABOUT THE COMPARISON BETWEEN PLATINUM-BASED DOUBLET AND SINGLE AGENT CHEMOTHERAPY IN PS 2 NSCLC PATIENTS

C.D. Rolfo[1], F. Passiglia[1], G. Bronte[2], S. Rizzo[2], I. Gil Bazo[3], E. Fiorentino[4], J.P. Van Meerbeeck[5], A. Russo[2] [1]Phase I- Early Clinical Trials Unit, Antwerp University Hospital, Edegem, BELGIUM, [2]2. Department of Surgical, Oncological and Oral Sciences, Section of Medical Oncology, Palermo University, Palermo, ITALY, [3]Medical Oncology, Clinica Universidad de Navarra, Pamplorna, SPAIN, [4]Department of Surgical, Oncological and Oral Sciences, Section of Surgical Oncology, Palermo University, Palermo, ITALY, [5]Thoracic Oncology, Multidisciplinary Oncology Center Antwerp (MOCA), Antwerp University Hospital, Edegem, BELGIUM

Background: Platinum-based doublet chemotherapy is still the standard 1st-line treatment for most EGFR wild-type NSCLC patients with performance status (PS) 0-1. However the treatment of PS2 patients is still controversial. Single-agent treatment with third-generation agents is recommended as the best option. Recently new prospective, randomized-phase III trials showed very interesting updates regarding the treatment of PS2 population. This meta-analysis aims to review all randomized trials comparing platinum-based doublets and single-agents in NSCLC PS2 patients.

Methods: Data from all published randomized trials, that compared efficacy and safety of platinum-based doublets to single agents in untreated NSCLC patients either wholly or partially dedicated to PS2, were collected by searching in PubMed and Cochrane Library. Pooled ORs were calculated for the 1-Year Survival-Rate (1-Y-SR), Overall Response Rate (ORR), and grade 3-4 (G3-4) hematologic toxicities.

Results: Five eligible trials (620 NSCLC PS2 patients) were selected among 1367 studies. Pooled analysis showed a significant improvement in ORR (OR: 3,243; 95% CI: 1,883-5,583) and 1-Y-SR (OR: 1,906; 95% CI: 1,281-2,836) in favor of platinum doublet chemotherapy. Hematologic toxicity data were obtained from 4 out of these 5 trials. G3-4 anemia (OR: 2,743; 95% CI: 1,359-5,536), neutropenia (OR: 7,956; 95% CI: 3,999-15,828) and thrombocytopenia (OR: 12,882; 95% CI: 4,901-33,857) were observed more frequently in patients receiving platinum.

Conclusions: This meta-analysis suggests that platinum-based combination regimens are superior to single-agent chemotherapy both in terms of ORR and survival-rate with increase of severe hematological toxicities. Carboplatin-based combination appears a feasible treatment option in first-line therapy of wild-type NSCLC PS2 patients. However we need to better understand which factors induce a worse PS, i.e. comorbidities or tumor

burden, to select a favorable subgroup of patients who could better tolerate platinum-based doublet chemotherapy.

Disclosure: All authors have declared no conflicts of interest.

106P
EFFICACY AND SAFETY OF BEVACIZUMAB IN ELDERLY PATIENTS WITH LUNG CANCER ADENOCARCINOMA

K.N. Syrigos, D. Vassos, M. Panagiotarakou, G. Tsoukalas, G. Athanasiadis, E. Sepsas, I. Gkiozos Oncology Unit GPP, Sotiria General Hospital, Athens School of Medicine, Athens, GREECE

Aim: Bevacizumab is a novel anti-angiogenic agent used in many advanced solid tumours, including non-squamous NSCLC. In contrast to clinical studies where enrolled patients are fit, many elderly NSCLC patients suffer from co-morbidities and often have history of a Cardiovascular Disease.

Methods: Medical records of 2672 patients diagnosed with NSCLC between 2001-2012 were screened. We identified and examined patients ≥75 years old treated with bevacizumab, for their demographics, clinical data and treatment details. We focused on those elderly patients with stable pre-existing cardiovascular disease.

Results: 356/2672 NSCLC patients received Bevacizumab at any treatment line. 33/382 (8,6%) were ≥75 years old. Of those, 29 had various co-morbidities including 19 patients with stable cardiovascular disease on medical treatment. In the 19 patients with Cardiovascular disease the male: female ratio was 17:2 and mean age 77 years (range 75-86). 8/19 patients had impaired renal function. All patients were of Performance Status ECOG 0/1. Median number of Bevacizumab cycles was 5 (range 2-11). 17/19 patients experienced ≥1 side effects (11 epistaxis and haemoptysis, 5 proteinuria, 4 hypertension) which led to treatment discontinuation in 5 patients. No major/fatal adverse events were noted. 8/19 patients (42%) showed radiological partial response and 5 (19%) stable disease (total disease control rate 61%). Median survival from initiation of Bevacizumab till death/last follow up was 7 months (range 2-28, 95% CI 5.14-12.55).

Conclusions: Treatment with Bevacizumab seems to be safe and effective in elderly NSCLC patients with controlled pre-existing cardiovascular disease and good performance status. These patients might benefit from participation in clinical trials similarly to younger NSCLC patients.

Disclosure: All authors have declared no conflicts of interest.

107P
EFFICACY AND SAFETY OF ERLOTINIB IN ELDERLY PATIENTS WITH LUNG CANCER ADENOCARCINOMA

K.N. Syrigos, P. Boura, D. Vassos, A. Vassias, A. Bastas, A. Boufas, I. Gkiozos Oncology Unit GPP, Sotiria General Hospital, Athens School of Medicine, Athens, GREECE

Aim: Besides chemotherapy, Erlotinib is another option in NSCLC patients especially in those with EGFR mutations. Elderly patients enrolled in trials are fit without co-morbidities, but in clinical practice most suffer from co-morbidities.

Methods: Medical records of 1221 patients diagnosed with NSCLC between 2008-2012 were screened. We examined patients ≥75 years for demographics, clinical data and Treatment details.

Results: 233/1221 NSCLC patients received erlotinib at any line. 53/233 (23%) were ≥75 years old. Male:female ratio was 34:19 and median age 79 years (range 75-88). NSCLC subtypes included 31 adenoca, 8 squamous cell, 9 NOS and 5 others. 50/53 patients had co-morbidities (≥2 in 46 patients, 1 in 4 patients). Main co-morbidities were cardiovascular disease (n=41), COPD (n=14), other cancer (n=10) and diabetes (n=8). 8 patients were tested for EGFR mutations (5 negative, 3 positive). Performance Status was satisfactory (ECOG 0-1) in 8 patients and poor (2-3) in 45 patients. 8 patients were treated with erlotinib 100mg and 45 patients with erlotinib 150mg (12 patients needed dose reduction). Complete follow up data were found in 46 patients. Mean duration of treatment was 79 days (range 9-662). 35/46 patients experienced side effects [rash n=29, diarrhea n=17] which led to treatment discontinuation in 12 patients. Patients with abnormal creatinine clearance (n=13) were more likely to stop treatment due to side effects (6/13 versus 6/33). 17/46 patients (37%) achieved disease control (5 PR –partial response, 12 SD- stable disease) and a time to progression (TTP) of 157 days (range 106-662, 95% CI 132.79-270,74) while 22/46 patients had PD as best response (TTP 49days, range 19-88, CI 44,67-64,97). 7patients were not evaluable (stopped Treatment due to side effects). All EGFR positive patients had disease control (2PR, 1SD).

Conclusions: Erlotinib is a valuable option in elderly NSCLC patients with co-morbidities, especially if they harbor EGFR mutations. Impaired renal function might be associated with propensity to side effects and early treatment discontinuation.

Disclosure: All authors have declared no conflicts of interest.

108P
TREATMENT COMPLIANCE, TOLERANCE AND EFFICACY IN ELDERLY PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER RECEIVING FIRST LINE CHEMOTHERAPY: A COMPARATIVE STUDY

G. Mountzios[1], M. Bakogeorgos[2], E. Mpournakis[2], P. Economopoulou[1], N. Kentepozidis[1], M.A. Dimopoulos[2] [1]Medical Oncology, 251 Airforce General Hopsital, Athens, GREECE, [2]Medical Oncology, University of Athens School of Medicine, Athens, GREECE

Aim: Elderly patients with advanced non-small cell lung cancer (NSCLC) tend to receive suboptimal treatment mainly due to fears of poor compliance and excessive toxicity.

Methods: Using the age of 70 years as the cut-off, we identified all elderly patients with advanced NSCLC who received first line chemotherapy between 2007 and 2012 in two tertiary cancer centers and compared them with their younger counterparts in terms of: i) adherence to treatment, including dose intensity (DI) and relative dose intensity (RDI), ii) toxicity and tolerance and iii) efficacy outcomes, including progression-free survival (PFS) and overall survival (OS). We evaluated the association between treatment schedule, age group and clinical outcome using logistic regression models.

Results: Among 292 eligible patients, complete data were available for 245, of whom 107 (43.7%) belonged to the elderly group. This group was associated with the presence of comorbidities ($p<0.0001$), non-smoking status ($p<0.001$), diagnosis based on cytology instead of biopsy or surgery ($p=0.047$) and with performance status of 2 or more ($p=0.012$). As compared to the younger, older patients were more likely to receive single-agent therapy (29.2% vs 8.0%, $p<0.001$), less likely to receive platinum-based combination chemotherapy (57.9% vs 80.3%, $p<0.001$), received fewer treatment cycles (median: 4 vs 5, $p=0.073$) and necessitated more days of hospitalization (median: 9 vs 6 days, $p=0.033$). Younger patients were more likely to receive cytotoxic drugs with optimal dosing, using the threshold of RDI >0.8 (49.6% vs 33%, $p=0.012$) and the threshold of RDI>0.9 (29.6% vs 16%, $p=0.015$). Substantial (Grade 3-4) toxicity was similar in both groups ($p=0.487$). There were no significant differences in efficacy outcomes between the two groups.

Conclusions: Although type, intensity and duration of first-line chemotherapy differ between elderly and younger patients with advanced NSCLC, this was not translated in significant differences in treatment efficacy or toxicity. These data further support the use of optimal treatment regimens in elderly patients with NSCLC

Disclosure: All authors have declared no conflicts of interest.

109P
EPIDERMAL GROWTH FACTORS TYROSINE-KINASE INHIBITORS (EGFR-TKI) EFFICACY IN NSCLC PATIENTS WITH HIGH POLYSOMY OF CHROMOSOME 7 AND EGFR/KRAS WILD TYPE TUMORS

F. Toffalorio[1], F. Conforti[1], G. Spitaleri[1], C. Catania[1], C. Noberasco[1], C. Lazzari[1], M. Barberis[2], F. de Marinis[1], T. De Pas[1] [1]Medical Oncology, European Institute of Oncology, Milan, ITALY, [2]Pathology Division, European Institute of Oncology, Milan, ITALY

Background: More than even before, the efficacy of epidermal growth factors tyrosine-kinase inhibitors (EGFR-TKI) in NSCLC patients carrying EGFR wild-type tumors has been under investigation. EGFR wild-type patients represent a large and heterogeneous group of patients. In this setting, the role played by high polysomy of chromosome 7 still remains controversial. Indeed, previous reports did not discriminate between chromosome 7 high polysomy and EGFR amplification and/or did not investigate the simultaneous presence of EGFR and KRas mutations.

Methods: We retrospectively collected data from 163 patients analyzed for EGFR status (mutation, amplification, chromosome 7 trysomy and polysomy), in addition to KRas mutation, between 2000 and 2010 in our Institute. EGFR-TKI was administered to 72 of them. All of them had previously received at least one line of chemotherapy. Objective responses and time to progression to EGFR-TKI were evaluated.

Results: Among the 163 samples analysed, 25 (15.3%) displayed high polysomy of chromosome 7, in presence of EGFR wild-type, absence of KRas mutation and EGFR amplification. Twelve patients, out of the 25 with high polysomy, received EGFR-TKI. The treatment led to a disease control in 10 of them (80%). One patient was lost to follow-up. In terms of overall response rate, we observed 2 PD, 4 PR and 5 SD. The mean time to progression was 8.9 months.

Conclusions: High polysomy of chromosome 7 characterizes 15% of tumors without EGFR mutations. Among the EGFR wild-type population, the evaluation of high polysomy of chromosome 7 could be a helpful tool to predict for benefit from EGFR-TKI.

Disclosure: All authors have declared no conflicts of interest.

110P
UNCOMMON EPIDERMAL GROWTH FACTOR RECEPTOR MUTATIONS IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

M. Oyaert[1], I. Demedts[2], E. Boone[1], J. Van Dorpe[3], E. De Laere[1], J. Breyne[1] [1]Molecular Diagnostics, AZ Delta Roeselare Menen, Roeselare, BELGIUM, [2]Pneumology, AZ Delta Roeselare Menen, Roeselare, BELGIUM, [3]Pathology, AZ Delta Roeselare Menen, Roeselare, BELGIUM

Aim: Classic activating mutations in the EGFR tyrosine kinase domain, such as L858R and deletions in exon 19, have been strongly associated with sensitivity to tyrosine kinase inhibitors (TKIs) in patients with Non-Small Cell Lung Cancer (NSCLC). Other mutations, e.g. T790M, show drug resistance. Detection of EGFR mutations has become an important issue for therapeutic decision-making in NSCLC. The clinical significance of uncommon EGFR mutations, however, remains poorly understood. The present study describes clinical outcomes of 6 patients with uncommon EGFR mutations, receiving TKI.

Methods: Three hundred and thirty patients with NSCLC (106 females aged 62.5 ± 1.1 years; 224 males aged 68.0 ± 0.6 years) were enrolled in the study from February 2011 until April 2013. FFPE tissue samples were screened for mutations using a High Resolution Melting technique, followed by Sanger sequencing of exons 18-21 of the EGFR gene. Mutation status was also tested using the Cobas® EGFR mutation test (Roche). Mutations found with HRM/sequencing but not with the Cobas® test and/or complex mutations, were considered as novel.

Results: EGFR mutations were found in 31/330 (9.4%) samples (18 female, 13 male). Nine mutations were considered as novel, not yet described mutations. Four mutations were singlet mutations (G735 (ex 19); V843L (ex 21); P699S (ex 18) and an ex 20 insertion), four were doublets (G719S + E709A (ex 18); G719S + E709K (ex 18); L858R + V689L (ex 18) and G719S + ex 20 insertion) and one patient had a triplet mutation (L858R + T790M + L730F). Six of them received TKIs. Two patients with singlet mutations receiving TKI, did not respond to their treatment. Patients with a G719S mutation in combination with an E709A or E709K mutation, showed stable disease upon TKI. Finally, two patients with complex mutations containing the activating L858R mutation in exon 21, showed partial response to treatment.

Conclusions: Novel singlet mutations showed a lack of response to TKIs. Complex mutations, harbouring a novel and a known mutation, showed the same response as described for the known mutation alone. This shows that using the commercial test for EGFR mutation analysis would have led to the same clinical outcome. The clinical significance of novel mutations remains unclear and poorly described and should be reported to support the decision making process in these patients.

Disclosure: All authors have declared no conflicts of interest.

111P
EGFR MUTATIONS AMONG LUNG ADENOCARCINOMA PATIENTS IN SERBIA – EGFR MUTATION INCIDENCE AND ITS CORRELATION WITH PATIENT DEMOGRAPHIC CHARACTERISTICS

B. Zaric[1], B. Perin[1], V. Kovcin[2], M. Cekic[3], D. Jovanovic[4], D. Radosavljevic[5], Z. Murtezani[6], M. Rancic[7], R. Jankovic[8], N. Vukobradovic-Djoric[9] [1]Clinic for Thoracic Oncology, Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica, SERBIA, [2]Outpatient Chemotherapy Department, Clinical Hospital Center Bezanijska Kosa, Belgrade, SERBIA, [3]Pulmolology, Clinic of Lung Diseases and TB, Knez Selo, SERBIA, [4]Institute of Lung Diseases, Clinical Center of Serbia, Belgrade, SERBIA, [5]Oncology, Institute of Oncology and Radiology of Serbia, Belgrade, SERBIA, [6]Oncology, Clinical Hospital Center Bezanijska Kosa, Belgrade, SERBIA, [7]Clinic of Lung Diseases and TB, Knez Selo, SERBIA, [8]Department of Experimental Oncology, Institute of Oncology and Radiology of Serbia, Belgrade, SERBIA, [9]Roche, Serbia, Belgrade, SERBIA

Aim: The detection of EGFR mutations in tumor tissues nowdays is guiding the treatment for advanced NSCLC. It is known that patients with lung adenocarcinoma have more frequent mutations, especially in population of women, non-smokers. The mutation L858R in exon 21 and the deletions in exon 19 account for >85% of all clinically important mutations.

Methods: The purpose of EGFR testing conducted in Serbia, is to assess the EGFR mutation rate among lung adenocarcinoma patients in Serbia in order to select group of patients suitable for treatment with erlotinib. Genomic DNA used for EGFR mutation analysis was isolated from FFPE tumor samples from 214 patients with NSCLC. For detection of EGFR mutations in exons 18-21 therascreen® EGFR PCR Kit and Cobas® EGFR Mutation Test were used.

Results: All tested patients had NSCLC, adenocarcinoma subtype, stage IIIb and IV. 214 patients were tested for EGFR mutations, male to female ratio 140(65%):74(35%), median age 63 years (range 36-83). EGFR mutations were detected in 30 patients (14,02% overall positivity rate). In tested male population, EGFR mutation rate is less than 10%, hence in tested female population, mutation rate is 23.6%. EGFR positivity rate varied between centers, with lowest EGFR mutation rate in southern Serbia(11.4%), folowing central Serbia(13.97%) and highest in northern Serbia(16,67%). Male to female ratio among EGFR positive patients was 13(41.4%):17(58,6%). Types of mutations detected were deletions in exon 19 in 18(60%) patients and L858R point mutation in exon 21 in 11(36.7%) patients, respectively. Insertion on exon 20 was detected in 1 patient.

Conclusions: EGFR mutation rate in Serbia among lung adenocarcinoma patient is 14,02%. Overall EGFR mutation rate in Serbia is in concordance with literature data, but lower in some parts of the country, which leads to conclusion that there is a need for better patient selection. Reason for lower mutation rate can lie in unknown smoking status of tested patients, and larger

proportion of male patients tested. Regarding characteristics of EGFR positive patients, we can conclude that EGFR mutations in Serbia are more frequent in female patients. Regarding type of mutations, more frequent type of mutation are deletions in exon 19.

Disclosure: N. Vukobradovic Djoric is a full time employee of Roche. All other authors have declared no conflicts of interest.

112P
ROLE OF EGFR MUTATIONAL STATUS IN RESPONSE TO FIRST-LINE CLASSICAL CHEMOTHERAPY IN PATIENTS WITH NON-SMALL-CELL LUNG CANCER

I. Franco[1], A. Antunes[1], S. Campainha[1], S. Conde[1], A.M. Barroso[2]
[1]Pulmonology, Centro Hospitalar Vila Nova de Gaia/Espinho, Vila Nova de Gaia, PORTUGAL, [2]Unidade de Pneumologia Oncológica, Centro Hospitalar de Vila Nova de Gaia/Espinho (CHVNG/E), Porto, PORTUGAL

Aim: Several studies showed that EGFR mutation is a predictor of epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) treatment response in patients with non-small-cell lung cancer (NSCLC). However, to what extent EGFR mutation status may influence the response to first-line chemotherapy regimens other than EGFR-TKI is not known. First-line treatment with EGFR-TKI was approved in Portugal in 2012. In our center, EGFR mutation analysis is performed to all NSCLC patients since 2006. The aim of this study was to evaluate the response to first-line classical chemotherapy – disease control, progression free survival (PFS) and overall survival (OS) – according to EGFR mutational status.

Methods: We retrospectively reviewed the medical records of 120 NSCLC patients – 6th ed. TNM stages IIIa (no radiotherapy), IIIb and IV - diagnosed and treated with first-line classical chemotherapy since 01.01.06 through 31.12.11. All patients underwent EGFR mutation analysis by direct DNA sequencing and were followed up until 31.10.13. Effect of EGFR mutations on PFS and OS was evaluated by Kaplan-Meier curves and disease control was evaluated by Odds Ratio.

Results: One hundred and twenty patients were included in the study: 72 (60%) men, 62.63+12.24 (mean+SD) years-old, 76 (63.5%) smokers or former smokers. EGFR mutations were detected in 17 (14.2%) patients. Median PFS after first-line chemotherapy was 12 months in EGFR mutated group versus 5 months wild-type group ($p = 0.021$). Median OS was 23 months in the EGFR mutated group versus 19 months in wild-type group ($p = 0.152$). Disease control was obtained in 82 patients (68%); EGFR mutation was associated to disease control - 2.402 (95% CI, 0.646-8.919).

Conclusions: In conclusion, EGFR mutation status seems to be a predictor of good response, not only to EGFR-TKI targeted therapy, but also to first-line classical chemotherapy, with a significant effect on PFS of NSCLCs patients. Nevertheless OS was not significantly different between both groups: deterioration of performance status or further changes of EGFR mutational status could explain these results.

Disclosure: All authors have declared no conflicts of interest.

113P
PALLIATIVE RADIATION DURING PEMETREXED PLUS CISPLATIN FIRST-LINE TREATMENT FOR ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC): PATIENT SAFETY IN THE JMDB AND PARAMOUNT TRIALS

G.V. Scagliotti[1], C. Gridelli[2], F. de Marinis[3], B. Biesma[4], M. Reck[5], B. San Antonio[6], A.H. Zimmermann[7], C. Visseren-Grul[8], N. Chouaki[9], L. Paz-Ares[10] [1]Clinical and Biological Sciences, University of Torino, Torino, ITALY, [2]Dept Oncology / Hematology, San Giuseppe Moscati Hospital, Avellino, ITALY, [3]First Oncological Pulmonary Unit, San Camillo Forlanini Hospital, Rome, ITALY, [4]Dept Pulmonary Diseases, Jeroen Bosch Hospital, Hertogenbosch, NETHERLANDS, [5]Thoracic Oncology, Hospital Grosshansdorf, Grosshansdorf, GERMANY, [6]Oncology, Eli Lilly and Company, Madrid, SPAIN, [7]Oncology, Eli Lilly and Company, Indianapolis, UNITED STATES OF AMERICA, [8]Oncology - Thoracic, Eli Lilly and Company, Houten, NETHERLANDS, [9]Oncology - Thoracic, Eli Lilly and Company, Paris, FRANCE, [10]Oncology, Seville University Hospital, Seville, SPAIN

Aim: The safety of palliative radiation (XRT) during first-line treatment with pemetrexed (Pem) plus cisplatin (Cis) was studied in a subset of pts in the JMDB (DB) and PARAMOUNT (PM) Phase 3 trials. Pts with stage IIIB/IV nonsquamous (NS) NSCLC (DB, n=618; PM, n=939) received up to 6 cycles and up to 4 cycles of induction therapy with Pem/Cis, respectively.

Methods: In both trials Pem (500 mg/m2) + Cis (75 mg/m2) were administered every 21 days. A subset of pts (DB, n=20; PM, n=45) also received palliative XRT. Safety was assessed via the incidence of adverse events (AEs) (CTCAE). All patients received oral folic acid, vitamin B_{12} and dexamethasone, consistent with the Pem label.

Results: Of pts who received palliative XRT during induction treatment, 90% of DB pts were male with an ECOG PS of 1 (90%) and a median age of 55 years; 58% of PM pts were male with an ECOG PS of 1 (69%) and a median age of 61 years. All patients except 1 in DB had stage IV disease. Bone was irradiated in 12/20 DB pts and 34/45 PM pts. Other locations (DB;PM) were: lymph node (0;2), mediastinum (3;2), chest wall (3;2), adrenal gland (0;1), intraocular (0;1), lung (1;1), brain (4;1), spinal cord (1;0) and abdomen (0;1). Total doses of XRT ranged from 8-50 Gy in both trials. The time between day 1 of last chemotherapy cycle and the start of palliative XRT ranged from 0-31 days in DB and 0-28 days in PM. Of 65 total pts, 12 (2:10) had ≥1 AE during XRT considered possibly related to Pem/Cis and/or XRT. Gr 2 anemia was the most common AE. Three pts had Gr 3/4 anemia. Five pts had Gr 1/2 nonhematologic toxicities. AEs during palliative XRT or within 2 weeks after the end of the last fraction in JMDB / PARAMOUNT (n=65).

***JMDB - 1 Gr 2 anemia; 1 Gr 2 radiation dermatitis**

Toxicity	Gr 1, n (%)	Gr 2, n (%)	Gr 3-4, n (%)
Anemia	1 (1.5)	*4 (6.1)	3 (4.6)
Leukocytes	0	2 (3.1)	0
Platelets	0	1 (1.5)	0
Rash/dermatitis	1 (1.5)	1 (1.5)	0
Rash/ desquamation	1 (1.5)	1 (1.5)	0
Radiation dermatitis	0	*1 (1.5)	0

Conclusions: In DB and PM, few pts with advanced NS NSCLC experienced AEs when treated with palliative XRT during Pem+Cis first line chemotherapy, and most events were Gr 1 / 2.

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114P
PEMETREXED MAINTENANCE THERAPY (PEM-MT) IN PATIENTS WITH ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (NSQ-NSCLC): A PRACTICE PATTERN ANALYSIS

V. Adam, L. Peeters, C. Dooms, K. Nackaerts, S. Lepers, C. Oyen, J. Vansteenkiste Respiratory Oncology Unit (Pulmonology), University Hospitals Leuven - Campus Gasthuisberg, Leuven, BELGIUM

Aim: The PARAMOUNT trial showed a significant improvement in overall survival (OS) with pem-MT in NSQ-NSCLC. After our pilot study (JTO 7:1291-5, 2012) on patients' perceptions on MT in a hypothetical context (i.e. before reimbursement of pem-MT in Q2, 2012), we now analysed the standard practice patterns (with reimbursed general implementation).

Methods: Retrospective database analysis of all consecutive pts with EGFR-wild-type NSQ-NSCLC who started cisplatin-pem from Jan 2012 till June 2013. Patients were stage IV at diagnosis or had a systemic relapse at least 1 year after initial (neo)adjuvant chemotherapy. RECIST assessment during MT was based on CT scan after 2 and after 4 cycles, and every 4 cycles thereafter. Endpoints of this analysis: uptake of pem-MT, tolerance, number of cycles, reason for discontinuation.

Results: We included 71 patients (93% stage IV; 86% adenocarcinoma). Thirty-seven pts (52%) did not receive MT. The main reasons were progressive disease (PD) during/after 1st line (n=21), toxicity (n= 7), worsening of performance status during/after 1st line (n=7, of whom 3 died), others (1 lost to follow-up, 1 switch to consolidating radiotherapy). 34 pts received MT, of whom 9 are still on treatment. Stop of MT was due to PD (n=16); adverse events (AEs, n=9): deterioration of renal function (n=4), haematological intolerance (n=3), oedema (n=1); patient request (n=1). The median and mean (range) number of MT cycles is 4 and 7 (1-26).

Conclusions: About 50% of 1st line cisplatin-pem pts continued with MT. Overall subjective tolerance of pem-MT was good, 7 of the 9 AEs leading to treatment discontinuation were lab toxicities, one main problem being cumulative renal toxicity (probably also related to repeated contrast-enhanced CT-scans to evaluate disease).

Disclosure: All authors have declared no conflicts of interest.

115P
MAINTENANCE LOW-DOSE GEMCITABINE VERSUS BEST SUPPORTIVE CARE IN ADVANCED AND METASTATIC NON-SMALL CELL LUNG CANCER: RANDOMIZED PHASE III TRIAL

A. Nagy, E. Fouad, K. Nasr, H. El-Ghazaly, A. Adel Clinical Oncology and Nuclear Medicine, Ain Shams University Faculty of Medicine, Cairo, EGYPT

Aim: To evaluate efficacy (defined in terms of prolongation of Time to Progression and Overall survival) and safety (as regard grade 3 and 4 toxicity)of low-dose gemcitabine as maintenance chemotherapy after first line gemcitabine/cisplatin in advanced and metastatic NSCLC.

Methods: This prospective phase III study included 120 patients with advanced and metastatic NSCLC (70.8% aging less than 60 years, 75.5% males, 59.2% with performance status 2, 75% with nonsquamous histology and 79.2% presented with stage IV 79.2%), who presented to Clinical Oncology and Nuclear Medicine Department, Ain Shams University Hospitals during the period from January 2010 to June 2012. All eligible patients started induction with gemcitabine/cisplatin. Patients who finished 4 cycles and showed response (CR-PR-SD) were randomized into two arms, Arm I (received gemcitabine 250 mg/m2 over 6 hours on days 1 & 8 every 3 weeks) and Arm II (received supportive care). Response was assessed by Revised RECIST guidelines every 2 cycles and toxicity by NCI criteria for common toxicities every cycle.

Results: The median TTP was 6.1 months (CI 5.3-6.6, p = 0.454) in Arm I and 5.8 months (CI 5.2-6.4, p = 0.454) in Arm II. The median OS were 9 months (CI 7.9-10.0. p = 0.994) and 8 months (CI 8.5-9.4, p = 0.994) in Arms I and II respectively. This trial showed that maintenance therapy with low dose gemcitabine was well tolerated with no grade 3 or 4 toxicity.The only significant toxicity was grade 2 anaemia in 8 patients (22.9%) in maintenance arm.

Conclusions: This trial did not show any statistical significance as regard TTP or OS between the 2 arms. The cause to this could be due to the smaller sample size or the use of low dose gemcitabine instead of conventional dose, the predominance of non-squamous histology and the predominance of PS 2.

Disclosure: All authors have declared no conflicts of interest.

116P
GEMCITABINE IN BRIEF STANDARD DOSE VERSUS PROLONGED LOW-DOSE INFUSION, BOTH COMBINED WITH CISPLATIN FOR ADVANCED NON-SMALL CELL LUNG CANCER

S.K. Beniwal[1], S.L. Jakhar[2], P.K. Bagri[2], N. Sharma[2], H. Kumar[2], A. Sharma[2], M. Singhal[2], D. Singh[2], G. Singh[2], A. Kapoor[2] [1]Medical Oncology, Acharya Tulsi Cancer Treatment and Research Institut, Bikaner, INDIA, [2]Radiation Oncology, Acharya Tulsi Regional Cancer Treatment and Research Institute, Bikaner, INDIA

Aim: Gemcitabine in low-dose prolonged infusion is a treatment with documented activity against a variety of tumors.The present study was conducted to evaluate the efficacy and safety of the combination of gemcitabine at a low-dose prolonged infusion in comparison with standard dose gemcitabine with cisplatin in chemonaive patients with advanced non-small cell lung cancer (NSCLC).

Methods: Eligible patients had non-small cell lung cancer in stage IIIB or IV, Eastern Cooperative Oncology Group(ECOG) 0-2, measurable disease, were chemonaïve and fulfilled the standard criteria for chemotherapy. Patients were randomly assigned 1:1 to receive 350mg/m2 gemcitabine in a 6-h infusion on days 1 and 8 and cisplatin at 80 mg/m(2) divided in 2 days on day 1and 2 (Arm I) versus gemcitabine 1000mg/m2 in 30 minutes on days 1 and 8 and cisplatin same schedule as Arm I (Arm II) (3-week cycle both). A total of 92 patients (65 men and 27 women, median age 54.5 years) were included and the two groups were balanced for prognostic factors.

Results: Histology was predominantly adenocarcinoma (55% of the patients). Patients had overall response rate (ORR) 41.3% and 36.9%(P-0.738), stable disease 32.6% and 34.8% (P-0.857) and progressive disease 26.1% and 28.3% (P-0.844) in standard arm and low-dose infusional arm respectively. Median progression-free survival was 5.5 months and 5.4 months, median overall survival was 10.2 months and 10.8 months, and 1-year survival was 40 % and 35.6% in standard arm and low-dose infusion arm respectively. Grade 3/4 toxicities were rare in both arm.

Conclusions: In NSCLC, gemcitabine low-dose prolonged infusion with cisplatin has low toxicity, especially thrombocytopenia, and has an activity comparable with gemcitabine given in higher dose in standard infusion. Low-dose gemcitabine may be preferred for incurable cancer among patients with poor economic status.

Disclosure: All authors have declared no conflicts of interest.

117P
WHOLE BRAIN RADIOTHERAPY WITH CONCURRENT TEMOZOLOMIDE FOR BRAIN METASTASIS IN NON-SMALL CELL LUNG CANCER: A SINGLE INSTITUTION, OPEN LABELED RANDOMIZED CLINICAL STUDY FROM SOUTH INDIA

S.S. Vadakke Puthiyottil, B.S. Mathew, P.G. Jayaprakash, C.D. Sivanandan, K. Ratheesan Radiation Oncology, Regional Cancer Centre Thiruvananthapuram, Trivandrum, INDIA

Aim: The mainstay of treatment for multiple Brain metastases (BM) is fractionated whole brain radiotherapy (WBRT). Concurrent Temozolomide (TMZ) with WBRT has been reported to improve response rates with non-significant prolongation of median survival. This study was intended to assess the efficacy of WBRT + TMZ in improving neurological progression free survival (PFS) for newly diagnosed patients with BM from Lung cancer.

Methods: Patients with radiologically proven multiple BM from Non Small Lung cancer (NSCLC) were included this study. Patients were randomly assigned to receive either WBRT of 20 Gy in 5 fractions with or without concurrent TMZ (75 mg/m2/d) for the 5 days. The primary end point was neurological PFS assessed clinically at 3 and 6 months after treatment. Survival curves were obtained by using the Kaplan-Meier method and were compared with the log-rank test.

Results: Between December 2011 and August 2013, 82 patients with NSCLC were enrolled. The mean age was 54.5years. There were 55 males and 27 females. 23 patients belonged to RTOG Recursive partitioning analysis (RPA) Class I and 59 to Class II. The PFS at 3 and 6 months were 38.46% and 23.77% for WBRT alone vs. 90.70% and 76.43% for WBRT with TMZ (p=0.00001). Subset analyses showed significantly better PFS for RTOG RPA Class-II (p-value 0.0143) receiving WBRT+TMZ.

Conclusions: The treatment of BM should be directed not only at improving survival but also improving the quality of life. While significant advances have been made for patients with solitary or limited (< four) BM with surgery and radio surgery, the outcome for patients with more advanced disease remains poor. This study demonstrated a significantly improved neurological PFS with the addition TMZ in patients with NSCLC with BM. Larger studies addressing this issue would be worthwhile considering the increasing incidence of BM owing to advances in systemic therapies, leading to prolonged survival for patients with lung cancer.

Disclosure: All authors have declared no conflicts of interest.

118P
INTRAPLEURAL HYPERTHERMIC CHEMOTHERAPY (IPHC) MAY ENHANCE SURVIVAL IN MALIGNANT PLEURAL DISSEMINATION

S. Sung[1], D.S. Noh[2], E. Yi[2], S.J. Park[2], H.C. Yang[2], S.C. Cho[2], K. Kim[2], C.L. Lim[2], S. Jheon[2] [1]Department of Thoracic and Cardiovascular Surgery, Seoul St Mary's Hospital, Seoul, KOREA, [2]Department of Thoracic and Cardiovascular Surgery, SNU Bundang Hospital, Seongnam, KOREA

Aim: Malignant pleural effusion or dissemination of lung cancer is detected in advanced cancer patients, and is generally associated with poor prognosis and poor survival. Palliative chemotherapy and or radiotherapy is not good enough to improve survival. Intrapleural perfusion hyperthermic chemotherapy (IPHC) provides direct effects to cancer tissue. The present study attempted to evaluate the efficacy and safety of IPHC.

Methods: From 2003 to 2012, 40 patients received IHPC for malignant pleural effusion or malignant pleural dissemination of lung cancer in a single institute. We excluded small cell lung cancer, multiple organ metastasis, N3 lymph node metastasis and additional procedure such as partial rib resection, decortication and other repeated surgery. A high dose cisplatin (150-200 mg/m^2 BSA) with saline was pooled into circuit and heated up to 43 degree Celsius. The cisplatin fluid filled the thoracic cavity nearly completely and was circulated with pump machine for 1 hour 30 minutes trying to maintain the temperature. Renal protective agents were adminstered perioperatively. We compared results with a chemotherapy-only group in terms of short-term survival and others.

Results: There were 40 patients in the IPHC and 36 in the chemotherapy-only groups.The mean age was 63.6±10.3 year (from 33 to 82). There was no statistical difference between two groups except age. The 2-year survival rate and 5-year survival rate of IPHC and the chemotherapy-only group were 65.0% and 12.5% versus 41.7% and 8.3%, respectively. We analysed prognostic factors and found SUV_{max} of post IPHC pleura of the patients who lived more than 2 years was less than that of the patients who lived less than 2 years (p-value=0.031). However preIPHC lung mass, preIPHC pleura SUV value, age, sex, chemotherapy, turmor size and nodela status did not have any influence on survival. Post IHPC complications were four acute renal failures(9.76%), two air-leaks (4.88%), two cardiac rhythm changes (bradycardia, atrial fibrillation, 4.88%) and gastrointestinal problem (2.44%). 16 patients received chemotherapy post procedure.

Conclusions: IPHC provides better survival compared with conventional chemotherapy. We suggest that IPHC is safe and effective for treatment of malignant pleural effusion or dissemination.

Disclosure: All authors have declared no conflicts of interest.

119P
THE EFFICACY AND TOXICITY OF CHEMOTHERAPY WITH BEVACIZUMAB FOR PREVIOUSLY TREATED PATIENTS WITH ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER

R. Itotani, T. Kitajima, D. Inoue, K. Takamatsu, M. Ishitoko, S. Marumo, M. Sakuramoto, M. Fukui Respiratory Disease Center, The Tazuke Kofukai Medical Research Institute Kitano Hospital, Osaka City, JAPAN

Aim: Bevacizumab (Bev) including chemotherapy is recommended as first line chemotherapy for patients with advanced non-squamous non-small cell lung cancer (non-Sq NSCLC). However there are few reports on the efficacy and toxicity of chemotherapy including Bev for previously treated patients with advanced non-Sq NSCLC. We conducted a retrospective cohort study to evaluate the efficacy and toxicity of chemotherapy including Bev for previously treated patients with advanced non-Sq NSCLC.

Methods: We examined advanced non-Sq NSCLC patients who were treated with chemotherapies including Bev as second or more lines at The Tazuke Kofukai Medical Research Institute Kitano Hospital between April 2010 and November 2013 in this study. The objective response rate (ORR), disease control rate (DCR), progression free survival (PFS) and adverse effects (AE) were investigated.

Results: A total of 41 patients received 60 chemotherapy regimens including Bev (median age 67 years old; gender male/female 22/19; clinical stage IIIA/IIIB/IV 3/4/34; Eastern Cooperative Oncology Group Performance Status (ECOG-PS) 0-1/2 58/2 regimens; lines of treatment 2nd line/3rd line/above 4th line 17/17/26 regimens; median number of cycles 4). The ORR and DCR were 14.8% and 80.4%, respectively. The median PFS time was 6.0 months. Toxicities of each regimens beyond Grade 3 in Common Terminology Criteria for Adverse events version 4.0 were as follows; neutropenia 30 (50%), thrombocytopenia 5 (8.3%), anemia 4 (6.7%), febrile neutropenia 2 (3.3%), anorexia 1 (1.7%), hypertension 7 (11.7%), proteinuria 2 (3.3%), skin disorder 3 (5.0%), pneumothorax 1 (1.7%) and bronchopulmonary hemorrhage 1 (1.7%, Grade 5). Most of these toxicities were acceptable except for one patient who had a fatal hemoptysis, and could be managed by some medications or only observation. During the treatment period, the patients' ECOG-PS didn't deteriorate except in 5 cases.

Conclusions: Chemotherapy including Bev seems to be mostly feasible and may provide favorable efficacy for previously treated patients with advanced non-Sq NSCLC. Further investigation is necessary to confirm this.

Disclosure: All authors have declared no conflicts of interest.

120P
CLINICAL RESULT OF IL-2 PLUS MELATONIN AND EPIGALLOCATECHIN GALLATE (EGCG) IN THE TREATMENT OF PATIENTS WITH NOT PREVIOUSLY TREATED ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

A.A. Tavartkiladze, Clinical Oncology, Georgian Cancer Research Center, Tbilisi, GEORGIA

Aim: The aim of our research is to study the efficiency of interleukin 2 (IL-2) plus melatonin and epigallocatechin gallate (EGCG) in the treatment of patients with not previously treated advanced non-small-cell lung cancer (NSCLC). Melatonin is a phylogenetically well-preserved molecule with diverse physiological functions. In addition to its well-known regulatory control of the sleep/wake cycle, as well as circadian rhythms generally, melatonin is involved in immunomodulation, hematopoiesis, and antioxidative processes. Recent human and animal studies have shown that melatonin also has important oncostatic properties. EGCG is a major catechin compound in tea extract and is also the most active form among the tea catechins in a variety of biological activities. For instance, EGCG has anticancerogenic, antioxidant, as well antimicrobal activities. Biological therapies are treatments that use natural body substances, or drugs that block them, to treat

cancer. IL-2 is a type of biological therapy for the treatment kidney cancer. It is also being evaluated in clinical trials for some other types of cancer including for NSCLC.

Methods: We have studied 34 patients with advanced not previously treated NSCLC. Each patient was administrated melatonin 40 mg/day orally (continually) in the evening, EGCG 1500 mg twice (750X2) daily (continually) and IL-2 intravenous 600,000 IU/kg day, over 5 days (repeated every 14 days). After one year we have studied using the FISH method the genetic profile (Genes: AKT1, ALK, BRAF, DDR2, EGFR, FGFR1, HER2, KRAS, MEK1, MET, NRAS, PIK3CA, PTEN, RET, ROS1) for the 34 patients.

Results: After one year from start of treatment 7 patients (20,58%) had survived (3 had partial response and 4 had stable disease). The genetic research showed the 7 surviving patients had amplification of the FGFR1 gene, while the other patients did not show genetic changes in the FGFR1 gene.

Conclusions: This research has very interesting implications for the development of the treatment of NSCLC showing FGFR1 amplification.

Disclosure: All authors have declared no conflicts of interest.

121P
NON-SMALL CELL LUNG CANCER (NSCLC) AMONG YOUNG ADULTS - SINGLE INSTITUTIONAL ANALYSIS OF DIAGNOSIS AND PROGNOSIS

M. Wollner[1], M. Moskovitz[2], D. Levy Faber[3], A. Agbarya[1] [1]Department of Oncology, Rambam Health Care Center, Haifa, ISRAEL, [2]Oncology, Rambam Health Caare Campus, Haifa, ISRAEL, [3]General Thoracic Surgery, Rambam Health Care Center, Haifa, ISRAEL

Aim: The median age of newly diagnosed patients with NSCLC is 70, only 1.7% of patients are diagnosed at age younger than 45. Data regarding the characteristic and prognosis of this group is scant and contradictive.

Methods: Retrospective analysis of medical records of patients with NSCLC, 45 year old and younger at diagnosis, treated at Rambam Health Care Campus.

Results: One hundred and sixteen patients under the age of 45 were treated for NSCLC between 2000-2013, third (36.6%) were non-smokers, 36% of arabic origin, 39% jewish of east-european origin. Relevant comorbidities had 16%. Histology: Adenocarcinoma represented 61%, and squamous cell carcinoma 16.4%. At diagnosis: locally advanced (25%) or metastatic (56%) disease. Median duration of symptoms was 9 weeks. Majority (76%) were in good performance status (PS ECOG 0-1), and only 25.9% had weight loss. The overall response rate to all lines of treatment was 44%. Response rate to first line chemotherapy was 41.3%. Median overall survival was 13.8 months, 17.4 months among non-smokers and 11.8 months among smokers. Survival was worse among patients with poor PS (18 vs. 4.8 months, $p<0.0001$), weight loss (16.8 vs. 7.2 months, $p=0.029$). Survival was significantly lower for patients presented at diagnosis with anemia, thrombocytosis, leukocytosis, hypoalbuminemia, elevated liver enzymes and elevated lactate dehydrogenase (LDH) levels. In multivariate analysis, leucocytosis and hypoalbuminemia at diagnosis predicted survival. Thirteen patients performed molecular analysis of tumor, 4 patients had EGFR mutation, 2 patients had ALK-EML rearrangement, 1 KRAS mutation, 1 RET mutation. Overall 7/13 patients had gene mutation predictive to treatment, and were treated with molecular targeted therapy accordingly.

Conclusions: This cohort of younger lung cancer patients had higher rates of advanced disease at diagnosis, adenocarcinoma histology, response to therapy, and lower rates of smoking than general population of patients with NSCLC, but no difference in survival. Prognostic factors significant for survival were PS and weight loss, anemia, thrombocytosis, leucocytosis, hypoalbuminemia, elevated liver enzymes and LDH at diagnosis. The rate of tumor gene mutations predictive to treatment was high, genetic tumor profiling is of particular importance among this group of patients.

Disclosure: All authors have declared no conflicts of interest.

122P
DIFFERENT EFFICACY BETWEEN TWO ERYTHROPOIESIS-STIMULATING AGENTS (ESAS) FOR CHEMOTHERAPY-INDUCED ANAEMIA (CIA) TREATMENT IN PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC): A SINGLE CENTER EXPERIENCE

A. Rodriguez Garzotto[1], S. Cortijo[2], C. Pernaut[1], I. Otero[1], G. Ruiz Ares[1], L. Parrilla[1], M. Blazquez Arroyo[1], J. Zugazagoitia[1], S. Ponce Aix[1] [1]Servicio de Oncologia Medica, University Hospital 12 de Octubre Medical Oncology, Madrid, SPAIN, [2]Servicio Farmacia, University Hospital 12 de Octubre Medical Oncology, Madrid, SPAIN

Aim: There are limited data on the relative effectiveness of biosimilar ESAs and other available ESAs for the treatment of CIA. In addition, it is unclear whether the most recent recommendations for more conservative use of ESAs to treat CIA are reflected in real-world clinical practice.

Methods: We analyzed 73 patients with NSCLC who were included in a retrospective audit of CIA treatment with ESAs in a large oncology centre in Spain, with patients treated by multiple physicians. The patients were treated for CIA with Binocrit® 40,000 IU QW (n=12), Binocrit® 30,000 IU QW (n=6), darbepoetin alfa 500 µg Q3W (n=36) or darbepoetin alfa 150 µg QW (n=19). In addition to overall haemoglobin (Hb) outcomes, comparisons were performed according to the different ESA treatments given. **Results:** The mean overall haemoglobin (Hb) at start of ESA treatment was 9.4 g/dL; the mean overall Hb level at the end of treatment was 10.6 g/dL. 36/73 patients (49%) achieved a Hb increase of at least 1 g/dL. There were no significant differences ($p>0.05$) between the groups in terms of Hb levels at the start of ESA treatment. At the end of treatment, however, the mean Hb level in the group treated with darbepoetin alfa 500 µg Q3W was significantly lower than that in the other three groups (Table). No drug-related adverse events were recorded.

ESA	Mean treatment duration (w)	Mean Hb at start of treatmen(g/dl)	Mean Hb at end of treatment (g/dl)
Darbepoetin 150 µg QW	4.16	9.2	11.3
Darbepoetin 500 µg Q3W	4.59	9.4	10.1
Binocrit 30,000 IU	3.50	9.4	11.1
Binocrit 40,000 IU	3.67	9.5	10.7

Conclusions: Our data indicate that Hb outcomes in a real-world clinical practice setting are similar for the ESA treatments used with the exception of Darbepoetin 500 µg Q3W, which achieved a significantly lower Hb at the end of treatment. We consider the use of ESAs in our centre to be conservative and safe, and to reflect the most recent change in ESA prescribing information and recommendations for more moderated use in patients with CIA (that is, use the lowest possible dose and duration of treatment necessary to avoid transfusions)

Disclosure: All authors have declared no conflicts of interest.

123TiP
STUDY 20070782: RANDOMIZED PHASE 3 TRIAL OF THE LONG-TERM SAFETY OF DARBEPOETIN ALFA IN PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC) WITH CHEMOTHERAPY-INDUCED ANEMIA (CIA)

P. Gascon[1], C.H. Barrios[2], D. Gordon[3], V. Hirsh[4], S. Orlov[5], K. Syrigos[6], C. Volovat[7], L. Zhang[8], C. Bohac[9] [1]Division of Medical Oncology, Hematology-oncology Department, Hospital Clinic, Barcelona University, Barcelona, SPAIN, [2]Department of Medicine,

PUCRS School of Medicine, Porto Alegre RS, BRAZIL, [3]Oncology, Cancer Care Centers of South Texas, San Antonio, UNITED STATES OF AMERICA, [4]Oncology, McGill University, Quebec, CANADA, [5]University N.a.academic I.p.pavlov of Moh and Sd of Rf, SBEI of HPE Saint Petersburg State Medical, St Petersburg, RUSSIAN FEDERATION, [6]Sotiria General Hospital, Athens School of Medicine, Athens, GREECE, [7]Oncology, Center of Medical Oncology, IASI, ROMANIA, [8]Medical Oncology, Sun Yat-Sun University Cancer Center, Guangzhou, CHINA, [9]Clinical Development, Amgen Inc., Thousand Oaks, UNITED STATES OF AMERICA

Background: Controlled trials have shown erythropoiesis-stimulating agents (ESAs) raise hemoglobin (Hb) and reduce transfusions in patients with CIA. While some suggestions of increased mortality and/or tumor progression have been raised in a few trials, most studies to date have not associated the use of ESAs with worse outcomes. As CIA often develops in lung cancer, studying ESA safety in NSCLC is warranted.

Trial design: Study 20070782 (NCT00858364) is a randomized, double-blind, non-inferiority trial comparing darbepoetin alfa with placebo currently enrolling patients with Stage IV NSCLC with CIA. Overall survival (primary endpoint) and progression-free survival (secondary endpoint) will be analyzed when approximately 2700 deaths occur. Other safety endpoints include tumor response and thromboembolic event rate. Superiority of darbepoetin alfa to placebo with respect to transfusion rates will be tested if non-inferiority is achieved for overall survival and progression-free survival. Patients (approximately 3000) from up to 500 world-wide sites will be randomized 2:1 to darbepoetin alfa (500 mcg) or placebo once-every-three-weeks until progression or end of chemotherapy. Eligibility criteria include ≥ 18 years, ECOG status ≤ 1, stage IV NSCLC, no prior adjuvant/neoadjuvant NSCLC therapy, ≥ 2 cycles first-line chemotherapy planned (≥ 6 weeks total), and screening Hb ≤ 11 g/dL. At Hb > 12 g/dL, study drug will be withheld until Hb ≤ 12 g/dL. Transfusions are allowed when medically indicated. As of October 31, 2013, active sites in the US, Europe, Latin America, and the Asia-Pacific region have enrolled 1234 patients. To date, an independent data monitoring committee has conducted 6 reviews of unblinded data (including a planned formal interim analysis to test for harm at 20% of the planned total number of 2700 deaths) and has recommended trial continuation without changes. Study 20070782 is the largest NSCLC clinical trial conducted and will provide comprehensive data on the benefit:risk profile of darbepoetin alfa in patients with CIA. We acknowledge the contributions of Jesús Cárdenas, David Henry, Jin-Hyoung Kang, Shona Nag, Martin Šmakal, H. Tilman Steinmetz, Gary Thomas, and Alex Fleishman. This is an Amgen Inc. sponsored study.

Disclosure: P. Gascon: No financial interest in the current research. I am not a stock holder or member of any advisory board of directors, corporate-sponsored research, or other substantive relationships. I have received honoraria from AMGEN for lecturing at meetings. C.H. Barrios: Steering committee participation and the conduct of research sponsored by AMGEM. D. Gordon: I own more than $50,000 in stock in Amgen ad receive paymnet for uties associated with the Steering Committee for the 782 Study. V. Hirsh: Member of an Advisory Board of Amgen and a member of Steering Committee for the trial. No financial conflicts. S. Orlov: Stock ownership: No Membership on an advisory board: No Corporate-sponsored research: Yes, Roche Other substantive relationships: No. C. Volovat: Stock ownership: No Membership on an advisory board: Yes, Roche and Amgen Corporate-sponsored research: Yes, Lilly and Roche Other substantive relationships: No L. Zhang: Stock ownership: No Membership on an advisory board: Yes, Roche, AZ, Amgen, Pfizer Corporate-sponsored research: Yes, Lilly and Roche Other substantive relationships: No. C. Bohac: I am an employee and stock holder of Amgen. All other authors have declared no conflicts of interest.

METASTASES FROM AND TO THE LUNG

124O

STEREOTACTIC ABLATIVE BODY RADIOTHERAPY (SABR) WITH FLATTENING FILTER FREE (FFF) MODE FOR NSCLC OLIGOMETASTATIC PATIENTS: FEASIBILITY AND OUTCOMES

P. Navarria[1], F. De Rose[1], A.M. Ascolese[1], E. Clerici[1], A. Tozzi[1], A. Fogliata[2], P. Mancosu[1], A. Gaudino[1], L. Cozzi[2], M. Scorsetti[1] [1]Radiotherapy and Radiosurgery, Humanitas Research Hospital, Rozzano, ITALY, [2]Physics, IOSI, Bellinzona, SWITZERLAND

Aim: Data in the literature suggest the existence of oligometastatic disease, a state in which metastases are limited in number and site. Different kinds of local therapies have been used for the treatment of limited metastases and in the recent years reports on the use of Stereotactic Ablative radiotherapy (SABR) are emerging and the early results on local control are promising. The aim of this study is the evaluation of local control, toxicity and overall survival in NSCLC oligometastatic patients underwent SABR

Methods: Between October 2010 and May 2013, 36 NSCLC patients for 58 lung lesions were treated at our Institution. SABR was performed in case of controlled primary tumor, long interval time from the first diagnoses (greater than 6-12 months), exclusion of surgery, and number of metastatic sites ≤ 5. The total dose prescribed varied according to tumor site and maximum diameter. Dose prescription was 48 Gy in 4 fractions for peripheral lesions, 60 Gy in 8 fractions for central lesions and 60 Gy in 3 fractions for peripheral lesions with diameter ≤ 2 cm.

Results: Radiological response was obtained in the vast majority of patients. The local control at 1, 2 and 3 years was 100%, 95% and 95% respectively. No pulmonary toxicity G3-G4, chest pain or rib fracture occurred. The median follow up was 38 months (range 6-57 months). Overall Survival (OS) at 1, 2 and 3 years was 90%,84% and 82% respectively.

Conclusions: SABR is feasible with limited morbidity. We believe that the discussion within a multidisciplinary team is of pivotal importance to select patients with better prognosis.

Disclosure: All authors have declared no conflicts of interest.

125P

BEVACIZUMAB SAFETY WHEN COMBINED WITH WHOLE-BRAIN RADIATION THERAPY (WBRT)

J. Arrondeau[1], C. Le Pechoux[2], S. Le Moulec[3], F. Barlesi[4], P. Lesueur[5], B. Besse[1] [1]Department of Medicine, Institut Gustave Roussy, Villejuif, FRANCE, [2]Department of Radiotherapy, Institut de Cancérologie Gustave Roussy, Villejuif, FRANCE, [3]Medical and Radiation Therapy, Hopital d'Instruction des Armées du Val-de-Grâce, Paris, FRANCE, [4]Multidisciplinary Oncology and Therapeutic Innovations Department, Assistance Publique Hôpitaux de Marseille, Marseille, FRANCE, [5]Oncology, Centre François Baclesse, Caen, FRANCE

Aim: Bevacizumab (bev.) based chemotherapy was approved for treatment of patients with metastatic non squamous non small lung carcinoma (NSCLC). In case of cerebral progression, whole-brain radiation therapy (WBRT) is offered. Because of its long half-life, bev. could increase with WBRT's toxicity. We reviewed toxicity and efficacy of WBRT when offered within 6 months after the last infusion of bev.

Methods: We report a retrospective, multicenter study of bev. followed by WBRT for NSCLC pts with inoperable brain metastasis. We collected data of pts, treated between 2009 and 2013 with BCT before WBRT, with a delay ≤ 6 months. Evaluation of neurologic symptoms was reported and toxicities were scored according to the version 4 common terminology criteria for adverse events.

Results: 28 pts were eligible. Median age was 45. Sex ratio was 1:1 (14 males, 14 females). 9 pts (32.1%) were never smokers. Median delay between brain metastasis and NSCLC diagnosis was 6.35 months (0-65 months). Median Graded Prognosis Assessment was 1,5 (0,5-3). 20 pts (71.4%) had neurologic symptoms before WBRT; mostly sensorimotor deficit (12 pts, 42.9%).

Bev. was in median used after 2,5 other treatments (1-8). The median dose of bev. was 15mg/kg and the median duration of treatment was 5.1 months (0.7-35 months). The median delay between brain metastasis diagnosis and WBRT was 6 months (0.1-25 months) and between BCT and WBRT was 12 days (0-143 days). Neurologic symptoms were stable during WBRT in 10 pts (35.7%), while the others had improvement or degradation of symptoms (8 pts, 28.6% each); one patient is dead during WBRT because of disease progression. Most common reported side-effects were intracranial hypertension symptoms (n=6 pts), grade 2 (n=1) or 3 (n=5), grade 2 seizure (n=2), grade 3 vertigo (n=1), grade 3 dizziness (n=1), and grade 2 intracranial bleeding (n=2). Radiologic brain metastasis assessment showed 1 complete response (3.6%), 7 partial responses, (25%) 9 stable diseases (32.1%), and 7 progressive diseases (25%). Then 10 pats had brain progression with median delay of 3.5 months (0.5-13 months). Median survival from WBRT was 3.15 months (0.1-36.8).

Conclusions: The combinaison of BCT and WBRT was not associated with increase toxicity, except in 2 patients with intracranial bleeding. Because of the limited number of pts, these results must be confirmed prospectively.

Disclosure: All authors have declared no conflicts of interest.

126P
SERUM MARKERS OF BONE REMODELING IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER AND BONE METASTASES

F. Lumachi[1], F. Mazza[2], A. Del Conte[3], G.B. Chiara[4], S.M.M. Basso[4] [1]Department of Surgery, Oncology & Gastroenterology, University of Padua, School of Medicine, Padova, ITALY, [2]Pneumology, S. Maria degli Angeli Hospital, Pordenone, ITALY, [3]Medical Oncology, S. Maria degli Angeli Hospital, Pordenone, ITALY, [4]Surgery 1, S. Maria degli Angeli Hospital, Pordenone, ITALY

Aim: Lung cancer is the most common cause of cancer death worldwide. In the USA, there were estimated to be 246,000 new cases and 164,000 deaths in 2013. Approximately, 80 % of lung cancers are carcinomas that are classified histologically as non-small cell lung cancer (NSCLC). The efficacy control for the treatment of bone metastases in NSLCLC is difficult and usually initiated later and with longer time between treatment cycles than the restaging of visceral or soft tissue metastases. The aim of this study was to evaluate the usefulness of bone formation serum markers bone alkaline phosphatase (bALP) and osteoprotegerin (OPG), and bone resorption serum markers tartrate-resistant acid phosphatase isoform-5b (TRACP 5b), carboxy terminal cross-linked telopeptide of type I collagen (CTX), and receptor activator of nuclear factor-κ ligand (RANKL) in patients with NSCLC and bone metastases.

Methods: Twenty-six patients with advanced NSCLC (21 men, 5 women, median age 74 years, range 57-79 years) scheduled for palliative chemotherapy were enrolled in the study. All patients underwent whole body (18)F-FDG PET/CT that showed the presence of bone metastases in 12 (cases). Controls (N=14) were patients with negative (18)F-FDG PET. The pre-treatment panel of serum markers was obtained in the entire study population. The results were expressed as positive or negative when they did not result within the reference range of each serum marker. The two-tailed Fisher exact probability test was used for testing results.

Results: TRAC5b (OR=0.09, 95%CI 0.01-0.56, p=0.016), RANKL (OR=0.13, 95%CI 0.02-0.78, p=0.044), and OPG (OR=0.13, 95%CI 0.02-0.76, p=0.047) exhibited a good sensitivity, whilst CTX (OR=0.20, 95%CI 0.04-1.06, p=0.11) and bALP (0.54, 95%CI 0.11-2.55, p=0.69) were not sensitive enough (cases vs. controls).

Conclusions: In patients with NSCLC and bone metastases the measurement of serum TRAC55, RANKL, and OPG could be useful in diagnosing advanced disease early. References Pollmann D, Siepmann S, Geppert R, Wernecke KD, Possinger K, Lüftner D. The amino-terminal propeptide (PINP) of type I collagen is a clinically valid indicator of bone turnover and extent of metastatic spread in osseous metastatic breast cancer. Anticancer Res. 2007; 27: 1853-1862.

Disclosure: All authors have declared no conflicts of interest.

MESOTHELIOMA AND OTHER TUMOURS

127O
PROGRAMMED CELL DEATH 1 LIGAND 1 EXPRESSION AND ASSOCIATION WITH SURVIVAL IN MESOTHELIOMA

A.S. Mansfield[1], T. Peikert[2], A. Roden[3], C. Krco[4], S. Harrington[5], H. Dong[5], E. Kwon[5] [1]Medical Oncology, Mayo Clinic, Rochester, MN, UNITED STATES OF AMERICA, [2]Pulmonology, Mayo Clinic, Rochester, MN, UNITED STATES OF AMERICA, [3]Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, UNITED STATES OF AMERICA, [4]Immunology, Mayo Clinic, Rochester, MN, UNITED STATES OF AMERICA, [5]Urology, Mayo Clinic, Rochester, MN, UNITED STATES OF AMERICA

Aim: Due to the role Programmed Cell Death 1 Ligand 1 (PD-L1, aka B7-H1) has in establishing immune tolerance, its associations with worse survival in patients with many human malignancies, and the availability of agents to target PD-1:PD-L1 interactions, we decided to investigate the expression of PD-L1 in mesothelioma with the goal of exploring whether it might serve as a therapeutic target.

Methods: We evaluated 224 cases of malignant pleural mesothelioma (MPM) diagnosed between the years of 1986 and 2003 for the expression of PD-L1 using immunohistochemistry. These tissue samples were obtained during diagnostic surgical pleural biopsies or therapeutic resections from patients with clinically diagnosed MPM. All cases were diagnosed as MPM by a pathologist. The mouse monoclonal anti-human B7-H1 (clone 5H1-A3) antibody was used at a dilution of 1:300. The location and percent of PD-L1 expression was scored for each sample by a pathologist. Cases with less than 5% expression were considered negative. Survival between groups was compared with Kaplan-Meier curves and the log-rank test. The associations of PD-L1 expression with outcome were assessed with Cox proportional hazards regression models.

Results: Eighty-nine of 224 samples (40%) expressed PD-L1. The median percent expression was 40% (10-70% interquartile range [IQR]). There were no significant differences in gender, age, decade of diagnosis, or lymphocytic infiltration between PD-L1 positive and negative patients; however, patients with PD-L1 positive tumors were less likely to be offered a therapeutic surgery due to greater extent of disease at presentation (p=0.001). Survival was significantly worse for patients with PD-L1 expression (6 months median, 4-9 mo. IQR) compared to those without PD-L1 expression (14 mo. median, 11-16 mo. IQR; p<0.0001). PD-L1 expression remained significantly associated with worse survival after adjusting for age, gender, lymphocytic infiltration, and therapeutic surgical intervention (risk ratio 1.73, 95% confidence interval 1.3-2.3; p=0.0002).

Conclusions: PD-L1 is expressed in a substantial proportion of MPMs and is associated with poor survival. PD-L1 expression may have important implications for the management of patients with MPM.

Disclosure: C. Krco: CK has patents pending in regard to B7-H1 as a prognostic marker. S. Harrington: SH has patents pending in regard to B7-H1 as a prognostic marker. H. Dong: HD has patents pending in regard to B7-H1 as a prognostic marker. E. Kwon: Both E. Kwon and the Mayo Clinic have received royalties greater from the licensing related to B7-H1. EK has patents pending in regard to B7-H1 as a prognostic marker. All other authors have declared no conflicts of interest.

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IDENTIFICATION OF A PROGNOSTIC MICRORNA SIGNATURE FOR PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA UNDERGOING EXTRAPLEURAL PNEUMONECTOMY

M.B. Kirschner[1], Y.Y. Cheng[1], S.C. Kao[1], N.J. Armstrong[2], B.C. McCaughan[3], N. van Zandwijk[1], G. Reid[1] [1]Asbestos Diseases Research Institute, University of Sydney, Sydney, AUSTRALIA, [2]School of Mathematics and Statistics, University of Sydney, Sydney, AUSTRALIA, [3]Cardiothoracic Surgical Unit, Royal Prince Alfred Hospital, Sydney, AUSTRALIA

Aim: So far, clinical factors have not been able to reliably predict which patient with malignant pleural mesothelioma may benefit from radical treatment approaches. We have investigated the possibility of using a microRNA expression signature as prognostic/predictive marker for patients undergoing extrapleural pneumonectomy (EPP).

Methods: Levels of 20 candidate microRNAs previously identified through microarray profiling of tumours from 'long and short survivors' after EPP were assessed by TaqMan assay-based RT-qPCR in RNA from 48 formalin-fixed paraffin embedded tumour tissue samples from patients following EPP. Multivariate Cox proportional hazard model selection was carried out using all available samples with likelihood ratio tests being used to determine improved fit. The performance of this best fit model was then compared to that of a model consisting of clinical factors (age, gender, histological subtype and stage) to evaluate the gain in predictive accuracy achieved by using microRNA levels (method of Schemper and Henderson).

Results: We identified 6 microRNAs: miR-221, -23a, -21, -31, -662 and -625-3p with prognostic potential. These microRNAs were significantly associated with prognosis (p-value <0.05). When applying a univariate log-rank model, higher tumour expression of miR-662 and lower tumour expression of the remaining microRNAs were associated with a survival benefit. The comparison of a model containing these microRNAs with a model of (only) clinical prognostic factors revealed a lower predictive inaccuracy (0.403 ± 0.031 vs 0.473 ± 0.031) for the microRNAs model. Combining clinical factors and microRNAs resulted in a gain of 0.076 further reducing the predictive inaccuracy to 0.397 ± 0.033, suggesting that the predictive inaccuracy can be decreased by using microRNA information.

Conclusions: This study has identified six microRNAs that seem to act as a prognostic signature with the potential to assist in better selection of MPM patients considered for EPP. Further validation of this model is essential.

Disclosure: All authors have declared no conflicts of interest.

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GAS5 LONG NON CODING RNA IN MALIGNANT PLEURAL MESOTHELIOMA

A. Renganathan[1], J. Kresoja[1], N. Echeverry[1], G. Ziltener[1], B. Vrugt[2], I. Opitz[3], R.A. Stahel[4], E. Felley-Bosco[1] [1]Laboratory of Molecular Oncology, University Hospital of Zurich, Zurich, SWITZERLAND, [2]Institute of Surgical Pathology, University Hospital of Zurich, Zurich, SWITZERLAND, [3]Division of Thoracic Surgery, University Hospital of Zurich, Zurich, SWITZERLAND, [4]Clinik and Policlinic of Oncology, Universitätsspital Zürich, Zurich, SWITZERLAND

Aim: Malignant pleural mesothelioma (MPM) is an aggressive cancer with short overall survival. Long noncoding RNAs (lncRNA) are a class of RNAs more than 200 nucleotides that do not code for protein and are part of the 90% of the human genome that is transcribed yet less well characterized. Earlier experimental studies showed GAS5 (growth arrest specific transcript 5) lncRNA deletion in asbestos driven mesothelioma. The function of GAS5 is not well known, but it has been shown to act as glucocorticoid receptor decoy and microRNA "sponge". Thus our aim is to investigate the possible role of the GAS5 in the growth of MPM.

Methods: Primary MPM cultures grown in serum-free condition in 3% oxygen or MPM cell lines grown in serum medium were used. Doxycycline inducible shGas5 clones were generated from ZL55SPT cells. Gene expression was quantified by qPCR. To investigate GAS5 promoter, 1kb sequence was inserted into pGL3 reporter plasmid and reporter activity was determined after transfection into MPM cells. Cell cycle length was determined by EdU incorporation assay. Localization of GAS5 lncRNA was identified by in situ hybridization. Expression of podoplanin and ki67 was identified by immunohistochemistry.

Results: GAS5 expression was lower in MPM cell lines compared to normal mesothelial cells. GAS5 was upregulated upon growth arrest induced by inhibition of Hedgehog or PI3K/mTOR signaling in in vitro MPM models. The increase in mRNA was accompanied by increased promoter activity. Silencing GAS5 increased the expression of glucocorticoid responsive genes GILZ and SGK1 and shortened the length of the cell cycle. Drug induced growth arrest was associated with GAS5 accumulation in the nuclei. Surprisingly, GAS5 was expressed at higher level in tumor tissue compared to non-tumoral tissue, was abundant in tumor quiescent cells and it was correlated to podoplanin expression.

Conclusions: Drug induced growth arrest increases Gas5 expression and decreasing levels of GAS5 shortens cell cycle in vitro. The higher GAS5 expression in MPM tissue compared to non-tumoral tissue is associated with cell quiescence and podoplanin expression. Because podoplanin and GAS5 mRNA sequence contain the same microRNA targets, this supports GAS5 lncRNA having an important role in growth-arrest and microRNA-"sponge" in MPM.

Disclosure: All authors have declared no conflicts of interest.

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POSITRON EMISSION TOMOGRAPHY (PET) AS A PROGNOSTIC FACTOR IN MALIGNANT PLEURAL MESOTHELIOMA (MPM)

S. Cedres[1], S. Ponce[2], J. Zugazagoitia[2], A. Navarro[3], A. Martinez[1], P. Martinez[1], F. Salva[3], C. Muñoz[2], G. Ruiz Ares[2], E. Felip[4] [1]Medical Oncology, Vall d´Hebron University Hospital. Universidad Autonoma de Barcelona, Barcelona, SPAIN, [2]Medical Oncology, Hospital 12 Octubre. Universidad Complutense, Madrid, SPAIN, [3]Medical Oncology, Vall d´Hebron University Hospital, Barcelona, SPAIN, [4]Oncologia Médica, Vall d`Hebron University Hospital Institut d'Oncologia, Barcelona, SPAIN

Aim: Malignant pleural mesothelioma (MPM) is an aggressive tumor linked to asbestos exposure and a marked increase in the incidence is predicted over the next decades in Europe and developing nations. We investigated the overall survival (OS) and variables affecting survival in patients (p) diagnosed of MPM.

Methods: Ninety-two patients diagnosed of MPM in Vall d´Hebron University Hospital and 12 Octubre University Hospital between November 2002 and September 2013 were retrospectively reviewed. Baseline factors analyzed were age, gender, performance status (PS), histology, stage, standard uptake value (SUV) and chemotherapy (CT). Survival data were calculated by the Kaplan-Meier method.

Results: Patient's characteristics: median age 68 years (31-88years), males 71.7%, PS 1:59.8%, asbestos exposure 57.6%, chest pain 73.9%, dyspnea 75%, clinical stage III 45% and IV 39%, epithelial subtype 69.6%. All patients were considered initially unresectable and 79.3% received CT in 1st line and 42.4 % in 2nd. PET study was performed to 31 patients with no previous talc pleurodesis. Median SUV was 7.2 and patients with epithelial histology presented lower SUV than no-epithelial group (11.9 vs 6.6, p=0.002). After a median follow up of 13 months the median OS was 13.3 months. We found significant increase in OS in patients with epithelial subtype (19.7 vs 5.0 months in no-epithelial, p<0.001), patients without chest pain (23.3 v 12.4, p=0.012), PS1 (13.3 vs 2.5 months in PS 2, p=0.011) and patients who received 2nd line CT (25.5 vs 9.6 months, p=0.003). In the group of patients underwent PET, SUV<7.2 was predictor of better survival regardless of histology (24.7 vs 7.6 months, for patients SUV<7.2, p=0.025) Although no significant, age, tumor stage, and response to CT were associated with better OS.

Conclusions: In our study with 92 MPM patients, epithelial subtype, chest pain, PS, and treatment with second line therapy are prognostic factors for survival. We demonstrated PET provides prognostic information independently of histology in advanced MPM.

Disclosure: All authors have declared no conflicts of interest.

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INTRAPLEURAL TREATMENT WITH HEDGEHOG ANTAGONIST IN A RAT BIOLUMINESCENT MODEL OF MESOTHELIOMA RECURRENCE

M. Meerang[1], O. Lauk[1], E. Felley-Bosco[2], S. Arni[1], B. Bitanihirwe[1], R.A. Stahel[2], W. Weder[1], I. Opitz[1] [1]Division of Thoracic Surgery, University Hospital Zurich, Zurich, SWITZERLAND, [2]Laboratory of Molecular Oncology, University Hospital of Zurich, Zurich, SWITZERLAND

Aim: Tumor recurrence remains a challenge after complete resection of malignant pleural mesothelioma (MPM). Stem cell activation by the hedgehog pathway was detected in MPM, thus we hypothesized that the local application of a hedgehog antagonist could suppress the growth of MPM after resection. Here, we aim to use an immuno-competent rat bioluminescent MPM model to test the efficacy of local intracavitary treatment with the FDA approved hedgehog antagonist in the prevention of MPM recurrence.

Methods: Cytotoxicity and colony formation assays were applied to determine sensitivity of rat MPM cells expressing luciferase (IL-45-luc) to the hedgehog antagonist in vitro. These cells were sub-pleurally inoculated to immune-competent rats. Tumor nodule was resected six day later and pneumonectomy was performed. The hedgehog antagonist was intra-cavitary administered using fibrin as a carrier (n=3) and compared to a control group receiving fibrin alone (n=2). Tumor growth was monitored daily after the treatment using an in vivo bioluminescent imager. The gene expression was analyzed by quantitative real time PCR.

Results: IL-45-luc cells express key molecules of hedgehog pathway. The hedgehog antagonist suppressed the growth of these cells in a dose dependent manner and inhibited the expression of hedgehog target genes in vitro. The expression of a hedgehog ligand was increased in vivo compared to in vitro condition. In vitro assay showed that the hedgehog antagonist was gradually released from fibrin over 7 days, however, in vivo only a trend in tumor growth suppression was observed at day 4 after treatment.

Conclusions: Compared to in vitro condition, in vivo environment induced increased expression of hedgehog ligand suggesting a role of the hedgehog pathway in this rat MPM model. Tumor recurrence was not significantly reduced after intrapleural administration of the hedgehog antagonist compared to control, however the number of animals was limited. Systemic treatment will be carried out to further investigate the efficacy of this drug in the immuno-competent rat MPM model.

Disclosure: All authors have declared no conflicts of interest.

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ENHANCING RISK STRATIFICATION IN PRIMARY MEDIASTINAL NONSEMINOMATOUS GERM CELL TUMORS (PMNSGCT): A 27-YEAR EXPERIENCE AT A TERTIARY CANCER CENTER

A. Necchi[1], S. Lo Vullo[2], P. Giannatempo[1], E. Farè[1], D. Raggi[1], N. Nicolai[3], L. Piva[3], P. Scanagatta[4], R. Salvioni[3], U. Pastorino[4] [1]Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, ITALY, [2]Clinical Epidemiology and Trials Organization Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, ITALY, [3]Surgery Urology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, ITALY, [4]Thoracic Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, ITALY

Aim: Mediastinal GCTs and PMNSGCTs poorly benefit from CT and half of patients (pts) still die for disease. Enhancing the risk stratification may result in tailoring a personalized treatment strategy since diagnosis.

Methods: Between 1985 and 2012, 87 pts with PM-GCT were treated at our center. Of them, pure seminomatous histology was excluded. Cox proportional hazards regression analysis was conducted to examine the prognostic impact of these candidate factors on overall survival (OS): type of 1st-line CT (high [HDCT] vs conventional dose [CDCT]), post-CT surgery, type of baseline elevated serum tumor marker (STM), presence of lung or liver-bone-brain metastases (LBB), STM response (still elevated vs normal or normalized), and histology (viable cancer [VC] vs necrosis/teratoma [NT]). OS curves were compared by Kaplan Meier method with the log-rank test.

Results: The study included 68 cases with PMNSGCT. Median age was 28.5 yrs (IQR: 23-35). 12 pts (17.7%) presented with mediastinal syndrome, 23 (33.8%) had lung and 7 (10.3%) LBB metastases. 12 pts received upfront HDCT and 45 pts (66.2%) underwent post-CT surgery. The final model of poor prognostic factors included no surgery (HR: 8.74, 95%CI, 1.77-43.01), surgery + VC (HR: 6.97, 95%CI, 1.46-33.30), and lung metastases (HR: 2.92, 95%CI, 0.99-8.64). The model demonstrated moderate discriminatory ability for OS (c-statistic=0.68). A risk stratification model based on the combination of these factors and accounting for a 50% five-year survival cutoff identified 2 groups (poor prognosis, N=28 vs good prognosis, N=26) with distinct overall survival curves ($p<0.001$). Pre-operative STM and final histology were not associated ($p=0.574$ at Chi squared test). 5-yr OS after receiving 2nd line CT (n=25) was 18.7% (95%CI, 7.9-44.5). Results are limited by small numbers.

Conclusions: Pts with PMNSGCT classified as having a good prognosis in this model had a fairly high survival estimate, while a strategy of consolidation CT for pts with poorest risk features warrants investigation, once the model is confirmed. The effect of surgery on survival was independent of post-CT STM, which also poorly predicted final histology.

Disclosure: All authors have declared no conflicts of interest.

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SOLITARY FIBROUS TUMOR OF THE PLEURA:SURGICAL TREATMENT ANALYSIS OUR CASES FROM SEPTEMBER 1999 TO DECEMBER 2013.

F. Gradica[1], E. Fype[2], F. Kokici[2], D. Argjiri[3], A. Leka[4], L. Lisha[1], Z. Perduka[5], I. Vata[1], A. Cani[2], P. Kraja[1] [1]Thorax Surgery Department, University Hospital of Lung Disease "Shefqet Ndroqi", Tirana, ALBANIA, [2]Reanimacion Anestesie, University Hospital "Shefqet Ndroqi", Tirane, ALBANIA, [3]Pneumology, University Hospital of Lung Disease 'Shefqet Ndroqi', Tirane, ALBANIA, [4]Imagery, University Hospital of Lung Disease "Shefqet Ndroqi", Tirana, ALBANIA, [5]Pneumology Service Rreshen, University Hospital of Lung Disease 'Shefqet Ndroqi', Tirane, ALBANIA

Aim: Solitary fibrous tumours (SFT) of the pleura are rare tumours, originated from the mesenchimal tissue. This tumours present unpredictable clinical course, probably related to their histological and morphological characteristics.We present our experiency in surgical treatment of our cases with solitary fibrous tumour of the pleura, from September 1999 to December 2013.

Methods: Twenty-five (25) patients affected by SFT of the pleura were referred to us for surgical resection in our clinic in SU"Shefqet Ndroqi" from September 1999 to December 2013. All the patients had chest radiographs, computerized tomogrphy, lung function tests and ECG, and biochemical study. All patients underwent a bronchoscopy prior surgery. The diagnosis was estabilish by Fine needle aspiration biopsy, VATS biopsy or open biopsy. Immunohistochemical reactions positive for CD34 did not perform in all patients.

Results: Surgical excision required 18 posterolateral thoracotomies, five anterior lateral thoracotomies and no one video-assisted thoracoscopy. Average tumor diameter was 8.5 cm range from (4-28 cm) and weight was 130 g,range from(20-1650 gram). In all our patients resections were complete. No intraoperative or perioperative medical or surgical complications occurred. Median hospital stay was 5 days while perioperative mortality rate was 0. Median follow-up was 70 months. Only one patient experienced tumour recurrence.

Conclusions: Surgical resection of benign solitary fibrous tumours is usually curative. Malignant solitary fibrous tumours generally have a poor prognosis. Clinical follow-up and radiological follow-up are indicated for both benign and malignant solitary fibrous tumours.

Disclosure: All authors have declared no conflicts of interest.