Caring Ambassadors Lung Cancer Program
Literature Review, May 2016

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

A Comparison of microCT and microPET for Evaluating Lymph Node Metastasis in a Rat Model. Flechsig P1,2, Kratochwil C3, Warth A4,2, et al. Mol Imaging Biol. 2016 Apr;18(2):243-8. doi: 10.1007/s11307-015-0890-0.

PURPOSE: The demand to optimize multidisciplinary treatment strategies in patients with benign and malignant diseases of the lung and other organs has led to the increased need of mechanistic proof-of-concept studies in preclinical small animal models using new non-invasive imaging methods. Therefore, we evaluated the role of microPET and microCT for mediastinal lymph node staging in an orthotopic lung cancer model in rats. **PROCEDURES:** Human lung cancer cells (NCI-H460) were injected transthoracically in nude rats (NIH-RNU). After 2 weeks of tumour growth, animals underwent multiphase contrast-enhanced microCT using ExiTron nano 12000 as a contrast agent and dynamic microPET using the tracer 2-deoxy-2-[(18)F]fluoro-D-glucose ([(18)F]FDG). Thereafter, animals were sacrificed for histological analysis. **RESULTS:** Late phase micro X-ray computed tomography (microCT) revealed the best delineation of lymph node metastases, as compared to earlier scans. In terms of an increased [(18)F]FDG uptake over time, dynamic micro positron emission tomography (microPET) delineated lymph node metastases and enabled metabolic examinations of the induced lung cancer metastases. **CONCLUSION:** The combination of contrast-enhanced microCT and dynamic microPET is feasible in rats for the visualization of mediastinal lymph node metastases.

Detection of EML4-ALK fusion gene and features associated with EGFR mutations in Chinese patients with non-small-cell lung cancer. Wen M1, Wang X1, Sun Y1, Xia J1, Fan L1, Xing H1, Zhang Z1, Li X1. Onco Targets Ther. 2016 Apr 5;9:1989-95. doi: 10.2147/OTT.S100303. eCollection 2016.

PURPOSE: Echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) and epidermal growth factor receptor (EGFR) define specific molecular subsets of lung cancer with distinct clinical features. We aimed at revealing the clinical features of EML4-ALK fusion gene and EGFR mutation in non-small-cell lung cancer (NSCLC). **METHODS:** We enrolled 694 Chinese patients with NSCLC for analysis. EML4-ALK fusion gene was analyzed by real-time polymerase chain reaction, and EGFR mutations were analyzed by amplified refractory mutation system.

RESULTS: Among the 694 patients, 60 (8.65%) patients had EML4-ALK fusions. In continuity correction χ (2) test analysis, EML4-ALK fusion gene was correlated with sex, age, smoking status, and histology, but no significant association was observed between EML4-ALK fusion gene and clinical stage. A total of 147 (21.18%) patients had EGFR mutations. In concordance with previous reports, EGFR mutation was correlated with age, smoking status, histology, and clinical stage, whereas patient age was not significantly associated with EGFR mutation. Meanwhile, to our surprise, six (0.86%) patients had coexisting EML4-ALK fusions and EGFR mutations. **CONCLUSION:** EML4-ALK fusion gene defines a new molecular subset in patients with NSCLC. Six patients who harbored both EML4-ALK fusion genes and EGFR mutations were identified in our study. The EGFR mutations and the EML4-ALK fusion genes are coexistent.

Hippo pathway effector YAP inhibition restores the sensitivity of EGFR-TKI in lung adenocarcinoma having primary or acquired EGFR-TKI resistance. Lee JE1, Park HS1, Lee D1, et al. Biochem Biophys Res Commun. 2016 Apr 20. pii: S0006-291X(16)30595-2. doi: 10.1016/j.bbrc.2016.04.089. [Epub ahead of print]
The efficacy of EGFR-tyrosine kinase inhibitors (TKIs) is significantly limited by various resistance mechanisms to those drugs. The resistance to EGFR-TKI is largely divided by two classes; acquired resistance after EGFR-TKI treatment, and primary resistance marked by cancer cell's dependence on other oncogene, such as KRAS. YAP has emerged as critical oncogene in conferring drug resistance against targeted therapy. In this study, we evaluated the role of YAP in primary and acquired EGFR-TKI resistance using gefitinib-resistant A549 and PC9 cells and their parental cell lines. Our study revealed that EGFR-TKI resistance is associated with enhanced YAP activity. Notably, YAP activation was independent of the Hippo pathway. We confirmed that AXL is a downstream target of YAP that confers EGFR-TKI resistance. And our results showed that YAP can induce ERK activation in lung adenocarcinoma. The combination of YAP inhibition with EGFR-TKI overcomes primary and acquired EGFR-TKI resistance. We also found increased YAP expression in human lung cancer after acquiring EGFR-TKI resistance. Collectively, we suggest a novel EGFR-TKI resistance mechanism involving YAP activation and suggest targeting YAP and EGFR simultaneously may be a breakthrough treatment of primary and acquired EGFR-TKI resistant lung cancer.

Lentivirus-mediated knockdown of TSP50 suppresses the growth of non-small cell lung cancer cells via G0/G1 phase arrest. Qiao WL1, Hu HY1, Shi BW1, Zang LJ2, Jin W3, Lin Q1. Oncol Rep. 2016 Apr 20. doi: 10.3892/or.2016.4763. [Epub ahead of print]
Non-small cell lung cancer (NSCLC) as the most frequently diagnosed lethal cancer remains the major cause of overall cancer-related death worldwide. Testes-specific protease 50 (TSP50) has been proved as a critical biomarker in various cancers, and we previously reported that TSP50 protein expression is overexpressed in clinical resected NSCLC tumor tissues and related to poor prognosis in NSCLC patients. Hence, the present study was designed to further investigate the potential oncogenesis mechanism of TSP50 in NSCLC cells. Real-time quantitative PCR, immunohistochemical assay and western blot analysis were used to analyze the TSP50 mRNA and protein expression in 20 NSCLC cases, and TSP50 expression was observed to have high levels in the NSCLC specimens and paired metastatic lymph node tissues when compared to the levels in corresponding normal lung tissues and normal lymph nodes. In the experiments in NSCLC cell lines, lentiviral short hairpin RNA (shRNA) delivery system was applied to knock down TSP50 in 95D cells, and the following investigations revealed that downregulation of TSP50 expression markedly reduced cell proliferation, colony formation and migration ability in vitro. Furthermore, the inhibition of TSP50 induced G0/G1-phase arrest and decreased expression levels of cell cycle relative markers CDK4, CDK6, and CyclinD1 and increased expression of p21 and p53 in 95D cells. **In conclusion,** this study indicates that TSP50 plays a significant role in NSCLC cell proliferation

and may act as a novel oncogene in the development and progression of NSCLC, offering a potential cancer therapeutic target for the treatment of NSCLC.

Treatment of experimental human breast cancer and lung cancer brain metastases in mice by macitentan, a dual antagonist of endothelin receptors, combined with paclitaxel. Lee HJ1, Hanibuchi M1, Kim SJ1, et al. Neuro Oncol. 2016 Apr;18(4):486-96. doi: 10.1093/neuonc/now037.
BACKGROUND: We recently demonstrated that brain endothelial cells and astrocytes protect cancer cells from chemotherapy through an endothelin-dependent signaling mechanism. Here, we evaluated the efficacy of macitentan, a dual endothelin receptor (ETAR and ETBR) antagonist, in the treatment of experimental breast and lung cancer brain metastases. **METHODS:** The effect of macitentan on astrocyte- and brain endothelial cell-mediated chemoprotective properties was measured in cytotoxic assays. We compared survival of mice bearing established MDA-MB-231 breast cancer or PC-14 non-small cell lung cancer (NSCLC) brain metastases that were treated with vehicle, macitentan, paclitaxel, or macitentan plus paclitaxel. Cell division, apoptosis, tumor vasculature, and expression of survival-related proteins were assessed by immunofluorescent microscopy. **RESULTS:** Cancer cells and tumor-associated endothelial cells expressed activated forms of AKT and MAPK in vehicle- and paclitaxel-treated groups in both metastasis models, but these proteins were downregulated in metastases of mice that received macitentan. The survival-related proteins Bcl2L1, Gsta5, and Twist1 that localized to cancer cells and tumor-associated endothelial cells in vehicle- and paclitaxel-treated tumors were suppressed by macitentan. Macitentan or paclitaxel alone had no effect on survival. However, when macitentan was combined with paclitaxel, we noted a significant reduction in cancer cell division and marked apoptosis of both cancer cells and tumor-associated endothelial cells. Moreover, macitentan plus paclitaxel therapy significantly increased overall survival by producing complete responses in 35 of 35 mice harboring brain metastases. **CONCLUSIONS:** Dual antagonism of ETAR and ETBR signaling sensitizes experimental brain metastases to paclitaxel and may represent a new therapeutic option for patients with brain metastases.

SCREENING, DIAGNOSIS AND STAGING

Negative EBUS-TBNA Predicts Very Low Prevalence of Mediastinal Disease in Staging of Non-Small Cell Lung Cancer. Taverner J1, Cheang MY, Antippa P, See K, Irving LB, Steinfort DP. J Bronchology Interv Pulmonol. 2016 Apr;23(2):177-80. doi: 10.1097/LBR.0000000000000234.
BACKGROUND: Confirmation of mediastinal disease (N2/3) in non-small cell lung cancer (NSCLC) generally precludes curative surgical management. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has become a routine first test in mediastinal staging of NSCLC; however, it remains unclear whether a negative EBUS-TBNA should be followed by mediastinoscopy before proceeding to surgery. Understanding the prevalence of metastases in lymph nodes with benign findings on EBUS-TBNA will inform decision making following negative EBUS-TBNA. **METHODS:** We examined a retrospective cohort of patients who underwent EBUS-TBNA before resection with mediastinal lymph node sampling for NSCLC between December 2009 and June 2014 in 3 hospitals in Melbourne, Australia. All patients had integrated positron emission tomography/computed tomography (PET/CT) before EBUS-TBNA. **RESULTS:** Eighty-two matched mediastinal lymph node stations were sampled in 57 patients by both EBUS-TBNA and surgical resection, 47 nodes in patients staged cN0/1 by PET/CT and 35 nodes in patients staged cN2/3. All patients had a negative EBUS-TBNA. Four malignant nodes were identified surgically (4.9% of lymph nodes). The mean size of malignant deposits was 5.5 mm. Per-node negative predictive value was 78/82=0.95. All malignant nodes were located in patients with moderate-high risk disease (cN2/3), giving a disease prevalence in cN2/3 patients of 11%, and 0% in cN0/1. In patients staged cN2, per-node NVP was 0.89. **CONCLUSION:** The prevalence of mediastinal

nodal disease following negative EBUS-TBNA is very low, at 4.9%. The per-node NVP of EBUS-TBNA is 0.95, decreasing to 0.89 in moderate-high risk patients. We suggest that a negative EBUS-TBNA of mediastinal nodes does not need to be confirmed by mediastinoscopy of those nodal stations, regardless of PET/CT findings.

The Lung Screen Uptake Trial (LSUT): protocol for a randomised controlled demonstration lung cancer screening pilot testing a targeted invitation strategy for high risk and 'hard-to-reach' patients. Quaife SL1, Ruparel M2, Beeken RJ3, et al. BMC Cancer. 2016 Apr 20;16(1):281. doi: 10.1186/s12885-016-2316-z.
BACKGROUND: Participation in low-dose CT (LDCT) lung cancer screening offered in the trial context has been poor, especially among smokers from socioeconomically deprived backgrounds; a group for whom the risk-benefit ratio is improved due to their high risk of lung cancer. Attracting high risk participants is essential to the success and equity of any future screening programme. This study will investigate whether the observed low and biased uptake of screening can be improved using a targeted invitation strategy. **METHODS/DESIGN:** A randomised controlled trial design will be used to test whether targeted invitation materials are effective at improving engagement with an offer of lung cancer screening for high risk candidates. Two thousand patients aged 60-75 and recorded as a smoker within the last five years by their GP, will be identified from primary care records and individually randomised to receive either intervention invitation materials (which take a targeted, stepped and low burden approach to information provision prior to the appointment) or control invitation materials. The primary outcome is uptake of a nurse-led 'lung health check' hospital appointment, during which patients will be offered a spirometry test, an exhaled carbon monoxide (CO) reading, and an LDCT if eligible. Initial data on demographics (i.e. age, sex, ethnicity, deprivation score) and smoking status will be collected in primary care and analysed to explore differences between attenders and non-attenders with respect to invitation group. Those who attend the lung health check will have further data on smoking collected during their appointment (including pack-year history, nicotine dependence and confidence to quit). Secondary outcomes will include willingness to be screened, uptake of LDCT and measures of informed decision-making to ensure the latter is not compromised by either invitation strategy. **DISCUSSION:** If effective at improving informed uptake of screening and reducing bias in participation, this invitation strategy could be adopted by local screening pilots or a national programme.

The IASLC Lung Cancer Staging Project: Proposals for Coding T Categories for Subsolid Nodules and Assessment of Tumor Size in Part-Solid Tumors in the Forthcoming Eighth Edition of the TNM Classification of Lung Cancer. Travis WD1, Asamura H2, Bankier AA3, et al. J Thorac Oncol. 2016 Apr 20. pii: S1556-0864(16)30335-5. doi: 10.1016/j.jtho.2016.03.025. [Epub ahead of print]
This article proposes codes for the primary tumor categories of adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA), and a uniform way to measure tumor size in part-solid tumors for the 8th edition of the tumor, node and metastasis (TNM) classification of lung cancer. In 2011 new entities of AIS, MIA and lepidic predominant adenocarcinoma (LPA) were defined and were later incorporated in the 2015 World Health Organization classification of lung cancer. To fit these entities into the T component of the staging system the Tis category is proposed for AIS, specifying Tis (AIS) if it is to be distinguished from squamous cell carcinoma in situ to be designated Tis (SCIS). We also propose MIA to be classified as T1mi. Furthermore, the use of the invasive size for T-descriptor size follows a recommendation made in three editions of the UICC TNM Supplement since 2003. For tumor size, the greatest dimension should be reported both clinically and pathologically. In nonmucinous lung adenocarcinomas, the computed tomography (CT) findings of ground glass versus solid opacities tend to correspond respectively to lepidic versus invasive patterns seen pathologically. However, this correlation is not absolute; so when CT features suggest nonmucinous AIS, MIA and LPA, the suspected diagnosis

and clinical staging, should be regarded as a preliminary assessment that is subject to revision after pathologic evaluation of resected specimens. The ability to predict invasive versus non-invasive size based on solid versus ground glass components is not applicable to mucinous AIS, MIA or invasive mucinous adenocarcinomas because they generally show solid nodules or consolidation on CT.

Biomarker Testing in Lung Carcinoma Cytology Specimens: A Perspective From Members of the Pulmonary Pathology Society. Roy-Chowdhuri S, Aisner DL, Allen TC, et al. Arch Pathol Lab Med. 2016 Apr 15. [Epub ahead of print]
The advent of targeted therapy in lung cancer has heralded a paradigm shift in the practice of cytopathology with the need for accurately subtyping lung carcinoma, as well as providing adequate material for molecular studies, to help guide clinical and therapeutic decisions. The variety and versatility of cytologic-specimen preparations offer significant advantages to molecular testing; however, they frequently remain underused. Therefore, evaluating the utility and adequacy of cytologic specimens is critical, not only from a lung cancer diagnosis standpoint but also for the myriad ancillary studies that are necessary to provide appropriate clinical management. A large fraction of lung cancers are diagnosed by aspiration or exfoliative cytology specimens, and thus, optimizing strategies to triage and best use the tissue for diagnosis and biomarker studies forms a critical component of lung cancer management. This review focuses on the opportunities and challenges of using cytologic specimens for molecular diagnosis of lung cancer and the role of cytopathology in the molecular era.

Morphological and molecular approach to synchronous non-small cell lung carcinomas: impact on staging. Schneider F1, Derrick V1, Davison JM1, Strollo D2, Incharoen P1, Dacic S1. Mod Pathol. 2016 Apr 15. doi: 10.1038/modpathol.2016.66. [Epub ahead of print]
Distinction between multiple primary cancers and intrapulmonary metastases in patients with synchronous multifocal lung cancer can be challenging. Histological and genotypic assessment of multifocal lung tumors have been suggested to influence the staging. The aim of this study was to determine the role of morphology and genotype in staging of surgically treated multifocal non-small cell lung carcinoma. Synchronous lung cancers from 60 patients (42 with adenocarcinoma and 18 with squamous cell carcinoma), clinically considered to represent intrapulmonary metastases, were histologically subtyped according to the 2015 World Health Organization classification of lung tumors and subjected to genotypic analysis (KRAS, EGFR, BRAF, PIK3CA, ALK, MET and ROS1 in adenocarcinoma and PIK3CA and p16 in squamous cell carcinoma). Concordance between clinical criteria and histological subtyping was identified in about 50% of cases ($P<0.0001$). Genotypically, 44% of adenocarcinomas and 60% of squamous cell carcinomas with identified molecular alterations were considered to be intrapulmonary metastases. Concordance between histological and molecular staging was observed in 89% of adenocarcinomas and 56% of squamous cell carcinomas. Univariate survival analyses failed to demonstrate significant differences in overall or cancer-specific survival in patients with adenocarcinoma and squamous cell carcinomas restaged according to histology and/or molecular profile. Lymph node metastases (N1/N2 vs N0) ($P=0.03$) and age >65 years ($P=0.05$) were associated with shorter overall survival. In addition, squamous cell carcinomas with p16 deletion showed shorter overall survival when compared with squamous cell carcinomas without p16 deletion ($P=0.05$). No correlation between other molecular alterations, clinico-pathological characteristics and prognosis was found. Our study demonstrates that a comprehensive genotypic and morphological assessment of surgically treated multifocal lung cancers is feasible but not sufficient to establish their clonal relationship and prognosis.

Initial Outcomes of a Lung Cancer Screening Program in an Integrated Community Health System. Miller AT1, Kruger P2, Conner K3, Robertson T4, Rowley B4, Sause W5, Ruckdeschel JC6, Blagev DP7. J Am Coll Radiol. 2016 Apr 28. pii: S1546-1440(16)00142-3. doi: 10.1016/j.jacr.2016.02.013. [Epub ahead of print]
PURPOSE: Lung cancer screening with low-dose CT (LDCT) demonstrated reduced mortality in the National Lung Screening Trial, yet there is debate as to whether the reported efficacy can translate into comparable effectiveness with community-based screening. The authors' purpose is to report the baseline patient characteristics and malignancy rate in the first 18 months after implementing a lung cancer screening program in an integrated community health system. **METHODS:** Patients were screened at 1 of 10 participating community-based centers within a 22-hospital system from 2013 to 2015. LDCT examinations were interpreted by 1 of 20 radiologists using structured reporting and an internally developed tracking system. Manual chart review was performed to ascertain the malignancy detection rate. **RESULTS:** A total of 357 patients were screened with LDCT. Of these, 80 patients were ineligible and 3 declined enrollment. The remaining 274 patients satisfied accepted screening criteria and were enrolled in the program. Malignancy was detected in a total of 11 enrollees (4.0%), 8 with lung cancer and 3 with extrapulmonary primary malignancies. Three patients (1.1%) were diagnosed with early-stage lung cancer and received definitive therapy. **CONCLUSIONS:** Early-stage lung cancer was detected with LDCT screening in an integrated community health system at a rate similar to other trials.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

Effect of Surgical Intervention on Survival of Patients With Clinical N2 Non-Small Cell Lung Cancer: A Veterans' Affairs Central Cancer Registry (VACCR) Database Analysis. Ganti AK1, Gonsalves W, Loberiza FR Jr, et al. Am J Clin Oncol. 2016 Apr;39(2):142-6. doi: 10.1097/COC.0000000000000040.
BACKGROUND: Optimal management of locally advanced non-small cell lung cancer (NSCLC) lacks consensus. A retrospective analysis of patient data entered in the Veterans Affairs Central Cancer Registry was conducted to evaluate these issues. **PATIENTS AND METHODS:** Data of patients with cT1-4, cN2, and cM0 NSCLC diagnosed in the VA Health System between 1995 and 2003 were evaluated. Age, sex, race, smoking history, TNM stage, treatment, and overall survival were abstracted. Survival was compared using multivariate Cox proportional hazards regression analysis. **RESULTS:** Of the 7328 patients analyzed, 7218 (98.5%) were male, 6061 (82.7%) were white, and 321 (4.4%) were never smokers. The treatment received included: none, 23.8%; chemotherapy alone, 14.3%; radiation alone, 23%; and chemoradiation (sequential or concurrent), 31.4%. Only 7.5% of patients had a surgical resection, with or without multimodality therapy. The median survival (months) of these patient groups were: surgery, 19.3; chemoradiation, 13; chemotherapy alone, 9.2; radiation alone, 7.3; and no treatment, 4 ($P<0.0001$). African Americans had a significantly decreased risk of mortality compared with whites (hazard ratio 0.92; 95% confidence interval, 0.87-0.98). **CONCLUSIONS:** Inclusion of surgical resection as a treatment modality was associated with a better overall survival. Also, African Americans appeared to do better than whites. These hypothesis-generating findings should be useful in the ongoing pursuit of better treatment strategies for locally advanced NSCLC.

Chest pain control with kinesiology taping after lobectomy for lung cancer: initial results of a randomized placebo-controlled study. Imperatori A1, Grande A2, Castiglioni M3, et al. Interact Cardiovasc Thorac Surg. 2016 Apr 29. pii: ivw110. [Epub ahead of print]

OBJECTIVES: Kinesiology taping (KT) is a rehabilitative technique performed by the cutaneous application of a special elastic tape. We tested the safety and efficacy of KT in reducing postoperative chest pain after lung lobectomy. **METHODS:** One-hundred and seventeen consecutive patients, both genders, age 18-85, undergoing lobectomy for lung cancer between January 2013 and July 2015 were initially considered. Lobectomies were performed by the same surgical team, with thoracotomy or video-assisted thoracoscopic surgery (VATS) access. Exclusion criteria (n = 25 patients) were: previous KT exposure, recent trauma, pre-existing chest pain, lack of informed consent, >24-h postoperative intensive care unit treatment. After surgery, the 92 eligible patients were randomized to KT experimental group (n = 46) or placebo control group (n = 46). Standard postoperative analgesia was administered in both groups (paracetamol/non-steroidal anti-inflammatory drugs, epidural analgesia including opioids), with supplemental analgesia boluses at patient request. On postoperative day 1 in addition, in experimental group patients a specialized physiotherapist applied KT, with standardized tape length, tension and shape, over three defined skin areas: at the chest access site pain trigger point; over the ipsilateral deltoid/trapezius; lower anterior chest. In control group, usual dressing tape mimicking KT was applied over the same areas, as placebo. Thoracic pain severity score [visual analogue scale (VAS) ranging 0-10] was self-assessed by all patients on postoperative days 1, 2, 5, 8, 9 and 30. **RESULTS:** The KT group and the control group had similar demographics, lung cancer clinico-pathological features and thoracotomy/VATS ratio. Postoperatively, the two groups also resulted similar in supplemental analgesia, complication rate, mean duration of chest drainage and length of stay. There were no adverse events with KT application. After tape application, KT patients reported overall less thoracic pain than the control group, the difference being significant on postoperative day 5 [median VAS, 2 (interquartile range, 1-3) vs 3 (2-5), $P < 0.01$] and day 8 [median VAS, 1 (0-2) vs 2 (1-3), $P < 0.05$]. Moreover, on postoperative day 30 persistence of chest pain (VAS ≥ 3) was reported less frequently by the KT group than by the control group (7 vs 24%; $P = 0.03$). **CONCLUSIONS:** KT after lung lobectomy is a safe and effective auxiliary technique for chest pain control.

Lobectomy versus stereotactic body radiotherapy in healthy patients with stage I lung cancer.
Rosen JE1, Salazar MC1, Wang Z2, et al. J Thorac Cardiovasc Surg. 2016 Apr 7. pii: S0022-5223(16)30035-6. doi: 10.1016/j.jtcvs.2016.03.060. [Epub ahead of print]
OBJECTIVES: Stereotactic body radiotherapy is an effective treatment for patients with early-stage non-small cell lung cancer who are not healthy enough to undergo surgery; however, the relative efficacy versus surgery in healthy patients is unknown. The National Cancer Database contains information on patient health and eligibility for surgery, allowing the long-term survival associated with lobectomy and stereotactic body radiotherapy to be compared in healthy patients with clinical stage I disease.
METHODS: The National Cancer Database was queried for patients who underwent lobectomy or stereotactic body radiotherapy for clinical stage I lung cancer between 2008 and 2012. Healthy patients were selected by excluding patients not offered surgery because of health-related reasons and only including patients documented to be free of comorbidities. **RESULTS:** A total of 13,562 comorbidity-free patients with clinical stage I lung cancer treated with lobectomy were compared with 1781 patients treated with stereotactic body radiotherapy. Time-stratified Cox proportional hazards models found lobectomy to be associated with a significantly better outcome than stereotactic body radiotherapy for both T1N0M0 tumors (hazard ratio, 0.38; 95% confidence interval, 0.33-0.43; $P < .001$) and T2N0M0 tumors 5 cm or less (hazard ratio, 0.38; confidence interval, 0.31-0.46; $P < .001$). In a propensity-matched analysis of 1781 pairs, lobectomy remained superior to stereotactic body radiotherapy (5-year survival 59% vs 29%, $P < .001$). **CONCLUSIONS:** Among healthy patients with clinical stage I non-small cell lung cancer in the National Cancer Database, lobectomy is associated with a significantly better outcome than stereotactic body radiotherapy. Further study is warranted to clarify the comparative effectiveness of surgery and stereotactic body radiotherapy across various strata of patient health.

Prognostic Significance of Programmed Cell Death Ligand 1 in Patients With Non-Small-Cell Lung Cancer: A Large Cohort Study of Surgically Resected Cases. Sun JM1, Zhou W2, Choi YL1, et al. **INTRODUCTION:** The aim of our analysis was to evaluate the prognostic effect of programmed cell death ligand-1 (PD-L1) expression in patients with non-small-cell lung cancer (NSCLC). **METHODS:** PD-L1 expression among 1070 surgically resected NSCLC specimens was evaluated by immunohistochemistry. Data were analyzed using Cox proportional hazard models, adjusting for age, sex, smoking status, histology, stage, and performance status. **RESULTS:** Sixty-eight patients (6%) were PD-L1 strong positive; 410 (38%) were PD-L1 weak positive. A significantly higher prevalence of PD-L1 positivity was observed among patients with squamous cell carcinoma and among stage IIIB/IV patients. PD-L1 expression may be associated with poorer overall survival, with an adjusted hazard ratio (HR) of 1.56 (95% confidence interval [CI], 1.08-2.26; p=0.02) for PD-L1 strong positive, 1.18 (95% CI, 0.96-1.46; p=0.12) for PD-L1 weak positive, and 1.23 (95% CI, 1.00-1.51; p=0.05) for the combined strong- and weak-positive groups compared with PD-L1 negative. Negative prognostic effect of PD-L1 expression was not statistically significant after adjusting for postsurgical chemotherapy or radiotherapy. Similar results were observed for progression-free survival. Among stage I patients, the disease recurrence rate was higher in the PD-L1-positive versus negative group (48% versus 27%, p<0.001), with an adjusted HR for disease-free survival of 2.01 (95% CI, 1.08-3.73; p=0.03) for PD-L1 strong positive and 1.57 (95% CI, 1.17-2.11; p=0.003) for PD-L1 weak positive compared with PD-L1 negative. **CONCLUSIONS:** Tumor PD-L1 expression may be associated with poor prognosis in patients with NSCLC, although its significance weakens when postsurgical therapy is considered.

Effects of dexmedetomidine on oxygenation and lung mechanics in patients with moderate chronic obstructive pulmonary disease undergoing lung cancer surgery: A randomised double-blinded trial. Lee SH1, Kim N, Lee CY, Ban MG, Oh YJ. Eur J Anaesthesiol. 2016 Apr;33(4):275-82. doi: 10.1097/EJA.0000000000000405.
BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a risk factor that increases the incidence of postoperative cardiopulmonary morbidity and mortality after lung resection. Dexmedetomidine, a selective α2-adrenoreceptor agonist, has been reported previously to attenuate intrapulmonary shunt during one-lung ventilation (OLV) and to alleviate bronchoconstriction.
OBJECTIVE: The objective is to determine whether dexmedetomidine improves oxygenation and lung mechanics in patients with moderate COPD during lung cancer surgery. **DESIGN:** A randomised, double-blinded, placebo-controlled study. **SETTING:** Single university hospital. **PARTICIPANTS:** Fifty patients scheduled for video-assisted thoracoscopic surgery who had moderate COPD. Patients were randomly allocated to a control group or a Dex group (n=25 each). **NTERVENTIONS:** In the Dex group, dexmedetomidine was given as an initial loading dose of 1.0μgkg over 10min followed by a maintenance dose of 0.5μgkgh during OLV while the control group was administered a comparable volume of 0.9% saline. Data were measured at 30min (DEX-30) and 60min (DEX-60) after dexmedetomidine or saline administration during OLV. **MAIN OUTCOME MEASURES:**
The primary outcome was the effect of dexmedetomidine on oxygenation. The secondary outcome was the effect of dexmedetomidine administration on postoperative pulmonary complications.
RESULTS: Patients in the Dex group had a significantly higher PaO2/FIO2 ratio (27.9±5.8 vs. 22.5±8.4 and 28.6±5.9 vs. 21.0±9.9 kPa, P<0.05), significantly lower dead space ventilation (19.2±8.5 vs. 24.1±8.1 and 19.6±6.7 vs. 25.3±7.8%, P<0.05) and higher dynamic compliance at DEX-30 and DEX-60 (P=0.0001 and P=0.0184) compared with the control group. In the Dex group, the PaO2/FIO2 ratio in the postoperative period was significantly higher (P=0.022) and the incidence of ICU admission was lower than in the control group. **CONCLUSION:** Dexmedetomidine administration may provide clinically

relevant benefits by improving oxygenation and lung mechanics in patients with moderate COPD undergoing lung cancer surgery.

PD-L1 and Tumor Infiltrating Lymphocytes as Prognostic Markers in Resected NSCLC.
Ameratunga M1, Asadi K2, Lin X3, Walkiewicz M4, Murone C2,4, Knight S5, Mitchell P1, Boutros P3,6,7, John T1,4,8,9. PLoS One. 2016 Apr 22;11(4):e0153954. doi: 10.1371/journal.pone.0153954. eCollection 2016.
INTRODUCTION: Immune checkpoint inhibition has shifted treatment paradigms in non-small cell lung cancer (NSCLC). Conflicting results have been reported regarding the immune infiltrate and programmed death-ligand 1 (PD-L1) as a prognostic marker. We correlated the immune infiltrate and PD-L1 expression with clinicopathologic characteristics in a cohort of resected NSCLC. **METHODS:** A tissue microarray was constructed using triplicate cores from consecutive resected NSCLC. Immunohistochemistry was performed for CD8, FOXP3 and PD-L1. Strong PD-L1 expression was predefined as greater than 50% tumor cell positivity. Matched nodal samples were assessed for concordance of PD-L1 expression. **RESULTS:** Of 522 patients, 346 were node-negative (N0), 72 N1 and 109 N2; 265 were adenocarcinomas (AC), 182 squamous cell cancers (SCC) and 75 other. Strong PD-L1 expression was found in 24% cases. In the overall cohort, PD-L1 expression was not associated with survival. In patients with N2 disease, strong PD-L1 expression was associated with significantly improved disease-free (DFS) and overall survival (OS) in multivariate analysis (HR 0.49, 95%CI 0.36-0.94, p = 0.031; HR 0.46, 95%CI 0.26-0.80, p = 0.006). In this resected cohort only 5% harboured EGFR mutations, whereas 19% harboured KRAS and 23% other. KRAS mutated tumors were more likely to highly express PD-L1 compared to EGFR (22% vs 3%). A stromal CD8 infiltrate was associated with significantly improved DFS in SCC (HR 0.70, 95%CI 0.50-0.97, p = 0.034), but not AC, whereas FOXP3 was not prognostic. Matched nodal specimens (N = 53) were highly concordant for PD-L1 expression (89%). **CONCLUSION:** PD-L1 expression was not prognostic in the overall cohort. PD-L1 expression in primary tumor and matched nodal specimens were highly concordant. The observed survival benefit in N2 disease requires confirmation.

Evolution of a Lung-Sparing Strategy with Sleeve Lobectomy and Induction Therapy for Non-small Cell Lung Cancer: 20-Year Experience at a Single Institution. Tagawa T1, Iwata T1, Nakajima T1, Suzuki H1, Yoshida S1, Yoshino I2. World J Surg. 2016 Apr;40(4):906-12. doi: 10.1007/s00268-015-3330-z.
BACKGROUND: To elucidate the evolution of a lung-sparing strategy with sleeve lobectomy (SL) and induction therapy for non-small cell lung cancer (NSCLC). **METHODS:** We retrospectively reviewed 205 patients with NSCLC who underwent pneumonectomy (PN, n = 54) or SL (n = 151) from 1994 to 2013. The study period was divided into four 5-year periods, and surgical trends were analyzed, focusing on the PN:SL ratio. **RESULTS:** PN was associated with a significantly advanced pathological stage, a larger tumor size and less pulmonary function compared with SL. The PN group had higher 30-day (3.7 vs. 0 %, p = 0.018) and 90-day (13.0 vs. 1.3 %, p = 0.0003) mortality than the SL group. The overall 5-year survival rate was significantly higher with SL (71.5 %) versus PN (42.8 %, p = 0.011) for patients with pN0-1. The ratio of PN among total surgeries decreased significantly over the four periods (1994-1998, 1999-2003, 2004-2008, and 2009-2013) from 5.63 % to 3.17, 1.40, and 1.38 %, respectively (p < 0.0001); in contrast, the PN:SL ratio increased significantly from 1.64 to 2.50, 3.71, and 5.44, respectively (p = 0.041). During the last period, when we introduced induction therapy, 38 of 651 who received surgery underwent induction therapy. The PN:SL ratios of those who did and did not undergo induction therapy were 15 (PN: 1, SL: 15) and 4.25 (PN: 8, SL: 34), respectively. **CONCLUSIONS:** A lung-sparing strategy with SL for NSCLC can decrease the PN rate to less than 2 % with less mortality. Induction therapy may facilitate SL and increase the PN:SL ratio.

Number of Ribs Resected is Associated with Respiratory Complications Following Lobectomy with en bloc Chest Wall Resection. Geissen NM1, Medairos R1, Davila E1, et al. Lung. 2016 Apr 23. [Epub ahead of print]
PURPOSE: Pulmonary lobectomy with en bloc chest wall resection is a common strategy for treating lung cancers invading the chest wall. We hypothesized a direct relationship exists between number of ribs resected and postoperative respiratory complications. **METHODS:** An institutional database was queried for patients with non-small cell lung cancer that underwent lobectomy with en bloc chest wall resection between 2003 and 2014. Propensity matching was used to identify a cohort of patients who underwent lobectomy via thoracotomy without chest wall resection. Patients were propensity matched on age, gender, smoking history, FEV1, and DLCO. The relationship between number of ribs resected and postoperative respiratory complications (bronchoscopy, re-intubation, pneumonia, or tracheostomy) was examined. **RESULTS:** Sixty-eight patients (34 chest wall resections; 34 without chest wall resection) were divided into 3 cohorts: cohort A = 0 ribs resected (n = 34), cohort B = 1-3 ribs resected (n = 24), and cohort C = 4-6 ribs resected (n = 10). Patient demographics were similar between cohorts. The 90-day mortality rate was 2.9 % (2/68) and did not vary between cohorts. On multivariate analysis, having 1-3 ribs resected (OR 19.29, 95 % CI (1.33, 280.72); p = 0.03), 4-6 ribs resected [OR 26.66, (1.48, 481.86); p = 0.03), and a lower DLCO (OR 0.91, (0.84, 0.99); p = 0.02) were associated with postoperative respiratory complications. **CONCLUSIONS:** In patients undergoing lobectomy with en bloc chest wall resection for non-small cell lung cancer, the number of ribs resected is directly associated with incidence of postoperative respiratory complications.

Clinical significance of the preoperative platelet count and platelet-to-lymphocyte ratio (PLT-PLR) in patients with surgically resected non-small cell lung cancer. Kim SH1, Lee HW2, Go SI3,4, Lee SI5, Lee GW4,6. Oncotarget. 2016 Apr 18. doi: 10.18632/oncotarget.8809. [Epub ahead of print]
BACKGROUND: The aim of this study was to assess the prognostic significance of the preoperative platelet count (PLT) and platelet-to-lymphocyte ratio (PLR) in patients with surgically resected non-small-cell lung cancer (NSCLC). **PATIENTS AND METHODS:** We retrospectively reviewed 202 patients treated for NSCLC between January 2002 and December 2007. Preoperative PLT and PLR scores were calculated using data obtained at the time of admission. Patients were assigned a PLT-PLR score of 0, 1, or 2 based upon the presence of thrombocytosis, an elevated PLR, or both. **RESULTS:** Patients with a PLT-PLR score of 2 had a significantly lower median overall survival (OS) [12.715 mo; 95% confidence interval (CI) 1.215-24.215] when compared with patients with PLT-PLR scores of 1 (52.238 mo; 95% CI 17.062-87.414, p = 0.002) or 0 (not reached, p < 0.001). Relapse-free survival (RFS) was also significantly decreased in patients with a PLT-PLR score of 2 (10.107 mo; 95% CI 3.388-16.826) relative to patients with a PLT-PLR score of 1 (27.214 mo; 95% CI 0-56.253, p = 0.002) or 0 (58.893 mo; 95% CI 32.938-84.848, p < 0.001). In multivariate analysis, a PLT-PLR score of 2 was an independent prognostic factor for poor OS (hazard ratio (HR) 3.473; 95% CI 1.765-6.835, p < 0.001) and RFS (HR 2.286; 95% CI 1.243-4.206, p = 0.008) compared with a PLT-PLR score of 0. **CONCLUSIONS:** Preoperative PLT-PLR scores can be useful for predicting disease prognosis in patients with surgically resected NSCLC. Further large prospective studies will be necessary to validate our findings.

Impact of Sublobar Resection on Pulmonary Function: Long-Term Results from American College of Surgeons Oncology Group Z4032 (Alliance). Kent MS1, Mandrekar SJ2, Landreneau R3, et al. Ann Thorac Surg. 2016 Apr 19. pii: S0003-4975(16)00082-5. doi: 10.1016/j.athoracsur.2016.01.069. [Epub ahead of print]
BACKGROUND: Sublobar resection (SR) in high-risk operable patients may result in a long-term decrease in pulmonary function. We previously reported 3-month pulmonary function outcomes from a

randomized phase III study of SR alone compared with SR with brachytherapy in patients with non-small cell lung cancer. We now report long-term pulmonary function after SR. **METHODS:** Pulmonary function was measured at baseline and at 3, 12, and 24 months. A decline of 10% or more from baseline in the percentage predicted forced expiratory volume of 1 percentage or in the diffusion capacity of the lung for carbon monoxide was considered clinically meaningful. The effect of study arm, tumor location, size, approach (video-assisted thoracoscopic surgery vs thoracotomy), and SR type (wedge vs segmentectomy) on pulmonary function was assessed using a Wilcoxon rank sum test. A generalized estimating equation model was used to assess the effect of each factor on longitudinal data, including all four time points. **RESULTS:** Complete pulmonary function data at all time points was available in 69 patients. No significant differences were observed in pulmonary function between SR and SR with brachytherapy, thus the study arms were combined for all analyses. A decline of 10% or more ($p = 0.02$) in the percentage predicted forced expiratory volume in 1 second was demonstrated for lower-lobe resections at 3 months but was not at 12 or 24 months. A decline of 10% or more ($p = 0.05$) in the percentage predicted diffusion capacity of the lung for carbon monoxide was seen for thoracotomy at 3 months but was not at 12 or 24 months. **CONCLUSIONS:** Clinically meaningful declines in pulmonary function occurred after lower lobe resection and after thoracotomy at 3 months but subsequently recovered. This study suggests that SR does not result in sustained decreased pulmonary function in high-risk operable patients.

Sublobar resection versus lobectomy for stage I non-small cell lung cancer: an appropriate choice in elderly patients? Fiorelli A1, Caronia FP2, Daddi N3, et al. Surg Today. 2016 Apr 16. [Epub ahead of print]

PURPOSES: The aim of this study was to evaluate whether sublobar resection could achieve recurrence and survival rates equivalent to lobectomy in high-risk elderly patients. **METHODS:** We conducted a retrospective multicenter study that including all consecutive patients (aged >75 years) who underwent operation for clinical stage I non-small cell lung cancer (NSCLC). The clinicopathological data, postoperative morbidity and mortality, recurrence rate and vital status were retrieved. The overall survival, cancer-specific survival and disease-free survival were also assessed. **RESULTS:** Two hundred and thirty-nine patients (median age 78 years) were enrolled. Lobectomies were performed in 149 (62.3 %) patients and sublobar resections in 90 (39 segmentectomies, 51 wedge resections). There were no differences in the recurrence rates following lobar versus sublobar resections (19 versus 23 %, respectively; $p = 0.5$) or the overall survival ($p = 0.1$), cancer-specific survival ($p = 0.3$) or disease-free survival ($p = 0.1$). After adjusting for 1:1 propensity score matching and a matched pair analysis, the results remained unchanged. A tumor size >2 cm and pN2 disease were independent negative prognostic factors in unmatched ($p = 0.01$ and $p = 0.0003$, respectively) and matched ($p = 0.02$ and $p = 0.005$, respectively) analyses. **CONCLUSIONS:** High-risk elderly patients may benefit from sublobar resection, which provides an equivalent long-term survival compared to lobectomy.

NSCLC - CHEMOTHERAPY

Navigating the Challenges of Adjuvant Chemotherapy in Older Patients with Early-Stage Non-Small-Cell Lung Cancer. Poudel A1, Sinha S1, Gajra A2. Drugs Aging. 2016 Apr;33(4):223-32. doi: 10.1007/s40266-016-0350-9.

Lung cancer is a disease of older adults. In the US and worldwide, more than 60 % of patients being diagnosed are over the age of 65 years. The preferred treatment of stage I-II non-small-cell lung cancer (NSCLC) is surgical resection. Adjuvant chemotherapy with a platinum-based combination is the standard of care for patients with early-stage NSCLC after surgery. However, there have been no large prospective studies to test the efficacy of adjuvant chemotherapy in the elderly, the population most

affected by lung cancer. The available evidence is limited to retrospective reviews of large population databases or post hoc analyses of prospective studies in age-unselected populations. This review aims to address the knowledge gap pertaining to the use of adjuvant chemotherapy in older patients with resected NSCLC. There are many barriers to use of adjuvant chemotherapy in older adults with NSCLC. The utilization of adjuvant chemotherapy amongst older adults has been slow but is improving. While the elderly may tolerate a lower dose intensity of chemotherapy compared with younger patients, they do garner benefit from adjuvant chemotherapy. There is a lack of a standardized tool to risk-stratify older patients for adjuvant chemotherapy after resection. Geriatric assessment may help guide decision making in the clinical practice setting. The principles of geriatric assessment and commonly employed tools for such assessment will be reviewed. Further, the emerging therapies in adjuvant treatment of lung cancer based on genetic mutations will be discussed.

Clinical efficacy of erlotinib, a salvage treatment for non-small cell lung cancer patients following gefitinib failure. Cho KM1,2, Keam B1,3, Kim TM1,3, Lee SH1,3, Kim DW1,3, Heo DS1,3. Korean J Intern Med. 2016 Apr 21. doi: 10.3904/kjim.2014.259. [Epub ahead of print]
BACKGROUND/AIMS: The purpose of this study was to identify predictive factors for erlotinib treatment in non-small cell lung cancer (NSCLC) patients following gefitinib failure. **METHODS:** Forty-five patients with NSCLC who were treated with erlotinib following gefitinib failure at Seoul National University Hospital between August 2005 and November 2011 were enrolled. Epidermal growth factor receptor (EGFR) mutation status, pathologic findings and other clinical factors, including response to tyrosine kinase inhibitors (TKIs) and progression-free survival (PFS), were evaluated. **RESULTS:** Of the 45 patients, 40 (88.8%) had adenocarcinoma. The following EGFR mutations were observed: five patients with a deletion of exon 19, six patients with an L858R mutation, three patients with wild-type EGFR, and 31 patients with unknown mutations. The response rate of erlotinib was 4.4%, and stable disease was 42.2%. The median PFS for erlotinib was 2.6 months (95% confidence interval, 1.4 to 3.7). Patients with a PFS $\geq$ 4 months during previous gefitinib treatment had a significantly longer PFS with erlotinib (3.3 months vs. 1.6 months, respectively; $p < 0.01$) than patients with PFS < 4 months with gefitinib. According to multivariate analyses, PFS $\geq$ 4 months for previous gefitinib treatment was significantly associated with prolonged PFS with erlotinib ($p = 0.04$). However, the response rate of gefitinib and treatment sequence were not associated with prolonged PFS with erlotinib ($p = 0.28$ and $p = 0.67$, respectively). **CONCLUSIONS:** Following rechallenge with the EGFR TKI erlotinib following gefitinib failure, patients who showed prolonged PFS with gefitinib benefit from erlotinib. However, further prospective studies are needed to confirm these findings.

Chemotherapy in elderly patients with nonsmall cell lung cancer. Veluswamy RR1, Levy B, Wisnivesky JP. Curr Opin Pulm Med. 2016 Apr 20. [Epub ahead of print]
PURPOSE OF REVIEW: Using chemotherapy in elderly nonsmall cell lung cancer (NSCLC) patients is often challenging given concerns of treatment-related toxicity. However, data have demonstrated that chemotherapy can lead to improved survival in this age group. In this review, we summarize existing data and discuss the role of chemotherapy in elderly patients with localized, locally advanced, and metastatic NSCLC. **RECENT FINDINGS:** Clear evidence-based guidelines for chemotherapy management in elderly patients is lacking given the limited prospective data available. However, there are more clinical trials investigating optimal chemotherapy agents and dosing schedules specific to the elderly. Comprehensive geriatric assessment-directed interventions are also being prospectively investigated to improve treatment selection for elderly patients. **SUMMARY:** Chronological age should not be a limiting factor for chemotherapy use in elderly NSCLC patients. Several studies have demonstrated similar survival benefits than in younger patients when chemotherapy is given as adjuvant treatment for localized disease; part of definitive treatment with radiation in locally advanced disease; and palliative treatment for

advanced NSCLC, however, at the cost of greater toxicity. Tolerability of chemotherapy in this heterogeneous group can be difficult to predict. Therefore, therapeutic decisions should be individualized based on performance status. Comprehensive geriatric assessment should be used to supplement performance status measures to minimize both under and overtreatment.

Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial.
Park K1, Tan EH2, O'Byrne K3, et al. Lancet Oncol. 2016 Apr 12. pii: S1470-2045(16)30033-X. doi: 10.1016/S1470-2045(16)30033-X. [Epub ahead of print]
BACKGROUND: The irreversible ErbB family blocker afatinib and the reversible EGFR tyrosine kinase inhibitor gefitinib are approved for first-line treatment of EGFR mutation-positive non-small-cell lung cancer (NSCLC). We aimed to compare the efficacy and safety of afatinib and gefitinib in this setting. **METHODS:** This multicentre, international, open-label, exploratory, randomised controlled phase 2B trial (LUX-Lung 7) was done at 64 centres in 13 countries. Treatment-naive patients with stage IIIB or IV NSCLC and a common EGFR mutation (exon 19 deletion or Leu858Arg) were randomly assigned (1:1) to receive afatinib (40 mg per day) or gefitinib (250 mg per day) until disease progression, or beyond if deemed beneficial by the investigator. Randomisation, stratified by EGFR mutation type and status of brain metastases, was done centrally using a validated number generating system implemented via an interactive voice or web-based response system with a block size of four. Clinicians and patients were not masked to treatment allocation; independent review of tumour response was done in a blinded manner. Coprimary endpoints were progression-free survival by independent central review, time-to-treatment failure, and overall survival. Efficacy analyses were done in the intention-to-treat population and safety analyses were done in patients who received at least one dose of study drug. This ongoing study is registered with ClinicalTrials.gov, number NCT01466660. **FINDINGS:** Between Dec 13, 2011, and Aug 8, 2013, 319 patients were randomly assigned (160 to afatinib and 159 to gefitinib). Median follow-up was 27·3 months (IQR 15·3-33·9). Progression-free survival (median 11·0 months [95% CI 10·6-12·9] with afatinib vs 10·9 months [9·1-11·5] with gefitinib; hazard ratio [HR] 0·73 [95% CI 0·57-0·95], p=0·017) and time-to-treatment failure (median 13·7 months [95% CI 11·9-15·0] with afatinib vs 11·5 months [10·1-13·1] with gefitinib; HR 0·73 [95% CI 0·58-0·92], p=0·0073) were significantly longer with afatinib than with gefitinib. Overall survival data are not mature. The most common treatment-related grade 3 or 4 adverse events were diarrhoea (20 [13%] of 160 patients given afatinib vs two [1%] of 159 given gefitinib) and rash or acne (15 [9%] patients given afatinib vs five [3%] of those given gefitinib) and liver enzyme elevations (no patients given afatinib vs 14 [9%] of those given gefitinib). Serious treatment-related adverse events occurred in 17 (11%) patients in the afatinib group and seven (4%) in the gefitinib group. Ten (6%) patients in each group discontinued treatment due to drug-related adverse events. 15 (9%) fatal adverse events occurred in the afatinib group and ten (6%) in the gefitinib group. All but one of these deaths were considered unrelated to treatment; one patient in the gefitinib group died from drug-related hepatic and renal failure. **INTERPRETATION:** Afatinib significantly improved outcomes in treatment-naive patients with EGFR-mutated NSCLC compared with gefitinib, with a manageable tolerability profile. These data are potentially important for clinical decision making in this patient population.

NSCLC - RADIOTHERAPY

Stereotactic Body Radiation Therapy as Salvage for Intrathoracic Recurrence in Patients With Previously Irradiated Locally Advanced Non-Small Cell Lung Cancer. Parks J1, Kloecker G, Woo S, Dunlap NE. Am J Clin Oncol. 2016 Apr;39(2):147-53. doi: 10.1097/COC.0000000000000039.

INTRODUCTION: The purpose of this study is to provide data on the outcomes of using stereotactic body radiotherapy (SBRT) as a means of salvage for non-small cell lung cancer (NSCLC) relapses previously treated with radiation. **MATERIALS AND METHODS:** The records of 128 consecutive patients treated with thoracic SBRT from 2009 through 2012 were retrospectively reviewed. Twenty-seven patients (29 lesions) treated with prior thoracic radiation for stage IIB-IIIB NSCLC with subsequent recurrences and retreated with SBRT were identified. **RESULTS:** The median prior radiation dose was 64.8 Gy (range, 45 to 74 Gy) with a median retreatment dose of 50 Gy (range, 30 to 54 Gy), corresponding to a biological equivalent dose of 100 Gy (range, 48 to 151 Gy), at a median time of 13.4 months from prior radiation. The mean follow-up after salvage SBRT was 22 months. Local failure following salvage was 11%, nodal failure was 37%, and distant failure was 30%. The local recurrence-free survival at 2 years was 72%. Out-of-field failure was predictive for worse local control (hazard ratio, 47.38; 95% confidence interval, 5.795-64.899). Progression-free survival at 1 year was 55% and 38% at 2 years. Overall survival at 2 years from SBRT salvage was 79%. Salvage biological equivalent dose ≥100 Gy was predictive of improved progression-free survival (48% vs. 18%, P=0.021) and overall survival (91% vs. 52%, P=0.004) at 2 years. The rate of symptomatic pneumonitis was 63% and chest wall pain reported was 26%. **CONCLUSIONS:** We observed improved outcomes following SBRT as a means of salvage for locally advanced recurrent NSCLC over traditional radiation therapy options. The toxicities were greater than expected from naive lung irradiation, but the adverse effects remained controlled with medications.

Phase II Trial of Stereotactic Body Radiotherapy for Stage I NSCLC: Survival, Local Control and Lung Function at 36 months. Navarro-Martin A1, Aso S2, Cacicedo J3, et al. J Thorac Oncol. 2016 Apr 18. pii: S1556-0864(16)30092-2. doi: 10.1016/j.jtho.2016.03.021. [Epub ahead of print]
PURPOSE: The long term impact of stereotactic body radiotherapy (SBRT) on respiratory function in patients with inoperable non-small cell lung cancer (NSCLC) has not been well-studied. The aim of this phase II trial was to assess local control, survival, and lung function at 36 months post-treatment. **METHODS AND MATERIALS:** From July 2008 to February 2012, 42 patients diagnosed with inoperable NSCLC with peripheral lesions were consecutively enrolled. Lung function testing included forced expiratory vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and diffusing capacity for carbon monoxide (DLCO). All lung function parameters were registered at baseline and evaluated prospectively post-SBRT every 6 months for 2 years and annually thereafter. **RESULTS:** Of the 42 initial patients, 4 were excluded. At 36 months post-SBRT, 22 patients were still evaluable (12 deaths and 4 patients lost to follow-up). At 36 months, local control was 94%. At 1, 2 and 3 years, respectively, OS rates were 92%, 75%, and 66%. Median OS was 57 months. Grade III acute toxicity was observed in 4 patients (10%). Chronic grade I toxicity was observed in all 38 cases (100%), with the most common type being pneumonitis (26 patients; 68%). Mean lung function parameters at baseline and at 36 months post-treatment were: FVC, 83% vs 79%; FEV1, 62% vs. 57%; and DLCO, 54% vs. 54 %. These changes were non-significant. **CONCLUSIONS:** In this trial, local control and survival rates following SBRT were very good. Treatment with SBRT had no significant impact on lung function at 36 months. These findings provide further support for the use of SBRT as a radical treatment for NSCLC. Lung toxicity is minimal, even in patients with poor pulmonary function prior to treatment.

Accelerated hypofractionated three-dimensional conformal radiation therapy (3 Gy/fraction) combined with concurrent chemotherapy for patients with unresectable stage III non-small cell lung cancer: preliminary results of an early terminated phase II trial. Ren XC1, Wang QY1, Zhang R1, et al. BMC Cancer. 2016 Apr 23;16(1):288. doi: 10.1186/s12885-016-2314-1.
BACKGROUND: Increasing the biological effective dose (BED) of radiotherapy for non-small cell lung cancer (NSCLC) can increase local control rates and improve overall survival. Compared with

conventional fractionated radiotherapy, accelerated hypofractionated radiotherapy can yield higher BED, shorten the total treatment time, and theoretically obtain better efficacy. However, currently, there is no optimal hypofractionated radiotherapy regimen. Based on phase I trial results, we performed this phase II trial to further evaluate the safety and preliminary efficacy of accelerated hypofractionated three-dimensional conformal radiation therapy(3-DCRT) combined with concurrent chemotherapy for patients with unresectable stage III NSCLC. **METHODS:** Patients with previously untreated unresectable stage III NSCLC received 3-DCRT with a total dose of 69 Gy, delivered at 3 Gy per fraction, once daily, five fractions per week, completed within 4.6 weeks. At the same time, platinum doublet chemotherapy was applied. **RESULTS:** After 12 patients were enrolled in the group, the trial was terminated early. There were five cases of grade III radiation esophagitis, of which four cases completed the radiation doses of 51 Gy, 51 Gy, 54 Gy, and 66 Gy, and one case had 16 days of radiation interruption. The incidence of grade III acute esophagitis in patients receiving an irradiation dose per fraction ≥2.7 Gy on the esophagus was 83.3 % (5/6). The incidence of symptomatic grade III radiation pneumonitis among the seven patients who completed 69 Gy according to the plan was 28.6 % (2/7). The median local control (LC) and overall survival (OS) were not achieved; the 1-year LC rate was 59.3 %, and the 1-year OS rate was 78.6 %. **CONCLUSION:** For unresectable stage III NSCLC, the accelerated hypofractionated radiotherapy with a total dose of 69 Gy (3 Gy/f) combined with concurrent chemotherapy might result in severe radiation esophagitis and pneumonitis to severely affect the completion of the radiotherapy. Therefore, we considered that this regimen was infeasible. During the hypofractionated radiotherapy with concurrent chemotherapy, the irradiation dose per fraction to esophagus should be lower than 2.7 Gy. Further studies should be performed using esophageal tolerance as a metric in dose escalation protocols.

Assessment of function and quality of life in a phase II multi-institutional clinical trial of fractionated simultaneous in-field boost radiotherapy for patients with 1-3 metastases.
Bauman G1, Yartsev S2, Roberge D3, et al. J Neurooncol. 2016 Apr 15. [Epub ahead of print]
We examined functional outcomes and quality of life of whole brain radiotherapy (WBRT) with integrated fractionated stereotactic radiotherapy boost (FSRT) for brain metastases treatment. Eighty seven people with 1-3 brain metastases (54/87 lung primary, 42/87 single brain metastases) were enrolled on this Phase II trial of WBRT (30 Gy/10) + simultaneous FSRT, (60 Gy/10). Median overall follow-up and survival was 5.4 months, 6 month actuarial intra-lesional control was 78 %; only 1 patient exhibited grade 4 toxicity (worsened seizures); most treatment related toxicity was grade 1 or 2; 2/87 patients demonstrated asymptomatic radiation necrosis on follow-up imaging. Mean (Min-Max) baseline KPS, Mini Mental Status Exam (MMSE) and FACT-BR quality of life were 83 (70-100), 28 (21-30) and 143 (98-153). Lower baseline MMSE (but not KPS or FACT-Br) was associated with worse survival after adjusting for age, number of metastases, primary and extra-cranial disease status. Crude rates of deterioration (>10 points decrease from baseline for KPS and FACT-Br, MMSE fall to <27) ranged from 26 to 38 % for KPS, 32-59 % for FACT-Br and 0-16 % for MMSE depending on the time-point assessed with higher rates generally noted at earlier time points (≤6 months post-treatment). Using a linear mixed models analysis, significant declines from baseline were noted for KPS and FACT-Br (largest effects at 6 weeks to 3 months) with no significant change in MMSE. The effects on function and quality of life of this integrated treatment of WBRT + simultaneous FSRT were similar to other published series combining WBRT + radiosurgery.

Protocol for the isotoxic intensity modulated radiotherapy (IMRT) in stage III non-small cell lung cancer (NSCLC): a feasibility study. Haslett K1, Franks K2, Hanna GG3, et al. BMJ Open. 2016 Apr 15;6(4):e010457. doi: 10.1136/bmjopen-2015-010457.
INTRODUCTION: The majority of stage III patients with non-small cell lung cancer (NSCLC) are unsuitable for concurrent chemoradiotherapy, the non-surgical gold standard of care. As the alternative

treatment options of sequential chemoradiotherapy and radiotherapy alone are associated with high local failure rates, various intensification strategies have been employed. There is evidence to suggest that altered fractionation using hyperfractionation, acceleration, dose escalation, and individualisation may be of benefit. The MAASTRO group have pioneered the concept of 'isotoxic' radiotherapy allowing for individualised dose escalation using hyperfractionated accelerated radiotherapy based on predefined normal tissue constraints. This study aims to evaluate whether delivering isotoxic radiotherapy using intensity modulated radiotherapy (IMRT) is achievable. **METHODS AND ANALYSIS:** Isotoxic IMRT is a multicentre feasibility study. From June 2014, a total of 35 patients from 7 UK centres, with a proven histological or cytological diagnosis of inoperable NSCLC, unsuitable for concurrent chemoradiotherapy will be recruited. A minimum of 2 cycles of induction chemotherapy is mandated before starting isotoxic radiotherapy. The dose of radiation will be increased until one or more of the organs at risk tolerance or the maximum dose of 79.2 Gy is reached. The primary end point is feasibility, with accrual rates, local control and overall survival our secondary end points. Patients will be followed up for 5 years. **ETHICS AND DISSEMINATION:** The study has received ethical approval (REC reference: 13/NW/0480) from the National Research Ethics Service (NRES) Committee North West-Greater Manchester South. The trial is conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP). The trial results will be published in a peer-reviewed journal and presented internationally.

Accelerated hypofractionated radiotherapy with concomitant chemotherapy in locally advanced squamous cell carcinoma of lung: evaluation of response, survival, toxicity and quality of life from a Phase II randomized study. Roy S1, Pathy S1, Mohanti BK1, Raina V2, Jaiswal A3, Kumar R4, Kalaivani M5. Br J Radiol. 2016 Apr 7:20150966. [Epub ahead of print]
OBJECTIVE: To evaluate the feasibility and efficacy of accelerated hypofractionated radiation with concomitant chemotherapy (AHFx-RT-CT) in locally advanced squamous cell carcinoma (SCC) of the lung. **METHODS:** 36 patients were enrolled in this study (CTRI/2013/11/004143). Patients in Arm A (n = 18) received neoadjuvant chemotherapy (NACT) (paclitaxel 200 mg m-2 and carboplatin area under the curve 5) followed by external radiotherapy (60 Gy/30 fractions/6 weeks). Patients in Arm B (n = 18) received NACT as in Arm A followed by AHFx-RT (48 Gy/20 fractions/4 weeks) with concomitant chemotherapy (cisplatin 30 mg m-2 weekly). Primary end points included comparative evaluation of overall locoregional response rates (ORRs) and progression-free survival (PFS). Secondary end points included toxicity, quality of life (QOL) and overall survival (OS). **RESULTS:** The median follow-up duration was 15 months. The ORR at first follow-up (72.2% vs 44%, p = 0.06) and at 1 year after treatment completion (61% vs 5.5%, p = 0.04) were superior in Arm B. The median PFS (17 vs 5.36 months; p = 0.053) and OS (24.73 vs 12.33 months; p = 0.007) were also superior in Arm B. Grade ≥3 acute pharyngitis/oesophagitis was less in Arm B (p = 0.05). Improvement of emotional function, cognitive function and chest pain was observed in Arm B. **CONCLUSION:** The study suggests that AHFx-RT-CT is feasible for locally advanced SCC of the lung with improved response rate, survival, QOL and favourable toxicity. Advances in knowledge: To the best of our knowledge, this is the first study comparing conventionally fractionated radiation with AHFx-RT-CT. Addition of low-dose weekly cisplatin as radiosensitizer may be the potential factor responsible for improved response rate, survival and favourable toxicity in the study arm despite lower biological effective dose.

Dose-Escalation Study of Thoracic Radiotherapy in Combination With Pemetrexed Plus Cisplatin in Japanese Patients With Locally Advanced Nonsquamous Non-Small Cell Lung Cancer: A Post Hoc Analysis of Survival and Recurrent Sites. Niho S1, Nokihara H, Nihei K, et al. Am J Clin Oncol. 2016 Apr;39(2):132-5. doi: 10.1097/COC.0000000000000030.
OBJECTIVES: We performed a post hoc analysis of progression-free survival (PFS), overall survival (OS), and recurrent sites in patients with locally advanced nonsquamous non-small cell lung cancer who

were enrolled in a phase I trial of combination chemotherapy consisting of pemetrexed plus cisplatin with concurrent thoracic radiotherapy. **METHODS:** Patients received pemetrexed (500 mg/m) plus cisplatin (75 mg/m) on day 1 every 3 weeks for 3 cycles plus concurrent thoracic radiotherapy consisting of 60 Gy (n=6) or 66 Gy (n=12); 4 to 6 weeks thereafter, patients received consolidation treatment with pemetrexed (500 mg/m) every 3 weeks for up to 3 cycles. We reviewed the medial records to collect data on progression, recurrent sites, late toxicity, and survival. **RESULTS:** No late radiation morbidity was observed. Thirteen patients (72%) exhibited disease progression: 8 patients had distant metastases, 8 patients had local recurrence (within the radiation field [n=6], outside the radiation field [n=2], and both [n=1]), and 3 patients had local recurrence plus distant metastases. The median PFS was 10.5 months (95% confidence interval [CI], 8.8-12.3), and the 3-year PFS rate was 28% (95% CI, 7.0-48.6). Ten of the 18 patients died of lung cancer. The median follow-up time for the censored cases was 42.8 months (range, 38.1 to 52.9 mo). The median OS was 27.3 months (95% CI, 13.1-41.6), and the 3-year OS rate was 50% (95% CI, 26.9-73.1). **CONCLUSIONS:** The median PFS and OS in our study were comparable to those of historical chemoradiotherapy controls.

A comparative study of the target volume definition in radiotherapy with «Slow CT Scan» vs. 4D PET/CT Scan in early stages non-small cell lung cancer. [Article in English, Spanish]
Molla M1, Anducas N2, Simó M3, et al. Rev Esp Med Nucl Imagen Mol. 2016 Apr 19. pii: S2253-654X(16)00025-1. doi: 10.1016/j.remn.2016.02.003. [Epub ahead of print]
OBJECTIVES: To evaluate the use of 4D PET/CT to quantify tumor respiratory motion compared to the «Slow»-CT (CTs) in the radiotherapy planning process. **MATERIAL AND METHODS:** A total of 25 patients with inoperable early stage non small cell lung cancer (NSCLC) were included in the study. Each patient was imaged with a CTs (4s/slice) and 4D PET/CT. The adequacy of each technique for respiratory motion capture was evaluated using the volume definition for each of the following: Internal target volume (ITV) 4D and ITVslow in relation with the volume defined by the encompassing volume of 4D PET/CT and CTs (ITVtotal). The maximum distance between the edges of the volume defined by each technique to that of the total volume was measured in orthogonal beam's eye view. **RESULTS:** The ITV4D showed less differences in relation with the ITVtotal in both the cranio-caudal and the antero-posterior axis compared to the ITVslow. The maximum differences were 0.36mm in 4D PET/CTand 0.57mm in CTs in the antero-posterior axis. 4D PET/CT resulted in the definition of more accurate (ITV4D/ITVtotal 0.78 vs. ITVs/ITVtotal 0.63), and larger ITVs (19.9 cc vs. 16.3 cc) than those obtained with CTs. **CONCLUSION:** Planning with 4D PET/CT in comparison with CTs, allows incorporating tumor respiratory motion and improving planning radiotherapy of patients in early stages of lung cancer.

Hypofractionated 3D radiotherapy for inoperable T1-3 N0-1 non-small-cell lung cancer. Mollà Armadà M1, Saez J2, Ramos M1, Giraldo A1, Seoane A2, Andreu J3, Simó M4, Giralt J1. Br J Radiol. 2016 Apr 7:20150824. [Epub ahead of print]
OBJECTIVE: This study assessed the toxicity and clinical outcomes of three-dimensional (3D) hypofractionated radiotherapy (HFRT) for medically inoperable T1-3 N0-1 non-small-cell lung cancer (NSCLC). **METHODS:** 34 patients with inoperable early-stage NSCLC were treated from August 2008 to April 2013. Prior to enrolment, patients were required to be evaluated by an experienced thoracic surgeon to determine the "operability". All received 57 Gy in 19 fractions followed by escalated doses of 3-Gy fractions, up to a total dose of 66 Gy using a 3D conformal technique. Toxicities were measured using the Common Terminology Criteria for Adverse Effects v. 4.0. **RESULTS:** The median follow-up was 33 months (7-74 months). Toxicity grades ≥3 were not observed. Local control (LC) was 80.4% at 2 years, whereas regional control (RC) was 78%. The overall survival (OS), time to progression (TTP) and time to distant metastasis (TTM) at 2 years were 60%, 59% and 80%, respectively. For patients with T1-2 N0 and a tumour size <45 mm (n = 19), rates of OS, TTP and TTM at 2 years were 71%, 75% and 94%,

respectively. LC and RC at 2 years were 85% and 94%, respectively. **CONCLUSION:** HFRT using 3.0-Gy fractions amounting to a total dose of 66 Gy is the recommended dose. A Phase 2 trial is warranted in order to assess the safety and efficacy of this fractionation scheme. Advances in knowledge: HFRT results in a favourable outcome in early-stage lung cancer without the usual restrictions in tumour size and/or location associated with previous treatment methods. No special equipment is required, therefore permitting its application in any centre.

Apparent diffusion coefficient (ADC) change on repeated diffusion-weighted magnetic resonance imaging during radiochemotherapy for non-small cell lung cancer: A pilot study. Weiss E1, Ford JC2, Olsen KM3, Karki K4, Saraiya S4, Groves R5, Hugo GD4. Lung Cancer. 2016 Jun;96:113-9. doi: 10.1016/j.lungcan.2016.04.001. Epub 2016 Apr 4.
OBJECTIVES: Serial diffusion-weighted magnetic resonance imaging (DW-MRI) during radiochemotherapy of non-small cell lung cancer (NSCLC) is analyzed to investigate the apparent diffusion coefficient (ADC) as a potential biomarker for tumor response. **METHODS:** Ten patients underwent DW-MRI prior to and at three and six weeks during radiochemotherapy. Three methods of contouring primary tumors (PT) were performed to evaluate the impact of tumor heterogeneity on ADC values: PTT: whole tumor volume; PTT-N: PTT-necrosis; PTL: small volume of presumed active tumor with low ADC value. Pretreatment and during-treatment absolute ADC values and ADC value changes were analyzed for PT and involved lymph nodes (LN). **RESULTS:** ADC values for PTT, PTT-N, PTL and LN increased by 8-14% (PT) and 15% (LN) at three weeks, and 19-26% and 23% at 6 weeks post initial treatment (p=0.04-0.002). Average percent ADC value increase was smaller than tumor volume regression (p=0.06-0.0005). Patients with overall survival <12 months had a lower increase of ADC values compared to longer surviving patients (p=0.008 for PTT). **CONCLUSIONS:**
Significant ADC value increases during radiochemotherapy for non-small cell lung cancer were observed. ADC value change during treatment appears to be an independent marker of patient outcome and warrants further investigation.

Impact of whole brain radiation therapy on CSF penetration ability of Icotinib in EGFR-mutated non-small cell lung cancer patients with brain metastases: Results of phase I dose-escalation study. Zhou L1, He J1, Xiong W1, et al. Lung Cancer. 2016 Jun;96:93-100. doi: 10.1016/j.lungcan.2016.04.003. Epub 2016 Apr 6.
OBJECTIVES: Whole-brain radiation therapy (WBRT) and epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are both treatment options for EGFR-mutated non-small cell lung cancer (NSCLC) patients with brain metastases. However, the dose-escalation toxicity and efficacy of combination therapy, and the effect of WBRT on cerebrospinal fluid (CSF) penetration of EGFR-TKIs are still unclear. **MATERIALS AND METHODS:** EGFR-mutated NSCLC patients with brain metastases were enrolled in this study, and the cohorts were constructed with a 3+3 design. The patients received icotinib with escalating doses (125-625mg, tid), and the concurrent WBRT (37.5Gy/15f/3weeks) started a week later. The CSF penetration rates of icotinib were tested before, immediately after, and 4 weeks after WBRT, respectively. Potential toxicities and benefits from dose-escalation treatment were analyzed. **RESULTS:** Fifteen patients were included in this study, 3 at each dose level from 125mg-375mg and 6 at 500mg with 3 occurred dose-limiting toxicities. The maximal tolerated dose of icotinib was 375mg tid in this combination therapy. There was a significant correlation between icotinib concentration in the CSF and plasma ($R(2)=0.599$, $P<0.001$). The CSF penetration rate of icotinib, from 1.2% to 9.7%, reached a maximum at 375mg (median, 6.1%). There was no significant difference for CSF penetration rates among the three test points (median, 4.1% vs. 2.8% vs. 2.8%, $P=0.16$). The intracranial objective response rate and median intracranial progression free survival are 80% and 18.9 months.

CONCLUSIONS: WBRT plus concurrent icotinib is well tolerated in EGFR-mutated NSCLC patients with brain metastases, up to an icotinib dose of 375mg tid. The icotinib CSF concentration seemed to have a potential ceiling effect with the dose escalation, and WBRT seemed to have no significant impact on CSF penetration of icotinib till 4 weeks after the treatment.

Dose escalation study of proton beam therapy with concurrent chemotherapy for stage III non-small cell lung cancer. Harada H1, Fuji H1, Ono A2, et al. Cancer Sci. 2016 Apr 25. doi: 10.1111/cas.12955. [Epub ahead of print]
The purpose of this study is to determine the recommended dose (RD) of proton beam therapy (PBT) for inoperable stage III non-small cell lung cancer (NSCLC). We tested two prescribed doses of PBT;66 Gy (relative biological effectiveness; RBE) in 33 fractions and 74 Gy (RBE) in 37 fractions in arms 1 and 2, respectively. The planning target volume (PTV) included the primary tumor and metastatic lymph nodes with adequate margins. Concurrent chemotherapy included intravenous cisplatin (60 mg/m2 , day 1) and oral S-1 (80, 100 or 120 mg based on body surface area, days 1-14), repeated as 4 cycles every 4 weeks. Dose-limiting toxicity (DLT) was defined as grade 3 or severe toxicities related to PBT during days 1-90. Each dose level was performed in 3 patients, and then escalated to the next level if no DLT occurred. When 1 patient developed a DLT, 3 additional patients were enrolled. Overall, nine patients (5 men, 4 women; median age, 72 years) were enrolled, including 6 in arm 1 and 3 in arm 2. The median follow-up time was 43 months, and the median progression-free survival was 15 months. In arm 1, grade 3 infection occurred in 1 of 6 patients, but no other DLT was reported. Similarly, no DLT occurred in arm 2. However, 1 patient in arm 2 developed grade 3 esophageal fistula at 9 months after the initiation of PBT. Therefore, we determined that 66 Gy (RBE) is the RD from overall clinical viewpoints.

SMALL CELL LUNG CANCER - SCLC

Growth suppression by MYC inhibition in small cell lung cancer cells with TP53 and RB1 inactivation. Fiorentino FP1, Tokgün E1, Solé-Sánchez S1, et al. Oncotarget. 2016 Apr 18. doi: 10.18632/oncotarget.8826. [Epub ahead of print]
Small cell lung cancer (SCLC) is the most aggressive type of lung cancer with high mortality. One of the MYC family genes, MYC, MYCL or MYCN, is amplified in ~20% of the SCLCs; therefore, MYC proteins are potential therapeutic targets in SCLC patients. We investigated the therapeutic impact of Omomyc, a MYC dominant negative, in a panel of SCLC cell lines. Strikingly, Omomyc suppressed the growth of all tested cell lines by inducing cell cycle arrest and/or apoptosis. Induction of G1 arrest by Omomyc was found to be dependent on the activation of CDKN1A, in part, through the TP73 pathway. Our results strongly indicate that SCLC cells carrying amplification of MYC, MYCL or MYCN are addicted to MYC function, suggesting that MYC targeting would be an efficient therapeutic option for SCLC patients.

Activation of the PI3K/mTOR Pathway following PARP Inhibition in Small Cell Lung Cancer. Cardnell RJ1, Feng Y2, Mukherjee S1, et al. PLoS One. 2016 Apr 7;11(4):e0152584. doi: 10.1371/journal.pone.0152584. eCollection 2016.
Small cell lung cancer (SCLC) is an aggressive malignancy with limited treatment options. We previously found that PARP is overexpressed in SCLC and that targeting PARP reduces cell line and tumor growth in preclinical models. However, SCLC cell lines with PI3K/mTOR pathway activation were relatively less sensitive to PARP inhibition. In this study, we investigated the proteomic changes in PI3K/mTOR and other pathways that occur following PAPR inhibition and/or knockdown in vitro and in vivo. Using reverse-phase protein array, we found the proteins most significantly upregulated following treatment with the PARP inhibitors olaparib and rucaparib were in the PI3K/mTOR pathway (p-mTOR, p-AKT,

and pS6) ($p \leq 0.02$). Furthermore, amongst the most significantly down-regulated proteins were LKB1 and its targets AMPK and TSC, which negatively regulate the PI3K pathway ($p \leq 0.042$). Following PARP knockdown in cell lines, phosphorylated mTOR, AKT and S6 were elevated and LKB1 signaling was diminished. Global ATP concentrations increased following PARP inhibition ($p \leq 0.02$) leading us to hypothesize that the observed increased PI3K/mTOR pathway activation following PARP inhibition results from decreased ATP usage and a subsequent decrease in stress response signaling via LKB1. Based on these results, we then investigated whether co-targeting with a PARP and PI3K inhibitor (BKM-120) would work better than either single agent alone. A majority of SCLC cell lines were sensitive to BKM-120 at clinically achievable doses, and cMYC expression was the strongest biomarker of response. At clinically achievable doses of talazoparib (the most potent PARP inhibitor in SCLC clinical testing) and BKM-120, an additive effect was observed in vitro. When tested in two SCLC animal models, a greater than additive interaction was seen ($p \leq 0.008$). The data presented here suggest that combining PARP and PI3K inhibitors enhances the effect of either agent alone in preclinical models of SCLC, warranting further investigation of such combinations in SCLC patients.

A phase II study of nintedanib in patients with relapsed small cell lung cancer. Han JY1, Kim HY2, Lim KY2, Hwangbo B2, Lee JS2. Lung Cancer. 2016 Jun;96:108-12. doi: 10.1016/j.lungcan.2016.04.002. Epub 2016 Apr 6.

OBJECTIVES: Nintedanib is an oral triple angiokinase inhibitor. This study was conducted to evaluate the efficacy and safety of nintedanib in patients (pts) with relapsed/refractory small cell lung cancer (SCLC). **PATIENTS AND METHODS:** Pts with an ECOG PS from 0 to 2 who exhibited progression after one or two prior chemotherapy or chemo/radiotherapy were enrolled. Pts received nintedanib 200mg BID daily in a 4-week cycle until progression or intolerable toxicity. The primary end point was the objective response rate (ORR). A two-stage design was employed. To continue to stage 2, ≥2 responders out of 22 pts were required. **RESULTS:** From Dec 2011 to June 2014, 24 pts were enrolled. Twenty-two pts completed treatment and were evaluable for response. The median follow-up was 9.7 (0.5-19.8) months. The median age was 64 (46-77) years. Twenty-two pts were male. Six pts had sensitive relapse. Eight pts received one prior chemotherapy. A median of one (range 1-5) cycle was administered. One pt had a partial response, and seven pts exhibited stable disease. The ORR was 5% (95% confidence interval [CI], 0.1-22.8). Median progression-free survival was 1.0 (95% CI, 0.9-1.1) month, and overall survival was 9.8 (95% CI, 8.4-11.2) months. The response criteria to proceed to full accrual were not met. The most frequent drug-related adverse events (AE) included hepatic enzyme elevation (86%), anemia (73%), anorexia (59%), and nausea (50%). Most AEs were mild and manageable. Grade 3 hepatic enzyme elevation occurred in 5 pts (23%). **CONCLUSIONS:** Nintedanib exhibited only limited activity with a manageable AE profile in relapsed or refractory SCLC (NCT01441297).

Is the canonical RAF-MEK-ERK signaling pathway a therapeutic target in SCLC? Cristea S1, Sage J2. J Thorac Oncol. 2016 Apr 28. pii: S1556-0864(16)30383-5. doi: 10.1016/j.jtho.2016.04.018. [Epub ahead of print]

The activity of the RAF-MEK-ERK signaling pathway is critical for the proliferation of normal and cancerous cells. Oncogenic mutations driving the development of lung adenocarcinoma often activate this signaling pathway. In contrast, pathway activity levels and their biological roles are not well established in small cell lung cancer (SCLC), a fast-growing neuroendocrine lung cancer subtype. Here we discuss the function of the RAF-MEK-ERK kinase pathway and the mechanisms leading to its activation in SCLC cells. In particular, we argue that activation of this pathway may be beneficial to the survival, proliferation and spread of SCLC cells in response to multiple stimuli. We also consider evidence that high levels of RAF-MEK-ERK pathway activity may be detrimental to SCLC tumors, including in part by interfering with their neuroendocrine fate. Based on these observations, we examine when small

molecules targeting kinases in the RAF-MEK-ERK pathway may be useful therapeutically in SCLC patients, including in combination with other therapeutic agents.

Survival analysis in second-line and third-line chemotherapy with irinotecan followed by topotecan or topotecan followed by irinotecan for extensive-stage small-cell lung cancer patients: a single-center retrospective study. Aktas G1, Kus T1, Kalender ME1, Sevinc A1, Camci C1, Kul S2. Onco Targets Ther. 2016 Apr 1;9:1921-6. doi: 10.2147/OTT.S101390. eCollection 2016.
PURPOSE: The number of patients who make it to receive third-line chemotherapy is increasing owing to the improvements in adverse-event management of chemotherapy for small-cell lung cancer (SCLC). Sequencing of optimal treatment for SCLC is still a challenge for oncologists. In this paper, we aim to present a different approach to the treatment of SCLC. **METHODS:** Between January 2008 and July 2014, all patients diagnosed with extensive-stage SCLC and treated with third-line chemotherapy at Gaziantep University Oncology Hospital were analyzed retrospectively. Disease control rates and progression-free survival (PFS) for first-, second-, and third-line chemotherapy, and overall survival (OS) were recorded. Survival analysis was calculated by using Kaplan-Meier method. **RESULTS:** A total of 255 SCLC patients were screened, and 25 of those patients who received third-line chemotherapy were included in this study. Median age was 57±10.131 years (range: 39-74 years). Disease control rates at first-, second-, and third-line chemotherapy were 92%, 68%, and 44%, respectively. Fourteen patients received irinotecan followed by topotecan, and eleven patients received topotecan followed by irinotecan. Second-line median PFS was statistically better in patients treated with irinotecan at second-line compared with those treated with topotecan (21 vs 12 weeks, P=0.018). Comparison of third-line median PFS of the two groups was not statistically significant (14 vs 12 weeks, P=0.986). Median OS was not statistically significant in patients who received irinotecan followed by topotecan vs those who received topotecan followed by irinotecan (18 vs 14 months, P=0.112). **CONCLUSION:** Sequential monotherapy with topotecan and irinotecan provides a considerable contribution to OS, and second-line irinotecan showed a better PFS, despite a similar OS, compared with topotecan.

PALLIATIVE AND SUPPORTIVE CARE

Oridonin inhibits gefitinib-resistant lung cancer cells by suppressing EGFR/ERK/MMP-12 and CIP2A/Akt signaling pathways. Xiao X1, He Z1, Cao W2, et al. Int J Oncol. 2016 Apr 15. doi: 10.3892/ijo.2016.3488. [Epub ahead of print]
Oridonin (Ori), a diterpenoid compound extracted from traditional medicinal herbs, elicits antitumor effects on many cancer types. However, whether Ori can be used in gefitinib-resistant non-small cell lung cancer (NSCLC) cells remains unclear. This study investigated the antitumor activity and underlying mechanisms of Ori. Results demonstrated that this compound dose-dependently inhibited the proliferation, invasion, and migration of the gefitinib-resistant NSCLC cells in vitro. Ori also significantly downregulated the phosphorylation of EGFR, ERK, Akt, expression levels of matrix metalloproteinase-12 (MMP-12), and the cancerous inhibitor of protein phosphatase 2A (CIP2A). In addition, Ori upregulated protein phosphatase 2A (PP2A) activity of gefitinib-resistant NSCLC cells. Ori combined with docetaxel synergistically inhibited these cells. Ori also inhibited tumor growth in murine models. Immunohistochemistry results further revealed that Ori downregulated phospho-EGFR, MMP-12, and CIP2A in vivo. These findings indicated that Ori can inhibit the proliferation, invasion, and migration of gefitinib-resistant NSCLC cells by suppressing EGFR/ERK/MMP-12 and CIP2A/PP2A/Akt signaling pathways. Thus, Ori may be a novel effective candidate to treat gefitinib-resistant NSCLC.

Weight Loss Associated with Platinum-Based Chemotherapy in Patients with Advanced Lung Cancer. Morio K, Minami T, Sozu T, Niki K, Kijima T, Uejima E, Morio K. Chemotherapy. 2016;61(5):256-61. doi: 10.1159/000443983. Epub 2016 Apr 1.
BACKGROUND: We examined whether the weight loss that occurs with platinum-based chemotherapy in lung cancer patients is associated with chemotherapy side effects, treatment completion rates and therapeutic effect. **METHODS:** We retrospectively reviewed charts of advanced lung cancer patients treated with ≥2 cycles of platinum-based chemotherapy. Patients were divided into 2 groups based on ≥5 or <5% weight loss. Relationships between weight loss and other variables were investigated. **RESULTS:** Among 114 patients, 18 (15.8%) experienced ≥5% weight loss. Significantly more patients with small-cell lung cancer (SCLC) than with non-SCLC were found to have ≥5% weight loss (30.8 vs. 11.4%, p = 0.023). Patients with ≥5% weight loss experienced higher incidences of grade 3-4 leukopenia (p = 0.008) and neutropenia (p = 0.005), and treatment completion rates were lower in this group (p = 0.035). Weight loss was not significantly associated with therapeutic effect. **CONCLUSION:** The weight loss in patients with advanced lung cancer receiving platinum-based chemotherapy is associated with SCLC, grade 3-4 leukopenia, neutropenia and a decrease in treatment completion rate.

Patterns of Palliative Care Consultation Among Elderly Patients With Cancer. Roeland EJ1, Triplett DP1, Matsuno RK1, et al. J Natl Compr Canc Netw. 2016 Apr;14(4):439-45.
BACKGROUND: The role of palliative care has expanded over the past several decades, although the oncology-specific regional evolution of this specialty has not been characterized at the population-based level. **METHODS:** This study defined the patterns of palliative care delivery using a retrospective cohort of patients with advanced cancer within the SEER-Medicare linked database. We identified 83,022 patients with metastatic breast, prostate, lung, and colorectal cancers. We studied trends between 2000 through 2009, and determined patient-level and regional-level predictors of palliative care delivery. **RESULTS:** Palliative care consultation rates increased from 3.0% in 2000 to 12.9% in 2009, with most consultations occurring in the last 4 weeks of life (77%) in the inpatient hospital setting. The rates of palliative care delivery were highest in the West (7.6%) and lowest in the South (3.2%). The likelihood of palliative care consultation increased with decreasing numbers of regional acute care hospital beds per capita. The use of palliative care consultation increased with increasing numbers of regional physicians. The use of palliative care decreased with increasing regional Medicare expenditure with a $1,387 difference per beneficiary between the first and fourth quartiles of palliative care use. **CONCLUSIONS:** Geographic location influences a patient's options for palliative care in the United States. Although the overall rates of palliative care are increasing, future effort should focus on improving palliative care services in regions with the least access.

Impact of self-reported physical activity and health promotion behaviors on lung cancer survivorship. Sloan JA1, Cheville AL2, Liu H3, et al. Health Qual Life Outcomes. 2016 Apr 29;14(1):66. doi: 10.1186/s12955-016-0461-3.
BACKGROUND: There is some initial evidence that an enhanced physical activity level can improve fquality of life, and possibly survival among patients with lung cancer. The primary aim of this project was to evaluate the impact of physical activity on the quality and quantity of life of lung cancer survivors. **METHODS:** Between January 1, 1997, and December 31, 2009, a total of 1466 lung cancer survivors completed a questionnaire with patient-reported outcomes for quality of life (QOL), demographics, disease and clinical characteristics, and a measure of physical activity (Baecke Questionnaire). Chi-square tests compared lung cancer survivors who reported being physically active versus not on a variety of the other covariates. Kaplan-Meier estimates and Cox models evaluated the prognostic importance of physical activity level on Overall Survival (OS). **RESULTS:** Roughly half of the lung cancer survivors had advanced stage disease at the time of survey. Treatment prevalence rates were 61, 54, and 33 % for

surgery, chemotherapy and radiotherapy, respectively. The majority (77 %) of survivors reported themselves as physically active. Physically active survivors reported greater activity across all individual Baecke items. Lung cancer survivor-reported QOL indicated the benefits of physical activity in all domains. Survivors receiving chemotherapy or radiation at the time of questionnaire completion were less likely to be physically active (74 and 73 % respectively). In contrast, 84 % of surgical patients were physically active. Disease recurrence rates were the same for physically active and inactive patients (81 % vs 82 %, $p = 0.62$). Physically active patients survived an average of 4 more years than those who were not physically active (8.4 years versus 4.4 years respectively, log rank $p < 0.0001$). **CONCLUSIONS:** Being physically active was related to profound advantages in QOL and survival in a large sample of lung cancer survivors.

Skeletal muscle radiodensity is prognostic for survival in patients with advanced non-small cell lung cancer. Sjøblom B1, Grønberg BH2, Wentzel-Larsen T3, et al. Clin Nutr. 2016 Apr 1. pii: S0261-5614(16)00101-1. doi: 10.1016/j.clnu.2016.03.010. [Epub ahead of print]
BACKGROUND & AIMS: Recent research indicates that severe muscular depletion (sarcopenia) is frequent in cancer patients and linked to cachexia and poor survival. Our aim was to investigate if measures of skeletal muscle hold prognostic information in advanced non-small cell lung cancer (NSCLC). **METHODS:** We included NSCLC patients with disease stage IIIB/IV, performance status 0-2, enrolled in three randomised trials of first-line chemotherapy (n = 1305). Computed tomography (CT) images obtained before start of treatment were used for body composition analyses at the level of the third lumbar vertebra (L3). Skeletal muscle mass was assessed by measures of the cross sectional muscle area, from which the skeletal muscle index (SMI) was obtained. Skeletal muscle radiodensity (SMD) was measured as the mean Hounsfield unit (HU) of the measured muscle area. A high level of mean HU indicates a high SMD. **RESULTS:** Complete data were available for 734 patients, mean age 65 years. Both skeletal muscle index (SMI) and muscle radiodensity (SMD) varied largely. Mean SMI and SMD were 47.7 cm2/m2 and 37.4 HU in men (n = 420), 39.6 cm2/m2 and 37.0 HU in women (n = 314). Multivariable Cox regression analyses, adjusted for established prognostic factors, showed that SMD was independently prognostic for survival (Hazard ratio (HR) 0.98, 95% CI 0.97-0.99, p = 0.001), whereas SMI was not (HR 0.99, 95% CI 0.98-1.01, p = 0.329). **CONCLUSION:** Low SMD is associated with poorer survival in advanced NSCLC. Further research is warranted to establish whether muscle measures should be integrated into routine practice to improve prognostic accuracy.

Using Perceived Self-efficacy to Improve Fatigue and Fatigability In Postsurgical Lung Cancer Patients: A Pilot Randomized Controlled Trial. Hoffman AJ1, Brintnall RA, Given BA, von Eye A, Jones LW, Brown JK. Cancer Nurs. 2016 Apr 29. [Epub ahead of print]
BACKGROUND: Fatigue remains a prevalent and debilitating symptom in persons with non-small cell lung cancer (NSCLC). Exercise has been shown to be effective in reducing fatigue, yet interventions are limited for postsurgical NSCLC patients. To date, while surgery is offered as a standard curative treatment for NSCLC, no formal guidelines exist for postsurgical rehabilitation. **OBJECTIVE:** This study focuses on the design and testing of a postsurgical intervention for NSCLC patients to promote perceived self-efficacy for fatigue self-management targeting cancer-related fatigue (CRF) severity and its associated fatigability through exercise. **METHODS:** A 2-arm randomized controlled trial was used to examine the impact of a 6-week rehabilitative CRF self-management exercise intervention on 37 NSCLC participants compared with 35 control group participants receiving usual care from diagnosis to 6 weeks' postsurgical hospital discharge. **RESULTS:** We exceeded goals for recruitment (66%), retention (97%), adherence (93%), and acceptability. Our 6-week exercise intervention demonstrated preliminary efficacy in significantly reducing CRF severity and fatigability as compared with usual care, with mean CRF levels restored to levels lower than presurgery. Likewise, the exercise group's functional performance

(physical and mental health scores) exceeded usual care. Furthermore, no adverse events were reported; participants had a mean age of 67 years and a mean of 8 comorbid conditions. **CONCLUSIONS:** An exercise intervention for postsurgical NSCLC patients is feasible, safe, and highly acceptable showing positive changes in CRF self-management. **IMPLICATIONS FOR PRACTICE:** To advance practice, testing of the effectiveness of this health-promoting self-management exercise intervention in a larger-scale randomized controlled trial is needed.

The relationship between coping strategies, quality of life, and mood in patients with incurable cancer. Nipp RD1, El-Jawahri A1, Fishbein JN2, et al. Cancer. 2016 Apr 18. doi: 10.1002/cncr.30025. [Epub ahead of print]
BACKGROUND: Patients with incurable cancer face many physical and emotional stressors, yet little is known about their coping strategies or the relationship between their coping strategies, quality of life (QOL), and mood. **METHODS:** As part of a randomized trial of palliative care, this study assessed baseline QOL (Functional Assessment of Cancer Therapy-General), mood (Hospital Anxiety and Depression Scale), and coping (Brief COPE) in patients within 8 weeks of a diagnosis of incurable lung or gastrointestinal cancer and before randomization. To examine associations between coping strategies, QOL, and mood, we used linear regression, adjusting for patients' age, sex, marital status, and cancer type. **RESULTS:** There were 350 participants (mean age, 64.9 years), and the majority were male (54.0%), were married (70.0%), and had lung cancer (54.6%). Most reported high utilization of emotional support coping (77.0%), whereas fewer reported high utilization of acceptance (44.8%), self-blame (37.9%), and denial (28.2%). Emotional support (QOL: $\beta = 2.65$, $P < .01$; depression: $\beta = -0.56$, $P = .02$) and acceptance (QOL: $\beta = 1.55$, $P < .01$; depression: $\beta = -0.37$, $P = .01$; anxiety: $\beta = -0.34$, $P = .02$) correlated with better QOL and mood. Denial (QOL: $\beta = -1.97$, $P < .01$; depression: $\beta = 0.36$, $P = .01$; anxiety: $\beta = 0.61$, $P < .01$) and self-blame (QOL: $\beta = -2.31$, $P < .01$; depression: $\beta = 0.58$, $P < .01$; anxiety: $\beta = 0.66$, $P < .01$) correlated with worse QOL and mood. **CONCLUSIONS:** Patients with newly diagnosed, incurable cancer use a variety of coping strategies. The use of emotional support and acceptance coping strategies correlated with better QOL and mood, whereas the use of denial and self-blame negatively correlated with these outcomes. Interventions to improve patients' QOL and mood should seek to cultivate the use of adaptive coping strategies.

Cachexia among US cancer patients. Arthur ST1, Van Doren BA1, Roy D1, Noone JM1, Zacherle E1, Blanchette CM1. J Med Econ. 2016 Apr 21:1-22. [Epub ahead of print]
BACKGROUND: Cancer cachexia is a debilitating condition and results in poor prognosis. The purpose of this study was to assess hospitalization incidence, patient characteristics, and medical cost and burden of cancer cachexia in the United States. **METHODS:** We used a cross sectional analysis of the Nationwide Inpatient Sample (NIS) for 2009. Five cancers reported to have the highest cachexia incidence were assessed. We estimated the hospitalization incidence related to cachexia by cancer type, and compared cost and length of stay and reported descriptive statistics for each cancer type, as well as compared differences between patients with and without cachexia. **RESULTS:** Risk of inpatient death was higher for patients with cachexia in lung cancer (OR = 1.32; CI = 1.20-1.46) and in all cancers combined (OR = 1.76; CI = 1.67-1.85). The presence of cachexia increased length of stay in lung (IRR = 1.05; CI = 1.03-1.08), Kaposi's sarcoma (IRR = 1.47; CI = 1.14-1.89) and all cancers combined (IRR = 1.09; CI = 1.08-1.10). Additionally, cachectic patients in the composite category had a longer hospitalization stay compared to non-cachectic patients (3-9 days for those with cachexia and 2-7 days for those without cachexia). The cost of inpatient stay was significantly higher in cachexic than non-cachexic lung cancer patients ($13,560 vs. $13,190; p<.0001), as well as cachexic versus non-cachexic cancer patients in general (14,751 vs. 13,928; p<.0001). **CONCLUSIONS:** Cachexia increases hospitalization costs and length of stay in several cancer types. Identifying the medical burden associated with cancer

cachexia will assist in developing an international consensus for recognition and coding by the medical community and ultimately an effective treatment plans for cancer cachexia.

COMPLEMENTARY & ALTERNATIVE THERAPY

Metastasized lung cancer suppression by Morinda citrifolia (Noni) leaf compared to Erlotinib via anti-inflammatory, endogenous antioxidant responses and apoptotic gene activation. Lim SL1, Mustapha NM2, Goh YM2, Bakar NA1, Mohamed S3. Mol Cell Biochem. 2016 Apr 22. [Epub ahead of print]

Metastasized lung and liver cancers cause over 2 million deaths annually, and are amongst the top killer cancers worldwide. Morinda citrifolia (Noni) leaves are traditionally consumed as vegetables in the tropics. The macro and micro effects of M. citrifolia (Noni) leaves on metastasized lung cancer development in vitro and in vivo were compared with the FDA-approved anti-cancer drug Erlotinib. The extract inhibited the proliferation and induced apoptosis in A549 cells (IC50 = 23.47 μg/mL) and mouse Lewis (LL2) lung carcinoma cells (IC50 = 5.50 μg/mL) in vitro, arrested cancer cell cycle at G0/G1 phases and significantly increased caspase-3/-8 without changing caspase-9 levels. The extract showed no toxicity on normal MRC5 lung cells. Non-small-cell lung cancer (NSCLC) A549-induced BALB/c mice were fed with 150 and 300 mg/kg M. citrifolia leaf extract and compared with Erlotinib (50 mg/kg body weight) for 21 days. It significantly increased the pro-apoptotic TRP53 genes, downregulated the pro-tumourigenesis genes (BIRC5, JAK2/STAT3/STAT5A) in the mice tumours, significantly increased the anti-inflammatory IL4, IL10 and NR3C1 expression in the metastasized lung and hepatic cancer tissues and enhanced the NFE2L2-dependent antioxidant responses against oxidative injuries. The extract elevated serum neutrophils and reduced the red blood cells, haemoglobin, corpuscular volume and cell haemoglobin concentration in the lung cancer-induced mammal. It suppressed inflammation and oedema, and upregulated the endogenous antioxidant responses and apoptotic genes to suppress the cancer. The 300 mg/kg extract was more effective than the 50 mg/kg Erlotinib for most of the parameters measured.

Acupuncture for Dyspnea in Lung Cancer: Results of a Feasibility Trial. Bauml J1, Haas A2, Simone CB 2nd3, Li SQ4, Cohen RB5, Langer CJ5, Mao JJ6. Integr Cancer Ther. 2016 Apr 24. pii: 1534735415624138. [Epub ahead of print]

PURPOSE: Dyspnea is a common and distressing symptom for patients with lung cancer (LC) because of disease burden, therapy toxicity, and comorbid illnesses. Acupuncture is a centuries-old therapy with biological plausibility for relief of dyspnea in this setting. This pilot study aimed to evaluate the feasibility and preliminary effectiveness of acupuncture for dyspnea among patients with LC. **METHODS:** Eligible patients had a diagnosis of LC and clinically significant dyspnea without a clear organic cause. The treatment consisted of 10 weekly acupuncture sessions, with a follow-up visit 4 weeks after therapy. The primary outcome was dyspnea severity as measured using a validated Numerical Rating Scale (NRS) of 0 to 10 (10 being "most severe shortness of breath imaginable"). **RESULTS:** We enrolled 12 patients in the study. The median age was 64.5 years; 66.7% of the patients were female, and 66.7% were Caucasians. Among those enrolled, 10 (83.3%) were able to complete all 10 acupuncture sessions. Acupuncture was well tolerated; adverse events were mild and self-limited. Mean (SD) dyspnea scores on the NRS improved from 6.3 (1.7) at baseline to 3.6 (1.9; $P = .003$) at the end of treatment and 3.2 (2.3; $P = .008$) at follow-up. Fatigue and quality of life also improved significantly with acupuncture ($P < .05$). **CONCLUSION:** Among patients with LC, acupuncture was well tolerated and exhibited promising preliminary beneficial effects in the treatment of dyspnea, fatigue, and quality of life. Performing a trial in this population appears feasible.

MISCELLANEOUS WORKS

The Effect of Receiving Treatment Within a Clinical Trial Setting on Survival and Quality of Care Perception in Advanced Stage Non-Small Cell Lung Cancer. Abu-Hejleh T1, Chrischilles EA, Halfdanarson TR, et al. Am J Clin Oncol. 2016 Apr;39(2):126-31. doi: 10.1097/COC.0000000000000029.

OBJECTIVES: Treatment outcomes of advanced stage (IIIB and IV) non-small cell lung cancer (NSCLC) are poor. In this study, we explore the survival outcomes and the perception of the quality of care delivered in stage IIIB and IV NSCLC patients treated within versus outside a clinical trial. **MATERIALS AND METHODS:** Data were obtained from the Cancer Care Outcomes Research and Surveillance Consortium (CanCORS). Baseline characteristics according to clinical trial participation were determined. The association between clinical trial enrollment and survival was assessed using a Cox proportional hazard model after adjusting for age, income, primary data collection and research site, comorbidities, self-reported performance status, presence of brain metastasis, stage IIIB versus IV, and cancer histology. **RESULTS:** Of 815 stage IIIB and IV NSCLC patients, 56 (7%) were enrolled in clinical trials. Median survival for the patients treated within versus outside a clinical trial was 20.5 versus 16.7 months, respectively (P=0.21). Using a multivariate survival model, clinical trial enrollment did not correlate with longer survival (P=0.81). Comparing patients according to clinical trial enrollment, patients treated within a clinical trial setting perceived a better overall quality of care (P<0.01). **CONCLUSIONS:** Management of stage IIIB and IV NSCLC patients within a clinical trial setting conveyed a perception of superior care that did not translate into survival benefit. These findings suggest that providing cancer care within a clinical trial should not imply a survival benefit when counseling stage IIIB and IV NSCLC patients about entering clinical trials.

Pan-cancer analysis of copy number changes in programmed death-ligand 1 (PD-L1, CD274) - associations with gene expression, mutational load and survival. Budczies J1,2, Bockmayr M1, Denkert C1,2, et al. Genes Chromosomes Cancer. 2016 Apr 22. doi: 10.1002/gcc.22365. [Epub ahead of print]

Inhibition of the PD-L1 (CD274) - PD-1 axis has emerged as a powerful cancer therapy that prevents evasion of tumor cells from the immune system. While immunohistochemical detection of PD-L1 was introduced as a predictive biomarker with variable power, much less is known about copy number alterations (CNA) affecting PD-L1 and their associations with expression levels, mutational load and survival. To gain insight, we employed The Cancer Genome Atlas (TCGA) datasets to comprehensively analyze 22 major cancer types for PD-L1 CNAs. We observed a diverse landscape of PD-L1 CNAs, which affected focal regions, chromosome 9p or the entire chromosome 9. Deletions of PD-L1 were more frequent than gains (31% vs. 12%) with deletions being most prevalent in melanoma and non-small cell lung cancer. Copy number gains most frequently occurred in ovarian cancer, head and neck cancer, bladder cancer, cervical and endocervical cancer, sarcomas, and colorectal cancers. Fine-mapping of the genetic architecture revealed specific recurrently amplified and deleted regions across cancers with putative biological and clinical consequences. We noted a strong correlation between PD-L1 CNAs and mRNA expression levels for most cancers and found tumors with PD-L1 gains to harbor significantly higher mutational loads compared to non-amplified cases (median: 78 non-synonymous mutations vs. 40, p=7.1e-69). Moreover, we observed that, in general, both PD-L1 amplifications and deletions were associated with dismal prognosis. In conclusion, PD-L1 CNAs, in particular PD-L1 copy number gains, represent frequent genetic alterations across many cancers, which influence PD-L1 expression levels, are associated with higher mutational loads, and may be exploitable as predictive biomarker for immunotherapy regimens.

Specialty pharmacy services for patients receiving oral medications for solid tumors. Stein J1, Mann J2. Am J Health Syst Pharm. 2016 Apr 28. pii: ajhp150863. [Epub ahead of print]
PURPOSE: Currently available oral oncology therapies are reviewed, and specialty pharmacy services for patients receiving these drugs are described. **SUMMARY:** Market introductions of new oral oncology drugs have increased substantially over the past decade, and 25-30% of all oncology agents in development are oral medications. Oral agents for treatment of breast cancer include capecitabine, lafatinib, and palbociclib. Several oral agents are used in treating patients with lung cancer driven by mutations of genes coding for anaplastic lymphoma kinase (ALK) and epidermal growth factor receptor (EGFR); currently available agents include the ALK inhibitors certinib and crizotinib and the EGFR inhibitors afatinib, erlotinib, and gefitinib. Four oral targeted therapies are used in the treatment of melanoma associated with the B-Raf proto-oncogene, BRAF: cobimetinib, dabrafenib, trametinib, and vemurafenib. Oral agents for treatment of prostate cancer include abiraterone acetate and enzalutamide. Oral agents for treatment of renal cell carcinoma include axitinib, everolimus, pazopanib, sorafenib, and sunitinib. Specialty pharmacy services for patients receiving oral oncology agents can include (1) providing patient counseling and education on adverse effects and self-management strategies, (2) processing prior-authorization requests and helping patients navigate copayment assistance programs, and (3) monitoring for medication toxicities and recommending dose adjustments as appropriate.
CONCLUSION: Many oral oncology medications have been introduced over the past 10-15 years, with many others in clinical development. Due to the complexity of initiating and monitoring patients receiving these oral therapies, specialty pharmacy services are an essential component of many patients' cancer care.