Caring Ambassadors Lung Cancer Program

Literature Review, January 2016

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Preclinical Investigation of the Novel Histone Deacetylase Inhibitor AR-42 in the Treatment of Cancer-Induced Cachexia. Tseng YC1, Kulp SK1, Lai IL1, et al. J Natl Cancer Inst. 2015 Oct 12;107(12):djv274. doi: 10.1093/jnci/djv274. Print 2015 Dec.

BACKGROUND: Cancer cachexia is a debilitating condition that impacts patient morbidity, mortality, and quality of life and for which effective therapies are lacking. The anticachectic activity of the novel HDAC inhibitor AR-42 was investigated in murine models of cancer cachexia. **METHODS:** The effects of AR-42 on classic features of cachexia were evaluated in the C-26 colon adenocarcinoma and Lewis lung carcinoma (LLC) models. Effects on survival in comparison with approved HDAC inhibitors (vorinostat, romidepsin) were determined. The muscle metabolome and transcriptome (by RNA-seq), as well as serum cytokine profile, were evaluated. Data were analyzed using mixed effects models, analysis of variance, or log-rank tests. All statistical tests were two-sided. **RESULTS:** In the C-26 model, orally administered AR-42 preserved body weight (23.9±2.6 grams, AR-42-treated; 20.8±1.3 grams, vehicle-treated; $P = .005$), prolonged survival ($P < .001$), prevented reductions in muscle and adipose tissue mass, muscle fiber size, and muscle strength and restored intramuscular mRNA expression of the E3 ligases MuRF1 and Atrogin-1 to basal levels ($n = 8$). This anticachectic effect, confirmed in the LLC model, was not observed after treatment with vorinostat and romidepsin. AR-42 suppressed tumor-induced changes in inflammatory cytokine production and multiple procachexia drivers (IL-6, IL-6Rα, leukemia inhibitory factor, Foxo1, Atrogin-1, MuRF1, adipose triglyceride lipase, uncoupling protein 3, and myocyte enhancer factor 2c). Metabolomic analysis revealed cachexia-associated changes in glycolysis, glycogen synthesis, and protein degradation in muscle, which were restored by AR-42 to a state characteristic of tumor-free mice. **CONCLUSIONS:** These findings support further investigation of AR-42 as part of a comprehensive therapeutic strategy for cancer cachexia.

Naringenin ameliorates inflammation and cell proliferation in benzo(a)pyrene induced pulmonary carcinogenesis by modulating CYP1A1, NFκB and PCNA expression.
Bodduluru LN1, Kasala ER2, Madhana RM2, et al. Int Immunopharmacol. 2016 Jan;30:102-10. doi: 10.1016/j.intimp.2015.11.036. Epub 2015 Dec 4.

Lung cancer is the major cause of cancer-related mortality and is a growing economic burden worldwide. Chemoprevention has emerged as a very effective preventive measure against carcinogenesis and several bioactive compounds in diet have shown their cancer curative potential on lung cancer. Naringenin (NRG), a predominant flavanone found in citrus fruits has been reported to possess anti-oxidative, anti-inflammatory and anti-proliferative activity in a wide variety of cancer. The aim of the present study is to divulge the chemopreventive nature of NRG against benzo(a)pyrene (B[a]P) induced lung carcinogenesis in Swiss albino mice. Administration of B[a]P (50mg/kg, p.o.) to mice resulted in increased lipid peroxidation (LPO), proinflammatory cytokines (TNF-α, IL-6 and IL-1β) with subsequent decrease in activities of tissue enzymic antioxidants (SOD, CAT, GPx, GR, GST) and non-enzymic antioxidants (GSH and Vit-C). Treatment with NRG (50mg/kg body weight) significantly counteracted all these alterations thereby showing potent anti-cancer effect in lung cancer. Moreover, assessment of protein expression by immunoblotting and mRNA expression by RT-PCR revealed that NRG treatment effectively negates B[a]P-induced upregulated expression of CYP1A1, PCNA and NF-κB. Further, the antiproliferative effect of NRG was confirmed by histopathological analysis and PCNA immunostaining in B[a]P induced mice which showed increased PCNA expression that was restored upon NRG administration. Overall, these findings substantiate the chemopreventive potential of NRG against chemically induced lung cancer in mice.

Whole exome sequencing reveals genetic variability among lung cancer cases sub-phenotyped for emphysema. Lusk CM1, Wenzlaff AS1, Dyson G1, et al. Carcinogenesis. 2015 Dec 30. pii: bgv248. [Epub ahead of print]

Lung cancer continues to be a major public health challenge in the United States, despite efforts to decrease the prevalence of smoking; outcomes are especially poor for African American patients compared to other races/ethnicities. Chronic obstructive pulmonary disease (COPD) co-occurs with lung cancer frequently, but not always, suggesting both shared and distinct risk factors for these two diseases. To identify germline genetic variation that distinguishes between lung cancer in the presence and absence of emphysema, we performed whole exome sequencing on 46 African American lung cancer cases (23 with and 23 without emphysema frequency matched on age, sex, histology and pack years). Using conditional logistic regression, we found 6,305 variants (of 168,150 varying sites) significantly associated with lung cancer sub-phenotype ($p \leq 0.05$). Next, we validated 10 of these variants in an independent set of 612 lung cancer cases (267 with emphysema, 345 without emphysema) from the same population of inference as the sequenced cases. We found one variant that was significantly associated with lung cancer sub-phenotype in the validation sample. These findings contribute to teasing apart shared genetic factors from independent genetic factors for lung cancer and COPD.

Single-cell detection of EGFR gene mutation in circulating tumor cells in lung cancer. Shuai S1, Yuliang D1. Yi Chuan. 2015 Dec;37(12):1251-7. doi: 10.16288/j.yczz.15-130.

Circulating tumor cells (CTCs) are cells that shed from a primary tumor and enter the peripheral blood circulation. The CTCs are closely associated with tumor development and metastasis because of its high heterogeneity. However, there are still no effective methods to detect single-cell heterogeneity of the CTCs. To this end, we developed a method to detect gene mutation in CTCs at the single-cell level and applied it to the detection of EGFR gene mutation in single lung cancer CTC. Specifically, the rare CTCs were captured from blood using an integrated microfluidic system, and then were released into a microchip with thousands of nanoliter wells to isolate single CTC. The single CTC was then transferred into a PCR tube under the microscope for single-cell genome amplification and detection of EGFR gene mutation. We firstly modified chip and capillary and optimized PCR conditions (annealing temperature, number of cycles) using non-small-cell lung cancer (NSCLC) cell lines A549, NCI-H1650 and NCI-H1975 as samples, which showed maximal amplification after 30 cycles with an annealing temperature at

59℃. We then successfully detected blood samples from NSCLC patients using this method. 5 CTCs were obtained from 2 mL patient's blood and the sequencing of EGFR exons 18, 19, 20 and 21 showed no mutations. Our results demonstrated that this method is sensitive enough to detect gene mutation in single CTC and has guiding significance in clinic research.

Molecular basis of antibody binding to mucin glycopeptides in lung cancer. Qu J1, Yu H2, Li F3, et al. Int J Oncol. 2016 Feb;48(2):587-94. doi: 10.3892/ijo.2015.3302. Epub 2015 Dec 18.
Glycopeptides bearing Tn epitopes are emerging targets for cancer diagnosis and immunotherapy. In this study, we analyzed membrane proteins containing O-glycosylated tandem repeat (TR) sequences in lung cancer patients of different types and stages, using gene microarray data in public domain. The expression of Tn and glycopeptide epitopes on the surface of lung cancer cell lines were studied by monoclonal IgG antibodies 14A, 16A, and B72.3. The binding of mAbs to synthetic glycopeptides were studied by surface plasmon resonance. Nine mucin mRNAs were found to be expressed in lung cancer patients but at similar level to healthy individuals. At protein level, a glycopeptide epitope on cancer cell surface is preferably recognized by mAb 16A, as compared to peptide-alone (14A) or sugar-alone epitopes (B72.3). 14A and 16A favor clustered TR containing more than three TR sequences, with 10-fold lower Kd than two consecutive TR. B72.3 preferrably recognized clustered sialyl-Tn displayed on MUC1 but not other O-glycoproteins, with 100-fold stronger binding when MUC1 is transfected as a sugar carrier, while the total sugar epitopes remain unchanged. These findings indicate that clusters of both TR backbones and sugars are essential for mAb binding to mucin glycopeptides. Three rules of antibody binding to mucin glycopeptides at molecular level are presented here: first, the peptide backbone of a glycopeptide is preferentially recognized by B cells through mutations in complementarity determining regions (CDRs) of B cell receptor, and the sugar-binding specificity is acquired through mutations in frame work of heavy chain; secondly, consecutive tandem repeats (TR) of peptides and glycopeptides are preferentially recognized by B cells, which favor clustered TR containing more than three TR sequences; thirdly, certain sugar-specific B cells recognize and accommodate clustered Tn and sialyl-Tn displayed on the surface of a mucin but not other membrane proteins.

Differential Serum Cytokine Levels and Risk of Lung Cancer between African and European Americans. Pine SR1, Mechanic LE2, Enewold L3, et al. Cancer Epidemiol Biomarkers Prev. 2015 Dec 28. pii: cebp.0378.2015. [Epub ahead of print]
BACKGROUND: African Americans have a higher risk of developing lung cancer than European Americans. Previous studies suggested that certain circulating cytokines were associated with lung cancer. We hypothesized that variations in serum cytokine levels exist between African Americans and European Americans, and increased circulating cytokine levels contribute to lung cancer differently in the two races. **METHODS:** Differences in ten serum cytokine levels, interleukin (IL)-1β, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, granulocyte macrophage colony-stimulating factor (GMCSF), interferon (IFN)-γ and tumor necrosis factor (TNF)-α between 170 African-American and 296 European-American controls from the National Cancer Institute-Maryland (NCI-MD) case-control study were assessed. Associations of the serum cytokine levels with lung cancer were analyzed. Statistically significant results were replicated in the prospective Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial and the Wayne State University (WSU) Karmanos Cancer Institute case-control study. **RESULTS:** Six cytokines: IL-4, IL-5, IL-8, IL-10, IFNγ, and TNFα, were significantly higher among European-American as compared to African-American controls. Elevated IL-6 and IL-8 levels were associated with lung cancer among both races in all three studies. Elevated IL-1β, IL-10 and TNFα levels were associated with lung cancer only among African Americans. The association between elevated TNFα levels and lung cancer among European Americans was significant after adjustment for additional factors. **CONCLUSIONS:** Serum cytokine levels vary by race and might contribute to lung cancer differently between African Americans

and European Americans. **IMPACT:** Future work examining risk prediction models of lung cancer can measure circulating cytokines to accurately characterize risk within racial groups.

Tumor-suppressive microRNA-29 family inhibits cancer cell migration and invasion directly targeting LOXL2 in lung squamous cell carcinoma. Mizuno K1, Seki N2, Mataki H1, et al. Int J Oncol. 2016 Feb;48(2):450-60. doi: 10.3892/ijo.2015.3289. Epub 2015 Dec 14.
Lung cancer remains the most frequent cause of cancer-related death in developed countries. A recent molecular-targeted strategy has contributed to improvement of the remarkable effect of adenocarcinoma of the lung. However, such treatment has not been developed for squamous cell carcinoma (SCC) of the disease. Our recent studies of microRNA (miRNA) expression signatures of human cancers showed that the microRNA-29 family (miR 29a, miR 29b and miR 29c) significantly reduced cancer tissues compared to normal tissues. These findings suggest that miR 29s act as tumor-suppressors by targeting several oncogenic genes. The aim of the study was to investigate the functional significance of miR 29s in lung SCC and to identify miR 29s modulating molecular targets in lung SCC cells. Restoration of all mature members of the miR 29s inhibited cancer cell migration and invasion. Gene expression data combined in silico analysis and luciferase reporter assays demonstrated that the lysyl oxidase-like 2 (LOXL2) gene was a direct regulator of tumor suppressive miR 29s. Moreover, overexpressed LOXL2 was confirmed in lung SCC clinical specimens, and silencing of LOXL2 inhibited cancer cell migration and invasion in lung SCC cell lines. Our present data suggested that loss of tumor-suppressive miR 29s enhanced cancer cell invasion in lung SCC through direct regulation of oncogenic LOXL2. Elucidation of the novel lung SCC molecular pathways and targets regulated by tumor-suppressive miR 29s will provide new insights into the potential mechanisms of oncogenesis and metastasis of the disease.

SCREENING, DIAGNOSIS AND STAGING

Management of Pulmonary Nodules by Community Pulmonologists: A Multicenter Observational Study. Tanner NT, Aggarwal J, Gould MK, Kearney P, Diette G, Vachani A, Fang KC, Silvestri GA. Chest. 2015 Dec 1;148(6):1405-14. doi: 10.1378/chest.15-0630.
BACKGROUND: Pulmonary nodules (PNs) are a common reason for referral to pulmonologists. The majority of data for the evaluation and management of PNs is derived from studies performed in academic medical centers. Little is known about the prevalence and diagnosis of PNs, the use of diagnostic testing, or the management of PNs by community pulmonologists. **METHODS:** This multicenter observational record review evaluated 377 patients aged 40 to 89 years referred to 18 geographically diverse community pulmonary practices for intermediate PNs (8-20 mm). Study measures included the prevalence of malignancy, procedure/test use, and nodule pretest probability of malignancy as calculated by two previously validated models. The relationship between calculated pretest probability and management decisions was evaluated. **RESULTS:** The prevalence of malignancy was 25% (n = 94). Nearly one-half of the patients (46%, n = 175) had surveillance alone. Biopsy was performed on 125 patients (33.2%). A total of 77 patients (20.4%) underwent surgery, of whom 35% (n = 27) had benign disease. PET scan was used in 141 patients (37%). The false-positive rate for PET scan was 39% (95% CI, 27.1%-52.1%). Pretest probability of malignancy calculations showed that 9.5% (n = 36) were at a low risk, 79.6% (n = 300) were at a moderate risk, and 10.8% (n = 41) were at a high risk of malignancy. The rate of surgical resection was similar among the three groups (17%, 21%, 17%, respectively; P = .69). **ONCLUSIONS:** A substantial fraction of intermediate-sized nodules referred to pulmonologists ultimately prove to be lung cancer. Despite advances in imaging and nonsurgical biopsy techniques, invasive sampling of low-risk nodules and surgical resection of benign nodules remain common, suggesting a lack of adherence to guidelines for the management of PNs.

Improved Lung Cancer Detection in Cardiovascular Outpatients by the Pulmonologist-based Interpretation of Chest Radiographs. Sakai M1, Kato A, Kobayashi N, Nakamura R, Okawa S, Sato Y. Intern Med. 2015;54(23):2991-7. doi: 10.2169/internalmedicine.54.4171. Epub 2015 Dec 1.
OBJECTIVE: Pulmonologists and cardiologists view chest radiographs differently. Lung cancer may therefore go undetected in patients referred to cardiovascular departments. We aimed to determine the clinical benefit of the additional interpretation of chest radiographs by pulmonologists in study involving cardiovascular outpatients. **METHODS:** A retrospective review of chest radiographs of outpatients attending a Japanese cardiovascular hospital between April 2000 and March 2010 was conducted. Lung cancer patients were categorized into 3 groups: group C, patients in whom tumors were detected by a cardiologist at the first visit; group P, patients in whom tumors were detected by the additional interpretation of a chest radiographs by a pulmonologist after a lesion was missed by a cardiologist; and group H, patients from an earlier period in which chest radiographs were only examined by a cardiologist. **RESULTS:** Cardiologists detected 9 cases of lung cancer in groups C and H from 2,430 and 2,288 radiographs, respectively. Pulmonologists detected 10 cases of lung cancer (group P) and 3 other malignancies that were previously undetected, giving a miss rate of 52.6% for the cardiologists. Tumor diameters were significantly smaller in group P than in group C or H. Furthermore, a significantly higher number of the tumors in group P were of an early stage and resectable, with more superposing structures than in groups C or H. **CONCLUSION:** The additional pulmonologist-based interpretations significantly increased the detection rate of operable tumors that mostly corresponded to the early T1 stage; this serves offers a potential clinical benefit in reducing the period of time from patient presentation to the diagnosis of lung cancer.

Using "residual" FNA rinse and body fluid specimens for next-generation sequencing: An institutional experience. Wei S1, Lieberman D1, Morrissette JJ1, Baloch ZW1, Roth DB1, McGrath C1. Cancer Cytopathol. 2015 Dec 18. doi: 10.1002/cncy.21666. [Epub ahead of print]
BACKGROUND: Tissue specimens are typically considered optimal for molecular testing; however, in the current era of personalized medicine, cytopathology specimens are increasingly recognized as potential sources for molecular testing. This is often accomplished by using cell block specimens and/or fine-needle aspiration (FNA) smear preparations. In this study, the authors investigated the feasibility, performance, and quality of "residual" FNA rinse and body effusion fluids used for next-generation sequencing (NGS). **METHODS:** Sequence data were generated from 17 malignancies in 16 patients from 13 FNA (10 lymph nodes, 1 lung, and 2 bone lesions) and 4 effusion (3 pleural and 1 pericardial) specimens. Malignancies included carcinomas (lung, breast, ovarian, and unknown primary), melanoma, and myeloma. Paired NGS testing was performed in 7 patients who had surgical biopsy or cell block specimens available. Routinely processed residual FNA rinse material and body fluids were used for DNA extraction and NGS (targeted gene panel). **RESULTS:** NGS was successfully performed on all 17 specimens. A significant amount of DNA was obtained from the residual FNA rinse (176.3 ng/μL) compared with the paired cell block slides (10.6 ng/μL). Two of the 10 lung adenocarcinomas (20%) demonstrated epidermal growth factor receptor (EGFR) mutations, including 1 leucine-to-arginine substitution at codon 858 (L858R) in exon 21 and 1 codon 2235_2249 deletion (resulting in an in-frame deletion of 5 amino acids from position 746 to 750 [glutamic acid, leucine, arginine, glutamic acid, and alanine]; E746_A750del) in exon 19. Three KRAS [Kirsten rat sarcoma viral oncogene homolog] mutations, 1 BRAF (v-Raf murine sarcoma viral oncogene homolog B1) mutation, and 1 NRAS (neuroblastoma RAS viral oncogene homolog) mutation were identified in the remaining lung adenocarcinomas. Patients who underwent paired testing demonstrated 100% concordant mutations. **CONCLUSIONS:** Targeted NGS can be performed on residual FNA rinse and body fluid specimens. This approach is particularly important when a paucicellular cell block or biopsy specimen is encountered.

Clinical implications of positive margins following non-small cell lung cancer surgery. Predina JD1, Keating J1, Patel N1, Nims S1, Singhal S1. J Surg Oncol. 2015 Dec 30. doi: 10.1002/jso.24130. [Epub ahead of print]
Positive margins following pulmonary resection of non-small cell lung cancer (NSCLC) occur in approximately 5-15% of patients undergoing a curative procedure. The presence of positive margins negatively impacts long-term outcomes by setting the stage for local and potentially distant disease recurrence. Despite major clinical ramifications, there are very few dedicated reports that examine the implications of positive margins following surgery for NSCLC. Furthermore, published series are typically retrospective studies from single institutions. In this review we analyze published data with special consideration of four pertinent questions: (i) what are the long term outcomes of a positive margin following pulmonary resection?, (ii) is intraoperative margin assessment by frozen section reliable?, (iii) what is the optimal distance of the tumor margin to the surgical margin?, and (iv) should adjuvant chemotherapy and/or radiation therapy be used in the setting of a positive surgical margin?

Role of race in oncogenic driver prevalence and outcomes in lung adenocarcinoma: Results from the Lung Cancer Mutation Consortium. Steuer CE1, Behera M1, Berry L2, et al. Cancer. 2015 Dec 22. doi: 10.1002/cncr.29812. [Epub ahead of print]
BACKGROUND: The discovery of oncogenic drivers has ushered in a new era for lung cancer, but the role of these mutations in different racial/ethnic minorities has been understudied. The Lung Cancer Mutation Consortium 1 (LCMC1) database was investigated to evaluate the frequency and impact of oncogenic drivers in lung adenocarcinomas in the racial/ethnic minority patient population. **METHODS:** Patients with metastatic lung adenocarcinomas from 14 US sites were enrolled in the LCMC1. Tumor samples were collected from 2009 through 2012 with multiplex genotyping performed on 10 oncogenic drivers (KRAS, epidermal growth factor receptor [EGFR], anaplastic lymphoma kinase (ALK) rearrangements, ERBB2 [formerly human epidermal growth factor receptor 2], BRAF, PIK3CA, MET amplification, NRAS, MEK1, and AKT1). Patients were classified as white, Asian, African American (AA), or Latino. The driver mutation frequency, the treatments, and the survival from diagnosis were determined. **RESULTS:** One thousand seven patients were included. Whites represented the majority (n = 838); there were 60 AAs, 48 Asians, and 28 Latinos. Asian patients had the highest rate of oncogenic drivers with 81% (n = 39), and they were followed by Latinos with 68% (n = 19), whites with 61% (n = 511), and AAs with 53% (n = 32). For AAs, the EGFR mutation frequency was 22%, the KRAS frequency was 17%, and the ALK frequency was 4%. Asian patients were most likely to receive targeted therapies (51% vs 27% for AAs). There were no significant differences in overall survival.
CONCLUSIONS: Differences were observed in the prevalence of oncogenic drivers in lung adenocarcinomas and in subsequent treatments among racial groups. The lowest frequency of drivers was seen for AA patients; however, more than half of AA patients had a driver, and those treated with targeted therapy had outcomes similar to those of other races.

Lung cancer screening: what do long-term smokers know and believe? Carter-Harris L1, Ceppa DP2, Hanna N2,3, Rawl SM1. Health Expect. 2015 Dec 23. doi: 10.1111/hex.12433. [Epub ahead of print]
OBJECTIVE: To explore knowledge and beliefs of long-term smokers about lung cancer, associated risk factors and lung cancer screening. **DESIGN:** Qualitative study theoretically framed by the expanded Health Belief Model based on four focus group discussions. Content analysis was performed to identify themes of knowledge and beliefs about lung cancer, associated risk factors and lung cancer screening among long-term smokers' who had and had not been screened for lung cancer. **METHODS:** Twenty-six long-term smokers were recruited; two groups (n = 9; n = 3) had recently been screened and two groups (n = 7; n = 7) had never been screened. **RESULTS:** While most agreed lung cancer is deadly, confusion

or inaccurate information exists regarding the causes and associated risk factors. Knowledge related to lung cancer screening and how it is performed was low; awareness of long-term smoking's association with lung cancer risk remains suboptimal. Perceived benefits of screening identified include: (i) finding lung cancer early; (ii) giving peace of mind; and (iii) motivation to quit smoking. Perceived barriers to screening identified include: (i) inconvenience; (ii) distrust; and (iii) stigma. **CONCLUSIONS:** Perceived barriers to lung cancer screening, such as distrust and stigma, must be addressed as lung cancer screening becomes more widely implemented. Heightened levels of health-care system distrust may impact successful implementation of screening programmes. Perceived smoking-related stigma may lead to low levels of patient engagement with medical care and decreased cancer screening participation. It is also important to determine modifiable targets for intervention to enhance the shared decision-making process between health-care providers and their high-risk patients.

Nonsquamous, Non-Small-Cell Lung Cancer Patients Who Carry a Double Mutation of EGFR, EML4-ALK or KRAS: Frequency, Clinical-Pathological Characteristics, and Response to Therapy.
Ulivi P1, Chiadini E2, Dazzi C2, et al. Clin Lung Cancer. 2015 Dec 1. pii: S1525-7304(15)00268-5. doi: 10.1016/j.cllc.2015.11.004. [Epub ahead of print]
BACKGROUND: Epidermal growth factor receptor (EGFR) and v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations, and echinoderm microtubule-associated protein-like 4 (EML4) anaplastic lymphoma kinase (ALK) translocation are generally considered to be mutually exclusive. However, concomitant mutations are found in a small number of patients and the effect of these on response to targeted therapy is still unknown. **PATIENTS AND METHODS:** We considered 380 non-small-cell lung cancer (NSCLC) patients who underwent nonsequential testing for EGFR and EML4-ALK translocation. KRAS mutation analysis was also performed on 282 patients. **RESULTS:** We found 1.6%, 1.1%, and 2.5% of patients who showed a double mutation comprising EGFR and EML4-ALK, EGFR and KRAS, and EML4-ALK and KRAS, respectively. Twenty-eight patients with EGFR mutation underwent first-line therapy with a tyrosine kinase receptor; a clinical benefit was observed in 81.8% of patients with EGFR mutations only and in 67% of those who also showed an EML4-ALK translocation. Twelve patients with an EML4-ALK translocation received crizotinib and 7 of these had disease progression within 3 months (2 had a concomitant KRAS mutation and 1 had a concomitant EGFR mutation). Two patients showed stable disease, 1 of whom also had a KRAS mutation. Two patients obtained a partial response and 1 had a complete response; all harbored an EML4-ALK translocation only. The median overall survival of patients who carried an EML4-ALK translocation alone or concomitant with a KRAS mutation was 57.1 (range, 10.7-not reached) and 10.7 (range, 4.6-not reached) months, respectively. **CONCLUSION:** Concomitant EGFR, EML4-ALK, or KRAS mutations can occur in NSCLC. Concomitant KRAS mutation and EML4-ALK translocation represents the most common double alteration and confers a poor prognosis.

Lung Cancer Screening With Low-Dose CT in the United States. Eberth JM1. J Am Coll Radiol. 2015 Dec;12(12 Pt B):1395-402. doi: 10.1016/j.jacr.2015.09.016.
The findings of the landmark National Lung Screening Trial (NLST)-showing a 20% reduction in lung cancer mortality when screening with low-dose CT (LDCT), compared with chest radiography-marked a turning point in the field of lung cancer screening, influencing organizational recommendations and leading to increasing acceptance of LDCT for screening of individuals at high risk for lung cancer. However, many practices and institutions have experienced barriers in their attempts to implement successful screening programs; these include challenges in maintaining the same high caliber of screening programs as those in the NLST, confusion regarding insurance reimbursement protocols, and a lack of resources to help physicians discuss the specifics of LDCT screening with their patients. To address these challenges, standards are being established to ensure consistent quality of screening programs, including

certification standards and protocols maintained by the ACR. In addition, the US Preventive Services Task Force's "B" rating, given to LDCT screening in late 2013, resulted in mandated private insurance coverage beginning in 2015 and the 2015 CMS coverage determination has spurred previously reluctant organizations to prepare for population-based screening. Despite these successes, protocols for billing and claims processing are still evolving and organizations are considering how best to implement the shared decision-making process required by CMS. Despite some procedural setbacks that have yet to be resolved, LDCT screening for individuals at high risk of lung cancer has grown substantially since its effectiveness was shown by the NLST in 2011.

Primary Care Providers and a System Problem: A Qualitative Study of Clinicians Caring for Patients With Incidental Pulmonary Nodules. Golden SE, Wiener RS, Sullivan D, Ganzini L, Slatore CG. Chest. 2015 Dec 1;148(6):1422-9. doi: 10.1378/chest.14-2938.
BACKGROUND: As lung cancer screening with low-dose CT scanning is implemented, an increasing number of people will be diagnosed with pulmonary nodules. Primary care clinicians care for the vast majority of these patients, but their experiences with communication and managing distress in this population are not well understood. **METHODS:** We conducted qualitative interviews of 15 primary care providers (PCPs) at two academic medical centers who care for patients with pulmonary nodules. We used qualitative description analysis, focusing on clinicians' information exchange and other communication behaviors. **RESULTS:** Most PCPs believed they had inadequate information to counsel patients regarding lung nodules, although this information is desired. PCPs were concerned patients could "fall through the cracks" but did not have access to a reliable system to ensure follow-up adherence. They were limited by time, knowledge, and resources in providing the preferred level of care. Most PCPs did not discuss the specific risk a nodule was lung cancer, in part because they did not have ready access to this information. PCPs believed most patients did not have substantial distress as a result of nodule detection. Most PCPs did not include patients when making decisions about the follow-up plan. **CONCLUSIONS:** PCPs often lack systemic resources to optimize patient-centered approaches when discussing incidental pulmonary nodules with patients. With the advent of lung cancer screening, pulmonologists can assist primary care colleagues by providing accurate information to counsel patients and assisting in managing conversations about the risk of cancer. Pulmonologists should support efforts to implement reliable systems to ensure adherence to follow-up.

The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the N Descriptors in the Forthcoming 8th Edition of the TNM Classification for Lung Cancer. Asamura H1, Chansky K, Crowley J, et al. J Thorac Oncol. 2015 Dec;10(12):1675-84. doi: 10.1097/JTO.0000000000000678.
INTRODUCTION: Nodal status is considered to be one of the most reliable indicators of the prognosis in patients with lung cancer and thus is indispensable in determining the optimal therapeutic options. We sought to determine whether the current nodal (N) descriptors should be maintained or revised for the next edition (8th) of the International Lung Cancer Staging System. **METHODS:** The new International Association for the Study of Lung Cancer lung cancer database was created from 94,708 patients diagnosed as having lung cancer between 1999 and 2010. Among these, 38,910 and 31,426 patients with non-small-cell lung carcinoma were available for an analysis of the clinical (c)N and pathological (p)N status, respectively. The anatomical location of lymph node involvement was defined by either the Naruke (for Japanese data) or American Thoracic Society (for non-Japanese data) nodal charts. Survival was calculated by the Kaplan-Meier method, and prognostic groups were assessed by a Cox regression analysis. **RESULTS:** The current N0 to N3 descriptors for both the cN and pN status consistently separated prognostically distinct groups. The 5-year survival rates according to the cN and pN status were 60% and 75% (N0), 37% and 49% (N1), 23% and 36% (N2), and 9% and 20% (N3), respectively. The

differences in survival between all neighboring nodal categories were highly significant for both the cN and pN status. With regard to pathological staging, additional analyses regarding the prognosis were performed by further dividing N1 into N1 at a single station (N1a) and N1 at multiple stations (N1b); N2 into N2 at a single station without N1 involvement ("skip" metastasis, N2a1), N2 at a single station with N1 involvement (N2a2), and N2 at multiple stations (N2b). The survival curves for N1b and N2a2 overlapped each other, and N2a1 had numerically a better prognosis than N1b, although the difference was not significant. Geographic difference in N-specific prognosis was observed for both c-settings and p-settings. This might have been because of the difference in the used nodal map, surgical technique, and pathologist's handling of the resected specimen. **CONCLUSIONS:** Current N descriptors adequately predict the prognosis and therefore should be maintained in the forthcoming staging system. Furthermore, we recommend that physicians record the number of metastatic lymph nodes (or stations) and to further classify the N category using new descriptors, such as N1a, N1b, N2a, N2b, and N3, for further testing.

Early Results From the Implementation of a Lung Cancer Screening Program: The Beaumont Health System Experience. Lanni TB Jr1, Stevens C, Farah M, Boyer A, Davis J, Welsh R, Keena D, Akhtar A, Mezwa D. Am J Clin Oncol. 2015 Dec 8. [Epub ahead of print]
PURPOSE: In 2010, a new study published by the National Lung Screening Trial showed a 20% reduction in mortality for those patients screened with low-dose computed topography (CT) versus x-ray. Recently, the Centers of Medicare and Medicaid have agreed to cover this service for those patients who meet the screening criteria. We compare the outcomes and costs associated with developing and implementing a lung cancer screening program. **MATERIALS AND METHODS:** One thousand sixty-five patients were screened from January 2014 to December 2014. These patients were screened on a low-dose CT screening protocol throughout Beaumont Health System. The American College of Radiology Lung Imaging Reporting and Data System (Lung-RADS) were used to assign the score for each patient. Screening eligibility criteria were based on the National Comprehensive Cancer Network guidelines. Downstream activity and revenue was determined after initial low-dose CT screening. **RESULTS:** At 1 year, 20 patients (1.6%) were diagnosed with lung cancer and another 15 patients were diagnosed with another form of cancer after screening. The median age, packs per day, and pack years smoked for all patients was 63, 1.0, and 39.0 years, respectively. Lung-RADS scores for all patients was 18% (1), 24.1% (2), 6.3% (3), and 5.4% (4). The net revenue for all activity after screening was $3.2 million.
CONCLUSIONS: The establishment of a low-dose CT lung cancer screening program improved the ability to screen patients as demonstrated by the number of patients screened and those diagnosed with a malignancy. These findings were also consistent with the findings from the National Lung Screening Trial study.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

Treatment Outcomes in Stage I Lung Cancer: A Comparison of Surgery and Stereotactic Body Radiation Therapy. Puri V1, Crabtree TD, Bell JM, et al. J Thorac Oncol. 2015 Dec;10(12):1776-84. doi: 10.1097/JTO.0000000000000680.
INTRODUCTION: The relative roles of surgery and stereotactic body radiation therapy in stage I non-small-cell lung cancer (NSCLC) are evolving particularly for marginally operable patients. Because there is limited prospective comparative data for these treatment modalities, we evaluated their relative use and outcomes at the population level using a national database. **METHODS:** Patient variables and treatment-related outcomes were abstracted for patients with clinical stage I NSCLC from the National Cancer Database. Patients receiving surgery were compared with those undergoing stereotactic body radiation

therapy (SBRT) in exploratory unmatched and subsequent propensity matched analyses. **RESULTS:** Between 1998 and 2010, 117,618 patients underwent surgery or SBRT for clinical stage I NSCLC. Of these, 111,731 (95%) received surgery, whereas 5887 (5%) underwent SBRT. Patients in the surgery group were younger, more likely to be males, and had higher Charlson comorbidity scores. SBRT patients were more likely to have T1 (versus T2) tumors and receive treatment at academic centers. Thirty-day surgical mortality was 2596 of 109,485 (2.4%). Median overall survival favored the surgery group in both unmatched (68.4 versus 33.3 months, $p < 0.001$) and matched analysis based on patient characteristics (62.3 versus 33.1 months, $p < 0.001$). Disease-specific survival was unavailable from the data set. **CONCLUSION:** In a propensity matched comparison, patients selected for surgery have improved survival compared with SBRT. In the absence of information on cause of death and with limited variables to characterize comorbidity, it is not possible to assess the relative contribution of patient selection or better cancer control toward the improved survival. Rigorous prospective studies are needed to optimize patient selection for SBRT in the high-risk surgical population.

Long-term survival following open versus thoracoscopic lobectomy after preoperative chemo-therapy for non-small cell lung cancer†. Yang CJ1, Meyerhoff RR1, Mayne NR1, et al. Eur J Cardiothorac Surg. 2015 Dec 30. pii: ezv428. [Epub ahead of print]
OBJECTIVES: Video-assisted thoracoscopic (VATS) lobectomy is increasingly accepted for the management of early-stage non-small cell lung cancer (NSCLC), but its role for locally advanced cancers has not been as well characterized. We compared outcomes of patients who received induction therapy followed by lobectomy, via VATS or thoracotomy. **METHODS:** Perioperative complications and long-term survival of all patients with NSCLC who received induction chemotherapy (ICT) (with or without induction radiation therapy) followed by lobectomy from 1996-2012 were assessed using Kaplan-Meier and Cox proportional hazard analysis. Propensity score-matched comparisons were used to assess the potential impact of selection bias. **RESULTS:** From 1996 to 2012, 272 patients met inclusion criteria and underwent lobectomy after ICT: 69 (25%) by VATS and 203 (75%) by thoracotomy. An 'intent-to-treat' analysis was performed. Compared with thoracotomy patients, VATS patients had a higher clinical stage, were older, had greater body mass index, and were more likely to have coronary disease and chronic obstructive pulmonary disease. Induction radiation was used more commonly in thoracotomy patients [VATS 28% (n = 19) vs open 72% (n = 146), $P < 0.001$]. Thirty-day mortality was similar between the VATS [3% (n = 2)] and open [4% (n = 8)] groups ($P = 0.69$). Seven (10%) of the VATS cases were converted to thoracotomy due to difficulty in dissection from fibrotic tissue and adhesions (n = 5) or bleeding (n = 2); none of these conversions led to perioperative deaths. In univariate analysis, VATS patients had improved 3-year survival compared with thoracotomy (61% vs 43%, $P = 0.010$). In multivariable analysis, the VATS approach showed a trend towards improved survival, but this did not reach statistical significance (hazard ratio, 0.56; 95% confidence interval, 0.32-1.01; $P = 0.053$). Moreover, a propensity score-matched analysis balancing patient characteristics demonstrated that the VATS approach had similar survival to an open approach ($P = 0.56$). **CONCLUSIONS:** VATS lobectomy in patients treated with induction therapy for locally advanced NSCLC is feasible and effective and does not appear to compromise oncologic outcomes.

Effects of dexmedetomidine on oxygenation and lung mechanics in patients with moderate chronic obstructive pulmonary disease undergoing lung cancer surgery: A prospective randomised double-blinded trial. Lee SH1, Kim N, Lee CY, Ban MG, Oh YJ. Eur J Anaesthesiol. 2015 Dec 24. [Epub ahead of print]
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). **INTERVENTIONS:** In the Dex group, dexmedetomidine was given as an initial loading dose of 1.0 μgkg over 10 min followed by a maintenance dose of 0.5 μgkgh during OLV while the control group was administered a comparable volume of 0.9% saline. Data were measured at 30 min (DEX-30) and 60 min (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.

Lobectomy for Non-Small Cell Lung Cancer by Video-Assisted Thoracic Surgery: Effects of Cumulative Institutional Experience on Adequacy of Lymphadenectomy.

Lee PC1, Kamel M2, Nasar A2, et al. Ann Thorac Surg. 2015 Dec 1. pii: S0003-4975(15)01581-7. doi: 10.1016/j.athoracsur.2015.09.073. [Epub ahead of print]

BACKGROUND: Because video-assisted thoracic surgery (VATS) lobectomies are increasingly being performed by thoracic surgeons, the adequacy of lymph node clearance by VATS compared with thoracotomy has been questioned, raising the possibility that patients are being understaged. One factor that may be overlooked in published studies is the learning curve of the surgeons and surgical volume in the adoption of VATS lobectomy. This study examined the effect of cumulative institutional VATS lobectomy experience on the adequacy of lymphadenectomy. **METHODS:** We retrospectively reviewed a prospective database to identify 500 consecutive patients who underwent VATS lobectomy for non-small cell lung cancer (NSCLC) at our institution between 2002 and 2012. For comparative purposes, the cohort was divided into halves, with an early group (first 250 cases) vs a late group (next 250 cases). Clinical and pathologic factors were analyzed. A propensity-matching analysis controlling for age, gender, pathologic stage, and percentage of forced expiratory volume in 1 second was done to compare survival and adequacy of lymphadenectomy. **RESULTS:** Patients operated on in the late group were significantly older (72 vs 69 years, p = 0.001) and had worse pulmonary functions (median forced expiratory volume in 1 second 83% vs 91%, p < 0.001; median diffusion capacity of the lung for carbon monoxide, 76% vs 85%, p < 0.001). Clinical and pathologic tumor sizes were significantly larger in the late group compared with the early group, with a median of 2.0 vs 1.8 cm (p = 0.002) for clinical T size and median of 2.1 vs 2.0 cm (p = 0.003) for pathologic T size. Patients in the late group had significantly more advanced clinical and pathologic stage distribution. The total number of lymph nodes and the number of nodal stations removed were significantly greater in the late group (p = 0.012) than in the early group (p < 0.001), and same results were obtained after propensity matching. No difference was seen in disease-free survival between the propensity-matched early vs late groups at 3 years (82% vs 85%, p = 0.187). **CONCLUSIONS:** For patients with NSCLC resected by VATS lobectomy, cumulative institutional experience significantly and positively affects the adequacy of lymphadenectomy. This may

be related to the initial surgeon's learning curve with VATS lobectomy. As the experience with VATS lobectomy becomes more mature, the procedure is increasingly being performed on older patients, often with more compromised pulmonary function and more advanced stage disease. Despite the expanded inclusion of older and sicker patients for VATS lobectomy, no compromise was seen in their disease-free survival.

Surgical Outcomes after Pulmonary Resection for Non-Small Cell Lung Cancer with Localized Pleural Seeding First Detected during Surgery. Yun JK1, Kim MA2, Choi CM2, et al. Thorac Cardiovasc Surg. 2015 Dec 15. [Epub ahead of print]
OBJECTIVES: Curative resection is not indicated for non-small cell lung cancer (NSCLC) with pleural seeding, which is classified as stage IV (M1a) disease. However, some patients with a presumably resectable main tumor are diagnosed with localized pleural seeding during surgery. **METHODS:** A retrospective analysis was performed of 3,975 patients who underwent surgery for NSCLC from 2000 to 2011. Among these cases, 78 (2.0%) patients had unexpected pleural seeding detected during surgery. Exploration with pleural biopsy was performed in 42 of these patients (exploration-only group) and pulmonary resection, including for the main tumor, was performed in 36 cases (resection group; sublobar resection in 12, lobectomy in 21, and pneumonectomy in 3 patients). Survival and cancer progression rates were estimated using the Kaplan-Meier method. Cox proportional hazard regression was used to evaluate prognostic factors associated with survival. **RESULTS:** Adenocarcinoma was the predominant histological type in both the exploration and resection groups (88.1 and 86.1%, respectively). Epidermal growth factor receptor expression was detected in 22 (52.4%) patients of the exploration group and 21 (58.3%) patients of the resection group. Baseline characteristics including age, sex, comorbidity, pulmonary function, and clinical T/N status were not significantly different between the two groups. There were no postoperative deaths in either group but postoperative complications occurred in two (4.8%) patients of the exploration group and three (8.3%) patients of the resection group. The overall 3- and 5-year survival rates in the exploration group were 41.1 and 15.2%, respectively, with a median survival time (MST) of 33 months, whereas they were 66.7 and 42.7%, respectively, in the resection group, with a 52-month MST ($p = 0.012$). Local and regional progression-free rates were significantly different ($p < 0.001$ and $p = 0.029$, respectively) between groups, whereas no difference was seen in the distant metastasis rates ($p = 0.957$). In multivariate survival analysis, surgical resection was the only significant prognostic factor ($p = 0.01$). **CONCLUSIONS:** Pulmonary resection including the main tumor, regardless of resection extent, may increase long-term survival for NSCLC patients with localized pleural seeding first detected during surgery, without a significant increase in hospital mortality or morbidity.

Impact of patient selection and treatment strategies on outcomes after lobectomy for biopsy-proven stage IIIA pN2 non-small cell lung cancer†. Yang CJ1, Adil SM1, Anderson KL1, et al. Eur J Cardiothorac Surg. 2015 Dec 30. pii: ezv431. [Epub ahead of print]
OBJECTIVES: We evaluated the impact of patient selection and treatment strategies on long-term outcomes of patients who had lobectomy after induction therapy for stage IIIA pN2 non-small cell lung cancer (NSCLC). **METHODS:** The impact of various patient selection, induction therapy and operative strategies on survival of patients with biopsy-proven stage IIIA pN2 NSCLC who received induction chemotherapy ± radiation followed by lobectomy from 1995 to 2012 was assessed using Cox proportional hazards analysis. **RESULTS:** From 1995 to 2012, 111 patients had lobectomy for stage IIIA pN2 NSCLC after chemotherapy ± radiation with an overall 5-year survival of 39%. The use of induction chemoradiation decreased over time; from 1996 to 2007, 46/65 (71%) patients underwent induction chemoradiation, whereas from 2007 to 2012, 36/46 (78%) patients underwent induction chemotherapy. The use of video-assisted thoracoscopic surgery (VATS) increased over the time period of the study, from

0/26 (0%) in 1996-2001, to 4/39 (10%) in 2002-07 to 33/46 (72%) in 2008-12. Compared with patients given induction chemotherapy alone, patients given additional induction radiation were more likely to have complete pathologic response (30 vs 11%, P = 0.01) but had worse 5-year survival in univariable analysis (31 vs 48%, log-rank P = 0.021). Patients who underwent pathologic mediastinal restaging following induction therapy but prior to resection had an improved overall survival compared with patients who did not undergo pathologic mediastinal restaging {5-year survival: 45.2 [95% confidence interval (CI): 33.9-55.9] vs 13.9% (95% CI: 2.5-34.7); log-rank, P = 0.004}. In multivariable analysis, the particular induction therapy strategy and the surgical approach used, as well as the extent of mediastinal disease were not important predictors of survival. However, pathologic mediastinal restaging was associated with improved survival (HR 0.39; 95% CI: 0.21-0.72; P = 0.003). **CONCLUSIONS:** For patients with stage IIIA pN2 NSCLC, the VATS approach or the addition of radiation to induction therapy can be selectively employed without compromising survival. The strategy of assessing response to induction therapy with pathologic mediastinal restaging allows one to select appropriate patients for complete resection and is associated with a 5-year overall survival of 39% in this population.

NSCLC - CHEMOTHERAPY

Induction or consolidation chemotherapy for unresectable stage III non-small-cell lung cancer patients treated with concurrent chemoradiation: a randomised phase II trial GFPC - IFCT 02-01. Fournel P1, Vergnenégre A2, Robinet G3, et al. Eur J Cancer. 2016 Jan;52:181-7. doi: 10.1016/j.ejca.2015.10.072. Epub 2015 Dec 12.

PURPOSE: The objective of this randomised phase II study was to evaluate the impact in terms of response and toxicities of induction or consolidation chemotherapy respectively before or after concurrent chemoradiotherapy in unresectable stage III non-small-cell lung cancer. **PATIENTS AND METHODS:** In the induction arm, patients received induction chemotherapy with cisplatin (80 mg/m(2)) and paclitaxel (200 mg/m(2)) on days 1 and 29 followed by a concurrent chemoradiotherapy (66 Gy in 33 fractions, cisplatin 80 mg/m(2) days 1, 29 and 57, vinorelbine 15 mg/m(2) days 1, 8, 29, 36, 57 and 64). In consolidation arm, the same concurrent chemoradiotherapy began on day 1 followed by two cycles of cisplatin and paclitaxel. **RESULTS:** One hundred twenty seven patients were randomised. The intent to treat response rates in induction and consolidation arms were 58% and 56% respectively. Median survival was 19.6 months in induction arm and 16.3 months in consolidation arm and 4-year survival rates were 21% and 30% respectively. Haematologic and non-haematologic toxicities were similar in both arms, except grade 3/4 oesophagitis, more frequent in consolidation arm than in induction arm (17% versus 10%). **CONCLUSION:** Cisplatin-based chemotherapy as induction or consolidation with concurrent chemoradiotherapy can be administrated safely. Response rates were similar in both arms with a trend in favour for consolidation arm for long-term survival.

Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Herbst RS1, Baas P2, Kim DW3, et al. Lancet. 2015 Dec 18. pii: S0140-6736(15)01281-7. doi: 10.1016/S0140-6736(15)01281-7. [Epub ahead of print]

BACKGROUND: Despite recent advances in the treatment of advanced non-small-cell lung cancer, there remains a need for effective treatments for progressive disease. We assessed the efficacy of pembrolizumab for patients with previously treated, PD-L1-positive, advanced non-small-cell lung cancer. **METHODS:** We did this randomised, open-label, phase 2/3 study at 202 academic medical centres in 24 countries. Patients with previously treated non-small-cell lung cancer with PD-L1 expression on at least 1% of tumour cells were randomly assigned (1:1:1) in blocks of six per stratum with an interactive voice-response system to receive pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg,

or docetaxel 75 mg/m2 every 3 weeks. The primary endpoints were overall survival and progression-free survival both in the total population and in patients with PD-L1 expression on at least 50% of tumour cells. We used a threshold for significance of p<0·00825 (one-sided) for the analysis of overall survival and a threshold of p<0·001 for progression-free survival. This trial is registered at ClinicalTrials.gov, number NCT01905657. **FINDINGS:** Between Aug 28, 2013, and Feb 27, 2015, we enrolled 1034 patients: 345 allocated to pembrolizumab 2 mg/kg, 346 allocated to pembrolizumab 10 mg/kg, and 343 allocated to docetaxel. By Sept 30, 2015, 521 patients had died. In the total population, median overall survival was 10·4 months with pembrolizumab 2 mg/kg, 12·7 months with pembrolizumab 10 mg/kg, and 8·5 months with docetaxel. Overall survival was significantly longer for pembrolizumab 2 mg/kg versus docetaxel (hazard ratio [HR] 0·71, 95% CI 0·58-0·88; p=0·0008) and for pembrolizumab 10 mg/kg versus docetaxel (0·61, 0·49-0·75; p<0·0001). Median progression-free survival was 3·9 months with pembrolizumab 2 mg/kg, 4·0 months with pembrolizumab 10 mg/kg, and 4·0 months with docetaxel, with no significant difference for pembrolizumab 2 mg/kg versus docetaxel (0·88, 0·74-1·05; p=0·07) or for pembrolizumab 10 mg/kg versus docetaxel (HR 0·79, 95% CI 0·66-0·94; p=0·004). Among patients with at least 50% of tumour cells expressing PD-L1, overall survival was significantly longer with pembrolizumab 2 mg/kg than with docetaxel (median 14·9 months vs 8·2 months; HR 0·54, 95% CI 0·38-0·77; p=0·0002) and with pembrolizumab 10 mg/kg than with docetaxel (17·3 months vs 8·2 months; 0·50, 0·36-0·70; p<0·0001). Likewise, for this patient population, progression-free survival was significantly longer with pembrolizumab 2 mg/kg than with docetaxel (median 5·0 months vs 4·1 months; HR 0·59, 95% CI 0·44-0·78; p=0·0001) and with pembrolizumab 10 mg/kg than with docetaxel (5·2 months vs 4·1 months; 0·59, 0·45-0·78; p<0·0001). Grade 3-5 treatment-related adverse events were less common with pembrolizumab than with docetaxel (43 [13%] of 339 patients given 2 mg/kg, 55 [16%] of 343 given 10 mg/kg, and 109 [35%] of 309 given docetaxel). **INTERPRETATION:** Pembrolizumab prolongs overall survival and has a favourable benefit-to-risk profile in patients with previously treated, PD-L1-positive, advanced non-small-cell lung cancer. These data establish pembrolizumab as a new treatment option for this population and validate the use of PD-L1 selection.

Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. Shaw AT1, Gandhi L2, Gadgeel S3, et al. Lancet Oncol. 2015 Dec 18. pii: S1470-2045(15)00488-X. doi: 10.1016/S1470-2045(15)00488-X. [Epub ahead of print]
BACKGROUND: Alectinib-a highly selective, CNS-active, ALK inhibitor-showed promising clinical activity in crizotinib-naive and crizotinib-resistant patients with ALK-rearranged (ALK-positive) non-small-cell lung cancer (NSCLC). We aimed to assess the safety and efficacy of alectinib in patients with ALK-positive NSCLC who progressed on previous crizotinib. **METHODS:** We did a phase 2 study at 27 centres in the USA and Canada. We enrolled patients aged 18 years or older with stage IIIB-IV, ALK-positive NSCLC who had progressed after crizotinib. Patients were treated with oral alectinib 600 mg twice daily until progression, death, or withdrawal. The primary endpoint was the proportion of patients achieving an objective response by an independent review committee using Response Evaluation Criteria in Solid Tumors, version 1.1. Response endpoints were assessed in the response-evaluable population (ie, patients with measurable disease at baseline who received at least one dose of study drug), and efficacy and safety analyses were done in the intention-to-treat population (all enrolled patients). This study is registered with ClinicalTrials.gov, number NCT01871805. The study is ongoing and patients are still receiving treatment. **FINDINGS:** Between Sept 4, 2013, and Aug 4, 2014, 87 patients were enrolled into the study (intention-to-treat population). At the time of the primary analysis (median follow-up 4·8 months [IQR 3·3-7·1]), 33 of 69 patients with measurable disease at baseline had a confirmed partial response; thus, the proportion of patients achieving an objective response by the independent review committee was 48% (95% CI 36-60). Adverse events were predominantly grade 1 or 2, most commonly constipation (31 [36%]), fatigue (29 [33%]), myalgia 21 [24%]), and peripheral oedema 20 [23%]). The

most common grade 3 and 4 adverse events were changes in laboratory values, including increased blood creatine phosphokinase (seven [8%]), increased alanine aminotransferase (five [6%]), and increased aspartate aminotransferase (four [5%]). Two patients died: one had a haemorrhage (judged related to study treatment), and one had disease progression and a history of stroke (judged unrelated to treatment). **INTERPRETATION:** Alectinib showed clinical activity and was well tolerated in patients with ALK-positive NSCLC who had progressed on crizotinib. Therefore, alectinib could be a suitable treatment for patients with ALK-positive disease who have progressed on crizotinib.

Adaptive neoadjuvant chemotherapy guided by 18F-FDG-PET in resectable non-small-cell lung cancers: the NEOSCAN trial. Chaft JE1, Dunphy M2, Naidoo J3, et al. J Thorac Oncol. 2015 Dec 24. pii: S1556-0864(15)00266-X. doi: 10.1016/j.jtho.2015.12.104. [Epub ahead of print]
INTRODUCTION: Although perioperative chemotherapy improves survival in patients with resectable lung cancers, systemic recurrence remains common. Neoadjuvant chemotherapy permits response assessment and opportunity to switch treatment regimens. Response measured by fluorodeoxyglucose PET correlates better than CT with clinical outcomes. The NEOSCAN trial assessed PET-measured response rate to alternative chemotherapy in patients with a suboptimal PET response after 2 cycles of neoadjuvant chemotherapy. **METHODS:** This phase 2 study enrolled patients with resectable stage IB-IIIA lung cancers (primary tumor >2 cm and SUVpeak≥4.5). Patients had a pretreatment FDG PET/CT before 2 cycles of cisplatin (or carboplatin) + gemcitabine (squamous) or pemetrexed (adenocarcinomas) then repeat PET/CT. If SUVpeak in the primary tumor decreased by ≥35%, patients continued the initial chemotherapy. Individuals with <35% PET response were switched to vinorelbine + docetaxel. Post operative radiotherapy was recommended to all patients with positive N2 nodes. A Simon-optimal two stage design was used to evaluate the primary endpoint of a PERCIST-defined response rate to vinorelbine + docetaxel in previously non-responding patients. **RESULTS:** 40 patients were enrolled. 15 patients (38%, 95% CI: 38-53%) had <35% decrease in SUVpeak and 13 received vinorelbine + docetaxel. The study met its primary endpoint with 10/15 (67%) PET metabolic responses to alternate therapy. Chemotherapy toxicities never precluded surgical exploration. **CONCLUSIONS:** Utilizing FDG PET/CT to assess response and change preoperative chemotherapy in non-responding patients can improve radiographic measures of response. This adaptive approach can also be used to test new drugs, attempting to optimize perioperative chemotherapy to achieve better long term outcomes.

Afatinib beyond progression in patients with non-small-cell lung cancer following chemotherapy, erlotinib/gefitinib and afatinib: phase III randomized LUX-Lung 5 trial. Schuler M, Yang JC, Park K, et al. Ann Oncol. 2015 Dec 8. pii: mdv597. [Epub ahead of print]
BACKGROUND: Afatinib has demonstrated clinical benefit in patients with non-small-cell lung cancer progressing after treatment with erlotinib/gefitinib. This phase III trial prospectively assessed whether continued irreversible ErbB-family blockade with afatinib plus paclitaxel has superior outcomes versus switching to chemotherapy alone in patients acquiring resistance to erlotinib/gefitinib and afatinib monotherapy. **METHODS:** Patients with relapsed/refractory disease following ≥1 line of chemotherapy, and whose tumors had progressed following initial disease control (≥12 weeks) with erlotinib/gefitinib and thereafter afatinib (50 mg/day), were randomized 2:1 to receive afatinib plus paclitaxel (40 mg/day; 80 mg/m2/week) or investigator's choice of single-agent chemotherapy. The primary end point was progression-free survival (PFS). Other end points included objective response rate (ORR), overall survival (OS), safety, and patient-reported outcomes. **RESULTS:** Two hundred and two patients with progressive disease following clinical benefit from afatinib were randomized to afatinib plus paclitaxel (n=134) or single-agent chemotherapy (n=68). PFS (median 5.6 versus 2.8 months, hazard ratio [HR] 0.60, P=0.003) and ORR (32.1% versus 13.2%, P=0.005) significantly improved with afatinib plus paclitaxel. There was no difference in OS. Global health status/quality of life was maintained with

afatinib plus paclitaxel over the entire treatment period. The median treatment duration was 133 and 51 days with afatinib plus paclitaxel and single-agent chemotherapy, respectively; 48.5% of patients receiving afatinib plus paclitaxel and 30.0% of patients receiving single-agent chemotherapy experienced drug-related grade 3/4 adverse events. Treatment-related adverse events were consistent with those previously reported with each agent. **CONCLUSION:** Afatinib plus paclitaxel improved PFS and ORR compared with single-agent chemotherapy in patients who acquired resistance to erlotinib/gefitinib and progressed on afatinib after initial benefit. LUX-Lung 5 is the first prospective trial to demonstrate the benefit of continued ErbB targeting post progression, versus switching to single-agent chemotherapy.

Pharmacogenetic analysis of advanced non-small-cell lung cancer patients treated with first-line paclitaxel and carboplatin chemotherapy. Park HS1, Lim SM, Cho A, Shin JG, Lee MG, Kim HR, Kim JH, Shin HJ, Cho BC. Pharmacogenet Genomics. 2015 Dec 4. [Epub ahead of print]
BACKGROUND: Genetic polymorphisms contribute toward interindividual variations in drug response. We investigated the effects of genetic polymorphisms on the clinical outcome of advanced non-small-cell lung cancer patients with first-line paclitaxel and carboplatin. **MATERIALS AND METHODS:** A total of 194 non-small-cell lung cancer patients were prospectively enrolled from January 2010 to January 2013. We genotyped 11 polymorphisms in seven genes involved in the glycolysis pathway and the related pharmacokinetic/pharmacodynamic pathway. Genetic associations with PET-SUV, survival outcome, and toxicity were analyzed, and in-vitro drug transport activity was measured in the oocyte system. **RESULTS:** Patients with the c.334 T>G and c.699 G>A homozygous variant in SLCO1B3 showed a higher incidence of grade 3/4 anemia (P=0.002). Transport activities of oocyte that overexpress the SLCO1B3 c.699 G>A variant showed a significantly decreased uptake of paclitaxel compared with the wild-type expressing oocytes. In addition, patients with GG/GA/AA genotypes of ABCB1, c.2677 T>G/A locus showed inferior progression-free survival (hazard ratio=1.49, P=0.017) compared with other genotypes. The GA genotype of HIF1A, c.1834 G>A locus was associated with inferior progression-free survival compared with the GG genotype (hazard ratio=2.47, P=0.008). **CONCLUSION:** This study showed that the SLCO1B3 c.699 G>A polymorphism may predict anemia and ABCB1, HIF1A polymorphism are highly predictive for worse survival in advanced NSCLC with first-line paclitaxel and carboplatin.

Non-small cell lung cancer cells acquire resistance to the ALK inhibitor alectinib by activating alternative receptor tyrosine kinases. Isozaki H1, Ichihara E2, Takigawa N3, et al. Cancer Res. 2015 Dec 30. pii: canres.1010.2015. [Epub ahead of print]
Crizotinib is the standard of care for advanced non-small cell lung cancer (NSCLC) patients harboring the anaplastic lymphoma kinase (ALK) fusion gene, but resistance invariably develops. Unlike crizotinib, alectinib is a selective ALK tyrosine kinase inhibitor (TKI) with more potent antitumor effects and a favorable toxicity profile, even in crizotinib-resistant cases. However, acquired resistance to alectinib, as for other TKIs, remains a limitation of its efficacy. Therefore, we investigated the mechanisms by which human NSCLC cells acquire resistance to alectinib. We established two alectinib-resistant cell lines that did not harbor the secondary ALK mutations frequently occurring in crizotinib-resistant cells. One cell line lost the EML4-ALK fusion gene, but exhibited increased activation of insulin-like growth factor-1 receptor (IGF-1R) and human epidermal growth factor receptor 3 (HER3), and overexpressed the HER3 ligand neuregulin 1. Accordingly, pharmacologic inhibition of IGF-1R and HER3 signaling overcame resistance to alectinib in this cell line. The second alectinib-resistant cell line displayed stimulated hepatocyte growth factor (HGF) autocrine signaling that promoted MET activation, and remained sensitive to crizotinib treatment. Taken together, our findings reveal two novel mechanisms underlying alectinib resistance that are caused by the activation of alternative tyrosine kinase receptors rather than by secondary ALK mutations. These studies may guide the development of comprehensive treatment

strategies that take into consideration the various approaches ALK-positive lung tumors use to withstand therapeutic insult.

NSCLC - RADIOTHERAPY

Clinical Trials Integrating Immunotherapy and Radiation for Non-Small-Cell Lung Cancer.
Daly ME1, Monjazeb AM, Kelly K. J Thorac Oncol. 2015 Dec;10(12):1685-93. doi: 10.1097/JTO.0000000000000686.
Methods of harnessing the immune system to treat cancer have been investigated for decades, but yielded little clinical progress. However, in recent years, novel drugs that allow immune recognition and destruction of tumor cells are emerging as potent cancer therapies. Building upon previous immunotherapy strategies that included therapeutic vaccines, recombinant cytokines, and other immunostimulatory agents, newer immunotherapy agents targeting immune checkpoints including programmed cell death 1, programmed cell death ligand-1, and cytotoxic T-lymphocyte-associated protein 4, among others, have garnered substantial enthusiasm after demonstrating clinical activity in a broad spectrum of tumor types. Trials evaluating immune checkpoint inhibitors in metastatic non-small-cell lung cancer (NSCLC) demonstrate robust and durable responses in a subset of patients. However, with overall response rates less than 20%, combinatorial strategies that extend the benefit of these agents to more patients are desirable. The integration of radiotherapy with immunotherapy is a conceptually promising strategy, as radiotherapy has potent immunomodulatory effects and may contribute not only to local control but may also augment systemic antitumor immune response. Preclinical data and case reports suggest the potential for robust clinical responses in metastatic NSCLC patients using this strategy, but prospective clinical trials evaluating the integration of radiation and immunotherapy are limited. The use of immunotherapy in nonmetastatic settings is also intriguing but understudied. We review the potential clinical settings of interest for the partnering of immunotherapy and radiation in NSCLC, including early stage, locally advanced, and metastatic disease, and review completed, accruing, and developing clinical trials.

Analysis of risk and predictors of brain radiation necrosis after radiosurgery. Zhuang H1, Zheng Y2, Wang J3, Chang JY4, Wang X1, Yuan Z1, Wang P1. Oncotarget. 2015 Dec 10. doi: 10.18632/oncotarget.6532. [Epub ahead of print]
In this study, we examined the factors contributing to brain radiation necrosis and its predictors of patients treated with Cyberknife radiosurgery. A total of 94 patients with primary or metastatic brain tumours having been treated with Cyberknife radiotherapy from Sep. 2006 to Oct. 2011 were collected and retrospectively analyzed. Skull based tracking was used to deliver radiation to 104 target sites. and the prescribed radiation doses ranged from 1200 to 4500 cGy in 1 to 8 fractions with a 60% to 87% isodose line. Radiation necrosis was confirmed by imaging or pathological examination. Associations between cerebral radiation necrosis and factors including diabetes, cardio-cerebrovascular disease, target volume, isodose line, prescribed dosage, number of fractions, combination with whole brain radiation and biologically equivalent dose (BED) were determined by logistic regression. ROC curves were created to measure the predictive accuracy of influence factors and identify the threshold for brain radiation necrosis. Our results showed that radiation necrosis occurred in 12 targets (11.54%). Brain radiation necrosis was associated by BED, combination with whole brain radiotherapy, and fractions (areas under the ROC curves = 0.892±0.0335, 0.650±0.0717, and 0.712±0.0637 respectively). Among these factors, only BED had the capability to predict brain radiation necrosis, and the threshold dose was 7410 cGy. In conclusion, BED is the most effective predictor of brain radiation necrosis, with a dose of 7410 cGy being identified as the threshold.

SMALL CELL LUNG CANCER - SCLC

The relationship between UGT1A1 gene polymorphism and irinotecan effect on extensive-stage small-cell lung cancer. Xiao XG1, Xia S1, Zou M1, Mei Q1, Zhou L1, Wang SJ1, Chen Y1. Onco Targets Ther. 2015 Dec 3;8:3575-83. doi: 10.2147/OTT.S95149. eCollection 2015.
AIMS: To analyze the distribution of uridine diphosphate glucuronosyltransferase (UGT)1A1 gene polymorphisms in Chinese patients with extensive-stage small-cell lung cancer (E-SCLC), and to evaluate correlations between the UGT1A1 gene polymorphisms and toxicity, and efficacy of irinotecan (CPT-11) based regimen in the patients with E-SCLC. **METHODS:** The study analyzed the distribution of UGT1A1*28/*6 gene polymorphisms by polymerase chain reaction amplification and pyrosequencing. The analysis of UGT1A1*28 and UGT1A1*6 gene polymorphisms was performed in 67 patients with E-SCLC admitted to the clinic in the Department of Oncology from June 2011 to January 2013. A total of 67 cases with E-SCLC treated with irinotecan (CPT-11)-based regimen were enrolled to observe the adverse events and efficacy during the chemotherapy, including objective response rate, progression-free survival (PFS) and overall survival (OS). The correlation between UGT1A1 gene polymorphisms and severe adverse events was analyzed. The influences of UGT1A1*6/*28 polymorphisms on objective response rate, PFS, and OS were also analyzed. **RESULTS:** The distribution of UGT1A1 genotypes among 67 patients was as follows: UGT1A1*28 wild-type (WT) genotype TA6/6 (56, 83.6%), heterozygous mutant genotype TA6/7 (11, 16.4%); UGT1A1*6 WT genotype G/G (45, 67.2%), heterozygous mutant genotype G/A (22, 32.8%); no significant difference of PFS and OS was observed between different genotypes. The incidence of grade 3 and 4 delayed diarrhea and neutropenia in the patients carrying UGT1A1*6 G/A mutation was higher than that in the WT genotype (36.4% vs 6.6% P=0.034; 27.2% vs 4.4% P=0.026, respectively). The incidence of grade 3 and 4 thrombocytopenia in the patients carrying UGT1A1*28 TA6/7 mutation was higher than that in the WT genotype (27.2% vs 1.8% P=0.017). The patients simultaneously carrying UGT1A1*28 TA6/7 and UGT1A1*6 G/A mutations were prone to suffering grade 3 and 4 delayed diarrhea and neutropenia. **CONCLUSION:** For irinotecan-based regimens in E-SCLC, the UGT1A1*28 and UGT1A1*6 locus mutations can be regarded as predictors for severe adverse events. We also found that neither clinical response nor prognosis was significantly associated with the UGT1A1 gene polymorphisms.

Synergistic killing of human small cell lung cancer cells by the Bcl-2-inositol 1,4,5-trisphosphate receptor disruptor BIRD-2 and the BH3-mimetic ABT-263. Greenberg EF1,2,3, McColl KS1,3, Zhong F1,3, Wildey G1,3, Dowlati A1,3, Distelhorst CW1,3. Cell Death Dis. 2015 Dec 31;6:e2034. doi: 10.1038/cddis.2015.355.
Small cell lung cancer (SCLC) has an annual mortality approaching that of breast and prostate cancer. Although sensitive to initial chemotherapy, SCLC rapidly develops resistance, leading to less effective second-line therapies. SCLC cells often overexpress Bcl-2, which protects cells from apoptosis both by sequestering pro-apoptotic family members and by modulating inositol 1,4,5-trisphosphate receptor (IP3R)-mediated calcium signaling. BH3-mimetic agents such as ABT-263 disrupt the former activity but have limited activity in SCLC patients. Here we report for the first time that Bcl-2-IP3 receptor disruptor-2 (BIRD-2), a decoy peptide that binds to the BH4 domain of Bcl-2 and prevents Bcl-2 interaction with IP3Rs, induces cell death in a wide range of SCLC lines, including ABT-263-resistant lines. BIRD-2-induced death of SCLC cells appears to be a form of caspase-independent apoptosis mediated by calpain activation. By targeting different regions of the Bcl-2 protein and different mechanisms of action, BIRD-2 and ABT-263 induce cell death synergistically. Based on these findings, we propose that targeting the Bcl-2-IP3R interaction be pursued as a novel therapeutic strategy for SCLC, either by developing BIRD-2 itself as a therapeutic agent or by developing small-molecule inhibitors that mimic BIRD-2.

Pleural Small Cell Lung Carcinoma: An Unusual Culprit in Pleural Effusion. Adejorin OD1, Sodhi A1, Hare FA1, Headley AS1, Murillo LC1, Kadaria D1. Am J Case Rep. 2015 Dec 30;16:912-5.
BACKGROUND: Small cell lung carcinoma (SCLC) usually presents as lung or mediastinal lesions. It is very rare for SCLC to present primarily as an isolated pleural effusion with no lung or mediastinal lesions. **CASE REPORT:** We report the case of a 77-year-old white male with a 60-pack year history of smoking, chronic obstructive pulmonary disease (stage IV), and asbestos exposure who presented with shortness of breath and left lateral chest pain for 7 days. On physical examination, he was very short of breath, with a prolonged expiratory phase on chest auscultation. Laboratory results were normal except for leukocytosis and chest radiograph revealing left-sided pleural effusion. Computerized tomography (CT) scanning of the chest with IV contrast showed left-sided pleural effusion without any lung or mediastinal lesions. Thoracentesis was performed and fluid was sent for analysis. Repeat CT chest/abdomen/pelvis, done immediately following thoracocentesis, did not show any masses or lymphadenopathy. Fluid analysis, including cytology and immunostain pattern, was consistent with small cell carcinoma. **CONCLUSIONS:** Small cell lung cancer presenting as an isolated pleural effusion is extremely rare. It requires close attention to cytology and immunohistochemistry of pleural fluid samples. It also has implications for management and should be managed as limited-stage SCLC.

The Role of Radiotherapy in the Treatment of Small-Cell Lung Cancer. Nosaki K1, Seto T2. Curr Treat Options Oncol. 2015 Dec;16(12):56. doi: 10.1007/s11864-015-0372-2.
OPINION STATEMENT: The standard therapy for limited disease small cell lung cancer (LD-SCLC) is concurrent chemoradiotherapy and prophylactic cranial irradiation (PCI) for those who achieve complete remission (CR) or good partial response (PR) with initial therapy. On the other hand, the standard therapy for extensive disease (ED-SCLC) is chemotherapy only. After the two phase III study conducted by Slotman et al., PCI with/without thoracic radiotherapy (TRT) is also recommended in the treatment of ED-SCLC. However, a Japanese phase III study failed to confirm the benefit of PCI for patients with ED-SCLC. All studies have demonstrated the effectiveness of PCI for preventing brain metastasis, but PCI seems to have a limited influence on OS. In the 2014 edition of the Guidelines for the Treatment of Lung Cancer from the Japan Lung Cancer Society (JLCS), use of PCI for patients with ED-SCLC has been changed from "recommended" to "not recommended". Appropriate selection of patients for PCI with/without TRT is very important. It is hoped that the characteristics of patients for whom PCI with/without TRT should be considered or avoided will be better defined in the future.

Positive Interaction Between Prophylactic Cranial Irradiation and Maintenance Sunitinib for Untreated Extensive-Stage Small Cell Lung Cancer Patients After Standard Chemotherapy: A Secondary Analysis of CALGB 30504 (ALLIANCE). Salama JK1, Gu L2, Wang X2, et al. J Thorac Oncol. 2015 Dec 24. pii: S1556-0864(15)00049-0. doi: 10.1016/j.jtho.2015.11.001. [Epub ahead of print]
BACKGROUND: Prophylactic cranial irradiation (PCI) has become a standard option for patients with extensive-stage small cell lung cancer (ES-SCLC). The Cancer and Leukemia Group B 30504 trial was a randomized phase II study of the effect of sunitinib versus placebo in ES-SCLC patients responding to platinum-based systemic therapy. The study required preenrollment brain imaging. PCI was provided at the discretion of treating physicians. We performed a secondary analysis of the Cancer and Leukemia Group B trial to determine the impact of PCI on patients with ES-SCLC. **METHODS:** Fisher's exact test and the Wilcoxon rank-sum test were conducted to identify the differences between patients receiving PCI and patients not receiving PCI. Kaplan-Meier analyses described progression-free survival (PFS) and overall survival (OS) for patients in the PCI and non-PCI groups. **RESULTS:** A total of 85 patients received maintenance therapy (41 received placebo and 44 received sunitinib). Patient characteristics were balanced between the PCI and non-PCI groups. The patients receiving PCI plus sunitinib had a

nonsignificant 2.7-month improvement in PFS (5.0 months versus 2.3 months, p = 0.14, hazard risk [HR] = 0.62, 95% confidence interval [CI]: 0.33-1.18) trending toward improved OS (8.9 months versus 5.4 months, p = 0.053, HR = 0.47, 95% CI: 0.22-1.03). PCI was associated with a trend toward improved median PFS (2.9 months versus 2.2 months, p = 0.096, HR = 0.69, 95% CI: 0.45-1.07) but not median OS (8.3 months in the PCI group versus 8.7 months in the non-PCI group, p = 0.76, HR = 1.07, 95% CI: 0.67-1.71). The patients receiving placebo had no improvement in PFS or OS with PCI. **CONCLUSIONS:** Trends toward improved PFS and OS were seen in patients receiving PCI and sunitinib, thus supporting the need for further prospective research evaluating the integration of maintenance systemic therapy and PCI for patients with ES-SCLC. Improved outcomes for patients with ES-SCLC after induction chemotherapy may require PCI, thoracic radiotherapy, and maintenance systemic therapy to achieve control of both intracranial and extracranial disease.

Utilization of Hyperfractionated Radiation in Small-Cell Lung Cancer and Its Impact on Survival.
Schreiber D1, Wong AT, Schwartz D, Rineer J. J Thorac Oncol. 2015 Dec;10(12):1770-5. doi: 10.1097/JTO.0000000000000672.
INTRODUCTION: Twice-daily radiation with concurrent chemotherapy is recognized as the standard of care for the treatment of limited stage small-cell lung carcinoma (SCLC), but its utilization in this setting is unclear. The objective of this study was to analyze modern patterns of treatment for limited stage SCLC and the impact on survival utilizing the National Cancer Database. **METHODS:** Between 1999 and 2012, there were 25,045 patients diagnosed with nonmetastatic SCLC who met the selection criteria, of whom 22,626 had survival data. Those receiving 45 Gy in 1.5 Gy fractions twice-daily (BID) were compared with those receiving 45 to 72 Gy in 1.8 or 2.0 Gy fractions. Overall survival was analyzed via Kaplan-Meier analysis and compared using the log-rank test. Multivariate Cox regression analysis was used to identify covariates associated with survival. **RESULTS:** The utilization of BID radiation overall was 11.3%. Treatment at an academic center was associated with a higher likelihood of receiving BID treatment (odds ratio: 2.29, 95% confidence interval [CI]: 1.95-2.69; p < 0.001). Median survival was 22.1, 17.2, 18.3, 19.2, and 19.5 months for patients receiving 45 Gy BID, 45 Gy once-daily, 46 to 59.4 Gy once-daily, 60 to 61.2 Gy once-daily, and 62 to 72 Gy once-daily, respectively (p < 0.001 for all pairwise comparisons to BID). On multivariate analysis, treatment at an academic center (hazard ratio: 0.88, 95% CI: 0.83-0.93; p < 0.001) and receipt of BID radiation (hazard ratio: 0.92, 95% CI: 0.86-0.98; p = 0.008) were associated with improved survival. **CONCLUSIONS:** The adoption of BID radiation remains very limited, but is more commonly utilized in the academic setting. In this hospital-based study, BID fractionation was associated with improved survival over once-daily fractionation, even at doses ≥60 Gy.

Bromodomain and hedgehog pathway targets in small cell lung cancer. Kaur G1, Reinhart RA2, Monks A2, Evans D2, Morris J3, Polley E4, Teicher BA5. Cancer Lett. 2015 Dec 10. pii: S0304-3835(15)00737-5. doi: 10.1016/j.canlet.2015.12.001. [Epub ahead of print]
Small cell lung cancer (SCLC) is an extremely aggressive cancer that frequently recurs. Twenty-three human SCLC lines were selected representing varied Myc status. Gene expression of lung cancer, stem-like, hedgehog pathway, and notch pathway genes were determined by RT2-PCR array and Exon 1.0 ST array. Etoposide and topotecan concentration response was examined. The IC50's for etoposide and topotecan ranged over nearly 3 logs upon 96 hrs exposure to the drugs. Myc status, TOP2A, TOP2B and TOP1 mRNA expression or topoisomerase 1 and topoisomerase 2 protein did not account for the range in the sensitivity to the drugs. γ-secretase inhibitors, RO429097 and PF-03084014, had little activity in the SCLC lines over ranges covering the clinical Cmax concentrations. MYC amplified lines tended to be more sensitive to the bromodomain inhibitor JQ1. The Smo antagonists, erismodegib and vismodegib and the Gli antagonists, HIP1 and SEN-450 had a trend toward greater sensitivity of the MYC amplified line.

Recurrent SCLC is among the most recalcitrant cancers and drug development efforts in this cancer are a high priority.

PALLIATIVE AND SUPPORTIVE CARE

Preclinical Investigation of the Novel Histone Deacetylase Inhibitor AR-42 in the Treatment of Cancer-Induced Cachexia. Tseng YC1, Kulp SK1, Lai IL1, et al. J Natl Cancer Inst. 2015 Oct 12;107(12):djv274. doi: 10.1093/jnci/djv274. Print 2015 Dec.
BACKGROUND: Cancer cachexia is a debilitating condition that impacts patient morbidity, mortality, and quality of life and for which effective therapies are lacking. The anticachectic activity of the novel HDAC inhibitor AR-42 was investigated in murine models of cancer cachexia. **METHODS:** The effects of AR-42 on classic features of cachexia were evaluated in the C-26 colon adenocarcinoma and Lewis lung carcinoma (LLC) models. Effects on survival in comparison with approved HDAC inhibitors (vorinostat, romidepsin) were determined. The muscle metabolome and transcriptome (by RNA-seq), as well as serum cytokine profile, were evaluated. Data were analyzed using mixed effects models, analysis of variance, or log-rank tests. All statistical tests were two-sided. **RESULTS:** In the C-26 model, orally administered AR-42 preserved body weight (23.9±2.6 grams, AR-42-treated; 20.8±1.3 grams, vehicle-treated; $P = .005$), prolonged survival ($P < .001$), prevented reductions in muscle and adipose tissue mass, muscle fiber size, and muscle strength and restored intramuscular mRNA expression of the E3 ligases MuRF1 and Atrogin-1 to basal levels ($n = 8$). This anticachectic effect, confirmed in the LLC model, was not observed after treatment with vorinostat and romidepsin. AR-42 suppressed tumor-induced changes in inflammatory cytokine production and multiple procachexia drivers (IL-6, IL-6Rα, leukemia inhibitory factor, Foxo1, Atrogin-1, MuRF1, adipose triglyceride lipase, uncoupling protein 3, and myocyte enhancer factor 2c). Metabolomic analysis revealed cachexia-associated changes in glycolysis, glycogen synthesis, and protein degradation in muscle, which were restored by AR-42 to a state characteristic of tumor-free mice. **CONCLUSIONS:** These findings support further investigation of AR-42 as part of a comprehensive therapeutic strategy for cancer cachexia.

Prevalence and Predictors of Inappropriate Delivery of Palliative Thoracic Radiotherapy for Metastatic Lung Cancer. Koshy M1, Malik R2, Mahmood U2, Husain Z2, Weichselbaum RR2, Sher DJ2. J Natl Cancer Inst. 2015 Sep 30;107(12):djv278. doi: 10.1093/jnci/djv278. Print 2015 Dec.
BACKGROUND: High-level evidence has established well-recognized standard treatment regimens for patients undergoing palliative chest radiotherapy (RT) for stage IV non-small cell lung cancer (NSCLC), including treating with fewer than 15 fractions of RT, and not delivering concurrent chemoradiation (CRT) because of its increased toxicity and limited efficacy in the palliative setting. **METHODS:** The study included patients in the National Cancer Database from 2004 to 2012 with stage IV lung cancer who received palliative chest radiation therapy. Logistic regression was performed to determine predictors of standard vs nonstandard regimens (>15 fractions or CRT). All statistical tests were two-sided. **RESULTS:** There were 46 803 patients in the analysis and 49% received radiotherapy for longer than 15 fractions, and 28% received greater than 25 fractions. Approximately 19% received CRT. The strongest independent predictors of long-course RT were private insurance (odds ratio [OR] = 1.40 vs uninsured, 95% confidence interval [CI] = 1.28 to 1.53) and treatment in community cancer programs (OR = 1.49, 95% CI = 1.38 to 1.58) compared with academic research programs. The strongest factors that predicted for concurrent chemoradiotherapy were private insurance (OR = 1.38 95% CI = 1.23 to 1.54) compared with uninsured patients and treatment in community cancer programs (OR = 1.44, 95% CI = 1.33 to 1.56) compared with academic programs. **CONCLUSIONS:** Approximately half of all patients with metastatic lung cancer received a higher number of radiation fractions than recommended. Patients with private insurance and treated in community cancer centers were more likely to receive longer courses of RT or

CRT. This demonstrates that a substantial number of patients requiring palliative thoracic radiotherapy are overtreated and further work is necessary to ensure these patients are treated according to evidenced-based guidelines.

Randomized Double-Blind Trial of Pregabalin Versus Placebo in Conjunction With Palliative Radiotherapy for Cancer-Induced Bone Pain. Fallon M1, Hoskin PJ2, Colvin LA2, et al. J Clin Oncol. 2015 Dec 7. pii: JCO.2015.63.8221. [Epub ahead of print]
PURPOSE: Cancer-induced bone pain (CIBP) affects one third of patients with cancer. Radiotherapy remains the gold-standard treatment; however, laboratory and clinical work suggest that pregabalin may be useful in treating CIBP. The aim of this study was to examine pregabalin in patients with CIBP receiving radiotherapy. **PATIENTS AND METHODS:** A multicenter, double-blind randomized trial of pregabalin versus placebo was conducted. Eligible patients were age ≥ 18 years, had radiologically proven bone metastases, were scheduled to receive radiotherapy, and had pain scores ≥ 4 of 10 (on 0-to-10 numeric rating scale). Before radiotherapy, baseline assessments were completed, followed by random assignment. Doses of pregabalin and placebo were increased over 4 weeks. The primary end point was treatment response, defined as a reduction of ≥ 2 points in worst pain by week 4, accompanied by a stable or reduced opioid dose, compared with baseline. Secondary end points assessed average pain, interference of pain with activity, breakthrough pain, mood, quality of life, and adverse events. **RESULTS:** A total of 233 patients were randomly assigned: 117 to placebo and 116 to pregabalin. The most common cancers were prostate (n = 88; 38%), breast (n = 77; 33%), and lung (n = 42; 18%). In the pregabalin arm, 45 patients (38.8%) achieved the primary end point, compared with 47 (40.2%) in the placebo arm (adjusted odds ratio, 1.07; 95% CI, 0.63 to 1.81; P = .816). There were no statistically significant differences in average pain, pain interference, or quality of life between arms. There were differences in mood (P = .031) and breakthrough pain duration (P = .037) between arms. Outcomes were compared at 4 weeks. **CONCLUSION:** Our findings do not support the role of pregabalin in patients with CIBP receiving radiotherapy. The role of pregabalin in CIBP with a clinical neuropathic pain component is unknown.

Prognostic value of health-related quality of life for overall survival in elderly non-small-cell lung cancer patients. Fiteni F1, Vernerey D2, Bonnetain F3, et al. Eur J Cancer. 2016 Jan;52:120-8. doi: 10.1016/j.ejca.2015.10.004. Epub 2015 Dec 10.
BACKGROUND: We investigated whether the health-related quality of life (HRQoL) score is a prognostic factor for overall survival (OS) in elderly patients with advanced non-small-cell lung cancer (NSCLC). **METHODS:** We included 451 NSCLC patients aged 70-89 years enrolled in the Intergroupe Francophone de Cancérologie Thoracique 0501 trial, using scores of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 at baseline to investigate the prognostic value of HRQoL for OS, in addition to conventional factors. Cox regression model was used for both univariate and multivariate analyses of OS. **RESULTS:** Global health status (GH) dimension score at baseline was associated with favourable OS when adjusted for clinical, functional, and histological factors (hazard ratio [HR]: 0.986; 95% confidence interval [CI]: 0.980-0.992). We distinguished three groups according to GH score: high (GH <46), intermediate (46 ≤GH ≤67), and low (GH >67) mortality risk. The median OS values were 14.5, 8.2, and 5.3 months in the low-, intermediate-, and high-risk categories, respectively (log-rank P <0.0001). In the high-risk group, doublet chemotherapy was not associated with favourable OS (HR: 0.70; 95% CI: 0.49-1.003; P=0.052), whereas in the intermediate- and low-risk groups, doublet chemotherapy was associated with favourable OS (HR: 0.72; 95% CI: 0.54-0.96; P=0.023 and HR: 0.50; 95% CI: 0.30-0.84; P=0.0089, respectively). **CONCLUSION:** This study supports the additional prognostic value of HRQoL data at diagnosis to identify vulnerable subpopulations in elderly NSCLC patients. HRQoL could thus be valuable in selecting patients who will benefit from doublet chemotherapy.

Reasons for palliative treatments in stage III non-small-cell lung cancer: what contribution is made by time-dependent changes in tumour or patient status? Robinson AG1, Young K2, Balchin K3, Owen T1, Ashworth A1. Curr Oncol. 2015 Dec;22(6):399-404. doi: 10.3747/co.22.2689.
INTRODUCTION: Stage iii lung cancer is the most advanced stage of lung cancer for which the potential of curative treatment is often discussed. However, a large proportion of patients are treated with palliative intent. An understanding of the time-dependent and -independent factors contributing to the choice of palliative-intent treatment is needed to help optimize patient outcomes. **METHODS:** This retrospective cohort study of patients with stage iii non-small-cell lung cancer (nsclc) newly diagnosed between 1 January 2008 and 31 December 2012 at the Cancer Centre of Southeastern Ontario collected data including patient demographics, clinical characteristics, tumour characteristics, treatment, and outcomes. **RESULTS:** Of 237 patients with stage iii nsclc included in the study, 130 were not treated with radical or curative intent (55%). Major time-independent variables cited for palliative-intent treatment included extreme age (5%), comorbidity (27%), patient choice (5%), and poor lung function (5%). Time-dependent variables included tumour progression on imaging (15%), weight loss (33%), performance status (32%), and the occurrence of a major complication such as hemoptysis, lung collapse, or pulmonary embolism (7%). A significant number of patients (20%) experienced a decline in performance status-to 2, 3, or 4 from 0 or 1-over the course of the diagnostic journey, and 12% experienced a transition from no weight loss to more than 10% weight loss. **CONCLUSIONS:** A significant proportion of patients receive palliative therapy for stage iii nsclc because of changes that occur during the diagnostic journey. Shortening or altering that pathway to avoid tumour growth or patient deterioration during care could allow for more patients to be treated with curative intent.

Distinct Characteristics of Small Cell Lung Cancer Correlate With Central or Peripheral Origin: Subtyping Based on Location and Expression of Transcription Factor TTF-1. Miyauchi E1, Motoi N, Ono H, Ninomiya H, Ohyanagi F, Nishio M, Okumura S, Ichinose M, Ishikawa Y. Medicine (Baltimore). 2015 Dec;94(51):e2324. doi: 10.1097/MD.0000000000002324.
Small-cell lung carcinoma (SCLC) is a type of lung cancer with neuroendocrine differentiation and a poor prognosis that is widely believed to arise in the central lung. Thyroid transcription factor-1 (TTF-1) is a peripheral marker of lung adenocarcinoma that is also highly expressed in SCLC. In this study, we examined whether SCLC is really a central-type tumor and the relationship between tumor location, TTF-1 expression and prognosis of SCLC.Ninety six SCLCs, diagnosed from biopsies or surgical materials, for which detailed computed tomography (CT) images were available, were collected consecutively from Japanese patients between 2004 and 2011. We examined the location of the primary tumor (central or peripheral) using thin-sliced CT, a TTF-1 immunohistochemical expression, and clinicopathology including prognosis.Of the 96 SCLCs, 74% (71/96) were of the peripheral type and found to have a significantly worse prognosis than central-type tumors. TTF-1 immunoreactivity was identified in 79 tumors (82%), 78% of which (62/79) were of the peripheral type and 22% of which were central. TTF-1 expression was significantly correlated with peripheral location ($P=0.030$). Multivariate analysis revealed that high TNM stages and the peripheral location were independent markers for poor survival.The majority of SCLCs were of the peripheral type. The peripheral-type SCLC expressed TTF-1 more frequently and had a poorer prognosis than central-type tumors did. Further analysis on original sites of SCLC, using molecular methodology, or based on another ethnicity, should be warranted.

Making the Grade: The Impact of Low-Grade Toxicities on Patient Preference for Treatment With Novel Agents. Castellanos EH1, Chen SC1, Drexler H1, Horn L1. J Natl Compr Canc Netw. 2015 Dec;13(12):1490-5.

BACKGROUND: Targeted therapies have shown clinical benefit in the treatment of solid tumors. The toxicity profiles and treatment duration and schedule of these agents differ considerably from those of traditional chemotherapy. Many studies of targeted therapies report sizeable numbers of grade 1 or 2 toxicities. We sought to determine whether anticipation of low-grade toxicities and treatment logistics impact patient willingness to undergo therapy. **PATIENTS AND METHODS:** A total of 209 patients with cancer (101 lung and 108 breast) were surveyed at the Vanderbilt-Ingram Cancer Center regarding willingness to comply with treatment based on anticipated efficacy, dosing convenience, and toxicity profiles. All toxicities were Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grade 1 and 2. Willingness to comply with treatment depending on toxicity, anticipated benefit, cancer type, and dosing convenience was compared. **RESULTS:** A substantial number of patients (2.9%-48.8%, depending on the toxicity described) professed unwillingness to undergo treatment because of anticipated grade 1 and 2 toxicities. Gastrointestinal and constitutional toxicities had a stronger negative impact on patient willingness to undergo therapy than dermatologic toxicity. Patients with lung cancer were significantly more likely to accept dermatologic and gastrointestinal toxicities than those with breast cancer. Willingness to tolerate toxicities correlated with expected benefit in terms of life expectancy and chance of cure. Lengthy travel distance for treatment negatively impacted willingness to undergo treatment. **CONCLUSIONS:** Anticipation of low-grade toxicities and dosing inconvenience negatively impacts patient willingness to be treated, which may affect adherence and therapeutic outcomes from therapy. Long-term tolerability should be considered when developing and assessing the impact of novel agents.

Prognosis, Treatment Benefit and Goals of Care: What do Oncologists Discuss with Patients who have Incurable Cancer? Raskin W1, Harle I2, Hopman WM3, Booth CM4. Clin Oncol (R Coll Radiol). 2015 Dec 14. pii: S0936-6555(15)00446-X. doi: 10.1016/j.clon.2015.11.011. [Epub ahead of print]
AIMS: Documentation of advance directives among patients with terminal cancer is known to be poor. Here we describe documentation of prognosis, treatment benefit and goals of care discussions in outpatients with advanced cancer. **MATERIALS AND METHODS:** All patients receiving first-line palliative chemotherapy for metastatic pancreas or lung cancers during 2010-2013 at the Cancer Centre of Southeastern Ontario were identified from electronic pharmacy records. Clinical notes from medical oncology were reviewed to identify documentation of discussions regarding prognosis, treatment benefit and goals of care. Differences between groups were tested using the chi-squared test. **RESULTS:** In total, 222 patients were included: 80% (177/222) with lung cancer and 20% (45/222) with pancreas cancer. Medical oncology notes documented discussion of prognosis in 64% (142/222), palliative intent of therapy in 82% (182/222), magnitude of treatment benefit in 29% (64/222) and goals of care in 4% (9/222) of patients. An estimate of survival was documented in 36% (79/222) of cases. Across medical oncology providers there was substantial variation in the frequency of discussing prognosis (range 33-90%, $P < 0.001$), treatment intent (range 55-100%, $P < 0.001$) and goals of care (range 0-17%, $P = 0.034$). In total, 41% (93/222) of patients were seen by palliative care; substantial medical oncology provider variation was observed (range 27-58%, $P = 0.020$). Referral rates to palliative care did not increase over time (41-44%, $P = 0.250$). **CONCLUSIONS:** In this cohort of ambulatory patients with an estimated life expectancy of 1 year or less, medical oncology documentation of prognosis, treatment benefit and goals of care was poor. Less than half the patients were seen by palliative care. Initiatives to improve documentation and referral to palliative care are needed.

Tai Chi Exercise for Cancer-Related Fatigue in Patients with Lung Cancer Undergoing Chemotherapy: A Randomized Controlled Trial. Zhang LL1, Wang SZ2, Chen HL3, Yuan AZ4. J Pain Symptom Manage. 2015 Dec 22. pii: S0885-3924(15)00989-6. doi: 10.1016/j.jpainsymman.2015.11.020. [Epub ahead of print]

OBJECTIVES: We aimed to assess the effectiveness of Tai Chi exercise for cancer-related fatigue (CRF) in patients with lung cancer undergoing chemotherapy. **METHODS:** We conducted a randomized trial of Tai Chi exercise as compared with low-impact exercise as a control intervention. Exercises were practiced every other day, a one-hour session for 12 weeks for each of the study groups. The primary endpoint was a change in total score of the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF). Secondary endpoints were changes in five subscale scores of the MFSI-SF. All assessments were repeated at three time points, T0: before first course of chemotherapy; T1: before third course of chemotherapy; and T2: at the end of the fourth course of chemotherapy. **RESULTS:** Between January 2012 and December 2014, 96 patients were enrolled in this trial. At six weeks and 12 weeks, the Tai Chi group had a lower MFSI-SF total score compared with the control group (59.5±11.3 vs. 66.8±11.9, $P<0.05$; 53.3±11.8 vs. 59.3±12.2, $P<0.05$). At six weeks, the Tai Chi group had lower MFSI-SF general subscale scores (18.1±4.6 vs. 20.4±4.5, $P<0.05$) and physical subscale scores (17.5±4.4 vs. 19.1±4.5, $P<0.05$), and higher MFSI-SF vigor subscale scores (14.5±3.3 vs. 11.6±3.4, $P<0.05$), compared with the control group. But no significant differences were found in emotional subscale (20.2±3.6 vs. 20.0±3.5, $P>0.05$) and mental subscale (18.2±4.0 vs. 18.9±3.9, $P>0.05$) scores between the Tai Chi group and the control group. At 12 weeks, the MFSI-SF subscale scores showed the same trends as at six weeks. **CONCLUSION:** Tai Chi is an effective intervention for managing cancer-related fatigue in patients with lung cancer undergoing chemotherapy, especially for decreasing general fatigue and physical fatigue, and increasing vigor.

Effectiveness of Chinese herbal medicine for cancer palliative care: overview of systematic reviews with meta-analyses. Chung VCh1,2, Wu X1,2, Hui EP1,3, et al. Sci Rep. 2015 Dec 16;5:18111. doi: 10.1038/srep18111.

Chinese herbal medicines (CHM) are often used in managing cancer related symptoms but their effectiveness and safety is controversial. We conducted this overview of meta-analyses to summarize evidence on CHM for cancer palliative care. We included systematic reviews (SRs) with meta-analyses of CHM clinical trials on patients diagnosed with any type of cancer. Methodological quality of included meta-analyses was assessed with the Methodological Quality of Systematic Reviews (AMSTAR) Instrument. Fifty-one SRs with meta-analyses were included. They covered patients with lung (20 SRs), gastric (8 SRs), colorectal (6 SRs), liver (6 SRs), breast (2 SRs), cervical (1 SR), esophageal (1 SR), and nasopharyngeal (1 SR) cancers. Six SRs summarized evidence on various types of cancer. Methodological quality of included meta-analyses was not satisfactory. Overall, favorable therapeutic effects in improving quality of life among cancer patients have been reported. Conflicting evidence exists for the effectiveness of CHM in prolonging survival and in reducing chemotherapy and/or radiotherapy related toxicities. No serious adverse effects were reported in all included studies. Evidence indicated that CHM could be considered as an option for improving quality of life among patients receiving palliative care. It is unclear if CHM may increase survival, or reduce therapy related toxicities.

Wenxia Changfu Formula () induces apoptosis of lung adenocarcinoma in a transplanted tumor model of drug-resistance nude mice. Ji XM1, Wu ZC2, Liu GW1, Yu HY1, Liu H3, Wang ZT4, Wei XH4, Ouyang B1. Chin J Integr Med. 2015 Dec 14. [Epub ahead of print]

OBJECTIVE: To explore the apoptosis mechanism of Wenxia Changfu Formula (, WCF) in reversing drug resistance of lung cancer in vivo. **METHODS:** Thirty model mice were randomly assigned to three groups: control group, cisplatin (CDDP) group, and WCF group. A transplanted tumor model of lung adenocarcinoma was established in all groups. Mice in the WCF group received intragastric administration of WCF (0.2 mL/10 g body weight) everyday in addition to CDDP intraperitoneally (5 mg/kg body weight) twice a week. The mice in the CDDP group received CDDP intraperitoneally (5 mg/kg body weight) twice a week, while the control group received normal saline intraperitoneally (0.2 mL/10 g body weight) everyday. The weight of the nude mice and respective tumors, tumor volume and tumor-inhibiting rate were measured. Electron microscopy was used to observe the existence of apoptosis body. Apoptosis index (AI) was detected by TdT-mediated dUTP nick end labeling staining. The expression of Fas and FasL mRNA was investigated by reverse transcription polymerase chain reaction, while immunohistochemistry was applied to detect the protein expression of Fas and FasL, caspase-3 and caspase-activated DNase (CAD), respectively. **RESULTS:** Compared with CDDP group and control group, WCF could signififi cantly reduce the tumor volume from the 19th day and alleviate the tumor weight ($P < 0.05$), and the apoptosis body was found in tumor cells in the WCF group. WCF could also enhance the level of AI, up-regulate the expression of caspase apoptosis pathway related protein caspase-3 and CAD, as well as the expression of Fas, FasL mRNA and protein ($P < 0.05$). **CONCLUSION:** WCF could improve the sensitivity of tumor cells to CDDP and reverse the drug resistance by inducing the apoptosis.

Phloretin exhibits an anticancer effect and enhances the anticancer ability of cisplatin on non-small cell lung cancer cell lines by regulating expression of apoptotic pathways and matrix metalloproteinases. Ma L1, Wang R1, Nan Y1, Li W1, Wang Q2, Jin F1. Int J Oncol. 2016 Feb;48(2):843-53. doi: 10.3892/ijo.2015.3304. Epub 2015 Dec 21.
Non-small cell lung cancer (NSCLC) accounts for 80-85% of all lung cancer cases and the prognosis of NSCLC patients is unsatisfactory since 5-year survival rate of NSCLC is still as low as 11%. Natural compounds derived from plants with few or no side effects have been recognized as alternative or auxiliary cure for cancer patients. Phloretin is such an agent possessing various pharmacological activities; however, there is scarce information on its anticancer effects on NSCLC. It was evaluated and confirmed, in the present study, that phloretin inhibited proliferation and induced apoptosis in A549, Calu-1, H838 and H520 cells in a dose-dependent manner, phloretin also suppressed the invasion and migration of NSCLC cells. We further confirmed that phloretin dose-dependently suppressed the expression of Bcl-2, increased the protein expression of cleaved-caspase-3 and -9, and deregulated the expression of matrix metalloproteinases (MMP)-2 and -9 on gene and protein levels. Besides, evaluations revealed that phloretin enhanced the anticancer effects of cisplatin on inhibition of proliferation and induction of apoptosis in NSCLC cells. Moreover, phloretin facilitated the effects of cisplatin on deregulation of Bcl-2, MMP-2 and -9, and upregulation of cleaved-caspase-3 and -9. In conclusion, the present study demonstrated that phloretin possessed anticancer effects and enhanced the anticancer effects of cisplatin on NSCLC cell lines by suppressing proliferation, inducing apoptosis and inhibiting invasion and migration of the cells through regulating apoptotic pathways and MMPs.

MISCELLANEOUS WORKS

Targeted Therapies for Non-Small Cell Lung Cancer: An Update on Epidermal Growth Factor Receptor and Anaplastic Lymphoma Kinase Inhibitors. Kreamer K1, Riordan D1. Clin J Oncol Nurs. 2015 Dec 1;19(6):734-42. doi: 10.1188/15.CJON.734-742.
BACKGROUND: The development of targeted therapies has revolutionized the treatment of advanced non-small cell lung cancer (NSCLC), with new clinical trials and therapies consistently providing new

information. This rapidly changing field mandates ongoing education for nursing professionals whose foremost priority is patient care. **OBJECTIVES:** This review aims to summarize the history and current status of targeted therapies for NSCLC, focusing on two types of drugs that have had the most impact to date. **METHODS:** The safety profiles of first- and second-generation EGFR and ALK inhibitors are described, and strategies for the management of the most commonly experienced adverse events are summarized. Information is also provided to help identify which patients might be eligible for treatment with EGFR or ALK inhibitors in addition to the implications of targeted therapies. **FINDINGS:** Therapies designed to target specific molecular features of individual tumor cells are one of the most important developments in treating NSCLC. The safety profiles of targeted therapies differ greatly from chemotherapy and present unique challenges to nurses. Education of nurses and patients on implementation of effective adverse event management and improvement in patient adherence will maximize the benefits of these drugs.

A Prognostic Model to Predict Mortality among Non-Small-Cell Lung Cancer Patients in the U.S. Military Health System. Lin J1, Carter CA, McGlynn KA, Zahm SH, Nations JA, Anderson WF, Shriver CD, Zhu K. J Thorac Oncol. 2015 Dec;10(12):1694-702. doi: 10.1097/JTO.0000000000000691. **INTRODUCTION:** Accurate prognosis assessment after non-small-cell lung cancer (NSCLC) diagnosis is an essential step for making effective clinical decisions. This study is aimed to develop a prediction model with routinely available variables to assess prognosis in patients with NSCLC in the U.S. Military Health System. **METHODS:** We used the linked database from the Department of Defense's Central Cancer Registry and the Military Health System Data Repository. The data set was randomly and equally split into a training set to guide model development and a testing set to validate the model prediction. Stepwise Cox regression was used to identify predictors of survival. Model performance was assessed by calculating area under the receiver operating curves and construction of calibration plots. A simple risk scoring system was developed to aid quick risk score calculation and risk estimation for NSCLC clinical management. **RESULTS:** The study subjects were 5054 patients diagnosed with NSCLC between 1998 and 2007. Age, sex, tobacco use, tumor stage, histology, surgery, chemotherapy, peripheral vascular disease, cerebrovascular disease, and diabetes mellitus were identified as significant predictors of survival. Calibration showed high agreement between predicted and observed event rates. The area under the receiver operating curves reached 0.841, 0.849, 0.848, and 0.838 during 1, 2, 3, and 5 years, respectively. **CONCLUSIONS:** This is the first NSCLC prognosis model for quick risk assessment within the Military Health System. After external validation, the model can be translated into clinical use both as a web-based tool and through mobile applications easily accessible to physicians, patients, and researchers.

Risk Adjusting Survival Outcomes in Hospitals That Treat Patients With Cancer Without Information on Cancer Stage. Pfister DG1, Rubin DM1, Elkin EB1, Neill US1, Duck E1, Radzyner M1, Bach PB1. JAMA Oncol. 2015 Dec 1;1(9):1303-10. doi: 10.1001/jamaoncol.2015.3151. **IMPORTANCE:** Instituting widespread measurement of outcomes for cancer hospitals using administrative data is difficult owing to lack of cancer-specific information such as disease stage. **OBJECTIVE:** To evaluate the performance of hospitals that treat patients with cancer using Medicare data for outcome ascertainment and risk adjustment and to assess whether hospital rankings based on these measures are altered by the addition of cancer-specific information. **DESIGN, SETTING, AND PARTICIPANTS:** Risk-adjusted cumulative mortality rates of patients with cancer were captured in Medicare claims data from 2005 through 2009 nationally and assessed at the hospital level. Similar analyses were conducted using Surveillance, Epidemiology, and End Results (SEER)-Medicare data for the subset of the United States covered by the SEER program to determine whether the inclusion of cancer-specific information (only available in cancer registries) in risk adjustment altered measured

hospital performance. Data were from 729 279 fee-for-service Medicare beneficiaries treated for cancer in 2006 at hospitals treating 10 or more patients with each of the following cancers, according to Medicare claims: lung, prostate, breast, colon, and other. An additional sample of 18 677 similar patients were included from the SEER-Medicare administrative data. **MAIN OUTCOMES AND MEASURES:** Risk-adjusted mortality overall and by cancer category, stratified by type of hospital; measures of correlation and agreement between hospital-level outcomes risk adjusted using Medicare data alone and Medicare data with SEER data. **RESULTS:** There were large survival differences between different types of hospitals that treat Medicare patients with cancer. At 1 year, mortality for patients treated by hospitals exempt from the Medicare prospective payment system was 10% lower than at community hospitals (18% vs 28%) across all cancers, and the pattern persisted through 5 years of follow-up and within specific cancer categories. Performance ranking of hospitals was consistent with or without SEER-Medicare disease stage information (weighted $\kappa \geq 0.81$). **CONCLUSIONS AND RELEVANCE:** Potentially important outcome differences exist between different types of hospitals that treat patients with cancer after risk adjustment using information in Medicare administrative data. This type of risk adjustment may be adequate for evaluating hospital performance, since the additional adjustment for data available only in cancer registries does not seem to appreciably alter measures of performance.

Necitumumab in Metastatic Squamous Cell Lung Cancer: Establishing a Value-Based Cost.
Goldstein DA1, Chen Q2, Ayer T2, et al. JAMA Oncol. 2015 Dec 1;1(9):1293-300. doi: 10.1001/jamaoncol.2015.3316.

IMPORTANCE: The SQUIRE trial demonstrated that adding necitumumab to chemotherapy for patients with metastatic squamous cell lung cancer (mSqCLC) increased median overall survival by 1.6 months (hazard ratio, 0.84). However, the costs and value associated with this intervention remains unclear. Value-based pricing links the price of a drug to the benefit that it provides and is a novel method to establish prices for new treatments. **OBJECTIVE:** To evaluate the range of drug costs for which adding necitumumab to chemotherapy could be considered cost-effective. **DESIGN, SETTING, AND PARTICIPANTS:** We developed a Markov model using data from multiple sources, including the SQUIRE trial, which compared standard chemotherapy with and without necitumumab as first-line treatment of mSqCLC, to evaluate the costs and patient life expectancies associated with each regimen. In the analysis, patients were modeled to receive gemcitabine and cisplatin for 6 cycles or gemcitabine, cisplatin, and necitumumab for 6 cycles followed by maintenance necitumumab. Our model's clinical inputs were the survival estimates and frequency of adverse events (AEs) described in the SQUIRE trial. Log-logistic models were fitted to the survival distributions in the SQUIRE trial. The cost inputs included drug costs, based on the Medicare average sale prices, and costs for drug administration and management of AEs, based on Medicare reimbursement rates (all in 2014 US dollars). **MAIN OUTCOMES AND MEASURES:** We evaluated incremental cost-effectiveness ratios (ICERs) for the use of necitumumab across a range of values for its cost. Model robustness was assessed by probabilistic sensitivity analyses, based on 10 000 Monte Carlo simulations, sampling values from the distributions of all model parameters. **RESULTS:** In the base case analysis, the addition of necitumumab to the treatment regimen produced an incremental survival benefit of 0.15 life-years and 0.11 quality-adjusted life-years (QALYs). The probabilistic sensitivity analyses established that when necitumumab cost less than $563 and less than $1309 per cycle, there was 90% confidence that the ICER for adding necitumumab would be less than $100 000 per QALY and less than $200 000 per QALY, respectively. **CONCLUSIONS AND RELEVANCE:** These findings provide a value-based range for the cost of necitumumab from $563 to $1309 per cycle. This study provides a framework for establishing value-based pricing for new oncology drugs entering the US marketplace.

Racial Differences in Tobacco Cessation and Treatment Usage After Lung Screening: An Examination of the National Lung Screening Trial. Kumar P1, Gareen IF2, Lathan C3, Sicks JD4, Perez GK5, Hyland KA6, Park ER5. Oncologist. 2015 Dec 28. pii: theoncologist.2015-0325. [Epub ahead of print]

BACKGROUND: Black smokers have demonstrated greater lung cancer disease burden and poorer smoking cessation outcomes compared with whites. Lung cancer screening represents a unique opportunity to promote cessation among smokers; however, little is known about the differential impact of screening on smoking behaviors among black and white smokers. Using data from the National Lung Screening Trial (NLST), we examined the racial differences in smoking behaviors after screening. **METHODS:** We examined racial differences in smoking behavior and cessation activity among 6,316 white and 497 black (median age, 60 and 59 years, respectively) NLST participants who were current smokers at screening using a follow-up survey on 24-hour and 7-day quit attempts, 6-month continuous abstinence, and the use of smoking cessation programs and aids at 12 months after screening. Using multiple regression analyses, we examined the predictors of 24-hour and 7-day quit attempts and 6-month continuous abstinence. **RESULTS:** At 12 months after screening, blacks were more likely to report a 24-hour (52.7% vs. 41.2%, $p < .0001$) or 7-day (33.6% vs. 27.2%, $p = .002$) quit attempt. However, no significant racial differences were found in 6-month continuous abstinence (5.6% blacks vs. 7.2% whites). In multiple regression, black race was predictive of a higher likelihood of a 24-hour (odds ratio [OR], 1.6, 95% confidence interval [CI], 1.2-2.0) and 7-day (OR, 1.5, 95% CI, 1.1-1.8) quit attempt; however, race was not associated with 6-month continuous abstinence. Only a positive screening result for lung cancer was significantly predictive of successful 6-month continuous abstinence (OR, 2.3, 95% CI, 1.8-2.9). **CONCLUSION:** Although blacks were more likely than whites to have 24-hour and 7-day quit attempts, the rates of 6-month continuous abstinence did not differ. Targeted interventions are needed at the time of lung cancer screening to promote abstinence among all smokers. **IMPLICATIONS FOR PRACTICE:** Among smokers undergoing screening for lung cancer, blacks are more likely than whites to have 24-hour and 7-day quit attempts; however, these attempts did not translate to increased rates of 6-month continuous abstinence among black smokers. Targeted interventions are needed at the time of lung cancer screening to convert quit attempts to sustained smoking cessation among all smokers.

Five-year survival in EGFR-mutant metastatic lung adenocarcinoma treated with EGFR-TKIs. Lin JJ1, Cardarella S2, Lydon CA2, Dahlberg SE3, Jackman DM4, Jänne PA4, Johnson BE5. J Thorac Oncol. 2015 Dec 24. pii: S1556-0864(15)00265-8. doi: 10.1016/j.jtho.2015.12.103. [Epub ahead of print]

INTRODUCTION: Activating mutations in the epidermal growth factor receptor (EGFR) predict for prolonged progression-free survival (PFS) in patients with advanced non-small cell lung cancer (NSCLC) treated with EGFR-tyrosine kinase inhibitors (EGFR-TKIs) versus chemotherapy. Long-term survival outcomes, however, remain undefined. The objective of this study was to determine the 5-year survival in these patients, and identify clinical factors associated with overall survival (OS). **METHODS:** Patients with EGFR-mutant metastatic lung adenocarcinoma treated with erlotinib or gefitinib at Dana-Farber Cancer Institute between 2002 and 2009 were included. OS was analyzed. **RESULTS:** Among 137 patients, median PFS and OS were 12.1 months (95% CI, 10.2-13.5 months) and 30.9 months (95% CI, 28.2-35.7 months), respectively. Twenty patients (14.6%) were 5-year survivors. In multivariate analysis, exon 19 deletions (hazard ratio [HR], 0.63; 95% CI, 0.44-0.91; $P = 0.01$), absence of extrathoracic (HR 0.62; 95% CI, 0.41-0.93; $P = 0.02$) or brain metastasis (HR 0.48; 95% CI, 0.30-0.77, $P = 0.002$), and non-current smoking status (HR 0.23; 95% CI, 0.09-0.59; $P = 0.002$) were associated with prolonged OS. Age, gender, stage at diagnosis, liver or bone or adrenal metastasis, specific TKI, and line of TKI therapy were not associated with OS. **CONCLUSIONS:** Our data suggest that the prevalence of 5-year survival among EGFR-mutant metastatic lung adenocarcinoma patients treated with erlotinib or gefitinib is 14.6%. Exon 19 deletions and absence of extrathoracic or brain metastasis are associated with prolonged survival.

Based on our findings, clinicians can gain an enhanced estimation of long-term outcomes in this population.

Racial and Ethnic Variations in Lung Cancer Incidence and Mortality: Results From the Women's Health Initiative. Patel MI1, Wang A2, Kapphahn K2, et al. J Clin Oncol. 2015 Dec 23. pii: JCO635789. [Epub ahead of print]
PURPOSE: This study aimed to evaluate racial/ethnic differences in lung cancer incidence and mortality in the Women's Health Initiative Study, a longitudinal prospective cohort evaluation of postmenopausal women recruited from 40 clinical centers. **METHODS:** Lung cancer diagnoses were centrally adjudicated by pathology review. Baseline survey questionnaires collected sociodemographic and health information. Logistic regression models estimated incidence and mortality odds by race/ethnicity adjusted for age, education, calcium/vitamin D, body mass index, smoking (status, age at start, duration, and pack-years), alcohol, family history, oral contraceptive, hormones, physical activity, and diet.
RESULTS: The cohort included 129,951 women-108,487 (83%) non-Hispanic white (NHW); 10,892 (8%) non-Hispanic black (NHB); 4,882 (4%) Hispanic; 3,696 (3%) Asian/Pacific Islander (API); 534 (< 1%) American Indian/Alaskan Native; and 1,994 (1%) other. In unadjusted models, Hispanics had 66% lower odds of lung cancer compared with NHW (odds ratio [OR], 0.34; 95% CI, 0.2 to 0.5), followed by API (OR, 0.45; 95% CI, 0.27 to 0.75) and NHB (OR, 0.75; 95% CI, 0.59 to 0.95). In fully adjusted multivariable models, the decreased lung cancer risk for Hispanic compared with NHW women attenuated to the null (OR, 0.59; 95% CI, 0.35 to 0.99). In unadjusted models Hispanic and API women had decreased risk of death compared with NHW women (OR, 0.30 [95% CI, 0.15 to 0.62] and 0.34 [95% CI, 0.16 to 0.75, respectively); however, no racial/ethnic differences were found in risk of lung cancer death in fully adjusted models. **CONCLUSION:** Differences in lung cancer incidence and mortality are associated with sociodemographic, clinical, and behavioral factors. These findings suggest modifiable exposures and behaviors may contribute to differences in incidence of and mortality by race/ethnicity for postmenopausal women. Interventions focused on these factors may reduce racial/ethnic differences in lung cancer incidence and mortality.

Chronic Disease Diagnosis as a Teachable Moment for Health Behavior Changes Among Middle-Aged and Older Adults. Xiang X1. J Aging Health. 2015 Dec 2. pii: 0898264315614573. [Epub ahead of print]
OBJECTIVE: To examine the impact of a new chronic disease diagnosis on substance use (i.e., smoking and drinking), utilization of preventive medical procedures, and physical activity among middle-aged and older adults. **METHOD:** Individual-level data came from 1996 to 2010 waves of the U.S. Health and Retirement Study. Disease diagnosis was ascertained from self-reports of physician-diagnosed diseases. A case-control difference-in-differences approach estimated in logistic regression was applied to test study hypotheses. **RESULTS:** After a diagnosis of chronic disease, participants decreased substance use and increased utilization of preventive medical procedures. Physical activity declined after a diagnosis of lung disease, cancer, and stroke. **DISCUSSION:** Chronic disease diagnosis may be an important teachable moment that can motivate individuals to adopt multiple risk-reducing health behaviors. Future research needs to elucidate the mechanisms through which disease diagnosis affects behaviors and test the modifying effect of time since diagnosis on intervention effectiveness.

Cancer incidence among Asian American populations in the United States, 2009-2011. Jin H1, Pinheiro PS1, Xu J2, Amei A2. Int J Cancer. 2015 Dec 13. doi: 10.1002/ijc.29958. [Epub ahead of print]
Cancer incidence disparities exist among specific Asian American populations. However, the existing reports exclude data from large metropoles like Chicago, Houston, and New York. Moreover, incidence rates by subgroup have been underestimated due to the exclusion of Asians with unknown subgroup.

Cancer incidence data for 2009 to 2011 for eight states accounting for 68% of the Asian American population were analyzed. Race for cases with unknown subgroup was imputed using stratified proportion models by sex, age, cancer site, and geographic regions. Age-standardized incidence rates were calculated for 17 cancer sites for the six largest Asian subgroups. Our analysis comprised 90,709 Asian and 1,327,727 non-Hispanic white cancer cases. Asian Americans had significantly lower overall cancer incidence rates than non-Hispanic whites (336.5 per 100,000 and 541.9 for men, 299.6 and 449.3 for women, respectively). Among specific Asian subgroups, Filipino men (377.4) and Japanese women (342.7) had the highest overall incidence rates while South Asian men (297.7) and Korean women (275.9) had the lowest. In comparison to non-Hispanic whites and other Asian subgroups, significantly higher risks were observed for colorectal cancer among Japanese, stomach cancer among Koreans, nasopharyngeal cancer among Chinese, thyroid cancer among Filipinos, and liver cancer among Vietnamese. South Asians had remarkably low lung cancer risk. Overall, Asian Americans have a lower cancer risk than non-Hispanic whites, except for nasopharyngeal, liver and stomach cancers. The unique portrayal of cancer incidence patterns among specific Asian subgroups in this study provides a new baseline for future cancer surveillance research and health policy.

Hospice Use, Hospitalization, and Medicare Spending at the End of Life. Zuckerman RB1, Stearns SC2, Sheingold SH3. J Gerontol B Psychol Sci Soc Sci. 2015 Dec 11. pii: gbv109. [Epub ahead of print]
OBJECTIVES: Prior studies associate hospice use with reduced hospitalization and spending at the end of life based on all Medicare hospice beneficiaries. In this study, we examine the impact of different lengths of hospice care and nursing home residency on hospital use and spending prior to death across 5 disease groups. **METHODS:** We compared inpatient hospital days and Medicare spending during the last 6 months of life using hospice versus propensity matched non-hospice beneficiaries who died in 2010, were enrolled in fee for service Medicare throughout the last 2 years of life, and were in at least 1 of 5 disease groups. Comparisons were based on length of hospice use and whether the decedent was in a nursing home during the seventh month prior to death. We regressed a categorical measure of hospice days on outcomes, controlling for observed patient characteristics. **RESULTS:** Hospice use over 2 weeks was associated with decreased hospital days (1-5 days overall, with greater decreases for longer hospice use) for all beneficiaries; spending was $900-$5,000 less for hospice use of 31-90 days for most beneficiaries not in nursing homes, except beneficiaries with Alzheimer's. Overall spending decreased with hospice use for beneficiaries in nursing homes with lung cancer only, with a $3,500 reduction. **DISCUSSION:** The Medicare hospice benefit is associated with reduced hospital care at the end of life and reduced Medicare expenditures for most enrollees. Policies that encourage timely initiation of hospice and discourage extremely short stays could increase these successes while maintaining program goals.

ALCHEMIST Trials: A Golden Opportunity to Transform Outcomes in Early-Stage Non-Small Cell Lung Cancer. Govindan R1, Mandrekar SJ2, Gerber DE3, et al. Clin Cancer Res. 2015 Dec 15;21(24):5439-44. doi: 10.1158/1078-0432.CCR-15-0354.

The treatment of patients with metastatic non-small cell lung cancer (NSCLC) is slowly evolving from empirical cytotoxic chemotherapy to personalized treatment based on specific molecular alterations. Despite this 10-year evolution, targeted therapies have not been studied adequately in patients with resected NSCLC who have clearly defined actionable mutations. The advent of next-generation sequencing has now made it possible to characterize genomic alterations in unprecedented detail. The efforts begun by The Cancer Genome Atlas project to understand the complexities of the genomic landscape of lung cancer will be supplemented further by studying a large number of tumor specimens. The Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST) is an NCI-sponsored national clinical trials network (NCTN) initiative to address the needs to refine therapy for

early-stage NSCLC. This program will screen several thousand patients with operable lung adenocarcinoma to determine whether their tumors contain specific molecular alterations [epidermal growth factor receptor mutation (EGFR) and anaplastic lymphoma kinase rearrangement (ALK)], making them eligible for treatment trials that target these alterations. Patients with EGFR mutation or ALK gene rearrangement in their tumor will be randomized to placebo versus erlotinib or crizotinib, respectively, after completion of their standard adjuvant therapy. ALCHEMIST will also contain a large discovery component that will provide an opportunity to incorporate genomic studies to fully understand the clonal architecture, clonal evolution, and mechanisms of resistance to therapy. In this review, we describe the concept, rationale, and outline of ALCHEMIST and the plan for genomic studies in patients with lung adenocarcinoma.