KEYNOTE LECTURES

1IN
LUNG CANCER SCREENING

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Lung cancer is a public health problem of global magnitude and the leading cause of cancer death worldwide. Primary prevention, i.e. effective ways to have smokers quit and effective ways to prevent adolescents to start smoking, are crucial to stop the epidemic, both in Europe and other parts of the world. At the same time, millions of men and women are presently at very high risk of developing lung cancer. With the new low-dose multi-detector computer technology available in the past decade, lung cancer screening may play an important role in reducing lung cancer mortality and morbidity in high risk populations. In the US, the National Lung Screening Trial (NLST) was the first large-scale lung screening project ever to show that offering lung (CT) screening to high risk persons lead to a significant 20% lung cancer mortality reduction (and 6.7% all-cause mortality reduction at a median 6.5-years of follow-up). In Europe, 5 population-based RCTs of lung cancer screening have now completed their recruitment with almost 30,000 enrollees. When considering whether lung cancer screening could or should be made available to the population, stringent standards must be applied. Early detection and prevention at public level does not guarantee effective prediction at an individual level, and to achieve positive outcomes we often need to implement programs for large groups of people, only some of whom will benefit. The newest criteria for early detection are therefore unambiguous. There must be substantial positive health outcomes in terms of additional years of life and a significant increase in treatment options. Secondly, any adverse effects must be limited in nature: the level of overdiagnosis and the side-effects need to be estimated and expressed in terms of quality-adjusted life-years gained. There must be a reasonable balance between costs and benefits and measures must be taken to ensure that implementation will not lead to substantial unintended effects (such as widespread inequality, or increased smoking due to a health certificate effect or false reassurance by the test result). In this keynote lecture I will provide an overview of the current European trials, debate the position where we are now on these 3 aspects, and provide detailed data from the NELSON-trial, the largest EU-lung cancer screening trial.

Disclosure: All authors have declared no conflicts of interest.

2IN
THE EVOLUTION OF MOLECULAR TARGETED TREATMENT

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The term "targeted therapy", in its most simple interpretation, implies that a drug target (generally molecular) is identified, is measurable with some reliability in a reproducible fashion, and that patients whose tumors are actionable for the target will derive more benefit than either unselected patients or patients with tumors not harbouring the molecular target in question. In fact, targeted therapy can be interpreted as including not only newer inhibitors of signal transduction or angiogenesis, but classic chemotherapeutic agents as well. And further, many patients with NSCLC continue to be treated in an unselected fashion even with so-called targeted agents, bevacizumab being the prime example. Thus at present, selection of chemotherapy regimens, or even so-called targeted therapies, for individual patients with NSCLC remains largely an empiric process. Nevertheless, developing molecular-based or pharmacogenomic (PG) approaches for selection of chemotherapy, or targeted therapies, through predictive biomarkers now appears feasible due to improved understanding of underlying molecular mechanisms. Although diverse terminology has been applied to molecular-directed selection of therapy on an individual patient basis (individualizing, customizing, or personalizing therapy), all rely on commonly shared principles for assessing tumor or host-related factors. In this presentation, emerging data regarding such approaches for treatment selection for non-small cell lung cancer (NSCLC) are addressed, focusing primarily on the process by which predictive biomarkers for drugs directed against newly discovered targets are identified and developed in a cohesive manner with the drug itself. Lessons learned ranging from preclinical models to randomized clinical trials testing these concepts are described, including limitations in the clinical setting of advanced stage disease. Methodological and technical aspects are elucidated, recommendations for clinical application are provided, and new directions in this field are projected.

Disclosure: All authors have declared no conflicts of interest.

MEET THE EXPERT SESSIONS

3IN
HIGH-RISK PATIENTS WITH ADVANCED NSCLC

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Lung cancer is more and more frequently diagnosed in elderly pts for 2 reasons: increase of life expectancy and increased risk of developing a cancer with age. Thus, median age of pts at diagnosis is now around 65–70 years. There has been for a long time some nihilism regarding elderly pts with advanced NSCLC as well from the pts themselves, their relatives and even doctors. Until recently there were no studies devoted to elderly pts and the body of knowledge came from trials including pts with no upper limit of age. In most of these studies, the results obtained in pts aged did not differ from those obtained in their younger counterparts. However, only hyperselected elderly pts were included and even though there was no upper limit of age, there were no very old pts. The 1st study devoted to pts aged >= 70 years was a randomization between vinorelbine (VNR) alone and best supportive care (BSC). There was a highly significant survival gain in the chemotherapy arm and single agent became the standard of care. The following studies compared single agent to non-platinum based doublet and the conclusion was that there was no advantage to doublet. As a consequence, the European recommendations in 2010 were to treat pts aged >=70 years with single agent therapy such as gemcitabine or VNR. In a recent IFCT trial comparing VNR or gemcitabine vs carboplatine + weekly taxol in 451 elderly PS 0–2 pts, there was a highly significant benefit of survival (MST 10.3 vs 6.2 mos) in the doublet arm. This result was seen in every prognostic subgroup and the new paradigm of treatment for pts aged 70–89 with PS 0–2 should probably be this doublet. Regarding PS 3 pts there is nowadays no recommendation for chemotherapy and BSC is probably indicated in most cases. PS 2 pts represent 25% of all lung cancer cases and even more in stage IV disease with a consistent poorer prognosis compared to PS 0–1 pts. Cisplatin is clearly contra-indicated. In a subgroup analysis of PS 2 pts, Lilenbaum demonstrated that there was a survival gain in favor of carboplatine-taxol vs taxol alone. Further studies resulted in similar conclusions. In molecularly unselected PS 2 pts, there is no advantage to targeted therapies as 1st line therapy. In conclusion, carboplatin-based doublet is probably the best for elderly and PS 2 pts but more dedicated studies are needed.

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4IN
RARE TUMORS OF THE LUNG

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Chest physicians, thoracic surgeons, and radiation oncologists are principally dealing with patients with primary lung carcinoma of usual histologies in their daily practice. They are mostly adenocarcinoma,

squamous cell carcinoma, small cell carcinoma, and large cell carcinoma of lung origin. However, according to the "WHO histological classification of tumours of the lung", lots of other primary and metastatic histologies are being recognized with their own pathobiological natures. Fundamental knowledge about these "rare tumours" might be reflected in a proper management of patients with such tumours despite their "rarity". WHO classification roughly divides tumours into the following categories: malignant epithelial tumours (including mesenchymal tumours), benign epithelial tumours, Lymphoproliferative tumours, miscellaneous tumours, and metastatic tumours. Among these, all the tumours except for malignant epithelial tumours and metastatic tumours are rarely encountered. One cautious note is that even a common subtype like adenocarcinoma includes rare variants such as "fetal adenocarcinoma", "colloid carcinoma", "mucinous cystadenocarcinoma", "signet ring adenocarcinoma", and "clear cell adenocarcinoma". As one of the subtypes of large cell carcinoma, "large cell neuroendocrine carcinoma" has been mentioned, and its clinicopathological profiles have recently been well characterized. However, this subtype comprises only 3% of whole resected cases ("rare") despite well-known recognition. Other rare but important histologies of epithelial tumours includes salivary gland tumours (mucoepidermoid carcinoma, adenoid cystic carcinoma, and epithelial-myoepithelial carcinoma) and sarcomatioid carcinoams. Rare mesenchymal tumours of the lung are angiosarcoma, inflammatory myofibroblastic tumour, and synovial sarcoma. Various types of lymphomas arise in the lung with different grade of malignancy. They are MALT lymphoma, diffuse large-cell lymphoma, and Hodgkin's disease. The modern molecular approach and biopsy technique obtaining enough amount of tumour tissue play the crucial role to establish the precise diagnosis for these rare tumours.

Disclosure: All authors have declared no conflicts of interest.

5IN
MEDIASTINAL STAGING: EBUS, EUS, MEDIASTINOSCOPY OR WHAT?

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Mediastinal lymph node (LN) involvement is present in 30 to 45% of newly diagnosed lung cancers. A subgroup of patients with positive mediastinal LN's benefit from surgical multimodality treatment. Therefore, mediastinal staging procedures can select patients for resection, based on both baseline and post-induction assessment. PET scan has largely improved mediastinal LN staging. However PET positive mediastinal findings should always be cyto-histologically confirmed. Due to the high NPV of PET scan, invasive staging can be omitted in patients with Stage I NSCLC. In central tumours, PET N1 nodes or CT-enlarged LN's invasive staging is recommended (De Leyn, 2007). Different techniques of invasive mediastinal staging are available. They vary in accuracy and procedure-related morbidity. Ultrasound-guided bronchoscopy with fine-needle aspiration (EBUS-FNA) and endoscopic esophageal ultrasound-guided FNA (EUS-FNA) are techniques that provide cyto-histological diagnosis and are minimally invasive. Although some studies have shown equal accuracy of EBUS and mediastinoscopy (Yasufuku, 2011), it is accepted in case of negative results of EBUS/EUS-FNA, an invasive surgical technique is indicated. A recent prospective study showed that combining endosonography and surgical staging compared with surgical staging alone resulted in greater sensitivity for mediastinal nodal metastasis end fewer unnecessary thoracotomies (Annema, 2010). For restaging in a surgical multimodality regimen, invasive techniques providing cyto-histological information are advisable despite the encouraging results with the use of re-PET/CT imaging. The accuracy of remediastinoscopy and EBUS/EUS-FNA is much lower than in baseline staging. Baseline staging of mediastinal LN's with endoscopic techniques and restaging after induction therapy with mediastinoscopy seems to be a valuable tool to select patients with N2 disease for surgical multimodality treatment. We conclude that optimal staging is a truly multidisciplinary process, with a variety of possible techniques, to be performed by experienced hands. The proficiency of the physician performing the procedure plays a role in varying sensitivity and specificity observed and each center has to adopt its own guidelines pending on their performance.

Disclosure: All authors have declared no conflicts of interest.

6IN
BRAIN AND BONE METASTASES MANAGEMENT

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Brain metastases (BM) are the most frequent neurologic complication related to cancer. The risk of developing BM varies according to primary tumor type, with lung cancer accounting for approximately one half of all brain metastases. The median survival time of untreated patients is approximately 1 month. With treatment, the overall median survival time after diagnosis is approximately four months. Head/brain scans with CT or MRI are the way that the vast majority of brain metastases are detected. Surgery plays important role for patients with a single BM and an operable lung cancer: relieving mass effect from a large symptomatic lesion, confirming the diagnosis when needed, improving local control. The most widely used treatment for patients with multiple brain metastases is whole brain radiotherapy (WBRT) with 30 Gy in ten 3 Gy fractions. Stereotactic radiosurgery treats only single BM with a precise delivery of a single, high dose of RT in a one-day session. Chemotherapy has traditionally played a limited role in thetreatment of BM because the most agents are either too large or hydrophilicto cross the blood–brain barrier. Temozolomide is a new orally administered alkylating agent that crosses the blood–brain barrier and attains therapeutic concentrations. Several phase II trials suggest that single agent temozolomide has modest activity in patients with recurrent or progressive brain metastases. Approximately 30-40% of NSCLC patients develop bone metastases. Bone metastases are associated with a significant increase in skeletal-related events (SREs). Traditionally, radiation therapy and surgery were the mainstays of treatment for patients with bone metastases. In recent years, however bisphosphonate have emerged as an additional treatment option. The principal mechanism of action is the suppression of bone resorption through the inhibition of osteoclast recruitment and adhesion. Actualy, the only bisphosphonate to have received worlwide approval for use in patients with lung cancer is zoledronic acid. The treatment with 4 mg of zoledronic acid reduces the proportion of patients with an SRE (38 vs 47%; p=0.039), and the rate of skeletal morbidity to 2,2 events/year vs 2,7 events/year for placebo (p=0.017).

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7IN
THYMOMA

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Thymic malignancies comprise thymomas and thymic carcinomas (TC), the latter also including neuroendocrine thymic tumors (NETT). The most used staging system (Masaoka) is based upon the surgical-pathologic local extent of invasion. The system presents some limitations for

TC and NETT, in which the rate of lymphatic spread is not negligible. For this reason, TNM-based systems have been proposed where the T descriptor is derived from the Masaoka classification, and the N descriptor is based upon the spread to the regional lymphnodes. A global effort is under way (ITMIG, IASLC, regional thymic interest groups of ESTS, EACTS, JART) to propose a consistent staging classification for the 8th edition of the TNM staging manual. The WHO histologic classification (A, AB, B1, B2, B3, TC, NETT) is widely recognized among the pathologists, but there are some gray areas which need clarification , including the inter-observer variability among B-types, the identification of type A thymomas with atypical features, the lack of a clear definition between B3 and TC. Treatment of thymic malignancies is stage-dependent. Stage I thymomas (encapsulated) are surgically treated with no further therapy. Stage II tumors are treated by upfront surgery followed by adjuvant therapy on a selective basis (high-risk tumors, including B2-B3 and TC). Stage III tumors which are deemed to be resectable should be approached with upfront surgery followed by adjuvant therapy in case of incomplete resection or high-risk tumors. Stage III tumors which are not resectable should undergo induction chemotherapy and surgery in case of response, followed by adjuvant radiotherapy. Stage IV tumors should be approached in a multidisciplinary setting with chemotherapy, surgery and postoperative radiotherapy. Sternotomy represents the standard surgical access, but small tumors can also be resected with a minimally-invasive approach (VATS, robotic), while in case of extended tumors resection of the neighboring structures is justified to achieve a complete resection. Very recently, promising reports have been published evaluating the efficacy of biologic (targeted) therapies in thymic tumors including EGFR inhibitors (cetuximab) in thymomas, KIT inhibitors (imatinib) in TC, somatostatin analogues (Octreotide) in octreotide-scan positive tumors.

Disclosure: All authors have declared no conflicts of interest.

THE EPIDEMIOLOGY OF LUNG CANCER

8IN
SMOKING AND LUNG CANCER

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9IN
THE BURDEN OF LUNG CANCER IN NON-SMOKERS

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The incidence of lung cancer in never-smokers in the United States and Europe is estimated in the range 10-15/100,000 person-years. The incidence of lung cancer among non-smoking women is higher in East Asia than in other regions (data in men are complicated by variability in the effect of tobacco smoking across regions). Recognized causes of lung cancer in never smokers include second-hand smoke, indoor radon, indoor coal burning for cooking and heating (mainly relevant to non-smoking Asian women), and exposure to occupational carcinogens. Suspected causes of lung cancer in never-smokers include chronic inflammatory conditions, outdoor air pollution, hormonal factors, and low intake of fresh fruits and vegetables. The distribution of histologic types of lung cancer in never-smokers is different from that of smokers, with a higher proportion of adenocarcinoma (62% vs. 19%), and lower proportion of squamous cell carcinoma (18% vs. 53%). Population attributable fractions for individual risk factors ranged from 0.40% to 19.93%, these estimates vary by geographic region and reflect the variable prevalence of exposure to known risk factors. In general, they are higher in East Asia than in Europe and North America. Genetic variants consistently associated with lung cancer susceptibility in never smokers are on chromosomes 5p15.33 (TERT and CLPTM1L genes) 6q and 13q31. The role of a locus identified in GWAS at 15q25 has not been confirmed in never-smokers.

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10IN
THE MOLECULAR PATHOGENESIS OF LUNG CANCER IN NEVER SMOKERS

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While lung cancer in smokers is the leading cause of cancer deaths in the world with about 900,000 deaths/year, lung cancer in lifetime never smokers (LCNS), with about 300,000 deaths per year, is the 7th leading cause of cancer deaths. LCNS shows major pathological, ethnic and gender differences, favoring adenocarcinoma histology, female gender and East Asian ethnicity. The major pathogenic cause(s) are largely unknown, with exposure to environmental exposure to tobacco smoke playing a minor role. Major molecular differences between lung cancers in smokers and NS have been demonstrated. The best studied changes include the relative frequency of EGFR mutations and ALK translocations in LCNS, the relative paucity of KRAS mutations, and differences in the spectrum of TP53 mutations. In addition, the methylation patterns of the two forms of cancers are different. Recent evidence suggests that global changes in copy number and the frequencies of mitochondrial mutations may also vary between these groups. Lung cancers in smokers and never smokers appear to be two distinct diseases arising in the same organ. These differences impact on diagnosis and clinical management.

Disclosure: All authors have declared no conflicts of interest.

11IN
ISSUES SURROUNDING GENDER

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For a long period of time lung cancer has been considered as a malignancy affecting only males, but epidemiological data have shown a dramatic increase of its incidence among women, mainly as a consequence of the huge spread of tobacco consumption. Considering that this increase in women continues worldwide, the incidence of lung cancer is projected to be identical in both sexes over the next decade. Gender differences in terms of susceptibility to carcinogens and natural history of the disease have been reported and several case-control studies suggested that women are more vulnerable to tobacco carcinogens than men. Histological subtypes also differ significantly according to gender being adenocarcinoma the commonest histologic subtype in women. Although tobacco smoking remains a significant risk factor for adenocarcinoma, approximately 20% of women with lung cancer are never smokers. The rate of lung cancer in never smokers is higher in women than in men, being the hormonal status one potential explanation for such difference. Estrogens may be involved in lung tumorigenesis through several mechanisms such as cell proliferation induced by ligand-estrogen receptor (ER) interaction, the cross-talk between estrogen receptors and other growth factor receptors (i.e. epidermal and insulin growth factor receptors). When compared with men, women are more likely to be younger (50 years old) at the time of diagnosis and to have a better survival at any stage and independently from the therapeutic approach. An improvement in understating genetic, metabolic, and hormonal factors that could affect the way women react to carcinogens and lung cancer represents a research priority.

Disclosure: All authors have declared no conflicts of interest.

PATHOLOGY: CHANGES IN MORPOHOLOGICAL AND MOLECULAR APPROACHES

12IN
MORPHOLOGICAL CLASSIFICATION OF ADENOCARCINOMA

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Morphology is the core approach to the classification of all lung cancers. The new IASLC/ATS/ERS recommendations for this classification reflects the fact that adenocarcinoma (AD) morphology is complex, it has important clinical and molecular associations, there was considerable confusion and misuse of the term bronchioloalveolar carcinoma (BAC) and the current WHO classification was not fully applicable to most AD diagnosis; that made on small biopsy/cytology samples. Most resected AD show a mixture of patterns; combinations of acinar (AC), solid (SOL), papillary (PAP) and BAC pattern that by WHO would be 'mixed type' AD. The dominance of particular patterns has implications for the tumour biology, behaviour and molecular pathology. A fifth micropapillary (MP) pattern has emerged, and is especially aggressive. The preponderance of SOL and MP patterns confers stage for stage, a poor prognosis, AC or PAP predominance an intermediate outcome while BAC predominant tumours are less aggressive. Studies have shown that this classification is reproducible. These differences should be exploited to select for adjuvant therapy trials, especially in Stage 1 disease. The WHO classification calls BAC a small lesion of pure BAC pattern with no metastatic potential, essentially AD in situ (AIS). Yet the term BAC is still used to describe invasive AD with a BAC component, most of which have metastatic potential and multifocal AD of diverse biology, differing histology (usually non-mucinous or mucinous cytology) and a distinctive, slowly progressive clinical course. Pathologists, surgeons and oncologists using the same term in different ways predicts miscommunication and clinical mishap. Thus, the following recommendations were made: · Drop the term BAC. · The BAC pattern is referred to as 'lepidic'. · Lepidic predominant AD has a favour prognosis, especially lesions <3cm with a non-lepidic component <5mm dia when 5YS is ~100% and the term minimally invasive AD (MIA) is recommended. · Multifocal lepidic AD are special types, especially when mucinous. Difficulty in AD diagnosis in small samples led to the term NSCLC-NOS in cases of doubt. Therapeutic choices now require its minimal use and predictive immunohistochemistry (IHC) is used to reduce NSCLC-NOS to under 10% of cases.

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13IN
MOLECULAR PATHOLOGY OF ADENOCARCINOMA

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The current therapeutic strategy for the lung cancer patients was shifted by EGFR-TKI treatment in combination with patient selection with EGFR mutation. In addition to such clinical impact, understanding EGFR mutations sheds new light on a landscape of the molecular pathogenesis of lung adenocarcinoma. EGFR mutation occurs in very early stage of cancer development, as it seen in a precursor lesion, atypical adenomatous hyperplasia. Invasive growth is driven by many genetic alterations, and EGFR gene amplification is revealed to be involved in this process. Invasive parts within individual tumors exclusively showed EGFR gene amplification in contrast to no amplification in the in-situ carcinoma component. Whereas the mechanism has not been elucidated, the gene amplification is closely associated with EGFR mutation, e.g., the amplification occurs mostly in EGFR-mutated tumors, and the mutated alleles are specifically amplified. The combination of mutated allele specific amplification and prevalence of gene amplification in invasive area could explain pseudo-heterogeneity of EGFR mutation that has been reported in the literature. As already known, not all adenocarcinomas harbor EGFR mutation, and EGFR is exclusively mutated in a subset of adenocarcinoma with TTF-1 expression. Recently, TTF-1 gene amplification is reported to be associated with metastasis, and the mutations of other addiction genes, including ALK, HER2 and BRAF, were also involved in this subset of adenocarcinoma. Interestingly, the subset of adenocarcinoma frequently develops in females and non-smokers. These findings could be integrated into a simple concept, a cellar lineage of lung adenocarcinoma. This concept is supported by molecular classification of lung cancer based on expression profiling.

Disclosure: All authors have declared no conflicts of interest.

14IN
IDENTIFYING GENOMICS-BASED THERAPEUTIC TARGETS IN LUNG CANCER

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Cancer is a disease of the genome; genetic lesions (gene mutations, gene copy-number changes, structural genetic changes, etc.) lead to irreversible changes in the intracellular signal transduction pathways that the tumor cells become dependent upon. A new class of cancer therapeutics targeting specific signaling pathways activated by genetic lesions has shown clinical success. Understanding the dependency associated with each genetic alteration is crucial in order to device specific inhibitory strategies to interfere with the activity of the respective oncogene or the pathways activated downstream of the oncogene. Such preclinical work can help expediting the preclinical-to-clinical transition of novel cancer therapeutics and to make them more effective. Similarly, linking drug response and clinical features of patients to genetic alterations is essential for a continuous re-assessment of the validity of such preclinical predictions. Our laboratory has created a conceptual framework as well as methodological strategies for approaching these needs. We have developed an international network for cancer genome analyses and we have developed a platform for functional cell biology analysis of the novel mutations that we discover. We have successfully applied this two-pronged approach to the discovery of cancer genotypes that are connected with drug response.

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15IN
DEVELOPMENTS IN GENE EXPRESSION SIGNATURES

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Normal cells are extremely complex, and their derangements during malignant transformation are even more so. It can also be observed that tumors exhibit a tremendous variability in their behavior in patients, from total chemoresistance and rapid progression and metastasis to indolence and lack of progression for years. While single genetic alterations are extremely important in guiding therapy today, it is impossible that understanding these single driver lesions, or even small numbers of them can allow for a complete understanding of cancer behavior and potential therapeutic interventions. In this context, "high content" analyses of the entire genetic sequence, methylation patterns, expression levels of tens of thousands of RNAs, both coding and non-coding, and proteomic patterns of expression and modification are being evaluated for an improved understanding of cancer beyond single driver mutations. These measurements are now technically feasible, however, these efforts are hampered by the huge number of data points and much smaller numbers of tumors available for analysis, and no signatures have found proven utility in the practical management of lung cancer patients to date. Many of the positive studies to date have also been hampered by severe methodological flaws ranging from systematic biases in sample collection, poor clinical annotation, inappropriate choice of cases to answer the hypothesis, and poor signature evaluation strategies. Some of these pitfalls, proposed solutions, and some of the promising candidate signatures under evaluation will be discussed.

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MESOTHELIOMA REVISITED

16IN
FUTURE MESOTHELIOMA RATES IN RELATION TO PAST AND CURRENT ASBESTOS EXPOSURE LEVELS

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We have calculated future worldwide mesothelioma rates from trends in national death rates published by the WHO. However, current mesothelioma rates, and hence predicted future rates based on them, reflect asbestos exposure levels 30 or more years ago when asbestos was still widely used. The public health benefit of regulations and continuing expenditure on asbestos monitoring and abatement within the European Community and elsewhere cannot be assessed, because it is not known how much asbestos released from older buildings is being breathed in by workers and the general population today, or what mesothelioma risks this will cause in the future. We are conducting two studies in the UK to answer these questions. MALCS (Mesothelioma and Lung Cancer Study): We are collecting lifetime occupational histories from mesothelioma and lung cancer patients born before 1965, together with lung samples for asbestos fibre counting by transmission electron microscopy (TEM). The results show a linear relationship between mesothelioma risk and asbestos lung burden. TIPS (The Inhaled Particles Study): The aim of TIPS is to determine the range of asbestos levels in the lungs of the general population, and of construction and other workers born since 1965, all of whom started work after 1980 when use of asbestos had virtually ceased in the UK. We are collecting lifetime occupational histories from pneumothorax patients, together with lung samples obtained at operation for TEM asbestos fibre counting. These data will determine the extent of continuing asbestos exposure due to current working conditions and in the general environment. In combination with the MALCS results, this will provide an estimate of future mesothelioma rates due to current occupational and environmental asbestos exposure levels in the UK. Similar studies are needed in other countries.

Disclosure: All authors have declared no conflicts of interest.

17IN
A MULTIDISCIPLINARY APPROACH

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Malignant pleural mesothelioma (MPM) is a uniformly fatal disease that has been recalcitrant to curative therapies. The median survivals of 8-18 months have, for the most part, led to a sense of frustration and nihilism in the medical and surgical community with regard to management of the disease, and the relatively small numbers of patients with mesothelioma have made it an orphan among other cancers with regard to research efforts and funding. This review will comment on the clinical presentation of the disease, and therapeutic options which are available at this time. The role, timing, degree, and availability of cytoreductive surgery in the context of a multimodality approach for MPM will be highlighted, and various strategies which incorporate adjuctive therapies either before, during or after the operation will be discussed. Newer cytotoxic chemotherapies, either alone or in combination, are reviewed with an emphasis on the increasing number of options with increased response rates that are becoming available for MPM patients. The results of protocols at selected centers which offer gene therapy, photodynamic therapy, hyperthermic chemotherapeutic perfusion, as well as intrapleural chemokines will be discussed, as well as newer preclinical approaches which base targeted therapies on novel molecular findings. In considering these newest novel approaches for the disease, the reader is encouraged to seek specialty consultation at centers that are concentrating programmatic efforts on mesothelioma in order to design translational-based approaches on preclinical findings. By using such an approach, the patient and his physician will find that there are considerably more options in the new century for mesothelioma than simply supportive care.

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18IN
BIOLOGY AND TARGETED APPROACHES

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Despite the continuing worldwide increase in the incidence of Mesothelioma and its very poor prognosis, the available therapeutic options remain extremely limited, reflecting an unmet need. Over the last few years, our understanding of the underlying biology of mesothelioma has increased substantially. This raises the possibility that more effective, targeted approaches for treating this cancer can be identified and implemented for patient benefit. Such approaches include 1) the re-targeting of conventional drug treatment based on emerging knowledge of somatic gene alterations which confer sensitivity or resistance 2) identifying novel vulnerabilities associated with oncogene addiction, and 3) synthetic lethal strategies. Examples of these strategies will be presented.

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STATE-OF-THE-ART STAGING

19IN
PET-CT IMAGING

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Positron Emission Tomography with computer tomography (PET-CT) and the clinical use of this imaging technology has developed rapidly during the last decade, especially in the field of lung cancer. The first PET-CT scanner was introduced in 2000 in the United States, combining the functional information from the PET scanner with anatomical structures obtained by CT. During the last decade app. 2000 PET/CT scanners have been installed in the United States (6.5 scanner per million people), 70 in Germany (1.2 scanner per million people) and 350 PET/CT scanners in Europe as a whole (0.4 scanner per million people). The role and potential impact of PET/CT in diagnosing and staging patients with non-small lung cancer is well established and incorporated in several clinical guidelines and recommendations. The European Society of Thoracic Surgery (ESTS) as well as the American College of Chest Physicians (ACCP) has published guidelines for proper preoperative mediastinal staging, both including a PET/CT examination. PET/CT is potentially hampered by a relatively high frequency of false positive findings; however, both specificity and sensitivity can be increased by detailed knowledge of patient history and side-by-side reading by an experienced radiologist and nuclear medicine physician. This presentation includes a brief introduction to the technology; including limitations and pitfalls. Through a presentation of recent meta-analyses as well as clinical studies, the role of PET/CT in staging patients with non-small cell lung cancer will be described and discussed. Current issues of controversies, e.g. the value of SUV and the use of low dose versus diagnostic CT will be addressed, as well as considerations on cost-effectiveness and future perspectives.

Disclosure: All authors have declared no conflicts of interest.

20IN
THE ROLE OF ENDOSCOPIC PROCEDURES

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Transesophageal endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) are novel techniques for the diagnosis and staging of lung

cancer. Worldwide, over one million patients with lung cancer are diagnosed annually of whom one third present with mediastinal metastases. Accurate diagnosis and staging is important for both prognostic and therapeutic reasons. Patients with non-small cell lung cancer (NSCLC) and mediastinal lymph node metastases or mediastinal tumour invasion (stage III) are preferably treated with chemo- radiation therapy, whereas patients without locally advanced disease are treated primarily by surgical resection of the lung tumour. Current mediastinal tissue staging of patients with NSCLC critically depends on surgical interventions, predominantly mediastinoscopy. EUS-FNA and EBUS-TBNA are incorporated in current guidelines as minimally invasive alternatives for surgical staging to demonstrate nodal metastases. Recently it has been shown that starting mediastinal staging with endosonography improves mediastinal nodal staging and reduces unnecessary thoracotomies in comparison to surgical staging by mediastinoscopy. In this talk the role of EUS-FNA and EBUS-TBNA for the diagnosis and staging of lung cancer will be evaluated. Indications of both methods will be addressed as well as the concept of complete echo-endoscopic staging of the mediastinum. The impact of EUS and EBUS on patient management will be discussed, in particular their role in preventing surgical staging procedures as well as the position of endosonography in non-small cell lung cancer staging algorithms.
Disclosure: All authors have declared no conflicts of interest.

21IN
SURGICAL TECHNIQUES

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The importance of correct staging is without debate, especially in patients with resectable lung cancer. False positive CT or PET findings may exclude curable patients from the best treatment option. If mediastinal lymph nodes are enlarged on CT scan or positive on PET scan indicating N2/ N3 disease this should be proven histologically. Despite newer techniques which are less invasive than surgical methods there is a role for mediastinoscopy - in guidelines still considered the goldstandard - or video-assisted thoracic surgery (VATS). Mediastinoscopy provides a larger amount of lymphatic tissue than non-surgical techniques (EBUS/EUS) which is important to exclude minimal metastatic disease. Compared to conventional mediastinoscopy video-assisted mediastinoscopy (VAM) has a number of advantages: due to bimanual dissection of the mediastinum more lymph nodes stations and complete lymph nodes can be removed with a lower complication rate. Standardisation and teaching of the method has been improved since implementation of the video technique which should therefore be the method of choice when performing mediastinoscopy. To prove mediastinal lymph node involvement and for selecting optimal stage-oriented therapy namely neoadjuvant therapy followed by surgery, the pathway could include EBUS/EUS for primary staging. For restaging after chemotherapy VAM should be performed followed by the definitive surgical procedure. The technique of VAMLA (video-assisted mediastinal lymphadenectomy) with en bloc resection of lymph node compartments further improves radicality and is seen a first step in patients eligible for VATS-lobectomy as dissection of the subcarinal region is facilitated and more complete. VATS as part of the staging procedure can be used in case of lymph nodes non accessible by mediastinoscopy and for exclusion of M1a disease or infiltration of viable structures. If pleural dissemination is confirmed immediate talc poudrage can be performed. Also, removal of a contralateral lesion to rule out metastatic disease may be indicated as lesions are not always malignancies.
Disclosure: All authors have declared no conflicts of interest.

22IN
WHICH TEST IS NEEDED FOR WHICH PATIENT?

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Pre-treatment staging for non-small cell lung cancer (NSCLC) nowadays is a multidisciplinary process involving imaging techniques, endoscopic and surgical procedures, and discussion of the findings at a multidisciplinary tumor board. The endpoint is maximal accuracy in order to avoid false positive interpretations leading to a false stage III or IV approach in early stage patients, or false negative findings leading to a false early stage approach in patients with locally advanced or advanced disease. CT-scan remains the non-invasive test with the best anatomical detail of tumour spread, but lacks information on the biological nature of the lesions. FDG-PET is able to add this information based on metabolic properties of tissues, but lacks fine spatial resolution. Therefore, contemporary imaging relies on combination of both, preferably in a fusion PET-CT scan, which is indicated for most patients with a potential for radical therapy. When distant metastasis is excluded, assessment of lymph node spread will usually direct the further therapy. The combined information of both CT and PET will guide the approach. Absence of suspect lymph nodes on both imaging tests has a high negative predictive value, and no further preoperative tests are needed, at least if the tumour is not centrally located. The same is true for patients with major lymph node involvement on their scan, histological confirmation is often not needed there. In all other cases, tissue verification by the most appropriate technique is warranted. The historical standard of mediastinoscopy is nowadays complemented and in quite some patients replaced by endoscopic techniques such as endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) or esophageal ultrasound fine needle aspiration (EUS-FNA). Each of these techniques remains important in modern staging algorithms [1]. A practical scheme for rational staging will be discussed.

[1] Vansteenkiste J, Dooms C, De Leyn P: Early stage NSCLC: challenges in staging and adjuvant treatment: evidence-based staging. Ann Oncol 21 Suppl 7:189-195, 2010.

Disclosure: All authors have declared no conflicts of interest.

BIOMARKERS AND THE IMPACT ON FUTURE CLINICAL TRIALS

23IN
MOLECULAR PORTRAITS/LANDSCAPE OF LUNG CANCER IN FRANCE

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Molecular profiling of tumor tissues, now a standard in the management of certain treatments, requires that molecular diagnostics be introduced into routine clinical practice. In the setting of NSCLC, EGFR mutation is a prerequisite for implementing gefitinib therapy, while ALK translocation is mandatory before the use of crizotinib. In anticipation of an increasing number of new available molecular tests, the French National Cancer Institute (INCa) and the French Ministry of Health decided as soon as 2006 to allocate specific funds for the development of a national network of 28 regional molecular genetics platforms. These facilities perform selected molecular tests free of charge for all patients in their region, regardless of the health institution where they are treated. In order to further increase the reactivity of this organization and to allow platforms to be immediately operational as soon as new targeted therapies are available for patients, a program of prospective detection of emerging biomarkers was set up. The program targets biomarkers for which clinical trials are currently ongoing for stratified subgroups of patients and was first launched for melanoma, lung and colorectal cancer. Since the beginning of 2011, lung tumor samples that are sent to a platform for EGFR mutation screening are also screened for BRAF, KRAS, PI3KCA and HER2 mutations, as well as for the EML4-ALK gene translocation. The table herebelow provides a summary of the activity in the French platforms in 2011.

Marker	Number of patients screened	Number of patients with a mutation	Mutation rate
EGFR activating mutation	20 761	2 009	9,6
RAS mutation	17 153	4 358	25,4
BRAF mutation	10 017	184	1,8
EML4/ALK translocation	4 543	208	4,6
PI3KCA mutation	5 329	111	2,1
HER2 Exon 20 mutation	7 731	69	0,9

Disclosure: All authors have declared no conflicts of interest.

24IN
THE LUNGSCAPE PROJECT

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Lungscape is a translational research project designed by ETOP. It aims to address the challenges of studying the molecular epidemiology of lung cancer by coordinating and harmonizing the procedures of a group of lung cancer specialists working in translational research across Europe and allowing analysis of larger series of cases. This initiative has the potential to expedite knowledge of the prevalence and context of current and emerging molecular biomarkers with clinical significance and facilitate more rapid translation of biomarker knowledge to the clinic. Lungscape is evolving in step-wise fashion, starting with a retrospective analysis of 2400 completely resected NSCLC in 12-15 institutions. The fundamental approach of Lungscape was to build a decentralized biobank (termed iBiobank) of samples from lung cancer patients with annotated clinical and pathological data and at least three years of documented follow-up. The virtual nature of iBiobank and the introduction of standardized biomolecular assessments - in which samples are tested using identical protocols across local laboratories- removes the need of transferring samples to a central location for evaluation. Lungscape consists of a master protocol, with defined modules to be added over time. The first module is a retrospective cohort study of ALK gene rearrangement aiming to describe prevalence, natural history, and genomic characteristics of patients in Europe harboring this rare genetic alteration, and to correlate this genetic alteration with long term outcome. A standardized IHC technique is used for screening with confirmation by FISH. Subsequent modules have been defined, including PI3K amplification, PTEN IHC, MET IHC and amplification, EGFR IHC and mutation and multiplex mutation testing. Lungscape will raise standards of translational research in ETOP and eventually lead to the building of comprehensive and practical diagnostic algorithms for personalized medicine.

Disclosure: All authors have declared no conflicts of interest.

25IN
BIOMARKERS AND IMPACT ON FUTURE CLINICAL TRIALS: A JAPANESE PERSPECTIVE

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Currently, lung cancer is regarded as a mixture of heterogeneous diseases rather than single entity of the disease in terms of prognosis and therapeutic response. Incorporating biomarkers that help distinguish different classes of lung cancer into clinical trials became very important in clinical trials. The discovery of EGFR mutations in 2004 as a predictive factor for EGFR tyrosine kinase inhibitors (TKI) made us appreciate importance of individualized approach to lung cancer. East-Asian people with lung cancer are blessed with higher incidence of EGFR mutation. A lot of data on EGFR mutation as a biomarker were generated from Japan. Among them, it is noteworthy that two randomized phase 3 studies that compared gefitinib with platinum doublet therapy for patients with EGFR mutation (WJTOG 3405 and NEJ 002) were performed in Japan. They both showed significantly longer PFS in the gefitinib arm. However, acquired resistance inevitably emerges after ~10 months even in such patients. Development of countermeasures for acquired resistance based on biomarkers is urgent clinical need. Japanese group headed by Prof. Mano found EML4-ALK fusion in 2007. It soon became evident that crizotinib, an ALK-TKI, was very active for this type of lung cancer in a phase I/II study conducted in US and Korea. Prof. Bang in Seoul kindly accepted many Japanese patients who were diagnosed as ALK+ through ALCAS (ALK Lung Cancer Study group) which Prof. Mano organized. Crizotinib will be approved soon in Japan. In the mean time, the Japanese Lung Cancer Society recently published "Guidance for ALK gene testing in lung cancer patients" to distribute right knowledge on diagnosis of ALK^+ lung cancer. In addition, newly identified targets such as DDR2 mutation, FGFR1 amplification, or ROS1 fusions also appear to belong to the same oncologic paradigm as EGFR or ALK. In planning future clinical trials, "ordinary" lung cancers and those with distinct targets should be handled separately. We have recently launched a randomized clinical trial comparing gefitinib with cisplatin plus vinorelbine as adjuvant treatment for resected stage II-III patients with EGFR mutation (IMPACT trial). However, it would be more difficult to deal with lung cancers with distinct molecular changes but with very low incidence.

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26IN
IMPACT OF BIOMARKERS ON CLINICAL TRIALS: A US PERSPECTIVE

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The discovery that the presence of a driver mutation in a tumor specimen from a person with lung cancer can be used to direct care has changed practice in the US. The latest version of the NCCN Guidelines advises routine testing for EGFR mutations and ALK rearrangements at diagnosis for all NSCLCs except those where the diagnosis of squamous cell lung cancer is certain. Initial treatment with erlotinib or crizotinib is recommend for mutation positive patients and chemotherapy selected based on histology for all others. This change in medical oncology practice has mobilized interventional radiologists, pulmonologists and thoracic surgeons to obtain tissue specimens adequate to permit mutation testing whenever lung cancer is suspected. A growing number are ordering these tests when the diagnosis of NSCLC is confirmed. Pathology departments have organized to triage specimens after the histologic diagnosis is made and to prepare and submit tissues for molecular tesing either within their own institutions or to the growing number of commercial laboratories. Once adequate material is received by the molecular lab the testing can be accomplished in days. Although there is no consensus, many laboratories perform EGFR and ALK testing in parallel to speed the process so the information can be used to guide care. Many methodologies are used to detect EGFR mutations but all use the FDA-approved FISH test to detect ALK positive cases. A growing number of laboratories utilize multiplex testing that includes all driver mutations (KRAS, PI3K, HER2, BRAF, AKT1, MEK1, NRAS, and MET amplification). As technology improves, an even larger number of genes will be assayed simultaneously to give a more comphrensive picture and provide the data even quicker. The availability if this information will change the conduct of clinical trials as the presence molecular abnormalities will be known when the patient first sees the oncologist and based on the swiftness of the crizotinib approval based on only 255 molecularly selected patients, eligibility for targeted therapy trials will increasingly

be restricted to individuals with the target, even in Phase 1. Since tumors from the majority of patients have a driver mutation, each can be directed to a clinical trial specific to their molecular lesion.

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OLIGOMETASTATIC NSCLC

27IN
THE CONCEPT OF OLIGOMETASTATIC NSCLC

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Of patients with NSCLC, approximately 20-50% will present with stage IV disease, often diagnosed with multiple dissemination sites in the brain, bone, liver, and adrenal glands. Abundant clinical and molecular research suggests that the process of metastasis proceeds in sequential steps, which eventually produces polymetastatic disease. With this view, there is an oligometastatic state of less biologically aggressive tumor behavior that lies between the completely absent and diffuse metastatic states. This intermediate state remains stable over time with limited metastatic spread. Because of the different lymphatic and vascular drainage patterns of NSCLC and the organ-specific enhancement or suppression of different tumor sites, there is a hierarchy for the oligometastatic state related to the time to metastasis, the number of metastases, and the location of the secondary sites. The paradigm of an oligometastatic state can be subdivided into a de novo intermediate stage of limited metastatic capacity and the limited remaining tumor deposits following the successful eradication of all other cancer metastatic tumors by systemic therapy. However, even with modern diagnostic imaging, it is not possible to determine or predict whether limited metastases represent a true oligometastatic state or a transitional stage to disseminated metastases. With the development of more effective and individualized systemic therapies, a novel approach for the diagnosis and treatment of patients with oligometastatic disease is needed. Part of the application of this expanded concept is reflected in the localized aggressive treatment for oligometastatic disease. Clinical trials are needed to further define recommendations to adjust different treatment modalities. However, it is clear that the rarity of oligometastatic disease in patients with NSCLC makes it unlikely that larger randomized prospective trials will be used to compare different treatment regimens with systemic therapy versus the combination of systemic therapy and local aggressive therapy. In conclusion, current retrospective data indicate a window of opportunity where local therapy using surgical or radiation treatments at secondary sites may improve long-term survival for a highly selected subset of patients.

Disclosure: All authors have declared no conflicts of interest.

28IN
BRAIN METASTASES

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Oligometastatic NSCLC - Brain metastases: Brain metastases (BM) are the most common intracranial tumours in adults, occurring in 20-40% of patients with cancer. Up to half of BM originate from lung primaries. In the last decade we have been faced with a new paradigm;

- The incidence of BM is increasing due to the use of improved systemic therapies.
- Improved imaging increases the likelihood of discovering and diagnosing occult BM. However most patients are diagnosed with multiple BM and less than 20% of patients have solitary BM at presentation based on MR imaging.
- BM present more often in the context of well controlled systemic disease and are more likely to be treatable than in the historic context of multi-organ metastatic disease.

In the context of stable thoracic and systemic disease treatment options for oligometastatic (OM) brain disease include surgery, stereotactic radiotherapy ± whole brain radiotherapy (WBRT) and systemic treatments.

Surgey: Surgery can play an important role in patients with BM and particularly patients with mass effect from a large symptomatic lesion. Randomised controlled trials with single BM have demonstrated that the addition of surgery to WBRT improves survival.

Stereotactic radiosurgery (SRS): SRS can be used as the sole treatment or as a 'booster therapy' in addition to WBRT to improve local control (1). Typically, SRS is reserved for patients with controlled extracranial disease and life expectancy >6 months, 1 to 4 BM, metastases less than 3cm in maximum diameter and metastases inaccessible for surgical resection. Although use of SRS has increased considerably in recent years there remains uncertainty with regard to the effectiveness of SRS alone and when to combine treatment options as well as how to appropriately select patients. The current questions are:

- Is SRS better than WBRT?
- Is SRS + WBRT better than SRS alone?
- Is SRS + WBRT better than WBRT alone?
- How does SRS compare to neurosurgery?

Systemic therapy: The role of systemic treatment is unclear in patients with OM and BM due to the lack of prospective studies in this group of patients. The efficacy of EGFR TKIs in BM patients has been suggested but the evidence is limited.

Disclosure: All authors have declared no conflicts of interest.

29IN
ADRENAL METASTASES

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Oligometastatic disease is considered a solitary extrapulmonary disease, potentially resectable. Adrenal metastases (M1) are a frequent site of solitary metastases from NSCLC but, should be treated? Is there any difference in survival with synchronous versus metachronous solitary adrenal metastasis?

The incidence in autopsies of adrenal metastasis caused by lung cancer (LC) is 18-42%. Even so, there are few patients who present solitary metastasis (M1) and operable LC.

Porte HL listed possible inclusion criteria to indicate surgery in patients with adrenal M1 of LC: the primary tumour has to be potentially controlled, not to include patients in stage III, to use explorations that confirm a solitary M1 before the surgery and to handle synchronous and metachronous M1 in similar way. In 2008 Tanvetyanon reviewed the studies published on adrenalectomy for synchronous metastases vs. metachronous ones. It includes 10 publications with a total of 114 patients. The median overall survival was lower in patients with synchronous metastases that in metachronous, 12 months vs. 31 months, (p=0.02). However, the estimated survival at 5 years was equivalent, 26% and 25% respectively. He observed lower survival in synchronous metastases may suggest a greater biological aggressiveness of the tumour and its metastases.

Our experience during the last 10 years: Seven patients has been considered, 4 men and 3 women between 38 and 71 years old (median 64 years) who underwent surgery in both the primary tumour and the adrenal metastasis. In 3 patients the resection of the metastases was performed synchronous to the primary tumour and in four patients resection was metachronous with an interval 10 to 39 months (median 25 months). The stage of the primary tumour was: IB in 1 patient, IIB in 1, IIIA in 2 and IV in 3 patients (N0 in two patients and N1 in one). Five patients underwent a lobectomy and two a pneumonectomy. The mean patient survival was 41 months (IC 95%:7–74) and the median survival of 20 months (IC 95%:7–32).

In conclusion, the resection of the adrenal solitary metastasis of pulmonary origin offers a life expectancy to consider. Multicentre studies with larger number of patients are required to establish the real utility of this resection compared to other systemic treatments.

Disclosure: All authors have declared no conflicts of interest.

30IN
SATELLITE NODULES, IPSI OR CONTROLATERAL LUNG METASTASES AND PLEURAL INVOLVEMENT

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According to the 2009 TNM classification of non–small cell lung cancers (NSCLC), second parenchymatous localizations are classified as T3 if located in the same lobe, T4 if located in a different lobe of the same lung, and M1a if located in the opposite lung, and aggregated in the group of multiple lung cancers (MLC). MLC represent up to 5% of all NSCLC and 10% of resected NSCLC. It is generally considered that determining if the second tumour is a second primary NSCLC or a lung metastasis would change staging, prognosis, and management. However, neither pathologic nor genetic analyses allow a clear distinction between a second primary and a lung metastasis. Furthermore, recent work emphasise the prognostic value of pathologic stage, but failed to demonstrate any correlation between histology discrepancy and prognosis. Resected MLC demonstrate a median survival of 30 months and a 5-year survival rate of 32%, whereas metastatic NSCLC treated exclusively with chemo and/or targeted therapies have a median survival of 6 to 12 months and anecdotic 5-year survival. Changing the staging by establishing the diagnosis of pulmonary metastasis of NSCLC is probably an important issue warranting further biologic research, but in the meantime, current management should include surgical resection of both tumours and radical mediastinal lymph node dissection whenever feasible. Metastatic pleural extension (M1a) of NSCLC includes malignant cells in the pleural fluid defining malignant pleural effusion, limited and localized pleural nodules defining limited metastatic pleural extension, and numerous and disseminated nodules defining pleural carcinomatosis. The finding of M1a extension is reported in 1-7% of patients with NSCLC, and usually precludes surgery. However, some limited and localized pleural nodules may be resectable. When an undiagnosed limited pleural malignant disease is discovered during thoracotomy, selected patients may undergo a complete surgical resection, with median and 5-year survivals of 15 months and 16%, as compared to 8 months and 4% after exclusive medical management. The long term results of complete surgical resection of both primary NSCLC and limited pleural nodules constitute a plea for the inclusion of surgery in multimodality treatment of NSCLC patients with M1a extension.

Disclosure: All authors have declared no conflicts of interest.

LOCALIZED THERAPY OF METASTATIC DISEASE TO THE LUNG

31IN
LOCAL TREATMENT FOR SYSTEMIC DISEASE: THE SURGICAL APPROACH

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Lung metastases occur in about 30 -50 % of all patients with solid tumors. About 30 % of this population has isolated lung metastases and these are potential candidates for a surgical resection. Other prerequisites for a curatively intended removal of lung metastases are that the primary tumor is controlled, that a complete resection of all lung metastases is technically and functionally possible, and that there are no other extra-pulmonary metastases with the exception of patients with colorectal carcinomas. In this selected group of patients the detection of liver metastases is no contraindication for the pulmonary resection as long as the liver lesion can be treated as well. Prognostic factors in patients with lung metastases are the type of the primary tumor, the disease-free interval between the primary tumor resection, and the detection of lung metastases as well as in a certain respect the number of metastases. The most significant prognostic factor, however, is the completeness of the pulmonary metastasectomy. Recently, new resection technologies have been developed. By the use of a "lung laser" the dissection of also multiple metastases as well as the resection of central lesions without anatomical resections (e.g. lobectomy) are possible. It has been shown that also multiple pulmonary metastases can be resected without major morbidity and zero mortality. In patients with isolated well-controlled metastases also minimal-invasive (VATS) resections are possible without formal thoracotomy. Overall 5-year survival rates after pulmonary metastasectomy vary between 20 and 45%.

Disclosure: All authors have declared no conflicts of interest.

32IN
THE ROLE OF STEREOTACTIC RADIOTHERAPY

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The hypothesis underlying the treatment of oligometastatic disease is that it represents a distinct clinical disease state, between loco-regionally confined and widely spread metastatic disease [Hellmann S, 1995]. For such patients, it has been postulated that complete metastasectomy is a curative treatment option. It is also been hypothesized that local therapy to the primary tumor site can retard distant disease progression and prolong survival in patients with metastatic disease [Morgan S, 2011]. Despite long-term survivals reported with ablative treatment for oligometastatic disease, the level of evidence to support such treatments is weak in many cases, often based on single-arm studies without appropriate controls. Stereotactic ablative radiotherapy (SABR) was first introduced more than a decade ago to treat stage I NSCLC. It entails the precise delivery of very high radiation doses in a short period of time, commonly in 3-8 fractions using co-called'risk-adapted' schemes, where smaller dose fractions are used when tumors in close proximity to critical normal organs. Local control rates in excess of 90% have been reported for lung tumors in prospective multicenter studies in Europe and North America. The growing interest and rapid spread of SABR has largely been driven by advances in radiotherapy planning and imaging techniques, both of which allow for increased treatment precision. The ability to perform outpatient SABR procedures without anesthesia is an additional advantage. As patterns of lung fibrosis after SABR can evolve up to more than 3 years post-treatment, such changes must be distinguished from tumor progression. The widespread use of SABR has set the scene for prospective randomized clinical trials to evaluate its role in metastatic disease to the lung. One approach would be to design trials that compare the use of a single ablative modality (e.g. SABR) plus standard care (which may be chemotherapy), versus only standard care. Another approach is to evaluate the combination of one or more ablative therapies (surgery, RFA, SART or combinations thereof) in combination with chemotherapy, versus chemotherapy alone. Such trials are necessary in order to ensure that what are apparently promising results with SABR in the treatment of pulmonary oligometastases are not solely due to patient selection.

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33IN
RADIOFREQUENCY ABLATION

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Today RFA is used primary lung neoplasms are close to those for surgical resection, in a curative intent in non-surgical or boarderline surgical candidates with T1A or T1B tumors. Inoperability is due to poor either respiratory function in relation do COBP in primary tumors, and iterative surgery or general comorbidities. Pre-ablation imaging work-up must be equivalent to a pre-surgical one, namely with PET_CT. Because size is strong redictive factor of success, the largest diameter of the tumor should be ideally smaller than 3 cm, and in any manner larger than 5cm. A review of 17 of the most recent publication demonstrated a median reported rate of complete ablation of 90%, even if high variability exists between publications with a range from 38% to

97%. Most studies report a statistically significant lower success rate of ablation with tumors larger than 2 to 3 cm in diameter. Oversizing ablation relative to the tumor improve complete ablation rate up to 96% at 18 months ablation when the ratio between the area of post-RFA ground glass opacity and the tumor area before treatment was at least 4. Ground glass opacity margins have been reported absent in 85% of post RFA CT of incompletely ablated tumors. Contact with a large vessel (>3 mm) has been reported by Hiraki et al and Gillams et al as a negative predictive factor of complete tumor ablation in lung. In our 8 years experience with 548 patients with 886 metastases from various origin treated in 622 RFA sessions, we were able to control 89.6% of the targeted metastases. The overall survival rate was 69.7% at 3 years. In multivariate analysis, number of metastases, size of metastases and disease free interval between primary tumor and occurrence of lung metastases significantly impact survival. Survival is close to surgical series. Tolerance was excellent with 10% chest tube placement and a median hospital stay of 3 days.
Disclosure: All authors have declared no conflicts of interest.

34IN
ISOLATED LUNG PERFUSION

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Surgical resection of lung metastases is a widely accepted procedure but due to local and distant recurrences reported 5-year survival rates are only 30 to 40% [1]. Main prognostic factors are histological type and complete resection. A better survival is reported in patients with a single metastasis and a disease-free survival of more than 3 years. Reoperations are feasible but often patients become inoperable due to insufficient pulmonary reserve and new treatment modalities are looked for. In some cases combined modality treatment is indicated. The maximal dose of intravenous chemotherapy is limited due to systemic side-effects, mainly haematological. As isolated limb and liver perfusion, isolated lung perfusion has the advantage of selectively delivering an agent into the lung while diverting the venous effluent [2]. Other related methods of delivering high-dose locoregional chemotherapy include embolic trapping (chemo-embolization) and pulmonary artery infusion without control of the venous effluent [2]. Isolated lung perfusion has proven to be highly effective in experimental models of pulmonary metastases with a clear survival advantage. Lung levels of cytostatic drugs are significantly higher after isolated lung perfusion compared to intravenous therapy without systemic exposure. Phase I human studies have shown that isolated lung perfusion is technically feasible with low morbidity and without compromising the patient's pulmonary function. Recently, promising long-term results have become available [3]. Further experimental and clinical studies are necessary to determine its definitive effect on local recurrence, long-term toxicity, pulmonary function and survival.

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STATE-OF-THE-ART: SUGGESTED TREATMENT ALGORITHMS

35IN
STATE OF THE ART: STAGE I AND II NSCLC

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Early stage non small cell lung cancer (NSCLC) includes patients with stage I (T1,T2a N0 M0) or stage II (T1,2 N1 M0 or T2b,T3 N0 M0). Approximately 30% of all patients present with stage I or stage II disease at diagnosis. Clinical experience based on large retrospective data indicates that the best chance of cure for patients with stage I and stage II lung cancer is surgical resection. The 5 year survival rates are 60 – 80% for stage I and 40 – 50% for stage II. Lobectomy including systematic lymph node dissection is adequate for most patients who tolerate this procedure. Lesser resection than lobectomy (sublobar resection) including lymph-adenectomy is indicated for small peripheral lesions (< 2cm) even in fit patients. However, local recurrence rate (when tumors <3cm are included) is increased two to three fold but long term survival differs only minimally. Additionally, patients who do not tolerate larger resection due to poor lung function may be treated by a segmentectomy as long as a radical resection can be achieved. Definitive radiotherapy by conventionally fractionated radiotherapy (>60Gy) or CHART for surgically inoperable patients is considered a good treatment modality. Stereotactic radiotherapy should be performed in centres with adequate equipment and experience. Surgery is best performed by thoracic surgeons with prominent focus on lung cancer treatment since perioperative mortality and long term survival are better compared to general surgeons who do the operation occasionally. The use of minimal invasive procedure by VATS is a highly valuable alternative to conventionnal procedures done by open thoracotomy. Recovery after surgery is faster and potential adjuvant chemotherapy is better tolerated. Intraoperative systematic mediastinal lymph node dissection is an integral part of the surgical treatment and allows accurate pathological staging. Platinum based adjuvant chemotherapy should be offered to patients with completely resected stage II lung cancer and good performance status. Adjuvant radiotherapy is not indicated in stage I and II R0 resected patients.
Disclosure: All authors have declared no conflicts of interest.

36IN
STATE OF THE ART: STAGE III NSCLC

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Lung cancer remains one of the most common malignancies and is the leading cause of cancer-related deaths in Europe and North America. In non-small cell lung cancer (NSCLC) the main curative therapeutic approach is surgery for early stages IA to IIB. However early stages constitute only 20-25% of all NSCLC patients, whereas the majority of patients initially present with locally advanced stages IIIA /IIIB or even with metastasized disease. Only small subsets of patients with the so called "minimal N2 disease" and some subgroups of T4 disease are widely accepted as potential candidates for surgical approaches. The majority of IIIA/IIIB patients were not considered for surgery and palliative systemic approaches consist of combinations of platinum-based chemotherapy and radiotherapy as standard of treatment. For locally advanced stages IIIA and IIIB NSCLC chemotherapy alone or associated with radiotherapy are used to downstage tumors and render them complete resectable. Cisplatin-based combination treatment found to achieve response rates of 50% to 75% in localized unresectable disease and eradication of micrometastasis were suggested. Preoperative radiotherapy resulted to sterilisation of mediastinal nodes so that patients with initial unresectable disease underwent surgery. Whereas a possible survival improvement related to induction treatment before surgery was suggested, several studies highlighted postoperative risks with increase of morbidity and mortality. Concurrent application of chemotherapy and radiation was considerably more toxic and recent results of EORTC 08941 and the Intergroup study 0139 have shown however, that the extent of surgery determines the postoperative mortality and that only in a subgroup of patients with lobectomy there was a survival benefit. In our experience pulmonary resection for locally advanced NSCLC after induction chemotherapy or chemoradiotherapy can generally be performed with acceptable morbidity and mortality. Patients should be carefully selected for operation especially with respect to their age, performance status and to their pulmonary and cardiovascular function tests. Future decision-making will have to take into account treatment morbidity and mortality and parameters of organ-sparing surgery following induction.
Disclosure: All authors have declared no conflicts of interest.

37IN
TREATMENT ALGORYTHMS FOR STAGE IV NSCLC

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A first-line treatment algorithm for stage IV NSCLC should consider as first step the presence of an activating EGFR mutation, to be screened in all adenocarcinoma histology, and in this case an anti-EGFR tyrosine kinase inhibitors (gefitinb or erlotinib) should be used. For EGFR wild-type or unknown NSCLC a subsequent step should consider patients age (over 70 years) and performance status (PS): platinum-based chemotherapy should be the preferred option in fit elderly PS 0-1 patients and adequate organ functions and single agent should be preferred in unfit elderly patients. In PS 2 patients either single agent or platin-based combinations are valid options. In patients under 70 years and PS 0-1 first-line platin-based chemotherapy for 4-6 cycles should be offered at diagnosis even to asymptomatic patients, deserving cisplatin combinations in fit PS 0-1 patients with adequate organ functions. Another crucial step for treatment algorithm is histology even if there is not a standard platin-based doublet. Two pre-planned subgroup analyses showed cisplatin and pemetrexed to be superior in non-squamous histology and inferior in squamous histology as compared to cisplatin and gemcitabine but without comparison with other doublets. Furthermore bevacizumab combined to platin-based chemotherapy is a treatment option for non-squamous histology only, due to safety concerns, in particular when carboplatin plus paclitaxel is the chemotherapy backbone. Cetuximab, if available, added to platin-based chemotherapy can be considered a treatment option for patients with high score (<200) EGFR IHC positive tumor. Switch maintenance with erlotinib or pemetrexed following completation of first-line chemotherapy is an option. Factors to consider in deciding for switch maintenance include histology, type and response to first line chemotherapy, residual toxicity, patient's symptoms and preference. Patients with tumour harbouring an activating EGFR mutation should receive EGFR TKI's as maintenance, if not yet received. Continuing maintenance with pemetrexed for patients receiving induction chemotherapy with cisplatin plus pemetrexed is a treatment option.

Disclosure: C. Gridelli: Honoraria as speaker bureau and advisory board member for Lilly, Roche, Merck.

38IN
STATE OF THE ART: SUGGESTED TREATMENT ALGORYTHMS FOR SMALL CELL LUNG CANCER TREATMENT

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Small-cell lung carcinomas (SCLC) represent less than 20% of all lung cancers. As it has a high propensity for early metastatic dissemination, less than a third of patients have limited disease (T0-4 N0-3 M0). As recommended by the ESMO lung cancer guidelines, the new TNM classification should be used for SCLC. Platin and etoposide-based chemotherapy is the cornerstone treatment for all patients. Response rates to both chemotherapy and radiotherapy are impressive but relapses are frequent as disease is often bulky at time of diagnosis. The current state-of-the-art treatment for M0 patients involves 4 to 6 cycles platin-etoposide based chemotherapy, combined with early thoracic radiotherapy administered concomitantly. Surgery can only be discussed in very selected patients with early disease. Because of the high risk of brain metastases, prophylactic cranial irradiation is indicated in responders and should be part of the standard management. The 5-year survival rate may reach 25% in M0 patients, but does not exceed 10% at 2 years in metastatic patients. Most patients relapse within the first two years, and there are few treatment options in second line as opposed to NSCLC. Drugs such as irinotecan, topotecan, amrubicin have shown efficacy in first or second line. Research for better identification of pathways that could be targeted with new drugs should continue. Pursuing clinical trials at all stages constitutes a challenge for thoracic researchers and oncologists.

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THE SPECTRUM OF NEUROENDOCRINE LUNG TUMORS

39IN
PATHOLOGICAL CLASSIFICATION

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A spectrum of neuroendocrine (NE) tumors (NET) of the lung exists, classified in the 2004 WHO scheme by combining architectural patterns (organoid versus diffuse growth) with the mitotic index and presence of necrosis. Typical carcinoids (TC) represent <1% of lung tumors and have a classical organoid (trabecular, acinar) pattern with polygonal, minimally atypical cells. Necrosis is always absent and mitoses are <2/10 high power fields (HPF). Small tumors with similar features, but < 5 mm in size are labelled tumorlets. Atypical carcinoids (ACs) are extremely rare, cigarette smoking-related low grade tumors, though often associated with regional and distant metastases. Their morphology overlaps that of TC, except that necrosis is present and/or the mitotic count is 2-10/10 HPF. Large cell NE carcinoma (LCNEC) partly resembles AC, but has large cells, extensive necrosis and a high mitotic index (>10/10 HPF). In the 2004 WHO scheme, LCNEC is classified with non-NE large cell carcinomas, from which it should be distinguished based on chromogranin or synaptophysin expression, in the absence of high molecular weight cytokeratins. Small cell lung carcinoma (SCLC) is the most common lung NET and is made of small cells with scant cytoplasm and condensed small nuclei: these features require a careful differential diagnosis with poorly differentiated squamous or basaloid carcinomas and other small cell tumors. "Combined NE carcinomas" rarely occur as an association of SCLC or LCNEC with a squamous or adenocarcinoma component. Focal NE differentiation in conventional squamous or adeno- carcinomas is not considered in this context, since no impact on prognosis has so far been demonstrated. The molecular profile of lung NETs has been extensively investigated to identify helpful diagnostic, prognostic and therapeutic predictive markers. Specific chromosomal alterations, oncogene mutations and cell cycle molecule disregulation have been documented, as well as the expression of receptors or factors targeted by bio- or chemo-therapeutic agents (eg somatostatin receptors, mTor pathway molecules, thymidylate synthase, topoisomerase, etc). All such data may ultimately provide a "molecular classification" of NETs to be integrated with morphology, for a future more appropriate therapeutic strategy.

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40IN
SURGICAL TREATMENT OF NEUROENDOCRINE LUNG TUMORS

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Bronchopulmonary neuroendocrine tumours consist of a spectrum of tumours (typical carcinoid, atypical carcinoid, large cell neuroendocrine and small cell lung cancer) that range from benign to malignant. As the tumours are rare, there are limited evidence on which clinicians able to use to guide management. Typical carcinoid tumours may present in the central airways and is usually managed by lung parenchymal sparing surgery. Peripheral carcinoid tumours, atypical carcinoid tumours and large cell neuroendocrine tumours are usually managed by surgical resection in patients with localised disease. In patients with advanced disease, treatment options include chemotherapy, radiotherapy, radionuclide therapy and biologic agents. The management of small cell lung cancer is usually non-surgical, however increasing number of centres are publishing good results with surgery, raising the question if surgery should be re-evaluated as a primary treatment modality. The prognosis of the tumours are largely dependant on cell type, and then by stage. Further study with international collaboration is required to allow us to advance our understanding and the management of our patients with this disease.

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41IN
DEVELOPMENTS IN SMALL CELL LUNG CANCER

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Very few developments have occurred in small cell lung cancer (SCLC) treatment and understanding of the biology of the tumor, in over 20 years. Although this is a tumor that is thought to be metastatic at the outset, the major improvements in survival have been obtained by the use of radiotherapy rather than the introduction of novel systemic treatments. Chest radiation given concomitantly to chemotherapy and prophylactic cranial irradiation (PCI) have both significantly improved survival of patients with limited disease. PCI was also able to significantly increase survival in extensive disease in a randomized trial. Among the systemic treatments available, no novel agent has received approval after topotecan for relapsed SCLC. A limited number of targeted agents have been tested in SCLC and so far the results have not been encouraging. A better understanding of the biology of this tumor will help devise novel strategies and identify potential targets for treatment. From CGH analysis of SCLC, it appears that this tumor has a very high number of genomic abnormalities which will potentially signify a high level of complexity and difficulty in finding driving oncogenic events. Exome sequencing programs are presently underway, which might shed some light onto the more common genetic abnormalities. Functional validation of these potential targets will need to be performed in adequate in vitro and in vivo models. Development of in vivo models that mimic more closely human SCLC has been attempted with some recent success.

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42IN
LARGE CELL NEUROENDOCRINE CARCINOMA: HOW SHOULD IT BE TREATED?

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LCNEC is an uncommon non-small cell lung cancer (NSCLC) sub-type accounting for up to 5% of all lung tumours, predominantly affecting males and smokers. Because LCNEC is uncommon the optimal management of the condition is unknown as trials have not been performed. Many series have reported outcomes of surgically resected patients and most report 5-year survival rates of <30%. Centres reporting stage-matched outcomes have demonstrated significantly inferior survival for LCNEC compared to other NSCLCs, approaching that of SCLC. The largest dataset comes from the SEER database, where survival from SCLC was worst, and other large cell carcinomas the best, with outcomes from LCNEC similar to other large cell carcinomas. Relapse rates are high, with brain a common relapse site. Several series have reported a potentially clinically meaningful benefit for platinum-doublet adjuvant chemotherapy, which has been also observed for stage 1 patients. Outcomes may vary by systemic therapeutic, with some reporting better outcomes with SCLC-like chemotherapy compared to NSCLC-like therapy. Further series support the notion that relapsed LCNEC is relatively chemo-refractory; a single-centre series, reported responses for chemonaive patients of 64% compared to 17% in previously treated patients. Data from JMDB suggest a benefit of pemetrexed in large cell carcinomas. However, this is likely a heterogenous group with large cell morphology including LCNECs. Preclinical data demonstrate that pemetrexed cytotoxicity is contingent on expression of thymidylate synthase, and the SCLC, squamous-subtype NSCLC, and LCNECs have highest TS expression compared to adenocarcinomas and other large cell NSCLC-types, suggesting that pemetrexed may therefore have limited activity in LCNECs. However, this needs prospective validation. Somatic molecular analyses have not identified common potentially druggable molecular aberrations, although one case reports a somatic EGFR exon 19 deletion that responded to gefitinib. In summary LCNEC is a rare high-grade NSCLC for which the international community has little robust data to make recommendations, and international collaborative working is urgently required.

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INDIVIDUALISED TREATMENT IN EARLY NON-SMALL CELL LUNG CANCER

43IN
FUNCTIONAL OPERABILITY: LESSONS LEARNED

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Assessment for pulmonary resection must include a preliminary cardiac evaluation. Patients deemed at prohibitive cardiac risk should be evaluated and treated as per American Heart Association/American Society of Cardiology guidelines. PpoDLCO is a reliable predictor of pulmonary complications and mortality. The correlation between FEV1 and DLCO is poor and more than 40% of patients with normal FEV1 may have reduced DLCO. A low ppoDLCO is a reliable predictor of cardiopulmonary morbidity and mortality but also in patients with normal respiratory function. Thus DLCO should be measured in all lung resection candidates. PpoFEV1 is not accurate in predicting surgical risk and residual pulmonary function in patients with pulmonary obstructive disease. One third of COPD patients improve their FEV1 3 months after pulmonary lobectomy. Thus poFEV1 should not be used alone for patients selection. Exercise testing allows global assessment of the physical fitness. Low-technology tests such as stair climbing test and shuttle walk test can provide only a rough estimation of the aerobic capacity of the patients. They are typically ideal as screening tests. Shuttle walk test tends to underestimate the exercise capacity at the lower range of VO2max, but there is a linear relationship between oxygen consumption and distance walked. Patients climbing less than 12m at stair climb test had a 2-fold and 13-fold higher rates of complications and mortality compared to those climbing higher than 22m. Cardiopulmonary exercise test provides several direct and derived measures that permit, in case of a limited aerobic reserve, to precisely identify possible deficits in the oxygen transport system. The recently published ERS-ESTS functional guidelines recommended its use in patients with cardiac co-morbidity or impaired pulmonary function or both, and in those patients with a reduced exercise tolerance at low-technology exercise tests. VO2peak greater than 20 ml/kg/min or 75% of predicted represents a safe threshold to undergo any kind of pulmonary resection. On the other hand, a value lower than 10 ml/kg/min or 35% of predicted usually contraindicates a major pulmonary resection.

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44IN
SURGICAL APPROACHES BEYOND LOBECTOMY AND PNEUMONECTOMY

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Lobectomy with bronchovascular reconstruction may allow radical resection in a number of lung cancer patients for whom simple lobar resection is not feasible and a pneumonectomy would be otherwise required. From a functional point of view, sleeve lobectomy (SL) is strictly indicated in patients who cannot withstand pneumonectomy (PN), but recent experiences have shown that the advantages of sparing lung parenchyma are evident also in patients without cardio-pulmonary impairment. Most studies show similar or better survival results for parenchymal sparing resections (including pulmonary artery reconstructions) if compared with PN. Moreover, in the analysis of 5-year survival according to stage and nodal status, SL results in higher survival rates for stages I, II and III, although the survival advantage in stage III appears to be limited and the benefit is not always confirmed for stage III-

N2 patients [Table 1]. Therefore the role of parenchymal sparing operations in patients with N2 disease still remains not completely defined. Postoperative morbidity and mortality data reveal overall better results for patients undergoing SL with respect to PN [Table1]. Looking at literature data, when morbidity is evaluated according to the type of complication, PN patients appear to experience a higher rate of cardiac complications, while SL patients show increased pulmonary and airway complications incidence. The preservation of lung parenchyma has been indicated by some authors as the possible cause of a theoretical increased risk for locoregional recurrence after SL. However, although in some experiences (Fadel'02) an higher local recurrence rate is reported for sleeve resection with advanced nodal status (N2), the few studies (Fadel'02, Terzi'02, Kim'05) analysing risk factors for recurrence, show that the tumor stage and the nodal status are the only negative predictive factors, rather than the type of operation performed. Table 1:

Author (year)	Stage I 5-yr (%) survival	Stage II 5-yr(%) survival	StageIII 5-yr (%) survival	Complications (%)	Postoperative mortality (%)	Local recurrence (%)
SLEEVE LOBECTOMY						
Gaissert ('96)	42	53	43	11	4	14
Tronc ('00)	63	48	8	16	1.6	22
Fadel ('02)	55	62	21	16	2.9	15
Terzi ('02)	60	32	22	14.5	12	5
Deslauriers ('04)	66	50	19	-	13	22
Kim ('05)	88	52	8	74.9	6.1	22
Ludwig ('05)	57	40	22	38	4.3	-
Takeda ('06)	45 (stage I-II)	45 (stage I-II)	21	45.2	1.6	9.7
PNEUMONECTOMY						
Gaissert ('96)	-	43	-	16	9	-
Deslauriers ('04)	50	34	22	-	5.3	35
Kim ('05)	75	36	38	44	4.1	6
Ludwig ('05)	45	42	13	26	4.6	-
Takeda ('06)	38 (stage I-II)	38 (stage I-II)	52	40.9	1.8	10.9

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45IN
WHAT CAN RADIOTHERAPY PROVIDE BEYOND THE STANDARD?

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The technical evolution that radiotherapy has witnessed of the last 5-10 years is impressive. Techniques that were considered as science fiction are now already outdated. Much of this evolution is due to the revolution in imaging and computer sciences, which we witness also in many other aspects in daily life. Due to these technical advances, more insight has been gained in fundamental biological processes and the rational combination of medications and radiotherapy. As a consequence, radiotherapy can now target very precisely stage I-II NSCLC to extremely high ablative doses. Stereotactic body radiotherapy is therefore now called Stereotactic Ablative Radiotherapy (SABR). In large prospective series, SABR results in even more than 95% freedom from local progression after 5 years. The fact that residual masses do not progress after such a long period, supports the idea that long-term local tumour control can indeed be obtained. Importantly, these results can be achieved in old and frail patients with very few side effects. Experience in The Netherlands shows that SABR can be introduced safely on a large scale in a standardised way. SABR is increasing used for new primary lung cancers and local recurrences after surgery. Radiotherapy plays an integral role in stage III NSCLC therapy, mostly in a multimodality setting. Technological advances and individualised dose prescriptions together with integration with molecular imaging allow the delivery of radical radiation doses in almost all patients. Severe late side effects are only rarely observed. Local tumour progression is seen in less than 30% of patients. Recent improvements such as volumetric arc therapy and intensive image-guided radiotherapy will allow the delivery of either higher doses to the tumour or less exposure of the normal tissues. The integration of molecular biology with radiotherapy offers great promises. Tumours with different radiosensitivities will be identified thus further individualising the treatment. Targeted agents combined with radiotherapy based on molecular rationale have the potential for improving cure. Finally, with proton therapy coming to maturity, sparing of normal tissues will become even more prominent.

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INDIVIDUALISED TREATMENT OF ADVANCED NSCLC WITH AVAILABLE AGENTS

46IN
CHEMOTHERAPY

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Chemotherapy remains the standard of care for the majority of patients with advanced non-small cell lung cancer (NSCLC). Recently there has been a shift to treat non-squamous NSCLC with platinum/pemetrexed and squamous cell cancer with platinum/gemcitabine however the choice is largely empirical. An increased understanding of the molecular biology of lung cancer is identifying factors that may predict benefit from, or resistance to individual chemotherapeutic agents. There is increasing evidence that patients with high thymidylate synthase may be resistant to pemetrexed, although randomised controlled trial data evaluating this factor in a treated vs control untreated population remain to be presented. High BRCA1 mRNA levels are associated with docetaxel sensitivity whilst high RRM1 levels may predict resistance to gemcitabine. A particular effort is being made globally to identify patients that are sensitive to and factors that predict for resistance to cisplatin, the most effective single agent in NSCLC. These include ERCC1 that in the adjuvant setting appears to identify patients resistant to cisplatin. These observations have proven difficult to confirm in advanced disease, nonetheless a number of avenues appear promising. Experimental models have shown that acquired resistance to cisplatin is associated with upregulation of CD133+, CD44+ and aldehyde dehydrogenase, factors associated with tumour stemness. There is an associated increase in SOX2, Nanog and OCTA. Furthermore upregulation of c-MET and ß-catenin indicate that platinum resistant cells may also have features associated with epithelial-mesenchymal transformation. The search for resistance markers has identified novel factors associated with DNA repair that may become targets for therapy. An example is the PARP protein family and the more recently identified factors MyRIP and hSSB1. Finally a number of miRNAs have been found to be associated with cisplatin resistance although their precise role in this process remains to be established. In summary in the future chemotherapeutic agents will be administered in a personalised manner to patients most likely to benefit from therapy, mechanisms will be targeted to overcome drug resistance and novel agents will emerge that in themselves will have activity through enhancing DNA damage and inducing apoptosis.

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47IN
EGFR (TKIS AND ANTIBODIES)

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Epidermal growth factor receptor (EGFR) is overexpressed in >70% of NSCLC and was proposed as a target by inhibition of cellular growth and proliferation. EGFR tyrosine kinase inhibitors (TKI) compete with ATP to

bind the EGFR TK domain and prevent downstream signalling, while monoclonal antibody (Mab) prevents dimerization of receptor. Total of 6 randomized studies comparing first line EGFR TKI with standard chemotherapy have demonstrated superiority in tumor response rate and progression free survival (PFS). Seventh study (LUX lung 3) comparing Afatinib, a second generation pan-HER TKI, with pemetrexexd/cisplatin will be presented in ASCO 2012. Possibility is that this will add a third EGFR TKI for first line treatment of patients with EGFR mutation. Another second generation TKI, Dacotinib, is being compared with erlotinib as second/third line therapy and KRAS negativity is a co-primary endpoint. EGFR TKI resistance is the major barrier to optimization of benefit from EGFR TKI. RECIST cristeria is used as the standard definition of TKI resistance, however, this may not be entirely applicable. ASPIRATION is an ongoing Asian study on the use of erlotinib beyond RECIST progression and results may provide insight on new set of criteria. IMPRESS is an Asian/Europe comparative study on continuation of TKI in combination with pemetrexed/carboplatin in patients who progressed on gefitinib. These studies help to establish future management of TKI resistance. A recent phase II study on combination of afatinib and cetuximab reported tumor response rate of 36% in patients with resistance to gefitinib or erlotinib. A phase III study is at planning stage. FLEX is a phase III study comparing combination of chemotherapy and cetuximab with chemotherapy that reported marginal OS benefit. However, positive result didn't gain authority approval for the Mab. Only in recent subgroup analysis, patients with high EGFR H-Score (>200) were found to have longer survival with the combination (12 vs 9.6 months), while there was no benefit in patients with low H-score. Data is being assessed by EMEA in this biomarker selected population. EGFR TKI is a standard first line therapy for patients with EGFR mutations and strategies against resistance are being investigated. Use of Mab may be limited to biomarker-selected population.

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48IN
VEGF INHIBITORS

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Dysregulation of angiogenesis in solid tumors enables tumor growth and metastasis. Receptors that mediate angiogenesis, and their ligands, have been identified; among these, vascular endothelial growth factor (VEGF) and its receptor tyrosine kinase play a central role. Besides bevacizumab which blocks VEGF binding to its receptors, various small-molecule tyrosine kinase inhibitors are currently in clinical development.

VEGF and VEGF receptor antibodies: A Metaanalysis which summarized the efficacy of the VEGF antibody bevacizumab in combination with platinum based chemotherapy in the available four randomized trials confirmed a significant improvement of Progression Free Survival (PFS) (HR 0.72; p<0.001) and Overall survival (OS) (HR 0.89; p=0.03) by treatment with bevacizumab. However also a significant increase in the frequency of characteristic side effects was noted (1). A randomized phase II trial which was performed in order to identify predictive markers for efficacy of bevacizumab and which look on a broad panel of serum and tissue based markers as well as dedicated imaging approaches couldn´t demonstrate any significant correlation between the baseline set of candidate markers (bFGF, E-Selectin, ICAM, PLGF, VEGF A, VEGFR 1, VEGFR 1) and response rate. However in an exploratory analysis a significant correlation between the VEGFA level and PFS was found. Further results especially regarding the dynamic marker sampling will be presented on upcoming meetings (2). In the field of Maintenance therapy the combination of Bevacizumab and Pemetrexed as Maintenance treatment demonstrated a significant improvement of PFS compared to the conventional Maintenance treatment with Bevacizumab (HR 0.5; p<0.001) in the AVAPERL trial (3). Currently Ramucirumab, a VEGF Receptor 2 antibody, is under clinical investigation in combination with chemotherapy in different stages of disease.

VEGF-TKI: In randomized phase III trials Motesanib as well as Sorafenib failed to induce a significant improvement of OS in combination with platinum based chemotherapy compared to chemotherapy alone in first-line treatment (4, 5, 6). A signal in PFS was seen in the "NEXUS" trial with Sorafenib and in the "MONET" trial with Motesanib. Treatment induced toxicity and mortality was higher in the squamous cell lung cancer populations. In second line treatment Vandetanib was investigated either in combination with chemotherapy (ZODIAC, ZEAL), as monotherapy compared to Erlotinib or as monotherapy compared to placebo after failure of a prior EGFR-TKI (ZEPHYR). The ZODIAC trial was the only trial which met the primary endpoint of PFS. All the other trials couldn´t confirm the results. However clinical activity of Vandetanib with improvement of response and PFS was seen in most of them. Sunitinib in combination with Erlotinib didn´t led to a significant improvement of OS compared to Erlotinib in the "Sun" trial but comparable to other approaches Response rate (RR) and PFS were improved (7). Similar results were seen in the recently presented "VITAL" trial which investigated the VEGF-Fusionprotein Aflibercept in combination with Docetaxel and showed a significant improvement of RR (23.3% v 8.9%, p<0.0001) and PFS (HR 0.82, p: 0.003) but no impact on OS (HR 1.01) compared to Docetaxel (8). Nintedanib (BIBF1120) another strong VEGF-TKI but also high inhibiting activities on the FGF-Receptor and PDGF-Receptor is currently in clinical investigation in two randomized phase III trials in combination with Docetaxel and Pemetrexed. First results are awaited for 2012.

Conclusion: Besides the confirmed efficacy of the anti VEGF antibody Bevacizumab in eligible patients the role of antiangiogenic TKI in treatment of NSCLC hasn´t been defined yet and is currently investigated in a large number of randomized phase III trials. One of the most important challenges for the future is the identification of predictive markers which might help to select patients who benefit from treatment with these new drugs.

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49IN
ALK INHIBITORS

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The EML4-ALK fusion gene is a validated oncogenic driver and therapeutic target in patients with non-small cell lung cancer (NSCLC). It is estimated to occur in around 4% of cases. Crizotinib (Pfizer), a small molecule tyrosine kinase inhibitor (TKI), is the first in class ALK inhibitor to be approved by the Food and Drug Administration in the United States for any line of treatment in patients with NSCLC bearing EML4-ALK. Single arm phase I/II trials of crizotinib in pretreated patients have demonstrated response rates of 50-60% with median durations of response ranging from 42-48 weeks. Toxicity is reported to be generally mild with predominantly visual and gastrointestinal effects. Randomised trials to compare crizotinib with first or second line standard chemotherapy are currently recruiting, as is an expanded phase II study (PROFILE-1005,-1007,-1014). Several other ALK inhibitors are in earlier stages of clinical development. These include the small molecule TKIs LDK378 (Novartis), ASP3026 (Astellas) and AP26113 (Ariad); and heat shock protein 90 inhibitors, IPI-504 (Infinity) and STA9090 (Synta). It is notable that crizotinib inhibits MET and AP26113 inhibits EGFR T790M in addition to ALK. The potential for these multitargeted agents to be of benefit to a broader spectrum of patients with NSCLC (lacking EML4-ALK) is of interest. This hypothesis is also being tested in a study of crizotinib combined with the pan-HER inhibitor, dacomatinib (Pfizer). EML4-ALK

appears to be associated with younger age, non-squamous histology, never or light former smoker and EGFR wildtype status but contradictory reports caution the restriction of testing to clinical subgroups. An emerging question is how best to diagnosis EML4-ALK, given its rarity, cost-effectively? Immunohistochemistry shows promise to identify cases for further definitive testing using fluorescent in situ hybridisation (FISH). Other areas of importance to now address in the clinical development of ALK inhibitors are how best to schedule with standard chemotherapy and/or radiotherapy, taking into account the prognostic and predictive role of EML4-ALK on standard treatments that are not targeting ALK, and resistance mechanisms.

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SCREENING AND CONSEQUENCES

50IN
GROUND GLASS LESIONS: HOW TODEAL WITH THEM

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Pulmonary nodules detected by low-dose CT lung cancer screening are classified into three types: a homogeneous ground-glass opacity type (pure GGO), a mixed GGO and a solid nodule type on thin-section CT images. A GGO is defined as a focal area of increased pulmonary attenuation through which normal parenchymal structures, such as airways, vessels, and interlobular septa, can be seen.1. The definition of radiological peripheral non-invasive lung adenocarcinoma; what is the candidate for the sublobar resection?Pathologically, lepidic growth pattern replacing bronchioalveolar epithelium without vascular invasion and lymphatic permeation is considered to non-invasiveness. Such lesion is visualized as GGO predominant nodule with little consolidation on preoperative thin-section CT scans. Therefore, the findings of thin-section CT scans can be used to predict non-invasive lung adenocarcinoma indicated for wide wedge resection. Multicenter JCOG 0201 study has demonstrated that both of the radiological criteria of C/T ratio ≤ 0.25 in T1a and 0.50 in T1ab on thin section CT tumor were able to define the homogeneous group of patients with superb prognosis before surgery. These patients were considered as the good candidates for limited resection.2. Management of CT-screening-detected Pulmonary NodulesThe tentative guidelines produced by the Japanese Society of CT Screening are as follows1) Mixed GGO type; A mixed GGO is sometimes seen on CT scans showing evidence of pneumonia, and in such cases a 3-month follow-up examination is recommended to determine whether the mixed GGO is persistent or not. If the size of a mixed GGO is < 10 mm, follow-up CT is an option instead of resection.2) Pure GGO type; If the size of a GGO is ≥ 15 mm, a diagnostic work-up is recommended. If the size of a GGO is ≥ 5 mm but < 10 mm, follow-up CTs at 3, 12, and 24 months are recommended. If the GGO increases in size or in density during follow-up, a diagnostic work-up is recommended. If the size of the GGO is ≥ 10 mm but < 15 mm, follow-up CT or resection depend on the hospital's criteria. If the GGO increases in size or density during follow-up, a diagnostic work-up is recommended. If the GGO is still stable at the time of the 24-month follow-up examination, further follow-up CT examinations are recommended.

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51IN
BIOMARKERS AND RISK MODELS FOR LUNG CANCER SCREENING

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The results of the NLST screening trial for lung cancer showed evidence of a 20% mortality reduction in the screened arm of the study. However, the long term success of future National Screening Programmes as early diagnosis tools will be dependent upon identifying populations at sufficient risk of developing the disease. The current lung cancer risk models include those of; Bach, Spitz, NELSON, LLP and the PLCO. The Liverpool Lung Project (LLP) Risk Model estimates an individual's 5-year absolute risk of lung cancer. The model was based on five epidemiological risk factors: smoking duration, prior diagnosis of pneumonia, family history of lung cancer, occupational exposure to asbestos and prior diagnosis of other cancer. Validation of the LLP Risk Model has been undertaken in the Harvard and European Early Lung Cancer (EUELC) case-control and LLP prospective cohort studies. There was evidence of good discrimination in Harvard (AUC= 0.76) and LLP cohorts (c-index= 0.77, 0.82), with no significant difference in discrimination by age, gender and smoking status. The LLP Risk model is used to select individuals from the UK Lung cancer CT screening trial (UKLS). The long term objective is to incorporate biomarkers based on susceptibility genes or acquired genetic and epigenetic changes into the risk models, to improve their level of discrimination. Early work on susceptibility genes has provided some evidence that the models may be improved, however currently the most promising are methylation and microRNA biomarkers in high risk individuals. Preliminary evidence points to the value of utilising a set of 6 methylation biomarkers as shown in the LLP case-control study of bronchial lavage specimens. Stratification of the results by cytology indicated that the best discriminatory algorithm is particularly useful for cytology negative subjects as there was a tremendous increase in sensitivity among this group of subjects (3% to 74%) with a moderate decrease in specificity (100% to 82%). The Sozzi team in Italy have demonstrated that miRNA expression profiling in plasma collected 1–2 y before the onset of disease, provided strong predictive, diagnostic, and prognostic signatures (AUC≥ 0.85) at the time of CT detection and in disease-free smokers enrolled in the screening trial.

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52IN
AN OVERVIEW OF EUROPEAN SCREENING STUDIES

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The US National Lung Screening Trial showed that low-dose computed tomography (LDCT) can significant reduce lung cancer mortality compared to chest X-ray. To confirm that LDCT screening is beneficial, several randomized controlled trials are ongoing in Europe. The largest of these, the Dutch-Belgian NELSON study, recruited 15,422 high risk persons to LDCT vs. no screening. NELSON mortality data are not yet available, but the study found volume-based determinations of growth were more reliable than visual two-dimensional assessments. A semi-automated volume-based growth determination method was often used, but often needed to be complemented by visual assessment. Preliminary results the Italian DANTE trial were published in 2009. This trial randomized 2472 participants to LDCT vs. annual clinical examination: the numbers of advanced and lethal lung cancers were identical in the two arms, so screening had no apparent benefit. The Italian Mild study (2208 screened subjects) compared one- with two-year screening intervals: preliminary data (personal communication) support a two-year interval. The Danish DLCST study assessed the impact of screening on participants' quality of life and smoking: screening per se did not favour stopping smoking and effective anti-smoking interventions were considered necessary; however screening did not facilitate smoking continuation either, as claimed by detractors of CT screening. The Italian Cosmos study, the largest non-randomized single centre study (5203 screened subjects), introduced a completely non-invasive diagnostic algorithm and assessed the utility of CT-PET in nodule management with satisfactory results. Cosmos data were used to develop a personalised predictor of lung cancer risk. This appears to reliably stratify participants after baseline so that the screening interval can be reduced in low risk individuals. Data from Cosmos and Mild also contributed to the development of sensitive and specific microRNA marker of early lung cancer, of potential use for first-line screening. These European initiatives have significantly increased

knowledge of issues related to lung cancer screening, and definitive data on mortality are awaited.
Disclosure: All authors have declared no conflicts of interest.

53IN
OPPORTUNITIES FOR PROGRESS FOLLOWING THE NATIONAL LUNG SCREENING TRIAL

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The recent NCI-sponsored, randomized trial of helical CT compared to chest X-ray screening in a high risk cohort was stopped as planned when a 20% reduction in lung cancer mortality was observed. This trial established that CT-based lung cancer screening fulfills a critical criterion as an effective cancer screening tool. The Dutch/Belgian screening study is ongoing and this study provides a significant opportunity to further enhance our understanding of the value of a defined diagnostic work-up approach, the use of nodule growth criteria for case selection and other related issues. Against this back drop, where does the field of screening go? The innovative approach for case detection employed by the NELSON study highlights how the efficiency of case detection can be improved. The recent IASLC screening statement points out the opportunity to refine the risk modeling in indentifying more appropriate potential lung cancer screening candidates. What are the core expectations for performance quality that should be expected of a lung cancer screening site? In this regard, as reported by van Klaveren and co-workers, volumetric determination of suspected lung cancers could enable efficient and accurate lung cancer case detection. How can an individual be assured that they are obtaining screening services from a site that also achieves such work-up accuracy? The surgical management of early stage lung cancers is increasingly employing video-assisted thoroscopic surgery. Recent studies demonstrate lower complications and more favorable operative mortality rates compared to standard, open thorocotomy approaches. Should a recommendation be made to standardize the use of minimally invasive approaches to reduce the possibility of over-treatment in the screening setting? Should the surgical management of screen detected tumors include molecular analysis of the tumor tissue to identifying patients at high risk of recurrence? As the evolution of effective and efficient early lung cancer management unfolds how such measures are added to standard of care for this new approach? Population-based care of early lung cancer is a new field. Given the controversies surround cancer screening in general, it is timely to proactively consider measures to allow more consistent success with improving lung cancer outcomes.
Disclosure: All authors have declared no conflicts of interest.

DEVELOPMENTS IN TARGETED THERAPY

54IN
OVERCOMING TKI RESISTANCE

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Aberrant signaling of physiological receptor tyrosine kinase (RTK) pathways plays a key role in distinct types of human cancers biology. In some specific tumours, a single genetic alteration was shown to be able to induce and sustain tumorigenesis, and can be thus referred to as “driver mutation”. This « oncogene addiction » was most often shown to be related to a RTK gene specific alterations, through mutations (EGFR, KRAS, BRAF, c-kit, PIK3CA), amplifications (MET, PIK3CA; FGFR) or translocations (EML4-ALK, BCR-ABL) increasing kinase activity and amplifying or initiating downstream signaling cascades. Best strategy to block RTK activation - using ATP competitive or allosteric TKIs, combined strategy of blockade of RTK or multi-TKI inhibitors - remains unsettled. Noteworthy, it has become obvious that almost all oncogene-addicted tumors become resistant to targeted treatments, sometimes rapidly, illuminating an intriguing and clinically relevant aspect of plasticity of cancer pathways. Collectively, TKIs can not be considered as a curative modality, even in the context of well-described and supposed circumscribed tumorigenic phenomenon. Two concepts are relevant for TKI resistance to date. First, the appearance of secondary mutations - acting as gatekeepers - in the same gene or in a downstream player of the pathway can impede or indirectly counterbalance the inhibition of the activated RTK, as reported for EGFR. Secondary, a « kinase switch », using a side-road to activate downstream interconnected canonical pathways, as demonstrated for MET amplification ability to confer resistance to EGFR TKIs by triggering the alternative oncogenic signaling through Erb3. Interestingly, TKI resistance remains poorly described, and the current evidences reveal a prominent lack of knowledge in most of the clinical situations encountered. In order to reach a personalized medicine, efforts should be maintained to comprehensively describe genomic events as well as their interactions in various types of tumours. However, there will be a strong need to focus on how these dynamic networks might respond and adapt to drug interference. TKI resistance deserves research priority, teaching us that facing complex interplays is likely to become the norm in establishing new approaches prone to circumvent resistance.
Disclosure: All authors have declared no conflicts of interest.

55IN
C-MET INHIBITORS

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The c-MET pathway is dysregulated in many human cancers and promotes tumor growth, invasion and metastasis. The MET receptor is activated by a number of mechanisms including protein overexpression, gene amplification gene mutation, protein overexpression and/or a ligand-dependent autocrine/paracrine loop. In addition, abnormalities in MET signaling is a poor prognostic factor. Thus, c-MET has been seen as an attractive target for cancer therapy. A wide variety of agents targeting different elements in the c-MET signaling pathway have been introduced into the clinic and are being explored in phase I, II and III clinical trials across multiple tumor types (Table 1). Clinical activity with minimal toxicity has been documented, albeit not as robust as anticipated. The most active compounds appear to be those with other targets in addition to c-MET.Predictive biomarkers are being explored. The current state of development of this class of compounds will be discussed.

TABLE 1: c-MET Inhibitors in the Clinic

TARGET	DRUG	STAGE OF DEVELOPMENT
SELECTIVE		
Oral TKI	Tivantinib, TAK-701, EMD1214063, EMD1204831,INCB28060, SGX-523, JNJ-38877605	Phase I – Phase III
Antibody	Rilotumumab, ficlatuzumab, onartuzumab, AMG-337	Phase I – Phase III
NON-SELECTIVE		**OTHE TARGETS**
Oral TKI	BMS-796302	Ron, Axl, VEGFR2, Flt3
	E7050	VEGFR2
	Cabozantinib	VEGFR2, Ret, Kit, Flt3, Tie2
	Crizotinib	Alk, Ron, Axl, Tie-2
	Foretinib	VEGFR2, Ret, Kit, Flt3, Tie2
Antibody		
	AMG-208	Ron

Disclosure: All authors have declared no conflicts of interest.

56IN

MTOR AND S6 KINASES AS BIOMARKERS/TARGETS IN LUNG CANCER

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Most patients die from lung cancer as a consequence of therapy resistant metastatic disease. Consequently, understanding the biological mechanisms that control multi-agent resistance and metastasis should provide novel therapeutic strategies and/or bio-markers to enable improved survival. Several growth factors have been implicated in lung cancer cell biology. Unless a particular growth factor/receptor is dominant it may be preferable to identify intracellular signalling target(s) that serve as a point of convergence in growth factor action. Western blot comparison of multiple signaling proteins in normal versus malignant lung cells revealed that mTOR, S6K1 and S6K2 are over-expressed in all tumours examined. We have shown that mTOR/S6K1 signalling is critical for mediating proliferation while S6K2 is a key inducer of multidrug resistance. Interestingly, in immunohistochemical tissue biopsy studies the expression levels of mTOR correlate with worse survival and elevated S6K2 appears to be predictive of poor response to therapy. Consequently, inhibitors of mTOR/S6K1 or S6K2 signalling may work best in those patients over-expressing these molecules. In a separate RNAi library based-screen we identified more than 50 novel kinases that control metastases. Amongst these silencing of p90 ribosomal S6 kinase 1 (RSK1) enhanced migration and invasion in vitro. Moreover silencing RSK1 promoted metastasis in vivo and its increased expression in primary tumours correlated with the presence of more metastasis in lung cancer patients. These findings suggest that RSK1 expression might serve as a biomarker predictive of disease progression.

Disclosure: All authors have declared no conflicts of interest.

57IN

TARGETING MEK AND BRAF IN NON-SMALL-CELL LUNG CANCER (NSCLC)

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Non-small-cell lung cancer (NSCLC) has recently been associated with molecular characteristics that have important implications in carcinogenesis and response to targeted therapies. Targeted therapies, if given to a patient subpopulation enriched by the presence of relevant molecular targets, can often abrogate cell signaling that perpetuates cancer progression. For instance, several molecular alterations have been defined as "driver mutations," such as mutations in EGFR, KRAS, and EML4-ALK fusion gene. Other key signaling pathways such as RAS/RAF/MEK, have also been identified as novel targets for lung cancer treatment. Constitutive ERK signaling is common in human cancer and is often the result of activating mutations in BRAF, RAS and upstream receptors. Missense BRAF kinase domain mutations are frequently observed in melanoma, colon and thyroid cancers and less frequently in lung (~5% in Adenocarcinomas and 1% in Sqamous carcinoma) and other cancer types. The vast majority involve a glutamic acid for valine substitution at codon 600 (V600E), which results in elevated BRAF kinase activity. Vemurafenib produced improved rates of overall and progression-free survival in melanoma patients with the BRAF V600E mutation. BRAF appears to be a druggable mutation that also defines subgroups of lung cancer patients. KRAS is frequently mutated in NSCLC (up to 30%), resulting in the activation of the MEK/ERK pathway. Targeting downstream effectors and MEK inhibition has been the subject of intense scientific and clinical research for some time now. Inhibitors of the pathway with selectivity for BRAF and MEK are now in Phase 1 and 2 clinical trials with promising early results. To maximize the likelihood of success with these agents, clinical trials enriched with patients whose tumors possess BRAF and RAS mutations have been proposed. This presentation reviews the current status of BRAF and MEK inhibitors with regard to their clinical development.

Disclosure: All authors have declared no conflicts of interest.

58IN

DEVELOPMENTS IN TARGETED THERAPY: FGFR1 INHIBITION IN LUNG CANCER

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Specific targeting of oncogenic protein kinases increasingly leads to treatment approaches in lung cancer superior to conventional chemotherapy. Such "druggable" targets have been almost exclusively identified in lung adenocarcinoma. Recently, within the Cologne Lung Cancer Genome Project, focal amplification of fibroblast growth factor receptor 1 (FGFR1) was identified in a large set of squamous cell carcinomas (SCC) of the lung using high resolution copy number analysis and confirmed by fluorescene in situ hybridization (FISH) in an independent cohort of SCC samples with high frequency (22%). Since the fibroblast growth factor receptor family plays a critical role in cell proliferation and survival in different tumor types, amplified FGFR1 represents an attractive target for the development of a personalized treatment approach in SCC of the lung. This was confirmed by the demonstration of growth inhibition and apoptosis induction by a FGFR inhibitor specifically in lung cancer cells harbouring amplified FGFR1 in vitro and by the induction of tumor shrinkage by this compound in a murine model of FGFR1 amplified lung cancer. Subsequently, a standardized reading and evaluation strategy for diagnosis of FGFR amplification in lung cancer tissue was developed using a two colour FISH assay. So far, several small molecules for FGFR inhibition have been developed and, partly, are clinically evaluated in different tumor types. The oral pan FGF-R kinase inhibitor BGJ398 is currently evaluated in a phase I first in man trial in adult patients with advanced solid malignancies (clinical trial protocol CBGJ398X2101). After discovery of FGFR1 amplification as frequent genetic alteration in SCC of the lung, this trial was opened for recruitment of FGFR1 amplified SCC of the lung and treatment of several patients has already been initiated. The evaluation of exclusively patients with FGFR1 amplification already in this early clinical development phase will rapidly answer the question whether FGFR1 amplification represents the first effective personalized treatment approach in SCC of the lung.

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UNRESOLVED ISSUES

59IN

HOW TO FOLLOW UP AFTER CURATIVE TREATMENT OF NSCLC

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Although surgery-based treatment strategies are those which offer the best chance for cure of a non-small cell lung cancer (NSCLC), five-year survival after a complete resection of a stage I-IIIA NSCLC varies between 20% and 70% depending on the stage of the disease. The purpose of follow-up is to early detect disease recurrence. There are no robust data published on the follow-up after surgery for NSCLC. It has never been demonstrated that follow-up after surgery for NSCLC detects earlier recurrences and/or improves life expectancy. Whether it is of interest and the optimal follow-up program are questions which remain unanswered. There are different international clinical

guidelines, reflecting rather expert opinions than evidence-based data. Most of them recommend regular clinic visits and thoracic imaging procedures, either chest X-ray or chest CT-scan. After a radiotherapy-based strategy, thoracic CT-scan has a poor discriminating capacity between recurrent tumour and post-treatment changes. PET-CT has been shown to be more accurate than CT after thoracic radiotherapy, especially if performed not earlier than 3 months after radiotherapy to avoid false-positive results due to post-radiotherapy inflammatory changes. PET-CT has been hypothesized to increase the proportion of recurrent diseases amenable for curative salvage treatment. A prospective evaluation suggested that PET-CT at 3 months after radiotherapy might be cost-effective, especially if only performed in asymptomatic patients. The best follow-up intervention needs to be evaluated through a robustly designed randomized control study, taking into account cost-effectiveness, patient-orientated outcomes such as quality of life and the penibility of follow-up procedures. A large randomised study, the IFCT 0302 study, is ongoing in France. It compares 2 follow-up programs in completely resected stage I-IIIa NSCLC, with overall survival as the primary end point. Patients are randomised between history + physical examination + chest X-ray and history + physical examination + chest X-ray + chest CT-scan + fiberoptic bronchoscopy (optional for adenocarcinomas).

Disclosure: All authors have declared no conflicts of interest.

60IN
N2 DISEASE

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N2 disease, according to the TNM staging system, is defined by the presence of metastatic disease in the ipsilateral mediastinal lymph nodes. Only selected patients with N2 disease may benefit from primary surgery; a careful preoperative work including CT scan PET and invasive procedures like EBUS and mediastinoscopy should be carried out to assess this parameter. In fact, the best treatment option for these patients include induction therapy followed by surgery. Preoperatively proven N2 disease requires a multidisciplinary approach with chemotherapy or chemoradiotherapy. However, in these patients, complete resection of the primary lesion still remains among the strongest prognostic factors for long term survival. Radical mediastinal lymphadenectomy should always be performed, since it is certainly an added value at least for correct staging. The impact of induction chemo-radiotherapy on postoperative morbidity is still being evaluated. However, after induction therapy, less extended resections and bronchoplastic reconstructions should be always considered to avoid pneumonectomy. When completely resected, occult N2 found at thoracotomy, skip metastases and single level N2 in selected locations are reported to portend a relatively encouraging outcome. In particular single level metastases within station 5 (AP window) has long been considered less unfavorable from the prognostic point of view, when compared to other sites.

Disclosure: All authors have declared no conflicts of interest.

61IN
PROPHYLACTICAL CRANIAL PCI IN NSCLC

No abstract received at time of going to press.

62IN
HOW TO IMPROVE THE OUTCOME WITH CHEMORADIOTHERAPY

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For patients with unresectable locoregionally advanced non small cell lung cancer (NSCLC) current standard treatment consists of concurrent chemoradiotherapy usually with cisplatin-etoposide or weekly low dose carboplatin-paclitaxel. Randomized studies have indicated no added benefit from the addition of induction or consolidation chemotherapy. Median survival times in recent multi-institutional trials have exceeded 20 months. Clinical and molecular factors contributing to the heterogeneity of clinical presentations are increasingly being recognized. Recent investigations have attempted to optimize radiation. A randomized trial testing the hypothesis that increasing total radiation doses from 60 Gy to 74 Gy would result in better locoregional control and increased survival times was closed early based on a futility analysis. An alternative hypothesis is that larger daily fraction sizes could lead to higher tumor cell kill. The CALGB is currently planning a Phase I trial of carboplatin-paclitaxel with concurrent radiation with daily fraction sizes beginning at 2.25 Gy and aiming in a sequential cohort design to escalate up to 3 Gy. There has also been interest in introducing novel chemotherapy agents. In particular for patients with non-squamous cell histology the use of pemetrexed as a radiation sensitizer is of interest. A large international randomized trial (PROCLAIM) is comparing concurrent chemoradiotherapy with cisplatin-etoposide vs. cisplatin-pemetrexed. Of note, both regimens can be administered at full chemotherapy doses thus optimizing systemic chemotherapy exposure. An alternative approach has been the use of targeted therapies. Anti-EGFR directed therapy with cetuximab is currently undergoing investigation. Pilot data utilizing tyrosine kinase inhibitors of EGFR have been disappointing. It is possible however that erlotinib or gefitinib in patients with EGFR mutations and similarly of crizotinib in patients with EML4-ALK fusion could lead to improved outcomes. Pilot trials investigating this approach are under discussion. The use of anti-angiogenic agents has been disappointing. Finally, the use of stereotactic body radiation therapy (SBRT) is being explored for patients with early stage disease as well as those with oligometastatic disease.

Disclosure: E.E. Vokes: Dr. Vokes is a consultant for Amgen, Avoa, Boehringer-Ingelheim, Genentech, and Novartis.

PREVENTION, EARLY DETECTION, EPIDEMIOLOGY, TOBACCO CONTROL

63O_PR
EFFECTIVENESS OF CHEST DIGITAL TOMOSYNTHESIS FOR EARLY DETECTION OF LUNG CANCER: FIRST–YEAR RESULTS FROM OBSERVATIONAL STUDY

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Objective: Screening with low-dose CT reduces mortality from Lung Cancer (LC); but, before public policy recommendations, cost-effectiveness and radiation adsorbed dose must be rigorously analyzed. Other strategies to select peoples who are best suited for CT must be searched. We present the 1st-year results of SOS Trial, an observational study using Digital Chest Tomosynthesis (DT) for early detection of LC. DT is limited angle tomography that allows reconstruction of multiple image planes and provides high-resolution images in coronal planes at radiation doses and costs much lower than CT.

Methods: Accrual started in December 2010 and ended in December 2011. Smokers or former smokers of at least 20 pack-years, aged 45–75 years, were considered potentially eligible and preassessed for eligibility during a telephone interview. Participants were requested to fill out a questionnaire on occupational history, smoking habits, past and present health conditions. Subjects were considered ineligible if they had history of previous malignancy within 5 years before accrual. All subjects enrolled had DT. One–yearly DT round was planned: one at baseline, and one yearly repeats. When suspicious pulmonary lesion is found on DT, first-line CT is warranted. Sample size of 2000 subjects was calculated on basis of incidence and mortality data reported in Piedmont Cancer Registry.

Results: At December 2011, a total of 1843 subjects were preassessed. 1703 (92%) subjects were finally enrolled; mean age 61 ys (95% CI, 48 – 73), active smokers 766 (77%). On first 1000 patients analyzed, at least one pulmonary abnormality was detected in 154 subjects, extrapulmonary abnormalities in 7 patients: effusions (2), pleural lesions (3), mediastinal lymph node

enlargement (2). 96 patients (9.6%) underwent first-line CT; false positive DT nodules were 32 (3.2%). LC detection rate was 1.1%.

Conclusion: DT detected non-calcified nodules in a percentage comparable to CT. Up until now LC was detected in 1.1% of cases. DT seems to be a promising first line tool for LC screening.

Table:

Comorbidities	658
Any abnormality in DT	154
First-line CT	96
Follo-up CT	53
CT/PET	16
Negative nodules for LC	7
Positive nodules for LC	11
Lobectomy	5
Pneumonectomy	1
STAGE	
IA	3
IB	2
IIB	1
IIIB	1
IV	4
HISTOLOGY	
Adenocarcinoma	7
Squamous cell	3
Carcinoid	1

Disclosure: All authors have declared no conflicts of interest.

64O_PR
LUNG CANCER RISK DETERMINATION WITH LOW COHERENCE ENHANCED BACKSCATTERING SPECTROSCOPY (LEBS) ANALYSIS OF BUCCAL MUCOSA

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Low dose CT may allow population screening for lung cancer (NEJM 2011). However, the low disease prevalence even in this enriched population results in a prohibitive false positive rate supporting need for better risk evaluation (Ann Int Med 2010). Field carcinogenesis represents a promising approach for cancer risk stratification. The buccal mucosa is in the smoking "field of injury" and represents a well established "molecular mirror of lung carcinogensis (Cancer Prev Res 2008). Our group has focused on using a novel optical technique, LEBS, to detect the micro-architectural consequences of the genetic/epigenetic alterations in field carcinogenesis (reviewed in Gastro 2011). We now assess the diagnostic ability of buccal LEBS analysis for lung cancer.

Methods: We performed a case-control study (n=63) using a training/blinded testing set design. Cases were pathologically confirmed primary lung cancer (mainly NSCLC) prior to any treatment. Controls were age/gender-matched smokers (current or past history). LEBS analysis was performed with a novel LEBS fiberoptic probe gently pressed to buccal mucosa. Five readings (each requiring 250 msecs) were obtained and analyzed by an investigator blinded to clinical data.

Results: Univariate analysis of our training set identified 5 markers that discriminated cases from controls (enhancement, spectral slope (SS), M, OHB and BVD with p values of 0.011, 0.015, 0.277, 0.0035 and 0.0024 respectively). These markers were not confounded by age, gender, smoking intensity, histological subtype or stage of disease. A prediction rule with only SS and BVP had excellent performance (AUROC=0.906). The training set determined threshold value yielded very encouraging results when prospectively applied to an independent testing set (sensitivity =100%, specificity=70%, PPV=81%, NPV=100%).

Conclusions: Buccal mucosal interrogation with our novel fiberoptic LEBS probe appears accurate in identifying lung cancer patients. While the modest sample size necessitates caution, the diagnostic performance along with the clinical practicality suggests that this minimally intrusive buccal LEBS approach represents a promising pre-screen for lung cancer.

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65O_PR
MIR-34C IS A POTENTIAL BIOMARKER FOR HISTOLOGICAL RESPONSE IN LUNG CANCER CHEMOPREVENTION STUDIES

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Endobronchial histology is currently considered the best intermediate endpoint for chemoprevention studies. While histologic grading is reproducible between specialized pathologists, more quantitative biomarkers of response would be desirable. We analyzed the expression of selected miRNA as potential surrogate biomarkers in the Iloprost lung cancer chemoprevention trial, which is the first to meet a pre-determined primary endpoint of histology improvement (Keith, Cancer Prev Res 2011). Matched biopsies (baseline-BL and the same site at follow-up-FU after 6 months of Iloprost or placebo) were obtained in 125 high-risk individuals who completed the trial: 40/35 and 25/25 current/former smokers in the Iloprost and placebo arm, respectively. We analyzed 496 biopsies including 4 matched biopsy pairs per patient: the best and the worst histology at BL and the 2 biopsies from same site at FU. Total RNA was extracted from formalin fixed paraffin embedded sections adjacent to the diagnostic section and 14 selected miRNA previously identified in high-grade bronchial preneoplasia were analyzed by qRT-PCR (Mascaux, Eur Resp J 2009). In the earlier and current studies, miR-34c expression was inversely correlated with BL histology grade ($r=0.36$, $p<0.001$, false discovery rate (FDR) <0.1). The current study demonstrated that the change in miR-34c expression between BL and FU biopsies was also inversely correlated with histology changes ($r=0.23$ $p=0.0003$, FDR<0.1) and this was independent of treatment arm or smoking status. In addition, a lower miR-34c expression at BL, and consequently its increase at FU, was significantly associated with histological response in the Iloprost ($p=0.0022$, FDR<0.1) and placebo arms ($p=0.0025$, FDR<0.1). The changes in miR-34c (a transcriptional target of p53) expression were inversely correlated with histological

changes at FU. In responders, miR-34c expression is significantly lower at BL and increased at FU, related with a worse histology at BL and its down-grading at FU. We conclude that the change in miR-34c expression in FU biopsies is correlated with histological response and may be a quantitative biomarker of response in lung chemoprevention studies.

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66O
AIRWAY OBSTRUCTION AND RESPIRATORY ILL-HEALTH IN A POPULATION AT INCREASED LUNG CANCER RISK

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Background: Lung cancer is clinically silent and more than two-thirds of lung cancers present at a late stage and less than 10% of people survive for 5 years. Detection of lung cancer at an early stage may then potentially increase survival rates. As lung cancer risk is associated with airflow obstruction and increases with decreasing FEV_1, in this study we are investigating the feasibility of detecting high risk individuals by identifying airflow obstruction and monitoring respiratory symptoms.

Method: This is a population-based cohort study, with subjects aged 40–75 and registered with GP practices in the Wythenshawe District of Manchester recruited between November 2010 and December 2011. Data on risk factors for lung cancer were obtained from a face-to-face interview together with spirometry. Respiratory symptoms were assessed using a questionnaire based on the Medical Research Council Questionnaire (MRCQ). The association between the risk factors for lung cancer and recorded airflow obstruction was examined at baseline.

Results: 2700 subjects were invited to participate. 273 (10.1%) subjects completed the baseline assessment and 260 (95.2%) completed spirometry. 175 participants (67.3%) reported no underlying respiratory disease. Ever smoking ($p<0.05$) but not exposure to passive smoke or occupational carcinogens and a family history of lung cancer was associated with airflow obstruction. Airflow obstruction was most severe (the lowest percentage of FEV_1 predicted) in smokers compared with non-smokers. 85 + 21, n=189 vs. 98 + 18, n=71, $p<0.05$). Airflow obstruction was significantly associated with chronic cough, cough with phlegm, wheezing and shortness of breath in smokers ($p<0.05$). Compared to asymptomatic participants, subjects with respiratory symptoms were strongly associated with airflow obstruction; for chronic cough OR 3.69 (95% CI 1.94 –6.99); for cough with phlegm OR 4.09 (95% CI 2.10–8.00); for wheezing OR 3.68 (95% CI 1.95–6.98) and for shortness of breath OR 4.40 (95% CI 2.30–8.42).

Conclusion: The community based study reaffirms that smokers with respiratory symptoms are at higher risk of having airflow obstruction, a powerful marker of lung cancer risk. Respiratory symptoms in smokers, with or without spirometry, may assist in targeting a high risk population for lung cancer screening.

Disclosure: All authors have declared no conflicts of interest.

67P
DO GENETIC POLYMORPHISMS OF GSTS ELEVATE THE RISK OF DEVELOPMENT OF LUNG ADENOCARCINOMA AND SQUAMOUS CELL CARCINOMA IN SLOVAK POPULATION?

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The Slovak Republic belongs to the countries with high incidence of lung cancer. Gene polymorphisms of the glutathione S-transferases (GSTs) may play a role in individual lung cancer susceptibility. In presented case-control study we investigate the incidence of polymorphism of GSTT1, GSTM1, GSTP1 genes and their combinations as possible predictive factors for identification of individuals with increased risk of formation and development of adenocarcinoma (AC) and squamous cell carcinoma (SCC) of lung in Slovak population. The study was conducted on 520 individuals consisting of 118 patients with adenocarcinoma, 112 patients with squamous cell carcinoma and 290 control individuals. GSTT1, GSTM1, GSTP1 gene polymorphisms were assayed by standard PCR and PCR-RFLP technique. The results of this study indicate that the GSTT1 null-genotype and combinations GSTT1 null and GSTM1positive, GSTT1 null and Ile/Val or Val/Val are associated with increased risk of lung adenocarcinoma in Slovak population. A significant association with 2.13 - fold increased risk was observed between lung adenocarcinoma and GSTT1 null genotype (95% CI = 1.29–3.51; p= 0.004). Also it was proved 2.17 times statistically higher risk for development of this histological type of lung cancer (95% CI =1.07–4.39; P = 0.046) in combination of GSTT1 null and GSTM1 positive genotypes and statistically significant risk with OR = 2.83 was observed in combination of GSTT1 null and Ile/Val or Val/Val genotypes (95% CI =1.34–6.01; P = 0.009). GSTT1, GSTM1, GSTP1 polymorphism did not show any significant association with SCC. Our study suggests that genetic make-up in metabolizing genes may increase susceptibility towards lung cancer development.

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68P
THE INFLUENCE OF GENETIC POLYMORPHISM OF CYP1A2, GSTT1, GSTM1, NAT2, MDR1 AND THEIR COMBINATIONS ON LUNG CANCER PREDISPOSITION

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One of the causes of tumor development is known to be disbalance of activation, inactivation and removal of toxic compounds. Change in the activity of xenobiotic biotransformation enzymes related to the existence of genetic polymorphism results in increased susceptibility of organism to deleterious effects and, in consequence, to a rise in a risk of developing various oncopathologies. On this connection it is necessary to take into account the total contribution of polymorphic variants of genes encoding enzymes of I and II xenobiotic biotransformation phases as well as P-glycoprotein in detecting predisposition to LC. The study comprised 118 LC patients undergoing treatment at Minsk Oncologic Dispensary over the period from 2003 to 2009. The control group includes 329 persons without oncopathology permanently living in the area of Belarus. PCR-RFLP and multiplex PCR methods were used for studying polymorphism of genes: CYP1A2 (C734A) – the activation

phase; GSTT1 (deletion), GSTM1 (deletion), NAT2 (C481T, G590A and G857A) – the detoxication phase and MDR1 (C3435T) – the removal phase. The examined individuals were divided into "fast" and "slow" acetylators according to the results of genotyping for three NAT2 sites (C481T, G590A and G857A). The combination of genotypes "734CACYP1A2/ GSTT1(+)/ GSTM1(+)/3435CTMDR1" was revealed to exert a protective effect when the genes CYP1A2 and MDR1 are represented with heterozygote and the genes GSTT1 and GSTM1 do not contain homozygous deletion. The risk of LC development is increased in the individuals with the genotype combinations "734AACYP1A2/GSTT1(-)" or "GSTT1(-)/3435CCMDR1". The combination "734AACYP1A2/GSTT1(-)/3435CCMDR1" and "734AACYP1A2/ GSTT1(-)/3435CC MDR1" is of the highest risk importance, especially when the carrier of such a combination is a "slow" acetylator. Thus, the study of genetic polymorphism of enzymes at all phases of xenobiotic biotransformation in an individual increases the degree of prognosis accuracy of his predisposition to LC. Association of homozygous GSTT1 gene deletion with predisposition to LC was detected in residents of Belarus. Combinations of polymorphic gene loci of biotransformation enzymes exert a modifying effect on risk importance of GSTT1 genotype in lung cancer development.

Disclosure: All authors have declared no conflicts of interest.

69P
USEFULNESS OF BONE RESORPTION MARKERS CTX, TRAP5B, AND PINP IN PATIENTS WITH NON-SMALL CELL LUNG CANCER AND BONE METASTASES. PRELIMINARY STUDY

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Background: Non-small cell lung carcinoma (NSCLC) is the most common lung cancer, which represents the major cause of cancer death worldwide. The early diagnosis of NSCLC is difficult, and the sensitivity of common serum tumor markers, such as carcinoembryonic antigen (CEA) and fragments of cytokeratin 19 (CYFRA 21-1), is low. Unfortunately, bone metastases (BMs) are common in patients with NSCLC, and their early detection and treatment may improve both disease-free interval and survival. Several serum biomarkers have been proposed for the detection of BMs, such as carboxy-terminal telopeptide of type I collagen (CTX), tartrate-resistant acid phosphatase isoform type 5b (TRAP5b), and amino-terminal propeptide of type I collagen (PINP), which are markers of bone resorption. The aim of this preliminary study was to evaluate the usefulness of a panel of serum biomarkers in patients with NSCLC and BMs.

Patients and methods: Sixteen patients (11 males, 5 females, median age 64 years, range 54-68) with NSCLC and BMs (cases), and 18 age- and gender-matched patients without BMs (controls) underwent serum CTX, TRAP5b, PINP, CEA, and CYFRA 21-1 measurements. CTX was measured by automated immunometric assay, TRAP5b and CEA by two-site enzyme-linked immunosorbent assay (ELISA), PINP by radioimmuno assay (RIA), and CYFRA 21-1 by immunochemiluminescent assay. The cut-off values were 400 pg/mL (CTX), 5 U/L (TRAP5b), 3.5 ng/mL (CEA), 65 µg/L (PINP), and 45 pg/mL (CYFRA 21-1), respectively.

Results: CTX (443.7±945.1 vs. 402.7±28.4 pg/mL, p=0.003), and PINP (75.9±11.4 vs. 64.1±7.5 µg/L, p=0.001), were significantly higher in patients with BMs, while the other markers did not differ (p=NS) between cases and controls. The sensitivity, specificity and accuracy were 73.7%, 86.7%, and 79.4% (OR=18.2, 95% CI 2.99-110.7, p<0.0001) for CTX; 30.4%, 76.2%, and 67.6% (OR=6.22, 95% CI 1.06-36.5, p=0.038) for TRAP5b; 72.2%, 81.2%, and 76.5% (OR=11.26, 95% CI 2.21-57.20, p=0.002) for PINP; 55.5%, 62.5%, and 58.8% (OR=2.08, 95% CI 0.53-8.23, p=0.29) for CEA; 65.0%, 78.61%, and 70.6% (OR=6.81, 95% CI 1.41-32.8, p=0.012) for CYFRA 21-1, respectively.

Conclusions: In patients with NSCLC, both CTX and PINP measurements can be useful in the detection of BMs.

Disclosure: All authors have declared no conflicts of interest.

70P
FURTHER VALIDATION OF DR-70 BLOOD BIOMARKER IN THE EARLY DETECTION OF NON-SMALL CELL LUNG CANCER

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Non-small cell lung Cancer (NSCLC) accounts for 85-90% of all lung cancers with a death rate of 85%. There is no routinely used blood biomarker test that can be used for lung cancer diagnosis with high sensitivity. Onko-Sure® is a regulatory approved blood test for detection and monitoring of lung cancer treatment/recurrence. It measures the accumulation of fibrin/fibrinogen degradation products in the serum using anti-DR-70 antibody. The purpose of this study was to further validate DR-70 utility in lung cancer early detection. A total of 232 serum samples were retrospectively obtained and were tested with DR-70. The samples were divided into two arms: confirmed healthy control (n= 120) and biopsy-confirmed NSCLC (n= 112). The data were analyzed to find the optimal cut point to differentiate the normal vs the cancer group along with sensitivity and specificity of the test. The data were further broken down into different stages followed by the analysis of sensitivity and specificity. The sensitivity and specificity achieved with DR-70 test at the cut point of 1.2 were 65.2% and 87.5%, respectively. A consistent high sensitivity was observed throughout all stages with the highest sensitivity reached for stage II (70.4%). Furthermore, DR-70 showed a sensitivity of 81.8% in acinar cell carcinoma, a subcategory of non-small cell lung cancer subcategories. Chest X-Ray is the routine first diagnostic step in lung cancer detection with the sensitivity of 78.3%; however, it misses lesions smaller than 1 cm. CT scan, with the sensitivity of 88.9%, may be ordered to further explore the situation which exposes the patient to further amount of radiation. In this study, DR-70 biomarker showed a high sensitivity for the detection of lung cancer which was in line with many previous studies. These findings highlight this test as an additional first line diagnostic tool that can be combined with X-ray to increase the diagnostic sensitivity. DR-70 showed 60% sensitivity in stage I of NSCLC, which will promise a higher sensitivity if used along with X-ray. An enhanced ability to diagnose NSCLC in an early stage should significantly improve prognosis, treatment options and survival rate for patients with lung cancer.

Disclosure: All authors have declared no conflicts of interest.

71P
EARLY DETECTION OF ENDOBRONCHIAL CARCINOMA USING AUTOFLUORESCENCE BRONCHOSCOPY

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Introduction: The earlier the stage we can detect lung cancer, the better for the patient's prognosis.

Objective: The objective of this study was to evaluate the benefit of using autofluorescence bronchoscopy for the detection and localization of endobronchial carcinoma.

Method: Autofluorescence bronchoscopy was used to examine 350 patients, aged 35 to 90 years ,who were either current or ex-smokers of more than 20 pack-years, and suspected of having lung cancer based on abnormal chest roentgenogram or computer tomogram of the chest.

Results: There were 262 men and 88 women with mean age of 64 years. One man and one woman developed carcinoma in situ, which was destroyed by electrocautery. Annual follow up by autofluorescence bronchoscopy was normal for the following 4 years for both patients.

Another man developed severe dysplasia which was ablated by using electrocautery. Open lung biopsy of left lower lobe lesion revealed bronchiolitis obliterans.

Conclusion: Autofluorescence bronchoscopy is able to enhance early detection of endobronchial cancer.

Disclosure: All authors have declared no conflicts of interest.

72P
LUNG CANCER (LC) RISKS IN WOMEN WITH PREVIOUS BREAST CANCER (BC): ANALYSIS OF CLINICOPATHOLOGICAL CHARACTERISTICS AND BIOMARKERS EXPRESSION

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Background: Several studies in BC patients (pts) suggest that older radiotherapy techniques and smoking are associated with an increased risk of developing LC in the ipsilateral lung especially with squamous cell histotype. Aim of this study is to evaluate if there are, in pts with previous BC, clinicopathological characteristics and a biomarkers profile, evaluated in BC and LC tissues, able to predict an increased risk of developing a subsequent LC. The BC and LC biomarkers profile will be compared with the biomarkers profile in pts with only BC or only LC.

Patients and methods: From 2006 to 2011, thirty-five pts with a previous BC were resected for LC. BC and LC tissues are currently used to evaluate the following biomarkers: Estrogen Receptors (ER), Progesterone Receptor (PgR), Aromatase, Human Epidermal Growth Factor Receptor 2 (HER 2), Ki-67, Breast Cancer 1(BRCA1), Breast Cancer 2(BRCA2), p53, Epidermal Growth Factor Receptor (EGFR), Kirsten Rat Sarcoma Viral Oncogene (KRAS) mutations, Excision Repair Cross-Complementing 1(ERCC1), Ribonucleotide Reductasi (RRM1), Thymidylate Synthase (TS) and class III β-tubulin (β-tub-III). Immunohistochemistry, Real-Time PCR and gene sequencing for mutations of EGFR and KRAS are used.

Results: The median age at diagnosis of BC was 55.5 years. The mean time between diagnosis of BC and LC was 6.25 years. Fourteen pts (40%) were never smokers, 8 pts (22%) were former smokers and 13 pts (37%) were smokers at the time of BC diagnosis. Twenty-four patients (69%) received adjuvant radiotherapy after BC resection and 14 of these pts (58%) had ipsilateral LC. Adenocarcinoma is the most common LC (26 pts, 74%) followed by squamous cell carcinoma (4 pts, 11%) and SCLC (3 pts, 9%). Biomarkers study are ongoing and the final results will be presented at the conference.

Conclusion: In this study adjuvant breast radiotherapy and smoking do not seem to be strictly associated with the development of LC in pts with a previous BC and adenocarcinoma is the most frequent LC histotype. The biomarkers study could increase our knowledge about the relationship between aetiological factors, individual susceptibility and gene-enviroment in developing a subsequent LC.

Disclosure: All authors have declared no conflicts of interest.

73P
LUNG CANCER IN MULTIPLE MALIGNANT NEOPLASMS

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Introduction: With the cancer risk 14.6% before the age of 65 yrs. belongs the Czech Republic to the most vulnerable amongst 185 countries. Proper clinical decision-making can add further support to the effort for prolonging survival of cancer patients with subsequent neoplasm in regard to an expected prevalence of 12,700 survivors of LC in 2015.

Material and methods: The primary and subsequent lung cancers (LC) based in the Czech Cancer Registry in 1976-2005 were analysed in relation to the occurence of cancers at other sites (ICD-10: C00-D48).The difference between cases and persons indicate the multiple malignant neoplasms (MMNs).

Results: Among total of 147,185 new LC in males collected during 1976-2005 years there were 3,278 (2.2%) primary and 8,849 (6%) subsequent cases. Among total of 29,208 new LC in females were 667 (2.3%) primary and 2,708 (9.3%) subsequent cases. The average interval between primary LC and subsequent neoplasms was 6.1 years. After primary LC the most frequent were 26,4% cancers of gastrointestinal and 16.1% urinary tract, 14.2% skin, 13% female genital and 13.2% other respiratory tract, 11.3% male genital and 11.2% breast. The most frequent preceding neoplasms before subsequent LC were 29.8% cancer of skin, 26% female genital, 16% breast, 13% of gastrointestinal, 12% urinary, 10.3% other respiratory tract. The 23,462 subsequent LC reported as a second cancer included early stages in 29.6% males and 27.9% females, advanced stages in 31.2% males and 31.3% females, unknown stages in 39.3% males and 40.8% females.

Conclusion: Individual treatment algorithms should pay more respect to the stage and prognostic markers of primary cancers. Most of subsequent cancers, particularly those of advanced stage could be prevented by the use of standards for follow-up care. The Czech screening programme and medical surveillance seems at present insufficient.

Disclosure: All authors have declared no conflicts of interest.

74P
COMPARISON OF SMOKING EFFECTS ON BLOOD CADMIUM LEVELS BETWEEN LUNG CANCER PATIENTS AND HEALTHY VOLUNTEERS (SMOKERS AND NON-SMOKERS) IN SYRIA

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Introduction: Cadmium (Cd) is heavy metal known to induce carcinogenesis by induction of reactive oxygen species resulting in alteration of DNA methylation or by over expression of the cellular proto-oncogene eEF1A2. The exact mechanism is currently not well established. Cigarette smoke inhalation is one of the routes for Cd exposure. The objective of this clinical study was to evaluate the effect of smoking on serum Cd levels and establish its relation to the development of lung cancer in the Syrian population.

Methods: Three groups were included in the study, comprising of lung cancer patients (n=40) with prior history of smoking, healthy smokers (n=23) and healthy non-smokers (n=23). The effect of smoking on serum Cd levels was compared between the groups by blood samples collection and analysis. Alpha-fetoprotein (AFP) levels were also measured for biomarker level estimation between them. Graphite furnace atomic absorption spectrometry and enzyme-linked immunosorbent assay were used to detect the Cd and AFP levels in serum, respectively. ANOVA test was used for comparison of serum Cd and AFP levels between them.

Results: The mean smoking history was 36.6 and 34.8 years in patients and healthy smokers respectively. Cd levels were highest in lung cancer patients (4.80±5.0 µg/L) followed by healthy smokers (2.06±1.04 µg/L) and least in the healthy non-smokers (0.87±0.43 µg/L). The difference in Cd levels between all the groups was statistically significant ($p<0.05$). Serum AFP levels in lung cancer patients (4.82±4.26 IU/mL) were marginally higher compared to healthy smokers (4.70±1.52 IU/mL) and healthy non-smokers (3.63±1.63 IU/mL) with no statistical significance.

Conclusions: High serum levels of Cd in smokers compared to non-smokers in this study further supports evidence that smoking is major source of Cd

exposure. And the significantly higher level of Cd in lung cancer patients with substantial smoking history is suggestive of its role in carcinogenesis.
Disclosure: All authors have declared no conflicts of interest.

75P
DEVELOPMENT OF A NATIONAL CLINICAL LUNG CANCER REGISTRY: NEED FOR COLLABORATIVE EFFORTS WITH ESMO/WHO

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Background: Data from lung cancer registry provides for health professionals/researchers and politics, detailed information on incidence, trend and survival statistics. Traditional cancer registries are population-based and seek to describe incidence, rates and trends of lung cancer within set populations. They supplement effectiveness of population-based registries in improving lung cancer patient care. Development of such databases is long awaited in India.
Objective: Our cancer NGO developed a primary plan in consultation with four divisional hospitals & the Health Ministry. We aim to establish a platform for the multi-clinician, multi-centric collation of clinical oncology datasets with lung cancer as a pilot disease entity. We plan to integrate this concept at major cancer institutes in Asia with expertise from ESMO/WHO. Proposal of intent has been approved at national level.
Methods: Here we relate our experience of an initiative aimed at establishing methodology, statistical analysis & control center for privacy, security and ownership concerns. We have developed national database but need participation of private cancer care institutes & naturopathy clinics. Total participants projected by 2013 are 46.
Conclusion: Our experience with this initiative over the past three years has shown that data can be collated centrally in a secure and private manner. Multicentre, multi-clinician collaboration is possible with Collaborative efforts with ESMO/WHO. But a major subject of concern is haphazard data/protocol maintenance by private entities. Most difficult data outsourcing was about survival statistics. A national lung cancer registry is a distant dream in resource-poor nations. But we have taken steps in a forward direction on this burning issue.
Disclosure: All authors have declared no conflicts of interest.

TRANSLATIONAL RESEARCH, BIOLOGY AND PATHOLOGY

76O
FISH FOR DETECTION OF PREDICTIVE ALK GENE REARRANGEMENTS IN HISTOLOGICAL NON-SMALL-CELL LUNG CARCINOMA SPECIMENS

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Background: The EML4-ALK fusion gene is an oncogenic driver mutation, which defines a small subgroup of lung adenocarcinomas (ADC) and predicts response to the dual ALK/MET inhibitor Crizotinib. The gold standard for detection of ALK gene rearrangements is fluorescence in situ hybridization (FISH). The goals of this study were 1) to test the performance of the recently FDA approved Vysis ALK Break Apart FISH Probe (Abbott Molecular, Inc.) on diagnostic non-small-cell lung carcinoma (NSCLC) specimens and 2) to test the prevalence of ALK-gene rearrangements in a western European population.
Materials and methods: 190 formalin fixed and paraffin embedded histological NSCLC specimens (101 small biopsies and 89 resection specimens), were retrospectively analysed by the new Vysis ALK Break Apart FISH Probe (Abbott Molecular, Inc.) according the guidelines of the manufacturer.
Results: FISH evaluation was successful in 165/190 NSCLC (87%), which included 117 ADC, 22 NSCLC favour ADC, 12 NSCLC not otherwise specified (NOS), 8 large cell carcinomas, 3 large cell neuroendocrine carcinomas, 2 adenosquamous carcinomas and one NSCLC favour squamous cell carcinoma. 22/190 NSCLC (11.6%) were not evaluable by FISH due to lack of adequate numbers of tumor cells and only 3/25 (1.6%) due to hybridization failure. This compares to a high 24% non-interpretable hybridizations in a previous series of 34 specimens that were analysed with a FISH assay not yet optimized for pulmonary biopsies. 5/165 NSCLC (3%), 3 ADC and 2 NSCLC NOS, were ALK FISH positive. These were lung cancers from 4 female and 1 male patients with a median age of 56 years (range 27-77).
Conclusion: The Vysis ALK Break Apart FISH Probe is well applicable to diagnostic NSCLC specimens with a highly improved hybridization success rate. The prevalence of ALK gene rearrangements of 3% in our unselected population of NSCLC is comparable to published data.
Disclosure: S. Savic: This study has been funded by Abbott Molecular, Inc, USA. L. Bubendorf: L.B. received speaker's honoraria from Abbott and Pfizer and research funds from Abbott, and attended advisory board meetings from Pfizer. All other authors have declared no conflicts of interest.

77O
LACE-BIO: VALIDATION OF THE PROGNOSTIC ROLE OF TUMOUR LYMPHOCYTIC INFILTRATION IN RESECTABLE NON-SMALL CELL LUNG CANCER

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Background: The benefit from platinum-based adjuvant chemotherapy (ACT) in non small cell lung cancer (NSCLC) was demonstrated in 4 randomized trials (IALT, JBR10, CALGB 9633 and ANITA). Following central review of 1587 NSCLC cases by one (EB: IALT) or two (EB, MT) specialized pathologists (WHO 2004 classification); there were 624 adenocarcinoma (ADC), 727 squamous cell carcinoma (SCC) and other 236 NSCLC (Other). Lymphocytic infiltration (intense infiltration: yes vs. no) was studied concurrently. Lymphocytic infiltration was a borderline favourable prognostic factor on overall survival (OS) in IALT (n=783 patients): hazard ratio (HR) 0.67, 95% confidence interval [0.46–0.98], p=0.04. (Brambilla; Lung Cancer 2005; 49 (Suppl. 2): S44). Therefore the LACE-Bio group performed a validation of these results on ANITA, JBR10 and CALGB trials.
Methods: Since there was no evidence of a different prognostic role in the chemotherapy and control arms in IALT (test of interaction between lymphocytic infiltration and treatment arm p = 0.85 on OS), the prognostic values were studied for validation in all patients with adjustment for treatment arm. Prognostic analyses were performed with Cox models stratified by trials and adjusted for treatment, sex, age, performance status, type of surgery, stage and histology.
Results: Out of 804 patients, 763 were evaluable. Intense lymphocytic infiltration was observed in 6% of the validation patients, ranging between 4 and 7% according to the trial, as compared to 11% in IALT. It was associated with histology: 10% in SCC and ~4% in ADC and other NSCLC (p=0.001). No association was found with the other covariates. Intense lymphocytic infiltration was correlated with longer overall and disease-free survival (HR=0.45 [0.24–0.85], p=0.01 and HR=0.44 [0.24-0.78], p=0005) without heterogeneity among trials.
Conclusion: Intense lymphocytic infiltration, found in only a minority of tumours, was validated as a favourable prognostic factor for survival in resectable NSCLC.
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Disclosure: All authors have declared no conflicts of interest.

78O
DRIVER GENE ALTERATIONS IN CHINESE NON-SMALL CELL LUNG CANCER PATIENTS

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Background: We aimed to define subgroups of patients with candidate driver genes in patients with non-small cell lung cancer.

Methods: Patients with primary lung cancer who underwent clinical genetic tests at Guangdong General Hospital were enrolled. Driver genes were detected by sequencing, high-resolution melt analysis, qPCR, or multiple PCR and RACE methods.

Results: 524 patients were enrolled in this study, and the differences in driver gene alterations among subgroups were analyzed based on histology and smoking status. In a subgroup of non-smokers with adenocarcinoma, EGFR was the most frequently altered gene, with a mutation rate of 49.8%, followed by EML4-ALK (9.3%), PTEN (9.1%), PIK3CA (5.2%), c-Met (4.8%), KRAS (4.5%), and BRAF (1.9%). The three most frequently altered genes in a subgroup of smokers with adenocarcinoma were EGFR (22.0%), KRAS (12.0%), and EML4-ALK (4.5%). We only found EGFR (8.0 %), c-Met (2.8%), and PIK3CA (2.6%) alterations in the non-smoker with squamous cell carcinoma (SCC) subgroup. PTEN (16.1%), PIK3CA (7.2%), and EML4-ALK (6.5%) were the three most frequently enriched genes in smokers with SCC. DDR2 and FGFR2 only presented in smokers with SCC (4.4% and 2.2%, respectively). Among these four subgroups, the differences in EGFR, KRAS, and PTEN mutations were statistically significant.

Conclusions: The distinct features of driver gene alterations in different subgroups based on histology and smoking status were helpful in defining patients for future clinical trials that target these genes.

Disclosure: All authors have declared no conflicts of interest.

79O_PR
RIBONUCLEOTIDE REDUCTASE SUBUNIT 2 (RRM2) PREDICTS SHORTER SURVIVAL IN RESECTED STAGE I-III NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS

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Background: Biomarkers can help in identifying patients (pts) with early-stage NSCLC with high risk of relapse and bad prognosis. The aim of this study was to investigate the relationship between the levels of expression of 7 biomarkers, clinicopathological characteristics and their prognostic significance.

Methods: Tumor tissue from 82 radically resected stage I-III NSCLC pts were consecutively collected to investigate the mRNA expression and protein levels of the following biomarkers: excision repair cross-complementation group 1 (ERCC1), breast cancer 1 (BRCA1), ribonucleotide reductase subunit 1 (RRM1), RRM2, p53R2, thymidylate synthase (TS) and class III beta-tubulin (β-Tub-III) using quantitative reverse transcriptase real-time PCR (qRT-PCR) and immunohistochemistry (IHC) with tissue microarray technique.

Results: In univariate analysis, p53R2 expression was significantly higher in adenocarcinoma (ADK) compared to squamous cell carcinoma (SSC) samples (p=0.002) and in stage I compared to stage II-III (p≤0.001). ERCC1 expression was significantly higher in female compared to male (p=0.03) and β-Tub-III expression was significantly higher in ADK than in SSC (p=0.03). Pts with lower RRM2 expression survived longer than pts with higher RRM2 expression (p=0.069). The multivariate analysis confirmed RRM2 as an independent prognostic marker of shorter survival (p= 0.031). The comparison of survival curves with qRT-PCR and IHC showed that there was similar results with a trend towards longer survival among ERCC1 negative pts, BRCA1 negative, p53R2 positive and among pts with low levels of RRM1 and RRM2 although the difference was not statistically significant in both methods. qRT-PCR and IHC have shown that β-Tub-III and TS had no significant impact on survival.

Conclusions: This is the first study that identifies RRM2 expression as a negative prognostic factor in resected stage I-III NSCLC. Moreover, we have demonstrated the different expression of p53R2 and β-Tub-III in ADK compared to SSC and higher expression of p53R2 in stage I compared to stage II-III pts.

Disclosure: All authors have declared no conflicts of interest.

80O_PR
SERUM PROTEOMIC CLASSIFIER FOR PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) TREATED WITH ERLOTINIB AND BEVACIZUMAB IN FIRST LINE: POOLED ANALYSIS OF PHASE II TRIALS SAKK19/05 AND NTR528

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Background: VeriStrat® proteomic classifier is a serum test utilizing mass spectrometry which reports two labels: VeriStrat Good (VSG) or VeriStrat Poor (VSP). Published data show VSG pts to perform better than VSP pts upon treatment with EGFR TKIs. We retrospectively explored VeriStrat's ability to separate pts with advanced non-squamous NSCLC treated in first-line with bevacizumab and erlotinib (BE) into better and worse progression-free survival (PFS) and overall survival (OS) groups.

Methods: Individual data and archived serum samples from 117 pts previously enrolled in 2 European phase II trials of first-line BE (NCT00354549 and NTR528) were analyzed. VeriStrat was performed centrally by Biodesix (USA). PFS and OS were evaluated using the Kaplan-Meier method; groups were compared using the log-rank test. The hazard ratio (HR) was assessed using Cox proportional hazards (CPH) models. For the multivariate analyses, both endpoints were analyzed using CPH and stepwise selection to check the importance of selected factors.

Results: Veristrat analysis performed in 117 pts sera from both trials classified 87 (74%) as VSG, 27 (23%) as VSP and 3 (3%) as "indeterminate". VSG and VSP demonstrated a statistically significant difference in OS ($p = 0.0027$, HR=0.480, 95% confidence interval (CI): 0.294–0.784) but significance for PFS was not reached ($p = 0.2632$, HR = 0.768, 95% CI: 0.482–1.223). PFS and OS were also assessed using multivariate analyses on the combined VSG and VSP pts. Stepwise selection indicated the following associations: smoking status ($p < 0.0001$) and histology (adenocarcinoma versus large cell carcinoma and not otherwise specified) ($p < 0.0001$) with PFS, VeriStrat classification ($p = 0.0042$) and smoking status ($p < 0.0001$) with OS.

Conclusions: These results support the notion that VeriStrat may be useful for clinical decision-making, representing a prognostic and potentially a predictive biomarker for treatment with EGFR TKIs. This predictive value of VeriStrat will be tested in a prospective clinical trial in advanced squamous cell lung carcinoma, sponsored by the European Thoracic Oncology Platform (ETOP).

Disclosure: O. Gautschi, A. Dingemans and S. Peters: honoraria from Roche for advisory boards. H. Roder: employment by Biodesix. All other authors have declared no conflicts of interest.

81O
UPFRONT GENOMIC TESTING FOR PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC) RECEIVING FIRST-LINE PLATINUM-BASED REGIMEN: PRELIMINARY RESULT OF THE MSN STUDY

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Background: Recent advances in lung cancer have identified potential driver mutations that may be targeted. To identify new predictors of response as well as novel targets for therapy, we have initiated a comprehensive large-scale re-sequencing analysis of genes potentially mutated in NSCLC.

Methods: Genomic DNA was extracted prospectively from untreated advanced NSCLCs. All tumors were obtained on IRB-approved protocols and after patients' consent (MSN trial "Melanoma –Small-cell lung cancer – Non-small cell lung cancer"). Pathology specimens were macrodissected in order to obtain more than 30% of tumor cells and, after DNA extraction, 96 selected exons from 30 genes were analyzed by Sanger sequencing. ALK rearrangements were detected by fluorescence in-situ hybridization. All results were discussed monthly in a molecular thoracic multidisciplinary staff. Second or third lines of treatment were adapted to mutation profiling.

Results: Thus far (between 09/01/2010 and 06/01/2011), 82 tumors have been analyzed for AKT, ALK, BRAF, EGFR, ERBB2, FGFR, GNAQ, HRAS, KIT, KRAS, MAP2K, MET, NOTCH1, PDGFRA, PI3KCA, PTEN, RET, STK11, TP53, and VHL mutations. The median age was 60 years (range 26-76), 29 (35%) were female, 58 (70%) had adenocarcinoma, 72 (67%) were former/current smokers. Nine patients had incomplete genomic analysis due mostly to insufficient tumor cells in the specimen or poor quality DNA. Median tumor cells ratio was 50%. Mutations were identified in 43/82 (52%) patients (EGFR: 9; KRAS: 10; STK 11: 8; BRAF: 4; MET: 2; PTEN: 2; ALK:2, NRAS: 1; ERBB2: 1; PIK3CA: 1…) of whom 11 had concurrent mutations. EGFR and KRAS mutations were mutually exclusive. No mutations were identified among 5 never smokers analyzed. The median time to complete testing for this initial phase was 30 days. Half of patients with genomic alterations were treated with molecularly targeted therapy based on their genetic alteration.

Conclusions: Mutational profiling of NSCLC is feasible, can distinguish relevant molecular subsets of lung cancer, and may present an impact on treatment at our cancer institute. Furthers sequencing are in progress and updated results will be presented in April 2012.

Disclosure: All authors have declared no conflicts of interest.

82PD_PR
CANCER-ASSOCIATED ONCOGENIC BARD1 ISOFORMS: FROM BIOMARKER EXPRESSION STUDIES TO DEVELOPMENT OF A BLOOD TEST FOR EARLY DETECTION OF LUNG CANCER

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The BARD1 protein binds to, stabilizes, and enhances the tumor suppressor functions of BRCA1. Highly upregulated expression of aberrant isoforms of BARD1, derived from differential splicing, was correlated with poor prognostic factors in breast and ovarian cancer (1, 2) and decreased patient survival in lung cancer (3). Previous and ongoing studies have shown that BARD1 isoforms are tumor drivers and act antagonistically to the E3 ubiquitin ligase functions of the BARD1-BRCA1 heterodimer. In particular, isoform BARD1β is promoting cell proliferation by stabilizing the Aurora kinases (4, 5). Since BARD1β and BARD1ϖ are specifically upregulated and correlated with poor prognosis in lung cancer (3) they might act as suitable biomarkers of lung cancer progression. To develop a blood test based on BARD1 isoforms, we performed ELISA tests with antibodies against different regions of BARD1 for the detection of BARD1 isoforms in the blood of lung cancer patients. We also generated a peptide library representing 40 epitopes mimicking BARD1 isoforms, for the detection of autoimmune antibodies recognizing epitopes expressed by BARD1 isoforms. BARD1 protein isoforms could be detected by ELISA in various serum samples, however, using peptides for capturing autoimmune antibodies directed against BARD1 isoforms seemed more promising. Serum samples from 60 non-small cell lung cancer (NSCLC) patients, obtained at time of diagnosis, and 40 control sera from phenotypically healthy volunteers, should significant differences between NSCLC cancer patients and controls. Applying a combination of seven peptides, lung cancer was detected with 87% sensitivity and 68% specificity. Thus, antibodies against BARD1 isoforms are telltales of lung cancer and their detection can be further developed towards a blood test. Experiments including larger patients and control group numbers, sera from patients with different types of lung cancer, as well as the comparison of this BARD1 isoform test with the standard test for lung cancer detection (CT scan), are currently ongoing, and should lead to optimized test conditions and a definition of the target patient set.

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Disclosure: I. Irminger-Finger: Author of patent submitted, scientific advisory of biotech company.

83PD_PR
DNA METHYLATION PROFILING DEFINES CLINICALLY RELEVANT BIOLOGICAL SUBSETS OF NON-SMALL CELL LUNG CANCER

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Purpose: NSCLCs comprise multiple distinct biological groups with different prognoses. Patients with epithelial-like (EL) tumors have a better prognosis and exhibit greater sensitivity to inhibitors of the EGFR pathway than patients with mesenchymal-like (ML) tumors. Here we test the hypothesis that EL NSCLCs can be distinguished from ML NSCLCs on the basis of global DNA methylation patterns.

Methods: To determine whether phenotypic subsets of NSCLC can be defined based on their DNA methylation patterns, we combined microfluidics-based gene expression analysis and genome-wide methylation profiling. We derived robust classifiers for both gene expression and methylation in cell lines and tested these classifiers in surgically resected NSCLC tumors. We validate our approach using quantitative RT-PCR and methylation specific PCR in FFPE biopsies.

Results: We show that patterns of methylation divide NSCLCs into EL and ML subsets as defined by gene expression and that these signatures are similarly correlated in NSCLC cell lines and tumors. We identify multiple DMRs, including one in ERBB2 and one in ZEB2, whose methylation status is strongly associated with an epithelial phenotype in NSCLC cell lines, surgically resected tumors, and FFPE biopsies from NSCLC patients who went on to fail front-line chemotherapy.

Conclusions: Our data demonstrate that patterns of DNA methylation can divide non-small lung cancers into two phenotypically distinct subtypes of

tumors and provide proof of principle that differences in DNA methylation can be used as a platform for predictive biomarker discovery and development.
Disclosure: D.S. Shames, K. Walter, T. Holcomb, L.C. Amler, G. Hampton, R. Yauch, R. Bourgon, P. Du are all employees of Genentech.

84PD
MAINTENANCE OF DNA REPAIR IN PREINVASIVE SQUAMOUS BRONCHIAL LESIONS

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Background: Preinvasive lesions occur frequently in squamous cell carcinoma (SCC) as the result of a stepwise accumulation of genetic and molecular alterations driving their progression at multicentric sites in the cancerization field. We have already shown that P53, cyclin D1 and E, Bcl2 and VEGF overexpression as well as telomere shortening are characteristics of these preinvasive states and progress from low grade to high grade lesions. We have also demonstrated a progressive escape from G2 cell cycle checkpoints (ATM, CHK2 phosphorylation) increasing the genetic instability.
Objective: We assessed the level of expression of DNA repair genes of the NER pathway (ERCC1, BRCA1, RRM1) in order to evaluate the capacity of DNA repair following DNA injury, toxics and drugs.
Methods: Immunohistochemical (IH) scores of ERCC1, BRCA1 and RRM1 were assessed in 28 patients with several preinvasive lesions in the bronchial tree in the vicinity of an invasive SCC. We examined 22 metaplasia, mild dysplasia and moderate dysplasia, 21 severe dysplasia and carcinoma in situ (CIS) and corresponding invasive SCC.
Results: IH scores were calculated by multiplying intensity (1-3) by percentage of positive cells (0-300). The cut-off of high level versus low level was determined by the median score of these expressions on the normal bronchial epithelium: 140, 100, 105, for ERCC1, BRCA1 and RRM1, respectively. The mean scores of metaplasia (190, 130, 133), mild dysplasia (220, 150, 150), moderate dysplasia (250, 180, 180), severe dysplasia (250, 200, 180) and their corresponding CIS (250, 200, 200) were observed for ERCC1, BRCA1 and RRM1, respectively, although the invasive SCC mean scores were 160, 170, 170, respectively. At the two ends of the spectrum, metaplasia/mild dysplasia and invasive carcinoma, a few lesions were of low score: 30%, 13%, 20% of metaplasia; 5%, 7%, 14% of mild dysplasia, 31%, 0%, 5% of SCC for ERCC1, BRCA1 and RRM1, respectively, whereas moderate, severe dysplasia and CIS displayed high level compared with normal bronchi.
Conclusion: There was a "cloche" phenomenon in the expression of DNA repair genes and overall a maintenance of DNA repair along the spectrum of preinvasive lesions. We conclude that genetic instability is not impaired through DNA repair gene loss in preinvasive squamous lesions.
Disclosure: All authors have declared no conflicts of interest.

85PD
A NEW MEDICAL DEVICE FOR IN-VIVO ISOLATION OF CIRCULATING TUMOR CELLS IN NON SMALL CELL LUNG CANCER (NSCLC) PATIENTS

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Background: In NSCLC, the number of circulating tumor cells (CTCs) is discussed as a prognostic and stratification biomarker, and could also judge the treatment efficacy. Currently, CTCs are isolated in vitro from small limited volumes of blood samples. Furthermore, results for NSCLC are scarce. The aim of the study was to assess a functionalized and structured medical wire (FSMW) for in vivo isolation of CTCs directly from the blood of NSCLC patients.
Material and methods: The device was inserted in a cubital vein through a standard iv cannula for 30 minutes. The interaction of target CTCs with the FSMW was mediated by an antibody directed against the epithelial cell adhesion molecule (EpCAM). To confirm the CTCs binding to the wire, the immunohistochemical staining against EpCAM as well as CD45 for negative cell selection was performed. There were 72 applications of the wire in 48 NSCLC patients staged from IA to IIIB and 12 non-cancer patients. Enumeration data from 34 NSCLC patients with 46 applications and 8 non-cancer patients were assessed.
Results: The device was well tolerated in all 72 applications without side effects. We obtained in vivo isolation of CTCs in 94 % NSCLC patients. The sensitivity was similar for early and late stage NSCLC patients. The median (range) of isolated EpCAM-positive CTCs was 13 (0-300). In the non-cancer patients, no CTCs were detected.
Conclusions: This proof of concept study may have important clinical implications, as the implementation of the device into clinical practice may improve early detection, prognosis and therapy monitoring of NSCLC patients.
Disclosure: Ms. Herold is a study coordinator for GILUPI GmbH. Dr. Morgenthaler is a CMO for GILUPI GmbH. Dr. Luecke is a CEO for GILUPI GmbH. All other authors have declared no conflicts of interest.

86PD
NEW SYNERGISM BETWEEN AZACITIDINE AND DASATINIB IN LUNG CANCER CELL TREATMENT

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Src is frequently overexpressed in human lung cancers and regulates the growth and survival of lung cancer cells in vitro. Nevertheless, clinical trials failed to demonstrate significant antitumor activity by Src inhibition alone in patients with advanced, pretreated lung cancer so far (reviewed in: Rothschild, Clin Lung Cancer 2010). We recently found that exogenous miR-29b expression sensitized lung cancer cells to to Src kinase inhibitors by targeting ID1 (Rothschild, Oncogene 2012). Because miR-29b is known to target DNA methyltransferase (DNMT), we speculated that pharmacological inhibition of DNMT may mimic the effects seen by miR-29b expression in response to Src tyrosine kinase inhibitors. To test our hypothesis, we studied the differential effect of Src kinase inhibiton (saracatinib and dasatinib) and DNMT inhibition (decitabine and azacitidine) on ID1 mRNA expression by RTqPCR in human lung cancer cell lines, and found that the reduction of ID1 mRNA was greater with combined Src and DNMT inhibition compared with inhibition of Src or DNMT alone. Then, we examined the effect of the novel combination on cell migration using scratch assays, and found that azacitidine at clinically relevant concentrations (100-1'000 nM) significantly increased the effect of dasatinib, compared with dasatinib alone. Moreover, the combination of azacitidine and dasatinib induced cell death as measured by alamar blue assay and clonogenic assay, whereas dasatinib was merely cytostatic as a single agent. These preliminary results support our hypothesis and justify further preclinical work on a new, rationally designed drug combination for the treatement of lung cancer.
Disclosure: All authors have declared no conflicts of interest.

87PD
THE ALK/MET INHIBITOR CRIZOTINIB INHIBITS EXPRESSION OF THE STEM CELL GENE ID1 AND MIGRATION OF MET-POSITIVE LUNG CANCER CELLS INDEPENDENTLY OF ALK-FUSION

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Background: Anaplastic lymphoma kinase (ALK) fusion-type oncoproteins are found in a subgroup of non-small cell lung cancer (NSCLC) (Soda 2007).The ALK inhibitor crizotinib (Xalkori®) is highly active in patients with ALK fusion-positive tumors (Shaw 2010). Crizotinib also targets MET and its downstream target SRC (Zillhardt 2010). We previously identified the inhibitor of differentiation 1 (ID1) as an important downstream effector of SRC (Gautschi 2008). ID1 and SRC are frequently expressed in NSCLC (Rothschild 2011). In the current study, we explored the effects of crizotinib on ID1 expression and cell migration in NSCLC cell lines.

Methods: Two ALK fusion-negative (A549, H460) and two ALK fusion-positive lung cancer cell lines (H2228, H3122) were incubated with crizotinib, the MET inhibitor PHA, or the SRC inhibitor saracatinib. ID1 mRNA levels were measured by quantitative real-time RT-PCR. Western blotting was performed for p-ALK, ALK, p-MET, MET, p-SRC, SRC and ID1. Migration assays were performed using A549 cells. Lentiviral vectors expressing shMET were used to stably knock-down MET expression.

Results: In the ALK-positive cell lines H2228 and H3122, crizotinib decreased ID1 mRNA, p-MET, and ID1 protein levels in a dose-dependent manner. In H2228 p-SRC levels were reduced upon crizotinib. PHA and saracatinib led to similar effects on ID1 expression as crizotinib. Expression of p-MET was detected in A549 cells, but not in H460 cells. A decrease of p-MET, p-SRC and ID1 upon crizotinib was detected only in A549 cells. Crizotinib as well as stable MET knock-down decreased ID1 and induced the level of p-SRC in H3122 cells. Stable MET knock-down decreased ID1 expression and the migratory potential of A549 cells in a similar way than crizotinib.

Conclusions: These preliminary results indicate that the effects of crizotinib on ID1 expression and cancer cell migration are associated with the presence of activated MET, rather than ALK fusion. Ongoing studies will determine whether crizotinib has clinical activity in ALK fusion-negative tumors that contain MET activation, and if compensatory reactivation of SRC mediates resistance to MET inhibitors.

Disclosure: S.I. Rothschild, M. Gugger and O. Gautschi: Honorary for advisory boards from Pfizer. All other authors have declared no conflicts of interest.

88PD
PROGNOSTIC IMPACT OF HYPOXIA-INDUCIBLE MICRORNA-210 IN PATIENTS WITH LUNG ADENOCARCINOMA

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Purpose: Hypoxia-inducible factor 1α (HIF-1α) is overexpressed in many tumors, including in non-small cell lung cancer (NSCLC). The importance of HIF-1α is based on its association with patient mortality. A study published in 2007 revealed that miR-210 is the most upregulated microRNA in hypoxic tissues, with roles in various functions such as apoptosis and tumor growth. Furthermore, miR-210 is regulated by HIF-1α. Since HIF-1α is associated with poor prognosis in NSCLC, we investigated miR-210 expression in vitro and in vivo to make correlations with NSCLC clinical characteristics, and thus investigate its potential as a prognostic factor.

Patients and methods: We used qRT-PCR to examine two NSCLC cell lines and 80 NSCLC tissue samples (62 adenocarcinomas, 18 squamous cell carcinomas) paired with 30 matched normal adjacent tissue samples. HIF-1α mRNA and miR-210 miRNA expression in NSCLC samples was analyzed to clarify the prognostic impacts in NSCLC. Furthermore, the effect of hypoxic induction of HIF-1α and miR-210 expression was compared between an adenocarcinoma cell line (A549) and a squamous cell carcinoma cell line (RERF-LC-AI).

Results: Both HIF-1α and miR-210 expression showed an inverse correlation with disease-free survival of NSCLC patients (p=0.007, p=0.001, respectively). Multivariate Cox analysis indicated miR-210 expression was an independent prognostic factor for disease-free survival (p=0.012). We further analyzed the prognostic significance of miR-210 expression by histological subtype and found it correlated with lymph node metastasis, late disease stages, and poor prognosis in patients with adenocarcinoma (p=0.034, p=0.019, p=0.021 respectively), whereas no relationship was found in patients with squamous cell carcinoma. In vitro, hypoxia induced much higher HIF-1α and miR-210 expression in adenocarcinoma cells than squamous cell carcinoma cells (p<0.001).

Conclusions: We determined that miR-210 is overexpressed in node-positive adenocarcinoma, and it is associated with poor clinical characteristics in adenocarcinoma, but not in squamous cell carcinoma. Our study provides the first evidence for the clinical impact of miR-210 in lung cancer and its importance as a prognostic biomarker.

Disclosure: All authors have declared no conflicts of interest.

89PD
ERCC1 AND BETA-TUBULIN III IN ADVANCED NSCLC PATIENTS TREATED WITH CISPLATIN-VINORELBINE

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Background: Platinum-containing chemotherapy remains as the standard treatment in advanced/metastatic non-small-cell lung cancer (NSCLC) patients (pts). Increased ERCC1 expression has been associated with resistance to platinum-based therapies, and beta-tubulin III (TUBB3) was shown to be involved in resistance to antimicrotubule agents. Here we studied these tumor markers in NSCLC pts treated with cisplatin-vinorelbine and correlated their expression with survival.

Methods: It is a retrospective study on pts diagnosed with advanced/metastatic NSCLC (TNM 6th ed), consecutively identified. All pts were treated with cisplatin 80 mg/m^2 d1 and vinorelbine 30 mg/m^2 d1, d8, d15, every 21 days, 4–6 cycles, in our Institution, between Sep/2002 and Oct/2008. ERCC1 (clone 8F1) and TUBB3 (clone TUJ1) expression were evaluated by immunohistochemistry, and biomarker expression was considered as high when more than 10% of tumor cells presented moderate to strong staining, nuclear or cytoplasmic, respectively. Overall survival (OS) was estimated by the Kaplan-Meier method and curves were compared with log-rank.

Results: 142 pts were studied; median age 63 y (34-87), 67% male and 86% current smokers. Adenocarcinoma (ADC, 58 pts, 43%), followed by squamous cell carcinoma (SCC, 50 pts, 37%) were the most frequent histologic types. 100 pts (71%) were staged as IV and 34 pts (24%) as IIIB. The median number of cycles was 4 (1-7). Median OS was 7.9 mo. Overall, high ERCC1 expression was observed in 61/104 pts (59%) and high TUBB3 expression in 55/109 pts (51%). According to histologic types, low ERCC1 expression was observed in 7/42 SCC pts (16%) and in 35/63 ADC pts (56%) (p=0.0004). Among ADC pts, 1-y OS rate was 28% and 47% in pts which tumors presented with high and low ERCC1 expression, respectively (HR 1.57, 95% CI

0.9-2.7, p=0.08). TUBB3 expression neither presented any difference between SCC and ADC types, nor any prognostic impact in terms of OS.
Conclusions: Low ERCC1 expression was observed more frequently in pts with advanced lung ADC and it was a favorable prognostic factor in ADC pts treated with cisplatin-vinorelbine.
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Disclosure: All authors have declared no conflicts of interest.

90PD
KI67 AS A PROGNOSTIC MARKER IN MALIGNANT PLEURAL MESOTHELIOMA

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Purpose: Malignant pleural mesothelioma (MPM) is an aggressive malignancy with increasing incidence. Despite the various immunohistochemistry markers used in mesothelioma pathology, there is only one pathological prognosticator accepted, namely the histological subtype. Therefore, we have investigated the prognostic value of the Ki76 mitotic index in MPM.
Patients and methods: The clinical relevance of the proliferation marker Ki67 was first studied in an Austrian cohort (AUT) of paraffin-embedded tissue samples from 55 MPM patients. Next, we confirmed these findings in an independent Hungarian cohort (HUN) of 42 patients. The results were documented as the percentage of tumor cells with nuclear Ki67 per high power field and correlated with the clinical outcome of the patients.
Results: Median percentage of Ki67 positive tumor cells was 10% for all patients, 10% for the AUT and 11% for the HUN cohort. Patients with low Ki67 index (≤ 10%) had a significantly longer overall survival than those with high Ki76 indices (AUT: hazard ratio [HR] 2.49, 95% confidence interval [CI] 1.30–4.79, p<0.01; HUN: HR 2.54, CI 1.26–5.13, p<0.01). In the multivariate analyses of the Austrian cohort (n=54) Ki67 index retained the prognostic power independent of gender, age, treatment, stage and histology. Treatment (HR 4.02, CI 1.82–8.90, p<0.01) and Ki67 index (HR 2.19, CI 1.07-4.47, p=0.03) were the remaining independent significant prognosticators in the multivariate Cox regression model. In this analysis biphasic histology showed a tendency for worse prognosis when compared to the epitheloid subtype (HR 1.96, CI 0.94-4.07, p=0.07).
Conclusion: This study reveals Ki67 index as an independent, reproducible prognostic factor in malignant pleural mesothelioma and warrants further prospective investigation in MPM patients.
Disclosure: All authors have declared no conflicts of interest.

91PD
ANALYTICAL PERFORMANCE AND WORKFLOW COMPARISON STUDY OF THREE METHODS FOR DETECTING EGFR MUTATIONS IN FORMALIN-FIXED PARAFFIN-EMBEDDED TISSUE (FFPET) SPECIMENS OF NON-SMALL CELL LUNG CANCER (NSCLC)

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Anti-EGFR tyrosine kinase inhibitors are indicated as first line therapy of metastatic EGFR–mutant NSCLC, so it is critical to have a robust, accurate and reproducible EGFR test method with rapid time to results. We conducted a 2-site method comparison study of 2 CE-IVD marked assays - 1) Allele - specific PCR-based cobas® EGFR Mutation Test, which detects 41 mutations in exons 18, 19, 20, and 21, and 2) ARMS-Scorpion PCR-based theraScreen® EGFR29 Mutation Kit, which detects 29 mutations in the same 4 exons - and 2x bi-directional Sanger sequencing. We tested 125 FFPET specimens of NSCLC with all 3 methods in a blinded manner; the cobas® test was performed at both sites. Positive (PPA) and negative (NPA) percent agreements were determined for the cobas® test vs. each of the other 2 methods. Specimens with discrepant results were tested using quantitative massively parallel pyrosequencing (454 GS-Titanium). Invalid rates, turnaround times and repeatability were assessed. PPA between cobas® and Sanger was 93.3%; NPA was 76.7%. Overall there were 13 discrepant results. Of 7 specimens that were mutation-positive by cobas® and negative by Sanger, 454 confirmed an exon 19 deletion in 3 cases and an exon 21 L858R mutation in 4 cases. Amongst the 6 discrepant specimens that were mutation-negative by cobas®and positive by Sanger, 5 cases were rare L861Q mutations, which the cobas test is not designed to detect. In one case Sanger detected an insertion in exon 20 and was called wild-type by 454. PPA between cobas® and therascreen® was 95.8% and NPA was 100%. There were 4 discrepant results, 3 of which represented L861Q mutations. Invalid rates were 0.4% for cobas®, 0% for therascreen® and 3.2% for Sanger. Approximate turnaround times were 1 day for cobas® and 7 days for Sanger for 24 samples, and 1 day for therascreen® for 10 samples. Repeatability of the cobas® test between the 2 sites was 99.2%. The invalid rates for the cobas® test and therascreen® were lower than Sanger sequencing. The cobas® and therascreen® assays showed a high degree of concordance, and both were more sensitive for the detection of exon 19 deletions and L858R mutations than Sanger. The cobas® test was highly reproducible between the two testing sites, had the greatest throughput and the shortest estimated turnaround time, and was the only assay with automated results reporting.
Disclosure: F. Lopez-Rios, B. Angulo, B. Gomez, D. Mair, R. Martinez, E. Conde, D. Gonzales de Castro: This study was funded by Roche Molecular Systems. Felice Shieh is an independent consultant for Roche Molecular Systems. Julie Tsai and Jeffrey Lawrence are full time employees at Roche Molecular Systems.

92PD
FEASIBILITY OF EPIDERMAL GROWTH FACTOR RECEPTOR MUTATION TESTING IN CYTOLOGY SAMPLES

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Background: Cytology samples obtained by endobronchial ultrasound (EBUS) fine needle aspiration (FNA), transoesophageal ultrasound (EUS) FNA, transthoracic (TT) CT guided FNA and bronchial washings are increasingly used to diagnose non-small cell lung cancer (NSCLC). Testing for the activating Epidermal Growth Factor Receptor (EGFR) mutations in these cytology samples can be challenging and is increasingly needed due to the lack of other adequate diagnostic material.
Aim: To compare the yield of testing for activating EGFR mutations in cytology samples versus histology samples in a consecutive series of patients (pts) with NSCLC diagnosed at Ghent University Hospital.
Methods: Medical files of pts with NSCLC in between December 2009 and December 2011 and tested for an activating EGFR mutation were reviewed. EGFR mutation testing was done with TheraScreen®: EGFR29 Mutation Kit – PCR based. Differences were evaluated using the Fisher's exact test.
Results: There were 99 patients tested for EGFR mutation: 69 (70%) had histology samples and 30 (30%) had cytology samples. Histology samples were surgical resection specimens (n=50) and biopsy samples (n=19). Cytology samples were EUS (n=2), EBUS (n=25), TT (n=1) and bronchial washing (n=2). In histology samples mutation test was not feasible in 3/69 (4%). In cytology samples mutation testing was not feasible in 8/30 (27%; p=0,003). In the surgical resection specimens only 1/50 (2%) samples could not be evaluated while this was 2/19 (11%; p=0,18) in the biopsy samples. The prevalence

of EGFR mutation was 13/66 (20%) in the histology specimens and 4/22 (18%; N.S.) in the cytology samples.
Conclusion: EGFR mutation testing in cytology specimens is feasible especially in EUS/EBUS FNA samples, but is associated with a higher rate of non-evaluable samples compared to histology specimens.

	Histology (n=69)				Cytology (***) (n= 30)	
	Resection Specimen (*) (n=50)		Biopsy (**) (n=19)			
	n	%	n	%	n	%
WT	37	74	16	84	18	60
Mutations	12	24	1	5	4	13
Non Evaluable	1	2	2	11	8	27

*Every specimen obtained by a surgical procedure ** Endobronchial biopsy or core biopsy *** EUS / EBUS / Transthoracic FNA (TT) / endobronchial washing

Disclosure: All authors have declared no conflicts of interest.

93PD
CTL ANTIGEN 4 (CTLA-4) AND KI67 AS PROGNOSTIC FACTORS IN RESECTED STAGE I-III NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS

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Background: CTLA-4 is a negative regulator of T-cell activation, the administration of anti-CTLA-4 monoclonal antibody therapy can reduce efficiently the migration and proliferation of hematologic and solid tumours. We previously reported that CTLA-4 is expressed by NSCLC cell lines providing evidence of its involvement in apoptosis induction upon engagement with soluble CTLA-4 ligands (Contardi E, Int J Cancer 2005). The aim of this study was to investigate the relationship between expression of CTLA-4 and other two markers functionally related to CTLA-4, β-catenin and Ki67, with clinicopathologic characteristics and overall survival (OS) to explore their prognostic significance.
Methods: We evaluated CTLA-4, β-catenin, Ki67 protein expression using specimens from 81 patients (pts) resected between 7/2005-3/2007 with stage I-III NSCLC. The median H-score, calculated using the formula (1 + I) x PC where I is the staining intensity and PC the percentage of tumor cells that stained at each intensity, of 20 and 160 was used as a threshold to define CTLA-4 and β-catenin overexpressing tumours respectively while a cut-off value of 15% was assumed to define Ki67 overexpression.
Results: CTLA-4 expression was positive in 47% of tumours, similar in males and females (47% vs 47%) and former-never or current smokers (46% vs 47%) while was significantly higher in non-squamous than in squamous carcinoma (53% vs 36%). Similar results were found for Ki67. We also assessed the association between CTLA-4 expression and Ki67: 51.1% of patients with Ki67≤15 showed CTLA-4 overexpression compared to 38.7% of patients with Ki67>15. Patients with lower Ki67 expression and higher CTLA-4 expression survived longer than those with a higher Ki67 expression (p= 0.069) and lower CTLA-4 expression (p=0.078). No significant association was seen between β-catenin and CTLA-4 and between β-catenin and survival.
Conclusion: In conclusion, we found that patients with higher expression of CTLA-4 and lower expression of Ki67 had better OS than patient with opposite result. This retrospective study represents the first investigation of CTLA-4 expression and Ki67 expression as possible prognostic factors for OS.
Disclosure: All authors have declared no conflicts of interest.

94P
SYSTEMATIC DETERMINATION OF EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATION STATUS IN PATIENTS WITH NEWLY NON SMALL CELL LUNG CANCER (NSCLS): ONE YEAR EXPERIENCE OF A SINGLE CENTER

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Background: Activating mutations in the epidermal growth factor receptor gene (EGFR) are associated with response to the tyrosine kinase inhibitors. Detection of EGFR mutations has become an important issue for therapeutic decision-making in non–small cell lung cancer. We implemented in our center a systematic determination of EGFR.
Methods: We have selected all patients with newly diagnosed non small cell lung cancer non squamous between January 2011 to December 2011. The objective was to evaluate the EGFR mutation status in a population of Hospital 12 de Octubre, Madrid, Spain. The TheraScreen EGFR 29 Mutation Test Kit (kit for detection of specific mutations, insertions, and deletions in the EGFR gene using real-time PCR) was used.
Results: Two hundred and fourteen patients were included, 74 (34.58%) women and 140 (65.42%) men; 206 (97.07%) non squamous (including adenocarcinoma, large cell carcinoma and other subtypes), 8 (2.93%) squamous cell carcinoma. Current smoker 64 (29.91%), former smoker 58 (27.1%), never smoker 43 (20.09%) and unknown 49 (22.9%). The tumor samples were paraffin embebed 92.36% and cytology 7.63%. Mutation(s) in the kinase domain (exon 18 to exon 21) of the EGFR gene were identified in 23 patients (10.75%). The mutation rate in women was 82.61% (19) and 17.39% (4) in men. Mutations were more frequent in adenocarcinoma 15 (65.22%), large cell carcinoma 7 (30.4%), former bronchiole-alveolar carcinoma 1 (4.35%) and no mutation was detected in squamous cell carcinoma. The proportion of positive mutations was 65.22% (15) in non smokers/former smokers and only 4.7% (2) in current smokers. Of the 23 patients with positive mutation 69.57% had exon 19 deletions, 26.09% had a mutation at exon 21, 4.35% had an insertion at exon 20, with no multiple mutation found. The median time to diagnosis was 4.05 days and we only had 1.4% patients with unevaluable tumour sample.
Conclusions: Systematic determination of EGFR in a public large center is feasible offering an acceptable time to result and with good performance. The prevalence of EGFR mutation was minor than reported previously due to the selection just by histology type. Nowdays EGFR mutation is been doing inside a larger molecular diagnosis platform in our center.
Disclosure: All authors have declared no conflicts of interest.

95P
FREQUENCY OF EGFR MUTATIONS IN NON-SMALL-CELL LUNG CANCER (NSCLC) FROM GREEK PATIENTS

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Background: NSCLC patients harboring activating somatic mutations within the tyrosine kinase (TK) domain of the epidermal growth factor receptor (EGFR) significantly benefit from EGFR targeted therapy. Treatment with the recently approved EGFR inhibitor IRESSA (gefitinib) leads to improved response and survival outcomes, therefore screening for EGFR mutations has

entered routine clinical practice. Several clinico-pathological factors correlate with these mutations including gender, smoking history, and histology. The frequency of EGFR mutations is also ethnicity-dependent, wherein the incidence in Asian populations is ~30%, while in Caucasians (Whites) it is lower, ~15%. However, limited data is available on intra-ethnic differences throughout Europe.

Aim: The aim of this study was to determine the frequency and spectrum of EGFR mutations in an unselected group of Greek NSCLC patients and investigate technical aspects of analysis.

Methods: We set up High Resolution Melting Analysis (HRMA) assays to identify mutations in exons 18-21 of the EGFR gene and validated their analytical sensitivity by making serial dilutions of samples with known mutations and tumor cell content (TCC). A total of 698 NSCLC patients were screened with HRMA for somatic EGFR mutations in exons 18-21 and mutation status was verified by bi-directional sequencing. ME-PCR (mutant enriched-PCR) was used in conjunction with standard bi-directional sequencing in a further 300 patients. Pathological review was obtained for all samples and macro-dissection was used to ensure a %TCC of >75% in all possible cases.

Results: The sensitivity of our HRM assays was found to be ≤1.5% Using HRMA and bi-directional sequencing a frequency of 19.05% was obtained; 105 x exon 19, 21 x exon 21, 6 x exon 20 and 1 x exon 18. Using ME-PCR the mutational frequency was 16.3%; 21 x exon 19, 22 x exon 21, 4 x exon 20 and 2 x exon 18.

Conclusions: Applying a very sensitive mutation detection technique in a large cohort of unselected Greek NSCLC patients in routine diagnostic practice, we obtained an overall mutation frequency of 19.05%. This mutation frequency is similar to that found by the SLADB and EURTAC studies in European populations. Differences in sensitivity between techniques suggest that more than one technique should be advised in routine diagnostic practice.

Disclosure: All authors have declared no conflicts of interest.

96P

ACTIVATING EGFR MUTATIONS IN PATIENTS WITH NON SMALL CELL LUNG CANCER: PREVALENCE AND PREDICTORS IN A CAUCASIAN SERIES

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Background: Somatic mutations in epidermal growth factor receptor (EGFR) gene predict for sensitivity to tyrosine kinase inhibitors (TKI's) in patients (pts) with advanced non small cell lung cancer (NSCLC). Most data were obtained in Asian pts.

Aim: To measure the prevalence and clinical distribution of EGFR mutations in a single institutional series of Caucasian pts from Ghent University Hospital.

Methods: Medical files between December 2009 and December 2011 were reviewed for activating EGFR mutation testing. (TheraScreen®: EGFR29 Mutation Kit – PCR based). Differences between mutation postives and negatives were evaluated using the Fisher's exact test.

Results: 99 patients were identified. Median age was 65 years. The test was not feasible in 11 (11%) due to inadequate sampling. So EGFR mutation prevalence was assessed in 88 (89%) of the samples. In 19% (17/88), an activating mutation was found (Mut+ group, n=17)): 8/17 (47%) L858R mutations, 8/17 (47%) exon 19 deletions and 1/17 (6%) exon 20 insertion. In wild type (WT) (Mut – group, n=71) 45% (32/71) were female while in the mutation positive group this was 88% (15/17; p<0.05). In wild type (WT) 8% (6/71) were never smokers while in the mutation positive group this was 53% (9/17; p<0.05). Median turnaround time was about 11 days (range 6-29).

Conclusion: In our series EGFR-mutation in Caucasians has a prevalence of 19% and is related to the female gender and a history of never smoking.

	Total (n= 88)	Mut – (n=71)	Mut + (n=17)	
Gender				P < 0.05
Female	47/88 (53%)	32/71 (45%)	15/17 (88%)	
Smoking History				P < 0.05
Never	15/88 (17%)	6/71 (8%)	9/17 (53%)	
Type Tumor				
Non Squamous	87/88	70/71	17/17	
Squamous	1/88	1/71	0/17	

Disclosure: All authors have declared no conflicts of interest.

97P

EXTERNAL QUALITY ASSESSMENT OF EGFR TESTING IN WESTERN FRANCE: A 2-YEAR EXPERIENCE

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Background: EGFR testing for NSCLC patients is routinely performed in France, within 28 regional platforms receiving a financial support from the French National Cancer Institute (INCa). In order to evaluate the quality of the tests performed in these plateforms, we developed an external quality assessment (EQA) protocol.

Method: 6 centers from the western France were involved. Altogether, these platforms perform 3.500 EGFR tests per year. The EQA scheme was based on the analysis of FFPE lung tumors. One stained section and one unstained 10 µm section prepared from 2 cases of NSCLC were sent by one of the 6 platforms to all the centers, every second month during the first year (2010), and every third month during year 2 (2011). Upon analysis, the following informations were collected: percentage of neoplastic cells in the samples, mutations tested, techniques used, and EGFR testing results.

Results: During this time period, 20 samples were analyzed by the 6 platforms. Slight differences in the estimation of the percentage of cancer cells in the samples were observed. Technically, different methods were used: pyrosequencing, HRM, allele-specific PCR, SNAPShot, standard sequencing. Despite these differences, concordant results were obtained for all the tested samples. Eight tumors were found to contain an EGFR mutation (4 exon 19 deletions and 4 p.L858R point mutations). The remaining 12 samples presented a wild type EGFR genotype.

Conclusion: Since the EQA did not rely on a single center, it was very cost-effective and not time consuming. It allowed to obtain a continuous evaluation of the platforms and provided useful informations on how the tests were performed. The main limitation was that we only used resection specimens and not lung biopsies (limited in size). We could complete this EQA by testing, in addition to clinical samples, DNAs prepared from cell lines harbouring known EGFR mutations, fixed and embedded as clinical samples.

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Disclosure: All authors have declared no conflicts of interest.

98P

CLINICAL AND IMMUNOLOGICAL EFFECTIVENESS OF DENDRITIC CELL IMMUNOTHERAPY IN LUNG CANCER PATIENTS: 5-YEARS FOLLOW-UP PERIOD

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Vaccination using dendritic cells (DC) represents a novel and promising method of lung cancer immunotherapy. Valuable proofs-of-principle have been obtained, which favor the use of DC in subsequent, more standardized clinical trials. Here, we represent a data of 5-years follow-up study of DC-vaccine immunotherapy effectiveness in non-small cell lung cancer (NSCLC) patients.

Material and methods: Ninety-four eligible patients with IIB-IIIA stage NSCLC were enrolled into the study. Patients were randomly allocated into two groups: 1st - patients who received DC-vaccine as immunotherapy after surgery (lobectomy, pneumonectomy), 2nd - control group of patients who received surgery only. Comparable groups were similar by age of the patients, histotypes of tumors, stages, volumes of surgical intervention. DC in amount $4{,}62 \pm 0{,}37 \times 10^6$ per injection were injected intravenously in 1–3 courses (6 months interval). One course consisted of 5 injections with one-month interval. Clinical and immunological monitoring of DC-vaccine immunotherapy was performed.

Results: DC-immunotherapy was well tolerated without significant toxicity. The comparatively superior survival of patients who received DC-vaccine immunotherapy in comparison with control group was found. During 1- year follow-up period 21,5% of patient died in 1st group, 33,8% of patients died in control (2nd) group (p=0.029). For patients in DC-vaccine group the 3-years survival rate was 49,1% in contrast to 33,1% in patients of control group (p=0.0085). At 5-years follow-up, we could observe that the difference in survival rates between two groups decreases, but remains statistically significant: 19,2% vs 13,6 % (p=0.0096). Interestingly, all patients (7 patients) who received 3 courses of DC-immunotherapy are alive without sign of disease during 29,5 ± 1.34 months. Patient-specific immune response evaluated by flow cytometric measurement of interferon-γproducing T-cells before and after vaccination revealed in 44,5% of patients.

Conclusions: Our study demonstrated that DC-vaccine immunotherapy could be conducted without major toxicity and induced tumor cell-specific immunological and clinical responses in NSCLC patients.

Disclosure: All authors have declared no conflicts of interest.

99P

CORRELATION OF ACTIVATED STAT3 EXPRESSION WITH CLINICOPATHOLOGIC FEATURES, RECEPTOR TYROSIN KINASE DOWNSTREAM SIGNAL PATHWAY AND EGFR/KRAS/ALK STATUSES IN LUNG ADENOCARCINOMA

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Background and object: Receptor tyrosine kinase (RTK) pathways play important roles in tumorigenesis and characteristics of lung adenocarcinomas, which has three downstream routes: Ras/Raf/ERK pathway, PI3K/Akt pathway and Jak/STAT pathway. Previously, we demonstrated that the activated PI3K-Akt pathway was relevant to advanced stages and phosporylated (p-) Akt was a poor prognosis marker. Here, to investigate STAT3 activation status and its correlation with clinicopathological features of lung adenocarcinoma, classified by oncogene changes (EGFR and KRAS mutations and EML4-ALK rearrangements).

Methods: Expression of p-STAT3 was detected by immunohistochemistry (IHC) in surgically-resected tumors from 212 invasive adenocarcinomas. Likewise, we analyzed expression of p-Akt, p-Erk1/2, p-mTOR, p-S6K, p-GSK3 as well as TTF-1, a cell lineage marker, and compared with clinicopathological features, EGFR/KRAS mutation status and EML4-ALK rearrangements, using univariate and multivariate analyses. Correlations of signal transduction molecules including p-STAT3 were analyzed using the Pearson's correlation coefficient.

Results: Positive p-STAT3 expression was detected in 149 of the 212 patients (70%). By the univariate analysis, p-STAT3 expression was significantly correlated with never smoking, lower stages, well histological differentiation, papillary rather than acinar histology, less lymphatic invasion, less vascular invasion, less pleural invasion, mutated EGFR and wild-type KRAS status. Among 111 patients with mutated EGFR, 88 (79%) patients had positive p-STAT3 expression. Six of 13 (46%) ALK rearranged tumors showed STAT3 activation. By the multivariate analysis using the logistic regression model, STAT3 activation was independently associated with never or light smokers (p=0.026) and the papillary rather than acinar structure (p=0.049). By the Pearson's correlation coefficient, positive correlation was identified between p-STAT3 and p-Erk1/2, p-S6K, p-GSK3 and TTF-1 expression.

Conclusion: The STAT3 activation was observed significantly in non-smokers, EGFR-mutated and KRAS wild-type cases, tumors of a TTF-1 positive lineage and about half of ALK rearranged tumors.

Disclosure: All authors have declared no conflicts of interest.

100P

PROGNOSTIC IMPACT OF PERIPHERAL AND LOCAL FOXP3+ REGULATORY T CELLS IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Purpose: Many kinds of mechanism involving immunosuppression in cancer patients have been reported to date. Regulatory T cells (Tregs), which express the master control transcription factor Foxp3, are thought to have a major role in hampering antitumor immune response. However, the clinical impact of Tregs in patients with lung cancer is still unclear. The aim of this study was to investigate the clinical significance of Tregs both in peripheral blood and in resected cancer tissue.

Experimental design: We analyzed peripheral blood mononuclear cells (PBMC) and resected specimens obtained from 65 patients with non-small cell lung cancer (NSCLC). Peripheral Tregs (pTregs) were detected as CD4+ and Foxp3+ cells by flow cytometry. Immunohistochemical staining for CD4, CD8 and Foxp3 expression was also performed quantitatively by analyzing three randomly selected fields from central regions (cCD4, cCD8 and cFoxp3), and interstitial regions of the tumors (iCD4, iCD8 and iFoxp3). Relationships between the expression frequencies in selected cells and clinicopathological parameters were statistically analyzed.

Results: The frequency of pTregs was significantly higher in patients who had pleural invasion (P=0.0049), vessel invasion (P=0.0009), lymphatic vessel invasion (P=0.0053), and recurrent disease (P=0.0112). Patients who had T1 factor had significantly higher frequency of cCD4 (P=0.0199) and cCD8 (P=0.0058), although cFoxp3 expression was not significant (P=0.0935). Patients who had high frequency of pTregs exhibited significantly poorer recurrence-free survival (P=0.0071). Multivariate analysis showed pTreg frequency was an independent prognostic factor (P=0.0458).

Conclusion: Although pathological analyses remains controversial, the frequency of pTregs in patients with NSCLC could be a useful prognostic biomarker.

Disclosure: All authors have declared no conflicts of interest.

101P
ERYTHROPOIETIN-RECEPTOR (EPOR) EXPRESSION AND THE TUMOR SPECIFIC EFFECT OF EPO TREATMENT IN LUNG CANCER

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Erythropoietin (EPO) is part of the standard care for lung cancer patients with anaemia but the clinical findings on the tumor related effects of this treatment are inconsistent. Hypoxic tumors are less sensitive to a number of anticancer therapies and hypoxia itself promotes progression. Nevertheless, the receptor of EPO (EPOR) can also be expressed on lung cancer cells that may support their survival and growth. Accordingly, we determined the expression of EPOR in lung cancer tissue samples and cells and investigated the effect of EPO treatment in vitro and in vivo using xenografts of human lung cancer cells. First, we analyzed bronchoscopy samples of 99 and 27 patients with NSCLC and SCLC, respectively. The expression of EPOR was measured in the tumor and adjacent non-tumorous samples of each patient by real-time PCR. Next, we measured the expression of EPOR in lung cancer cell cultures. Finally, we characterized the proliferation of EPO treated lung cancer cell cultures and the tumor growth and vascularization in mice carrying xenograft subcutaneous human lung cancer cell tumors and treated with recombinant human EPO. The expression of EPOR was significantly higher in the NSCLC bronchoscopy samples when compared to SCLC. Nevertheless, we found no significant association between EPOR expression levels and survival. Although a number of lung cancer cell lines expressed EPOR, EPO treatment had no effect on in vitro cell proliferation. Importantly, EPO treatment of mice with xenograft tumors resulted in increased proliferation of endothelial cells in the tumor and decreased tumor size. Our study suggests that EPO can support the proliferation of intratumoral endothelial cells. This, in turn, can result in better perfusion of tumor tissue, decrease tumor hypoxia and improve the therapeutic efficacy of anti-cancer treatment. However, further studies are needed to establish the effect of EPO treatment on the clinical outcome of lung cancer.

Disclosure: All authors have declared no conflicts of interest.

102P
SIRT1 REGULATES ENDOTHELIAL DLL4/NOTCH SIGNALING IN MURINE LEWIS LUNG CANCER MODEL

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Introduction: Sirtuin 1 (SIRT1), nicotinamide adenine dinucleotide 1 (NAD1)-dependent class III histone deacetylase (HDAC), acts as a key regulator of vascular endothelial homeostasis, angiogenesis, and endothelial dysfunction. However, underlying mechanism of SIRT1-mediated lung cancer angiogenesis remains unknown.

Methods: We established lewis lung cancer (LLC) xenograft model in endothelial cell-restricted SIRT1, SIRT1 (H363Y) (SIRT1 mutant that lacks deacetylase activity) transgenic mice and wild type C57BL/6J mice. Lung cancer derived-vascular endothelial cells (ECs) were isolated from xenograft tumor of SIRT1 transgenic mice. Quantitative chromatin immunoprecipitation (qChIP) analysis was used to confirm the binding of SIRT1 and Notch1.

Results: SIRT1 deacetylase activity reduced the abundance of acetylated Notch1 intracellular domain (N1IC). qChIP analysis demonstrated SIRT1 directly controled Notch1 expression by recruiting to the proximal promoter region of Notch1. Knockdown of SIRT1 by siRNA exhibited markedly enhanced activity of N1IC and up-regulated expressions of Notch1 target genes HEY1 and HEY2 in lung cancer derived-ECs. Sprouting angiogenesis was reduced after knock-down of SIRT1. However, exposure to Notch inhibitor, DAPT (N-[N-(3, 5-difluorophenacetyl)-L-alanyl]-S- phenylglycine t-butyl ester), abrogated the inhibition of angiogenic response in SIRT1 siRNA-transfected lung cancer derived-ECs. Consistent with in vitro findings, expression of SIRT1 was inversely associated with N1IC expression through its deacetylation activity and that deacetylase-defective mutant of SIRT1 (SIRT1 H363Y) had no effect on N1IC in vivo. Compared to SIRT1 transgenic mice, tumor growth in SIRT1 H363Y transgenic mice was much slower and similar to that in wild type mice. Blocking deacetylase activity of SIRT1 using HDAC inhibitor, nicotinamid (NAM), resulted in decreased tumor growth in the SIRT1 transgenic mice. The stunted tumor growth in SIRT1 H363Y transgenic mice was associated with decreased tumor vascularization.

Conclusions: SIRT1 facilitates endothelial branching and proliferation by down-regulation of Notch signaling, thereby promoting vascular growth and tumor vessel density.

Disclosure: All authors have declared no conflicts of interest.

103P
MASPIN EXPRESSION IS A FAVOURABLE PROGNOSTIC FACTOR IN NON-SMALL CELL LUNG CANCER

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Background: Maspin is a unique member of the serine protease inhibitor superfamily that suppresses tumour growth, angiogenesis and metastasis. The aim of our study was to evaluate the prognostic impact of maspin expression in resected non-small cell lung cancer (NSCLC) patients.

Patients and methods: From 1996 to 2001, 439 patients underwent radical surgery for NSCLC at Polytechnic University of Marche Region. Maspin expression was detected as cytoplasmic and nuclear staining of neoplastic cells. For the cytoplasmic staining the cases were classified as follows: negative (<5%), low positive (5-50%) and high positive (>50%). Moreover, in the positive cases, the intensity of the staining was also considered and scored as 1+ (low), 2+ (medium) and 3+ (high). A similar classification was used for nuclear staining; in this case, the intensity was not considered.

Results: The analysis showed that smoking history, pathological stage of disease, N status, histological grading, sex and ECOG performance status had a prognostic impact on overall survival (OS). Expression of maspin was also found to be an independent prognostic factor. A statistically significant longer OS was seen in patients with higher as compared with lower expression of nuclear maspin (p=0.0098) and a poorer OS was present in patients with a higher intensity of cytoplasmic staining (p=0.024). Nuclear expression of maspin was also found to be an independent prognostic factor at multivariate analysis.

Conclusion: The results of this study suggest that over-expression of maspin is correlated with a favourable prognosis in NSCLC and may be a useful clinical marker in this disease.

Disclosure: All authors have declared no conflicts of interest.

104P
CANCER STEM CELLS (CSCS) SENSITIVITY ASSAY FOR METASTATIC NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS

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Background: Current data suggest that cancer stem cells (CSCs) are responsible for tumor development, growth and progression. The inefficacy of conventional therapies might be ascribed to the stem cell population explaining cancer chemoresistance and the high frequency of relapse in the majority of

tumors. In the present study we investigated whether CSCs could be isolated in patients with metastatic NSCLC and whether in vitro CSCs sensitivity assay could identify an effective treatment.
Materials and methods: CSCs were isolated from effusions or fresh cancer tissue from primary tumor or metastasis of NSCLC patients progressing after standard therapies. CSCs were propagated in vitro and tested for different chemotherapeutic drugs or targeted agents. The more effective treatment inducing highest CSCs mortality rate, was further administered to the patients.
Results: The study included 17 patients with a median age of 58 years (range 27-81). The procedure for CSCs isolation was repeated in two patients (two and three times, respectively). CSCs were obtained from liver metastases in 16 cases (80%), pleural biopsy in 1 case (5%), lung nodule excision in 1 case (5%) and by pleural or peritoneal effusion in 2 cases (10%). CSCs were successfully isolated in 13 patients (76%). Failure in CSCs isolation might be attributed to inadequate material (6 cases) or contamination (1 case). CSCs sensitivity assay was performed in 6 cases (30%), with a median of 6 drugs or combinations tested (range 4–10). The median time required for sensitivity assay results was 40 days (range 30–46).
Conclusion: Our preliminary data indicate that CSCs isolation and in vitro sensitivity assay are feasible in patients with metastatic NSCLC. Efficacy analysis is ongoing and definitive data will be available for the meeting.
Disclosure: All authors have declared no conflicts of interest.

105P
INHIBITION OF ACTIVIN SIGNALS IMPAIRS GROWTH OF MALIGNANT PLEURAL MESOTHELIOMA CELLS

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Background: Malignant pleural mesothelioma (MPM) is a highly aggressive and therapy-resistant tumor with rising incidence related to asbestos exposure. Growth factors of the activin family are deregulated in a number of malignancies including HCC, NSCLC and esophageal cancer. Here we show that activin signals may contribute to aggressiveness of MPM cells.
Methods: Expression of activin subunits and activin receptors was determined in 10 MPM cell lines by QPCR. Moreover, activin βA (INHBA) expression was analyzed by immunohistochemistry (IHC) in MPM tissue samples (n=53). To determine whether INHBA gene expression can be epigenetically regulated via promotor demethylation and/or histone acetylation, cells were treated with 5-azacytidine and/or Trichostatin A. For functional analyses, MPM cells were exposed to exogenous activin A, siRNA-mediated INHBA silencing or activin receptor inhibitors. MTT and clonogenic growth assays were used to assess cell proliferation and survival. Cell migration was analyzed by scratch and transwell assays, and Smad2 phosphorylation by Western blots.
Results: Expression analysis revealed high expression of activin βA and activin receptors in most MPM cell lines. IHC in paraffin-embedded tissue sections of MPM patients showed a significant association of activin A expression with epitheloid histology ($P < 0.05$), but not with patient survival, stage or nuclear Ki67 expression. Within tumors with biphasic histology, activin A was predominantly present in the epithelial compartment.With regard to the consequences of promotor demethylation or histone acetylation on INHBA gene expression, no clear evidence for repression of INHBA in MPM was found. Treatment with activin A lead to a strong induction of Smad2 phosphorylation in MPM cell models and stimulated growth and clonogenicity in a subset of cell lines. Silencing of INHBA in contrast lead to reduced growth, clonogenic survival and migration, demonstrating the important role of INHBA expression for MPM cells. Targeting activin receptors with two different kinase inhibitors (SB431542, A8301) confirmed these results. **Conclusions:** These data suggest that deregulated INHBA expression contributes to the malignant phenotype of MPM cells and that activin signals should be further evaluated as therapeutic targets.
Disclosure: All authors have declared no conflicts of interest.

106P
VOLATILE FINGERPRINTS OF LUNG CANCER SPECIFIC GENETIC MUTATIONS

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Gene profiling became a key role for accurately classifying tumors in individual patients, for predicting the response to the available treatments and for personalizing cancer treatment. Common techniques require tissue specimen and thus are invasive, time consuming and may delay therapy. Here, we report on a new concept for profiling of genetic mutations of (lung) cancer cells. Headspace samples of several cell lines with specific well-defined genetic mutations (EGFR and KRAS mutations and ALK fusion) were studied and compared. The headspace VOCs from the cell lines was collected using passive sampling badges containing Tenax TA as a sorbent material in duplicates throughout the whole incubation time. The headspace was then exposed to a vacuum chamber containing an array of four cross-reactive gold nanoparticles (GNPs) coated with organic capping for blind samples of various genetic mutations. The signals collected from the GNP sensors were analyzed using a discriminant factor analysis (DFA). The nature and chemical composition of the VOCs associated with each of the investigated genetic mutations was explored and determined through complementary chemical analysis and discussed in terms of metabolic pathways. Based on the new profiling approach, we present a volatile fingerprint assay based on nine binary tests that improved the number of correctly identified samples in a blind test. While the reported concept was obtained through in vitro studies, as a way to eliminate confounding factors that are associated with clinical samples or patients/animals, it is reasonable to assume that similar findings could be detected directly from blood or the exhaled breath samples. Those will allow immediate testing to predict a clinical benefit from targeted therapy. The reported approach could help guiding treatments by tracking genetic alterations, so that patients could benefit from safer, more timely and effective interventions that improve survival and quality of life while reducing hospitalizations caused by unnecessary invasive procedures.
Disclosure: All authors have declared no conflicts of interest.

107P
MUTATIONAL PROFILE AND EPITHELIAL-MESENCHYMAL TRANSITION PHENOTYPE IN SARCOMATOID CARCINOMA OF THE LUNG

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Background: Sarcomatoid carcinoma (SC) of the lung include, according to the 2004 WHO classification, pleiomorphic carcinoma, spindle cell carcinoma, and giant cell carcinoma. They predominate in smokers, and are characterized by Epithelial to Mesenchymal Transition (EMT) properties and a dismal prognosis; however no specific therapy has been proposed to date for locally advanced and metastatic cases.
Objectives: The purpose was to determine if SC could be sub-divided in adenocarcinomas and squamous cell carcinoma subtypes to better guide mutation analyses, and to characterize their mutational and EMT profiles, in order to define new potential therapeutic targets.
Methods: TTF1, P63 and CK 5-6 staining were performed in 22 SC of the lung. K-Ras, EGFR and LKB1 mutations were analysed by sequencing,

FGFR1 amplification and EML-ALK rearrangement by FISH, and EMT phenotype by immunohistochemistry regarding pan-cytokeratins, vimentin, E cadherin, snail, FAK and mTOR expressions.

Results: All tumors but one concerned smokers. Seven out of 22 harbored an adenocarcinomas immunophenotype with TTF1 expression, 8 an SCC phenotype with P63 positivity, one had an adenosquamous profile, and 6 were TTF1-/P63-. None were EGFR mutated, but 4 with ADC immunophenotype were K-Ras mutated, one case being also LKB1 mutated. None was FGFR1 amplified or ALK rearranged. Pancytokeratin and E-cadherin expressions predominated in SC with ADC and SCC immunophenotype, and in epithelial component of pleiomorphic carcinoma and in giant cell carcinoma; they were lost in mesenchymal component, in contrast with vimentin and snail, which negatively regulates E Cadherin, which were also expressed mainly in TTF1-/P63- SC. FAK, involved in cellular migration, and mTOR, in cellular proliferation downstream of LKB1 inactivation, were widely expressed in all sarcomatoid carcinoma.

Conclusions: As expected, only K-ras and LKB1 mutations were observed in our series of SC arising in smokers, and only in cases with ADC immunophenotype, justifying an immunosubtyping of SC to guide mutation analyses; EMT phenotype characterizes SC, as well as FAK and mTOR overexpression, the latter representing a potential therapeutic target, which needs to be further evaluated in larger series.

Disclosure: All authors have declared no conflicts of interest.

108P
POTENTIAL ASSOCIATION OF PLATELET FACTOR 4 (PF4) WITH ANGIOGENESIS IN NON-SMALL CELL LUNG CANCER (NSCLC)

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Plasma chemokines are significant in developing theories concerning the biology of NSCLC. PF4 appears to be important in the regulation of angiogenesis associated with tumourigenesis, bet the role of PF4 in angiogenesis in NSCLC is unknown. We report the results of clinical study aimed to reveal association between PF4 plasma levels and development of NSCLC. The study involved 30 patients with early stage NSCLC who underwent pulmonary resection. Paired blood samples were collected intraoperatively – peripheral venous blood sample, representing systemic circulation and pulmonary venous blood sample from lobar pulmonary vein that received drainage directly from the tumor, representing tumor circulation. Additional peripheral blood samples from patients with metastatic NCSLC (n=10) and healthy controls (n=10) were collected. Plasma PF4 levels were determined by ELISA. PF4 levels were significantly higher in the peripheral blood samples compared to pulmonary blood samples (median 13001 pg/mL vs. 11489 pg/mL) (p=0.001). The median PF4 level was 10509 pg/mL in patients with metastatic NSCLC and 10691 pg/mL in healthy individuals with no difference between groups (p=0.86). At the same time PF4 levels were higher in peripheral blood of early stage NSCLC patients compared to patients with metastatic NSCLC (p=0.041) and healthy controls (p=0.021). In the local tumor microenviroment, net angiogenesis is determined by an imbalance in the over-abundance of angiogenic, compared with relative under-expression of angiostatic factors. PF4 binds to heparin-like molecules and other sulphated glycosaminoglycans that are required for the binding of proangiogenic factors modulating the effect of proangiogenic growth factors. The up-regulation of PF4 in peripheral blood could be a way of systemic response in order to counterbalance angiogenic growth factors. Reduced PF4 levels observed in tumor draining blood could indicate that angiostatic effect of PF4 was not able to counterbalance the angiogenic growth factors present in the tumor. The changes in PF4 may have the potential to convey valuable clinical information about the angiogenic potential of the tumor, and be an additional tool for a non-invasive diagnosis.

Disclosure: All authors have declared no conflicts of interest.

109P
DEVELOPMENT OF A NOVEL RT-PCR ASSAY FOR THE DETECTION OF EML4-ALK FUSION GENES IN FFPE SPECIMENS

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Background: EML4-ALK is a fusion-type protein tyrosine kinase identified recently in a subset of human lung carcinomas and seems to be a promising candidate for a therapeutic target as well as for a diagnostic molecular marker in NSCLC. Indeed, ALK kinase inhibitors (Crizotinib PF0234-1066, Pfizer) have already been developed and have been reported to be efficient only in patients positive for the *EML4-ALK* fusion. To date, several EML4-ALK variants have been identified in lung cancer samples. A variety of methods have been used for the detection of these fusions, including IHC, FISH, and RT-PCR, which is the only method that can distinguish between different variants. Existing RT-PCR methods though, are designed to amplify large cDNA fragments and are inadequate for the analysis of formalin-fixed paraffin-embedded (FFPE) tissues which produce cDNA fragments of limited size. Thus, we designed an RT-PCR assay that can detect all published EML4-ALK variants and is suitable for use with this commonly available material.

Methods: The study included FFPE specimens from NSCLC patients without EGFR and K-RAS mutations. Pathological review was obtained for all samples and macro-dissection was used to ensure a tumor cell content of >75%. Detection of all EML4-ALK fusions was achieved using a multiplex RT-PCR. Specific primers that enhance specifically *EML4-ALK* transcripts 1, 2, 3a, 3b, 4, 5a, 5b, 6, 7, "4", and "5" were designed. DNA sequencing analysis was performed to confirm the specificity of the obtained PCR products. The sensitivity of the method was calculated by adding to 1&mug RNA serial dilutions of the synthetic DNA fragments. It was found that up to 22 copies of the translocation can be detected per & mug of RNA. We are currently increasing our sample size of Greek patients and are in collaboration with other centres to further understand the clinical impact of the variant spectrum.

Results: None of the 96 FFPE specimens tested so far, was positive for the *EML4-ALK* fusion. Control *EML4-ALK* FISH positive samples were positively subtyped using RT-PCR and sequencing.

Conclusions: We designed a robust multiplex RT-PCR assay that permits the sensitive detection of all published *EML4-ALK* variants. It's suitable for use with commonly available materials such as FFPE speciments, cytological speciments and other aspirates.

Disclosure: All authors have declared no conflicts of interest.

110P
THE CLINICAL UTILITY OF PLASMA DNA QUANTIFICATION IN NSCLC DIAGNOSTICS AND RADICAL THERAPY EFFECTIVENESS MONITORING

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Background: Increased concentrations of free DNA are detectable in peripheral blood of most cancer patients including non-small cell lung cancer (NSCLC). Our aim was to evaluate the clinical value of plasma

DNA quantification for early NSCLC diagnostics and assessment of radical therapy effectiveness.

Methods: Plasma DNA concentration was measured in 60 resectable NSCLC patients (stage I-IIIA) prior and following the radical treatment using real-time PCR. Patients with distinctive scenarios of chronic respiratory inflammation (34 COPD, 35 sarcoidosis and 32 persistent asthma) were included into the study to assess the diagnostic accuracy of plasma DNA quantification in NSCLC detection. 10 orthopedic patient undergoing hip joint surgery and 40 healthy volunteers comprised control groups.

Results: NSCLC patients (8.0 ng/ml) demonstrated significantly higher mean plasma DNA concentration with respect to patients with chronic respiratory inflammation (3.4 ng/ml), orthopedic patients (3.0 ng/ml) and healthy controls (2.3 ng/ml; $p<0.0000$). The cut-off point of >2.8 ng/ml provided 90% sensitivity and 80,5% specificity in discriminating NSCLC from healthy individuals (AUC=0.89, $p<0.0001$). However, 56% specificity and 90% sensitivity were calculated, when patients with chronic respiratory inflammation were also considered (AUC=0.80, $p<0.0001$). Similar raise in plasma DNA levels was detected a week after the surgery in either resected NSCLC (68.7 ng/ml, $p<0.0000$) or orthopedic patients (28.4 ng/ml, $p<0.0015$). NSCLC patients with no disease recurrence during 3-6 month follow-up showed significant reduction in plasma DNA levels (2.8 ng/ml), whereas in relapsed subjects plasma DNA levels were significantly higher than baseline values.

Conclusions: The diagnostic power of our quantitative plasma DNA test, though quite satisfactory, needs further improvement to meet early-diagnosis requirements in NSCLC. Drastic increase of plasma DNA concentration following resection surgery in NSCLC did not result from malignancy, but the surgical trauma. In the post-operative long-term follow up quantitative analysis of plasma DNA seemed to discriminate relapse-free patients from recurrent ones proving its potential usefulness for radical NSCLC therapy effectiveness monitoring.

Disclosure: All authors have declared no conflicts of interest.

111P
UROKINASE-TYPE PLASMINOGEN ACTIVATOR AND INHIBITOR AS PROGNOSTIC MARKERS IN PATIENTS WITH NON-SMALL CELL LUNG CANCER AND LYMPH NODE METASTASES

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Background: Several biological markers have shown their usefulness in patients with lung cancer. Urokinase-type plasminogen activator (u-PA) is a member of the serine protease, an extracellular matrix protease strictly related to tumor aggression. It is localized on the tumor cells surface by binding to a specific receptor (u-PAR), which regulates the proteolytic activity around the cells. Plasminogen activator inhibitor 2 (PAI-2) regulates the u-PA activity. The expression of u-PA and PAR is elevated in malignant tumors, while low levels of PAI-2 expression correlates with the presence of metastases. We retrospectively assayed the expression of u-PA, u-PAR, and PAI-2 in specimens from non-small cell lung carcinoma (NSCLC), with the aim of evaluating possible relationship between these prognostic markers and the presence of lymph node metastasis.

Materials and methods: Paraffin-embedded archival tumor tissues from 59 patients with NSCLC were used to assess by immunohistochemical staining expressions of u-PA and u-PAR, and to measure by enzyme-linked immunosorbent assay levels of PAI-2 antigen. The analysis was performed by reverse transcriptase polymerase chain reaction (RT-PCR). Patients were 42 (71.2%) males and 17 (28.8%) females, with a median age of 62 years (range 54-68). LN metastases were found in 25 (42.3%, Group A) patients, while 34 (57.7%, Group B) were node-negative (pN0). A positive-staining area of more than 10% was considered as a positive result. The Pearson chi-square (χ^2) test was used to compare data.

Results: Positive markers (A vs. B) were found in 15 of 25 vs. 24 of 34 (u-PA), 13 of 25 vs. 23 of 34 (u-PAR), and 10 of 25 vs. 24/34 (PAI-2) specimens, respectively. A significant relationship between u-PAR positivity and LN metastasis ($\chi^2=0.019$, $p=0.018$) was found, while both u-PA ($\chi^2=0.396$, $p=0.283$) and u-PAR ($\chi^2=0.223$, $p=0.171$) were not related to LN status.

Conclusions: In patients with NSCLC, u-PAR seems to be the key molecule for extracellular matrix degradation enzyme and the target molecule of cancer metastasis prevention, representing a sensitive marker of prognosis.

Disclosure: All authors have declared no conflicts of interest.

112P
A MODIFIED VIMENTIN HISTOLOGIC SCORE HELPS RECOGNIZE PULMONARY SARCOMATOID CARCINOMA IN SMALL BIOPSY SAMPLES

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Introduction: Little is known on the use of a modified vimentin histologic score (M-VHS) for confirming stable epithelial-mesenchymal transition (EMT) and hence the final diagnosis of pulmonary sarcomatoid carcinoma (PSC) in small biopsy samples. As PSC are life-threatening tumors, an improvement in their diagnostic recognition in small-sized tumor samples is clinically warranted.

Methods: Vimentin expression was assessed by immunohistochemistry in both preoperative biopsy samples and paired surgical specimens from 20 pleomorphic carcinomas, two pulmonary blastomas and one carcinosarcoma. A M-VHS was devised multiplying three independently assessed parameters, i.e. the percentage of positive cells (as assessed semiquantitatively by quintiles, from 0 to 5) by the intensity (as compared to internal positive controls: low [1] vs. strong [2]) and the distribution pattern within the cytoplasm (partial [1] vs. diffuse [2]). So settled, the V-MHS ranged from 0 to 20 (maximum value resulting from 5x2x2). Forty-six consecutive cases of non-small cell lung carcinomas (NSCLC) were used as cancer control group for validating M-VHS.

Results: No differences in M-VHS were found between biopsies and surgical specimens of PSC, so confirming the occurrence of stable EMT and hence the specific diagnosis of PSC, whereas the M-VHS in the 46 NSCLC was by far significantly lower ($p<0.0001$). All types of PSC shared the same M-VHS. Poorly differentiated NSCLC showing marked pleomorphism with spindling and giant cell changes but not stable EMT did exhibit a significantly increased V-MHS.

Conclusions: M-VHS helped morphology to render more definite diagnoses on small biopsies of PSC, thus permitting a more planned approach to the recognition and the treatment of this life-threatening tumor subset.

Disclosure: All authors have declared no conflicts of interest.

113P
THYMIDYLATE SYNTHASE GENE POLYMORPHISMS AND LUNG ADENOCARCINOMA IN SERBIA

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Purpose: Thymidylate synthase (TS) is necessary for DNA synthesis through catalyzing the conversion of dUMP to dTMP using folate as a methyl donor. The TS promoter has a 28bp double or triple tandem repeat polymorphism (2R, 3R) related to TS protein expression. 2R/2R homozygotes, as well as guanine to cytosine transition in the second repeat of the 3R allele, are associated with lower TS expression. Previous studies have suggested that TS activity is a prognostic factor in non-small cell lung cancer. The aim of the study was to analyze the association of TS gene polymorphisms with lung adenocarcinoma in Serbian patients.
Methods: A case-control study including 56 late-stage lung adenocarcinoma patients and 53 healthy subjects was performed. Standard PCR and restriction fragment length polymorphism analysis were used for TS genotyping. Depending on the presence of high (3RG) or low (2R, 3RC) expression alleles, TS functional groups were subclassified into HH (3RG/3RG), HL (2R/3RG, 3RG/3RC) and LL (2R/2R, 2R/3RC, 3RC/3RC) groups. Descriptive analyses included genotype and allelic frequencies; the odds ratio (OR) and the 95% confidence interval (CI) were calculated as an estimate of relative risk.
Results: The distribution of the polymorphic variants in patients vs. controls was 12.5% vs. 9.4% for HH, 12.5% vs. 16.9% for HL and 75% vs. 73.6% for LL. The frequencies of alleles in patients vs. controls were 0.18 vs. 0.17 for H, and 0.81 vs. 0.82 for L. There was no significant difference in LL+HL vs. HH ($\chi 2 = 0.042$; OR = 0.73; 95% CI, 0.22 – 2.46). A non-significant difference in LL vs. HL+LL genotype distribution was observed between patients and controls ($\chi 2 = 0.0025$; OR = 1.08; 95% CI, 0.46 – 2.54).
Conclusions: We found no significant association between the TS polymorphisms and the risk of lung adenocarcinoma occurrence in Serbia. As this study is limited by a relatively small sample size, a further large case-control study including analysis of gene-gene interactions with genes coding for other folate metabolism enzymes is needed. Finding a potential correlation between these polymorphisms and lung adenocarcinoma occurrence could contribute to the earlier detection of this disease.
Disclosure: All authors have declared no conflicts of interest.

114P
ATM DEFICIENCY IN NON SMALL CELL LUNG CANCER CELL LINES

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Background: Ataxia telangiectasia mutated (ATM) is a multifunctional DNA damage signaling protein. Loss of ATM function, as seen in patients with ataxia telangiectasia, causes a cancer predisposition and radiation sensitivity. We have previously reported that PARP inhibition is a useful therapeutic approach in mantle lymphoma cells deficient in ATM. Recent reports suggest that ATM is commonly mutated in non-small cell lung cancers (NSCLC). We have also shown that loss of ATM expression in early resected NSCLC confers a poor prognosis. We hypothesize that ATM-deficient NSCLC cells will be sensitive to irradiation, and will not be able to activate DNA repair mechanisms. ATM expression and activity is likely to have therapeutic implications in NSCLC, as it may serve as a potential guide for successfully selecting patients for radiotherapy as well as for PARP inhibition.
Methods: The NSCLC cell lines NCI-H23, NCI-H226, NCI-H460, and A549 were used in this study. ATM expression was assessed in each cell line by western blot. ATM functionality was determined by examining active phosphorylated ATM following irradiation of the cells and by interrogating downstream targets of ATM including p53, checkpoint kinase 2 (ChK2), and KRAB-associated protein 1 (KAP1). After characterizing each NSCLC cell line, the biological effects of PARP-1 inhibition and gamma-irradiation on viability these cells was examined using the clonogenic survival assay.
Results: Expression level of ATM varies significantly between NSCLC cell lines with H23 being the most ATM deficient. This ATM deficiency correlated with increased sensitivity to radiation and an altered sensitivity to PARP inhibition.
Conclusion: Our preliminary results indicate differences in ATM functionality between different NSCLC cell lines following irradiation and that targeting ATM deficient NSCLC tumour is a rational therapeutic strategy. Results of the downstream activity of ATM in these cells, and the biological consequences of ATM deficiency will be presented and discussed.
Disclosure: All authors have declared no conflicts of interest.

115P
AN INDUCIBLE SYSTEM TO STUDY CHEMOTHERAPY RESISTANCE IN NON-SMALL CELL LUNG CANCER

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Introduction: Occurrence of chemotherapy resistance is a major obstacle in the treatment of non-small cell lung cancer (NSCLC). Inhibition of translesion synthesis DNA polymerase κ sensitizes NSCLC tumors to cisplatin and reduces the formation of chemotherapy resistance. DNA polymerase κ consists of the catalytic subunit REV3 and the structural subunit REV7. Surprisingly, we found that lentiviral-based short hairpin RNA–mediated depletion of REV3 per se suppresses colony formation of lung, breast, mesothelioma, and colon tumor cell lines, whereas control cell lines and a normal mesothelial primary culture are less affected. We showed that inhibition of REV3 expression per se in cancer cells leads to an accumulation of persistent DNA damage.
Aim: The aim of this project is to develop a system, which allows us to study how REV3 depletion per se and in combination with chemotherapy affects human NSCLC tumor growth in a mouse xenograft model.
Results: A549 NSCLC cells were transfected with two plasmids, one encoding a tetracycline repressor and the other plasmid encoding a short hairpin RNA targeting REV3 under the control of a promoter containing a tetracycline repressor binding site. After initial analysis of REV3 mRNA expression by real-time PCR, we selected 2 clones with inducible inhibition of REV3 expression and 2 clones containing the corresponding scrambled construct. Detailed analysis revealed that the inducible inhibition of REV3 expression was highest 72 hours after doxycycline addition. At this time point, levels of histone H2AX phosphorylation, a marker for DNA damage, were increased by REV3 depletion whereas scrambled control clones were not affected. Additionally, inducible inhibition of REV3 expression significantly reduced colony formation.
Significance: Translesion synthesis DNA polymerase κ is the main extender from mismatches formed after treatment with DNA-damaging agents and is thereby a major contributor to the occurrence of chemotherapy resistance. Additionally, our previous findings indicate that depletion of REV3 can be applied for susceptible cancers as a potential monotherapy. The inducible system will allow us to study the effect of REV3 depletion per se and in combination with chemotherapy in the in vivo setting.
Disclosure: All authors have declared no conflicts of interest.

116P
T-TYPE CALCIUM CHANNELS IN NON SMALL CELL LUNG CANCER

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Background: Calcium signaling is known to regulate cell proliferation via numerous channels and pathways. A newly emerging therapeutic target in

cancer research is the t-type calcium channel. These channels exist in three isoforms, Ca(v)3.1, 3.2, and 3.3, and are typically expressed in epithelia only during development. T-type channels have been implicated in esophageal, breast and ovarian cancers but their role in lung cancer has not been thoroughly investigated. We set out to assess the expression, function and effect of these channels in NSCLC cell lines.

Methods: In vitro studies were conducted using A549, H23, H226, H460, H522, and H1299 NSCLC cell lines. Expression of Ca(v)3.1 and 3.2 was assessed by Western blot analysis and location by microscopy imaging. Functional analyses were conducted using patch clamp studies, which can detect the unique t-current generated by the channels. The effects of two known channel inhibitors, Mibefradil and NNC-55-0396 on proliferation were examined using the XTT assay.

Results: All NSCLC lines tested expressed one or both of the t-type calcium channel isoforms, with H226 having the greatest Ca(v)3.1 expression and H460 having the most 3.2. However, not all lines had functional channels, which was partly explained by the location within the cell. Preliminary XTT results suggest the inhibitors can influence the proliferation of these cell lines in vitro, but their effect is dependent upon function.

Conclusion: T-type calcium channels may influence proliferation of NSCLC cell lines. Further inquiry into the clinical significance of t-type channel expression in NSCLC patients is currently underway using the Glans-Look Lung Cancer Database, in which expression in resected tumors is correlated with patient outcome.

Disclosure: All authors have declared no conflicts of interest.

117P
SEX DIFFERENCES IN CXCR4 SUBCELLULAR LOCALIZATION AND ACTIVITY IN NON-SMALL CELL LUNG CANCER

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Background: CXCR4 is a chemokine receptor that is commonly misexpressed in various cancer types, and has been shown to have a direct role in the migratory and invasive abilities of metastatic cancer cells when activated by its ligand, SDF-1 (CXCL12). Clinical outcome data from our lab has shown that CXCR4 is overexpressed in some lung adenocarcinomas and has an adverse effect on overall patient survival, but this effect is only observed in female patients. Some evidence has suggested that SDF-1 and estrogen receptor activity cooperate to regulate each other in a feedback loop, however it is unclear what the effect of this is on CXCR4 activity in lung cancer cells.

Objectives and methods: To address the mechanism behind these apparent sex differences, we selected several non-small cell lung cancer (NSCLC) cell lines, derived from both male and female sources, and interrogated them for CXCR4 expression and activity. Expression of CXCR4 in the cell lines was assessed by western blot and quantitative RT-PCR, and subcellular localization was determined by fluorescence immunohistochemistry. We further assayed CXCR4 functionality by looking at downstream activation of the MAPK and AKT pathways, as well as performing migration and invasion assays in the presence of SDF-1.

Results and conclusions: Our preliminary data shows that CXCR4 is expressed in all cell lines tested, and inhibition of either CXCR4 or SDF-1 with small inhibitors or with blocking antibodies revealed that CXCR4 activity increases migration of the NSCLC cell lines tested. Results from these experiments and others to illustrate the sex differences in CXCR4 activity will be presented and discussed, along with evidence potentially linking estrogen receptor expression and activity to CXCR4 function.

Disclosure: All authors have declared no conflicts of interest.

118P
ASSOCIATION OF METHYLENETETRAHYDROFOLATE REDUCTASE GENE POLYMORPHISM WITH SUSCEPTIBILITY TO LUNG ADENOCARCINOMA IN SERBIA

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Purpose: Methylenetetrahydrofolate reductase (MTHFR) is an important enzyme of the folate metabolism and is involved in the process of carcinogenesis. Cytosine to thymine transition at nucleotide 677 (C677T) yields a thermolabile variant of this enzyme with reduced activity. Previous studies have suggested that MTHFR activity is a prognostic factor in non-small cell lung cancer. The aim of this study was to analyze the association of MTHFR polymorphism with lung adenocarcinoma in Serbia.

Methods: A case-control study including 55 late-stage lung adenocarcinoma patients and 53 healthy subjects was performed. Restriction fragment length polymorphism analysis was used for MTHFR genotyping. Descriptive analyses included genotype and allelic frequencies; the odds ratio (OR) and 95% confidence interval (CI) were calculated as an estimate of relative risk. The Hardy-Weinberg equilibrium was tested using the $\chi 2$ test. Significance was considered for $p < 0.05$.

Results: The distribution of C677T genotypes in patients and controls did not deviate from the Hardy-Weinberg equilibrium. The distribution of the polymorphic variants in patients vs. controls was 61.8% vs. 24.5% for CC, 32.7% vs. 62.3% for CT and 5.5% vs. 13.2% for TT. The frequencies of alleles in patients vs. controls were 0.78 vs. 0.56 for C, and 0.22 vs. 0.44 for T. A nonsignificant difference in CT+CC vs. TT genotype distribution was observed between patients and controls ($\chi 2 = 1.12$; OR = 2.64; 95% CI, 0.63 – 11.08). For CC vs. TT+CT genotype distribution a significant difference was observed between patients and controls ($\chi 2 = 13.79$; OR = 4.98; 95% CI, 2.14 – 11.61).

Conclusions: An increased frequency of the C allele in Serbian lung adenocarcinoma patients compared to healthy controls was detected. Moreover, a significant corelation between the homozygous CC genotype and lung adenocarcinoma occurence was found. As this study was performed on a relatively small sample size further validation is necessary. Finding a potential correlation between MTHFR gene polymorphisms and lung adenocarcinoma could contribute to earlier detection of this disease.

Disclosure: All authors have declared no conflicts of interest.

119P
PHOSPHOLIPID PROFILING OF NON-SMALL CELL LUNG CANCER BY IMAGING MASS SPECTROMETRY

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Purpose: Lipidomics may provide a new direction to study cancer by identifying some tumor-specific markers, leading to elucidation of the mechanism of tumorigenesis and identification of therapeutic targets. We identified novel differentially-expressed lipids between the normal and tumor tissues from the same patients that may provide insights into diagnosis, prognosis, and therapeutic targets for patients with non-small cell lung cancer.

Methods: We performed an imaging MALDI lipidomic study to gain the unique lipid alterations that are characteristic of non-small cell lung cancer. Imaging MALDI mass spectrometry integrated histopathology and lipid expression. Frozen cancer tissues and matched normal lung tissues were sliced to a thickness of 10μm and transferred onto a conductive glass slide. The matrix for lipid imaging was binary matrix. After laser scanning by MALDI-TOF equipped with a smart beam laser, the images were

created for single masses and classified members of lipids at 200μm spatial resolution. Based on the spatial distribution, region specific lipids on a tissue can be identified by either MALDI-TOF/TOF or Liquid chromatography (LC)-MS/MS. Classified mass markers selectively labeled tumor and normal regions of non-small cell lung cancer. Unsupervised and supervised analysis of image data correlated with histologically stained image.

Results: We identified 17 phopholipid species, differentially expressed in normal and cancer area from the same patients with non-small cell lung cancer. We found 12 phopholipids showing upregulated expression and 5 phopholipids showing significant down-regulated expression in the tumor tissues from the patient with non-small cell lung cancer.

Conclusions: We successfully showed the feasibility of MALDI imaging as a useful tool for the analysis of lipid profiles using lung tissue sections.

Disclosure: All authors have declared no conflicts of interest.

120P
THE SERUM LEVELS OF HE4 ARE CLOSELY ASSOCIATED WITH PULMONARY ADENOCARCINOMA PROGRESSION

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Objectives: The human epididymis 4 (HE4) gene product, also known as Whey-Acidic-Protein (WAP) four-disulfide core domain protein 2 (WFDC2), was identified as the transcript expressed in the epididymis and respiratory tract. We previously reported that HE4 is also expressed in pulmonary adenocarcinoma. The purpose of this study was to investigate serum levels of HE4 as biological marker in pulmonary adenocarcinoma.

Materials and methods: In trained set, 102 patients with pulmonary adenocarcinoma underwent surgery in our institute from 2008 to 2011 were evaluated. 58 healthy controls and 16 benign lung disease were compared. In the validation set, we used 105 patients with pulmonary adenocarcinoma operated between 2000 and 2007. Postoperative change of serum HE4 levels were investigated in 35 patients. The level of HE4 was determined with ELISA and compared with clinicopathological factors.

Results: In the trained set, sera in lung adenocarcinoma were significantly higher than in healthy controls. Receiver operating curve (ROC) showed that HE4 was a good discriminator of lung adenocarcinoma (cutoff point, 50.3pM, Area under curve (AUC), 0.825; 95% confident interval (CI) 0.76-0.89, p<0.001). In the validation set, no significant correlation was found between serum HE4 levels and clinicopathological factors including age, gender, tumor size, and nodal status. However, positive rate of HE4 showed the tendency to correlate to the staging (36.5% in stage I, 57.1% in stage II, 50% in stage III and 100% in stage IV, p=0.057). Furthermore, postoperative change of HE4 serum levels showed significant correlation between increase and recurrence. Although 6 of 16 patients with postoperative increase recurred, only one of 19 patients with decrease or no change HE4 serum levels recurred after operation (p=0.032). The five-year overall survival rate was 60.4% in the HE4-positive group, compared with 91.9 % in the HE4-negative group (p=0.008).

Conclusions: These data showed that HE4 expression in sera is associated with progression of pulmonary adenocarcinoma and a possible biomarker.

Disclosure: All authors have declared no conflicts of interest.

121P
RELATIVE INTENSITY OF TP53 MUTATION IS ASSOCIATED WITH INTRATUMOR GENETIC HETEROGENEITY AND THE PROGNOSIS OF PATIENTS WITH EARLY STAGE NON-SMALL CELL LUNG CANCERS

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A large number of studies have evaluated the impact of TP53 mutations on the prognosis of patients with non-small cell lung cancer (NSCLC); however, the results of these studies are still controversial. Recently, considerable intratumor heterogeneity for genetic alterations has been demonstrated in various human cancers, including lung cancer. In the present study, we evaluated TP53 mutations in NSCLCs and observed remarkable variations in the values of the relative intensity (RI, intensity of the peak of the mutated allele/intensity of the peak of the non-mutated allele) of TP53 mutations. We also examined whether the RI values were associated with the intratumor heterogeneity of TP53 mutations. In addition, we evaluated the relationship between the presence of TP53 mutation and survival outcome. TP53 mutation was not significantly associated with survival of the patients. However, when tumors with TP53 mutation were categorized into two groups, those with a low- and high-intensity of the mutation, the latter group had significantly worse survival compared to those with wild-type TP53 (adjusted hazard ratio = 2.58, 95% confidence interval = 1.21–5.48, P = 0.01), whereas the former group did not. These results suggest that intratumor genetic heterogeneity may be an important factor in determining the role of TP53 mutation on the prognosis of NSCLC patients.

Disclosure: All authors have declared no conflicts of interest.

122P
LUNG CANCER INCIDENCE, EXPRESSION OF TUMOUR SUPPRESSOR PROTEIN P53 AND ANTI-APOPTOTIC SURVIVING AND SURVIVAL IN CHROMIUM EXPOSED INDIVIDUALS

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Workers chronically exposed to hexavalent chromium have higher incidence of lung cancer. Our study investigates incidence of lung cancer types, age of onset of the disease and surviving time among chromium exposed workers (smelters, tapers, crane operators) in comparison to non-exposed persons. We analysed 77 chromium exposed workers and 104 male controls with diagnosed lung cancer. The average exposure time among workers was 18.38 years (range 1–41 years). For investigation of possible role of surviving and p53 protein we used immohistochemical visualisation. It was found out that chromium exposure decreases the age at the onset of the disease of 4.18 years. Significant difference between the age at the onset of the disease was found between smokers and non-smokers (P=0.008) in the control group. Non-exposed non-smokers had explicitly higher age at the onset of the illness in relation to other groups. In exposed group the significant effect of smoking on the age at the disease onset was not found (P=0.775). Small cell lung carcinoma (SCLC) forms 25.71% of all cases in chromium exposed workers and 16.34%

in non exposed individuals. The survival time of patients with NSCLC and SCLC within non-exposed were 12.33 and 17.75 month respectively and in exposed group 14.8 and 4.44 month respectively. No correlation was found between the age at the diseases onset and time of exposure. There was negative correlation between surviving and p53 expression. We did not find any correlation between expression of analysed proteins and survival time. Occupational exposure to chromium was identified as an important risk factor of lung cancer even overlaying effect of smoking. Both chromium exposure and smoking decrease the age at the diseases onset. Higher percentage of SCLC was found in chromium exposed individuals.

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Disclosure: All authors have declared no conflicts of interest.

123P

CC-CHEMOKINE LIGAND 18 INDUCES EPITHELIAL TO MESENCHYMAL TRANSITION IN LUNG CANCER A549 CELLS AND ENHANCES THE METASTATIC POTENTIAL

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Lung cancer is one of the leading causes of cancer-related death worldwide with more than a million deaths per year. The poor prognosis is mainly based on the highly aggressive behavior of this entity, associated with an early metastasis. Although the exact mechanisms are still unknown, the process of epithelial to mesenchymal transition (EMT) seems to play an important role. We already demonstrated that CCL18, a primate specific chemokine, is highly elevated in patients with lung cancer and correlates with the survival time of patients with adenocarcinoma of the lung. Therefore we hypothesized that CCL18 induces EMT in this histological subtype. We investigated the effect of CCL18 on A549, an adenocarcinoma cell line of the lung, on EMT maker and studied also the effects of CCL18 on cell functions such as migration, invasion, chemotaxis, chemoresistance and proliferation.

Exposure of A549 lung cancer cells to CCL18 in various concentrations decreases the epithelial marker E-cadherin, whereas S100A4, a marker of the mesenchymal phenotype increases. According to these changes SNAIL1, one of the most important transcriptional regulators of EMT, was also induced and increases depending on the given CCL18 dose. The proliferation rate declines after exposure to CCL18 dose dependently to a maximum of 40%. The chemotactic capability after CCL18 exposure increased about 50%. Therefore CCL18 may be an interesting target in therapy of NSCLC.

Disclosure: All authors have declared no conflicts of interest.

124P

THE ROLE OF MELATONIN ON THE EXPRESSION OF NITRIC OXIDE SYNTHASE IN NSCLC CELL CULTURE IN VITRO

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Experimental research has confirmed that melatonin plays an important role both as an oncopreventive agent and an oncotherapeutic medication. It is confirmed that during an oncological disease the quantity of melatonin in blood plasma compared with its normal level decreases, and the more anaplastic a malignant cell is, the less melatonin it contains. The same parallel can be traced in malignant cells regarding expression of the enzyme participating in the nitric (II) oxide synthesis (uNOS). Namely, the more anaplastic the malignant tumor cell is, the lower the expression of uNOS it manifests. Moreover, it was confirmed that the less uNOS the cell contains, the more aggressively the cancer develops and the less sensitive it is towards pharmacological therapy. We studied the quality of expression of uNOS in cell cultures derived from the biopsy material of lung squamous cell cancer - SCLC (G3 and G4) (17 cases) by the western blotting method; reagent u-NOS antibody Catalog Number GTX73127 (GeneTex). Results were compared with the expression of uNOS in the pavement epithelium culture of the healthy human bronchi. The changes in uNOS expression after administering melatonin (after 10-day incubation in 5% CO_2 incubator) were studied. Results were compared with the quality of expression of uNOS in initial samples.

Results were the following: 1. uNOS expression in SCLC cell cultures (mostly, in G4 cases) is decreased dramatically - by 53% compared with control samples. 2. Upon melatonin administration, uNOS expression is moderately increased in G4 malignant cells (by 31% compared with initial samples) and sharply increased in G3 malignant cells (by 62% compared with initial samples). We may conclude that melatonin is involved in the complex processes of the body's anti-cancer fight and this issue requires a more thorough research.

Disclosure: All authors have declared no conflicts of interest.

125P

THE EFFICACY OF PEMETREXED-BASED TREATMENT FOR ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC), AS CORRELATED WITH THE PATHOLOGIC FEATURES OF TUMORS

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Introduction: Non-squamous lung carcinoma has been reported to benefit from cisplatin-pemetrexed compared to cisplatin-gemcitabine treatment. This finding enhanced efforts to sub-classify NSCLC histologically. We were interested to examine the efficacy of pemetrexed-based systemic treatment as correlated with the pathologic features of tumors.

Methods: NSCLC patients that were treated with pemetrexed-based chemotherapy in a single center during 2007-2011 were identified by a database search. Pathology records were reviewed and tumor morphology, immunohistochemistry (IHC) results for TTF1, CK7, p63, CK5/6 and level of differentiation were recorded. Progression free survival (PFS) and overall survival (OS) were recorded from the medical charts. Outcome was correlated with pathologic features by logrank test.

Results: A total of 98 patients treated by a pemetrexed-based regimen were identified. 17 patients with incomplete follow up data were excluded, as well as 18 patients with incomplete pathology data, leaving 63 patients for our analysis. IHC and level of differentiation was available for part of the patients (see table), non allowing prognostic evaluation. Comparing the patients with a diagnosis of adenocarcinoma based on microscopic description to those with a diagnosis of non-squamous cell carcinoma based on IHC, PFS was similar (6.7 vs 4.4 months, p=0.4, HR=0.75). OS was significantly better for adencocarcinoma bearing patients (non-reached vs 10.2 months, p=0.0006, HR=0.18, 0.006-0.25).

Conclusions: A pathologic diagnosis of adenocarcinoma implies better survival compared to a diagnosis of non-squamous cell carcrinoma based on IHC, among advanced NSCLC treated with a pemetrexed-based chemotherapy regimen. Larger patient cohorts, as well as cohorts not treated with pemetrexed, need to be examined to elucidate prognostic vs predictive implication of the pathologic method of diagnosis.

IHC/ differentiation	Patients with data available (%)*	Positive (%)	Negative (%)
TTF1	47 (75)	42 (89)	5 (11)
CK7	33 (52)	31 (94)	2 (6)
P63	15 (24)	4 (27)	11 (73)
CK5/6	21 (33)	3 (14)	18 (86)
Level of differentiation	20 (32)	Well to moderate; 7 (35)	Poor to undifferentiated; 13 (65)

*Percent of the patients with clinical and pathological data (N=63).

Disclosure: All authors have declared no conflicts of interest.

126P

SEQUENTIAL USE OF VINORELBINE (V) FOLLOWED BY GEFITINIB (G) INDUCES A SYNERGISTIC EFFECT IN NON-SMALL CELL LUNG CANCER (NSCLC) CELL LINES

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Background: Preclinical studies with tyrosine kinase inhibitors (TKI) demonstrate that these agents enhance the antitumor activity of cytotoxic chemotherapy although several clinical studies in NSCLC patients have failed to achieve survival improvement in an unselected population. Aim of this study is to identify potential addictive, synergistic or antagonist effects between V and G in vitro as a rationale for further investigation in the clinical setting.

Methods: Human lung cancer cell lines with wild-type (A-549) and mutant-type EGFR genes (NCI-H1975) were used as in vitro models to evaluate the antitumor activity of G and V using three different schedules: G followed by V, V followed by G and the two drugs concomitantly. We also evaluated the antiproliferative efficacy of repeated weekly V doses along with sequential or continuous G.

Results: In our evaluation of the growth inhibition effect on A-549 and NCI-H1975 of three different schedules, we observed that the V-G sequence was more potent than either the G-V sequence or the concomitant administration of the two drugs. On NCI-H1975 a clear synergistic effect was found at highest concentration of V with every concentration of G tested only in the sequence of V followed by G. This result was confirmed when we evaluated the optimal combination of V and G. The most effective antiproliferative result was found when V was given with the sequential administration of G. A frankly synergistic growth inhibitory effect was observed only when A-549 and NCI- H1975 were first exposed to V (day 1 and day 8) and then treated with G (from day 9 to day 21) compared with V alone or G in continuous.

Conclusion: This study suggests that the schedule of V followed by G is superior to other sequences with V and G in treating NSCLC cell line. This finding is encouraging as a proof of the possible benefit of combining an EGFR targeting compound with a cell cycle specific drug and could be a rationale for a new treatment strategy in patients with advanced EGFR mutated NSCLC. The molecular mechanisms involved in the synergistic effect between V and G against NSCLC cells will be the object of study in the near future.

Disclosure: All authors have declared no conflicts of interest.

Exceptional Acceptance

251P

GANETESPIB: AN EFFECTIVE STRATEGY TO OVERCOME CRIZOTINIB RESISTANCE IN ALK-DRIVEN CANCERS

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Background: The EML4-ALK rearrangement represents nearly 40,000 non-small cell lung carcinoma (NSCLC) patients worldwide each year. While targeted ALK inhibitors such as crizotinib have shown clinical efficacy the vast majority of patients will develop resistance, reinforcing the need for new therapies. One such strategy is to target the molecular chaperone ALK depends on for protein stabilization. Indeed, inhibition of Hsp90 by ganetespib has shown an encouraging 50% objective response rate in patients with advanced ALK+ NSCLC. To determine if ganetespib can be an effective strategy for ALK inhibitor resistance, we evaluated its activity alone or in combination with crizotinib in crizotinib-sensitive and -resistant cancer cells harboring ALK fusions.

Methods: H2228 and H3122 NSCLC cells, which express EML4-ALK, were treated with ganetespib, crizotinib or the combination, and cell viability and signaling cascades were assessed both in vitro and in vivo. To generate models of crizotinib resistance, H2228 NSCLC, H3122 NSCLC and NPM-ALK-expressing BaF3 cells were exposed to various crizotinib concentrations. Fifteen different ALK kinase domain substitutions were identified in the BaF3 cells; clonal NPM-ALK/BaF3 cells were made for each resistance mutation and assayed for sensitivity to ganetespib.

Results: Ganetespib was significantly more potent than crizotinib in both H2228 and H3122 NSCLC cells. The combination of ganetespib with crizotinib resulted in complimentary inhibition of MAPK signaling and strong synergistic anticancer activity in vitro and in vivo. In crizotinib resistant H2228 and H3122 cells, ganetespib displayed low nanomolar activity equivalent to that observed in the parental population. Ganetespib treatment induced the degradation of wild type and all 15 mutant forms of ALK, resulting in potent cell death.

Conclusions: Ganetespib effectively destabilizes EML4-ALK in crizotinib sensitive cells and multiple clinically validated ALK mutants in crizotinib resistant cells. The complementary actions of directed ALK inhibition with crizotinib and indirect ALK inhibition with ganetespib result in synergistic anticancer activity and warrants further study.

Disclosure: All Synta employees disclose that they have financial interest in Synta. All St. Jude employees declare no conflict of interest.

DIAGNOSIS AND IMAGING

127P

THE DIAGNOSTIC ROLE OF ENDOBRONCHIAL ULTRASOUND IN PERIPHERAL LUNG CANCER LESIONS

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Background: Endoscopic diagnosis and pathological findings remain the benchmark for diagnosis of lung cancer. Endobronchial ultrasound (EBUS) is a minimally invasive technique that expands the view of the bronchoscopist beyond the lumen of the airway. The sensitivity of transbronchial diagnosis of lung cancer showed superiority of EBUS guided bronchoscopy through successful placement of probes compared to fluoroscopic guidance only.

Objective: Introducing EBUS guided bronchoscopy to localize the peripheral pulmonary lesions (PPL), we attempted to evaluate the feasibility, efficacy and safety of its application in the diagnosis of peripheral lung cancer lesions.

We compared diagnostic yields of EBUS guided bronchoscopy according to diameter, location of lesions and different type of sampling procedures.
Patients and methods: At the Institute for Pulmonary Diseases of Vojvodina, Serbia 120 patients with PPL underwent EBUS between April 2010 and November 2011. A radial ultrasound probe (20MHz Km-BS20-26R) was used. The probe was connected to an endoscopic ultrasound system (EU-ME-1, Olympus, Japan). Our sampling procedures were transbronchial biopsy (TBB), catheter biopsy and brush biopsy.
Results: The lesions (14–59mm measured on CT) were visualized by EBUS in 99 patients (82%). The overall sensitivity in the diagnosis of PPL was 0.73. Overall diagnostic yield for lesions <30 mm was 0.34 and for lesions > 30 mm was 0.66. Prevalence of malignancy was 68%. Sensitivity of TBB (0.86), exceeds the other two sampling procedures-catheter biopsy 0.37 and brush biopsy 0.33. Multivariate analysis revealed that the diameter and the location of the peripheral lung cancer lesions were independent predictors of diagnostic sensitivity of EBUS guided bronchoscopy.
Conclusions: EBUS guided bronchoscopy is effective for diagnosing peripheral lung cancer lesions. The diameter, type of sampling procedures and the identification of the bronchus leading to the lesions were valuable as factors related to a higher diagnostic sensitivity with this procedure.
Disclosure: All authors have declared no conflicts of interest.

128P
THE ROLE OF BLIND PLEURAL BIOPSY IN DIAGNOSIS OF PLEURA

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Introduction: Blind percutaneous pleural biopsy has traditionally been performed to investigate the etiology of exudative pleural effusion. The aim of study was to prove the importance of blind pleural biopsy in diagnosis of possible lung cancer.
Material and methods: The study included 100 patients (63 male, 37 female; median age: 67) with pleural effusion of unknown etiology which was located in the right side in 60 patients, and in the left side in 40 patients. A blind pleural biopsy was performed on every patient with three as the least number of samples of tissue, which were sent for PH verification.
Results: In seven patients (7%) we proved pleuritis specifica (TBC). In 23 patients (23%) a malign PH finding was found. There were 11 patients (47%) with adenocarcinoma, 6 patients (26%) with clearly non-defined carcinosis of pleure, 2 patients (8,7%) with mesothelioma pleure, 1 patient (4,3%) with metastasis of ductal invasive breast carcinoma, 1 patient (4,3%) with metastasis of non-hodgkin lymphoma, 1 patient (4,3%) with metastasis of medullar carcinoma of the thyroid and 1 patient (4,3%) with NSCLC.
Conclusion: Closed pleural biopsy using a Tru-cut needle is effective for the specific diagnosis of exudative pleural effusion. In our study needle biopsy obtaining pleural tissue was diagnostic in approximately 23% of patients presenting with malignant effusion in the sample. Blind pleural biopsy is a relatively safe procedure with several limitations (painful, unpleasant) and a low percentage of positive result. But it is still a very acceptable, possible and safe method for the diagnosis of uncommon pleural effusion.
Disclosure: All authors have declared no conflicts of interest.

129P
IDENTIFICATION AND CHARACTERIZATION OF PROTEINS ISOLATED FROM MICROVESICLES IN MALIGNANT PLEURAL EFFUSIONS

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Microvesicles (MVs, also known as exosomes, ectosomes, microparticles) are released by various cancer cells, including lung, colorectal and prostate carcinoma cells. MVs released from tumor cells and other sources accumulate in the circulation and in pleural effusion (PE). Although recent studies have shown that MVs play multiple roles in tumor progression, the potential pathological roles of MV in pleural effusion, and their protein composition, are still unknown. In this study we report the first global proteomic analysis of highly purified MVs derived from pleural effusion in the patient with non-small-cell-lung-cancer (NSCLC). Using nano-LC–MS/MS following 1-D SDS-PAGE separation, we identified a total of 912 MV proteins with high confidence. Three independent experiments on three patients showed that MV proteins from PE were distinct from MV obtained from other malignancies. Bioinformatics analyses of the MS data identified pathologically relevant proteins and potential diagnostic makers for NSCLC, including lung-enriched surface antigens and proteins related to EGFR signaling. These findings provide new insight into the diverse functions of MVs in cancer progression and will aid in the development of novel diagnostic tools for NSCLC. Abbreviations: MV, microvesicle; NSCLC, non small cell lung cancer; PE, pleural effusion; LC, liquid chromatography; MS/MS, tandem mass spectrometry
Disclosure: All authors have declared no conflicts of interest.

130P
THE RADIOLOGICAL INCIDENCE OF RILI (RADIATION-INDUCED LUNG INJURY) AND ITS CORRELATION WITH DOSIMETRIC AND CLINIC PARAMETERS

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Radiation-induced lung injury (RILI) is the most common side effect after radiation therapy for lung cancer. It is known that the radiological finding of RILI is not always associated with the clinical manifestation of pneumonitis, and it is also not clear if it correlates with a decrease of patient's pulmonary function. In this study, we analyzed the predictive value of dosimetric parameters and Pulmonary Function Tests (PFTs) and their correlation with the radiological incidence of radiation-induced lung injury (RILI). Data from 64 patients with non-small cell lung cancer (NSCLC), stage I-IIIB, treated with (chemo)-radiation in our Institution from 2005 to 2010 were analysed. Eligibility criteria were: presence of visible tumor on a diagnostic chest CT scan, availability of CT scans before irradiation and at 3–6 months follow-up, baseline PFTs, with at least forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), total lung capacity (TLC), functional residual capacity (FRC) and vital capacity (VC) at 2–4 months follow-up. Data from patients were analysed. The worsening of pulmonary function was evaluated comparing PFTs performed before and after radiotherapy. Thirty-two patients (50%) developed radiation-induced changes in lung tissue. Logistic regression was performed to verify whether the commonly used lung dosimetric constraints could be predictive of RILI. MLD was found to be the strongest predictor of RILI (Odds Ratio: 1.20; 95% CI: 1.04 – 1.39; p: 0.012), but even V20, V30, V5, omolateral V20 proved to be significantly related to the onset of RILI. Moreover, the prescribed total dose was significantly associated with RILI. No patient showed clinical signs or symptoms of pneumonitis nor any worsening of PFTs resulted in clinically significant decrease of patient's respiratory performance. Our study confirmed the important role of dosimetric parameters for the prediction of lung toxicity. It also proved that the radiological finding of RILI does not necessarily correlate with a worsening of the patient's respiratory performance, or other respiratory symptoms, especially when treatment planning has been performed complying with the lung dosimetric constraints.
Disclosure: All authors have declared no conflicts of interest.

131P
THE MULTI-DISCIPLINARY APPROACH TO NEW LUNG CANCER CASES

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Introduction: Cancer care is increasingly delivered by multidisciplinary teams. As more and more treatment options emerge, the complexity of managing a lung cancer patient (pt) has evolved. The multi-disciplinary team meeting (MDM) is, for the majority of incident lung cancer cases, the platform from which treatment decisions are determined. We reviewed all new lung cancer cases where a multidisciplinary discussion was performed at our institution.

Methods: A prospectively maintained database was retrospectively reviewed for all new lung cancer cases discussed at the chest MDM from July 1st 2011 to December 31st 2011. Clinicopathological variables, e.g. histological subtype, tumour stage, smoking status and ECOG performance status were recorded. Treatments offered, and key performance indicators such as time to review from multi-disciplinary referral as well as time to treatment from established diagnosis and discussion were documented.

Results: A total of 61 new lung cancer cases were recorded, including 20 female and 41 male patients (pts). Thirteen (21%) pts were treated with surgical resection, and did not necessitate further therapy. Thirty eight percent had stage IV disease at diagnosis. Seven pts were referred directly to palliative care only from the meeting. Of the 29 pts referred to Medical Oncology for consideration of systemic therapy, 2 declined treatment themselves while 9 pts (31%) were deemed unfit by the assessing physician on the basis of worsening performance status and co-morbidities. Of those who proceeded to systemic chemotherapy, time from referral to review averaged at 7 days, & time from referral to treatment was 14–17 days.

Conclusion: While the rationale behind the MDM is the involvement of all key specialities in making clinical decisions on individual pts, the consensus reached at such a meeting is not always in reality the best option for a particular pt. Multidisciplinary discussions promote more evidence-based recommendations and improved treatment timing, as proven by our single institution experience. However, one size does not fit all. Treatment recommendations at such meetings fail to address pt preference as well as co-morbidities, and wider social and psychological issues.

Disclosure: All authors have declared no conflicts of interest.

EARLY STAGE AND LOCALLY ADVANCED NSCLC

132O
SHOULD RADIOLOGICALLY "SOLID" TUMOR BE VALID FOR LIMITED RESECTION IN SMALL-SIZED LUNG CANCER?

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Background: Small-sized lung cancers showing a wide area of ground-grass opacity (GGO) on thin-section computed tomography (CT) are considered to be a good candidate for limited surgical resection, because of its minimally invasive nature. On the other hand, the validity for limited resection of radiologically "solid" tumors is still controversial in small-sized non-small cell lung carcinoma.

Methods: Between 2008 and 2010, 680 consecutive patients underwent pulmonary resection for lung cancer. Findings of preoperative computed tomography were reviewed for all 680 patients and categorized into three parts: pure GGO, mixed GGO, and pure solid. All patients were evaluated with positron emission tomography (PET) and maximum standardized uptake value (SUVmax) was recorded. Several clinicopathological features were investigated for detecting predictors for hilar or mediastinal lymph node metastasis. Uni- or multivariate analyses were used for evaluating the relationship between those factors and lymph node metastasis.

Results: There were 227 patients with lung cancer showing solid or mixed GGO appearance on thin-section CT scan. Among them, nodal involvement was found pathologically in 42 (26%) patients with pure solid tumors in contrast to 4 (6%) patients with mixed GGO tumors (p=0.0002). Among 131 patients with clinical T1a tumors, there were 94 (71.8%) patients with solid tumor, and nodal involvement was observed in 15 (16.0%) in this group. Multivariate analysis elucidated the following predictors for no lymph node metastasis: mixed GGO tumor, presence of air bronchogram, low CEA level and low SUVmax. Among 94 T1a tumor showing pure solid, CEA level and SUVmax were the significant predictors for lymph node involvement by tumor based on multivariate analysis (p=0.0148, 0.0177). The frequency for lymph node metastasis was approximately 27% for patients having lung cancer with pure "solid" and high SUVmax even for T1a tumor.

Conclusions: Lymph node metastasis is frequently observed for pure "solid" lung cancer, especially when tumor shows high SUVmax. If limited surgery is indicated for solid lung cancer, the thorough intraoperative evaluation of lymph nodes is inevitable for preventing locoregional failure.

Disclosure: All authors have declared no conflicts of interest.

133O
LUNG CANCER WITH SCATTERED CONSOLIDATION: NEW RADIOLOGICAL INDEPENDENT CATEGORY OF PERIPHERAL LUNG CANCER ON THIN-SECTION COMPUTED TOMOGRAPHY

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Background: The extent of ground glass opacity (GGO) on thin-section computed tomography (CT) has been reported to be a good prognostic marker for lung cancer. However it is not rare to experience difficulty in measuring the size of GGO. Thus we investigated clinicopathological features in lung cancer of which GGO is difficult to measure.

Materials and methods: A retrospective study was conducted on consecutive 572 patients with resected lung cancer of clinical stage IA between 2004 and 2011. All patients underwent preoperative CT and authors reviewed radiological findings for all cohorts. Lung cancers having difficult GGO to measure are selected and their clinicopathological features are investigated. To elucidate characteristic findings, clinicopathological features on other lung cancers were also investigated and compared with each other.

Results: There were 71 (12.4%) patients with lung cancer of which GGO is difficult to measure. All of these lung cancers showed GGO and consolidation on thin-section CT. The consolidation was not easily measurable because of its scattered distribution, so we defined it as lung cancer with scatterd consolidation (LCSC). Of those, there were no nodal metastases at all. The frequency of pathological lymphatic and/or vascular invasion were significantly less observed (p<0.0001). In multivariate analysis for predictors of lymphatic and vascular invasion, new category "LCSC", CEA (≥5ng/ml), tumor size (>20mm) and C/T ratio (>0.5) were independent predictors significantly. And four categories (GGO group, LCSC, Part Solid group and Pure Solid group) are more graduated, more invasive and these distributions were significantly different (p<0.0001)(Table 1). **Conclusions:** New category "LCSC" has been proposed and this resolved the problem that we can't measure the

C/T ratio because of scattered consolidation. LCSC was independent category and minimally invasive lung cancer. We could decide each strategy for c-stage IA non-small cell lung cancer, classifying these four categories. Table 1:

	GGO group 0<C/T ratio≤0.5	LCSC	Part Solid group 0.5<C/T ratio<1	Pure Solid group C/T ratio=1
P-N1 or 2	0%	0%	8.5%	25%
Lymphatic invasion (+)	5.5%	16.9%	38.7%	69.5%
Vascular invasion (+)	3.2%	7.0%	30.2%	65.8%

Disclosure: All authors have declared no conflicts of interest.

134O
THE SIZE OF CONSOLIDATION ON THIN-SECTION COMPUTED TOMOGRAPHY IS A BETTER PREDICTOR OF SURVIVAL THAN THE MAXIMUM TUMOR DIMENSION IN RESECTABLE LUNG CANCER

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Background: Ground glass opacity (GGO) is a preoperative prognostic factor in resectable lung cancer. However, the impact of GGO on the T factor in the TNM staging system remains unclear and the maximum tumor dimension is also an uncertain measurement for assessing the prognosis of early lung cancer with a mixture of consolidation and GGO. Thus, we sought to determine which is a better prognostic factor in clinical stage IA lung cancer patients, the size of the solid component on thin-section CT scan or the conventional maximum tumor dimension.

Patients and methods: Between January 2004 and January 2011, 398 consecutive patients with lung cancer that measured less than 30 mm in diameter underwent surgical resection at our hospital. Univariate and multivariate analyses were performed by the logistic regression procedure to determine the relationship between pathologic lymph node metastasis-positive status and clinical or radiological findings such as the maximum dimensions of consolidation and the tumor, the presence of air bronchogram, pleural indentation and the preoperative serum carcinoembryonic antigen (CEA) level.

Results: Of the 398 patients, 59 (14.8%) had pathologic lymph node metastasis. Univariate analysis revealed four significant predictors of pathological nodal involvement: the presence of air bronchogram, the size of consolidation, the maximum tumor dimension and the preoperative CEA level ($p<0.01$, respectively). In a multivariate analysis, the size of consolidation and the presence of air bronchogram were significant predictors of nodal metastasis ($P<0.01$, respectively). Among 56 patients with lung cancers that showed consolidation larger than 20mm and no air bronchogram, 26 (46.4%) had nodal metastasis.

Conclusion: The maximum dimension of consolidation was an independent unfavorable prognostic factor, regardless of the maximum tumor dimension. This could lead to the more accurate prediction of pathological lymph node metastasis with both GGO and a solid component. It may also be useful for identifying candidates for limited surgical resection such as segmentectomy with nodal dissection in early lung cancers.

Disclosure: All authors have declared no conflicts of interest.

135O
STEREOTACTIC BODY RADIOTHERAPY (SBRT) USING VOLUMETRIC MODULATED ARC THERAPY (VMAT) WITH FLATTENING FILTER FREE (FFF) MODALITY FOR MEDICALLY INOPERABLE EARLY STAGE NON SMALL-CELL LUNG CANCER (NSCLC): A PROSPECTIVE SINGLE INSTITUTIONAL EXPERIENCE

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Purpose: To evaluate preliminary results and toxicity of SBRT using Volumetric Modulated Arc Therapy (VMAT) with Flattening Filter Free (FFF) beams modality for stage I NSCLC patients.

Methods and materials: Of the one hundred twenty-two consecutive patients with inoperable early-stage NSCLC that underwent SBRT at our Institution, in the last year 36 were treated with VMAT-FFF beams. For all patients a pretreatment CT scan and a whole-body [18F]-fluorodeoxyglucose positron emission tomography/ computed tomography (CT-PET) were acquired to rule out any other sites of disease. A pathologic diagnosis was available for 18/36 (50%). Prescription dose was 48 Gy in 4 consecutive fractions for all patients. Clinical outcome was evaluated by CT scan and CT-PET. The incidence of pneumonitis was graded according to the NCI CTCAE v3.0 scale.

Results: Median follow up was 9 months (range 3-14 months). Response was recorded in 35/36 patients (97.2%). Particularly, at the first follow up (3 months) 18/36 (50%) had complete remission and 13/36 (36%) partial remission major than 50%. No local recurrence occurred. At the last follow up all patients were alive. No pulmonary toxicity of grade 2 or greater was recorded. No chest pain toxicity occurred. Removal of the flattening filter (FF) increased the dose rate. The median beam-on time (BOT) was reduced by 75% passing from about 8 minutes (with FF modality) to 2 minutes (with FFF modality).

Conclusions: SBRT for early-stage NSCLC resulted in excellent local control with minimal toxicity. VMAT technique improved target coverage while minimizing higher dose to normal tissue with respect to coplanar beam arrangements. Furthermore, the BOT was significantly reduced in FFF modality with a subsequent increase of patient comfort and reduction of intra-fraction motion. In our experience SBRT with VMAT-FFF resulted in an earlier radiological response compared to FF modality though a longer follow-up is needed to assess the effective outcome incidence.

Disclosure: All authors have declared no conflicts of interest.

136O
EARLY RESPONSE AFTER 40 GY TO CONCURRENT RADIOCHEMOTHERAPY (RTCT) AFTER INDUCTION CHEMOTHERAPY STRONGLY PREDICTS COMPLETE RESPONSE, TIME TO PROGRESSION AND OVERALL SURVIVAL IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: To evaluate the impact of early response after 40 Gy of RTCT on unresectable stage III NSCLC outcome.

Methods: 85 patients (pts), treated from 2004 to 2011 were included in this study. Pts received 2 cycles of induction chemotherapy (CT): cisplatin (C) and docetaxel (D) followed by concurrent RTCT: 66–70 Gy, 6 weekly cycles of CD.

An early assessment by CT-scan was planned at 40–46 Gy. Pts with complete and partial response (RECIST criteria) were considered as early responders (ER) while pts with stable or progressive disease were considered as non-responders (NR). Median follow-up was 29.5 months [range: 3.9–84.1].
Results: Median age was 64 [range: 41–83], 52/85 of pts (61%) were male, 44/85 (52%), 33/85 (39%) had adenocarcinoma or squamous cell carcinoma respectively, 82/85 (96%) had performans status 0 or 1, 51/85 (60%) and 34/85 (40%) were stage IIIB or IIIA respectively. 82/85 (96%) received the planned 2 induction cycles, 80/85 (80%) completed > 4 concurrent cycles and mean radiation dose received was 58 Gy [range: 36–70]. 64% of pts were ER (54/85), all with partial response. T status at baseline was the only factor associated with ER: 77% (33/43) of pts staged T1-T3 were ER vs. 50% (21/42) of pts staged T4 (p=0.014). Among the 30 pts who achieved CR, 26 were ER (48%) and 4 were NR (14%) (p=0.02). Median time to progression (TTP) was 18 months in the ER group vs. 7 months in the NR group (p<0.001). Median overall survival (OS) was 24.5 months [%95CI: 12–36], with 36 and 14 months for ER and NR respectively (p<0.0001). Independent variable for better OS in multivariate analysis was only ER (HR=0.34 [%95CI: 0.18–0.64], p=0.001). Independent variables for better TTP in multivariate analysis were stage IIIA (HR=0.32 [%95CI: 0.16-0.62], p<0.0001), surgery (HR=0.29 [%95CI: 0.10–0.85], p=0.025) and ER (HR=0.42 [%95CI: 0.23–0.75], p=0.004).
Conclusion: ER had a significant better TTP and OS than NR. Since the likelihood of complete response in NR is low and toxicity is significant, the benefit of the RTCT completion in these pts is questionable. Those results incite to compare in NR the completion of RTCT vs. second-line CT in a prospective trial.
Disclosure: All authors have declared no conflicts of interest.

137O_PR
IMAGING EARLY RADIOTHERAPY (RT)-INDUCED CHANGES OF PROLIFERATION IN PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC) USING FLT-PET

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Background: [F-18]Fluorothymidine (FLT) is a promising biomarker of response to RT. 2 pilot studies in NSCLC have reported FLT PET uptake changes at variable time points during concurrent chemo-RT (Everitt 2009, Vera 2011). It is unknown, whether FLT uptake decreases early during RT alone and whether such changes exceed test-retest variability.
Methods: FLT-PET imaging is performed in NSCLC patients (pts) scheduled for radical RT twice at baseline (scans 1, 2) to assess reproducibility and after 3–10 RT fractions (scan 3), to assess response. Serial blood samples for analysis of circulating cell death biomarkers are also taken (M30/65). Data are dynamically acquired for 60min on the TrueV PET/CT scanner. 45–60 minute images are reconstructed using 3D-OSEM, smoothed with a 4mm Gaussian filter. Tumours are manually delineated on PET-CT images by a specialist thoracic radiologist. SUV reproducibility is measured as (SUV2-SUV1)/(SUV1+SUV2)*200. RT response is calculated as % change relative to single/average baseline value.
Results: 14 evaluable pts had a total of 31 scans: 10 male, 4 female, age 47-83, Stage II(1), III (10), III/IV(3) NSCLC treated with radical RT (12 pts: 55Gy in 20 fractions (#), 1pt: 66Gy in 33#, 1pt: 50Gy in 20#). 5 pts are evaluable for reproducibility and 12 for response. Pre-treatment scans were done within 2-6 days and on-treatment scans 6-15 calendar days after day1 RT (4-11 fractions, 11-30Gy). 38 lesions were delineated: 14 primary tumours (6-214cm^3, median 70cm^3) and 24 nodes (2-22cm^3, median 7cm^3) Mean absolute SUVmean reproducibility was 8.1% (primaries 7.6%, nodes 8.3%). Following RT malignant lesion SUVmean change ranged from +3.1 to -53.6% (average -33.6%, primaries -24.9%, nodes -39.4%). SUVmax average reproducibility was 12.2% and response -36.5%.
Conclusions: RT induces early decreases in tumour FLT uptake which exceed baseline reproducibility. We observed less average decrease in primary tumour uptake compared to previous report using comparable RT dose but with concomitant chemotherapy (SUVmax decrease >40%) (Everitt, 2009). Recruitment is ongoing and blood biomarker and updated imaging, including kinetic, results will be reported.
Disclosure: P. Koh: PK Koh is supported by a Cancer Research UK and AstraZeneca clinical fellowship grant. O. Ataman: Ozlem Ataman is an AstraZeneca employee. All other authors have declared no conflicts of interest.

138PD
A CASE-REFERENT STUDY FOR EVALUATING THE EFFECTIVENESS OF LUNG CANCER SCREENING IN VARESE, ITALY

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Background: The effect of chest x-ray (CXR) screening at population level on mortality from lung cancer (LC) has not been studied adequately and is an unresolved issue.
Aim: We applied a case-referent design to evaluate the effect of a five annual CXR screening programme on LC mortality, in a clearly defined population-based cohort of smokers.
Methods: In July 1997 we invited all smokers of >10 pack-years eligible for LC screening who lived in 50 communities of the Varese Province, to participate in a nonrandomized screening by annual CXR exam for five years. 5,815 smokers (the cohort) were invited. 21% of the cohort (1,244 subjects) self-select to participate in screening; 79% did not participate. The cohort was followed-up through December 2006, all LC deaths being recorded. For each case, one referent was sampled from the cohort. The referent, alive at the time of case death, was matched to case for birth year and gender. The screening history of cases and referents was evaluated. The crude LC risk of death in the screened relative to the unscreened subjects was estimated as odds ratio (OR), as follows: Crude OR = (n. sets of case screened, referent not screened)/(n. sets of case not screened, referent screened). To adjust for self-selection bias, we applied Duffy's formula (Appl Stat 2002; 51:235–43), using LC incidence as adjusting factor.
Results: Crude OR was 0.79 (95%CI, 0.47-1.32), suggesting a LC mortality reduction of 21% in screened versus unscreened subjects. After adjustment for self-selection, the effect increased to 41% (OR = 0.59; 95%CI, 0.35-0.99) (table).
Conclusion: CXR screening reduced LC risk of death in a population-based cohort of ever smokers. Adjustment for screenee's self-selection enhanced the LC mortality reduction.

Table. Case-referent sets and CXR screening history

Set	n.	%
Case and referent both screened	12	7.0
Case screened, referent not screened	26	15.1
Case not screened, referent screened	33	19.2
Case and referent both not screened	101	58.7
Total	172	100
Crude OR of LC death	0.79 (95%CI, 0.47-1.32)	
Adjusted OR of LC death	0.59 (95%CI, 0.35-0.99)	

Disclosure: All authors have declared no conflicts of interest.

139PD
DETECTION OF PREMALIGNANT BRONCHIAL LESIONS CAN BE IMPROVED BY COMBINATION OF AUTOFLUORESCENCE IMAGING (AFI) AND NARROW BAND IMAGING (NBI) VIDEOBRONCHOSCOPY

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Background: The search for most efficient bronchoscopic imaging tool in detection of early lung cancer is still active. The major aim of this study was to determine sensitivity, specificity, positive (PPV) and negative predictive value (NPV) of each technique and their combination in detection of premalignant bronchial lesions.

Patients and methods: This was a prospective trial that enrolled 96 patients with indication for bronchoscopy. Major indications were: radiological suspicion for lung cancer, surveillance of patients after surgery, evaluation of known malignancy, positive sputum cytology and prolonged cough. In each patient at least one but no more than 3 biopsies were taken from places identified as pathological under white light videobronchoscopy (WLB), AFI, NBI or their combination. At least one, but no more than 3 biopsies were taken randomly from places that appeared normal under each technique. Lesions were classified as visually positive if pathological fluorescence was observed under AFI or, dotted, tortuous and abrupt ending blood vessels were identified under NBI. Squamous metaplasia, mild, moderate or severe dysplasia and CIS were regarded as histologically positive lesion were.

Results: Sensitivity, specificity, PPV and NPV of WLB in detection of premalignant lesions were 26.5%, 63.9%, 34.4% and 54.9% respectively, corresponding values for AFI were 52%, 79.6%, 64.6% and 69.9% respectively, for NBI were 66%, 84.6%, 75.4%, 77.7%, respectively, while corresponding values for combination of NBI and AFI were 86.1%, 86.6%, 84.6%, and 88% respectively. Combination of NBI and AFI significantly improves sensitivity when compared to each individual technique ($p<0.001$). When specificity is of concern combination of techniques improves specificity of WLB ($p<0.001$), specificity of AFI ($p=0.03$) but it has no significant influence on specificity of NBI ($p=0.53$).

Conclusion: combination of NBI and AFI in detection of premalignant bronchial lesions increases both sensitivity and specificity of each technique. However more prospective, randomized data are needed to validate and confirm these findings.

Disclosure: All authors have declared no conflicts of interest.

140PD_PR
BREATH ANALYSIS FOR DISTINGUISHING MALIGNANT FROM BENIGN PULMONARY NODULES USING NANO ARTIFICIAL OLFACTORY SYSTEM

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The overreaching goal of this study is to tailor a novel Nano Artificial Olfactory System (NaNose®) in order to compare the signatures and compositions of exhaled VOCs in people with solitary pulmonary nodules (SPNs) as a part of a fast, non-invasive diagnostic method. Breath samples were collected from 74 volunteers with SPNs in a cross-sectional comparative survey conducted in University of Colorado Cancer Center and Denver Veterans Affairs Medical Center (Denver, CO, USA). The exhaled breath was analyzed by the NaNose® and, for comparsion, by GC-MS for determining the chemical nature of the VOCs. Pattern recognition methods were used then to analyze the results obtained from GC-MS and NaNose® and to correlate the results with the clincal data. Discriminant function analysis of the signals of the sensor array containing 5-nm gold nanoparticle sensors and HBC-functionalized random network carbon nanotube sensors discriminated benign from malignant single pulmonary nodules (SPNs) in a high-risk cohort based on lung cancer related VOCs profiles ($p<0.0001$; accuracy 88±2%). Further, it discriminated NSCLC from SCLC ($p=0.0015$; accuracy 94±1%) and between early vs. advanced disease ($p<0.0001$; accuracy 88±2%). Further studies are required as to evaluate such non-invasive approach in SPNs positive patients in the post NLST-era. The results provide a launching pad towards obtaining an inexpensive, compact tool that is amenable to widespread screening and that has a potential for direct and real-time.

Disclosure: All authors have declared no conflicts of interest.

141PD
DISCRIMINATION OF CLINICAL STAGES IN NON-SMALL CELL LUNG CANCER PATIENTS BY SERUM HSP27 AND HSP70: A MULTI-INSTITUTIONAL CASE-CONTROL STUDY

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Introduction: Lung cancer represents a major healthcare problem and biomarkers for detection are not available. We have recently described that patients with manifest COPD evidence elevated levels of serum heat shock proteins (HSPs). Based on these data, we speculated whether HSPs are also increased in lung cancer patients.

Methods: Serum levels of HSP27, pHSP27 and HSP70 in patients with early (n=34) and advanced (n=72) NSCLC were determined by ELISA. Healthy smokers (n=24), healthy never-smoker volunteers (n=33) served as control population.

Results: Serum levels of HSP27 were elevated in NSCLC patients diagnosed at an early or advanced stage when compared with both healthy control groups ($P<0.005$ and $P<0.0001$ respectively). Moreover, HSP27 levels could differentiate between early vs. advanced stage NSCLC ($P=0.0021$). Serum levels of HSP70 were also significantly elevated in patients with NSCLC diagnosed at an early or at an advanced stage when compared with either healthy control groups ($P=0.0028$ and $P<0.0001$ respectively). In univariate logistic regression models including healthy subjects and patients with NSCLC, HSP70 had an area under the curve (AUC) of 0.779 ($P<0.0001$) and HSP27 showed an AUC of 0.870 ($P<0.0001$).

Conclusion: Our data suggest that serum HSP27 levels might serve as a possible tool to discriminate between early and advanced stage NSCLC.

Disclosure: All authors have declared no conflicts of interest.

142PD
FDG-PET/CT FOR RESPONSE EVALUATION IN LOCALLY ADVANCED NSCLC PATIENTS – A PILOT STUDY

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Introduction: About 25% of non small cell lung cancer (NSCLC) patients have locally advanced disease and can potentially be cured with chemo-radiotherapy. This treatment is usually accompanied by high complication rates and

some patients die shortly after the end of intensive treatment course. Being able to predict who could benefit from this intensive treatment strategy can help us improve the outcome and avoid highly toxic, unbeneficial treatments. Recently, PERCIST 1.0 was proposed as criteria for standardization of evaluating response by FDG-PET/CT. The purpose of this study was to investigate the usefulness of PERCIST 1.0 in NSCLC patients in the daily routine by evaluating whether PET/CT will add more valuable prognostic information that could help tailor patient treatment accordingly.
Methods: 21 consecutive patients diagnosed with locally advanced NSCLC, who had both a baseline PET/CT scan and an evaluation PET/CT scan performed after 1–4 cycles of chemotherapy (carboplatine / vinorelbine), prior to curative intended radiation therapy, at our institution from September 2009 until march 2011. The PET/CT scans were analyzed by one experienced evaluator semi-quantitatively according to the recently proposed PERCIST 1.0 criteria for evaluation of response to treatment, by Wahl et al. (Patient outcome was not known to the evaluator, at the time of evaluation.) The change in SUL peak at the evaluation scan was calculated as according to the PERCIST 1.0, and compared to progression free survival (PFS).
Results: The percentage change in SUL peak and the resulting response categories progressive metabolic disease (PD), stable metabolic disease (SMD) and partial metabolic disease (PMR) correlate well with Time to progression. Patients with PMR and SMD had statistically significant longer time to progression (11 months SE 1.8) as compared to (4 months SE 1.5) in patients who had PD.
Conclusion: Response by PERCIST 1.0 evaluated early in the course of curatively intended chemo-radiotherapy can be used to predict PFS, and progression at the early evaluation prior to radiotherapy predicts a poor outcome and may in the future be considered a valid indicator for change of therapeutic strategy.
Disclosure: All authors have declared no conflicts of interest.

143PD
NSCLC: RADIATION DOSE - TUMOR SIZE RELATED, ACCELERATED (1,8 GY BID) RADIOTHERAPY – FINAL RESULTS OF A PROSPECTIVE STUDY

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Purpose: Final results of a prospective study, correlating radiation dose to tumor size.
Methods: Doses to primary tumors were adjusted along increasing tumor size in 4 groups (<2.5 cm / 2.5-4.5 cm / 4.5-6.0 cm / >6.0 cm). ICRU-doses of 73.8 Gy/ 79.2 Gy/ 84.6 Gy/ 90.0 Gy, respectively, were applied. Involved nodes received a median dose of 59.4 Gy (54,0-75,6 Gy). Fractional doses 1,8 Gy bid. Conformal target splitting technique was used mostly. 2 cycles platin-containing chemotherapy were given before radiotherapy (preferential interval to RT <10 days). Primary end points are local and regional tumor control, secondary endpoints are survival and tolerability. 2004 – 2009: 160 consecutively referred, unselected patients with 164 histologically/ cytologically proven NSCLC were enrolled; Stage I: 38 patients; II: 6 pts.; IIIA: 69 pts.; IIIB: 47 pts. Weight loss >5%/3 months: 38 pts. (24%). Patients were rigorously followed for locoregional tumor control (by periodic CT and/or PET scan) and toxicity.
Results: Minimum follow-up time is 24,8 months, median follow-up time 38 months for patients alive (range 24,8–96). We observed 32 local recurrences, distributed in the described tumor size groups as follows: 2/27, 20/ 94, 7/30 and 3/13. Ten patients failed regionally only. The local / regional tumor control rates at 2 years are 77% / 93%, respectively. Median overall survival (OS) time is 28,0 months, 2- and 5-year overall survival rates for all patients are 57% and 19%, respectively. For stage III patients, median OS is 24,3 months, 2-/ 5-year OS rates 51% / 18%, respectively. 2 treatment-related deaths (progressive pulmonary fibrosis) occurred in patients with pre-existing pulmonary fibrosis. Further acute toxicity was mild: pneumonitis grade 3 (n=6); esophagitis grade 2/ 3 (n=16/ 8). Late esophageal toxicity grade 3 (n=1). No further late toxicity scored >grade 1. As in 94% locoregional recurrences occured within 2 years, these figures can be regarded as final results.
Conclusions: Dose-escalated accelerated radiotherapy following induction chemotherapy is well tolerated. Locoregional tumor control and survival compare favourably with the results of simultaneous chemo-radiotherapy, which is considered 'state of the art' for non-resected NSCLC.
Disclosure: All authors have declared no conflicts of interest.

144PD
TRIMODALITY TREATMENT INCLUDING RADICAL SURGERY IN ADVANCED STAGE NON-SMALL CELL LUNG CANCER – A RETROSPECTIVE, EXPLORATIVE STUDY

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Background: Advanced stage non-small cell lung cancer (NSCLC) is a fatal disease, characterized by N2/N3 lymph nodes and/or locally advanced tumor. In clinical stage III NSCLC the role of surgical resection – combined with induction treatment – remains controversial. We aimed to assess the clinical outcome of patients undergoing a trimodality therapy regime (induction chemoradiotherapy and radical resection) for advanced stage NSCLC.
Methods: We retrospectively reviewed the medical files of all consecutive patients undergoing induction chemoradiotherapy followed by curative resection between 1998 and 2010 at our institution.
Results: A total of 49 patients received induction chemo- and radiotherapy followed by radical surgery, including 11 patients (22.4%) with pancoast tumors. The patients comprised 34 (69.4%) men and 15 (30.6%) women with a mean age of 54.5 years at the time of resection. Three segmental resections, 24 lobectomies, 3 bilobectomies, and 20 pneumonectomies (11 extra- and 9 intrapericardial) were performed. In 48 patients a complete resection (R0) was achieved. 21 (42.9%) patients had a postoperative complication, ranging from 29.2% after lobectomy to 63% after pneumonectomy (p=0.23). No deaths occurred within 30 days. Overall 3-year survival rate was 45%. Overall disease free survival (DFS) was 10.14 months (95%CI 4.76 – 15.51). In patients with pneumonectomy 3-year survival was significantly better than in patients with lobectomy (55% vs. 32%, p=0.039; HR 0,386; 95% CI 0,153 – 0,976).
Conclusion: Within a trimodality therapy including radical surgery favorable results for patients in advanced stage non-small cell lung cancer can be achieved. In this series survival in patients undergoing pneumonectomy tended to be superior to patients with lobectomy.
Disclosure: All authors have declared no conflicts of interest.

145P
ADJUVANT CISPLATINUM-DOCETAXEL CHEMOTHERAPY IN STAGE IB-II RESECTED NSCLC PATIENTS: THE TOLEDO TRIAL

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To evaluate the tolerability of four cycles of adjuvant docetaxel plus cisplatin in patients with completely resected stage IB-II NSCLC. This multicenter, open, parallel-group study was conducted in 15 hospitals in Belgium and 3 hospitals in the Netherlands between Dec 2005 and Sept 2010. The trial was designed as a randomized phase II trial with stratification according to stage IB versus II and 2:1 randomization between cisplatin + docetaxel arm (Cis and Doc both 75 mg/m2 on day 1) ("experimental arm") versus a 3 w schedule cisplatin + vinorelbine arm (Cis 80 mg/m2 on day 1; VRB 25 mg/m2 on days 1 and 8) ("reference arm"). The primary endpoints were success of treat-

ment delivery (defined as at least 3 cycles of CT with a relative dose intensity of 80 % or above) and toxicity (any non-hematological grade 4 toxicity).
Results: 101 of 104 randomized patients (69 Cis-Doc, 35 Cis-VRB) started the allocated treatment and were included in the intent-to-treat analysis (68 Cis-Doc, 33 Cis-VRB). In arm Cis-Doc 52 patients (76%) achieved 3 cycles with relative dose intensity of both cisplatin and docetaxel ≥ 80%. In arm Cis-VRB 23 patients (70%) completed 3 cycles with relative dose intensity of both cisplatin and vinorelbine ≥ 80% In arm Cis-Doc 46 patients (68%) experienced grade 3-4 hematological toxicity (neutropenia and febrile neutropenia) whereas 36 patients (53%) reported non-hematological grade 3 adverse events (mainly gastro-intestinal events and fatigue). 1 patient (1%) had grade 4 CNS cerebrovascular ischemia (unlikely related to study treatment). In arm Cis-VRB 26 patients (79%) had grade 3–4 hematological toxicity and 14 patients (42%) non-hematological grade 3 toxicity. No treatment-related deaths were observed.
Conclusions: This randomized Ph II study shows:
a: A larger than expected proportion of patients receiving the reference arm (Cis-VRB) , possibly due to the 3 weeks schedule
b: The high percentage (80%) of successful administration of the experimental arm (Cis-Doc) in adjuvant approach, and manageable toxicities .
Follow-up for progression free and overall survival is currently ongoing. These results should be confirmed in larger randomized trials focused on survival analysis.
Disclosure: All authors have declared no conflicts of interest.

146P
MID-VENTILATION BASED PTV MARGINS IN STEREOTACTIC ABLATIVE RADIOTHERAPY (SABR): A CLINICAL EVALUATION

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Introduction: State of the art in SABR includes the acquisition of a four dimensional (4D) planning CT scan. Conventionally, an Internal Target Volume (ITV) is generated from this 4D CT to account for respiratory motion during treatment delivery. An alternative approach is to plan on the mid-ventilation (midV) CT (frame of the 4D CT with the tumor closest to its time average mean position) and use a Clincal Target Volume to Planning Target Volume (PTV) expansion based on a margin recipe, to simultaneously account for respiratory motion and other geometrical uncertainties[1]. This approach leads to considerably smaller margins especially for patients with larger tumor motion. The purpose of this study was to evaluate the validity of this approach.
Materials and methods: Two hundred patients (107 males, 93 females) treated between June 2006 and March 2010 were analyzed. Mean age was 73 years; tumor stage was T1 in 167 patients, T2 in 30 patients and lung metastases in 3 patients. Tumors were located in the right and left upper lobe in 73 and 70 patients, right middle lobe in 4 patients, right and left lower lobe in 30 and 23 patients. In all patients a 4D CT was acquired and subsequently the midV CT scan was selected. Tumor amplitudes were determined in left-right (LR), cranio-caudal (CC) and anterior-posterior (AP) direction, and used to calculate patient specific PTV margins[2]. Patients were generally treated with 3x18 Gy using static Intensity Modulated Radiotherapy or Volumetric Modulated Arc Therapy using online 3D/4D Cone Beam CT guidance.
Results: After a median follow up of 17.8 months, local recurrence (within the PTV) occurred in 4 patients. In this patient cohort the median LR, CC and AP peak-to-peak amplitude were 2 mm (range 0-9), 4 mm (0-39) and 3 mm (0-14), respectively. The median 3D vector length was 6.9 mm (0-39). In case of local recurrence the median 3D vector length was 7.4 mm (3-13.9), with in every quartile one event.
Conclusion: An excellent local control of 98% was established using the MidV approach combined with online image guidance using SABR in early stage lung cancer. This provides strong support to incorporate respiratory motion directly into the PTV instead of using an ITV.
[1]Wolthaus et al. IJROBP, 2008
[2]Sonke et al. IJROPB, 2009
Disclosure: All authors have declared no conflicts of interest.

147P
RADIOFREQUENCY (RF) ABLATION AS ALTERNATIVE THERAPY FOR EARLY STAGE LUNG CANCER AND SINGLE METASTASIS: OUR EXPERIENCE IN 26 PATIENTS NOT ELIGIBLE FOR SURGERY

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Objectives: Surgery is the treatment of choice for localized primary lung cancer and single metastasis. Unfortunately many patients are excluded from surgery because of risks related to age and comorbidities. We retrospectively analyzed our experience to evaluate RF ablation as an alternative procedure in these selected cases.
Methods: From 2008 to 2011, 26 patients aged between 63 and 88 underwent CT-guided RF ablation for single pulmonary lesion. 13 patients were affected by primary cancer stage I-II (N0), 10 by single metastasis arising from tumor already resected and 3 by advanced stage (IIIB-IV) lung cancer. These 3 cases underwent RF ablation for hemoptysis or pain palliation. Patients were excluded from surgery due to comorbidities (21), advanced stage (3) or refusal (2). 22 patients presented a smaller than 3 cm lesion. They required a single needle passage; the others required 2-3 passages. Patients were followed-up with CT in the first 6 months and subsequently with PET/CT. Data were analyzed by the Kaplan-Meier method.
Results: Complete necrosis was always obtained in smaller than 3 cm lesions. In 15 cases we registered a post-procedure pneumothorax; 11 required a drainage. The medium hospital stay was 3 days. At follow-up 10 deaths were recorded (9 for recurrence). The median survival was 30 months. Survival was 100% at 6 months, 95.2% at 12 months, 71.9% at 24 months and 21.6% at 32 months. There were relapses in all patients with lesions bigger than 3 cm, in 4 with primary cancer smaller than 3 cm, and in 3 with metastasis. Disease-free survival was 25 months divided as follows: 100% at 6, 86.3% at 12, 47.4% at 24 and 17.8% at 32 months. Palliation cases obtained symptom remission for 6 months.
Conclusions: Our data suggest RF ablation as a successful alternative in selected patients with high surgical risks. Its therapeutic efficacy appears to be limited to single lesions smaller than 3 cm.
Disclosure: All authors have declared no conflicts of interest.

148P
DIFFERENTIAL CLINICAL CHARACTERISTICS OF OPERATED PATIENTS WITH LUNG SQUAMOUS CELL CARCINOMA AND ADENOCARCINOMA

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Background: Squamous cell carcinoma (SCC) and adenocarcinoma (ADC) comprise 50-80 % of non-small cell carcinomas of lung. Recent studies have shown differences in molecular networks between SCC and ADC subtypes. Moreover, chemotherapeutic treatment of SCC and ADC is nowadays different, which emphasizes need of accurate diagnostics.
Hypothesis and aims: We hypothesized that lung SCC and ADC may have various clinical characteristics. Our aim was to compare the clinical features of the patients with SCC and ADC, who had been operated and diagnosed by histology.
Material and method: A retrospective study material consisted of 232 patients who were treated by surgical lung operation in Oulu University

Hospital, Oulu, Finland, between the years of 1998 and 2007. Diagnoses were confirmed by histological evaluation of lung resection material. The clinical data was gathered systematically by using a specific form that was planned for the study. Clinical, histological and radiological data was re-evaluated by pulmonologists as well as pulmonary radiologists and pathologists.
Results: Of the 130 patients with SCC and 102 patients with ADC, 59 were women and 173 men. Proportion of women was 14.6% in SCC and 39.0% in ADC. 96.9% of SCC patients were ex- or current smokers while 75.5% of ADC patients were smokers and 15.7% non-smokers. Survival of the patients with SCC was 50.9 months when that of the ADC patients was 43.2 months. 6.2% of SCC and 7.8% of ADC patients had a family history of cancer. 79.2% of SCC patients and 45.0% of ADC patients got sole surgical treatment. 6.2% of surgically treated SCC patients and 25.5% of ADC patients were given adjuvant chemotherapy. Common symptoms at the time of diagnosis in patients with SCC and ADC were cough (39.2% versus 18.6%), hemoptysis (23.0% versus 9.8%) and dyspnoea (23.1% versus 16.7%).
Conclusion: Clinical characteristics of the patients with SCC and ADC showed variable features with differential sex, survival, smoking habits and symptoms. We concluded that SCC and ADC are clinically, and not only by molecular biology and histology, differently behaving lung diseases.
Disclosure: All authors have declared no conflicts of interest.

149P
CLINICAL, MOLECULAR FEATURES AND PROGNOSIS IN A SERIES OF PATIENTS (PTS) NEVER-SMOKERS WITH RESECTED NON-SMALL CELL LUNG CANCER (NSCLC)

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Purpose: Describe the clinical and pathological features of NSCLC from never-smokers and correlate the clinical and molecular findings with prognosis.
Methods: From March 1996 to September 2011, 26 never-smoker patients with NSCLC were treated at our institution with radical surgery. We analized the tumor samples from these patients who underwent complete resection. Molecular data available for EGFR (real-time PCR) and ALK (FISH) were collected retrospectively from medical records.
Results: Twenty-six pts were identified: 22 pts (85%) were female. All were Caucasian and never-smokers. Median age was 69 years (range 33-82) and 100% were adenocarcinoma (ADC). According to the TNM 7TH edition the p-stage was: IA, 7.6% (2 pts); IB, 38.4% (10 pts); IIA, 7.6% (2 pts); IIB, 11.5% (3 pts); IIIA, 26.9% (7 pts); IIIB, 7.6% (2 pts). Neoadjuvant chemotherapy (CT) was administered in 4 pts, adjuvant CT in 7 pts and adjuvant radiotherapy (RT) in 2 pts. Median overall survival (OS) was 32.79 months (m) (range 2.96–189.01) and median disease free survival (DFS) was 16.63 m (range 2.96–115.46). Fifteen pts had recurrence disease (57.7%), with a relapse-free interval of 14.1 m (range 6.25–78.94): local disease in 7 pts (47%) and distant disease in 8 pts (53%). Median overall survival among patients who relapsed was 35.76 m (range 4.80-189.01). Molecular analysis was performed in 13 pts (EGFR-mutation status was determined in 12 pts and ALK in 7 pts). We found EGFR-mut in 9/12 pts (3 pts with exon 19 delection, 6 pts with mut exon 21 L858R) and ALK positive in 1/7 pts. First-line treatment used in 11 pts: 4 pts (36%) received platin-based CT with partial response (PR) in 3 pts. 7 pts (64%) received target therapy achieving PR in 2 pts and complete response (CR) in 2 pts.
Conclusion: Absence of smoking history defined a subset of NSCLC population characterized by female gender, adenocarcinoma histology and a great portion of molecular alterations. Most of these patients present an oncogene alteration with available target therapies.
Disclosure: All authors have declared no conflicts of interest.

150P
EFFECT OF RADICAL TREATMENT ON EXERCISE CAPACITY AND MUSCLE FORCE IN PATIENTS WITH INTRATHORACIC CANCER

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Introduction: Radical treatment in patients (pts) with intrathoracic cancer aims to prolong life and restore quality of life. Data on its effect on exercise capacity and muscle force after radical treatment are scarce.
Aim: To investigate the effect of radical treatment on exercise capacity, muscle force and quality of life in a cohort of consecutive pts with newly diagnosed lung cancer or pleural mesothelioma.
Methods: In pts with c-stages I-IIIB lung cancer or c-stage I-II mesothelioma pulmonary function, exercise capacity, peripheral muscle force and quality of life were assessed before and either 6 weeks (w) after surgery when applied as sole therapy, or 2 w after combined modality therapy (any combination of chemotherapy with radical radiotherapy and/or surgery). Data are presented as median with 95% CI and compared with Wilcoxon's test.
Results: 117 pts (86 male, age: 64 years (47 – 77), BMI: 25 kg/m^2 (18 – 34), 40% COPD; 35 pack years (0 - 70)), 105 NSCLC, 6 SCLC and 6 mesothelioma were enrolled in the study: 50% underwent surgery as sole therapy, 12% surgery + chemotherapy, 24% chemotherapy + radiotherapy, 10% surgery + chemotherapy + radiotherapy and 4% radiotherapy only. 24 pts dropped out and 18 are still under treatment. The maximal exercise capacity and 6MWD decreased significantly after treatment (from 100 Watt (48 – 184) to 82 Watt (38 – 147) and the 6MWD from 515 m (388 – 632) to 482 m (328 – 617)). Fatigue and pain increased significantly after treatment (VAS pain from 1 points (0 – 9) to 2 points (0 – 8) and FACT-F from 9 points (3 – 30) to 13 points (3 – 33)).
Conclusion: Radical therapy for intrathoracic cancer significantly affects exercise capacity, muscle force, pain and fatigue. Mature data on all patients will be available at the meeting.

	Before treatment	After treatment
FEV_1 (%pred.)	88 (54 – 116)	72(48 – 106)*
VC (%pred.)	101 (92 – 111)	87 (72 – 104)*
$DL_{,CO}$ (%pred.)	73 (43 – 125)	55 (30 – 106)*
VO_2max (%pred.)	69 (39 – 109)	58 (33 – 83)*
VO_2max/kg (ml/min/kg)	20 (12 – 30)	16 (10 – 26)*
6MWD (%pred.)	77 (59 – 95)	63 (51 – 95)*
QF (%pred.)	67 (33 – 107)	61 (28 – 96)*
Max.Load (%pred.)	79 (43 – 137)	64 (30 – 115)*

*P<0.05

Disclosure: All authors have declared no conflicts of interest.

151P
EARLY CEREBRAL RELAPSE IN PATIENTS UNDERGOING RADICAL TREATMENT FOR NON-SMALL CELL LUNG CANCER

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Background: Despite complete surgical resection of primary non-small cell lung cancer (NSCLC), brain metastases are frequent causes of initial recurrence. We evaluated the incidence of brain metastases in patients who underwent complete resection for NSCLC followed by adjuvant chemotherapy (ACT) and factors associated with risk of brain relapse.

Methods: The records of 180 patients who underwent curative-intent surgery and ACT for NSCLC from 2005 to 2009 and enrolled in the follow-up program were reviewed. All of patients were neurologically intact at the initial staging. Patients who had brain metastases at the time of diagnosis were excluded from analysis. The incidence of brain metastases was estimated using the Kaplan-Meier method. A univariate analysis assessed factors associated with the development of brain metastases.
Results: 178 patients were evaluable. Median age 64±7,7 years, 96(53,3%) were male and 84(46,7%) female. Median follow-up of all patients was 41 months. Brain metastases as the sole site of first relapse was observed in 17 (9,6%) patients. ACT was given to 94,1% of them. Postoperative pathological stage distribution was: stage Ib, 2 patients (11,8%), stage IIa, 3 patients (17,6%); stage IIIa, 11 patients (64,7%); stage IV (T2bN0M1a), 1 patient (5,9%). Adenocarcinomas, squamous cell carcinomas and large cell carcinomas were found in 10(58,8%), 4(23,5%), 3(17,6%) of patients, respectively. The 2 years actuarial rate of brain metastases was 11,7%. All of the patients developed brain metastases within 18 months after complete resection of primary lung tumor. On univariate analysis, postoperative higher stages (≥IIIa) of NSCLC (Relative risk [RR]=3,3; 95% confidence interval (CI) 1.2–9.1; logrank p=0,0001), larger (>3cm) tumor size (RR=1,9; 95% CI, logrank p=0,006) were associated with significant increased risk of brain metastases.
Conclusion: The patients with operable NSCLC without neurological symptoms at the time of diagnosis have a high incidence of early intracranial recurrence. We consider that brain imaging should be included as essential part of preoperative evaluation in patients with large tumor size (>3cm).
Disclosure: All authors have declared no conflicts of interest.

152P
ACCELERATED HYPOFRACTIONATED RADIOTHERAPY IN INOPERABLE LUNG CANCER USINGTOMOTHERAPY: THE LAUSANNE EXPERIENCE

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Purpose/objective: To asses the feasibility and the acute toxicity of accelerated radiotherapy in medically inoperable, non-small-cell lung cancer patients using an hypofractionated RT schema by helical Tomotherapy, maintaining the dose at the organs at risk (BED2GY) below the values of conventional radiotherapy.
Material/methods: Between March 2011 and December 2011, 13 patients were enrolled to receive accelerated hypofractionated radiotherapy. Patients had documented I or IIA stage non-small-cell lung cancer. Multiphase chest computed tomography simulation scan was performed in all cases. The dose prescription for the ITV was 60Gyin 5 bi-weekly fractions. Dose to the organs at risk did not exceed normal tissue tolerance limits. Acute toxicity was registered using the CTCAE,v 3.0.
Results: Median follow up was 6 months. No acute grade 3 toxicity was observed. All patients were alive at their last follow up with no evidence of disease-progression.
Conclusions: Preliminary data demonstrate the feasibility of bi weekly treatment of the tumor by accelerated hypofractionated intensity-moudulated radiotherapy, without major toxicity. Further long follow up is needed.
Disclosure: All authors have declared no conflicts of interest.

153P
PATTERNS OF RECURRENCE AFTER TREATMENT WITH CONTINUOUS HYPERFRACTIONATED ACCELERATED RADIATION THERAPY IN NON-SMALL CELL LUNG CANCER

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Introduction: CHART is a novel method of radiotherapy delivery, which would combat the accelerated repopulation of tumour cells during radiotherapy. Continuous Hyperfractionated Accelerated Radiation Therapy (CHART) using 54 Gy given in 1.5 Gy fractions, 3 times daily for 12 consecutive days has been compared with conventional radiotherapy (60 Gy in 6 weeks). This resulted in a 9% absolute improvement in 2 year survival. (29% v 20%, p=0.004, hazard ratio=0.77) for CHART. However, 61% of the patients treated with CHART died with disease in the chest and 50% had distant metastatic disease. We retrospectively studied the patients treated by CHART in our centre, to evaluate the outcome and observe patterns of recurrence.
Methods: The medical records of patients treated with CHART for stage I-III-B between 2004–2009 were reviewed. Disease recurrence in tumour bed, ipsilateral hilum, and/or mediastinum was considered a local/regional recurrence (LRR). Nodal failures were defined as a new or enlarging LN>1 cm on short axis on CT. The actuarial rates of LRR and distant recurrence were estimated using the Kaplan-Meier method. Time to disease recurrence and overall survival were evaluated.
Results: 37 patients were treated with CHART between January 2004 and January 2009. Most patients treated were stage 1A or stage 1B suggesting increased use of concurrent chemoradiotherapy for bulky tumours and locally advanced stage disease. 43% of patients recurred during the study period. 66% of the recurrences were locoregional. Brain and pleura were the other sites of recurrence. Median time to recurrence was 35 months. (CI: 17 – 53.) Median survival for patients was 21 months, which meets the standard of 16.5 months set by the pivotal CHART trial. Estimated 2-year survival is 46.5%, within this cohort, compared with 29% in the 1997 trial. There was also a trend for poorer short-term survival, if over the age of 70, although this was not statistically significant (p=0.7)
Conclusion: In spite of the relative early stage disease of the patient cohort, a significant proportion had local recurrence. This might suggest the need for further dose escalation or the need for combination with radiosensitising agents.
Reference: Saunders et al. CHART versus conventional radiotherapy in non-small-cell lung cancer: a randomised multicentre trial. Lancet 1997; 350: 161-165.
Disclosure: All authors have declared no conflicts of interest.

154P
LONG-TERM RESULTS OF COMBINED TREATMENT WITH POSTOPERATIVE ACCELERATED HYPERFRACTIONATED RADIOTHERAPY IN OPERABLE LUNG CANCER

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The role of post-operative radiotherapy (PORT) in radically resected non-small cell lung cancer treatment is still under discussion. New methods of radiotherapy are necessary for increase of results of the combined treatment. The study included 40 patients (pts) with NSCLC stage II-III and intrathoracic lymph nodes metastases (N1-2), which in the period from 1998 to 2004 completed a combined treatment with PORT in the accelerated hyperfractionated regimens. From subsequent analysis excluded two patients who died of postoperative complications within 4 months after the operation. All the pts were performed radical surgery an adequate level (20 lobectomy, 16 pneumonectomy, 2 bilobectomy), 13 pts received accelerated hyperfractionated radiotherapy: 1.25 Gy, 2 fractions a day, other 25 patients: accelerated hyperfractionated radiotherapy on the uneven pattern of crushing daily dose 2 fractions 1 and 1.5 Gy to a total dose 45–50 Gy (86,6-94 units TDF) in all patients, which is equivalent to a dose of 52–56 Gy with conventional fractionation. The median age was 55 years (39–69 years). Stage II disease was diagnosed in 16 pts, III in - 22. Radiation therapy began 3-5 weeks after surgery. Radiation esophagitis occurred in 58% pts (Grade 1 - in 14 pts, grade 2 - in 6, grade 3 - y 2), one pt had an unplanned

interruption for 14 days due to esophagitis. The clinical signs of radiation pneumonitis in the final stages of treatment were observed in 7 (18.4%) pts. The overall 3-year and 5-year survival was 42% and 29%, respectively. Characteristically, 50% of pts died from progression of underlying disease in the first 1.5 years after surgery, and distant metastases were detected in 14 of them, which corresponds to 37% of all enrolled in the study. This may indicate a high risk of subclinical distant metastases in N1-2 stages. Local recurrences were observed in 13% of pts. It is known for the death of 6 (15.8%) patients with concomitant diseases of the heart, blood vessels and lungs. Combined treatment with postoperative accelerated hyperfractionated radiotherapy can achieve relatively satisfactory survival rates against a background of moderate radiation reactions.

Disclosure: All authors have declared no conflicts of interest.

155P
EXTENSIVE VS LIMITED SURGERY IN SENIOR LUNG CANCER PATIENTS

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Surgery remains the only potentially curative options for treatment of NSCLC. The number of elderly patients with lung cancer at a curative stage is growing. There is a need for additional refinement in the selection process and postoperative care in this growing subgroup. The aim of our study was to determine the influence of type of surgical resection on postoperative outcome in elderly patients.

Patients and methods: We performed retrospective review of the clinical records of all senior patients (>70years) with lung tumors operated on thoracic department in 2000–2005. Patient with lung metastases and benign lesions, received perioperative chemo and/or-radiotherapy were excluded. All cases were re-staged according to the 7th edition of the TNM classification. Ppo-FEV1 was estimated according ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (2009). The patients were divided in 2 groups - those who underwent pneumonectomy (group-1; 26 patients) and after lung resection (group-2; 13 patients after lobectomy and 1 patient after wedge resection). Survival rates were calculated according to the Kaplan-Meier method.

Results: Histology type of tumors, pathological classification and preoperative comorbidities status was compared in both groups. One patient in group-1 died from perioperative complication and no one in group-2. One or more minor complications occurred in 7 patients of group-1 and two patients of group-2. Pulmonary ventilation time during pneumonectomy - 178±5.6 min. (ppo-FEV1 from 28% till 56.37%), pulmonary ventilation time during lobectomy was 156±7.2 min. (ppo-FEV1 from 50% till 88%). However group-2 patients have statistically significant better survival (median 26,33 month) compared with group-1 patients (median 17,83 month) (p=0.045).

Conclusions: Older age should not be considered contraindication for lung resection and surgery can be performed at acceptable risk in elderly patients. Additional functional evaluation is indicated in specific subgroup of elderly lung cancer patients.

Disclosure: All authors have declared no conflicts of interest.

156P
EFFICACY AND SAFETY OF MULTIMODALITY THERAPY OF LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER AT THE BRITISH COLUMBIA CANCER AGENCY

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Background: Surgery following concurrent cisplatin-based chemotherapy and radiation (trimodality therapy) for locally advanced non-small cell lung cancer (NSCLC) remains controversial, with high mortality associated with trimodality therapy in some landmark trials. In this retrospective study, we evaluated the feasibility, safety, and efficacy of trimodality and bimodality therapy over an 11 year period at an academic center where the treatment plan was reached by multi-disciplinary conference consensus.

Methods: Between January 1999-2010 at the Vancouver Cancer Centre, 177 patients were identified with locally advanced NSCLC treated with platinum and etoposide chemotherapy and ≥40Gy radiation therapy, with or without surgical resection. Patient characteristics extracted included sex, age, weight loss, performance status, race, smoking history, tumor stage, histology and location, method of mediastinal staging, chemoradiation treatment details, hemoglobin, albumin, and LDH. Outcome measures included overall survival, disease relapse, pathological response rate and treatment associated morbidity and mortality.

Results: See table below.

Conclusions: Locally advanced NSCLC patients treated with concurrent bimodality chemoradiation in this series achieved survival outcomes similar to those reported in the literature. Multi-disciplinary selection for trimodality therapy was associated with better survival and low treatment related mortality. The selection process does not allow assessment of the contribution of surgery to efficacy. However, the safety and favourable survival of trimodality therapy for patients so selected is sufficient for this model of care to continue as a standard at BCCA.

		Bimodality (N=131)	Trimodality (N =46)
Sex	Female	45%	63%
	Male	55%	37%
Age	Median (years)	60	61
	Range	32–82	40–73
Weight loss	<5%	73%	89%
	5–10%	18%	9%
	>10%	9%	2%
PS	0	26%	43%
	1	63%	52%
	2	8%	4%
	3	3%	0%
Race	Asian	23%	11%
	Caucasian	71%	89%
Smoking history	Current	52%	50%
	Former	30%	39%
	Non-smoker	18%	11%
Stage	IIB	4%	11%
	IIIA	56%	63%
	IIIB	40%	24%
Histology	SCC	34%	33%
	Adeno	33%	50%
	Other	33%	17%
Surgical details	Pneumonectomy	–	35% (20% L & 15% R)
	Lobectomy	–	65%
Complications	Hospitalization	24%	11%
	Death on treatment	5%	2%
Survival	Median OS	19.6 months	68 months
	5-year OS	17.5%	53.2%

Disclosure: All authors have declared no conflicts of interest.

157P
COMPARATIVE EVALUATION OF GEMCITABINE/ CARBOPLATIN AND CISPLATIN/ETOPOSIDE WITH CONCURRENT CHEMORADIATION IN LOCALLY ADVANCED NON SMALL CELL CARCINOMA LUNG IN TERMS OF RESPONSE AND TOXICITIES

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Objectives: To assess the impact of these protocols on 1) Locoregional control of disease. 2) overall survival of the patients 3) Time to disease progression 4) Toxicity associated with these two regimens.
Study Design: Hospital based, prospective case controlled simple randomised study.
Material and methods: A total of 60 histopathologically proven patients were taken, randomised into two arms with 30 patients in each arm, the baseline parameters of patients in each arm were well balanced with regard to various clinical and demographic parameters. In arm 1 patient received three cycles gemcitabine and carboplatin followed by concurrent chemo radiation with cisplatin (as radiosensitizer) followed by three more cycles of the same drugs. Similarly Arm 2 received three cycles of cisplatin and etoposide followed by concurrent chemo radiation with cisplatin followed by three more cycles of same drugs. After completion of treatment patients were followed three monthly and evaluated for response and toxicities. Student T test and Kaplan Meier methods were used for survival analysis.
Results: Out of 60 patients, forty six patients were male and 4 patients were female, more than 85% patients were smokers. The common presenting symptoms were cough (77%) and hemoptysis (37%). Most common histology in both arms was squamous cell carcinoma (90%).On completion of treatment, there was (33.3%) complete response and (56.7%) partial response in study group and 30.0% complete response and 53% partial response in control group. Toxicities noted in study arm are neutropenia (57%) anaemia (20%) and thrombocytopenia (30%) as compared to control group in which neutropenia (23%) anaemia (26%) and thrombocytopenia (3.3%).In control group renal toxicity and oesophagitis was (13.3%) and (23%) and in study group(3.3%) and (16.7 %) respectively. DFS was (33.3%) in study and (26.7%) in control.
Conclusions: Gemcitabine and carboplatin provides marginal survival benefits with acceptable and manageable toxicity profiles as compared to cisplatin and etoposide in locally advanced Non Small cell ca lung.
Disclosure: All authors have declared no conflicts of interest.

158P
OUR FIRST EXPERIENCE WITH THE INTEGRATION OF POSITRON EMISSION TOMOGRAPHY IN RADIATION THERAPY PLANNING OF NON SMALL CELL LUNG CANCER

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Background: Positron emission tomography (PET) with [^{18}F] fluoro-2-deoxy-d-glucose (FDG) has proven to be a valuable diagnostic and staging tool for non small cell lung cancer (NSCLC).
Purpose: To prospectively study the integration of ^{18}FDG-PET in radiation therapy planning and its impact on the planning target volume (PTV), target coverage, and lung toxicity in patients with NSCLC.
Methods: Twenty three patients presenting with stages I-III NSCLC on CT, referred for radical radiation therapy, underwent both ^{18}FDG-PET and CT simulation procedures on the same day. CT and a ^{18}FDG-PET were obtained in treatment position in an integrated PET/CT scanner, and coregistered images were used for three-dimensional conformal radiation therapy planning (3DCRT). First, volume delineation was performed on the CT data. In a second step, the corresponding PET data were used as an overlay to the CT data to define the gross tumor volumes (GTV) and planning target volumes (PTV). Delineation was done independently by radiation oncologist and nuclear radiologist. Standard margins were applied to each GTV to generate a PTV, and standardized treatment plans were designed and calculated for each PTV. The two 3DCRT plans for each patient were compared with respect to the GTV, PTV, mean lung dose (MLD) and volume of normal lung receiving ≥20 Gy (V20).
Results: Of the 23 patients who were planned with 3DCRT, PET increased the radiation therapy volume in 14 patients (61%). PET helped to distinguish tumor from atelectasis in 5 patients with atelectasis. In 4 of 23 (17%) patients, ^{18}FDG-PET information changed management strategy. These patients were diagnosed with metastatic disease based on ^{18} FDG-PET and received palliative radiation therapy. Increases in the target volumes led to increases in the MLD and V20. Decreases in the target volumes in the patients with atelectasis led to decreases in these lung toxicity parameters.
Conclusions: The information provided by ^{18}FDG-PET would have contributed to a substantial reduction of the GTV. This applies particuarly for patients with tumor-associated atelectasis. Radiation targeting with fused ^{18} FDG-PET and CT images resulted in alterations in radiation therapy planning in over 70% of patients by comparison with CT targeting.
Disclosure: All authors have declared no conflicts of interest.

159P
RADIATION-INDUCED LUNG INJURIES COMPLICATED BY ABSCESS FORMATION

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In some cases radiation therapy given to patients with locally advanced lung cancer is complicated by destructive processes with cavitations in the lung. Between 2006 and 2011 12 patients (pts) with radiation pneumonitis and pneumofibrosis grade 4 complicated by abscess formation were treated. All pts had previously received chemoradiotherapy for lung cancer to a total dose 50-70 Gy. After anticancer treatment it took from 6 months to 4 years for a cavity to form. Destructive cavities sized maximally 9-16 cm had communications with bronchi of various caliber. The Karnofsky index (PS) was at first visit from 30% to 60% (on the average 40%). Pts with chronic destructive processes treated in an inpatient setting, where anti-inflammatory steroid and nonsteroid, broncholitic, mucolytic and antiaggregant agents were administered along with disintoxication, anesthetic, haemostatic, antitussive drugs, artificial hypotension and cavity sanation. The mentioned agents were administered until the pain relief, normalization of the body temperature, stabilization of the general condition, alleviation of cough and dyspnea were achieved. Then, substitutive, metabolic, reparative and immune agents were added and treatment was performed until the PS reached a stable value of 60-80%. This approach improved the clinical and radiological symptomatology, reduced the number of complications, exacerbations and hospitalizations associated with them, improved the exercise tolerance and quality of life. After treatment PS increased to 60-80% in all the pts. 9 pts are alive at the present time (5 pts have lived 5 years, 4 pts have lived 2 years since the beginning of follow-up). After cavity formation 3 pts lived 2, 2.5 and 3 years, respectively. Their deaths resulted from pulmonary hemorrhage. Work experience with radiation pneumonitis and pneumofibrosis complicated by pulmonary suppuration suggests that it is necessary to use all the available methods of delivering drugs to the lung cavity on the background of complex step-by-step systemic therapy. Such therapeutic methods do not remove the empyema or abscess cavities. However, they improve quality of life and extend life expectancy for pts.
Disclosure: All authors have declared no conflicts of interest.

160P
LARGE CELL NEUROENDOCRINE CARCINOMA: RETROSPECTIVE ANALYSIS OF 24 CASES FROM 4 ONCOLOGY CENTERS IN TURKEY

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Background: Large cell neuroendocrine carcinoma (LCNEC) of the lung is classified as variant of large cell lung carcinoma by the World Health Organization. However the clinical and biological behaviours of LCNEC resemble small cell lung carcinoma (SCLC) with high mitotic index and positivity of tumor cells with neuroendocrine markers. Because small series were reported in the literature, there is no consensus about management of this subset. In the present study we evaluated the incidence and prognosis of LCNEC in four oncology centers in Turkey.

Materials and methods: We analyzed 24 patients with diagnosis of LCNEC from the medical data of 3138 non-small cell lung cancer patients who were diagnosed and treated between 2008-2010 in 4 different medical oncology centers in Turkey.

Results: Median age was 56 (range; 36-64), most of the patients were male and three of them were women. Ten out of 24 patients (41.6%) had locally advanced or metastatic disease so operation could not be performed. Five patients (20.8%) were staged as stage I, 6 (25%) with stage II, 5 (20.8%) with stage III and 8 (33.3%) with stage IV. All patients had a history of smoking. Twelve patients (50%) received chemotherapy post-operatively. At a median of 14.4 months of follow-up (range; 3-59) median OS and PFS times were 32.7 and 9.5 months, respectively. TNM stage and the performance of surgery were significantly related with both OS and PFS ($p<0.05$).

Conclusion: LCNEC was diagnosed generally post-operatively. Prognosis of LCNEC is poor so surgery alone is not sufficient for long survival, and adjuvant chemotherapy has been suggested.

Disclosure: All authors have declared no conflicts of interest.

161P
CASE STUDIES OF PULMONARY RESECTION FOR LARGE-CELL NEUROENDOCRINE CARCINOMA

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Aims: The World Health Organization (WHO) currently classifies large-cell neuroendocrine lung carcinoma (LCNEC) as a distinct subtype of pulmonary large-cell carcinoma. However, the survival after surgical-resection of LCNEC appears to be substantially worse than for other non-small-cell carcinoma (NSCLC), resembling more the survival of small-cell carcinoma. The question remains whether LCNEC is best treated the same as other NSCLC. LCNEC is rare and every case that is treated should be analyzed carefully.

Methods: The records of 5 LCNEC (2.6%) out of 195 patients, who underwent an intended curative resection for lung cancer in our institute during a 10-year period beginning in December 2002, were reviewed. The patients consisted of 5 male current smokers, with a median age of 70 years (64-82). The clinical stages were 2 in stage IB, 2 in stage IIA, and 1 stage IIIA. All patients underwent an anatomical resection with systematic lymph node dissection or lymph node sampling. One patient with positive mediastinal lymph node had neoadjuvant chemotherapy and received postoperative radiation to the mediastinal area. Median follow-up time was 31 months (15-68).

Results: The two patients with clinical stage IIA were upgraded to pathological stage IIIA after operation. One of them who was pathological stage IIIA died of cerebral infarction without cancer recurrence 2 years after the operation. The neoadjuvant chemotherapy of 3 courses (cisplatin + gemcitabine) for a patient with positive mediastinal lymph node reduced node size. Recurrence of disease was observed in two patients with pathological stages IB and IIIA. They died at 55 and 15 postoperative months, respectively. They received systemic chemotherapy for recurrent diseases and one of them received adrenalectomy for adrenal metastases.

Conclusion: Neoadjuvant chemotherapy should be considered only as complementary technique to surgery for LCNEC. The role of adjuvant therapy for LCNEC should be examined in a larger trial.

Disclosure: All authors have declared no conflicts of interest.

162P
CLINICOPATHOLOGICAL FEATURES, TREATMENT MODALITIES AND SURVIVAL ANALYSES OF PATIENTS WITH NON SMALL CELL LUNG CANCER: A SINGLE CENTER EXPERIENCE IN TURKEY

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Aim: We aimed to analyse the clinicopathological features, treatment modalities and also survival of cases with NSCLC.

Methods: Seven hundred and thirty-eight patients followed in a period of 10 years with a diagnosis of NSCLC at the Department of Medical Oncology, Ankara Oncology Education and Research Hospital were included. Overall survival (OS) was calculated with Kaplan Meier survival analyses by using log-rank test.

Results: The majority of patients (87.3%) were male and 12.7% of them were female. The rate of smoking was 84.6%. The most frequent initial symptoms were dyspnea (76%), cough (70%), asthenia (53%) and weight loss (49%). ECOG performance status (PS) of patients were PS 0, 2.2%, PS 1, 44.6%, PS 2, 39.3% and PS 3, 13.9% respectively. The most common histological types were squamous cell carcinoma (39.8%) and adenocarcinoma (34.4%). The majority of patients (89.9%) were diagnosed in locally advanced and metastatic stages. The most common sites of metastasis were bone and brain. Five-year OS rate was 10.5% for the entire cohort. In 11.9% of patients surgery could be performed with pneumenectomy in 16, lobectomy in 61 and segmentectomy in 3 patients. Radiotherapy (RT) was administered to 73.8% of patients and 35 of them had adjuvant RT, 190 had primary RT, 351 had paliative RT. Seventy-three of patients treated with RT received chemotherapy (CT). Twenty-eight of them were treated with CT as adjuvant setting and 3 of them received neoadjuvant CT. A total of 489 patients were treated with first line palliative CT, 159 second line palliative and 35 third line palliative CT. In 17.2% of the patients only supportive treatment was carried out. Univariate analysis indicated that the presence of metastasis, ECOG PS, primary RT, primary CT and palliative CT were important prognostic factors for OS. In the multivariate analysis, ECOG PS (HR; 1.42, $p<0.001$), primary RT (HR; 1.97, $p<0.001$), palliative CT (HR; 1.70, $p<0,001$) and the presence of metastasis (HR; 1.42, $p=0,005$) were found to be important prognostic indicators for OS.

Conclusions: Our results showed that the majority of our patients were male, most of them were younger than 65 years and the most common histopathological subtype was squamous cell carcinoma. It was found that surgery in early stage, systemic CT and RT in advanced stage prolonged OS and improved the symptoms.

Disclosure: All authors have declared no conflicts of interest.

Exceptional Acceptance

250O_PR

A NEW GENETIC SIGNATURE DEFINING TWO PROGNOSTIC GROUPS AMONG PATIENTS WITH COMPLETELY RESECTED EARLY NON-SMALL CELL LUNG CANCER

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Objectives: Among patients with completely resected early (I and II) non small cell lung cancer (NSCLC), 25-30% develops recurrence within 5 years. Biology behaviour of tumours seems to define different prognosis even among these early patients. The aim of this study was to look for a group of genes defining subgroups of patients with different prognosis.

Methods: Patients with completely resected early NSCLC were eligible for the study.

Those cases receiving adjuvance were excluded. Patients with previous oncological history were not considered for the study either. RNA was extracted from frozen samples with more than 70% tumor cells. Tumors were analyzed using microarray expression 4x44 K (Agilent). The data were normalized and subjected to unsupervised analysis (clustering and k-means) to classify samples based on expression profiles. Association of identified molecular subgroups with clinical, pathological and molecular variables and disease free survival (DFS) was analyzed.

Results: Eighty-four patients were selected (60 stage I and 24 stage II). All of them were homogeneously operated on in the same institution by the same surgical team. Systematic lymph node dissection was performed in all cases. Neither histological subtype nor tumor stage was associated with DFS. We identified two molecular subgroups of NSCLC based on 50 genes. Most of them encode proteins directly or indirectly related to B lymphocytes (as immunoglobulin molecules, CD79a, CD19, POU2AF1 or pERp1). Other proteins as TNFRSF17, SLAM7F, CD139; CXCL13, IRF4, CD27, Pim-2 or CD38, although nonrestricted to B cells, are strongly associated with B cell homeostasis, proliferation and survival. Disease free survival was significantly better for the group of good prognosis [Hazard Ratio 3.4 (CI 95%: 1.6 – 7.3; p= 0.001)]. An external dataset (n=162) was used to validate our molecular classification based on these 50 genes.

Conclusions: Expression of these 50 genes could make up a new genetic signature for NSCLC. It could define subgroups of patients with different prognosis among those with completely resected early-staged NSCLC. Immunosurveillance seems to be important in tumoral behaviour among analyzed patients.

Disclosure: All authors have declared no conflicts of interest.

ADVANCED NSCLC

163O_PR

BIOMARKERS OF TORCH TRIAL ON FIRST-LINE ERLOTINIB FOLLOWED BY SECOND-LINE CHEMOTHERAPY IN ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS

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Background: TORCH was a randomized phase 3 trial, conducted in Italy and Canada, comparing 1st-line erlotinib followed at progression by cisplatin/gemcitabine vs. the standard reverse sequence in unselected patients (pts) with advanced NSCLC. Primary endpoint was overall survival (OS); 900 pts were planned. The study was stopped after 760 pts, as the first interim analysis showed inferiority of the experimental arm. Exploratory analyses for EGFR activating mutations (mut), KRAS mut and EGFR gene copy number (GCN) were conducted after study closure, on 319 (42%) tumor samples available.

Methods: EGFR exon19 deletions were identified using PCR fragment analysis on macro-dissection enriched tumor DNA, with positive cases confirmed by sequencing. EGFR exon 21 and KRAS codons 12/13 were analysed by sequencing. Mutations were confirmed in independent PCR products and EGFRL858R negative cases were confirmed by MassARRAY (Sequenom). EGFR GCN was evaluated by FISH, classified by Colorado system.

Results: Pts with known marker status were distributed similarly between arms. EGFR and KRAS mut and EGFR GCN status were known in 275 (36%), 276 (36%) and 196 (26%) pts respectively. Mutations were found in 39/275 (14%) for EGFR and 73/276 (26%) for KRAS; 102/196 (52%) pts had high EGFR GCN tumors. No significant imbalances between arms were noted. EGFR mut was significantly more common in females, East Asians and never smokers; KRAS mut was less common in never smokers. There was no interaction between any biomarker and treatment efficacy for OS and total PFS (progression-free survival after both lines). For first PFS, only EGFR mut but neither KRAS mut nor EGFR GCN showed significant interaction with treatment. Pts with EGFR mut had improved first PFS with erlotinib (HR 0.60, 95%CI 0.30-1.20) compared to EGFR wild type (WT) pts (HR 2.07, 95%CI 1.58-2.71; interaction p=0.006). Among EGFR WT pts, there was no interaction between EGFR GCN and treatment efficacy.

Conclusion: Pts with EGFR mut experienced greater benefit from erlotinib followed by 2nd-line chemotherapy, while EGFR WT pts derived greater benefit from standard sequence of 1st-line chemotherapy prior to erlotinib.

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KRAS MUTATIONAL STATUS IMPACT PROGRESSION FREE SURVIVAL OF PATIENTS TREATED WITH PLATINUM BASED CHEMOTHERAPY IN NSCLC

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Background: KRAS mutations in NSCLC are supposed to indicate a poor prognosis and poor response to anticancer treatment. However, such evidence is only drawn from retrospective series giving controversial results. Moreover, it is possible that the various KRAS mutations differently affects prognosis, carcinogenesis and drug response as demonstrated in preclinical setting. Aim of this study is to prospectively assess the prognostic value of KRAS mutations in NSCLC patients treated with a first line platinum containing regimen. This is a properly planned ancillary study within the TAILOR trial (NCT00637910) which is mainly focused on the second line.

Methods: Tissue and blood samples were collected at diagnosis in the whole cohort of registered patients. KRAS status was centrally determined with standard direct sequencing and KRAS genotype was assessed by real time PCR. The primary hypothesis is a difference in PFS according to KRAS mutational status; the impact of the three more frequent KRAS substitutions (G12C, G12V, and G12D) was also explored. The analysis was planned at occurrence of 200 events (HR≥1.49, power 80%, 2-tailed alpha 10%), in a Cox model adjusting for Performance Status and radical surgery.

Results: Out of 565 patients registered, 341 (60.5%) were evaluable for KRAS and 85(25%) were mutated. At a median follow-up of 17 months KRAS mutated patients showed a statistically significant worse PFS (HR 1.42 95%CI 1.06-1.94; p=0.02). No differences among doublets were observed in KRAS mutated patients. The most frequent KRAS mutations were: G12C (36.4%), G12V (21.1%), G12D (16.4%), others (25.9%). Prognostic differences among variants are observed. Final genotype analyses are ongoing.

Conclusions: This is the first prospective, pre-planned and adequately sized evaluation of KRAS in NSCLC. Patients mutated for KRAS seem to have a higher risk of progressing. These results suggest that KRAS mutation epidemiology in this setting highly differs from that of colon cancer. Clinical data suggest that tailored strategies for these patients are warranted and our preclinical studies will help in clarifying the molecular mechanisms.

Disclosure: All authors have declared no conflicts of interest.

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ACTIVITY OF THE PAN-HER TYROSINE KINASE (TK) INHIBITOR DACOMITINIB (PF-00299804) IN REFRACTORY NONADENOCARCINOMA (NON-A) NON-SMALL CELL LUNG CANCER (NSCLC) AND COMPARED WITH ERLOTINIBIN THE 2ND-/3RD-LINE SETTING

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Introduction: In the BR21 study of erlotinib (E) in 2/3rd line NSCLC,[1] median overall survival (OS) was 6.7 months and median progression-free survival (PFS) 2.2 months. Inferior outcome was demonstrated for patients (pts) with non-A versus adenocarcinoma. Dacomitinib, an irreversible inhibitor of human epidermal growth factor receptors (HER)-1/EGFR, -2, and -4 TKs, was evaluated in phase (P) II trials in i) chemotherapy (CT) and EGFR TKI-refractory KRAS wild-type NSCLC[2] as a single agent and ii) versus E in 2nd-/3rd-line NSCLC.[3] Here results for non-A pts are reported.

Methods: 16 pts in the US PII CT and EGFR-TKI refractory study and 65 pts (dacomitinib = 32; E = 33) in the global randomized PII 2nd-/3rd- line study had non-A histology. Pts were ECOG PS = 0–2; the dacomitinib starting dose was 45 mg QD. The primary endpoint was objective response rate (ORR; RECIST) for the refractory study and PFS for 2nd-/3rd- line. Other endpoints were ORR, PFS, OS, patient-reported outcomes, safety, pharmacokinetics, and exploratory biomarkers.

Results: Of the 16 refractory non-A pts (12 squamous), 1 had a PR. Clinical benefit rate (CBR) (CR, PR or SD ≥24 weeks) was 18.8% (95% CI: 4.0, 45.6), median PFS was 11.1 weeks (95% CI: 5.6, 17.9), median OS was 26.6 weeks (95% CI: 9.9, 35.9); survival at 6 months and at 1 year was 50.0% (95% CI: 24.5, 71.0) and 21.9% (95% CI: 5.6, 44.9), respectively. For 2nd-/3rd- line non-A pts, there was a non-significant trend in favor of dacomitinib [HR 0.65, i.e. 54% improvement (95% CI: 0.36, 1.18), 2-sided P=0.152; with a median PFS of 8.7 weeks for dacomitinib compared with 8.0 weeks for E]. For OS, the HR was 0.74 (95% CI: 0.41, 1.34), 2-sided P=0.323; CBR was 21.9% (7/32; 1 PR, 1 CR) for dacomitinib and 9.1% (3/33) for E.

Conclusions: Dacomitinib demonstrated activity in non-A pts after progression on E and 1–2 prior CTs, and comparable activity to E in the 2nd-/3rd- line setting. These findings support a potential role for a pan-HER TKI in non-A NSCLC and ongoing PIII studies in this population.

1. Shepherd et al NEJM 2005;353:123
2. Campbell et al ASCO 2010 abstr 7596
3. Ramalingam et al ESMO 2010 abstr 365 PD

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EVALUATION OF SYMPTOM IMPACT OF DACOMITINIB (PF-00299804) VS ERLOTINIB IN PATIENTS WITH ADVANCED NSCLC AFTER CHEMOTHERAPY FAILURE: RESULTS FROM A PHASE 2 RANDOMIZED CLINICAL TRIAL

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Introduction: NSCLC patients (pts) experience many cancer-related symptoms (sx; eg, cough, dyspnea, pain, hemoptysis, fatigue). Decreasing tumor burden may reduce/delay these sx and favorably impact global Health Related Quality of Life (HRQOL). Dacomitinib is an irreversible, small molecule inhibitor of EGFR/HER-1, HER-2, and HER-4 tyrosine kinases. In a global multicenter, open-label randomized phase 2 study (NCT00769067) of 2nd/3rd-line NSCLC, dacomitinib showed improved progression-free survival (PFS; primary objective), hazard ratio 0.66 (95% CI, 0.47, 0.91), 2-sided P=0.012, and manageable toxicity vs erlotinib.[1] Here we report impact on core lung cancer sx.

Methods: Pts progressing after 1–2 prior chemotherapies were randomized 1:1 to dacomitinib (45 mg) vs erlotinib (150 mg) orally QD. A secondary objective was to explore HRQOL. Disease/treatment-related sx were recorded using the EORTC QLQ-C30 and QLQ-LC13 and scored using the scoring manual.[2] Scores were summarized by the mean (and 95% CI) for each group and plotted over time. Mean changes from baseline (Cycle 1, Day 1) were also reported for each group.

Results: Between Nov 2008 and Oct 2009, 188 pts were randomized. Baseline scores were similar between the 2 treatments and on-study completion rates were high (above 84%). Key NSCLC sx were improved in pts receiving dacomitinib vs erlotinib with clinically meaningful improvements (>10 points on 100 point scale). The difference in mean change from baseline favored dacomitinib at most time points (Table).

Conclusions: Dacomitinib demonstrated favorable clinical benefit vs erlotinib and improvements in common NSCLC sx. Such findings are important when considering the totality of benefit of a potential new therapy.

1. Ramalingam et al ESMO 2010 365PD
2. Fayers et al EORTC QLQ-C30 scoring manual. EORTC publications 2001

Table: 166O

Mean change from baseline within treatment arms for dacomitinib/erlotinib: higher positive scores = worsened symptom*

Symptom (n)	Baseline (dacomitinib/ erlotinib)	D10–14	Week 4	Week 8	Week 12	Week 16
Fatigue (88/89)	39/38	0/3 (79/70)	1/7 (79/78)	1/12 (61/61)	−5/8 (44/37)	−2/6 (37/24)
Pain (90/88)	28/33	1/2 (79/70)	0/4 (80/78)	3/2 (62/61)	2/3 (43/37)	4/3 (37/24)
Dyspnea single item (90/88)	33/35	−4/−4 (79/70)	−5/−3 (80/78)	−4/6 (61/61)	−8/3 (44/37)	−5/1 (37/24)
Dyspnea 3-item (89/88)	34/33	−6/0 (78/67)	−2/−1 (79/77)	−1/1 (61/61)	−6/1 (43/37)	−8/1 (36/21)
Coughing (89/88)	43/41	−7/0 (78/70)	−13/−3 (79/77)	−13/0 (61/61)	−16/−5 (43/37)	−19/0 (36/22)
Pain in chest (89/88)	23/27	-5/−5 (78/69)	−9/−6 (79/77)	−8/−1 (61/61)	−8/−2 (43/37)	−5/5 (36/21)
Pain in arm or shoulder (89/88)	25/23	−1/−2 (78/69)	−2/3 (79/77)	−5/7 (61/61)	−2/4 (43/37)	−6/3 (36/22)

*Data are rounded to nearest whole number

Disclosure: J. O'Connell and R. Mundayat: I am an employee of Pfizer Oncology and hold stock in Pfizer Oncology. A. Bottomley: I have served Pfizer Oncology in an advisory role and have received research funding from Pfizer Oncology. S.S. Ramalingam: Advisory role – AVEO, Abbott, Astellas, Lilly, Genentech, Boehringer Ingelheim, Pfizer Oncology. M. Boyer: Advisory role – Pfizer Oncology, Boehringer Ingelheim Honoraria – Pfizer Oncology, Boehringer Ingelheim, Eli Lilly, Amgen Research funding – Pfizer Oncology. K. Park: I have served Pfizer Oncology in an advisory role. F. Blackhall: I have served Pfizer Oncology in an advisory role and have also received honoraria, research funding and other remuneration [travel expenses] from Pfizer Oncology. A. Campbell: At the time that the research was undertaken, both myself and an immediate family member were employees of Pfizer Oncology and both of us held stock in Pfizer Oncology.

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CLINICAL BENEFITS OF SEQUENTIAL ADMINISTRATION OF DOCETAXEL AND INTERMITTENT ERLOTINIB AS A SECOND-LINE THERAPY FOR ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC), A PHASE II RANDOMIZED STUDY

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Background: Patients (p) with advanced NSCLC have few treatment options after progressing to 1st-line platinum doublet chemotherapy (PDC). Several preclinical and phase I studies have suggested that sequential administration of erlotinib (E) and docetaxel could avoid possible negative interactions and optimize the benefit obtained against NSCLC. This randomized phase II was designed to address the clinical benefit obtained with the use of sequential administration of docetaxel and intermittent E.

Methods: 70 p with advanced NSCLC progressing to previous PDC for advanced disease were randomized (1:1):

- Group A (n = 34): Docetaxel 75 mg/m^2 day 1 and intermittent E (day 2-16), up to 4 cycles, followed by E in monotherapy
- Group B (n = 36): E in monotherapy.

Treatment was administered until unacceptable toxicity or disease progression. Primary endpoint: rate of p free of progression at 6 months; secondary endpoints: progression-free survival (PFS), overall survival (OS), disease control rate (DCR) and safety. The study has completed enrolment. At the date of cut-off for this communication, data of 60 patients were available: 30 in Group A/30 in Group B.

Results: Baseline characteristics: non-adenocarcinoma (60.3%), current/former smokers (95%), male (90%) and stage IV (87.9%). 6 months PFS: 13.5% in the sequential arm. PFS: 2.7 months (m) in Group A (95% CI 2.1 – 3.8) and 2 m in Group B (95% CI 1.7 – 2.4) p value 0.08. Median OS: 11.0 m (95% CI 4.5 – 13.4) in group A and 4.7m (95% CI 2.5 – 6.6) in Group B with a p value 0.02. DCR: 44.4% in the experimental group whereas in the E one was 30.8%. Adverse events (AEs), including skin rash and diarrhea, were all generally tolerable. Of interest, the low number of p developing neutropenia in the D + E arm.

Conclusions: Although the primary objective has not been met, an encouraging benefit on survival has been shown in the exploratory analysis, with a median overall survival of 11 months for patients treated with the sequential regimen. Final data will be presented during the meeting.

Disclosure: All authors have declared no conflicts of interest.

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EFFECT OF DENOSUMAB VERSUS ZOLEDRONIC ACID ON OVERALL SURVIVAL IN PATIENTS WITH LUNG CANCER AND BONE METASTASES: RESULTS FROM A RANDOMIZED PHASE 3 STUDY

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Background: Denosumab (XGEVA®) is a fully human RANKL antibody approved to prevent skeletal-related events in patients with solid tumors and bone metastasis. We now present overall survival (OS) data for patients with lung cancer and bone metastases who participated in a phase 3 trial of denosumab versus zoledronic acid (ZA) for preventing SREs in patients with bone metastasis from solid tumors (except breast and prostate) or with multiple myeloma.

Methods: Patients were equally randomized to receive either a monthly subcutaneous denosumab injection (120 mg) or intravenous ZA (4 mg; dose adjusted for renal function). Daily calcium and vitamin D supplements were recommended. An exploratory analysis was conducted to assess OS among patients with lung cancer, including both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), who received either denosumab or ZA.

Results: A total of 811 patients with lung cancer (702 NSCLC; 109 SCLC) enrolled. The mean age of patients was 61 years; most were male (71%) and Caucasian (88%). 89% of patients in both treatment groups received prior chemotherapy. 85% of denosumab and 80% of ZA patients had an Eastern Cooperative Oncology Group (ECOG) status of 0 or 1. OS was prolonged with denosumab over ZA for all patients with lung cancer as well as the subgroups with NSCLC and SCLC (Table). The difference in OS observed between treatment groups was not affected by prior chemotherapy or difference in ECOG status between the groups. Adverse event (AEs) rates among these patients were similar between groups (96.8% denosumab, 95.4% ZA). Serious AEs occurred less frequently with denosumab (66.0%) than ZA (72.9%). Osteonecrosis of jaw was balanced (0.7% denosumab, 0.8% ZA; P=1.0). Hypocalcemia AE rates were 8.6% denosumab and 3.8% ZA.

Conclusion: Denosumab treatment is associated with significantly improved overall survival versus zoledronic acid in patients with lung cancer.

Table. Median Months of Overall Survival in Lung Cancer Patients Treated With Denosumab or ZA

Subgroup	Denosumab	ZA	Hazard Ratio (95% CI)	P-value
All lung cancer patients (n = 811)	8.9 months	7.7 months	0.80 (0.67–0.95)	0.01
NSCLC (n = 702)	9.5 months	8.1 months	0.78 (0.65–0.94)	0.01
Squamous cell carcinoma (n = 163)	8.6 months	6.4 months	0.68 (0.47–0.97)	0.035
Adenocarcinoma (n = 400)	9.6 months	8.2 months	0.80 (0.62–1.02)	0.075
SCLC (n = 109)	7.6 months	5.1 months	0.81 (0.52–1.26)	0.36

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Disclosure: G. Scagliotti: Dr. Scagliotti has received honoraria from Eli Lilly, Roche, and AstraZeneca. P. Woll: Dr. Woll is an advisory board member for Amgen. I. Jacobs: Dr. Jacobs is employed by and owns stock and stock options in Amgen. All other authors have declared no conflicts of interest.

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LONG-TERM SURVIVORS WITH ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (NSNSCLC) TREATED WITH FIRST-LINE (1L) CHEMOTHERAPY (CT) PLUS BEVACIZUMAB (B) AND MAINTENANCE (MTC) B

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Background: B plus CT followed by mtc B has been shown to improve outcomes in patients (pts) with nsNSCLC. In the clinical setting, some pts are able to receive prolonged mtc treatment (Tx) with B. The aim of our research was to explore their clinical characteristics, in order to assess the behavior of these pts who benefit most from B.

Methods: In 30 Spanish institutions we studied retrospectively data from 104 pts with advanced nsNSCLC receiving long-time mtc B defined by a median PFS ≥ 9 months (m), which represents an increase in PFS of approximately 50%, as compared with historical data. Clinical and histological characteristics, Tx received, ORR, median PFS and OS, and safety data were recorded.

Results: Pts characteristics: median age 57 years (yr); caucasian: 98%; ECOG PS 0/1/2 (%): 61/38/2; male: 61%; current/former/never smokers (%): 36/45/19; baseline hypertension (HTN)/cardiovascular disease (%): 24/9; adenocarcinoma: 82%; stage IV: 84%; 84% of pts presented ≤2 metastatic sites; central tumor location: 30%; tumor cavitation: 4%; among 40 pts tested, 8% presented activating EGFR mutations. 1L CT was: carboplatin/cisplatin doublets (%): 57/43; median no. of cycles for CT/B and mtc B was 6 and 18, respectively. Median B dose was 7.5 mg/kg. ORR: 83%. Of 71% of pts who had evidence of PD to 1L, 90% received second-line (2L) Tx. 77% of pts who progressed to 2L, received a third-line (3L). B was maintained in 26% and 24% of pts receiving 2L and 3L. Median PFS: 15 m (CI 95%:14-16); median OS: 31 m (95% CI: 22-39). 1 and 2 yrs survival rates (%): 97 (95% CI: 93 - 100) and 62 (95% CI: 51 - 73). Most frequent B related toxicities (%): gr 1/2 epistaxis (22/0), gr 1/2 HTN (12/6), grade 1/2/3 asthenia (2/6/4) and gr 1/2/3 proteinuria (3/3/1).

Conclusions: To our knowledge, these are the first data reported of long-term survivors with advanced nsNSCLC treated with 1L CT/B plus long-time mtc B. Although prospective evaluation is required, the outstanding median OS (31 m) and 2-yr survival (62%) point out the importance of selecting Tx and the role of mtc B after 1LB. B was very well tolerated, without significant life-threatening toxicities. Subgroup analyses will be presented.

Disclosure: J.V. Cardona: J.V. Cardona works for Roche Farma, S.A. as Medical Manager. All other authors have declared no conflicts of interest.

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RESULTS OF THE FIRST ITALIAN EXTERNAL QUALITY ASSURANCE SCHEME FOR SOMATIC EGFR MUTATION TESTING IN NON-SMALL-CELL LUNG CANCER

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Background: Assessment of the mutational status of the epidermal growth factor receptor (EGFR) is mandatory in order to choose the most appropriate first-line treatment for non-small-cell lung cancer (NSCLC) patients. The Italian Association of Medical Oncology (AIOM) and the Italian Society of Pathology and Cytology (SIAPEC) started an external quality assessment (EQA) scheme for EGFR testing in 2011.

Methods: Ten specimens (3 biopsies and 7 surgical specimens) with known EGFR mutation status were validated in 3 referral laboratories and then provided to 47 laboratories participating in the EQA. Participating laboratories registered at the website, and were requested to perform DNA extraction and analysis using their usual method and to submit their results within a 4 week timeframe. A board of experts from AIOM and SIAPEC evaluated the results according to a pre-defined scoring system that assigned 2 points to the correct genotype and 0 points to false-negative or false-positive results. The threshold to pass the EQA was set at >18/20 points. Centers failing to pass the I round were offered to participate to a II round that was organized with the same rules of the I round.

Results: All the centers participating to the EQA submitted the results within the timeframe. DNA sequencing (79%) was the main methodologies

used by the participants, while few centers used Pyrosequencing (17%) or the Real Time PCR (4%). A significant number of analytical errors was observed, including both false-negative and false-positive results. Fourteen out of 47 centers (30%) did not pass the I round having reached a score ≤18 points. A difference was observed between the testing methods: 0/10 laboratories that used Pyrosequencing or Real Time PCR failed, whereas 14/37 (38%) laboratories that employed PCR/sequencing made analytical errors. Eight of the 14 centers that failed in the I round passed the II round. Overall, 41/47 (87%) of the Italian centers passed the EGFR EQA.

Conclusions: The results of this first Italian quality assessment for EGFR testing in NSCLC suggest that EGFR mutational analysis is performed with good quality in the majority of Italian centers.

Disclosure: All authors have declared no conflicts of interest.

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THE RELEVANCE OF DISEASE STABILIZATION (SD) AS A SURROGATE END-POINT IN ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS TREATED WITH ERLOTINIB (E) IN SECOND/THIRD LINE

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Background: SD has often been viewed as a result of uncertain clinical value. With the advent of E in advanced NSCLC, increasing numbers of patients (pts) achieve SD as a best response. In clinical practice is a common observation an high proportion of SD pts receiving E with durable SD. The aim of this analysis was to compare the PFS and OS in pts with advanced NSCLC who achieved confirmed SD or complete/partial response (CR+PR) after second/third line treatment with E.

Methods: Data from 684 italian pts, entered into the TRUST trial (Tiseo M et al. Lung Cancer 2008), were analyzed. E was given orally at 150 mg per day and was continued until disease progression, development of unacceptable toxicity or patient's refusal. We define confirmed SD (cSD) if the patients' PFS was ≥5 months (response to E were per-protocol evaluated every two months) and reconfirmed SD (rSD) if the patients' PFS was ≥8 months.

Results: Pts characteristics: median age 67 years (31-89); females/males = 219/465 pts (32%/68%); never/former smokers = 191/493 pts (28%/72%); squamous/adeno/BAC/large cell/NOS = 163/361/26/21/113 pts (24%/53%/4%/3%/16%); PS 0-1/2-3 = 557/127 pts (81%/19%). In 83 pts (12%) E was given as first-line therapy in pts unable to receive chemotherapy; 305 pts (45%) had received 1 prior line and 296 (43%) 2 prior lines of chemotherapy. Four hundred and twenty-eight pts were evaluable for response in second/third line: CR+PR were 44 (10%) and 226 pts (53%) obtained a SD with 139 pts (32%) with cSD and 83 pts (19%) with rSD. The median PFS estimates (with 95% CI) were 13.1 months (9.8-16.4) for CR+PR pts, 9.9 months (8.2-11.4) for cSD pts and 14 months (12-16) for rSD. The median OS estimates (with 95% CI) were 24.0 months (17-31) for CR+PR pts, 17.9 months (14.4-21.5) for cSD pts and 24.9 months (18.1-31.7) for rSD.

Conclusions: Our findings demonstrate for the first time the relevance of achieving disease stabilization with E treatment. Pts obtaining cSD or rSD had durable PFS and OS comparable, particularly for rSD, with PFS and OS of those having CR+PR.

Disclosure: P. Venturino: Roche employee. All other authors have declared no conflicts of interest.

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CO-DEVELOPMENT OF A FOLATE RECEPTOR TARGETED DRUG CONJUGATE (EC145) AND A FOLATE RECEPTOR TARGETED IMAGING AGENT (EC20) IN THE TREATMENT OF ADVANCED ADENOCARCINOMA NSCLC

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Background: The folate receptor (FR) is overexpressed on many epithelial cancers, including adenocarcinoma of the lung. EC145 is a conjugate of folate that is coupled chemically to desacetylvinblastine hydrazide (DAVLBH), specifically targets the FR. EC20 uses the identical folate-targeting moiety but is conjugated to a technetium-chelating agent to allow for in vivo imaging and identification of tumor FR status. This phase 2 study evaluates the potential use of the ^{99m}Tc-EC20 agent to select advanced FR-positive lung cancer patients to be treated with EC145.

Methods: Patients with adenocarcinoma of the lung, ECOG PS 0-2 progressive after ≥ 2 prior therapies, and had ≥ 1target lesion expressing FR on the EC20 scan, were eligible. EC145 was administered at 1 mg IV daily x 5 for 3/4 weeks for 2 cycles, and then at 2.5 mg IV TIW on weeks 1 and 3 every 4 weeks for 6 cycles. The primary endpoint of the study was clinical benefit response (CBR) defined as the ability to receive ≥ 4 courses of therapy. Secondary endpoints included response rate (RR), progression-free survival (PFS), and overall survival (OS).

Results: 43 patients were enrolled and received ≥ 1 dose of EC145; 70% had ≥ 3 prior therapies. CBR was observed in 26% of patients, and one (2.3%) had a PR. Superior clinical benefit response and survival was observed in patients in which all target lesions expressed FR (FR++)compared to those who had at least one but not all target lesions positive for FR (FR+), 50% vs. 14% and 10.8 vs. 3.4 months, respectively. The most common drug-related AEs were fatigue (37%) and constipation (33%), with no grade 4 toxicity. The majority of patients discontinued therapy due to progressive disease, and none due to toxicity.

Conclusions: Intriguing efficacy results were seen in heavily pre-treated patients who had all target tumor lesions expressed FR by EC20 scan (FR++). ^{99m}Tc-EC20 scan offers a non-invasive way to select patients that are most likely going to benefit from treatment with EC145. A randomized phase 2 study of EC145 and EC145 plus docetaxel vs. docetaxel in FR++ 2nd line adenocarcinoma lung cancer will start shortly.

Disclosure: M.J. Edelman: I have received research funding and consultant honoraria from Endocyte. P. Bonomi, W. Harb, S. Pal, R. Boccia, M. Kraut, J. Rogers, B. Conley, E. Garon: Research funding from Endocyte. D. Morgenstern: Employee of Endocyte.

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EGFR EXON 20 INSERTION MUTATIONS IN NSCLC: FREQUENCY AND TREATMENT OUTCOMES WITH EGFR DIRECTED TKIS

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Introduction: Among EGFR gene mutations, exon 19 deletions and exon 21 point mutations are the most common. These are often termed classic activating mutations due to their enhanced sensitivity to EGFR TKI. However, not all mutations have the same effect. There is growing evidence that exon 20 insertions are a unique type of EGFR mutations. Its true frequency within the larger EGFR mutated NSCLC pool is unknown, with reports describing frequency from 1 to 10%. Although limited, most reports indicate that patients (pts) with exon 20 insertions are not as responsive to TKI as pts with classical activating mutations. The aim of our study was to evaluate frequency of exon 20 insertions and treatment outcomes in pts harbouring these types of mutations treated with EGFR directed TKIs.

Patients and metods: 803 pts with pathologically confirmed adenocarcinoma or NSCLC not other specified were routinely screened for EGFR mutations between years 2009-2011 in Slovenia. A commercially available kit (TheraScreenKit ®) was used for mutation analysis. 150 out of 803 pts (18.6 %) were positive for EGFR mutations and 21 (14%) had exon 20 insertions. Among them 11 pts (52%) were treated with TKIs (erlotinib or gefitinib) for advanced disease, 9 pts received TKIs as 1st line therapy and 2 as 2nd line therapy. Clinicopathological and follow-up data were retrospectively collected from medical charts.

Results: The frequency of exon 20 insertions within EGFR mutated pts pool was 14 %. Most of the pts harbouring these mutations were females 12 (57%), never smokers (44%) and 91.0% had adenocarcinoma. According to the RECIST criteria, none of 11 pts responded to TKI therapy; in 7 pts (63.6%) stagnation was achieved and 4 pts (36.4%) had disease progression. Median PFS from TKI treatment initiation was only 2.5 months.

Conclusion: The frequency of exon 20 insertions in routinely screened collective of NSCLC pts is low. The low radiographic response and short PFS indicate lower sensitivity of these type of EGFR mutations to the treatment with TKI, especially compared to high response rates of around 70% and long PFS rates of 9-13 months reported in pts harbouring classic activating EGFR mutations.

Disclosure: All authors have declared no conflicts of interest.

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PROGNOSTIC EFFECT OF EXCISION REPAIR CROSS-COMPLEMENTATION GROUP 1 (ERCC1) IN PLATINUM TREATED ADVANCED NON-SMALL CELL LUNG CANCER

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Purpose: Although current treatment option for advanced non–small-cell lung cancer (NSCLC) relies on cisplatin-based chemotherapy, individualized approaches to therapy may improve response or reduce unnecessary toxicity. Excision repair cross-complementing 1 (ERCC1) has been associated with cisplatin resistance. We hypothesized that assigning cisplatin based on pretreatment ERCC1 expression (both protein and mRNA) would improve response and survival.

Patients and methods: From March 2009 to April 2010, 61 chemotherapy naïve stages IIIB and IV NSCLC patients were enrolled. ERCC1 protein and mRNA expression was detected from pretreatment biopsies by Immunohistochemistry and real-time quantitative PCR assays, respectively. Patients received cisplatin based regimen in the form of cisplatin plus (etoposide or gemcitabine or docetaxel or vinorelbine).The primary end point was the impact of ERCC1 expression on PFS and OS.

Results: All biopsy specimens (61) were candidate for mRNA detection; 31 patients (50.8%) showed positive ERCC1 expression while only 52 biopsy specimens were candidate for protein detection; 34 patients (65.4%) showed positive ERCC1 expression. Complete concordance among the RT-QPCR and IHC for detection of ERCC1 expression was detected in 38 out of the 52 cases (73%). Positive ERCC1 expression was associated with short PFS ($P < 0.001$ for mRNA and $P = 0.001$ for protein). Positive ERCC1 expression was associated with short OS ($P = 0.001$ for mRNA and $P = 0.003$ for protein). Also, positive ERCC1 expression was associated with poor response to cisplatin based chemotherapy ($P < 0.001$ for mRNA and $P = 0.027$ for protein).

Conclusions: This prospective study further validates ERCC1 as a reliable biomarker for customized chemotherapy in advanced NSCLC patients and shows that high expression of ERCC1 by IHC or RT-PCR was significantly associated with poor outcome in advanced NSCLC patients treated with platinum based chemotherapy.

Disclosure: All authors have declared no conflicts of interest.

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INCORPORATING CRIZOTINIB INTO CLINICAL PRACTICE AS A NEW STANDARD OF CARE (SOC) IN ALK-POSITIVE NON-SMALL CELL LUNG CANCER (NSCLC)

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The EML4 –ALK gene fusion was identified in NSCLC in 2007 and has a prevalence of 3–5% in NSCLC of largely adenocarcinoma histology. Crizotinib (Xalkori®) is an oral, ATP-competitive, small molecule ALK and MET receptor tyrosine kinase inhibitor, which has developed as a potential new SOC for ALK-positive NSCLC. Following promising early activity, in 2008 a Phase 1 protocol (PROFILE 1001; NCT00585195, Pfizer), was expanded via an ALK-positive NSCLC cohort (confirmed by break-apart FISH assay). An open-label, multicenter, phase II study of crizotinib in advanced ALK-positive NSCLC (PROFILE 1005; NCT00932451, Pfizer) was initiated in 2010. A total of 119 (PROFILE 1001) and 136 (PROFILE 1005) patients with ALK-positive NSCLC were evaluable for safety and efficacy. Median age was 51 and 52 years, respectively, and most patients were pretreated. Clinical antitumor activity was dramatic, with rapid and durable responses (Table). ORRs were independent of age, gender, number of prior regimens and ECOG performance status, and far exceeded the ORRs of 16.3% and 9.7% in patients who received 1st- and 2nd-line chemotherapy, respectively, prior to crizotinib. Updated median PFS for PROFILE 1001 (excluding 1st-line patients) will be presented. The most common treatment-related AEs were Grade 1 vision disorder (62%), nausea (53%), diarrhea (43%), and vomiting (40%). Visual effects were transient with no effect on activities of daily living. Grade 3 or 4 treatment-related AEs included increased ALT/AST, pneumonitis, neutropenia and lymphopenia. Based on these data, crizotinib and the break-apart ALK FISH assay were simultaneously approved by the FDA for the treatment of advanced ALK-positive NSCLC in 2011. US NCCN, CAP-IASLC-AMP, and Japanese lung cancer biomarker guidelines have since recommended routine screening of patients with NSCLC for ALK-positivity. Crizotinib could therefore now be considered SOC in these patients.

Table:

	PROFILE 1001	PROFILE 1005
Evaluable patients	n=116	n=133
Objective Response Rate (ORR; PR+CR)	61% (95% CI: 52%, 70%)	51% (95% CI: 42%, 60%)
Median Duration of Response	42 weeks	48 weeks
Median Duration of Treatment	32 weeks	22 weeks
Median Progression-free Survival (PFS)	10 months (95% CI: 8.2, 14.7)	Not yet available

Disclosure: J. Soria: I have served Pfizer Oncology in an advisory role and have also received honoraria from Pfizer Oncology. F. Blackhall: I have served Pfizer Oncology in an advisory role and have also received honoraria, research funding and other remuneration [travel expenses] from Pfizer Oncology. B. Solomon: I have served Pfizer Oncology in an advisory role and have also received honoraria and research funding from Pfizer Oncology.
L. Crino: I have received honoraria from Pfizer Oncology. G. Scagliotti: Advisory role - Eli Lilly Honoraria - Eli Lilly, AstraZeneca, Roche. C. Huang Bartlett and K. Wilner: I am an employee of Pfizer Oncology and hold stock in Pfizer Oncology. S.I. Ou: I have received honoraria, research funding and other remuneration from Pfizer Oncology

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PRELIMINARY EXPOSURE RESPONSE (ER) ANALYSIS OF CRIZOTINIB IN PATIENTS WITH ALK-POSITIVE ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Crizotinib (Xalkori®) is a first-in-class oral ALK inhibitor, which was approved by the Food and Drug Administration for the treatment of advanced *ALK*-positive non-small cell lung cancer (NSCLC). ER analyses were conducted for efficacy and safety endpoints from two crizotinib trials.
Methods: Data from 255 patients receiving crizotinib 250 mg BID in two clinical studies (A8081001: n=119; A8081005: n=136) were analyzed. Logistic regression was used for safety endpoints (ALT elevation, neutropenia, fatigue) and objective response rate (ORR); Cox regression was used for progression-free survival (PFS; study 1001 only). Exposure was measured by model-predicted average steady state concentration and observed geometric mean trough concentration. The models included potential confounders and effect modifiers. To identify factors to predict low exposure, a model-building approach was used and models were fit separately for each study.
Results: In both studies, a positive ER relationship was observed for ORR. The odds ratios comparing lowest sextile exposure group to the median exposure were 2.15 (95% CI: 1.19–3.86) and 1.69 (95% CI: 1.01–2.81) for studies 1001 and 1005, respectively. In addition, PFS showed a positive ER relationship, though it was not statistically significant. No clinically meaningful ER relationships were found for safety endpoints. There were trends toward higher risk of neutropenia with higher exposure ($p>0.05$ in both studies). There were trends toward less risk of fatigue ($p<0.05$, study 1005 only) and less risk of ALT elevations ($p<0.05$, study 1001 only) with higher exposure. Low average daily dose (ADD) was the primary driver of low exposure. In both studies, the lowest ORR was observed in the lowest sextile exposure group, which included most subjects with ADD less than 450 mg (90% of the nominal 500 mg). In study 1001, there was a trend of correlation with use of CYP3 inducers and low exposure.
Conclusions: This preliminary ER analysis of crizotinib showed favorable benefit-risk assessment at the recommended 250 mg BID dose regimen.

Disclosure: J. French: I have served Pfizer Oncology in an advisory role and also hold stock in Pfizer Oncology as a consequence of being a former employee of Pfizer Oncology. W.W. Tan, D. Kang, A. Bello and P. Selaru: I am an employee of Pfizer Oncology and hold stock in Pfizer Oncology. All other authors have declared no conflicts of interest.

177P
IN SEARCH OF A BETTER THERAPEUTIC APPROACH TO NSCLC: THE ROLE OF EML4-ALK TRANSLOCATION

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The study of molecular characteristics of NSCLC plays an increasing role in choosing the best therapy. In addition to the use of TKIs in the first –line treatment of EGFR mutated NSCLC advanced disease, now arises the use of crizotinib in tumors with EML4-ALK translocation. The EGFR mutation and EML4-ALK are mutually exclusive, the latter being more frequent in non-smokers with non-squamous histology. The study of these characteristics with the best benefit to the patient is only possible with a structured methodology that enables its systematic and timely execution.
Aim: To present the methodology used during 2011 in our service to carry out cytogenetic and molecular study of NSCLC. Demographics, clinical, cytogenetic and molecular characterization of the study population.
Methodology: In all new cases of NSCLC, the EGFR exons 18-21 were sequenced. After sequencing, the non-smokers or former smoker patients with wild-type EGFR and non-squamous histology were subjected to FISH analysis to investigate the EML4-ALK rearrangement. It was made a descriptive statistical analysis of demographics, clinical, cytogenetic and molecular features of the study population.
Results: EGFR was sequenced in 138 cases of NSCLC, 98 (71%) were male. The most common histology was adenocarcinoma - 92 cases (67%), followed by squamous cell carcinoma - 29 patients (21%) and poorly differentiated NSCLC - 17 (12%). Regarding smoking, 52 patients were active smokers and 40 non-smokers and 46 former smokers. At diagnosis, stage IV - 79 patients (57%) was the most frequent. The EGFR was mutated in 16 patients - mutation rate of 11.5%. 57 patients were eligible for the study EML4-ALK. In five of these, the material available was insufficient for diagnosis. We found two positive cases (3.8% rate of translocation), both adenocarcinomas – one male former smoker patient and one non-smoker female patient.
Discussion: With these results it appears that one of the problems in the search of EML4-ALK is the suitability of the samples, as in 8.8% of cases, the study was not possible. The rate of translocation found is consistent with the literature. The use of a systematic strategy allows the molecular characterization of tumors in order to a correct and timely therapeutic management.
Disclosure: All authors have declared no conflicts of interest.

178P
THE MANCHESTER LUNG CANCER GROUP EXPERIENCE OF EGFR MUTATION ANALYSIS AND TREATMENT OUTCOMES

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The presence of Epidermal Growth Factor Receptor (EGFR) activating mutations in patients with NSCLC was first described in 2005. Tumours exhibiting these mutations show sensitivity to treatment with an oral Tyrosine Kinase

Inhibitor. Testing for EGFR mutations in patients with non-squamous NSCLC began in the Greater Manchester and Cheshire network in the last quarter of 2009. We audited the notes of consecutive patients who were identified with an activating EGFR mutation by the Central Manchester Genetics Laboratory between November 2009 and October 2011. A total of 110 mutations were identified in tumour tissue from 98 patients. 13.6% were in exon 18, 38.2% in exon 19, 15.4% in exon 20 and 32.8% in exon 21. 65% of patients were female. The median age was 69 years (36-89). Notes were available for 78 patients, 56 of whom received treatment with an EGFR TKi. 5 had previously received radical treatment and 17 never received treatment. 6.4% were current smokers, 41% were ex-smokers, 29.6% had never smoked and smoking history was not documented in 23%. An initial response to treatment was seen in 75%, with stable disease in 15%.The mean duration of treatment was 7.5 months (2 weeks – 18 months), with 23 patients still receiving a TKi at the time of data analysis. The most commonly seen toxicities were diarrhoea and rash. Only 1 patient had no documented toxicity from their TKi. 16 patients (28%) had treatment discontinued or interrupted because of toxicity. In 8 of these, treatment was re-introduced at a reduced dose, and 3 patients went back to full dose. Our results confirm that treatment with a TKi is effective for patients with EGFR mutations, with a side effect profile consistent with published data.

Disclosure: All authors have declared no conflicts of interest.

179P
CAN MUTATIONS OF EGFR AND KRAS OF SERUM BE PREDICTIVE AND PROGNOSTIC MARKERS IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)?

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Background: The status of Epidermal growth factor receptor (EGFR) and Kirsten ras (KRAS) mutations have been used widely in management of patients with non-small cell lung cancer (NSCLC). However, it may be difficult to get tumor tissue for analyzing the status of EGFR and KRAS mutation in large proportion of patients with advanced disease

Patients and methods: We obtained pairs of tumor and serum samples from 57 patients with advanced NSCLC, between March 2006 and January 2009. EGFR mutation status from tumor samples and KRAS mutation status from serum samples was analyzed by genomic polymerase chain reaction and direct sequence and EGFR mutation status from serum samples was determined by the peptide nucleic acid locked nucleic acid (PNA-LNA) PCR clamp.

Results: EGFR mutations were detected in the serum samples of 11 patients and in the tumor samples of 12 patients. Fourteen patients revealed KRAS mutation in the serum sample. EGFR mutation status in the serum and tumor samples was consistent in 50 (87.7%) of the 57 pairs (correlation index; 0.62 $P<0.001$). Only 5 of 57 (8.7%) patients showed mutation of both EGFR and KRAS in serum sample. Twenty-two of 57 patients (38.5%) received EGFR-TKIs as any line therapy. The response for EGFR-TKIs was significantly associated with EGFR mutations in both tumor samples and serum samples ($p<0.05$). The status of KRAS mutation in serum was not predictive for the response of EGFR-TKI ($p>0.05$). There was no significant differences in OS according to the status of EGFR mutations in both serum and tumor samples ($p>0.05$) and KRAS mutations in serum samples ($p>0.05$).

Conclusion: The status of EGFR and KRAS mutation in serum was not prognostic in patients with advanced NSCLC. However, the clinical usefulness of EGFR mutation of serum as a selection marker for EGFR-TKIs sensitivity in NSCLC might be allowed, not KRAS mutation.

Disclosure: All authors have declared no conflicts of interest.

180P
EGFR MUTATION IN AUSTRIAN PATIENTS WITH NSCLC: A RETROSPECTIVE STUDY

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Introduction: Point mutations of the Epidermal growth factor receptor (EGFR) in non-small cell lung cancer (NSCLC) predicts the response to tyrosine kinase inhibitors. Commonly mutations occur more in never smokers, adenocarcinomas, women and East Asians. In the largest European screening trial the frequency of caucasian Spanish patients was 16.6% (1). However, the frequency of EGFR mutations in NSCLC from Austrian patients is unknown.

Aim: To evaluate the prevalence of EGFR mutation in Austrian patients with NSCLC.

Methods: From January 2010 to October 2011 tumor tissue from bronchoscopy, CT-guided and ultrasound guided biopsies and surgical specimen with histological type of Adenocarcinomas (AC) and NSCLC NOS (Not Otherwise Specified) excluding squamous cell carcinomas and large cell carcinomas were tested for EGFR mutations from 4 hospitals in Austria with high expertise in the management of lung cancer. The mutation detection was performed in one specialisted laboratory with the TheraScreen EGFR29MutationKit from DxS on a Light Cycler 480.

Results: 581 patients (550 AC, 31 NOS) were tested. EGFR mutations were found in 87 patients (14.97 %). 71 patients (12.22 %) carried an activated Mutation (Exon 19 Deletion and Exon 21 L858R).

Conclusion: These results indicate that Austrian patients with NSCLC harbor somatic EGFR mutations at a frequency similar to other European caucasian patients with NSCLC. **Reference:** [1] Screening for epidermal growth factor receptor muations in lung cancer. Rosell et al. NEJM 361 (10) 2009 **Disclosure:** All authors have declared no conflicts of interest.

181P
EGFR MUTATION AND TYROSINE KINASE INHIBITOR (TKI) TREATMENT IN A DANISH (CAUCASIAN) POPULATION OF ADVANCED NSCLC PATIENTS AT ODENSE UNIVERSITY HOSPITAL 2010-11

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Background and method: The multi disciplinary lung cancer team at Odense University Hospital has since July 2010 recommended a test for EGFR mutation in patients with advanced adenocarcinoma prior to possible chemotherapy. Out of 348 new cases with lung cancer from our primary uptake area, 98 consecutive patients have been tested until November 2011. Nine patients (9.2%) had the mutation. In female never-smokers and ex-smokers the mutation rate was 26.9%. In the same period the test (TheraScreen DxS, Qiagen) has also been applied in patients with relapse and in patients referred from other hospitals. Out of a total number of 199 tested, 21 subjects with EGFR-mutation have been found. We here report the treatment and outcome for these patients.

Material: Among the 21 patients 19 were females and 2 males. One patient was a current smoker, the remaining pts. were either never-smokers (7 pts.) or ex-smokers (13 pts.). Sixteen pts. were treated with a TKI, 12 of them as first line treatment. Five pts. with mutation did not receive TKI: Two died before treatment could start and two were assessed would not benefit

from the treatment. One underwent curative intended chemo-radiotherapy. Performance status of the 16 treated pts were PS 0: 2 pts., PS 1: 9 pts. and PS 2: 5 pts.

Results: As of January 2012, 7 pts were still treated with TKI. Sixteen months being the longest follow up time. Mean follow up time was 7 months. Seven pts had progression after 2, 5, 6, 7, 8, 8 and 11½ months of treatment. Two pts died without known progression within 1 and 2 months respectively. The mean progression free survival was 8.2 months and the mean overall survival OS 15.4 months.

Discussion: We found a mutation rate of 10.5 % among the tested pts. The mutation positive subgroup is typically non-smoking females. The patients treated had 8 months of PFS though many patients were still being successfully treated at end of inquiry. Further follow-up must show the long term effect of TKI on EGFR mutated tumors but the results so far are encouraging.

Disclosure: All authors have declared no conflicts of interest.

182P
ARCHER: A RANDOMIZED DOUBLE-BLINDED PHASE III STUDY OF DACOMITINIB (PF-00299804) VERSUS ERLOTINIB FOR ADVANCED (ADV) NON-SMALL CELL LUNG CANCER (NSCLC)

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Introduction: Human epidermal growth factor (HER/EGFR) family receptor signalling regulates tumor cell proliferation, invasion, angiogenesis, metastasis, and apoptosis. Selective, reversible EGFR/HER1 tyrosine kinase inhibitors (TKI) are used for the treatment of unselected patients (pts) with adv NSCLC after failure of 1st-line chemotherapy (CT) and in pts with EGFR-mutated NSCLC. A randomized phase II trial compared dacomitinib, an orally available irreversible pan-HER TKI, with erlotinib, in pts who had received 1–2 prior systemic therapy regimens for adv NSCLC. Dacomitinib demonstrated significantly longer progression-free survival (PFS) vs erlotinib in the overall population (12.4 vs 8.3 weeks; HR=0.66, p=0.012), with benefit consistent across several clinical and molecular subgroups. Median PFS in the KRAS wild-type (wt) subgroup was 16.1 vs 8.3 weeks for dacomitinib and erlotinib, respectively (HR=0.55, p=0.006).

Methods: ARCHER is a randomized, double-blinded, phase III clinical trial comparing the efficacy and safety of dacomitinib with erlotinib in pts with locally adv or metastatic NSCLC (pathologically confirmed radiologically measurable disease), 1–2 prior CT regimens, ECOG PS 0–2, and tissue available for molecular analysis. Approximately 800 pts will be randomized to receive dacomitinib 45 mg or erlotinib 150 mg orally once daily. The primary endpoint is PFS with overall survival, objective response rate, duration of response, safety and tolerability, and pt reported outcomes of health-related quality of life and disease-/treatment-related symptoms as secondary endpoints. Efficacy will be analyzed in two co-primary populations: (1) all enrolled pts with adv NSCLC, and (2) pts with KRAS wt NSCLC. Study design provides 90% and 80% power to detect ≥33% and ≥45% improvement in PFS in all pts receiving dacomitinib vs erlotinib, and in pts with KRAS wt NSCLC, HR ≤0.75 and 0.69 using a 1-sided stratified log-rank test at a significance level of 0.015 and 0.01, respectively. The final primary analysis stratified log-rank test will include baseline ECOG PS, KRAS mutation status and EGFR mutation status as stratification factors.

Disclosure: V. Antic: I am an employee of Pfizer AG and have stock ownership in Pfizer AG. M. Boyer: Advisory role - Pfizer Oncology, Boehringer Ingelheim Honoraria - Pfizer Oncology, Boehringer Ingelheim, Eli Lilly, Amgen Research funding - Pfizer Oncology. T. Mok: Advisory role - AstraZeneca, Roche, Eli Lilly, Merck Serono, Eisai, BMS, AVEO, Pfizer Oncology, BeiGene Honoraria - AstraZeneca, Roche, Eli Lilly, Merck Serono, Eisai, BMS, AVEO, Pfizer Oncology, BeiGene Research funding – AstraZeneca. K. O'Byrne: Advisory role and honoraria - Pfizer Oncology. L. Paz-Ares: I have served Pfizer Oncology in an advisory role and have received honoraria from Pfizer Oncology. S.S. Ramalingam: Advisory role - AVEO, Abbott, Astellas, Lilly, Genentech, Boehringer Ingelheim, Pfizer Oncology. J. Liang and I. Taylor: I am an employee of Pfizer Oncology and hold stock in Pfizer Oncology. S. Letrent: Both myself and an immediate family member are employees of Pfizer Oncology and hold stock in Pfizer Oncology

183P
GGCP041/09: A GALICIAN STUDY OF SECOND-LINE ERLOTINIB IN PATIENTS WITH ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (NSNSCLC)

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Background: Efficacy of oral erlotinib has been conclusively established in 2nd line setting (BR.21 and TRUST studies) and the outcomes are similar to those provided by other approved chemotherapeutical agents (TITAN study). Higher responses rates have been found in p with Asian ethnicity, adenocarcinoma, women and never smokers, where predictive EGFR mutations occur more frequently; even though erlotinib has a significant effect on survival in all subgroups of patients. This observational study evaluates the efficacy of 2nd line erlotinib in unselected p with nsNSCLC in 4 Galician institutions.

Methods: Unselected p with advanced nsNSCLC were treated with 150 mg/day of erlotinib as 2nd line therapy until unacceptable toxicity or progressive disease. EGFR mutational status was retrospectively tested when feasible, and serum carcinoembryonic antigen (CEA) monitored during the treatment period.

Results: Baseline characteristics of 45 p included at the time of this analysis: mean age of 61.7 yrs. (range: 38-83); 80% male; 73.3% adenocarcinoma; 71.1% stage IV; 7/69/24% PS ECOG 0/1/2; 29/33/38 % never/current/former smokers. EGFR activating mutation testing was performed in 24 p (53%) and 2 positive cases were found (8%), both with metastatic adenocarcinoma (stage IV). The median PFS was 3.3 (95% CI: 1.6-5.1) and the median OS 10 months (95% CI: 7.5-12.5). Among p without EGFR mutations, erlotinib conferred a median OS of 8.1 months (95% CI: 1.4-14.9). Out of 31 p evaluable, radiologic response was achieved in 7 p (22.6%), for an overall disease control rate of 45.2%. No unexpected toxicities were reported: 60 % of p experienced cutaneous toxicity (6.6% grade ¾), 22.2% asthenia (4.4% grade ¾) and 17.8% diarrhea (2.2% grade ¾). Only 3 p discontinued due to adverse events.

Conclusions: This study confirms the efficacy and safety of 2nd line erlotinib in a clinical practice scenario and the outcomes in p with non-squamous NSCLC are equivalent to those reported with the chemotherapy for salvage therapy. Moreover, the absence of mutations does not preclude the benefit from the drug. Updated data of the study will be presented.

Disclosure: All authors have declared no conflicts of interest.

184P

TREATMENT WITH EGFR TYROSINE KINASE INHIBITORS BEYOND PROGRESSION IN LONG-TERM RESPONDERS TO ERLOTINIB IN ADVANCED NON-SMALL CELL LUNG CANCER: A CASE-CONTROL STUDY OF OVERALL SURVIVAL

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Introduction: Some patients with advanced NSCLC show prolonged disease stabilization on treatment with an EGFR-tyrosine kinase inhibitor (TKI) such as erlotinib. It is so far not clear how to treat patients who progress after prolonged response to erlotinib. We hypothesized that TKI therapy beyond progression with added chemotherapy, radiotherapy or best supportive care (BSC) may improve survival compared to chemotherapy, radiotherapy or BSC alone.
Patients and methods: We retrospectively analyzed all NSCLC patients treated with erlotinib at our institutions since 2004 who progressed after at least stable disease on erlotinib for at least six months (n=41). Twenty-seven patients were treated with TKI beyond progression (TKI patients), of whom 24 received erlotinib and 3 afatinib. Fourteen patients did not receive further TKI treatment after progression (controls). Overall survival (OS) from progression on TKI and OS from diagnosis of lung cancer was analyzed for the whole population and case-control subpopulations of pairs matched for gender, smoking status, and histology.
Results: Treatment with TKI and chemotherapy was well tolerated with no increase in grade 3 and 4 toxicities. TKI-patients had a significantly longer OS from progression on TKI (case control: median 21.0 vs. 3.0 months, HR 0.175) and longer OS from diagnosis of lung cancer (case control: median 28.5 vs. 15.3 months, HR 0.335).
Conclusions: In long-term erlotinib responders, treatment with TKI beyond progression in addition to chemotherapy or radiotherapy is feasible and well tolerated with limited toxicity. TKI-treatment beyond progression leads to prolonged OS compared to treatment with TKI-free chemotherapy or radiotherapy.
Disclosure: All authors have declared no conflicts of interest.

185P

GEFITINIB AND ERLOTINIB IN ADVANCED NON-SMALL –CELL LUNG CANCER (NSCLC) PATIENTS: A RETROSPECTIVE REVIEW FROM THE HOSPITAL UNIVERSITARIO CENTRAL DE ASTURIAS

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Background: Gefitinib (G) and erlotinib (E), both specific tyrosin kinase Inhibitors (TKIs) have demonstrated efficacy in second and third line treatment of patients with NSCLC. The aim of this study has been to report the experience of a single centre with the utilization of these agents in an unselected population.
Methods: A retrospective analysis was carried out from August 2002 to March 2008 of patients with advanced NSCLC treated with G or E. Criteria of response and toxicity were those recommended by OMS and Kaplan and Meier method for determination of median progression free (PFS) and overall survival (OS).
Results: 131 patients were treated with TKI (17 with Gefinitib and 114 with Erlotinib). Patients treated with Gefitinib (G) received all 250 mg/day and 150 mgs of median with Erlotinib (E) (50-150). Epidemiological characteristics were as follow (G/E); median of age (55(38-74)/60(37-80)), Karnosfky (70(50-100)/70(50-100)), lines of previous chemotherapy (2(1-6)/2(1-5)). Percentage of males (76/68), stage IV (88/89), never smokers (29/29) and non-squamous histology (88/80). Among 131 patients considered evaluable for activity, there were 6% objective responses rate (ORR) in the G and 17% in E group with an additional 47% of disease stabilization with G and 36% with E group. The median PFS and overall survival with G were 73 and 282 days, with E 90 and 210, respectively.Never smokers,development of rash, diarrhoea, EGFR mutation and prior chemotherapy response or stabilization were independent variables related longer ORR, PFS and OS. The most important toxicities grade 1-2 were (G/E; %): rash (59/63), diarrhoea (18/21), pneumonitis (0/1), pancreatitis (0/1) and grade 3-4 toxicities (0/20).Dose reduction and/or delay of treatment were required in any patients with G and 18% with E.
Conclusion: In this retrospective analysis the efficacy of G and E in terms of ORR and survival have been confirmed in an unselected group of patients with advanced NSCLC. The TKI gefitinib seems to have similar efficacy but with a better profile of toxicity than erlotinib.
Disclosure: All authors have declared no conflicts of interest.

186P

DRUGS FREE OF CHARGE IN LUNG CANCER TRIALS: AN ANALYSIS OF PHARMACEUTICAL COST SAVINGS

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Background: The cost of new anticancer drugs has dramatically increased in recent years. The global financial crisis forces to implement countermeasures in order to limit pharmaceutical expenses. Sponsored clinical trials that provide drugs free of charge may be a useful tool in order to reduce drug costs. The aim of this analysis is to evaluate the effect of clinical trials on pharmaceutical expenditure savings.
Methods: We evaluated the cost of drugs administered in clinical practice and in clinical trials (considering only the standard regimens that were administered also in clinical practice) in 2010 at the Lung Cancer Unit of the National Institute for Cancer Research in Genova, Italy. The cost of drugs was calculated on the price charged at our Institute in 2010. The supposed cost of experimental treatments replacing standard therapy was converted in the cost of the treatments that would have been chosen in clinical practice, considering histology, line of treatment and number of administered cycles.
Results: From 1/1/10 to 12/31/10, 197 patients affected by lung cancer or pleural mesothelioma were treated. 152 patients (77.6%) received treatment in clinical practice or in non-sponsored trials (18 patients in 4 trials), while 44 (22.4%) received a standard treatment in one of the 12 sponsored clinical trials recruiting in 2010. The total number of administered cycles was 579, of which 436 (75.3%) in clinical practice or non-sponsored trials and 143 (24.7%) in sponsored clinical trials. The overall cost of care (excluding supportive care and hospitalization) was 990.688,69 Euro. The cost of drugs administered in clinical practice or in non-sponsored trials was 725.665 Euro (73,2%), while the cost of drugs administered in clinical trials was 265.023,69 Euro (26,8%).
Conclusions: Participation in sponsored clinical trials in which drugs are provided free of charge offers substantial savings on drug expenditure; furthermore, this analysis does not take into account the grant which covers the cost per patient of radiological and laboratory exams, as well as operating costs of the study (study coordinators, research nurses, sub-investigators).
Disclosure: All authors have declared no conflicts of interest.

187P

EFFECT OF ENOBOSARM ON OVERALL SURVIVAL IN A PHASE IIB STUDY IN NSCLC PATIENTS WITH >8% WEIGHT LOSS

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Background: At diagnosis, up to 50% of lung cancer patients have substantial weight loss, increasing to >80% prior to death. Much of this weight loss is attributed to muscle wasting-leading to a decline in physical function and other detrimental effects. Studies show that NSCLC patients with wasting at diagnosis are less able to tolerate chemotherapy, have worse outcomes and shorter survival. The negative impact of wasting underscores the importance of preventing and treating this condition early. We conducted a Phase IIb, randomized, double-blind, placebo-controlled, study to evaluate the effect of

enobosarm, a selective androgen receptor modulator, on muscle wasting and physical function in patients with cancer.
Methods: Subjects (n=159) were randomized to oral enobosarm or placebo for 16 weeks. Subjects were males >45y and postmenopausal females, had experienced ≥2% weight loss in the 6 months prior to randomization, and had NSCLC, colorectal cancer, non-Hodgkin's lymphoma, chronic lymphocytic leukemia or breast cancer. The primary endpoint was change in total lean body mass. We report on overall survival in the entire study population and NSCLC cohort based on weight loss of > or ≤8% in the 6 months prior to randomization.
Results: In placebo subjects (ITT), overall survival was significantly (P=0.003, log rank) reduced in subjects with >8% weight loss compared to subjects with ≤8% weight loss. Among NSCLC subjects (n=61) placebo subjects with >8% weight loss demonstrated a similar survival disadvantage (P=0.04); 4 month Kaplan-Meier estimates 100% vs 49% ±14.8%. In enobosarm treated subjects in the ITT and NSCLC groups, baseline weight loss did not negatively affect survival.
Conclusions: Preceding weight loss among NSCLC patients not treated with enobosarm is predictive of decreased survival. NSCLC subjects randomized to placebo with >8% weight loss at baseline were 2x more likely to die than subjects with ≤8% weight loss. In the enobosarm group baseline weight loss was not predictive of survival. These data suggest that enobosarm may overcome the negative prognostic effect of >8% weight loss. Further research is needed to assess the effect of enobosarm on overall survival.
Disclosure: S. Dodson: I am member of senior leadership and own stock in the GTx. M. Hancock and M.A. Johnston: I am an employee and own stock in GTx, Inc. M. Steiner: I am CEO, on the board and own stock in GTx, Inc.

188P
EFFECT OF ENOBOSARM, A SELECTIVE ANDROGEN RECEPTOR MODULATOR, ON PHYSICAL FUNCTION IN NSCLC PATIENTS WITH MUSCLE WASTING

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Background: Muscle wasting in cancer patients leads to decline in physical function. At diagnosis, >50% of lung cancer patients have substantial wasting, increasing to >80% prior to death. Data shows that NSCLC patients with muscle wasting are less likely to tolerate chemotherapy, have worse outcomes and shorter survival. This has detrimental consequences early in a patient's malignancy, underscoring the importance of diagnosing and treating this condition at an early stage. Literature shows that a 10% improvement in physical function is a substantial clinically meaningful benefit. We conducted a randomized, double-blind, placebo-controlled study to evaluate the effect of enobosarm on muscle wasting in physical function in patients with cancer.
Methods: Subjects (n=159) were randomized to oral enobosarm or placebo for 16 weeks. Subjects were males >45y and postmenopausal females, with ≥2% weight loss in 6 months prior to randomization and had NSCLC, colorectal cancer, non-Hodgkins lymphoma, chronic lymphocytic leukemia, or breast cancer. The primary endpoint was change in lean body mass and QOL and physical function as secondary endpoints. For this analysis, clinical benefit is defined as 10% improvement in physical function.
Results: 103 subjects (MITT) had stair climb assessed at baseline and week 16. Enobosarm subjects demonstrated clinical benefit compared to placebo (P=0.03). Among NSCLC subjects, 28 were included in the physical function analysis. 78% treated with enobosarm responded compared to 30% treated with placebo (P=0.02). Physical function was postitivley correlated with QOL as assessed by the FAACT questionnaire further substantiating clinical benefit (Spearman correlation coefficient = 0.60, P=0.001).
Conclusions: Enobosarm was well tolerated ad showed statistically significant & clinically relevant improvement in physical function and NSCLC subjects. Clinical benefit in stair climb power correlated with a clinically relevant improvement in quality of life. These data provide evidence that enobosarm may play an important role in management NSCLC by improving physical function & quality of life.
Disclosure: S. Dodson: I am a member of senior leadership and own stock in GTx, Inc. M. Hancock and M.A. Johnston: I am an employee and own stock in GTx, Inc. M. Steiner: I am the CEO, on the board and own stock in GTx, Inc.

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PLEURO-PULMONARY TUBERCULOSIS FOLLOWING CHEMOTHERAPY FOR LUNG CANCER IN A HIGH TUBERCULOSIS PREVALENCE COUNTRY

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Background: Chemotherapy (CTx) is a risk factor for occurrence of infections. Tuberculosis (TB) is a common infection in high prevalence countries. Data on TB incidence following CTx for lung cancer (LC) is limited. The current study was conducted to assess the incidence of pleuro-pulmonary TB following CTx for LC at a tertiary care institute in North India.
Methods: Retrospective data analysis of newly diagnosed LC patients receiving CTx over a three-and-half year period. Diagnosis of TB was made by presence of suggestive clinico-radiological features (fever, cough, pleuritic chest pain, new parenchymal infiltrates or new onset pleural effusion on chest imaging) along with demonstration of acid fast bacilli (AFB) in sputum/pleural fluid/bronchoalveolar lavage (BAL) fluid and/or growth of Mycobacterium tuberculosis on culture. For biopsy/cytology specimens, diagnosis of TB was established by demonstration of granulomatous inflammation with AFB. Descriptive statistics are used.
Results: Of 763 patients diagnosed during the study period, those excluded from analysis were 14 who did not receive any form of definitive treatment, 23 with non-bronchogenic histologies and 64 who received oral EGFR-TKIs as first line (sole) treatment for non-small cell LC. Among the remaining 662 LC patients who received CTx and comprised the study population, six (0.9%) patients developed TB (four pulmonary and two pleural). Diagnosis was by sputum microscopy, BAL fluid microscopy and pleural biopsy in two patients each. TB involved right lung/pleura in five patients and all patients developed TB on same side as primary tumor. All patients were treated with standard four drug anti-tubercular therapy. Demographic, treatment and survival profile is presented in table.
Conclusions: Incidence of pleuro-pulmonary TB following CTx for LC is low even in a high prevalence country like India. Occurrence of TB on same side as primary tumor in all patients warrants further studies for causality and mechanism determination.
Patient Characteristics:

Age^	**47.3 (15.6) years**
Males	5 (83.3%)
Current/ex-smokers	3 (50.0%)
Histology	
Squamous	2 (33.3%)
Small cell	2 (33.3%)
Non-squamous NSCLC	2 (33.3%)
Stage IIIB-IV at LC Dx	4 (66.7%)
Extra-thoracic metastasis at LC Dx	3 (50.0%)
Baseline performance status of ECOG 0-1	5 (83.3%)
Cycles of chemotherapy*	4.5 (2-6)
Objective response to chemotherapy	
Partial response	4 (66.7%)
Stable disease	2 (33.3%)
Time interval between LC Dx and TB Dx*	144 (56-317) days
Time interval between last chemotherapy cycle and TB Dx*	55 (36-182) days
Overall survival*	312 (200-504) days
Survival after TB Dx*	174 (100-199) days

^Mean (standard deviation); *Median (inter-quartile range); LC = lung cancer; TB = tuberculosis; Dx = diagnosis

Disclosure: All authors have declared no conflicts of interest.

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EFFICACY AND FEASIBILITY OF GEMCITABINE AND CARBOPLATIN AS FIRST-LINE CHEMOTHERAPY IN ELDERLY PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Although platinum-based chemotherapy is a standard first-line treatment in advanced non-small cell lung cancer (NSCLC), further research for the safety and efficacy of combination chemotherapy in elderly patients has been required. The purpose of this study was to evaluate the efficacy and safety of gemcitabine and carboplatin as first-line treatment in elderly patients with advanced NSCLC and to evaluate the prognostic factors.

Methods: Eligibility included: 1) age 70-89, 2) histologically confirmed NSCLC, 3) chemotherapy-naive, 4) advanced disease with stage IIIB or IV, 5) ECOG PS 0-2, 6) adequate organ function. Patients received intravenous carboplatin (AUC=5) on day 1 and gemcitabine (1000 mg/m^2) on days 1 and 8, every 3 weeks. Response evaluation was done every 6 weeks with RECIST criteria and toxicity was evaluated with NCI-CTCAE.

Results: Between May 2007 and Oct 2011, 40 patients were enrolled. Median age was 73.9 years (range: 70.0–84.6), and there were 27 men (67.5%). 37 patients (92.5%) had ECOG PS 0-1 and 3 patients (7.5%) had PS 2. Histology was squamous cell carcinoma (42.5%) and adenocarcinoma (57.5%). The median number of cycles was 4 (range: 1-6). Best responses were partial response in 22 (55.0%) patients and stable disease in 13 (32.5%). Overall response rate was 55.0% (95% CI: 39.8–69.3). The median progression-free survival (PFS) and overall survival (OS) were 5.9 months (95% CI: 4.5-7.3) and 9.6 months (95% CI: 8.2–11.0), respectively. 6-month PFS rate and 1-year survival rate were 49.0% (95% CI 32.9–62.5) and 34% (95% CI: 22.1-50.5), respectively. Grade 4 hematologic toxicities were neutropenia (7.5%), thrombocytopenia (7.5%) and anemia (5.0%). Frequent non-hematological toxicities were fatigue (40.0%), stomatitis (15.0%), and nausea/vomiting (10.0%), which were predominantly Gr 1/2. Histologic subtype of adenocarcinoma was a significant prognostic factor for PFS (p=0.024) and also had favorable tendency to OS.

Conclusions: Gemcitabine and carboplatin combination chemotherapy can be considered as an effective and manageable treatment option in elderly advanced NSCLC patients with good performance status.

Disclosure: All authors have declared no conflicts of interest.

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MANAGEMENT OF ELDERLY ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS: ANALYZING "REAL-LIFE" PRACTICE PATTERNS

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Background: In advanced EGFR wild-type NSCLC, platinum-doublet chemotherapy (CT) combinations are commonly accepted as the reference regimens for fit patients (pts), with demonstrated improvement in overall survival, quality of life and symptom control. Greater than 40% of advanced NSCLC pts are aged ≥ 70 yrs and evidence supports benefit of the elderly population with combination CT in those with a good performance status (PS) and limited comorbidities. Given the paucity of data in the non-clinical trial setting, we explored the practice patterns in managing this subpopulation in a large North American cancer centre.

Methods: A population-based, retrospective, chart review was conducted in elderly (≥ 70 yrs) advanced EGFR wild-type or unknown NSCLC pts who were diagnosed in Northern Alberta, Canada from 2007 to 2009. Baseline clinical characteristics, treatments, toxicity data, and patient outcomes were collected.

Results: From 2007 to 2009, 349 elderly pts with stage IV NSCLC were diagnosed. Age range was 70 to 93 yrs with a median of 76 yrs. Two-hundred ninety pts (83%) received best supportive care (BSC) alone; key factors influencing this decision were poor PS (ECOG PS ≥ 2; 75%), patient choice (14%), and significant comorbidities (8%). Of 59 elderly pts (17%) who received CT, 51 (86%) received platinum-doublet CT with a median of 4 cycles per patient. A significant proportion (44%) had delays in administration of CT due to hematologic and non-hematologic toxicities. This resulted in dose reductions for 14% of elderly pts. Although there was not a CR, 7 pts (12%) had a PR, and 26 pts (27%) had SD for a disease-control rate of 38%. Median overall survival (OS) was 11.6 months for those receiving CT and 2.3 months for BSC alone (1-yr OS of 49% and 12%, respectively).

Conclusions: This study demonstrates that in the elderly Albertan population, a significant majority of pts do not receive CT, primarily due to poor PS. This possibly explains the underrepresentation of these pts in lung cancer clinical trials. For those elderly pts who are fit to receive CT, survival is comparable to the broader population of advanced NSCLC but is hindered by toxicities and subsequent delays in CT administration. Further interrogation into the risk to benefit ratio determinants are needed.

Disclosure: All authors have declared no conflicts of interest.

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EFFICACY AND SAFETY OF PEMETREXED AS SECOND-LINE TREATMENT IN ELDERLY PATIENTS (PTS) WITH ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (NSCLC): A RETROSPECTIVE ANALYSIS

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Background: In elderly pts with advanced NSCLC, and no major co-morbidities, chemotherapy or target agents, are the standard of care in second-line treatment, after a first platinum-based regimens. No randomized clinical trial evaluating age related efficacy and safety of pemetrexed.

Patients and methods: We retrospectively analysed elderly pts (≥65), with no major co-morbidities, with diagnosis of non-squamous advanced/metastatic NSCLC, treated with pemetrexed (500 mg/m2, d 1, every 3 wks), after first-line platinum-based chemotherapy. In an exploratory analysis, we considered the following factors in order to evaluate a potential influence on response and safety: age (<75 vs ≥75), adenocarcinoma (adk) histology vs other non-squamous carcinoma (non-SCC), performance status (0 vs 1/2), presence of brain metastases.

Results: 65 elderly pts (median age 71, range 60 to 85) were evaluated. Pts were (%): male 72; stage IV 77; ECOG PS 0/1-2 58/42; adk/large cell/other non-SCC 77/8/15; previous cisplatin/carboplatin 56/44; brain metastases 26. Median cycles of pemetrexed were 5.8. ORR was 43.1%. CR was reached in 2 pts (3.1%); PR in 26 pts (40%), SD in 27 pts (41.6%) and PD in 10 pts (15.3%). The overall population median PFS was 4.1 months (95% CI: 2.9 - 5.4). Median PFS (months) according to different factors resulted: 2.9 vs 4.2 (p=0.18) in pts with brain metastases vs no; 4.4 vs 1.4 (p<0.0001) for adk vs other non-SCC and in pts with ECOG PS 0 vs 1/2 was 4.6 vs 2.5 (p=0.009). No significant PFS differences between the age groups (<75 vs ≥75) were observed (4.4 vs. 3.5; p = 0.7). Low incidence of clinically significant grade (G) 1/2 adverse events (AEs) occurred. G3 hematologic AEs were (%): anemia 4.6; neutropenia 9.2; piastrinopenia 6.2. G3 non-hematologic AEs were (%): fatigue 9.2, nausea 4.6; vomiting, diarrhea, rash, mucositis and > ALT were under 2%. No pts developed neurosensory toxicities.

Conclusion: Long-term survival and good tolerability resulted in our elderly pts treated with pemetrexed in second-line; in this setting, single agent may be recommended too, in pts with a good ECOG PS, independently from age.

Disclosure: All authors have declared no conflicts of interest.

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ROLE OF COMBINED ERLOTINIB AND TEMOZOLAMIDE IN ADENOCARCINOMA LUNG WITH BRAIN METASTASES IN ELDERLY PATIENTS

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Aims: To evaluate the feasibility and tolerance of Erlotinib and Temozolamide in elderly patients of adenocarcinoma lung with brain metastases.

Background: Brain metastases are found in ~10-25% at the time of diagnosis, and ~40-50% of all patients with lung cancer develop brain metastases during the course. Most patients present with multiple lesions. Brain metastases are usually associated with poor outcomes and shortened survival of 6 months or less. Standard treatment options include symptomatic therapy with steroids and whole-brain radiotherapy (WBRT). The poor outcomes and relapses following WBRT alone indicate a need for new therapeutic options.

Material amd methods: A total of 9 elderly patients of biopsy proven adenocarcinoma lung with brain metastases (on MRI) were analyzed from July 2010 to December 2011 with respect to patient's characteristics, chemotherapy, radiotherapy and treatment outcomes. The patients' age ranged from 58 to 75 years. All the patients were planned for palliative radiation of 30 Gy/10#/2 weeks to local disease with WBRT of 20 Gy/5#/1 week with concurrent Temozolamide@ 75mg/m2 followed by assessment for further therapy after 3 weeks of radiation. All the patients were evaluated 3 weekly for assessment of symptom relief and improvement or progression.

Results: All the patients completed the scheduled radiation with oral steroids. After 3 weeks all the patients were started on Erlotinib@ 150 mg, daily and Temozolamide@ 150-200 mg/m2, D1-5, 4 weekly. 3 of the patients progressed and died between 3 and 6 months. 1 patient defaulted during the radiation therapy and another after completion of 6 cycles of oral chemotherapy. Only 4 patients could complete the 12 cycles of oral chemotherapy with Temozolamide and Erlotinib, 4 weekly. Only 1 patient needed dose reduction of Erlotinib to 100 mg due to grade III rashes in 3rd cycle. Side effects were managed conservatively in rest. The patients who improved after local and brain RT have shown to tolerate the further oral chemotherapy. These patients are still alive with the metastatic disease.

Conclusion: The combination of Erlotinib with temozolomide represents a promising strategy for treating brain metastases in adenocarcinoma lung and appears to be safe and tolerable.

Disclosure: All authors have declared no conflicts of interest.

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ERLOTINIB AS FRONTLINE TREATMENT FOR ELDERLY PATIENTS (P) WITH ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (NSNSCLC): GGCP044/09 STUDY

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Background: NSCLC is primarily a disease of older people with a median age of approximately 70 years (y) at diagnosis. Platinum combination chemotherapy (CT) has shown to be more effective than single agents but it is associated with more toxicity. Erlotinib is an EGFR TK inhibitor with a favourable toxicity profile and its oral administration makes it suitable to treat elderly p. No much is known about its efficacy and toxicities in this subpopulation, often under-represented in clinical trials. This Galician study aims to evaluate the efficacy and safety of erlotinib as 1st-line treatment (Tx) for elderly p with advanced nsNSCLC.

Material and methods: Elderly p (≥70 years old) with stage IIIB/IV nsNSCLC were included in this prospective observational study. Erlotinib was orally administered at a dose of 150 mg daily until disease progression or intolerable toxicity. PFS (primary objective) and OS were measured from time of diagnosis.

Results: A total of 31 p were enrolled. Baseline characteristics: Mean age 78 y (range 70-85); female 67.7%; adenocarcinoma (including BAC) 90.3%; never/current/former smokers (%): 54.8/16.1/22.6 (6.5% unknown), stage IV 84%; ECOG PS 0/1/2 (%): 6.4/45.2/48.4. The median PFS was 6.4 and the median OS was 9.9 months. Out of 26 evaluable p, 8 had PR and 8 SD, for an ORR of 30.8% and a DCR of 61.6%. The most common adverse event was skin rash, 38.7% (9.6% grade 3-4), diarrhoea, 25.8% (3.2% gr. 3-4) and asthenia, 19.3% (no gr 3-4 were reported). 5 p (16.1%) needed dose reduction and 3 p withdrew the Tx due to grade 3 diarrhoea, eye perforation and esofaghitis, respectively.

Conclusions: These results in real-life settings confirm that erlotinib is an active and well tolerated agent as frontline Tx in elderly p (≥70) in nsNSCLC. Response rate is similar to that achieved with CT in younger people; benefit in PFS is modest, but median OS is acceptable, taking into account that half of the p had a PS of 2. EGFR mutation testing should be strongly encouraged among elderly p.

Disclosure: All authors have declared no conflicts of interest.

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A PHASE II STUDY OF WEEKLY PACLITAXEL COMBINED WITH CARBOPLATIN VERSUS THE STANDARD EVERY 3-WEEKS PACLITAXEL AND CARBOPLATIN FOR ELDERLY PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED NON-SMALL CELL LUNG CANCER

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Background: Paclitaxel and platinum-based chemotherapy is considered to be a standard approach for locally advanced and metastatic non-small cell lung cancer (NSCLC). In recent years, paclitaxel on a weekly schedule in combination with carboplatin has been widely used because it is associated with a lower incidence of neuropathy and myelosuppression. Otherwise, only a few studies are available in elderly patients with NSCLC.

Purpose: The aim of our study was to evaluate the efficacy and safety of weekly paclitaxel combined with carboplatin compared with the classic 3-weekly schedule of paclitaxel and carboplatin as initial therapy and the feasibility of subsequent maintenance therapy versus observation in elderly patients with locally advanced (stage IIIB) and metastatic (stage IV) NSCLC.

Methods: Eighty-six patients ≥ 65 years with stage IIIB-IV NSCLC were randomly assigned to one of the following arms: arm1, paclitaxel 90 mg/m^2 weekly for 3 of 4 weeks with carboplatin (area under the curve {AUC} =6) on day 1 of each 4 week cycle; and arm 2, paclitaxel 200 mg/m^2 with carboplatin (AUC=6) on day 1 of each 3-week. After four cycles of chemotherapy, those with objective response or stable disease were randomized to weekly paclitaxel (70mg/m^2, 3 of 4 weeks) or observation as maintenance therapy. Primary end point was response while second end points included survival and toxicity.

Results: All patients were evaluable for response, overall responses were recorded in 42.9% in arm 1 versus 31.8% in arm 2; stable disease was 38.1% in arm 1 versus 27.3% in arm 2 and progressive disease was 19% in arm 1 versus 40.9% in arm 2. The median time to progression and median survival times were 7 months and 10.8 months in arm 1 versus 5.6 months and 9 months in arm 2, respectively. The 1-year survival rates were 47.6% in arm 1 versus 36.4% in arm 2. Grade 3/4 anemia was more common in arm 1 (23.8%) than arm 2 (9.1%). Grade 3/4 neutropenia and febrile neutropenia

occurred in 14.3% and 4.7% in arm 1 versus 22.7% and 9.1% in arm 2. Grade 2/3 neuropathy occurred in 4.7% in arm 1 versus 13.6% in arm 2.
Conclusions: Efficacy was similar between the weekly regimen and the standard regimen of carboplatin and paclitaxel for elderly patients with advanced NSCLC and may be advantageous based on its favorable tolerability profile.
Disclosure: All authors have declared no conflicts of interest.

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A PHASE I-II EVALUATION OF THE SAFETY AND EFFICACY OF THE ORAL HSP90 INHIBITOR DEBIO 0932 IN COMBINATION WITH SOC IN FIRST- AND SECOND-LINE THERAPY OF STAGE IIIB OR IV NSCLC - THE HALO STUDY (HSP90 INHIBITION AND LUNG CANCER OUTCOMES)

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Background: Debio 0932 is an oral second-generation Heat shock protein 90 (HSP90) inhibitor, structurally unrelated to geldanamycin. In pre-clinical models and in the recently completed dose-escalation part of a Phase I study (NCT01168752), Debio 0932 has shown promising signs of efficacy in Non Small-Cell Lung Cancer (NSCLC). Further investigations into the potential role of Debio 0932 in NSCLC are warranted.
Study design: This study will include patients with advanced NSCLC (Stage IIIb or IV) without known EGFR mutation, and will consist of three parts. Part A is an open-label dose escalation study of Debio 0932 in combination with standard of care (SOC) in patients who are candidates for first-line- or second-line treatment. First-line SOC consists of cisplatin + gemcitabine in case of squamous histology, and cisplatin + pemetrexed in case of non-squamous histology. Second-line SOC consists of docetaxel. Part B is a randomized, double-blind, placebo-controlled study of Debio 0932 in combination with first-line SOC in 138 patients who did not receive previous systemic treatment for advanced NSCLC. Patients who subsequently develop progressive disease in Part B will enter into Part C, in which a second randomization will assign patients to double-blind treatment with docetaxel + placebo or docetaxel + Debio 0932. Approximately 100 patients are expected to enter Part C. Part B has a primary endpoint of PFS at 6 months; key secondary endpoints include best overall response rate, duration of objective response, change in tumour size from baseline until 6 months, and OS. Part C has a primary endpoint of change in tumour size from baseline until 6 months; key secondary endpoints include best overall response rate, duration of objective response, PFS at 6 months, and OS. Potential pharmacogenomic, tumour pharmacogenetic, proteomic, and pharmacogenetic factors predictive of response to Debio 0932 will be assessed.
Conclusion: This international multi-center study will investigate the role of Debio 0932 in the first- and second line treatment of advanced NSCLC. Study results are expected in 2014.
Disclosure: H. van Ingen and D. Purcea: I am an employee of Debiopharm. S. Brienza and L. Paz-Ares: I am a consultant to Debiopharm.

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BEVACIZUMAB (B), CISPLATIN (C) AND PEMETREXED (P) PLUS MAINTENANCE B IN CHEMO-NAïVE PATIENTS (PTS) WITH ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (NSNSCLC): A PHASE II STUDY

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Background: B in combination with platinum doublets followed by continuation maintenance with B prolongs survival and delays progression in chemo-naïve pts with advanced (nsNSCLC). P in combination with C is efficacious in advanced nsNSCLC as frontline treatment. This phase II study aims to evaluate the efficacy and safety of B, C and P plus maintenance B in chemo-naïve pts with advanced nsNSCLC.
Methods: Chemo-naïve pts with unresectable stage IIIB or IV nsNSCLC were treated of C (75 mg/m^2), P (500 mg/m^2), and B (7.5 mg/kg) on day 1 every 21 days up to 6 cycles. Pts with response or stable disease (SD) received maintenance B (7.5 mg/kg) every 21 days until disease progression or unacceptable toxicity. The primary endpoint was median progression free survival (PFS). Secondary endpoints included objective response rate (ORR), overall survival (OS), safety and analysis of K-ras mutations and plasma VEGF levels.
Results: From 4/09 to 12/11, 27 pts were enrolled in the study. Data of 21 pts are presented. Median age was 58 years (range 42-74); male/female (%): 81/19; ECOG 0/1 (%): 5/95; adenocarcinoma/large cell carcinoma (%): 95/5. Median follow-up is 4.7 months. 53% of pts received at least 6 cycles of treatment and 20% received up to 12 cycles. Among the 15 pts assessable for response, the ORR was 47% (95% CI, 21-73) and disease control rate was 87%. Median PFS was 6.0 months (95% CI, 1.9-7.5). Grade 3/4 hematologic toxicity was neutropenia (9%/0). Most frequent grade 3/4 non-hematologic toxicities were fatigue (29%/0), venous thrombosis (14%/0), pulmonary embolism (9%/0) and dyspnea (5%/5%). There were no grade 3/4 hemorrhagic events. Data on survival and the analysis of K-ras mutations and VEGF levels will be presented.
Conclusions: Treatment with B, C and P plus maintenance B is feasible and effective as front-line treatment of pts with advanced nsNSCLC. These data provide further evidence that B may be used in combination with multiple standard, platinum-based doublets in this setting.
Disclosure: All authors have declared no conflicts of interest.

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MAINTENANCE THERAPY FOR ADVANCED NON-SMALL CELL LUNG CANCER: HOW DOES MY PATIENT FEEL ABOUT IT?

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Introduction: Several randomized trials on maintenance therapy (MT) for metastatic non-small cell lung cancer (NSCLC) have demonstrated benefit in progression-free survival. Recent data also showed a significant overall survival (OS) gain for MT with pemetrexed or erlotinib. Yet, in this non-curative treatment setting, the benefit has to be weighed against the potential burden of treatment. In the absence of data regarding patients' preferences towards MT, we undertook a patient survey.
Methods: This pilot study surveyed patients with stage IV NSCLC scheduled for standard first-line platinum-based doublet chemotherapy outside of a therapeutic clinical trial. The survey could be carried out in a a 'neutral' hypothetical context, i.e. without consequences for MT, as it was performed in the (short) timeframe where MT was not reimbursed in Belgium, and as this was made clear when the patients agreed to participate. The patients had a questionnaire at baseline, after two, and after four cycles of chemotherapy, always before the result of tumour response assessment was known. Ten questions covering the overall attitude towards MT, the clinical benefit expected by patients, the acceptance of side-effects, and the modes of administration were autonomously completed by the patients.
Results: Thirty patients were included. Overall, patients had a positive attitude towards MT. At baseline, 60% were in favour, 40% were unsure, and no single patient was opposed. MT resulting in an OS benefit of six, three or one month, respectively, was considered worthwhile by 83%, 67%, and 43% of patients, respectively. With some decrease of these percentages over time, especially for the OS benefit of one month. Effects on symptom control were crucial for about 90% of the patients at any timepoint. There was a slight preference for oral versus i.v. administration. Side effects were accepted by the majority as long as they were mild to moderate.

Conclusion: Our survey showed that metastatic NSCLC patients are in general in favour of MT. They expect either an OS benefit of at least several months, or better symptom control, in balance with mild to moderate side effects.

Disclosure: J. Vansteenkiste: Holder of Eli-Lilly Chair in Respiratory Oncology at Leuven University (research funding). All other authors have declared no conflicts of interest.

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A PHASE II STUDY OF PEMETREXED IN HEAVILY PRETREATED NON-SQUAMOUS NON-SMALL-CELL LUNG CANCER: HANSHIN ONCOLOGY GROUP 001

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Background: Pemetrexed has shown substantial activity in non-squamous non-small-cell lung cancer (NSqNSCLC) and is one of the current standard agents in second-line settings due to its efficacy and favorable tolerability profile. We conducted phase II study to evaluate the safety and efficacy of pemetrexed in Japanese patients with previously treated, advanced NSqNSCLC.

Patients and methods: Patients with stage IIIB (wet) or IV NSqNSCLC, performance status (PS) 0/1/2, previous two to five regimens of chemotherapy were enrolled and received pemetrexed (500 mg/m^2 Day 1, every 21 days) until disease progression. The primary endpoint was progression-free survival (PFS). The secondary endpoints included overall survival (OS), objective response rate (ORR), disease control rate (DCR), and safety. The trial has been registered at UMIN-CTR (www.umin.ac.jp/ctr/index/htm), registration identification number UMIN000002467.

Results: From August 2009 to May 2010, 46 patients were enrolled: median age 65 yrs; 52% women; PS 0/1/2 26%/67%/7%, respectively; no. of previous treatment regimens were 2/3/4/5 in 48%/26%/24%/2%, respectively; EGFR activating mutation status was positive/wild/unknown for 30%/48%/22%, respectively. Median duration of follow-up was 13.5 months, with 80% patients progressed and 50% deceased. Median of 7 cycles of pemetrexed was administered. Median PFS was 4.2 months (95%CI: 3.3, 6.4). Median OS was 15.8 months (95%CI: 10.7, NA). ORR was 8.7% (95%CI: 2.4, 20.8) and DCR was 63.0% (95%CI: 47.5, 76.8) (CR 0%, PR 8.7%, SD 54.3% and PD 28.3%, by monitoring committee). In a total of 261 cycles of therapy, G3/4 neutropenia was observed in 7%/3% cycles, G3/4 anemia in 1%/0% cycles, and G3/4 thrombocytopenia in 1%/0% cycles, respectively. The most common G3/4 non-hematologic adverse events were hyperkalemia (2%) and elevation of aminotransferase (2%).

Conclusions: Treatment with pemetrexed in previously treated Japanese NSqNSCLC patients is feasible and shows encouraging activity.

Disclosure: All authors have declared no conflicts of interest.

200P
CARBOPLATIN AND PEMETREXED FOR NON-SQUAMOUS NON-SMALL CELL LUNG CANCER – OVERALL SURVIVAL AND TOXICITY

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Cisplatin/pemetrexed has been shown to be superior to cisplatin/gemcitabine in terms of overall survival for NSCLC with non-squamous cell histology. Although cisplatin is advantageous when compared to carboplatin from a survival point of view, the toxicity is also more pronounced, and carboplatin is often preferred in palliative treatment. In clinical trials, patients are highly selected, and results from randomised trials does not always transform to clinical practice. In this retrospective study we examine how patients with advanced, non-squamous NSCLC respond to treatment with carboplatin plus pemetrexed (C/P). The study included all patients diagnosed with advanced or metastatic NSCLC (not eligible for concomitant chemo-radiation) treated with C/P in the first-line setting. Chemotherapy cycles were repeated every 3 weeks for up to 4 cycles. Patients were CT-scanned at baseline, after 3 cycles of chemotherapy and approximately every third month hereafter. Assessments of toxicity were made according to the common toxicity criteria (CTC, version 3.0). From November 2009 to December 2010, a total of 83 patients received first-line treatment with C/P. Following first line therapy, 17 patients went on to receive curative intended radiation, survival data is only shown for the remaining 66 patients.

Performance status	N	Median overall survival, mths
0	28	13.6
1	29	8.0
2	8	10.8
3	1	3.0

Adverse event	N	%
Neutropenic fever, grade3+	3	4
Nausea, grade 3+	2	2
Transfusion of RBC's	17	20
Trombocytopenia, grade 4	3	4

In our study an OS of 10.0 months was observed for patients in ECOG PS of 0 or 1. The corresponding OS in a Norwegian study of C/P was 8,7 months (ECOG PS=0-1). A recent study which compared C/P with C/docetaxel showed an OS in the C/P arm of 14.9 months (ECOG PS=0-2). Toxicity rates were similar to those observed in clinical trials.

Disclosure: All authors have declared no conflicts of interest.

201P
PREDICTIVE FACTORS FOR LONG-TERM RESPONSE TO PEMETREXED TREATMENT IN ADVANCED NON-SQUAMOUS, NON-SMALL-CELL LUNG CANCER PATIENTS

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Introduction: This study intended to identify the novel predictive factors affecting the duration of the response and survival rates in pemetrexed treatment in advanced non-squamous, non-small cell lung cancer.

Method: We performed a retrospective analysis of the clinical and pathology data of all consecutive patients with advanced non-squamous, non-small-cell lung cancer treated with pemetrexed as a

second or further line of treatment between June of 2003 and June of 2010. The primary objective was progression-free survival, and secondary objectives were response rate, disease control rate, and overall survival.

Results: Two hundreds and seventeen patients were enrolled. Median age at diagnosis was 63.2. Male patients represented 51.6% and patients in the never-smoker category accounted for 53.9% of all patients. In 176 patients (81.1%), adenocarcinoma was confirmed histologically. Pemetrexed was used as a second-line therapy in half of all patients (108 patients, 49.8%). The overall response rate was 15.6% and the disease control rate was 59.4%. Median progression-free survival was 3.0 months and median overall survival was 10.3 months. In a multivariate analysis, good performance status and non-exposure to gemcitabine were independent predictive factors of progression-free survival. Pemetrexed was well tolerated in most patients, except for one patient who showed grade 3 hematologic toxicity. Treatment-related discontinuation due to pemetrexed-related adverse events was rare (3.7%).

Conclusion: The performance status and whether a patient had been exposed to gemcitabine were significant predictive factors of progression-free survival.

Disclosure: All authors have declared no conflicts of interest.

202P
THE EFFECT OF PEMETREXED CONTAINING REGIMES ON OVERALL SURVIVAL IN NON-SQUAMOUS NSCLC

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Background: Scagliotti's paper in 2008 suggested that pemetrexed and cisplatin (pem-cis) produces longer overall survival (OS) compared to gemcitabine and cisplatin (gem-cis) in non-squamous NSCLC. (12.6 vs 10.9 months). However, Gronberg's paper in 2009 comparing pemetrexed and carboplatin (pem-carbo) and gemcitabine and carboplatin (gem-carbo) showed no difference in OS (7.8 vs 7.5 months). NICE guidance in Sep 2009 permits the use of pem-cis in 1st line locally advanced or metastatic non-squamous NSCLC. This retrospective study examines the effect of the NICE guidance on overall survival in non-squamous NSCLC.

Methods: We included all non-squamous NSCLC patients registered in our centre between 1st Sep 2008 and 1st April 2011. Those treated with palliative chemotherapy were identified and their clinical records examined. Overall survival (OS), progression free survival (PFS) and chemotherapy toxicities were recorded. Data was analysed using SPSS.

Results: 111 patients were included in the study. 26 patients received pemetrexed containing regimes. 20 of these patients received pem-carbo due to a number of factors including patient co-morbidities and infusion time. PFS in those receiving pemetrexed regimes was 3.8 months (CI 2.6 – 5.1) and 5.8 months for other platinum doublets (CI 4.5 – 7.2). Median OS was 13.7 months for those receiving pemetrexed regimes (CI 9.1 – 18.3) and 10.5 months for those receiving platinum doublets (CI 8.4 – 12.7). Pem-carbo did not appear inferior to pem-cis in PFS or OS. Overall, grade 3 or 4 toxicities were lower than reported in the clinical trials but haematological toxicities were high in the pem-cis patients.

Conclusions: Overall survival in this study matches those reported in the Scagliotti paper and is better than those reported in the Gronberg paper despite the high frequency of carboplatin containing regimes. Small numbers mean that no significant differences were found but the data supports the use of pemetrexed regimes in non-squamous NSCLC.

Disclosure: All authors have declared no conflicts of interest.

203P
CLINICAL PROFILE AND PATTERNS OF PROGRESSION (PD) OF PATIENTS (PTS) WITH ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (NSNSCLC) TREATED WITH FIRST LINE BEVACIZUMAB (B): AVVA STUDY

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Background: B in combination with platinum doublets prolongs survival and delays PD in chemo-naïve pts with advanced nsNSCLC and its safety profile has been widely described in clinical trials. In this study we aim to evaluate the behavior, clinical profile and patterns of PD of real-life nsNSCLC pts treated with B in 44 Spanish institutions.

Methods: AVVA is a multicenter, epidemiological study to define the clinical profile (gender, age, PS, histology, stage, comorbidities, tumor load, Tx, response and tolerability) and describe the patterns of PD. Pts diagnosed with advanced nsNSCLC and evidence of PD after treatment (Tx) with standard chemotherapy (CT) plus B up to 6 cycles followed by maintenance B were included.

Results: Data of 158 pts are presented. Clinical profile was: median age 58 years (range 34-79); male 65%; stage IV 91%; adenocarcinoma 77%; ECOG PS 0/1/≥2 (%): 35/56/9; never/current/former smokers (%): 23/40/37. 64% of pts presented relevant concomitant disease at baseline (27% cardiovascular disease, 24% pulmonary disease). Tx received: B plus carboplatin-doublet/cisplatin-doublet/other (%) 70/25/5. Median no. of cycles for CT/B: 6/9. Patterns of PD: 44% presented high tumor load (tumor diameter ≥55mm and ≥5 lesions); 97% of pts presented intra-thoracic disease, 53% presented extra-thoracic disease and 13% only pulmonary disease. High tumor load was associated with extra-thoracic disease ($p<0.05$). ORR was 53% (95% CI: 45-61) and disease control rate was 85%. Best response was achieved after a median of 4 cycles (range 1-16). ECOG 0/1 at PD (%): 15/50. Median PFS was 7.7 months (95% CI: 7.3-8.1). No differences were found in ORR or PFS according to tumor load and intra/extra-thoracic disease. Grade 3/4 toxicities were: venous thrombosis (3.2%/0), proteinuria (0.6%/0), hemoptysis (0.6%/0), pulmonary embolism (0/0.6%) and mucositis (0.6%/0).

Conclusions: B was effective in this real-life patients' population, irrespective of tumor load and location of the disease. These results confirm the well-established safety profile and the efficacy of B as frontline Tx in nsNSCLC.

Disclosure: All authors have declared no conflicts of interest.

204P
INCREASE IN THE ERYTHROCYTE MEAN CORPUSCULAR VOLUME (MCV) IN NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS TREATED WITH PEMETREXED-BASED CHEMOTHERAPY

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Introduction: Pemetrexed (Pem) is approved for maintenance chemotherapy (MTX) in patients (pts) with advanced NSCLC. Pem MTX has become a common practice either alone or in combination with bevacizumab (Bev).

Because Pem is well tolerated, pts can remain on therapy for a prolonged period. We report an increase in the erythrocyte MCV without megaloblastic anemia and without apparent clinical significance.
Method: 45 non-squamous NSCLC pts previously treated with Pem-based therapy either as initial treatment followed by MTX Pem or Pem/Bev or second line (2nd) therapy were studied. MCV values were collected and those pts whose MCV were above normal range (80-98 fl) at one point during therapy are reported. All patients received daily folic acid (FA) and vitamin B12 (VitB12) at least every 3 cycles of Pem. FA, VitB12, homocysteine (Hom), and methylmalonic acid (MMA) levels were measured on those pts still on active MTX who also had high MCV.
Results: 41 pts received platinum/Pem/Bev triplet as initial therapy followed by Pem/Bev or Pem MTX, 2 pts with Pem/Bev as 2nd line, and 2 pts with Pem alone as 2nd. Median age: 64 years old (34-84); 27 pts males; 29 pts (64%) Hispanic. 27 pts (60%) developed an elevated MCV (range: 98.1-114). For the entire cohort, median # cycles of Pem given 12 (range: 2-38). In those pts who had high MCV, the median # of Pem cycles given was 12 (range: 5-38). All pts had normal or low MCV prior to therapy. 32 pts had progressed and are not longer on MTX. 8/13 pts on active MTX had high MCV; 5 of these 8 pts were available for FA, VitB12, MMA, and Hom measurement. All values were within normal limits. The MCVs of these 5pts were: 101.6, 100, 102.1, 102.2, and 104.8 from baseline values of: 74.4, 89.3, 92.8, 89.7, and 89.6, respectively. The hemoglobin levels of these pts were 12.2, 13.2, 15.4, 11.4, and 11 g/dL, respectively with normal WBC and platelets.
Discussion: Pem is a structural analogue of FA and uses the same biochemical machinery as natural folates for membrane transport and intracellular polyglutamation. We report here patients treated with Pem for a prolonged periodwith proper FA and VitB12 supplementation that have an increased MCV with no abnormal levels of co-factors. Pem induces macrocytosis by a thymidylate-independent mechanism. This observation will be further validated in the other pts still on Pem-based MTX.
Disclosure:
E.S. Santos and L. Raez: Eli Lilly Speaker Bureau; no other conflict of interest to declare. J.E. Gomez: Eli Lilly Speaker Bureau. No other relationship to disclose. All other authors have declared no conflicts of interest.

205P
CLINICAL USEFULNESS OF PULMONARY FUNCTION TEST IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER RECEIVING CHEMOTHERAPY

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Background: Chemotherapy for non-small ling cancer (NSCLC) induces some change in pulmonary function. Baseline and Changes in specific pulmonary function tests may be useful for prediction in survival.
Methods: A retrospective review of a prospective database of patients with NSCLC who underwent platinum-based first-line chemotherapy, had pulmonary function tests performed both before and after therapy was performed. In this study, patients who were treated with radiotherapy or lung resection were omitted. Baseline values and change in the pulmonary function test (PFT) before and after treatment were entered into a multivariate model in which the dependent variable was survival.
Results: There were 53 patients. Significant improvements ($p < 0.05$) were recorded after chemotherapy in forced expiratory volume in 1 second %pred. (FEV1, 8.04%pred.), FEV1/ forced vital capacity (FEV1/FVC, 4.09%pred.) and forced expiratory flow 25–75%pred. (FEF25-75%, 14.69%pred.). Lung diffusion for carbon monoxide adjusted with hemoglobin (DLCO adjusted) was significantly impaired after chemotherapy (−10.02%; p=0.002). There was no significant difference in change of PFT according to tumor response and regimen. Univariate analysis of the factors affecting survival revealed that response to chemotherapy, baseline FVC %pred., FEV1 %pred., FEV1/FVC and FEF25-75% in liter, changes after chemotherapy in residual volume (RV) in liter and DLCO adjusted were significant for survival. On multivariate analysis, progressive disease after chemotherapy (HR 15.323; 95% CI 3.846-61.042; p<0.001) and decrease is 8% or less in DLCO adjusted (HR 3.082; 95% CI 1.302-7.298; p=0.010) were factors for reduced survival.
Conclusions: A decrease in DLCO adjusted after chemotherapy may predict survival, especially if the decrease is 8% or less. These results should be considered in the patients with advanced NSCLC who underwent chemotherapy.
Disclosure: All authors have declared no conflicts of interest.

206P
SPIROMETRY IN PATIENTS WITH STAGE IV NON-SMALL CELL LUNG CANCER (NSCLC)

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Background: Symptom control is paramount in the palliative management of stage IV NSCLC. Given the common risk factor of smoking, patients with NSCLC are likely to have concurrent chronic obstructive pulmonary disease (COPD). Once stage IV NSCLC is diagnosed, the familiar focus tends to be palliation using chemoradiotherapy. The investigation and treatment of co-existing COPD may be neglected resulting in incomplete management of dyspnoea. We sought to determine the frequency of spirometry in patients being worked up for stage IV NSCLC in a tertiary oncology unit.
Method: Records of 130 current/ ex-smokers with stage IV NSCLC were reviewed. Symptoms at first consultation, co-morbidities, possible contributing factors to dyspnoea, use of bronchodilators as well as the results of any spirometry performed within six months prior or post first review were recorded. Global initiative for chronic obstructive lung disease (GOLD) staging system was used to document COPD severity [stage I Forced Expiratory Volume (FEV) I ≥ 80%, stage II 50-80%, Stage III 30-50%, Stage IV <30%].
Results: Median age was 66.5 years (37-87) and 69% were male. At first consultation, 61/130 (46%) patients complained of dyspnoea. Of these, 75% (46/61) were not known to have prior COPD. Only 14/46 (30%) were referred for spirometry, resulting in 10/14 (71%) being diagnosed with COPD (40% GOLD stage I, 20% stage II, 20% stage III, 10% stage IV). Twenty eight of the 46 patients had at least one other known factor potentially contributing to dyspnoea. Eighteen patients were breathless without a clear cause. However, only 6/18 (33%) were referred for spirometry and 4/6 patients (66%) had COPD. The median pack years smoked was 37. Only 3/46 (6.5%) breathless patients were on bronchodilators at the time of first consultation as a result of spirometry in the context of their cancer diagnosis.
Conclusion: A minority of patients (30%) with stage IV NSCLC and dyspnoea without known COPD underwent spirometry; 71% had COPD when tested. COPD is a clear contributor to dyspnoea in this group of patients and warrants timely investigation and intervention. Any patient with a smoking history should have spirometry during work up for stage IV NSCLC, regardless of other contributors to dyspnoea.
Disclosure: All authors have declared no conflicts of interest.

207P
SIMPLE MULTIPLES OF MEDIAN OVERALL SURVIVAL (OS) MAY NOT ESTIMATE SURVIVAL IN PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC) TREATED WITH FIRST-LINE EGFR-TARGETED AGENTS

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Introduction: For patients with incurable cancer, being able to estimate prognosis remains important. Previous work has shown that simple multiples of the median OS can estimate survival in patients with lung and breast cancer receiving palliative chemotherapy[1,2]. We investigated whether this is true for NSCLC patients treated with first-line EGFR-targeted agents.
Methods: We used similar methods to previous authors[1]. We initially confirmed our methodology in an analysis of 11 first-line chemotherapy trials for

NSCLC. We then analysed all trials where at least 50 patients received first line therapy with only EGFR-targeted agents. We extracted data on a range of survival points (90%, 75%, 50%, 25% & 10%) from survival curves. We compared these with calculated multiples (0.25, 0.5, 2 and 3) of the median OS.
Results: We identified 10 trials utilising EGFR targeted agents which met our criteria and included an OS curve. 5 trials used gefitinib, 5 used efitinib. Table 1 summarises the results. Only 48% of estimates of survival were within 0.75-1.33 times the actual value. This is significantly worse than the agreement seen with conventional cytotoxic agents. In particular, 82% of the estimated values were incorrect for the worst case scenario (90% percentile), largely as a result of over-estimation.
Conclusions: This work shows that the relationship between median OS and other survival points, which holds for patients treated with chemotherapy, may not hold for those treated with first-line EGFR-targeted agents. Kiely et al[1] observed that in patients treated with chemotherapy, the survival distribution was closely approximated by an exponential distribution. The incongruence of our results with this relationship suggests that EGFR-targeted agents may impact differently on OS.
References: 1. Kiely et al. JCO February 1, 2011 29.4 456-463 2. Alam et al. 13th World Conference on Lung Cancer, 2009

Table 1: Median OS & proportion of actual survival to estimated survival at different survival points.

	Median OS Weeks	90%	75%	25%	10%
Chen 2012	51	**2.6**	1.3	0.8	NA
Ebi 2008	51	**2.1**	**1.5**	1.0	NA
Hesketh 2008	22	**1.4**	1.2	0.9	**0.5**
Jackman 2007	48	**1.5**	1.3	1.2	NA
Maemondo 2010	134	**0.7**	0.8	NA	NA
Mitsudomi 2010	134	**0.7**	0.8	NA	NA
Mok 2008	80	**1.5**	0.9	NA	NA
Rossel 2009	122	1.3	1.1	**1.8**	NA
Satoh 2011 standard dose	110	0.9	0.9	**1.4**	NA
Satoh 2011 Low dose	141	**0.5**	**0.7**	1.0	NA
Stinchcombe 2011	26	**1.6**	**1.9**	1.0	1.0

Values in bold lie outside 0.75 – 1.33 range. NA: Missing Data
Disclosure: All authors have declared no conflicts of interest.

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FOLATE-CONJUGATED MESOPOROUS SILICA NANOPARTICLES FOR CYTOSOLIC PHOSPHOLIPASE A2α TARGETED NONSMALL LUNG CANCER THERAPY

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We developed a targeted anticancer drug delivery system based on folate-conjugated rattle-type SiO_2 hollow mesoporous spheres combining receptor-mediated targeting moieties. Mesoporous silica nanoparticles functionalized by surface hyper branching polymerization of poly (ethylene imine), PEI, were further modified by introducing both fluorescent and Folic acid (FA) ligands, with the aim of specifically targeting cancer cells. The internalization of the particles in cell lines expressing different levels of folate receptors was studied. Flow cytometry was used to quantify the mean number of nanoparticles internalized per cell. Four times more particles were internalized by cancer cells expressing folate receptors as compared to the normal cells expressing low levels of the receptor. Pyrrolidine-2, an anticancer drug, was introduced into MSNs. The release of Pyrrolidine-2 from MSN-FA had a sustained release pattern, and the Pyrrolidine-2 loaded MSN-FA exhibited greater cytotoxicity, apoptosis and $cPLA_2\alpha$ activity than free Pyrrolidine-2 and Pyrrolidine-2 loaded MSNs due to the increase of cell uptake of anticancer drug delivery vehicles mediated by the FA receptor. Therefore, we conclude that folate-conjugated mesoporous spheres have potential for targeted anticancer drug delivery for cancer therapy.
Disclosure: All authors have declared no conflicts of interest.

209P
WHY IS CHEMOTHERAPEUTIC INTERVENTION SUCH A RELATIVELY RARE OCCURRENCE IN STAGE IV NSCLC?

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Introduction: Nearly 40% of NSCLC patients present at diagnosis with stage IV disease. Because they represent a significant percentage of lung cancer cases and have the most guarded prognoses, improving patient care in this group would have a meaningful clinical impact. Standard 1st line treatment with a platin-based doublet has been shown to significantly extend survival, but experience at our institution suggests that many stage IV NSCLC patients do not receive any systemic treatment at all. Potential reasons for not receiving cytotoxic treatment are poor performance status, advanced age, and travelling distance. The goal of this study was to ascertain why stage IV NSCLC patients do or do not receive chemotherapy.
Methodology: All patients diagnosed with stage IV NSCLC at the Tom Baker Cancer Centre in 2003-2006 were included (n=832). Demographic information was extracted from the Glans-Look Database and clinical data was retrieved from medical charts. Patient history was reviewed for referral patterns, oncology consultations, if chemotherapy was offered, and, if not, why it was declined. We calculated travel distance of each subject to the medical centre using patient's postal codes and Google™ software.
Results: Of the 832 patient cohort, only 193 patients (23.2%) received systemic treatment (21.0% no treatment, 55.8% RT only, 16.2% chemo and RT, and 7.0% chemo only). Patients who received systemic treatment had a MOS of 11 months while those who did not had an MOS of 2.3 months. Preliminary results show that ECOG status was the primary stated reason for not receiving chemotherapy followed by rapid progression, death before first medical oncologist appointment, and concerns regarding age and comorbidities. Rural location was not indicated as a factor. However, within the full cohort we found an inverse correlation between driving distance to the Cancer Centre and use of systemic therapy.
Conclusion: A range of factors influence the administration of chemotherapy in stage IV NSCLC. Some, such as rapid disease progression, are less susceptible to modification. However, the importance of ECOG status and travel distance suggests that the development of less toxic therapies and the creation of rural treatment centres may encourage greater uptake of systemic treatment in this patient group. Full results will be presented.
Disclosure: All authors have declared no conflicts of interest.

210P
THE RELATION BETWEEN LEUCOCYTOSIS AND OVERALL SURVIVAL IN ADVANCED STAGE NON SMALL CELL LUNG CANCER

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Introduction: Non small cell lung cancer (NSCLC) is a heterogeneous clinical entity that can have different clinical behaviours even within the same stage of disease. Since prognosis is quite dismal especially in advanced stages of diseases, more attention has been focused on the identification of prognostic factors. Performance status of the patient, stage of disease and weight loss are classical prognostic factors for advanced stage NSCLC, but still new factors are needed. In some recent studies tumor related leucocytosis has been found to be a negative prognostic factor for overall survival in advanced stage NSCLC patients. In this study, we aimed to evaluate the relation between

pretreatment leucocyte levels and overall survival in advanced stage NSCLC patients.

Material-method: The files of advanced stage and histologically proven NSCLC patients, who had admitted to and been treated in our clinic between March 2008 and March 2011, were evaluated retrospectively. Demographical datas, diagnosis date, performance status at diagnosis, stage, pretreatment leucocyte levels, date of last visit or death of all patients were noted. The exclusion criteria were concomitant infections, bone marrow metastasis at diagnosis or administration of steroids.

Results: The files of 95 advanced stage NSCLC patients were evaluated. 14 were female (%14,7) and 81 were male (%85,3). Median age was 63 (37-88) in the whole group, 70 (42-78) in females and 63 (37-88) in males. According to pretreatment leucocyte values, the patients were divided into 4 subgroups. The values were ≤10000/mm3 in Group 1, >10000- ≤15000/mm3 in Group 2, >15000-≤20000/mm3 in Group 3 and >20000/mm3 in Group 4. The subgroups were similar with respect to age, sex and performance status of the patients (p levels were 0,295; 0,753 and 0,362 respectively). Median survival was 13,3 months in Group 1, 8,6 months in Group 2, 5,7 months in Group 3 and 0,9 months in Group 4. There was a significant difference for overall survival between the groups (p:0,000).

Conclusion: In this study pretreatment leucocytosis is shown to be a negative prognostic factor for overall survival stage in advanced stage NSCLC patients. This relation is more pronounced as the pretreatment leucocyte levels increase.

Disclosure: All authors have declared no conflicts of interest.

211P
NEUROENDOCRINE TUMORS OF THE LUNG: RETROSPECTIVE CLINICAL DATA AND CURRENT TRIALS

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Objective: Neuroendocrine tumors (NET) of the lung can be divided in typical carcinoid (TC), atypical carcinoid (AC), large cell neuroendocrine carcinoma (LCNEC) and small cell lung carcinoma (SCLC). TC, AC, and LCNEC are rare tumors with a reported prevalence of approximately 3% among surgically resected lung cancers. However, there is only little information on the exact prevalence of lung NET and no treatment standards exist. Targeted therapies such as mTOR inhibitors and somatostatin analogs are discussed as promising approach. Here we present retrospective clinical data on lung NET from one institution and current clinical trials as new treatment options.

Patients and methods: Retrospective analysis of 1690 surgically resected lung cancer patients was performed in Lungenklinik Merheim (January 2007–December 2010). For patients with a diagnosis of TC, AC, LCNEC, and LCNEC with SCLC we compared the data in terms of age, sex, smoking habits, tumor stage, and survival.

Results: Among the resected patients, 35 (2,1%) were diagnosed with TC, 8 with AT (0,5%), 32 with LCNEC (1,9%) and 8 with LCNEC/SCLC (0,5%). LCNEC highly correlated with smoking and patients were diagnosed at a later stage compared to those with carcinoids. Patients with TC and AC happened more likely to be women, never-smokers and were mainly diagnosed in Stage I. There was no significant difference in age between these groups. The mTOR inhibitor RAD001 and the somatostatin analog SOM230 have proven efficacy for treatment of NETs. Based on the need for treatment options of patients with advanced lung NET, the following trials have been set up: A combination trial of RAD001 and carboplatin/paclitaxel for patients with advanced LCNEC is actively recruiting patients in 10 German study sites. In addition, a 3-arm phase II study to evaluate the efficacy and safety of SOM230 and RAD001 alone or in combination in the treatment of patients with advanced (unresectable or metastatic) TC and AC of the lung and thymus will start shortly.

Conclusions: Lung NET is rather rare. Retrospective analysis of the presented data allows us to differentiate between these patients in terms of prognosis. The importance of clinical trials is recognized and will be addressed in two clinical trials.

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212P
HYPERBARIC OXYGENATION WITH CHEMOTHERAPY IN TREATMENT OF PATIENTS WITH NSCLC

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Background: By the time of diagnosis more than 75% of all lung cancer patients have locally advanced or metastatic process. According to WHO, at different stages of treatment to 80% of lung cancer patients need chemotherapy. Malignant neoplasm lead to the development of tissue oxygen deficiency or directly related to acute or chronic hypoxia. Hypoxia of normal tissues is a one of the reasons of chronic anemia in patent with advanced NSCLC. We conducted an analysis of toxicity of chemotherapy in patients with NSCLC by means of chemotherapy concurrently with hyperbaric oxygenation.

Materials and methods: Between October 2010 and November 2011 42 patients with advanced NSCLC were treated with chemotherapy regimen (Cisplatin 75mg/m2 on day 1 + Etoposide 120mg/m2 in 1, 3, 5 days). Cycles repeated every 21 days. We used two hyperbaric pressure chambers: BLKS 303MK and BLKS-307 Khrunichev. Hyperbaric oxygenation procedures are held under pressure 1.3 atm for 40 minutes, 1 time a day every day for 5 consecutive days. All the patients were divided into 2 groups. 15 patients received chemotherapy only. 27 patients received chemotherapy simultaneously with hyperbaric oxygen therapy. 15 patients received chemotherapy only. Patients were not given any prophylaxis of neutropenia. Toxicity was evaluated with Common Toxicity Criteria, Version 3.0.

Results: Grade 2 anemia was reported in 28% patients treated with chemotherapy and hyperbaric oxygenation and in 40% patients treated with chemotherapy only. The beneficial effect of hyperbaric oxygenation was also demonstrated by a quick recovery of hemoglobin levels than in controls. We evaluated the dose intensity of chemotherapy. Dose reductions and increased periods between cycles of chemotherapy are associated with poor outcomes of chemotherapy. Dose intensity in patients received chemotherapy with hyperbaric oxygenation was 92%, but in group of chemotherapy only dose intensity was 81%.

Conclusions: This results show that hyperbaric oxygenation procedures with the chemotherapy reduced grade of anemia in patients with advanced NSCLC.

Disclosure: All authors have declared no conflicts of interest.

213P
BODY MASS INDEX (BMI), IS IT A PROGNOSTIC FACTOR IN METASTATIC NON SMALL LUNG CANCER?

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Background: Cancer cachexia adversely affects survival and quality of life. The aim of our study was to establish the correlation between low BMI and survival in Moroccan patients with metastatic non small cell lung cancer (NSCLC).

Methods: We reviewed 115 cases of metastatic NSCLC diagnosed between January 2007 to June 2011 at the Medical Oncology Department at Hassan II University Hospital. Low BMI was defined as < 18.5 kg/m2.
Results: Median age was 57 ± 10 years. 83, 5% of patients were men. 81% of patients were treated with platinum based chemotherapy. 36% had a low BMI at diagnosis. The mean BMI among patients with low BMI was 17 Kg/m². Low BMI was more frequently associated with hypoalbuminemia (p=0,008). However, it was not correlated to age, sexe, performance status, number of metastatic sites involved. The median duration of follow-up was 7.4 months (1-99 months). Low BMI was significantly correlated to OS in patients with metastatic NSCLC (median of 5 versus 8 months, p =0, 01). The median of DFS was shorter (4 versus 6 months), but not significantly different (p=0, 15). No significantly increased toxic death rates were observed among patients with low BMI (p=0.27).
Conclusion: Low BMI could be a prognostic marker to predict unfavorable OS in patients with metastatic NSCLC.
Disclosure: All authors have declared no conflicts of interest.

214P
PROGNOSTIC FACTORS FOR SURVIVAL OF SYMPTOMATIC PATIENTS WITH MALIGNANT PLEURAL EFFUSION WHO UNDERWENT PALLIATIVE TALC PLEURODESIS

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Background: Pleural carcinomatosis usually represents the final common pathway in several metastatic diseases, especially breast, ovarian, and colonic cancer, leading to malignant pleural effusion (MPE). This complication is common in several patients with advanced malignancy, and usually leads patients to suffer from significant dyspnea, which may reduce their quality of life. Several interventions have shown to be useful to palliate the symptoms, including video-assisted thoracoscopic (VATS) pleural drainage, and talc or chemical pleurodesis. In patients with MPE, pleurodesis prevents re-accumulation of the effusion and thereby of symptoms. There is no evidence for an increase in mortality following talc pleurodesis, but factors affecting survival of treated patients are unclear. The aim of this study was to evaluate prognostic factors for survival of symptomatic patients with MPE.
Patients and methods: Thirty-five patients (median age 70 years, range 42-83) with MPE underwent VATS, evacuation of the pleural fluid, and talc pleurodesis. There were 25 (71.4%) males and 10 (28.6%) females, and the causes of MPE were breast or ovarian cancer, non-small cell lung carcinoma, and malignant pleural mesothelioma in 14, 12, and 9 cases, respectively. The relationship of factors to survival was analyzed calculating the log-rank test using Kaplan-Meyer method. The Cox's regression model was also used.
Results: Overall, the mean follow-up was 9.8±8.7 months, while the median postoperative survival for the entire group was 15.5 months (95% CI 2-29). We did not find (log-rank test) any relationship between both gender (p=0.53) and underlying malignancy associated with MPE (p=0.89, 0.48, and 0.36 for secondary cancer, lung cancer, and mesothelioma, respectively) and survival. Similarly, no correlation was found (Cox's regression) between both age of the patients (p=0.44) and quantity of pleural fluid (p=0.88) and survival.
Conclusions: Our results show that the prognosis of patients with MPE who underwent palliative talc pleurodesis is independent of age, gender, type of malignancy, and amount of pleural effusion, suggesting the usefulness to treat all patients with symptomatic MPE.
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215P
ZOLEDRONIC ACID ROLE IN SRES PREVENTION: AN ADVANTAGE FOR ALL PATIENTS WITH ADVANCED NSCLC AND BONE METASTASES?

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Introduction: The purpose of this study is to investigate the impact of Zoledronic Acid (ZA) administration in prevent SREs in pts with advanced non-small cell lung cancer (A-NSCLC).
Methods: We observed retrospectively 148 pts, whose 135 valued, with NSCLC and BM diagnosed (2007-2010) at the same time of the primary tumor or later during the treatment. The effectiveness of treatment with ZA was valued in terms of time at the diagnosis of bone metastasis and time at first or second SREs during the treatment. Furthermore we valued the effectiveness of treatment to relieve pain (Visual Analogic Scale) and improve Quality of Life (EORTC-QoL Scale).
Results: We analyzed 135/148 pts. Median age was 61 years. After diagnosis of BM, pts was treated with ZA at the standard dose of 4 mg every 28 days. In 53% BM was observed at the time of diagnosis of primary disease, in 47% during the chemotherapy. SREs never occurred in 31 pts (44%) with stadium IV for bone metastasis; 14 pts (47%) with stadium IV for metastasis in other sites and then on bone; 8 pts (23,5%) with early stage in progression on bone.The first SRE occurred at the time of the diagnosis in 29 pts (41%) with stadium IV for bone metastasis; in 12 pts (40%) with stadium IV for metastasis in other sites and subsequent bone progression; in 18 pts (53%) with early stage in which bone progression occurred during chemotherapy or follow-up. During the treatment with ZA experienced the first SRE: 11 pts (15%) with stadium IV for bone metastasis, after 2 months; 4 pts (13%) with stadium IV for metastasis in other sites, after 4,5 months; 8 pts (23,5%) with early stage and subsequent bone progression, after 5 months. Bone pain was observed in 80% of pts and in 60% it decreased during the treatment with ZA associated with improved QoL.
Conclusions: This retrospective analysis about role of Zoledronic Acid to prevent SREs in NSCLC pts with BM shows that pts in stadium IV for bone metastasis at the time of diagnosis or occurred during treatment have major probability to never experienced SRE rather than at the time of bone diagnosis or during treatment. In these pts the treatment with ZA could soothe bone pain and improve Quality of Life.
Disclosure: All authors have declared no conflicts of interest.

216P
SURGICAL OUTCOMES OF ADVANCED NSCLC (STAGE IIIB & IV)

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Background: The role of surgery in stage IIIB or IV NSCLC (AJCC 6th edition) patients is very limited. But stage shifting to operable patients with stage IIIA or IV NSCLC to IIIA in the AJCC 7th edition has been made. So we analyzed the long term results of the surgical resection for the operable patients with stage IIIB or IV NSCLC in a single institute.
Methods: From January 1990 to December 2009, 102 patients with stage IIIB (T4) NSCLC and the 36 patients with stage IV (separate tumor in ipsilateral different lobe) NSCLC were operated on in a Korean cancer center. We retrospectively analyzed the long-term survival and the risk factors for long-term survival of the 138 patients.
Results: Some 59 (42.7%) patients had major organ invasion in the mediastinum; separate tumor in ipsilateral different lobes were seen in 43 (31.1%) patients and satellite nodule in the same lobe were seen in 36 (26%) patients among the 138 stage IIIB or IV NSCLC patients with surgery. N0 stage was 42 (30.4%) patients, N1 stage was 29 (21%) patients and N2 stage was 67 (48.6%) patients. Lobectomy was performed in 56 (40.5%) patients, bilobctomy was

performed in 14 (10.1%) and pneumonectomy was performed in 68 (49.2%). Complete resection was achieved in 123 (89.1%) and operation mortality rate was 6.5% (9/138 patients). Median survival was 34 months and 5-year and 10-year survival rates were 34.6% and 21.9%, respectively. Recurrence, surgery alone, N2 stage, and incomplete resection were risk factors of long-term survival in multivariate analysis.

Conclusion: Although the role of surgery in stage IIIB, IV NSCLC patients is very limited, the long-term outcomes of surgical resection of these patients are tolerable in our Korean cancer center. So we thought the shifting of stage of the group with operable stage IIIB or IV NSCLC to IIIA is appropriate.

Disclosure: All authors have declared no conflicts of interest.

SCLC AND THYMOMA

217P

PRIMARY LOCATION OF SMALL CELL LUNG CANCER (SCLC) AND TTF-1 EXPRESSION: ARE MOST SCLCS REALLY OF HILAR ORIGIN?

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Backgroud: Small cell lung cancer (SCLC) has been believed to occur at the hilar part of lung. Thyroid transcription factor-1 (TTF-1), a transcription factor for alveolar cell differentiation, is expressed in terminal bronchiolar cells and alveolar type II cells, and is therefore a marker of peripheral lung cells. TTF-1 is expressed in 80-97% in SCLC as well as in 63%-84% of adenocarcinoma, suggesting SCLC is of the origin of peripheral lung cells. However, the fact of frequent TTF-1 expression in SCLC is not consistent with the long-standing notion that SCLC is derived from hilar neuroendocrine cells such as Kultschitzky cells. In this study, we examined whether or not SCLC is really a hilar type tumor and TTF-1 would have prognostic relevance.

Methods: 96 consecutive patients with SCLC, of which detailed CT pictures were available and were diagnosed with biopsies and/or surgical materials during 2004-2011, were enrolled. SCLCs diagnosed only by cytology were excluded. We evaluated the location of primary tumor (central or peripheral) by CT at diagnosis. Tumors originating at a segmental or more proximal bronchus were classified to be of hilar type, whereas lesions arising at distal to segmental bronchi were of peripheral type. Expression of TTF-1 was detected immunohistochemically using formalin-fixed paraffin-embedded specimens. Disease-specific survival was obtained for all the cases.

Results: 72 of 96 SCLCs (75%) proved to be of peripheral type. The nuclear immunoreactivity of TTF-1 was identified in 79 tumors (82%). Among these, 69 (87.3%) were peripheral type. TTF-1 expression was significantly correlated with the peripheral location of primary tumor (P<0.001). The hilar type tumors without TTF-1 expression (n=14) had significantly better median survival time than those with TTF-1 expression or of peripheral type (n=82) (21.0 vs 50.3 months respectively; P=0.032).

Conclusions: TTF-1 expression was strongly associated with peripheral location. SCLC of hilar type and without TTF-1 expression showed significantly better prognosis. SCLC may be classified into two subtypes: hilar and peripheral types with different prognosis.

Disclosure: All authors have declared no conflicts of interest.

218P

TIME TO TREATMENT FAILURE IN LIMITED DISEASE SMALL-CELL LUNG CANCER PATIENTS WITH POOR INITIAL PERFORMANCE STATUS WHO RESPONDED TO CHEMORADIOTHERAPY

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Background: Limited disease (LD) small cell lung cancer (SCLC) can only rarely be cured by chemoradiotherapy (CRT). Dose- and time density is a crucial aspect for efficient treatment of SCLC. Optimal local control is important due to the low sensitivity of recurrent disease to any treatment. In these conditions knowledge about timing of recurrence can help optimize follow up and enhance effectiveness of the second-line therapy.

Patients and methods: 125 LD SCLC patients with initial performance status (PS) WHO 2-3 who responded to CRT were retrospectively reviewed. Conventionally fractionated thoracic irradiation (TRT) was applied in the concurrent (group 1) or sequential (group 2) mode. Time from initial diagnosis and treatment close to the local relapse, any distant and brain recurrence was recorded and analysed.

Results: Median time from initial diagnosis to local relapse was 376 (95% CI: 260 – 492) and 401 (95% CI: 241 – 560) days (p = 0.8); to any distant recurrence 275 (95% CI: 178 – 372) and 298 (95% CI: 241 – 355) days (p = 0.7) and to brain recurrence 330 (95% CI: 216 – 444) and 273 (95% CI: 221 – 325) days (p = 0.7) in the concurrent and sequential group respectively. Median time from end of chemotherapy to local relapse was 200 (95% CI: 132 – 268) and 309 (95% CI: 174 – 444) days (p = 0.5); to any distant recurrence 151 (95% CI: 71 – 231) and 157 (95% CI: 105 – 209) days (p = 0.7) and to brain recurrence 123 (95% CI: 15 – 231) and 151 (95% CI: 101 – 201) days (p = 0.7) in group 1 and 2 respectively. Median time from end of TRT to local relapse was 316 (95% CI: 231 – 401) and 196 (95% CI: 127 – 265) days (p = 0.3); to any distant recurrence 180 (95% CI: 74 – 286) and 84 (95% CI: 31 – 137) days (p = 0.2) and to brain recurrence 213 (95% CI: 104 – 322) and 73 (95% CI: 17 – 129) days (p = 0.2) in the group 1 and 2 respectively. Patients treated with concurrent CRT developed brain metastases more often (19/51, 37% versus 15/74, 20%, p < 0.049), however there was a clear trend to different temporal distribution of brain recurrence in the concurrent and sequential group (p = 0.084).

Conclusion: Using a time analysis we defined relevant intervals from initial diagnosis and treatment end to onset of recurrence disease to further optimize a follow-up protocol in LD SCLC patients responded to CRT.

Disclosure: All authors have declared no conflicts of interest.

219P

COMPARATIVE EVALUATION OF CONCURRENT VERSUS SEQUENTIAL CHEMORADIATION IN LIMITED STAGE SMALL CELL LUNG CANCER -TERTIARY CARE CENTRE (AIIMS) EXPERIENCE

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Objectives: To study overall survival, response and toxicities associated with two arms, and to consider timing of thoracic radiotherapy in small cell lung cancer. Frequency of metastasis after Prophylactic Cranial Irradiation.

Material and methods: 60 patients with small cell lung cancer were studied over a period of three years from March 2008 to October 2011. Thirty patients in each arm, both arms were well balanced in terms of patients characteristics. Arm one received three cycles of chemotherapy (cisplatin and etoposide) followed by thoracic radiation of 45Gy by AP/PA portals followed by three cycles of chemotherapy. In second arm radiation was started from day 1 of chemotherapy (cisplatin and etoposide), both groups completed six cycles of chemotherapy. After completion of primary treatment, PCI was done in patients with complete response.

Results: The concurrent chemotherapy arm showed better survival than the sequential arm (p=0.31).The median survival was 28 months in the concurrent arm and 20 months in the sequential arm. Two year survival rate was 56.3% in the concurrent arm versus 32% in the sequential arm. More toxicities were seem in the concurrent arm compared with the sequential arm. Frequencies of brain metastasis after PCI in SCT-RT and CCT-RT patients were 14.9% and 7.1%, respectively.

Conclusions: Concurrent chemoradiation seems better than sequential chemoradiation, however the results are not statistically significant. As compared to sequential chemoradiation, concurrent chemoradiation showed more toxicity. Outcomes may improve further by applying PCI at earlier stages.
Disclosure: All authors have declared no conflicts of interest.

220P
SUBGROUP ANALYSIS OF OVERALL SURVIVAL ACCORDING TO THE DURATION OF CHEMORADIOTHERAPY IN LIMITED DISEASE SMALL-CELL LUNG CANCER PATIENTS WHO RESPONDED TO MULTIMODALITY TREATMENT

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Background: Chemoradiotherapy (CRT) represents a standard treatment in limited disease (LD) small cell lung cancer (SCLC). Timing of thoracic irradiation (TRT) as an obligatory part of CRT has been the subject of several randomised trials. When considereing only trials with concurrent platinum-based CRT, several meta-analyses reported significantly improved overall survival (OS) when a short interval between the first day of chemotherapy and the last day of TRT was documented. In our previous study we demonstrated that duration of CRT correlates with OS in LD SCLC patients with poor initial performance status. To search for optimal CRT duration a subgroup analysis of OS in LD SCLC patients responded to multimodality treatment was performed.
Patients and methods: 147 LD SCLC patients with initial PS WHO 1-3 who responded to CRT were retrospectively reviewed. Conventionally fractionated thoracic irradiation (TRT) was applied in the concurrent or sequential mode. Platinum- as well as non platinum-based chemotherapy was used. Duration of CRT was defined as a time from initial diagnosis to the date of last treatment applied for LD SCLC without inclusion of PCI. Survival was analysed according to the Kaplan-Meier method and measured from the date of initial diagnosis. Surviving patients were censored at the date of last follow-up. Survival curves for each subgroup were compared using the log-rank test.
Results: According to the CRT duration 147 patients were divided into four subgroups: 1 - (up to 100 days) 19 (13%) patients, 2 - (101 – 150 days) 18 (12%) patients, 3 - (151 – 200 days) 49 (33%) patients and 4 - (201 days and more) 61 (42%) patients, respectively. Median survival for the entire cohort was 510 (95 CI: 434 – 586) days: 602 (95 CI: 261 – 943) days in subgroup 1, 325 (95 CI: 258 – 392) days in subgroup 2, 532 (95 CI: 441 – 623) days in subgroup 3 and 524 (95 CI: 415 – 633) days in subgroup 4. However, difference in median survival between the subgroups did not reach significance.
Conclusion: Our results show that the subgroup of patients who have completed CRT up to 100 days from initial diagnosis demonstrate a potentially better survival compared to the rest of cohort but the difference was not significant. Further studies powered to determine the impact of CRT duration on survival in LD SCLC patients are initiated.
Disclosure: All authors have declared no conflicts of interest.

221P
WEEKLY DIVIDED CARBOPLATIN COMBINED WITH IRINOTECAN IN PATIENTS WITH SMALL-CELL LUNG CANCER AS THE FIRST-LINE TREATMENT

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Background: Systemic chemotherapy is a mainstay of treatment in patients with small-cell lung cancer (SCLC). However, adverse effects of chemotherapeutic agents, especially platinum-based, cause neutropenia, infection, sepsis, and even death. Weekly divided platinum-based chemotherapy in concurrent chemo-radiation of non-small cell lung cancer is an acceptable regimen. We tested the feasibility of divided platinum-based chemotherapy in SCLC without concurrent radiation.
Materials and methods: Patients with chemotherapy-naive SCLC received carboplatin 2 AUC combined with irinotecan (60mg/m^2) at day 1, 8, and 15 every 4 weeks for 4 cycles at an out-patient department. The primary endpoint was evaluation of overall response rate, and secondary endpoints were treatment-related serious adverse events and discontinuation of chemotherapy due to side effects.
Results: Thirty (25 extensive stage and 5 limited stage) patients were enrolled. Complete response, partial response, stable disease, and progressive disease were 5 (16.7%), 21 (70.0%), 1 (3.3%), and 3(10.0%), respectively. Serious adverse events happened 5 times in 2 patients; 1 patient stopped chemotherapy due to side effects.
Conclusions: Weekly divided carboplatin combined with irinotecan is a feasible regimen in previously untreated SCLC patients.
Disclosure: All authors have declared no conflicts of interest.

222P
TOPOTECAN AND CAV CHEMOTHERAPY FOR RECURRENT SCLC: THE WEST OF SCOTLAND EXPERIENCE

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SCLC has a high response rate to first line chemotherapy but response is short lived. Oral topotecan is licensed for second line chemotherapy and in October 2009 was approved for the West of Scotland. Clinical trials have shown that IV topotecan is comparable to CAV, oral topotecan has a survival advantage over best supportive care and oral topotecan and IV topotecan have similar efficacy. A retrospective case note review was undertaken of 63 patients who received oral topotecan or IV CAV second line for recurrent SCLC during time period October 2009 to April 2011. Results were analysed using SPSS version 19. 39.3% of patients were given oral topotecan and 60.3% IV CAV. Overall survival for patients receiving topotecan was 13 weeks (95% CI, 6.9 – 19.1) versus 24 weeks (95% CI, 18.3 –29.7) (log rank $p< 0.001$). of the 25 patients who received topotecan for cycle 1 only 33.3% of patients received full dose, 2.3 g/m2 days 1-5. Furthermore, only 18.5% received equivalent of 4 cycles of topotecan, 33.3% 1 cycle, 44.4% 2 cycles and 3.7% 3 cycles. In comparison, 92.7% of patients received full dose of CAV for cycle 1. 12.2% received 1 cycle of CAV, 31.7% received 2 cycles, 39% 3 cycles and 2.4% for both 5 and 6 cycles. Myelosuppression was the most common dose limiting toxicity with 29% of patients experiencing this with topotecan versus 12.2 % with CAV. However, neutropenic sepsis was similar in both groups 17% in CAV and 12.9% in topotecan patients. 19.5% of CAV patients developed infections requiring dose delays versus 6.5% in topotecan group. Grade 3 fatigue was similar in both groups 12.2 % in CAV and 16.1% in topotecan group. The patients who received topotecan second line had significantly lower survival rates than those receiving CAV. One of the reasons for this is concern of haematological toxicity resulting in sub-optimal dosing of topotecan and thus, oncologists opting to prescribe CAV second line rather than topotecan. Most of the patients in this case series did not start with full dose topotecan and yet still experienced high rates of myelosuppression. The CAV patients tolerated higher equivalent doses than the topotecan patients.
Disclosure: All authors have declared no conflicts of interest.

223P

SMALL CELL LUNG CANCER: BETTER THAN ITS REPUTATION? A POPULATION BASED STUDY

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Introduction: This study was undertaken to identify patients with small cell lung cancer (SCLC) who were alive five years or more after the diagnosis in a National, unselected population (Norway).
Methods: During 2000-2005 lung cancer was diagnosed in 8 253 men and 5 188 women. The proportion of SCLC was 1 274 (15.1%) in men and 996 (19.2%) in women. The completeness of the Cancer Registry of Norway is 99%. All reports on patients diagnosed as having limited or disseminated SCLC and who were alive five years or more were reviewed and eventually revised by pathologists at 17 different institutions.
Results: 94 patients with SCLC were alive more than 5 years after diagnosis. Of these surgical resection was performed in 12 cases. The distribution between disseminated and limited was 6% and 94%, respectively. In 45 cases the diagnosis was based on bronchoscopy and histology. After pathology review the initial diagnosis of SCLC were sustained in 75 patients while 15 were revised.
Conclusion: After revision of specimen 3.2% of patients with SCLC were alive more than 5-year after diagnosis. This group should be looked closer at 1) for further confirmation of diagnosis and 2) for prognostic biomarkers.
Disclosure: All authors have declared no conflicts of interest.

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MULTIMODAL APPROACH TO THE MANAGEMENT OF THYMOMA AND THYMIC CARCINOMA: MONO-INSTITUTIONAL EXPERIENCE

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Purpose: To evaluate the role of radiation therapy (RT) in patients with thymoma and thymic carcinoma in terms of toxicities, loco-regional control and survival.
Materials and methods: Between December 2003 and March 2011, 44 consecutive patients were treated with radiotherapy for thymoma or thymic carcinoma. Each patient was evaluated, before and after treatment, by a multidisciplinary team including medical oncologists, radiation oncologists and thoracic surgeons. The patient's general condition, the histologic classification (WHO) and stage of disease were considered for the definition of the most appropriate treatment. Surgery plus chemotherapy (CT) and RT was performed in 27/44 (61%) of patients, CT and RT in 8/44 (18%) and surgery and adjuvant radiation therapy in 9/44 (21%). The median radiation dose was 54 Gy (range 44-60 Gy). Clinical outcome was evaluated by means of CT scan. The incidence of pneumonitis was graded according to the NCI CTCAE v3.0 scale.
Results: The median follow up was 48 months (range 14 -94 months). No "in field" recurrence occurred. No pulmonary toxicity greater than G2 was observed. Minor toxicity occurred: radio-dermatitis G1 in 3 (7%) patients, dysphagia G2 in 11/44 (25%), and fatigue in 9/44 (20%). Overall-survival at five years was 75%, distant metastases were found in 5/44, all in thymic carcinoma cases.
Conclusions: Although the population of the study included patients with thymoma and thymic carcinoma with different stages of disease, local control and survival are satisfactory with minimal toxicities. Due to the high sensitivity of thymoma and thymic carcinoma to radiation therapy there is much interest in evaluating the role of RT in the treatment of this rare tumour.
Disclosure: All authors have declared no conflicts of interest.

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MULTIDISCIPLINARY MANAGEMENT OF THYMOMA: A SINGLE INSTITUTIONAL EXPERIENCE-LARGE SERIES

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Background: Thymoma is the most common tumour of the anterior mediastinum. Surgery is the mainstay of treatment, with adjuvant radiation recommended for invasive thymomas. Because of its indolent natural history and rarity, prospective randomized trials may not be feasible hence the best possible evidence can be large series. A retrospective analysis of thymoma patients managed at our institution is presented.
Methods: All patients presenting to Thoracic disease management group at Tata Memorial Centre during 2006-2011 were screened. Amongst 115 patients with histo-pathological confirmation of thymoma, 62 patients' medical records could be retrieved and presented in this study. Masaoka staging and WHO classification was used. The clinical and therapeutic factors and follow up parameters were recorded and survival was calculated. Effect of prognostic factors was compared.
Results: Sixty two patients were identified (36M, 26F; age 22-84, median 51.5 years). Majority (57%) of thymoma were stage I-II and 82% of thymic carcinoma were stage III-IV. WHO classification showed 10/23/18/18/13/18% were subtypes A/AB/B1/B2/B3/C respectively. Mean tumour size was smaller in patients with myasthenia (5.3cm) than the entire group (7.6cm). Neoadjuvant therapy was offered to five unresectable stages III or IVa patient's with 40% resectability rates. Median overall survival was 60 months (Inter quartile-range 3-44 months) with overall survival rate (OS) at 3 year being 90%. Resectable tumours had better outcomes (94%) than nonresectable (81%) at 3 years (p=0.1). Three year overall survival was 96% for stage I-II, 91% for stage III, and 69% for stage IV. Stage was the only significant (p=0.01) prognostic factor on multivariate analysis. Myasthenia gravis did not negatively influence survival (88% Vs 91%; p=0.85) and corroborates with literature.
Conclusion: Thymoma with associated paraneoplastic syndromes presents as early whereas thymic carcinoma as advanced disease. Staging is an important prognostic factor. Treatment of thymoma depends on the resectability of the disease and surgery is the mainstay of therapy. Aggressive multimodality treatment should be offered to advanced stage patients and yields good survival rates.
Disclosure: All authors have declared no conflicts of interest.

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THE ESCALATION OF PNEUMOTOXICITY IN TREATMENT OF LOCALLY ADVANCED MALIGNANT THYMOMA AND THE EFFECT OF PENTOXIFYLLINE

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Purpose: Malignant thymoma belongs among rare neoplasms. The optimal therapy for locally advanced malignant thymoma (LA MT) is controversial. Locally advanced stages and postoperative residual disease of tumorous portion are great risks for patients. Adjuvant therapy using chemotherapy (CT) and radiotherapy (RT) brings contradictory results. This management can be limited by escalation of pneumotoxicity.
Methods: Between 1998 - 2008 we assessed and retrospectively analysed 18 patients who were treated postoperatively by the CT and RT. The treatment took place in the following sequence: surgery (S) + CT ± RT. The CT regimens were used: (cDDP+doxorubicin+etoposide or cyclophosphamide) and (ADOC: doxorubicin+cDDP+vincristine+cyclophosphamide). Planned

radiation doxorubicin+cDDP+vincristine+doses ranged from 50-60 Gy. Side effects were classified according to CTC v 3.0.

Results: The median age at the time of histopathological verification was 58 (range 38 to 75). Three patients (17%) underwent biopsy only. Fifteen patients (83%) in clinical stages III and IVa underwent the resection to various extent. The number of applied chemotherapy cycles was 4 - 8. Radiation doses were applied in the range of 45-68 Gy. Radiation pneumonitis (RP) of grade 1/2 was observed in 13 patients (72%) and grades 3/4 in 6 patients (33%), in the group ADOC in 5 patients (83%). The best local control of the disease was observed in the group treated with the sequence of S+CT+RT using the ADOC chemotherapy regimen. In this group the median time to tumor progression was 38 vs 17 months against the others, respectively (p=0.0001). However, in these patients the escalation of toxicity with severe manifestation of RP, that resulted in post-irradiation fibrosis, was observed. The manifestations of RP were softened by oxygenotherapy, antibiotics, corticoids and pentoxifylline (PE). Median time to recover RP grade 3/4 was 4.9 vs 2.8 months with the application of pentoxifylline.

Conclusions: Postoperative intensive treatment with chemotherapy and radiotherapy in patients with LA MT leads to an improvement of the local control of the disease. The escalated toxicity, mainly the radiation pneumonitis, can be reduced by the application of pentoxifylline.

Disclosure: All authors have declared no conflicts of interest.

MESOTHELIOMA

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UPDATED ANALYSIS OF EORTC 08983: A RANDOMISED TRIAL OF RALTITREXED AND CISPLATIN VERSUS CISPLATIN IN MALIGNANT PLEURAL MESOTHELIOMA

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Background: EORTC 08983 randomised 250 chemotherapy-naive patients with advanced pleural mesothelioma to receive cisplatin 80 mg/m² IV on day 1, alone (arm A) or combined with raltitrexed 3 mg/m² IV (arm B) (Van Meerbeeck, J Clin Oncol 2005; 23:6881-9).

Method: An unplanned updated overall survival (OS) analysis based on the data as of May 5, 2011. OS is defined as time from randomisation to death from any cause.

Results: After a median follow up of 98 months, 118/124 participants in arm A and 115/126 in arm B were deceased. Seventeen (6 and 11) patients were censored at the last date known to be alive: 12 (4 and 8) had their survival status not updated due to sites not responding, 2 in arm B are alive and 3 (2 and 1) are lost to follow up. Progressive disease was the cause of death in 87% of deaths in both arms. The median survival time in arm B is 11.4 months (95% CI 9.5 - 13.7) as compared to 8.8 months (7.7- 10.7) on arm A.The hazard ratio is 0.77 (95% CI0.6 -1.0) in favour of arm B. The p-value for the log-rank test is 0.0491, which is still below the nominal cut-off value of 0.049266 alpha level that was used at the time of the final analysis.

Conclusions: the results of this updated analysis confirm the superior efficacy of the raltitrexed/cisplatin combination over cisplatin alone in the first line palliative treatment of patients with malignant pleural mesothelioma.

Disclosure: H. Phillips: H Phillips is an employee of Hospira UK Ltd, producer of raltitrexed. All other authors have declared no conflicts of interest.

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PROLONGED SURVIVAL OF PATIENTS WITH LOCALISED MALIGNANT PLEURAL MESOTHELIOMA AFTER HIGH DOSE HEMITHORACIC RADIOTHERAPY TO AN INTACT LUNG

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Introduction: Mesothelioma patients will obtain best palliation with treatment that controls their enlarging tumour masses, which originate in the pleura of one hemithorax and spread into surrounding organs, producing distressing local symptoms of pain and respiratory impairment. As most are unsuitable for extrapleural pneumonectomy and chemotherapy provides poor local control, we postulated that high doses of radiotherapy to large volumes would provide the best and most durable symptom relief.

Methods: In 2003 our institution began a prospective program of high dose radiotherapy for mesothelioma patients using new technological advances and precision targeting of all viable tumour with ^{18}F-FDG PET scans. We believed that radiation toxicity could be limited by advanced techniques with 3-D treatment planning and delivery. All patients had histologically confirmed malignant pleural mesothelioma of any subtype, confined to one hemithorax with normal lung, liver and renal function. None had undergone a pneumonectomy.

Results: From 2003 to 2011, 44 patients aged 37-76 received doses of 45-60 Gy to part or all of one complete hemithorax over 6 weeks, using 3D-conformal or, in 27 cases, intensity-modulated radiotherapy (IMRT). 84% had advanced stage III-IV disease on planning PET scans. 21 had a pleurectomy/decortication, 16 a pleurodesis and 5 only a biopsy. 19 were chemotherapy-naive and 22 had progressed after palliative chemotherapy. Median survival of all patients was 22 mths from diagnosis (range 7-91). Survival is 80%, 39% and 7% at 1, 2 and 5 years, and 15 are still living. 26 deaths were from progressive disease (in 25 outside the irradiated volume), mostly in the contralateral lung or the ipsilateral lung that had been excluded from radiotherapy in our early patients while we established our normal tissue tolerance constraints. Apart from one debatable death from pneumonitis, there were no grade 4 or 5 toxicities.

Conclusions: Many believe mesothelioma to be radioresistant and that toxicity is prohibitive if high doses are given with the affected lung in situ. Our experience provides clear evidence that radiation is arguably the most effective single targeting agent for mesothelioma and new technologies including IMRT allow high doses to be delivered safely to large volumes. Survival is not compromised.

Disclosure: All authors have declared no conflicts of interest.

229O_PR
GLYCOPEPTIDE SERUM MARKERS FOR MALIGNANT PLEURAL MESOTHELIOMA DIAGNOSTICS

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Background: Malignant pleural mesothelioma (MPM) is an aggressive cancer of the pleura caused by asbestos exposure. Recent therapeutic advances

have raised growing interest in the identification of serum accessible diagnostic markers for MPM. Here, we used mass-spectrometry (MS) based technologies for the identification and clinical verification of glycopeptide MPM candidate biomarkers in serum. Glycopeptide MPM candidate biomarkers were selected from a pool of glycopeptides discovered through comparison of the surfaceome of MPM with control cell lines. The clinical significance of the selected glycopeptides was verified by using Selected Reaction Monitoring (SRM) in serum from cohorts of MPM patients and controls.

Methods: The surfaceome of four MPM (epithelioid and biphasic) and four control (pleura and lung adenocarcinoma) cell lines was investigated by using Cell Surface Capturing (CSC) technology and label free quantitative mass spectrometry. Glycopeptides detected in higher abundance in the MPM surfaceome were selected for SRM-based quantitative analysis in patient sera enriched for N-glycopeptides.

Results: Surfaceome analysis revealed 500 N-glycopeptides, corresponding to more than 300 cell surface N-glycoproteins from MPM-derived cell lines. 56 candidate biomarker peptides were selected for initial SRM quantification and verification in serum of patient cohorts. The cohorts consisted of 25 MPM patients (13 epithelioid and 12 biphasic, stage I-IV), 25 healthy donors and 25 non-small-cell lung cancer patients (16 adenocarcinoma and 9 squamous, stage III-IV) matched per sex and age. We verified the robustness of our approach based on serum analysis of the mesothelioma marker soluble mesothelin–related protein (SMRP).

Conclusion: The relative quantitative investigation of the MPM surfaceome revealed serum accessible potential MPM candidate biomarkers. SRM technology enables now the parallel verification of glycopeptide candidate biomarkers in serum samples of selected patient cohorts. A multiplexed 56 peptides SRM-assay for MPM was established and evaluated in 75 serum samples.

Disclosure: All authors have declared no conflicts of interest.

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ASSESSMENT OF CIRCULATING MIRNAS AS POTENTIAL BIOMARKERS FOR MALIGNANT PLEURAL MESOTHELIOMA (MPM)

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The definitive diagnosis MPM often depends on the availability of a biopsy of sufficient size. The identification of a biomarker that can be easily measured in blood with a potential use in the early detection setting would represent an important step forward. Recently it has been shown that microRNAs (miRNAs) detectable in serum or plasma represent a class of potential new biomarkers. In this study we investigated the ability of certain miRNAs in plasma and serum to serve as a diagnostic marker for MPM. Using Agilent 8x15k miRNA microarrays we profiled miRNA expression in plasma samples from healthy volunteers and patients with MPM. Candidate miRNAs identified in the arrays were validated by TaqMan assay-based quantitative real-time PCR or using the OpenArray real-time PCR platform. Microarray-based expression profiling of plasma from 5 MPM patients and 3 healthy controls identified 17 miRNAs with significantly differential abundance in the two sample groups. Validation of these miRNAs in a series of plasma samples from 15 MPM patients and 13 controls (healthy controls and patients with coronary artery disease) revealed that levels of miR-625* are not only significantly elevated in plasma of MPM patients (4-fold higher, p=0.004), but are also able to discriminate between MPM patients and controls with an accuracy of 82.4 %. Furthermore, levels of two miRNAs previously reported to be associated with MPM, miR-29c* and miR-92a, were also elevated in our MPM series however without reaching statistical significance. Assessing levels of miR-625* in serum of another series of MPM (N= 30) and asbestosis (n=10) confirmed that miR-625* was significantly (p=0.023) elevated only in serum of MPM patients and was able to discriminate between cases and controls with an accuracy of 79.3 %. Finally, miR-625* was also found to be present at significantly higher levels (2-fold higher, p= 0.006) in tumour specimen from 18 MPM patients who underwent extrapleural pneumonectomy than in normal mesothelium (pericardial tissue). Taken together these data provide evidence that miR-625* has the potential to serve as a novel blood-based biomarker for MPM.

Disclosure: All authors have declared no conflicts of interest.

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RATIONAL FOR A PHASE I CLINICAL STUDY USING FAP SPECIFIC RE-DIRECTED T CELLS IN MESOTHELIOMA PATIENTS

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Introduction: In re-directed T cells, the antigen-specificity of T cells is engineered through introduction of a chimeric antigen receptor (CAR). CARs consist of an antigen-binding molecule, a trans-membrane domain and a signalling domain. In this project, we generated re-directed T cells that recognise Fibroblast Activation Protein (FAP). FAP is expressed in the tumour stroma of the majority of carcinomas and is thought to be a key player in promoting tumour growth and malignancy. Here, we investigate the therapeutic potential of anti-FAP re-directed T cells targeting human malignant pleural mesothelioma (MPM), which usually express FAP on the tumour cells.

Methods: Human peripheral mononuclear cells (PBMCs) were isolated by Ficoll gradient centrifugation followed by Magnetic Activated Cell Sorting (MACS) of CD8+ T cells. Purified T cells were retrovirally transduced to express the FAP-specific CAR. The anti-FAP CAR constists of a single-chain fragment recognising FAP, a human IgG domain and CD3z and CD28 signalling domains. To test antigen-specificity and functionality of anti-FAP re-directed T cells, their capacity to lyse targets and produce interferon γ (IFN-γ) in an antigen-specific manner was assessed in vitro. Furthermore, FAP as target for re-directed T cells was analyzed in MPM and healthy human tissue by immunohisto-chemistry and immune fluorescence microscopy.

Results: FAP expression was detected in all histological subtypes of human MPM in the tumour cells and in the tumour stroma. Expression of FAP-specific CARs has been confirmed on 293T cells as well as on human CD8+ T cells. In vitro characterisation showed specific target cell lysis by anti-FAP re-directed T cells Furthermore, re-directed T cells secreted antigen-specifically IFN-γ.

Conclusion: We generated functional anti-FAP re-directed T cells and indentified FAP as a target molecule in MPM. Experiments are under way to demonstrate antigen-specific functionality in FAP positive tumours in vivo. We plan to start a pilot phase I trial in 2012 to investigate the safety of anti-FAP re-directed T cells in patients with MPM, who are not eligible for multi-modal therapy and not in need for immediate palliative chemotherapy.

Disclosure: All authors have declared no conflicts of interest.

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EVALUATION OF DIFFERENT EXTERNAL RADIOTHERAPY TECHNIQUES FOR THE TREATMENT OF MALIGNANT PLEURAL MESOTHELIOMA AFTER EXTRAPLEURAL PLEUROPNEUMONECTOMY

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Background and Purpose: Postoperative radiotherapy reduces local relapses of malignant pleural mesothelioma after radical surgery. Comparative

planning for intensity modulated radiotherapy (IMRT) volumetric intensity modulated arc therapy (VMAT) and proton therapy (PT) was performed.
Material and methods: Eight patients treated with IMRT or VMAT after extrapleural pleuropneumonectomy (EPP) were replanned with PT and either with VMAT or either with IMRT. A comparison of dose homogeneity (DH), target volume (TV) coverage, mean and maximal dose to organs at risk (OAR) was performed. Robustness of each technique was evaluated in respect to the dose distribution variation in respect of air cavity volume decrease.
Results: Dose coverage and DH of the planning target volume (PTV) were similar for IMRT, VMAT and PT for the volume covered by >95% (V95) and <5% (V105). The mean dose (md) to the contralateral kidney, contralateral lung, liver, heart, and spinal cord was significantly reduced with PT compared to IMRT and VMAT. A decrease of V13 and V20 for the lung was observed for VMAT in comparison to IMRT. After EPP, air cavities were common (range 0 – 1250 cm^3), decreasing up to 20cm^3/day. The photons plans were more robust than PT plans, in respect to the PTV coverage (V90, V95), when air volume decreased in the resected lung. VMAT plans were less affected than IMRT plans, if changes in the air cavity volumes occurred.
Conclusion: Both, proton and photon plans achieved good target coverage and DH. PT accomplished additional dose sparing of all OARs compared to IMRT or VMAT, and VMAT showed better results than IMRT. PT dose distributions were more susceptible to changing air cavities during the treatment period emphasizing the need for replanning and adaptive RT for PT.
Disclosure: All authors have declared no conflicts of interest.

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A PHASE 2 STUDY OF SORAFENIB AFTER FIRST LINE PLATINUM CONTAINING COMBINATION CHEMOTHERAPY IN MALIGNANT MESOTHELIOMA

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Background: The incidence of mesothelioma is rising, with a predicted peak in the UK expected in 2020. Cisplatin and pemetrexed first line confers a survival benefit, but with a median progression-free survival of only 5.7 months. Sorafenib inhibits the raf/MEK/ERK signalling pathway, as well as tyrosine kinases including receptors for VEGF which are present at particularly high circulating levels in mesothelioma patients. Antibodies to VEGF, VEGFR1 & VEGFR2 inhibit mesothelioma growth.
Methods: Sorafenib at 400mg BD was assessed in a single arm multi-centre phase 2 study. A Simon 2-stage design was used. Eligible patients had received prior platinum combination chemotherapy. The primary endpoint was progression-free survival (PFS) at 6 months assessed by CT using modified RECIST. Published reference values for PFS in mesothelioma (Francart et al. 2006 J Clin Oncol) provide a benchmark of 28% progression-free at 6 months.
Results: A total of 53 patients have been treated, 41 male and 12 female. Primary histology was epithelioid (37), sarcomatoid (2), mixed (7). No histological sub-group was recorded in 7 patients. 96% of patients had a performance status of 0 or 1. The most frequent adverse events were fatigue, hand-foot syndrome, diarrhoea and hypertension. Overall treatment was well tolerated with few grade 3 and no grade 4 toxicities. At 6 months 34% of patients were progression free, despite all patients having already received prior chemotherapy. A total of 5 patients remained on study beyond one year.
Conclusions: Sorafenib is well tolerated in patients with mesothelioma after completion of platinum containing chemotherapy. PFS compares favourably to that reported for other targeted agents in this disease.
Disclosure: All authors have declared no conflicts of interest.

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THIRD, FOURTH AND SUBSEQUENT LINES IN MALIGNANT MESOTHELIOMA

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Introduction and objectives: Malignant mesothelioma is a low incidence neoplasm whose natural history is poorly modified by treatments received. The objective is to analyze the potential impact of third-line treatment and subsequent survival of patients.
Material and methods: The study includes cases of malignant mesothelioma diagnosed in our hospital during the period between 2003 and 2010 treated with palliative chemotherapy. The variables recorded were: age, sex, PS, smoking, asbestos, histological subtype, stage, treatment, progression-free survival (PFS) and overall survival (OS). Statistical analysis was performed using SPSS.
Results: 38 patients were included (73.7% men and 26.3% women) with a mean age of 68.7 years; 15.8% smokers and 44.7% former smokers. 31.6% had contact with asbestos. 52.6% had PS1 and 7.9% PS2 at diagnosis. Histology: 39.5% epithelial, 26.3% sarcomatous, 5.3% mixed and 28.9% undifferentiated. 52.6% were stage III and 44.7% stage IV. OS was 17.5 months with a PFS of 8.57 months. 15 patients received three or more lines of treatment. These had an average age of 64.6 years and 66.7% were men; 13.3% were smokers and 40% former smokers; 26.7% had contact with asbestos, 60% PS0 and 40% PS1. Histology: 40% epithelial, 20% sarcomatous, 13.3% mixed and 26.7% undifferentiated. The OS was 28.62 months with PFS 9.72 months. The PFS of patients with PS 0 was 23.16 months versus 13.89 months for patients with PS 1-2 (p 0.05). Difference in OS between patients treated with 1 or 2 lines versus those treated with 3 or more lines was 18.28months (28.62m vs 10.34m, p 0.01).
Conclusions: Patients treated with 3 or more lines of chemotherapy have a higher OS. This difference may be due to chemotherapy or patient characteristics. In the subgroup of patients treated with 3 or more lines of chemotherapy the percentage of patients with PS 0 is higher (39.5% versus 60%) acting as a prognostic factor. No other prognostic factors have been identified by the small sample available. New clinical and molecular analysis attempted to be made.
Disclosure: All authors have declared no conflicts of interest.

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RETROSPECTIVE ANALYSIS OF CLINICOPATHOLOGIC AND SURVIVAL DATA OF MALIGNANT PLEURAL MESOTHELIOMA (MPM) PATIENTS IN A SINGLE CENTER SERIES

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Background: 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 in our institution.
Methods: Forty nine patients diagnosed of MPM in Vall d´Hebron University Hospital between November 2002 and September 2011 were retrospectively reviewed. Baseline factors analyzed were age, performance status (PS), histology, stage, chemotherapy (CT), neutrophil to lymphocyte ratio (NLR) and tumor markers. Survival data were calculated by the Kaplan-Meier method.

Results: Patient's characteristics: median age 68 years (31-88years), males 75.5%, PS 1: 67.3%, asbestos exposure 53.1%, chest pain 77.6%, dyspnea 75.5%, pleural effusion 91.8%, clinical stage III: 55.1%, epithelial subtype 71.4% and NLR>5 in 44.9% of all patients. CA125 was elevated in 15/23 p, CEA in 2/32 p and Ca 15.3 in 10/16 p. All patients were considered initially unresectable and 71.4% received CT in 1st line and 34.7% in 2nd. Response rate in 1st line was 75.3% (PR:27%, SD 48.3%) and in 2nd line 46.7% (PR:6.7%, SD 40%). After a median follow up of 9.2 months the median OS was 15.2 months. We found significant increase in OS in patients with epithelial subtype (23.4 vs 5.0 months in no-epithelial, p<0.001), PS1 (14.7 vs 2.2 months in PS 2, p=0.036), NLR ≤5 (26.5 vs 13.4 months, p=0.025) and patients who received 2nd line CT (8.9 and 26.4 months p second line, p=0.05). Although no significant, age, tumor stage, absent thoracic pain and response to CT were associated with better OS. Patients with tumor markers elevated at baseline were followed during CT and we only found changes in Ca15.3≥20% over baseline in concordance with radiological response (increase Ca15.3 in 6/6 p progression, decrease 1/1 p with response and no changes 2/2 p with stable disease).

Conclusion: In our series of 49 MPM patients, epithelial subtype, PS, NLR and treatment with second line therapy are prognostic factor for survival. Ca15.3 warrants further study to clarify its potential use as a marker of chemotherapy efficacy in p with MPM.

Disclosure: All authors have declared no conflicts of interest.

236P
PROGNOSIC FACTORS AFFECTING SURVIVAL IN MALIGNANT MESOTHELIOMA (ANALYSIS OF 125 SUBJECTS)

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Determining the pre-treatment prognostic factors in malignant pleural mesothelioma (MPM) is of importance in terms of both estimating the course of disease and determining the patients who are candidate to multimodal therapy. Aim of the current study was to determine the prognostic factors affecting survival in the patients with MPM. One hundred and twenty five patients who had been diagnosed histologically as having MPM over the past 5 years were evaluated retrospectively. Relationships of survival of the patients with their age, gender, exposure to asbestos, smoking history, platelet, hemoglobin, leukocyte (WBC), serum lactate dehydrogenase (LDH) values, their histology, performance scores and stage of disease were examined. Advanced clinical stage, N2 nodal involvement and presence of distant metastasis were found to be related to survival. Sarcomatous histology was found to be poor prognostic factor independently of other factors. We showed that histological subtype and stage of disease were the most important parameters in planning the treatment, especially in determining the patients who were candidate multimodal treatment and estimating the prognosis.

Disclosure: All authors have declared no conflicts of interest.

237P
CLINICO-PATHOLOGICAL CHARACTERISTICS OF IRANIAN PATIENTS WITH MALIGNANT MESOTHELIOMA REFERRED TO "NATIONAL RESEARCH INSTITUTE OF TUBERCULOSIS AND LUNG DISEASE": A SINGLE INSTITUTE STUDY FROM IRAN

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Malignant Mesothelioma (MM) is a malignancy of the pleura with a dismal prognosis despite multimodality treatments such as extrapleural pneumonectomy (EPP), chemotherapy and radiation therapy. Approximately 70% of MM is associated with documented asbestos exposure. This study provides a general overview on Iranian patients' characteristics, referred to our Thoracic Surgery and/or Oncology Clinics within past 13 years.

Results: In this retrospective study, clinico-pathological data of 58 patients with definite diagnosis of MM was retrieved and analyzed. These patients belonged to different geographical regions of Iran. This study showed that male to female ratio of patients was 2.22 (40/18) with mean age of 53.13±11.43 years (range 25-75). Most Common presenting symptoms were dyspnea (65.5%), cough (20.7%) and chest pain (13.8%). The majority of patients had regionally invasive or metastatic disease at the time of diagnosis (stage IB: 1.7%, stage II: 32.8%, stage III: 15.5%, stage IV: 50%). The histologic subtypes were: epithelioid: 51.7% (n=30), biphasic 10.3% (n=6), sarcomatoid 3.4% (n=2), Lymphohistiocytic 1.7% (n=1) and in 32.8% (n=19) the subtype was not determined. EPP, EPP followed by adjuvant chemotherapy (+/- radiation therapy) and chemotherapy alone were performed in 8.6 % (n=5), 8.6% (n=5) and 79.4 % (n=46) of patients, respectively. Two patients didn't undergo any treatment. Smoking history was positive in 41.4% (n=24) of patients and only 17.2% (n=34) of them had documented asbestos exposure.

Conclusion: We speculate that the most Iranian patients referred to our institute were diagnosed in advanced stages. Furthermore, in view of less common documented exposure to asbestos in Iranian patient, other environmental, genetic factors, along with viral oncogens (e.g. SV-40) presumably contribute to development of MM in majority of Iranian patients. More studies in this regard are warranted.

Disclosure: All authors have declared no conflicts of interest.

238P
THE BURDEN OF MESOTHELIOMA MORTALITY: ESTIMATION AS THE FIRST STEP TO PREVENTION

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Background: Mesothelioma is a rare cancer that principally affects the pleura and is almost always caused by asbestos exposure. The disease is rapidly fatal; most of those affected dying within a year of diagnosis. Mesothelioma incidence has increased in South East England of which East Kent is a major part, particularly for men aged over 70 years, reflecting areas of asbestos use in shipbuilding and industry in the past.

Methods: Work-related cancers are largely preventable. The aim of the study is to estimate the current burden of cancer in the area of East Kent in the UK attributable to occupational factors, and identify carcinogenic agents, industries and occupations for targeting risk prevention. Data of all cases diagnosed at East Kent Hospitals NHS Trust were collected retrospectively from April 2009 to March 2010.

Results: There were a total of 15 cases in East Kent Hospital NHS trust, UK over the period of one year which is a significantly high number as compared to previous years, the current population being 614,576. All of them were male. Median age was 74 years and median survival from diagnosis was 8.9 months. All of them had histological or cytological confirmation and 85% had documented evidence of definite or probable exposure to asbestos. There were seven cases that were treated with chemotherapy and 6 patients had advanced malignancy and received radiotherapy and 2 patients with advanced malignancy had palliative treatment only. No patient had radical surgery and there was minimal difference in relative survival between men with localised and non-localised disease stage.

Conclusion: In Great Britain, where asbestos use continued later than many other countries, the peak is anticipated to occur later between 2011 and 2115. Between 1981 and 2000, North East England and South East England were the areas with the highest standardised mortality ratios. Cancer networks, especially those with primary care trusts with high incidence, need to be aware of this disease and ensure that risk reduction strategies and services are in place to assist these patients. More research is needed to understand the interrelationships of prognostic factors, treatment choices and survival, and to determine the best care and support for these patients and their families.

Disclosure: All authors have declared no conflicts of interest.

METASTASES

239O
STEREOTACTIC BODY RADIOTHERAPY (SBRT) USING VOLUMETRIC MODULATED ARC THERAPY (VMAT) WITH FLATTENING FILTER FREE (FFF) MODE FOR LUNG METASTASES IN OLIGOMETASTATIC PATIENTS: A PROSPECTIVE SINGLE INSTITUTIONAL EXPERIENCE

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Purpose: Data on the use of stereotactic body radiation therapy (SBRT) in oligometastatic patients are emerging and the early results on local control are promising. Aim of this study was to evaluate results and toxicity of SBRT using VMAT-FFF in lung metastatic patients from different primary tumors.

Methods and materials: One hundred forty-five consecutive patients treated between October 2010 to September 2011 were included. The most common primary cancers were lung and colon-rectal. One hundred sixty-seven SBRT were performed. All patients had oligometastatic disease. Dose prescription was 48 Gy in 4 consecutive fractions for peripheral lesions with maximum diameter < 3 cm, 60 Gy in 6 consecutive fractions for central lesions and 32 Gy in 4 consecutive fractions for lesions with maximum diameter between 3 and 5 cm or in case of multiple lesions in the same lung. Clinical outcome was evaluated by CT scan and CT-PET. The incidence of pneumonitis was graded according to the NCI CTCAE v3.0 scale.

Results: Median follow-up was 9 months (range 3-14). Response was recorded in 134/167 lesions (80%). At the last follow up 132/155 of patients (85%) were alive. No pulmonary toxicity of grade 2 or greater was recorded. No chest pain toxicity occurred. Removal of the flattening filter (FF) increased the dose rate. The median beam-on time (BOT) was reduced by 75% passing from about 8 minutes (with FF modality) to 2 minutes (with FFF modality).

Conclusion: SBRT is a feasible, safe and effective local treatment option for pulmonary metastases in patients with contraindications to surgery or for palliation of symptomatic pulmonary metastases. VMAT technique improved target coverage while minimizing higher dose to normal tissue with respect to coplanar beam arrangements. Furthermore, the BOT was significantly reduced in FFF modality with a subsequent increase of patient comfort and reduction of intra-fraction motion. In our experience SBRT with VMAT-FFF resulted in a good radiological response though a longer follow-up is needed to assess the effective outcome incidence and to select patients with better prognosis.

Disclosure: All authors have declared no conflicts of interest.

240O
SIGNIFICANCE OF LOW DOSE DISTRIBUTION IN DEVELOPING RADIATION PNEUMONITIS AFTER HYPOFRACTIONATED RADIOTHERAPY USING HELICAL TOMOTHERAPY FOR PULMONARY METASTASES

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Hypofractionated radiotherapy (HRT) has been commonly used for pulmonary metastases since tumorcidal dose can be accurately delivered to the target without increasing dose to adjacent normal lung. However, radiation pneumonitis (RP) is still a major problem and sometimes a fatal complication after HRT. To determine the relationship of normal lung volume and different levels of radiation dose in clinically significant RP, we retrospectively investigated the data from patients treated with HRT using helical tomotherapy for lung metastases. Total 45 patients were included and median age was 53 years old. Average number of pulmonary metastases was 4.7 (range, 1~10) and median 50 Gy (range, 30~60 Gy) was delivered to PTV (planning target volume) in 10 fractions during 2 weeks. RP was diagnosed by chest X-ray or computed tomography after HRT and its severity was determined by CTCAE version 4.0. A ROC (Receiver Operating Characteristic) curve of MLD (mean lung dose) and Vn (volume percentage of lung receiving more than n Gy; range V5~V50 in 5 Gy interval) was investigated to find the cutoff values, the sensitivity and the specificity. And we compared the average values of Vn and MLD in two groups of the patients who suffered from grade II or more RP (Gr.II-RP) and the patients who didn't experience RP. The Gr.II-RP was developed in 12 patients (26.6%). In the patients, MLD, V5, V10, V15, V25 and V30 showed significance in developing Gr.II-RP ($p<0.05$). Among these, MLD and V5 were most powerfully significant. And their cutoff points, sensitivity and specificity were 13.79 Gy, 75.0% and 69.7%, respectively in MLD ($p=0.009$) and 80.75%, 75% and 63.6%, respectively in V5 ($p=0.004$). The other parameters such as age, sex, performance status, number of targets, sum of PTVs' volumes, previous thoracic RT, chemotherapy, total dose, daily dose and even NTCP were not statistically significant in developing any RP. And the mean values of Vn below V30 and average MLD of two groups were statistically different ($p<0.05$). In present study, the Vn less than V30 and the MLD were thought important to develop Gr.II-RP. So, we have to try to decrease not only MLD but also the lower dose distribution area less than V30 for safe HRT using helical tomotherapy in multiple pulmonary metastases. However, further clinical study should be required to confirm this outcome.

Disclosure: All authors have declared no conflicts of interest.

241O
SCREENING FOR BRAIN METASTASIS (BM) IN PATIENTS (PTS) WITH STAGE III NON-SMALL CELL LUNG CANCER (NSCLC): HAS MAGNETIC RESONANCE IMAGING (MRI) AN ADDITIVE VALUE COMPARED TO COMPUTED TOMOGRAPHY (CT)?

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Introduction: 30% of pts with NSCLC present with stage III disease and are candidates for treatment with curative intent. As the brain is a common site for dissemination, excluding BM is important before starting aggressive treatment. Current guidelines advise to perform a post contrast MRI or a contrast enhanced CT (CE-CT) of the brain in these pts. MRI is in small studies, including not only stage III NSCLC, reported to be superior to CT in diagnosing occult BM. However, CT and MR technology have evolved. If CE-CT performed in the same setting as the standard whole body ^{18}F-deoxyglucose-positron emission tomography (^{18}FDG-PET-CT) could lead to the same yield of BM detection as ^{18}FDG-PET-CT with low dose CT (LD-CT) and separately MRI, a substantial gain in time and resources could be expected. The aim of this retrospective study is to investigate the additive value of MRI to CT when both are performed in standard work-up.

Methods: All pts who underwent ^{18}FDG-PET-CT in the diagnostic work-up for lung cancer between January 2008 and September 2011 were reviewed. Pts with stage III disease without taking into account results of brain MRI or CT and who were candidates for curative treatment were selected. Pts with neurological symptoms that required brain imaging were excluded. The CE- or LD-CT was compared to the MRI to investigate whether additional asymptomatic BM were detected on MRI. Development of BM within a year after negative MRI was scored.

Results: From the 510 ^{18}FDG-PET-CT's performed, 429 pts were diagnosed with NSCLC. 3 pts had occult BM on CE-CT but otherwise no metastasis. 97/429 pts had stage III and were eligible for curative treatment. 77/97 (79%) pts underwent a MRI (MRI not made because of for example diagnostic work-up elsewhere or contra-indication for MRI), 45/77 (58%) CE-CT and 32/77 (42%) LD-CT. In none of the CE-CT pts BM were detected on MRI. In 5/32 LD-CT pts (16%) BM were detected on MRI. 9/77 pts (12%) without BM on MRI at diagnosis developed BM within a year, 2/9 (22%) were already progressive outside the brain.
Conclusion: In this retrospective study it seems that there is no additive value of MRI when ^{18}FDG-PET-CT with CE-CT is performed in the diagnostic work-up of neurologically asymptomatic stage III NSCLC pts in order to exclude BM. A prospective trial is thus warranted.
Disclosure: All authors have declared no conflicts of interest.

242O
PULMONARY METASTASECTOMY: AN ANALYSIS OF TECHNICAL AND ONCOLOGICAL OUTCOME IN 301 PATIENTS

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Resection of lung metastasis is a growing field in thoracic surgery. Currently no randomized trial exists to guide physicians in this field. Indication and technique therefore vary dependent on personal conviction. The aim of this analysis was to evaluate the technical and oncological outcome of pulmonary metastasectomy. We retrospectively analysed all patients who underwent pulmonary metastasectomy in our department between January 2005 and June 2010. Follow-up was accomplished by maintenance in the outpatient clinics of our medical-center or by questionnaire of the after-caring physicians. We identified 301 patients who underwent curative intended pulmonary metastectomy. In 62 patients (20.6%) the Nd-YAG laser was used. Despite significantly higher numbers of resected lesions in laser-assisted resections compared with wedge and anatomical resections (median 7.0 vs. 2.0; $p<0.01$) there was no significant difference in surgical and overall morbidity exept for pneumonia (11.3% vs. 2.9%; $p<0.01$). Follow-up was completed for 85.4% of patients. After median follow-up of 20.2 months (range 0 to 75.5 months) 42.5% of patients suffered from recurrence. Mean disease-free interval was 12.9 months (range 0 to 60.6 months). There was a significant correlation between tumor-free resection margin ($p<0.01$), number of metastases ($p<0.02$) and disease-free survival in univariate analysis. Although we found a significant difference between laser and non-laser resections regarding classification as R0 ($p<0.01$), we did not find a significant correlation between surgical technique and disease-free interval ($p=0.09$). Regression analysis confirmed tumor-free resection margins to be the only significant independant factor influencing disease-free survival ($p<0.03$). The number of metastases no longer reached significance ($p=0.09$).The technique used for resection ($p=0.34$) did not have an influence. Despite the higher number of resectable lesions in laser-assisted metastasectomy the complication rate was not increased except for the rate of pneumonia. Even though laser-resected lesions were more frequently classified as non R0-resections the technique did not have an influence on disease-free interval. The number of metastasis seems to be of minor importance.
Disclosure: All authors have declared no conflicts of interest.

243O
OUTCOMES OF REPEATED METASTASECTOMY FOR PULMONARY RECURRENCE IN COLORECTAL CANCER

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Background: The consensus remains insufficient about repeated metastasectomy for pulmonary recurrence from colorectal cancer. In this study, we evaluated outcomes of repeated metastasectomy in these patients.
Materials and methods: From 1995 to 2009, 99 patients had undergone a pulmonary metastasectomy from colorectal cancer at our institute. Over a median follow-up of 39.7 months, 31 patients received second metastasectomy (21 wedge resections, 5 segmentectomies, 4 lobectomies, and 1 chest wall resection). Of these, ten had over 3 nodules, and six had bilateral metastases. The median disease-free interval was 16.0 months. Among these 31 patients, 21 showed pulmonary recurrence again and of those, 11 patients underwent third resection (9 wedge resections, and 2 lobectomies).
Results: There was no postoperative mortality. Of the 31 patients who underwent second metastasectomy, overall and disease-free 3-year survival rates were 59.5% and 32.0%, respectively, after second operation. Of the 11 patients who received third metastasectomy, overall survival rate was 45.0% at 3 years after third operation.
Conclusions: Repeated pulmonary resection after first metastasectomy can be performed without severe complications and provides good prognosis in patients with recurrent metastasis from colorectal cancer. Our outcomes suggests that the aggressive but parenchyma-saving metastasectomy can improve the results of repeated pulmonary metastasectomy in patients with multiple and bilateral pulmonary metastases.
Disclosure: All authors have declared no conflicts of interest.

244P
REIRRADIATION USING HELICAL TOMOTHERAPY FOR LOCALLY RECURRENT NON-SMALL-CELL LUNG CANCER AND METASTATIC LUNG CANCER

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Purpose: To evaluate clinical efficacy of re-irradiation using Helical Tomotherapy for locally recurrent non small cell lung cancer or metastatic lung cancer.
Methods and materials: Between March 2006 and April 2011, 16 cases with non-small cell lung cancer or metastatic lung cancer who developed local recurrence after stereotactic body radiation therapy (SBRT) using Helical Tomotherapy. 5 patients had non-small cell lung cancer and 10 patients had multiple metastatic lung cancer. All patients received previous sequential chemoradiotherapy (median dose; 50 Gy). We defined the gross tumor volume (GTV) as recurrent tumor mass on CT and planning target volume (PTV) as an anatomical extension of GTV was defined 0.5~1 cm margin from GTV. Median dose to GTV and PTV was 45 Gy (45~61.2 Gy) and 40 Gy (35~57.5 Gy). The treatment schedule of helical tomotherapy was from 10 fractions to 28 fractions during 2-6 weeks. The response was evaluated at 1 month after completion of treatment and then every 2, 3 months thereafter. RECIST (Response Evaluation Criteria in Solid Tumors) was used to determine response of tumor and CTCAE (Common Terminology Criteria for Adverse Events) v3.0. was used to evaluated treatment toxicity .
Results: Median follow-up was 8 months (2–16 months) and median age was 49.5 years. Median time from initial treatment to recurrence was 8.5 months (2-36 months). Treatment response rate was 56.3 % (PR; 9/16 cases). Disease control time was median 3.5 months (1-16 months) and median 6 months (1-16 months) in non-small-cell lung cancer. Median overall survival amounted to 9.1 months. All patients showed grade I radiation peumonitis. Acute toxicity was grade II esophagitis in 1 patient and grade III esophagitis in 1 patient. Late toxicity was grade III radiation peumonitis in 1 patient 7 months later.

Conclusion: Palliative and salvage re-irradiation using Helical Tomotherapy may be suggested as an effective and safe treatment in locally recurrent non-small-cell lung cancer or metastatic lung cancer with previous radiotherapy. More cautious patient selection could increase the benefit of reirradiation using Helical Tomotherapy.
Disclosure: All authors have declared no conflicts of interest.

245P
BI- AND TRI-MODALITY APPROACH IN TREATMENT OF LUNG METASTASES OF OSTEOSARCOMAS AND SOFT TISSUE SARCOMAS

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Surgery in treatment of pulmonary metastases of sarcomas of bones and soft tissues has the increasing value. For improvement of results its combination with other antitumor methods are necessary. Since 2004 in our Center after revealing of isolated pulmonary metastases of malignant tumors at different steps of combined treatment, as well as in the process of follow-up for patients (pts), a multimodality treatment including preoperative distant radiotherapy, induction and/or consolidation chemotherapy and open surgical metastasectomies is performed. Preoperative radiotherapy is carried out in 3 Gy fractions twice a day with an interval of 4 hours, 3 treatment days per week to a total dose 30 Gy on biggest metastatic lesions. Metastasectomies and manipulations in the pulmonary parenchyma are performed with surgical neodymium YAG laser MY 40 (wave length 1318 nm). From April 2004 to December 2011, in thoracic and radiology departments MRRC 33 patients (15 women and 18 men) aged from 16 to 70 years, with malignant osteosarcomas and soft tissue sarcomas, who had pulmonary nodules revealed by x-ray and CT multimodality treatment was carried out. 9 pts had initially metastatic tumors with lung lesions in other cases metastases were reveled after treatment of primary tumor. The primary malignancies were presented: 1) osteosarcoma - 13 pts; 2) chondrosarcoma - 3 pts; 3) soft tissue sarcomas - 17 pts. A total 57 surgeries were performed, 13 pts had bilateral surgeries, the maximum number of surgeries in one patient was 6. The largest number of metastases in one surgery was 103. Time of observation for patients from the first surgery in the lungs amounted to: In the group of pts (n=13) with osteosarcomas - from 10 to 90 months, 6 pts died with disease progression; All pts with chondrosarcoma (n=3) died with disease progression from 3 up to 22 months; In the group of pts (n=17) with soft tissue sarcoma from 1 to 90 months, 4 pts died with disease progression. There was no treatment related mortality. Thus, precise resection of neodymium YAG laser combining with radio- and chemotherapy is adequate and functional sparing treatment method in lung metastases of sarcomas. Such surgeries do not only increase the survival rate of patients, but also maintain their quality of life.
Disclosure: All authors have declared no conflicts of interest.

246P
RISK FACTORS FOR LUNG METASTASES FROM INVASIVE DUCTAL BREAST CARCINOMA. A CASE-CONTROL STUDY AT FIVE-YEAR FOLLOW-UP IN A POPULATION OF WOMEN WHO UNDERWENT CURATIVE SURGERY

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Background: Breast cancer (BC) accounts for about one-third of cases of cancer in women. BC occurs predominantly in elderly women, continue to be one of the most common causes of cancer death, and mainly metastasizes to the skeleton and lung. Although complete excision of primary tumor improves survival in patients with advanced metastatic disease, pulmonary metastasectomy plays a role in the management of patients. However, patients with small metastasis have a better overall survival, and thus the early detection of lung metastases (LM) is crucial. Indeed, in several studies, risk factors (RFs) such as age, stage of the disease, serum tumor markers, and other biological parameters obtained from pathological specimen, have been evaluated. The aim of this study was to analyze their role in differentiating patients at risk of having LMs among a cohort of women with BC.
Patients and methods: We retrospectively reviewed data regarding a series of 348 women (median age 60 years, range 28-85) who underwent curative surgery for pT1-2, N0-1 (stage I and IIA) invasive ductal breast carcinoma. During five-year follow-up, 15 (4.3%) patients developed LMs (cases), and 39 (11.2%) other type of cancer relapse, while 294 (84.5%) were disease-free (controls). The followings parameters were considered: age of the patients, size of the tumor (T), axillary lymph node (AN) status (N), estrogen (ER) and progesterone (PR) receptor negativity, human epidermal growth factor receptor 2 (HER2) and nuclear antigen Ki67 overexpression, adjuvant chemotherapy. Odds ratio (OR) estimates and the associated 95% confidence interval (CI) were obtained, and the significance level was set at $p<0.01$.
Results: Age<50 (OR=4.55, 95%CI 1.58-13.05, p=0.005), and N1 status (OR=8.03, 95%CI 2.48-25.98, p=0.0002) were statistically significant RFs for LM from BC. Tumor size>2 cm (T2) (OR=2.90, 95% CI 1.02-8.27, p=0.041), and ER negativity (OR=3.51, 95% CI 1.21-10.17, p=0.018) were weak RFs, while PR negativity (OR=2.01, 95% CI 0.70-5.73, p=0.14), HER2 (OR=1.48, 95% CI 0.49-4.49, p=0.32) and Ki67 (OR=1.72, 95% CI 0.59-4.99, p=0.23) overexpression, and no chemotherapy administration (OR=1.06, 95% CI 0.35-3.20, p=0.55) were independent of LMs onset.
Conclusions: N1 patients aged <50 have a significantly increased (>8-fold) risk of developing LMs.
Disclosure: All authors have declared no conflicts of interest.

MISCELLANEOUS

247P
CONSUMER INVOLVEMENT IN CANCER RESEARCH: A NETWORK EXAMPLE

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Background: Involvement of consumers and the general public is an important means of improving cancer services. How to involve consumers in cancer research has not previously been documented. The objective of this study was to explore different ways of involving consumers in cancer research in one regional network.
Methods: We formed a Consumer Research Partnership (CRP) in 2009 of around 25 members consisting of consumers and the professionals who wish to help in both promoting and participating in consumer involvement in cancer research. This study evaluated the activities of the CRP from March 2010 to March 2011. We used the following indices to judge the level of consumer involvement: number of projects involving consumers through the group, types of projects, level of involvement and the methods of involving consumers.
Results: Fifteen projects were submitted to the CRP group during the 12-month period studied. Of these, 8 projects were clinical trials, 3 were qualitative research projects, 2 were patients' surveys and 2 were non-randomised interventional studies. Seven projects requested consumer

involvement on patient information sheets for clinical trials. Out of these 7 applications, 3 also requested consumers' help in designing research questionnaires and another 3 requested that consumers should be involved in their project management group. In addition, 4 projects involved consumers in the proposal development phase and another 4 projects asked for advice on how to increase trial recruitment, conduct patient interviews or help with grant applications.

Conclusions: The creation of the CRP and this audit of its activity has documented how consumers can be involved in cancer research at all levels. In particular, consumers have a role to play in advising on patient information sheets and in designing/managing clinical projects.

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Disclosure: All authors have declared no conflicts of interest.

248P
ANALYZING PALLIATIVE CARE ISSUES FOR TERMINALLY ILL LUNG CANCER PATIENTS: IDENTIFYING DEFICITS AND NEEDS OF STAKEHOLDERS IN THE INDIAN HEALTHCARE SYSTEM

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Objectives: Our Cancer NGO aims to analyze palliative care issues/needs & their status. ESMO/WHO urgently need to focus on the development of palliative care for lung cancer patients. For developing nations this approach will certainly have a positive impact on lung cancer management. NGOs working in remote areas can develop policy paper for implementation in the rural/tribal areas.

Method: Our NGO volunteers & nurses conducted this pilot study in six rural villages of India. 7 nurses, 2 physicians & 1 counselor participated. 146 Patients, 34 caregivers, 18 spiritual/community leaders participated. Relief of distressing symptoms was reported in 80%. Responses on palliative care were analyzed using questionnaires, while community/spiritual leaders participated through focus group discussions. 90% of participants expressed a need for a model that incorporates palliative services into the mainstream of medical therapy which should be emphasized as the standard care approach.

Results/findings: Poor wellbeing, appetite, pain and fatigue were most prevalent symptoms reported by the patients. 50% of the patients reported severe pain and 9% reported no pain. Spiritual pain control had the highest correlation to QOL in comparison to functional, emotional, physical and social wellbeing. 90% of patients and caregivers reported free communication about illness. We also need to modify attitudes of caregivers towards psychosocial needs of lung cancer patients & their families. Lung cancer care hospitals must have separate departments for handling these issues.

Conclusions/Recommendation: This study gives a demographic picture of terminal cancer patients and family caregivers in the public healthcare system and some aspects of palliative care. Resource-poor nations need NGOs to develop such programs in the absence of government-run healthcare setups. We NGO activists need the ELCC conference to discuss our project ideas/concerns/difficulties with senior researchers from USA/Europe. ESMO must take the initiative in propagating such efforts in developing nations. Development of a comprehensive lung cancer service program is a distant dream in resource poor nations. We NGO patient advocates need international funding support for palliative care programs.

Disclosure: All authors have declared no conflicts of interest.

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ANALYZING KNOWLEDGE, PERCEPTION AND ATTITUDES OF NURSES: IN CARE OF LUNG CA PATIENTS

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Objectives: [1] To assess knowledge, perception and attitudes of nurse in cancer-NGO. Set-up on nursing care of lung-cancer-patients. [2] To improve lung-cancer-care which is a prevalent disease in rural/tribal population of the developing world among all age groups and sex. Nurses caring for individuals with cancer have an important role in assessing patient needs and providing necessary care. The cancer nurse is key in promoting both patient/family coping and adaptation through interventions of 1) patient education, 2) symptom management, and 3) therapeutic support. Cancer nursing is specialty practice and requires knowledge and skills beyond general preparation.

Methods: From October 2010: Questionnaires based study consisted of two sections. 1] Information about respondents. 2] Methods to elicit nurse's knowledge perception and attitudes in care of cancer patients. All questionnaires were returned and analyzed using simple statistical method. We also designed framework for orientation/CME that would novices to experts in providing nursing care for cancer patients. This presentation outlines role of cancer nurse, impact on patient outcomes and education required for competent practice.

Result: N=23 nurses aged between 20-35 years enrolled from district hospital & rural catholic mission in rural/tribal India. 18 females, 5 males. knowledge, perception and attitudes of nurses towards cancer care is minimal with only 10 showing special skill, perception and good attitudes towards caring for cancer patients as opposed to 9 with little knowledge and low perception to caring for cancer patients and the remaining 4 with no specific knowledge and perception towards nursing care of cancer patients.

Conclusion: Oncolo gy nursing is an important specialty but neglected. There are limited training centers in India. Resources are scarce for such initiatives. Trained nurses can improve QOL of cancer patients. Oncology training programs and motivation will improve the knowledge perception and attitudes of nurses in the cancer patient's care. This presentation will describe role of cancer-nurses, impact on patient QOL, and education required for competent clinical care of cancer patients.

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