Caring Ambassadors Lung Cancer Program
Literature Review, October 2018

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Preclinical studies reveal that LSD1 inhibition results in tumor growth arrest in lung adeno-carcinoma independently of driver mutations. Macheleidt IF1,2, Dalvi PS1,2, Lim SY1,2, et al. Mol Oncol. 2018 Sep 16. doi: 10.1002/1878-0261.12382. [Epub ahead of print]
Lung adenocarcinoma (LUAD) is the most prevalent subtype of non-small cell lung cancer. Despite the development of novel targeted and immune therapies, the five-year survival rate is still only 21%, necessitating more efficient treatment regimens. Lysine-specific demethylase 1 (LSD1) is an epigenetic eraser which modifies histone 3 methylation status, and is highly overexpressed in LUAD. Using representative human cell culture systems and two autochthonous transgenic mouse models, we investigated inhibition of LSD1 as a novel therapeutic option to treat LUAD. The reversible LSD1 inhibitor HCI-2509 significantly reduced cell growth with an IC50 of 0.3 to 5 µM in vitro, which was linked to an enhancement of histone 3 lysine methylation. Most importantly, growth arrest, as well as inhibition of the invasion capacities, were independent of the underlying driver mutations. Subsequent expression profiling revealed that the cell cycle and replication machinery were prominently affected after LSD1 inhibition. In addition, our data provide evidence that LSD1 blockade significantly interferes with EGFR downstream signaling. Finally, our in vitro results were confirmed by preclinical therapeutic approaches, including the use of two autochthonous transgenic LUAD mouse models driven by either EGFR or KRAS mutations. Importantly, LSD1 inhibition resulted in significantly lower tumor formation and a strong reduction in tumor progression, which were independent of the underlying mutational background of the mouse models. Hence, our findings provide substantial evidence that tumor growth of LUAD can be markedly decreased by HCI-2509 treatment, suggesting its use as a single agent maintenance therapy orcombined therapeutical application in novel concerted drug approaches.

CircRNA hsa_circ_100395 regulates miR-1228/TCF21 pathway to inhibit lung cancer progression. Chen D1,2, Ma W3, Ke Z1, Xie F4. Cell Cycle. 2018 Sep 13:1-11. doi: 10.1080/15384101.2018.1515553. [Epub ahead of print]
Circular RNA (circRNA) is shown to participate in various tumors, including lung cancer. Although a few circRNAs involved in lung cancer are reported, whether circRNA negatively regulates lung cancer

development remains elusive. In this study, we showed hsa_circ_100395 expression was decreased in lung cancer tissues. Besides, hsa_circ_100395 level was inversely correlated with TNM stage and metastases in lung cancer and low hsa_circ_100395 expression in patients predicted poor prognosis. Overexpression of hsa_circ_100395 dramatically inhibited lung cancer cell proliferation, arrested cell-cycle progression and reduced cell migration and invasion in vitro. Xenograft experiments showed that hsa_circ_100395 overexpression delayed tumor growth in vivo. Mechanistically, we showed hsa_circ_100395 serves as a sponge for miR-1228 targeting TCF21 in lung cancer. Rescue assays indicated that hsa_circ_100395 regulates lung cancer cell proliferation, migration and invasion through modulating miR-1228/TCF21 pathway. Altogether, our study reveals a novel regulatory loop that hsa_circ_100395/miR-1228/TCF21 axis modulates lung cancer development. **ABBREVIATIONS:** circRNA: circular RNA; miRNA: microRNA; RNA-FISH: RNA fluorescence in situy bridization; qRT-PCR: Reverse transcription and quantitative real-time PCR.

[Benzyl Isothiocyanate Induces Apoptotic Cell Death Through Mitochondria-dependent Pathway in Gefitinib-resistant NCI-H460 Human Lung Cancer Cells In Vitro.](#) Huang YP1, Jiang YW2, Chen HY2, et al. Anticancer Res. 2018 Sep;38(9):5165-5176. doi: 10.21873/anticanres.12839.
BACKGROUND/AIM: Gefitinib is used to treat patients with lung cancer, but in some patients, the disease becomes gefitinib-resistant. Benzyl isothiocyanate (BITC), found in cruciferous vegetables, has shown anticancer activity in many human cancer cell lines. However, the effects of BITC on gefitinib-resistant NCI-H460 lung cancer cells in vitro have not been investigated. **MATERIALS AND METHODS:** The effects of BITC on gefitinib-resistant NCI-H460 lung cancer cells were investigated in vitro. Flow cytometric assay was used for determining the total viable cell number, apoptotic cell death, the production of reactive oxygen species (ROS) and Ca2+, mitochondriaI membrane potential (Ψm) and caspase-3, -8 and -9 activities. Furthermore, 4', 6-diamidino-2-phenylindole staining was used to examine chromatin condensation in NCI-H460 and NCI-H460/G cells. **RESULTS:** BITC reduced total viable cell number via the induction of apoptotic cell death, that was also confirmed by annexin V/propidium iodide double staining assay. BITC increased ROS and Ca2+ production, reduced Ψm and increased caspase-3, -8 and -9 activities in both NCI-H460 and NCI-H460/G cells. Western blotting assay also showed that BITC increased expression of cleaved caspase-3 and -9, cytochrome c, BCL2-associated X protein, endonuclease G, poly (ADP-ribose) polymerase, growth arrest and DNA-damage protein 153, caspase-7 and activating transcription factor 6 alpha, but reduced apoptosis-inducing factor and caspase-9, BH3-interacting domain death agonist, calpain 1, glucose-regulated protein 78 and inositol requiring enzyme 1 alpha in NCI-H460/G cells. **CONCLUSION:** BITC-induced apoptotic cell death appears to occur via caspase- and mitochondria-dependent pathways in both cell lines.

SCREENING, DIAGNOSIS AND STAGING

[Effect of a pulmonary nodule fact sheet on patient anxiety and knowledge: a quality improvement initiative.](#) Koroscil MT1, Bowman MH1, Morris MJ1, Skabelund AJ1, Hersh AM1. BMJ Open Qual. 2018 Sep 14;7(3):e000437. doi: 10.1136/bmjoq-2018-000437. eCollection 2018.
INTRODUCTION: The utilisation of chest CT for the evaluation of pulmonary disorders, including low-dose CT for lung cancer screening, is increasing in the USA. As a result, the discovery of both screening-detected and incidental pulmonary nodules has become more frequent. Despite an overall low risk of malignancy, pulmonary nodules are a common cause of emotional distress among adult patients.
METHODS: We conducted a multi-institutional quality improvement (QI) initiative involving 101 participants to determine the effect of a pulmonary nodule fact sheet on patient knowledge and anxiety. Males and females aged 35 years or older, who had a history of either screening-detected or incidental solid pulmonary nodule(s) sized 3-8 mm, were included. Prior to an internal medicine or pulmonary

medicine clinic visit, participants were given a packet containing a pre-fact sheet survey, a pulmonary nodule fact sheet and a post-fact sheet survey. **RESULTS:** Of 101 patients, 61 (60.4%) worried about their pulmonary nodule at least once per month with 18 (17.8%) worrying daily. The majority 67/101 (66.3%) selected chemotherapy, chemotherapy and radiation, or radiation as the best method to cure early-stage lung cancer. Despite ongoing radiographic surveillance, 16/101 (15.8%) stated they would not be interested in an intervention if lung cancer was diagnosed. Following review of the pulmonary nodule fact sheet, 84/101 (83.2%) reported improved anxiety and 96/101 (95.0%) reported an improved understanding of their health situation. Patient understanding significantly improved from 4.2/10.0 to 8.1/10.0 (p<0.01). **CONCLUSION:** The incorporation of a standardised fact sheet for subcentimeter solid pulmonary nodules improves patient understanding and alleviates anxiety. We plan to implement pulmonary nodule fact sheets into the care of our patients with low-risk subcentimeter pulmonary nodules.

Implications of the Eighth Edition of the TNM Proposal: Invasive vs. Total Tumor Size for the T Descriptor in Pathologic Stage I-IIA Lung Adenocarcinoma. Kameda K1, Eguchi T2, Lu S3, Qu Y4, Tan KS5, Kadota K6, Adusumilli PS7, Travis WD8. J Thorac Oncol. 2018 Sep 6. pii: S1556-0864(18)33037-5. doi: 10.1016/j.jtho.2018.08.2022. [Epub ahead of print]
INTRODUCTION: The eighth edition of the tumor, node, and metastasis (TNM) staging system included the proposal that the T descriptor be determined according to the invasive component, excluding lepidic component, for nonmucinous lung adenocarcinomas. We sought to conduct a clinicopathologic comparative analysis of the newly proposed classification using invasive size versus total tumor size. **METHODS:** Patients who underwent lung resection for primary lung adenocarcinoma with pathologic stage (p-Stage) I-IIA (based on total size [t]) were reviewed (n=1704). Pathologic invasive size was measured, and tumors were reclassified using invasive size (i). Cumulative incidence of recurrence (CIR) and lung cancer-specific cumulative incidence of death (LC-CID) were analyzed using a competing-risks approach. Prognostic discrimination by p-Stage(t) and p-Stage(i) was evaluated using a concordance index (C-index). **RESULTS:** The use of invasive size resulted in downstaging in 377 of 1704 patients (22%), with twice as many patients with p-Stage IA1 (IA1[i] vs. IA1[t]: 389 [23%] vs. 195 [11%]). However, outcomes were similar between the two groups (IA1[i] vs. IA1[t]: 5-year-CIR, 11% vs. 13%; 5-year LC-CID, 5% vs. 7%). Prognostic discrimination by p-Stage(i) was better than by p-Stage(t) (C-index for p-Stage[i] vs. p-Stage[t]: recurrence, 0.614 vs. 0.593; lung cancer-specific death, 0.634 vs. 0.621). **CONCLUSIONS:** When invasive size, rather than total size, was used for the T descriptor, a larger number of patients were classified with a favorable prognosis (p-Stage IA1) and better prognostic discrimination of p-Stage I-IIA nonmucinous lung adenocarcinomas was achieved.

Challenges to Educating Smokers About Lung Cancer Screening: a Qualitative Study of Decision Making Experiences in Primary Care. Greene PA1, Sayre G2,3, Heffner JL4, Klein DE5, Krebs P6,7, Au DH2,3,8, Zeliadt SB2,3. Cancer Educ. 2018 Sep 1. doi: 10.1007/s13187-018-1420-y. [Epub ahead of print]
We sought to qualitatively explore how those at highest risk for lung cancer, current smokers, experienced, understood, and made decisions about participation in lung cancer screening (LCS) after being offered in the target setting for implementation, routine primary care visits. Thirty-seven current smokers were identified within 4 weeks of being offered LCS at seven sites participating in the Veterans Health Administration Clinical Demonstration Project and interviewed via telephone using semi-structured qualitative interviews. Transcripts were coded by two raters and analyzed thematically using iterative inductive content analysis. Five challenges to smokers' decision-making lead to overestimated benefits and minimized risks of LCS: fear of lung cancer fixated focus on inflated screening benefits; shame, regret, and low self-esteem stemming from continued smoking situated screening as less averse

and more beneficial; screening was mistakenly believed to provide general evaluation of lungs and reassurance was sought about potential damage caused by smoking; decision-making was deferred to providers; and indifference about numerical educational information that was poorly understood. Biased understanding of risks and benefits was complicated by emotion-driven, uninformed decision-making. Emotional and cognitive biases may interfere with educating and supporting smokers' decision-making and may require interventions tailored for their unique needs.

Usefulness of complementary next-generation sequencing and quantitative immunohistochemistry panels for predicting brain metastases and selecting a treatment outcomes of non-small cell lung cancer. Machado-Rugolo J1, Fabro AT2, et al. Hum Pathol. 2018 Sep 12. pii: S0046-8177(18)30352-6. doi: 10.1016/j.humpath.2018.08.026. [Epub ahead of print]
To demonstrate the usefulness of complementary next-generation sequencing (NGS) and immunohistochemistry (IHC) counting, we analyzed 196 patients with non-small cell lung cancer (NSCLC) who underwent surgical resection and adjuvant chemotherapy. Formalin-fixed paraffin-embedded samples of adenocarcinoma (ADC), squamous cell carcinoma (SqCC), and large-cell carcinoma (LCC) were used to prepare tissue microarrays and were examined by protein H-score IHC image analysis and NGS for oncogenes and proto-oncogenes and genes of tumor suppressors, immune checkpoints, epithelial-mesenchymal transition factors, tyrosine kinase receptors, and vascular endothelial growth factors (VEGFs). In patients with brain metastases, primary tumors expressed lower PIK3CA protein levels. Overexpression of TP53 and a higher PD-L1 protein H-score were detected in patients that underwent surgical treatment followed by chemotherapy as compared to those that underwent only surgical treatment The absence of brain metastases was associated with wild-type sequences of genes EGFR, CD267, CTLA-4, and ZEB1. The combination of protein overexpression according to IHC and mutation according to NGS was rare (i.e., represented by a very low percentage of concordant cases), except for TP53 and VEGF. Our data suggest that protein levels detected by IHC may be a useful complementary tool when mutations are not detected by NGS and also support the idea to expand this approach beyond ADC to include SqCC and even LCC, particularly for patients with unusual clinical characteristics. Conversely, well-pronounced immunogenotypic features appeared to predict the clinical outcome after univariate and multivariate analyses. Patients with a solid ADC subtype and mutated genes EGFR, CTLA4, PDCD1LG2, or ZEB1 complemented with PD-L1 or TP53 protein lower expression that only underwent surgical treatment, who develop brain metastases, may have the worst prognosis.

Lung cancer screening: an emerging cancer control issue presents opportunities for an awareness campaign in rural Michigan. Springer SM1, McFall A2, Hager P2, Percy-Laury A3, Vinson CA3. Cancer Causes Control. 2018 Sep 18. doi: 10.1007/s10552-018-1080-6. [Epub ahead of print]
Lung cancer is the leading cause of cancer deaths in the United States representing about 25% of all cancer deaths. The risk from smoking has increased over time with racial/ethnic minorities and disadvantaged populations having higher smoking rates and experiencing greater burden of lung cancer compared to other populations. Rural populations, in particular, experience higher rates of tobacco usage associated with increased incidence of lung cancer. National efforts to identify lung cancer in its early stage would greatly benefit high-risk populations, consequently reducing advanced cancers and potentially decreasing smoking rates. In 2013, lung cancer screening with low-dose computed tomography was recommended by the US Preventive Services Task Force for early detection of lung cancer. These guidelines were developed after the results of the National Lung Screening Trial. The National Lung Screening Trial study showed a 20% reduction in deaths of participants who were current or former heavy smokers who were screened with low-dose computed tomography versus those screened by chest X-ray. In response to this evidence and using state lung cancer burden data and local smoking rates as a guide, Michigan implemented a lung cancer screening awareness campaign in the rural

northern, lower peninsula. Awareness of lung cancer screening was increased through the use of a variety of media including gas station/convenience store small media, digital media, radio broadcast media, and the use and marketing of a website that provided lung cancer screening information and resources.

[**Clinical utility of reflex testing using focused next-generation sequencing for management of patients with advanced lung adenocarcinoma.**](#) Miller TE1, Yang M2, Bajor D3, et al. J Clin Pathol. 2018 Sep 18. pii: jclinpath-2018-205396. doi: 10.1136/jclinpath-2018-205396. [Epub ahead of print]
AIMS: The growing number of genomically targeted therapies has made genomic testing an important part of the care for patients with non-small cell lung cancer. However, limited tissue availability, cost and long turnaround times can create barriers to efficient genomic testing and subsequent treatment. Effective approaches to reduce these barriers are needed. **METHODS:** 302 advanced lung adenocarcinomas from consecutive patients seen at University Hospitals Cleveland Medical Center (UHCMC) were tested inhouse using a hybrid DNA/RNA next-generation sequencing (NGS) panel. Sample testing was reflexed from pathology for all stage III or IV tumours. Genomic alterations were tiered according to their clinical relevance and reported with guideline-recommended therapies. Clinical implications of genomic testing results were assessed by manual chart review. **RESULTS:** With a sample cohort consisting of 64% biopsies, 16% excisions/resections and 20% fine needle aspirations, the assay was reliable with a 95% success rate. The average turnaround time from receipt of unstained formalin-fixed paraffin embedded slides to reporting was 4.8±2.1 days, half of the recommended 10 days and similar to single-gene testing. Alterations with Food and Drug Administration-approved or the National Cancer Center Network guideline-recommended targeted therapies were found in 18% of cases. Within this group, 60% of patients went on genomically driven therapies. **CONCLUSIONS:** We found our reflexed inhouse NGS assay to be reliable, cost-effective and efficient. Incorporation of reflex testing with our NGS assay led to an expansion of successful genomic profiling for all guideline-recommended alterations, and by including an expanded number of alterations within our panel we obtained clinically useful information outside the guidelines without changing cost or efficiency. This approach has enabled UHCMC clinicians to efficiently initiate genomically driven therapies for patients with lung adenocarcinoma.

[**A national survey of primary care physicians: Perceptions and practices of low-dose CT lung cancer screening.**](#) Eberth JM1,2,3, McDonnell KK4, Sercy E1,2, Khan S2, Strayer SM5, Dievendorf AC4, Munden RF6, Vernon SW7. Prev Med Rep. 2018 May 22;11:93-99. doi: 10.1016/j.pmedr.2018.05.013. eCollection 2018 Sep.
Soon after the National Lung Screening Trial, organizations began to endorse low-dose computed tomography (LCDT) screening for lung cancer in high-risk patients. Concerns about the risks versus benefits of screening, as well as the logistics of identifying and referring eligible patients, remained among physicians. This study aimed to examine primary care physicians' knowledge, attitudes, referral practices, and associated barriers regarding LDCT screening. We administered a national survey of primary care physicians in the United States between September 2016 and April 2017. Physicians received up to 3 mailings, 1 follow-up email, and received varying incentives to complete the survey. Overall, 293 physicians participated, for a response rate of 13%. We used weighted descriptive statistics to characterize participants and their responses. Over half of the respondents correctly reported that the US Preventive Services Task Force recommends LDCT screening for high-risk patients. Screening recommendations for patients not meeting high-risk criteria varied. Although 75% agreed that the benefits of LDCT screening outweigh the risks, fewer agreed that there is substantial evidence that screening reduces mortality (50%). The most commonly reported barriers to ordering screening included prior authorization requirements (57%), lack of insurance coverage (53%), and coverage denials (31%). The most frequently cited barrier to conducting LDCT screening shared decision making was patients' competing health priorities (42%). Given the impact of physician recommendations on cancer screening

utilization, further understanding of physicians' LDCT screening attitudes and shared decision-making practices is needed. Clinical practice and policy changes are also needed to engage more patients in screening discussions.

[Consolidation/Tumor Ratio on Chest Computed Tomography as Predictor of Postoperative Nodal Upstaging in Clinical T1N0 Lung Cancer.](#) Moon Y1, Park JK2, Lee KY3, Namkoong M2, Ahn S2. World J Surg. 2018 Sep;42(9):2872-2878. doi: 10.1007/s00268-018-4543-8.

BACKGROUND: In clinical T1N0 peripheral lung cancers, lymph node upstaging is occasionally encountered postoperatively. However, nodal upstaging is rare in lung cancers presenting as ground-glass opacities. The aim of this study was to determine if lymph node upstaging could be reliably extrapolated from parameters such the consolidation/tumor ratio of chest computed tomography. **METHODS:** We conducted a retrospective study of 486 patients treated for peripheral clinical T1N0 non-small cell lung cancer, each undergoing lobectomy with mediastinal lymph node dissection. We compared preoperative variables in the pathologic N0 and nodal upstaging groups, analyzing such variables to determine factors predictive of lymph node upstaging. **RESULTS:** Of the 486 patients studied, lymph node upstaging occurred in 42 (8.6%). In the upstaging group, the mean nodule diameter exceeded that of the pathologic N0 group (2.3 vs 1.9 cm, respectively; $p < 0.001$), and the mean consolidation/tumor ratio was larger in the upstaging group than the pN0 group (0.95 vs 0.68, respectively; $p < 0.001$). Nodule diameter and consolidation/tumor ratio emerged as significant predictive factors for lymph node upstaging after surgery in a multivariate analysis (hazard ratio [HR] 2.259, $p = 0.039$; HR 173.645, $p = 0.001$, respectively). **CONCLUSIONS:** Consolidation/tumor ratio and nodule diameter are significant predictive factors of postoperative lymph node upstaging. The higher the consolidation/tumor ratio and smaller the nodule diameter, the less likely the occurrence of postoperative lymph upstaging would be in clinical T1N0 peripheral non-small cell lung cancer.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

[Video-assisted thoracoscopic surgery for lung cancer after induction therapy.](#) Matsuoka K1, Yamada T1, Matsuoka T1, Nagai S1, Ueda M1, Miyamoto Y1. Asian Cardiovasc Thorac Ann. 2018 Sep 24:218492318804413. doi: 10.1177/0218492318804413. [Epub ahead of print]

BACKGROUND: Although thoracoscopic surgery is widely performed for early-stage lung cancer, only a few small studies have evaluated the role of video-assisted thoracoscopic surgery in patients with locally advanced lung cancer who had received preoperative chemotherapy. **METHODS**: Among 1655 patients who underwent anatomical lung resection for lung cancer between January 2009 and December 2014 in our institution, we retrospectively examined the short- and long-term outcomes of 110 (6.6%) who had undergone induction therapy. Thoracoscopic surgery was performed in 79 of these patients and thoracotomy in 31. **RESULTS:** In the thoracoscopic group, conversion to a thoracotomy was required in 4 patients. More combined resections were included in the thoracotomy group, and combined resection of large vessels or the carina was carried out only via a thoracotomy. Postoperative complications of grade 3 or above were found in 15 (13.6%) patients, and there was no significant difference in the incidence of postoperative complications between the 2 groups. The 3- and 5-year survival rates for the patients overall were 58.6% and 50.3%, respectively. Although there was no significant difference in overall outcome between the 2 groups, the patients with postoperative ypN2 status in the thoracoscopic group had a significantly better outcome than those in the thoracotomy group. **CONCLUSION:** Although video-assisted thoracoscopic surgery was not suitable for central advanced lung cancer requiring angioplasty or

carinal resection, it seems to be useful for patients with locally advanced lung cancer who had undergone induction therapy, especially patients with peripheral lung cancer and mediastinal lymph node metastasis.

Optimization of routine testing for MET exon 14 splice site mutations in non-small cell lung cancer patients. Descarpentries C1, Leprêtre F2, Escande F1, et al. J Thorac Oncol. 2018 Sep 6. pii: S1556-0864(18)33038-7. doi: 10.1016/j.jtho.2018.08.2023. [Epub ahead of print]
INTRODUCTION: Genomic alterations affecting splice sites of MET exon 14 were recently identified in non-small cell lung cancer (NSCLC) patients. Objective responses to MET tyrosine kinase inhibitors have been reported in these patients. Thus, detection of MET exon 14 splice site mutations represents a major challenge. So far, most of these alterations were found by full-exome sequencing or large capture-based NGS panels, which are not suitable for routine diagnosis. **METHODS:** Aiming to provide a molecular testing method applicable in routine practice, we first developed a fragment-length analysis for detecting deletions in introns flanking MET exon 14. Second, we designed an optimized targeted next generation sequencing (NGS) panel called CLAPv1, covering the MET exon 14 and flanking regions in addition to the main molecular targets usually covered in genomic testing. In patients with MET exon 14 mutations, MET gene amplification, gene copy number and MET receptor expression were also determined. **RESULTS:** Among 1514 formalin-fixed paraffin-embedded NSCLC samples, non optimized NGS allowed detection of MET exon 14 mutations in only 0.3% of the patients, and fragment length analysis detected deletions in 1.1% of the patients. Combined, the optimized CLAPv1 panel and fragment length analysis implemented for routine molecular testing revealed MET exon 14 alterations in 2.2% of 365 additional NSCLC patients. MET gene amplification or high gene copy number were observed in 6 out of 30 patients (20%) harboring MET exon 14 mutations. **CONCLUSIONS:** These results demonstrate that optimized targeted NGS and fragment-length analysis improve detection of MET alterations in routine practice.

Air Leak Management Program with Digital Drainage Reduces Length of Stay after Lobectomy. Mayor JM1, Lazarus DR2, Casal RF3, Omer S1, Preventza O4, Simpson K1, Jimenez E1, Cornwell LD5. Ann Thorac Surg. 2018 Sep 12. pii: S0003-4975(18)31246-3. doi: 10.1016/j.athoracsur.2018.07.029. [Epub ahead of print]
BACKGROUND: Air leaks can impede recovery from lung resection. To help prevent and manage air leaks, we developed a comprehensive program that includes using precompression of lung staple lines, sealant, fissure-less video-assisted thoracoscopic (VATS) lobectomy, a digital-drainage system, and endobronchial valve placement for prolonged air leak. We assessed the effect of this program on prolonged air leaks, hospital length of stay (LOS), and chest tube days in our high-risk veteran population. **METHODS:** Using a prospectively maintained database, we retrospectively analyzed data from 226 patients who underwent lung resection for cancer by VATS lobectomy in a Veterans Affairs center. Patients were divided into 2 groups. Group A (n=134; historical controls) underwent lobectomy from July 2009 through October 2013; Group B (n=92; intervention group) underwent lobectomy from November 2013 through July 2016 and received care per the comprehensive program. **RESULTS:** The median hospital LOS was significantly shorter in Group B than in Group A patients (5 days versus 6 days, respectively; p=0.0001). Group B had a shorter median chest tube duration (2 days versus 3 days; p=0.027). Prolonged air leak (> 5 days) occurred in 5.4% of Group B and 9.7% of Group A patients (p=0.24). Prolonged LOS (>14 days) was less frequent in Group B (1.1%) than in Group A (8.2%) (p=0.030). Multivariable analysis showed that predictors of decreased air leak duration, chest tube duration, and LOS included undergoing surgery in the later time period (Group B). **CONCLUSIONS:** Our comprehensive program was associated with reduced chest tube days and hospital LOS.

[**Postoperative complications decrease the cost-effectiveness of robotic-assisted lobectomy.**](#) Kneuertz PJ1, Singer E2, D'Souza DM2, Moffatt-Bruce SD2, Merritt RE2. Surgery. 2018 Sep 26. pii: S0039-6060(18)30560-9. doi: 10.1016/j.surg.2018.08.024. [Epub ahead of print]

BACKGROUND: Cost of robotic-assisted (RATS) lobectomy remains a major concern. We sought to define variability in cost and factors associated with increased hospital expenses after RATS lobectomy for early stage non-small cell lung cancer. **METHODS:** We performed a retrospective review of patients who underwent RATS lobectomy for stages I-IIIA non-small cell lung cancer at a single institution between 2012 and 2014. Clinical outcomes were linked to hospital financial data. Linear regression analysis was used to test the impact of patient factors and postoperative outcomes on cost.
RESULTS: A total of 137 patients underwent RATS lobectomy, predominantly for stage IA (73%, n = 100). Overall in-hospital morbidity was 29.2% (n = 40), median length of stay was 5 days (range 1-27 days). Postoperative cost accounted for approximately 50% of total cost of hospitalization and varied significantly (mean $9,618.38 ± $10,779.65), resulting in an average total hospital cost of $19,565 (±$11,620.42). Male sex and upper lobe predominant disease were independently associated with increased cost, whereas higher preoperative diffusing capacity of lung for carbon monoxide (DLCO) was cost-protective. Hospital expenses associated with prolonged hospitalization were $2,376.23 per day (95% CI $2,178-2,573.60). The most common complication associated with increased cost was atrial fibrillation ($5,609.13; 95% CI $2,095.42-$9,122.84). Postoperative atelectasis requiring bronchoscopy, respiratory failure, pulmonary embolism, and reoperation were seen less frequently in this cohort of patients but were associated with significant additional cost. **CONCLUSION:** Hospital cost of RATS lobectomy can vary significantly. In addition to patient risk factors, differences in cost are mainly driven by postoperative events. Initiatives aimed to reduce common yet expensive complications have the potential to improve overall cost-effectiveness of RATS lobectomy.

[**Predicting Lung Function Following Lobectomy: A New Method to Adjust for Inherent Selection Bias.**](#) Ontiveros N1, Eapen-John D2, Osorio N1, et al. Respiration. 2018 Sep 26:1-12. doi: 10.1159/000490258. [Epub ahead of print]

BACKGROUND: Predictions that overestimate post-lobectomy lung function are more likely than underestimates to lead to lobectomy. Studies of post-lobectomy lung function have included only surgical patients, so overestimates are overrepresented. This selection bias has led to incorrect estimates of prediction bias, which has led to inaccurate threshold values for determining lobectomy eligibility.
OBJECTIVE: The objective of this study was to demonstrate and adjust for this selection bias in order to arrive at correct estimates of prediction bias, the 95% limits of agreement, and adjusted threshold values for determining when exercise testing is warranted. **METHODS:** We conducted a retrospective study of patients evaluated for lobectomy. We used multiple imputations to determine postoperative results for patients who did not have surgery because their predicted postoperative values were low. We combined these results with surgical patients to adjust for selection bias. We used the Bland-Altman method and the bivariate normal distribution to determine threshold values for surgical eligibility. **RESULTS:** Lobectomy evaluation was performed in 114 patients; 79 had lobectomy while 35 were ineligible based on predicted values. Prediction bias using the Bland-Altman method changed significantly after controlling for selection bias. To achieve a postoperative FEV1 > 30% and DLCO ≥30%, a predicted FEV1 > 46% and DLCO ≥53% were required. Compared to current guidelines, using these thresholds would change management in 17% of cases. **CONCLUSION:** The impact of selection bias on estimates of prediction accuracy was significant but can be corrected. Threshold values for determining surgical eligibility should be reassessed.

Procedure-Specific Risk Prediction for Recurrence in Patients Undergoing Lobectomy or Sublobar Resection for Small (≤2 cm) Lung Adenocarcinoma: An International Cohort Analysis. Bains S1, Eguchi T2, Warth A3, et al. J Thorac Oncol. 2018 Sep 22. pii: S1556-0864(18)33119-8. doi: 10.1016/j.jtho.2018.09.008. [Epub ahead of print]
PURPOSE: To develop and validate procedure-specific risk prediction for recurrence following resection for early-stage lung adenocarcinoma (ADC) and investigate risk prediction utility in identifying patients who may benefit from adjuvant chemotherapy (ACT). **BASIC PROCEDURES:** In patients who underwent resection for small (≤2 cm) lung ADC (lobectomy, 557; sublobar resection, 352), an association between clinicopathological variables and risk of recurrence was assessed by a competing risks approach. Procedure-specific risk prediction was developed based on multivariable regression for recurrence. External validation was conducted using cohorts (N=708) from Japan, Taiwan, and Germany. The accuracy of risk prediction was measured using a concordance index (C-index). We applied the lobectomy risk prediction approach to a propensity score-matched cohort of patients with stage II-III disease (n=316, after matching) with or without ACT and compared lung cancer-specific survival between groups among low or high-risk scores. **MAIN FINDINGS:** Micropapillary pattern, solid pattern, lymphovascular invasion, and necrosis were involved in the risk prediction following lobectomy, and micropapillary pattern, spread through air spaces, lymphovascular invasion, and necrosis following sublobar-resection. Both internal and external validation showed good discrimination (C-index in lobectomy and sublobar resection: internal, 0.77 and 0.75; and external, 0.73 and 0.79). In the stage II-III propensity score-matched cohort, among high-risk patients, ACT significantly reduced the risk of lung cancer-specific death (subhazard ratio 0.43, p=0.001), but not among low-risk patients. **PRINCIPAL CONCLUSIONS:** Procedure-specific risk prediction for patients with resected small lung ADC can be used to better prognosticate and stratify patients for further interventions.

NSCLC – SYSTEMIC THERAPIES (CHEMOTHERAPY, TARGETED THERAPY, AND IMMUNOTHERAPY)

Immune checkpoint inhibitors in non-small-cell lung cancer: current status and future directions.
Yan YF1, Zheng YF2, Ming PP3, Deng XX1, Ge W4, Wu YG5. Brief Funct Genomics. 2018 Sep 20. doi: 10.1093/bfgp/ely029. [Epub ahead of print]
Since 2015, immunotherapies, especially immune checkpoint inhibitors (ICIs), have made great breakthroughs in non-small-cell lung cancer (NSCLC). Among them, nivolumab, pembrolizumab and atezolizumab have been granted US Food and Drug Administration approval for NSCLC. It is imperative to combine ICIs with chemotherapy, radiotherapy, antivascular therapy and targeted therapy. But in the bright future, there are two problems. One is how to use biomarkers to select the beneficiaries. The other is how to achieve a balance between drug effectiveness and safety. There are now seven drugs targeting the programmed death-1/programmed death ligand-1 (PD-1/PD-L1) and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) pathways that have been or are expected to enter clinical treatment. This review focuses on these drugs and summarizes clinical trials that have been reported or that ongoing ones have already entered the recruiting state.

Progression-Free-Survival and Overall Survival beyond 5 years of non-small cell lung cancer patients with synchronous oligometastases treated in a prospective phase II trial (NCT 01282450).
De Ruysscher D1, Wanders R2, Hendriks LE3, et al. J Thorac Oncol. 2018 Sep 22. pii: S1556-0864(18)30935-3. doi: 10.1016/j.jtho.2018.07.098. [Epub ahead of print]
BACKGROUND: Two randomized studies demonstrated an increased progression-free survival (PFS) by adding a radical local treatment to systemic therapy in responding patients with oligometastatic non-small cell lung cancer (NSCLC), but long-term data are lacking. We updated the results of our previous phase II trial with a minimal follow-up exceeding 7 years. **METHODS:** Prospective single-arm phase II

trial. The main inclusion criteria were pathologically proven NSCLC stage IV with less than five metastases at primary diagnosis, amendable for radical local treatment (surgery or radiotherapy). No previous response to systemic treatment was needed. **RESULTS:** Forty patients were enrolled, 39 of whom were evaluable (18 men, 21 women); mean age was 62.1 ± 9.2 years (range, 44-81). Twenty-nine (74%) had N2 or N3 disease; 17 (44%) brain, seven (18%) bone, and four (10%) adrenal gland metastases. Thirty-five (87%) had a single metastatic lesion. Thirty-seven (95%) of the patients received chemotherapy as part of their primary treatment. Median overall survival (OS) was 13.5 months (95% CI 7.6-19.4); 1-, 2-, 3-, 5-, 6- year OS was 56.4%, 23.3%,12.8%, 10.3%, 7.7 % and 5.1%, respectively. Median progression-free survival (PFS) was 12.1 months (95% CI 9.6-14.3); 1-, 2-, 3-, 5-, 6- year OS was 51.3%, 13.6%, %,12.8%, 7.7%, 7.7 % and 2.5%, respectively. Only three patients (7.7%) had a local recurrence. **CONCLUSIONS:** In patients who were not selected according to response to systemic treatment, the PFS at 5 years was 8 %. Entering patients in trials combining local therapy with novel systemic agents (e.g. immunotherapy) remains mandatory.

[A Phase II Trial of Osimertinib in the Second-Line Treatment of Non-small Cell Lung Cancer with the EGFR T790M Mutation, Detected from Circulating Tumor DNA: LiquidLung-O-Cohort 2.](#)
Park CK1, Cho HJ1, Choi YD2, Oh IJ1, Kim YC1. Cancer Res Treat. 2018 Sep 7. doi: 10.4143/crt.2018.387. [Epub ahead of print]
PURPOSE: Administering the best treatment after failure of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy requires knowledge of resistance status. In this trial, treatment efficacy of osimertinib was assessed in patients with non-small cell lung carcinoma (NSCLC) harboring the T790M resistance mutation, detected from circulating tumor DNA (ctDNA) with unknown tumor mutation status. **MATERIALS AND METHODS:** To extract ctDNA from plasma, 15 mL of peripheral blood was withdrawn and centrifuged immediately before storage. CobasTM version 2 and PANA MutyperTM were used for ctDNA genotyping. Patients with T790M, detected from ctDNA, were enrolled and they received a once-daily administration of osimertinib, 80 mg. The primary endpoint was objective response rate (ORR), and secondary endpoints were ctDNA test sensitivity, progression-free survival (PFS), duration of response (DoR), and safety (ClinicalTrials.gov, Identifier: NCT02769286). **RESULTS:** Eighty patients with acquired resistance to prior EGFR-TKI therapies were screened. ctDNA of 21 patients showed T790M positivity, and 19 patients were enrolled. In the response-evaluable population (n=15), ORR was 66.7% (10/15). Median PFS was 8.3 months (95% confidence interval [CI], 7.9-8.7) and median DoR was 6.8 months (95% CI, 5.3-8.3) in the intent-to-treat population (n=19). No subject experienced drug-related adverse event of grades ≥ 3 or required dose reduction. The sensitivity of the ctDNA tests was 56.8% using both methods and 45.9% with either method from the estimated T790M-positive cases. **CONCLUSION:** Osimertinib has favorable efficacy in patients with NSCLC harboring T790M, detected from ctDNA with unknown tumor mutation status, in whom disease had progressed during prior EGFR-TKI therapy.

[Hyperprogressive Disease in Patients With Advanced Non-Small Cell Lung Cancer Treated With PD-1/PD-L1 Inhibitors or With Single-Agent Chemotherapy.](#) Ferrara R1, Mezquita L1, Texier M2, et al. JAMA Oncol. 2018 Sep 6. doi: 10.1001/jamaoncol.2018.3676. [Epub ahead of print]
IMPORTANCE: Hyperprogressive disease (HPD) is a new pattern of progression recently described in patients with cancer treated with programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors. The rate and outcome of HPD in advanced non-small cell lung cancer (NSCLC) are unknown. **OBJECTIVES:** To investigate whether HPD is observed in patients with advanced NSCLC treated with PD-1/PD-L1 inhibitors compared with single-agent chemotherapy and whether there is an association between treatment and HPD. **DESIGN, SETTING, AND PARTICIPANTS:** In this multicenter retrospective study that included patients treated between August 4, 2011, and April 5, 2017,

the setting was pretreated patients with advanced NSCLC who received PD-1/PD-L1 inhibitors (8 institutions) or single-agent chemotherapy (4 institutions) in France. Measurable disease defined by Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) on at least 2 computed tomographic scans before treatment and 1 computed tomographic scan during treatment was required. **INTERVENTIONS:** The tumor growth rate (TGR) before and during treatment and variation per month (ΔTGR) were calculated. Hyperprogressive disease was defined as disease progression at the first evaluation with ΔTGR exceeding 50%. **MAIN OUTCOMES AND MEASURES:** The primary end point was assessment of the HPD rate in patients treated with IO or chemotherapy. **RESULTS:** Among 406 eligible patients treated with PD-1/PD-L1 inhibitors (63.8% male), 46.3% (n = 188) were 65 years or older, 72.4% (n = 294) had nonsquamous histology, and 92.9% (n = 377) received a PD-1 inhibitor as monotherapy in second-line therapy or later. The median follow-up was 12.1 months (95% CI, 10.1-13.8 months), and the median overall survival (OS) was 13.4 months (95% CI, 10.2-17.0 months). Fifty-six patients (13.8%) were classified as having HPD. Pseudoprogression was observed in 4.7% (n = 19) of the population. Hyperprogressive disease was significantly associated with more than 2 metastatic sites before PD-1/PD-L1 inhibitors compared with non-HPD (62.5% [35 of 56] vs 42.6% [149 of 350]; P = .006). Patients experiencing HPD within the first 6 weeks of PD-1/PD-L1 inhibitor treatment had significantly lower OS compared with patients with progressive disease (median OS, 3.4 months [95% CI, 2.8-7.5 months] vs 6.2 months [95% CI, 5.3-7.9 months]; hazard ratio, 2.18 [95% CI, 1.29-3.69]; P = .003). Among 59 eligible patients treated with chemotherapy, 3 (5.1%) were classified as having HPD. **CONCLUSIONS AND RELEVANCE:** Our study suggests that HPD is more common with PD-1/PD-L1 inhibitors compared with chemotherapy in pretreated patients with NSCLC and is also associated with high metastatic burden and poor prognosis in patients treated with PD-1/PD-L1 inhibitors. Additional studies are needed to determine the molecular mechanisms involved in HPD.

[Brief Report: Increased Hepatotoxicity Associated with Sequential Immune Checkpoint Inhibitor and Crizotinib Therapy in Patients with Non-Small-Cell Lung Cancer.](#) Lin JJ1, Chin E1, Yeap BY1, et al. J Thorac Oncol. 2018 Sep 8. pii: S1556-0864(18)33040-5. doi: 10.1016/j.jtho.2018.09.001. [Epub ahead of print]

INTRODUCTION: Immune checkpoint inhibitors (ICIs) are standard therapies in advanced non-small-cell lung cancer (NSCLC). While genotype-directed tyrosine kinase inhibitors (TKIs) represent the standard of care for subsets of oncogene-driven NSCLC, patients may receive ICIs during their disease course. The impact of sequential ICI/TKI therapy on the risk of hepatotoxicity has not been described. **METHODS:** Patients with advanced ALK/ROS1/MET-driven NSCLC treated with crizotinib, with or without preceding ICI, were identified. The cumulative incidences of crizotinib-associated grade 3+ transaminase elevations (per the Common Terminology Criteria for Adverse Events version 4.0) were compared. **RESULTS:** We identified 453 patients with NSCLC harboring an oncogenic alteration in ALK, ROS1, or MET who were treated with crizotinib (11 with, 442 without prior ICI). Among 11 patients treated with ICI followed by crizotinib, five (cumulative incidence, 45.5%; 95% confidence interval [CI], 14.9-72.2) developed grade 3 or 4 ALT elevation, and four (36.4%; 95% CI, 10.0-64.2) developed grade 3 or 4 AST elevation. In comparison, among 442 patients who received crizotinib only, grade 3 or 4 ALT and AST elevations occurred in 34 (8.1%; 95% CI, 5.7-11.0; P <0.0001) and 14 patients (3.4%; 95% CI, 1.9-5.5; P <0.0001), respectively. There were no grade 5 transaminitis events. All cases of hepatotoxicity following sequential ICI and crizotinib use were reversible and nonfatal, and no case met Hy's law criteria. **CONCLUSIONS:** Sequential ICI/crizotinib treatment is associated with a significantly increased risk of hepatotoxicity. Careful consideration and monitoring for hepatotoxicity may be warranted in patients treated with crizotinib following prior ICI.

[**Correlation of PD-L1 expression with tumor mutation burden and gene signatures for prognosis in early stage squamous cell lung carcinoma.**](#) Yu H1, Chen Z2, Ballman K2, et al. J Thorac Oncol. 2018 Sep 22. pii: S1556-0864(18)33116-2. doi: 10.1016/j.jtho.2018.09.006. [Epub ahead of print]

PURPOSE: Anti-PD1/PD-L1 immunotherapy has demonstrated success in the treatment of advanced non-small cell lung cancer (NSCLC). Recently, PD1/PD-L1 blockade also has demonstrated interesting results in small trials of neo-adjuvant treatment in Stage IB-IIIA NSCLC. In addition, several clinical trials using anti-PD1/PD-L1 as an adjuvant or neo-adjuvant treatment in resectable stage NSCLC patients are ongoing. However, few analyses of anti-PD1/PD-L1 immunotherapy related biomarkers in early stage squamous cell lung carcinoma (SqCLC) have been reported. In this study, we evaluated PD-L1 protein expression, tumor mutation burden, and expression of an immune gene signature in early stage SqCLC, providing data for identifying the potential role for anti-PD1/PD-L1 treatment in early stage SqCLC patients. **EXPERIMENTAL DESIGN AND RESULTS:** A total of 255 early stage SqCLC patient specimens were identified within the Strategic Partnering to Evaluate Cancer Signatures (SPECS) program participating centers. PD-L1 protein expression by IHC was evaluated using the Dako PD-L1 22C3 pharmDx kit on the Dako Link 48 auto-stainer. Tumor Mutation Burden (TMB) was calculated based on data from targeted genome sequencing. The T-effector and IFN-γ gene signature was determined from Affymetrix gene chip data from frozen specimens. The prevalence of PD-L1 expression was 9.8% at a tumor proportion score (TPS) cutoff of ≥ 50%. PD-L1 mRNA and PD-L2 mRNA positively correlated with PD-L1 protein expression on tumor cells (TCs) and tumor-infiltrating immune cells (TIICs). PD-L1 protein expression on TIICs was correlated with the T-effector and IFN-γ gene signature (P<0.001), but not with TMB. For tumor cells, all of these biomarkers were independent of each other. And neither PD-L1 protein expression, TMB, or T-effector and IFN-γ gene signatures were independently prognostic for patient outcomes. **CONCLUSIONS:** Evaluation of PD-L1 expression, TMB, and T-effector and IFN-γ gene signatures in the early-stage SqCLC cohort were found to be independent of each other and none were associated with overall survival. Results also support the hypothesis that PD-L1 expression is regulated by an intrinsic mechanism on tumor cells and an adaptive mechanism on immune cells.

[**Atezolizumab Treatment Beyond Progression in Advanced Non-Small Cell Lung Cancer: Results From the Randomized, Phase III OAK Study.**](#) Gandara DR1, von Pawel J2, Mazieres J3, et al. J Thorac Oncol. 2018 Sep 11. pii: S1556-0864(18)33043-0. doi: 10.1016/j.jtho.2018.08.2027. [Epub ahead of print]

INTRODUCTION: Cancer immunotherapy may alter tumor biology such that treatment effects can extend beyond radiographic progression. In the randomized, Phase III OAK study of atezolizumab (anti-PD-L1) versus docetaxel in advanced non-small cell lung cancer, overall survival (OS) benefit with atezolizumab was observed in the overall patient population, without improvement in objective response rate (ORR) or progression-free survival (PFS). We examine the benefit-risk of atezolizumab treatment beyond progression (TBP). **METHODS:** 850 patients included in the OAK primary efficacy analysis were evaluated. Atezolizumab was continued until loss of clinical benefit. Docetaxel was administered until RECIST v1.1 disease progression (PD)/unacceptable toxicity; no crossover to atezolizumab was allowed. ORR, PFS, and post-PD OS, target lesion change, and safety were evaluated. **RESULTS:** In atezolizumab-arm patients, ORR was 16% versus 14% and median PFS was 4.2 versus 2.8 months per immune-modified RECIST (imRECIST) versus RECIST v1.1. The median post-PD OS was 12.7 months (95% CI: 9.3, 14.9) in 168 atezolizumab-arm patients continuing TBP, 8.8 months (95% CI: 6.0, 12.1) in 94 patients switching to non-protocol therapy and 2.2 months (95% CI: 1.9, 3.4) in 70 patients receiving no further therapy. Of the atezolizumab TBP patients, 7% achieved a post-progression response in target lesions and 49% had stable target lesions. Atezolizumab TBP was not associated with increased safety risks. **CONCLUSIONS:** Within the limitations of this retrospective analysis, the post-PD efficacy and

safety data from OAK are consistent with a positive benefit-risk profile of atezolizumab TBP in patients performing well clinically at the time of PD.

[Alectinib versus crizotinib in treatment-naïve anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study.](#) Gadgeel S1, Peters S2, Mok T3, et al. Ann Oncol. 2018 Sep 12. doi: 10.1093/annonc/mdy405. [Epub ahead of print]
BACKGROUND: The phase III ALEX study in patients with treatment-naïve advanced anaplastic lymphoma kinase mutation-positive (ALK+) non-small-cell lung cancer (NSCLC), met its primary endpoint of improved progression-free survival (PFS) with alectinib versus crizotinib. Here we present detailed central nervous system (CNS) efficacy data from ALEX. **PATIENTS AND METHODS:** Overall, 303 patients aged ≥18 years underwent 1:1 randomization to receive twice-daily doses of alectinib 600 mg or crizotinib 250 mg. Brain imaging was conducted in all patients at baseline and every subsequent 8 weeks. Endpoints (analyzed by subgroup: patients with/without baseline CNS metastases; patients with/without prior radiotherapy) included: PFS, CNS objective response rate (ORR), and time to CNS progression. **RESULTS:** In total, 122 patients had Independent Review Committee-assessed baseline CNS metastases (alectinib, n = 64; crizotinib, n = 58); 43 had measurable lesions (alectinib, n = 21; crizotinib, n = 22), and 46 had received prior radiotherapy (alectinib, n = 25; crizotinib, n = 21). Investigator-assessed PFS with alectinib was consistent between patients with baseline CNS metastases [hazard ratio (HR) 0.40, 95% confidence interval (CI): 0.25-0.64] and those without (HR 0.51, 95% CI: 0.33-0.80, P interaction = 0.36). Similar results were seen in patients regardless of prior radiotherapy. Time to CNS progression was significantly longer with alectinib versus crizotinib and comparable between patients with and without baseline CNS metastases ($P < 0.0001$). CNS ORR was 85.7% with alectinib versus 71.4% with crizotinib in patients who received prior radiotherapy, and 78.6% versus 40.0%, respectively, in those who had not. **CONCLUSION:** Alectinib demonstrated superior CNS activity and significantly delayed CNS progression versus crizotinib in patients with previously untreated, advanced ALK+ NSCLC, irrespective of prior CNS disease or radiotherapy.

[Landscape of EGFR -dependent and -independent resistance mechanisms to osimertinib and continuation therapy post-progression in EGFR-mutant NSCLC.](#) Le X1, Puri S2, Negrao MV1, et al. Clin Cancer Res. 2018 Sep 18. pii: clincanres.1542.2018. doi: 10.1158/1078-0432.CCR-18-1542. [Epub ahead of print]
PURPOSE: Osimertinib was initially approved for T790M positive NSCLC and, more recently, for first-line treatment of EGFR-mutant NSCLC. However, resistance mechanisms to osimertinib have been incompletely described. **EXPERIMENTAL DESIGN:** Using cohorts from MD Anderson Lung Cancer Moonshot GEMINI and Moffitt Cancer Center Lung Cancer databases, we collected clinical data for patients treated with osimertinib. Molecular profiling analysis was performed at the time of progression in a subset of the patients. **RESULTS:** In the 118 patients treated with osimertinib, 42 had molecular profiling at progression. T790M was preserved in 21 (50%) patients and lost in 21 (50%). EGFR C797 and L792 (26%) mutations were the most common resistance mechanism and were observed exclusively in T790M-preserved cases. MET amplification was the second most common alteration (14%). Recurrent alterations were observed in 22 genes/pathways, including PIK3CA, FGFR, and RET. Preclinical studies confirmed MET, PIK3CA, and epithelial-to-mesenchymal transition (EMT) as potential resistance drivers. Alterations of cell cycle genes were associated with shorter median PFS (4.4 vs 8.8 months, p=0.01). In 76 patients with progression, osimertinib was continued in 47 cases with a median second progression-free survival (PFS2) was of 12.6 months; 21 patients received local consolidation radiation with median PFS of 15.5 months. Continuation of osimertinib beyond progression was associated with a longer overall survival compared to discontinuation (OS 11.2 vs 6.1 months, p=0.02). **CONCLUSIONS:** Osimertinib resistance is associated with diverse, predominantly EGFR-independent genomic alterations.

Continuation of osimertinib post-progression, alone or in conjunction with radiotherapy, may provide prolonged clinical benefit in selected patients.

[**Efficacy and safety analysis of the German expanded access program of osimertinib in patients with advanced, T790M-positive non-small cell lung cancer.**](#) Stratmann JA1, Michels S2, Hornetz S3, et al. J Cancer Res Clin Oncol. 2018 Sep 22. doi: 10.1007/s00432-018-2754-x. [Epub ahead of print]
PURPOSE: Osimertinib, a third-generation irreversible mutant-selective inhibitor of EGFR kinase activity was clinically evaluated in the AURA trials, where it showed high clinical efficacy and a favorable toxicity profile in patients with acquired exon 20-EGFR pT790M mutation. We provide the clinical data of the German expanded access program that further characterizes the efficacy and safety of osimertinib in a heterogeneous patient population outside clinical trials. **METHODS:** We performed a retrospective data analysis on patients who were included into the German osimertinib EAP.
RESULTS: Of 81 patients enrolled, 51 patients (62.9%) with sufficient case report form data were available for efficacy and safety analysis. Unconfirmed overall response rate was 80.0% with 2 patients (3.9%) achieving a complete remission and 37 patients (72.5%) having a partial remission. Disease control rate was 95.9% and only two patients showed refractory disease. Disease control rate did not correlate with clinical characteristics and was independent of number as well as type of the previous therapy line(s). Estimated progression-free survival was 10.1 months (95% CI 9.2-11.0 months). Osimertinib showed a favorable toxicity profile with no dose reductions in our observation period, even in patients with low performance status. Median survival from first diagnosis to data cut-off was 47.3 months (95% CI 43.3-51.9 months). Repeated tissue/liquid biopsy of three patients in our cohort who showed disease progression revealed an amplification of MET. **CONCLUSIONS:** We confirm safety and efficacy of osimertinib with high response rates among all subgroups, including patients with poor performance status and multiple prior therapy lines. Amplification of MET might mediate acquired resistance to osimertinib.

[**Impact of BRAF Mutation Class on Disease Characteristics and Clinical Outcomes in BRAF-Mutant Lung Cancer.**](#) Dagogo-Jack I1, Martinez P2, Yeap BY3, et al. Clin Cancer Res. 2018 Sep 17. pii: clincanres.2062.2018. doi: 10.1158/1078-0432.CCR-18-2062. [Epub ahead of print]
PURPOSE: BRAF mutations are divided into functional classes based on signaling mechanism and kinase activity: V600-mutant kinase-activating monomers (class I), kinase-activating dimers (class II), and kinase-inactivating heterodimers (class III). The relationship between functional class and disease characteristics in BRAF-mutant non-small cell lung cancer (NSCLC) has not been fully explored.
EXPERIMENTAL DESIGN: We performed a retrospective analysis of BRAF-mutant NSCLCs treated at two institutions from 2005-2017 to determine clinicopathologic characteristics, progression-free survival (PFS) on chemotherapy, and overall survival (OS). **RESULTS:** We identified 236 patients with BRAF-mutant NSCLC (n=107 class I, n=75 class II, and n=54 class III). Patients with class II or III mutations were more likely to have brain metastases (p≤0.01) and RAS co-alterations (p≤0.001). Compared to class I, PFS on chemotherapy was shorter for class II (p=0.069) and class III (p=0.034). OS was shorter for class II and III (Class I: 40.1 months, Class II: 13.9 months, Class III: 15.6 months; I vs II: p<0.001, I vs III: p=0.023); however, this difference was driven by fewer extra-thoracic metastases and higher use of targeted therapies in class I patients. When patients treated with targeted therapy and those with thoracic-only metastases were excluded, there was no difference in OS across the three classes. **CONCLUSIONS:** BRAF-mutant NSCLC is a heterogeneous disease that encompasses three distinct functional classes. Classes II and III have aggressive clinical features leading to less favorable outcomes. The distinct biological characteristics of class II and III tumors suggest that class-specific therapies may be necessary to effectively target these molecular subsets.

IMPORTANCE: Treatment choice for lung squamous cell carcinoma could be aided by identifying predictive biomarkers. **OBJECTIVE:** To assess whether patient outcomes in the LUX-Lung 8 trial were associated with ERBB gene family member aberrations in tumor specimens. **DESIGN, SETTING, AND PARTICIPANTS:** Ad hoc secondary analysis of the LUX-Lung 8 trial conducted at 183 centers in 23 countries from March 30, 2012, to January 30, 2014. Eligible patients had stage IIIB or IV lung squamous cell carcinoma with progressive disease after 4 or more cycles of platinum-based chemotherapy. Tumor genetic analysis (TGA) was performed using next-generation sequencing in a cohort enriched for patients with progression-free survival (PFS) of more than 2 months. Epidermal growth factor receptor (EGFR) expression levels were assessed by immunohistochemistry in a separate cohort of patients from the LUX-Lung 8 population. Associations of PFS and overall survival (OS) with ERBB gene alterations and EGFR expression levels were assessed. This analysis was conducted from February 26, 2015, to June 12, 2017. **INTERVENTIONS:** Patients were randomized 1:1 to treatment with afatinib dimaleate (40 mg/d; n = 398) or erlotinib hydrochloride (150 mg/d; n = 397). **MAIN OUTCOMES AND MEASURES:** Overall survival, PFS, pooled and individual ERBB gene mutations, ERBB copy number alterations, and EGFR expression. **RESULTS:** Tumor specimens from 245 patients were eligible for next-generation sequencing (TGA subset: 132 patients treated with afatinib; 113 patients treated with erlotinib). In this population, outcomes were improved with afatinib vs erlotinib treatment (PFS: median, 3.5 vs 2.5 months; hazard ratio [HR], 0.69; 95% CI, 0.51-0.92; P = .01; OS: median, 8.4 vs 6.6 months; HR, 0.81; 95% CI, 0.62-1.05; P = .12). Of 245 patients in the TGA subset, 53 (21.6%) had tumors with 1 or more ERBB mutations. Among afatinib-treated patients, PFS (median, 4.9 vs 3.0 months; HR, 0.62; 95% CI, 0.37-1.02; P = .06) and OS (median, 10.6 vs 8.1 months; HR, 0.75; 95% CI, 0.47-1.17; P = .21) were longer among those with ERBB mutation-positive disease than among those without. The presence of HER2 mutations was associated with favorable PFS and OS following afatinib vs erlotinib treatment. There was no apparent association between copy number alteration or EGFR expression level and outcome. **CONCLUSIONS AND RELEVANCE:** Next-generation sequencing may help identify patients with lung squamous cell carcinoma who would derive additional benefit from treatment with afatinib. The role of ERBB mutations, particularly HER2 mutations, as predictive biomarkers for afatinib treatment in this setting warrants further evaluation.

BACKGROUND: The objective of this study was to assess cost and effectiveness of osimertinib in treating newly diagnosed advanced non-small cell lung cancer with an epidermal growth factor receptor (EGFR) mutation from a public payer's perspective in the U.S. and China. **MATERIALS AND METHODS:** Markov models were developed to compare three treatment strategies: first-line use of osimertinib, first-line use of the standard first-generation EGFR-tyrosine kinase inhibitor (EGFR-TKI) followed by the second-line use of osimertinib, and the standard first-generation EGFR-TKI therapy (standard care [SOC]). Clinical data, cost, and utility data were mainly derived from published literatures. Deterministic and probabilistic sensitivity analyses were conducted to assess the robustness of the incremental cost per quality-adjusted life year (QALY) between the treatments. **RESULTS:** The resultant incremental cost per QALY gained for the first-line osimertinib versus SOC was $312,903 in the U.S. and

$41,512 in China. The incremental cost per QALY for the second-line osimertinib versus SOC was $284,532 in the U.S. and $38,860 in China. The probability of the SOC strategy being cost-effective is 1.0 if the willingness to pay threshold is below $150,000/QALY in the U.S. and below $30,000/QALY in China. **CONCLUSION:** Osimertinib as first-line treatment could gain more health benefits in comparison with standard EGFR-TKIs or second-line use of osimertinib. However, because of the high cost of treatment, the cost-effectiveness analyses were not in favor of the first-line use of osimertinib from a public payer's perspective in the U.S. and China. **IMPLICATIONS FOR PRACTICE:** Osimertinib as first-line treatment yielded the greatest health outcomes but is not a cost-effective strategy for lung cancer in the U.S. and China. The price of osimertinib has a substantial impact on economic outcomes.

[A Randomized, Open-Label, Phase II Study Comparing Pemetrexed Plus Cisplatin Followed by Maintenance Pemetrexed versus Pemetrexed Alone in Patients with Epidermal Growth Factor Receptor (EGFR)-Mutant Non-small Cell Lung Cancer after Failure of First-Line EGFR Tyrosine Kinase Inhibitor: KCSG-LU12-13.](#) Yoo KH1,2, Lee SJ1, Cho J3, et al. Cancer Res Treat. 2018 Sep 3. doi: 10.4143/crt.2018.324. [Epub ahead of print]
PURPOSE: The optimal cytotoxic regimens have not been established for patients with non-small cell lung cancer (NSCLC) who develop disease progression on first-line epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI). **MATERIALS AND METHODS:** We conducted a multi-center randomized phase II trial to compare the clinical outcomes between pemetrexed plus cisplatin combination therapy followed by maintenance pemetrexed (PC) and pemetrexed monotherapy (P) after failure of first-line EGFR-TKI. The primary objective was progression-free survival (PFS), and secondary objectives included overall response rate (ORR), overall survival (OS), health-related quality of life (HRQOL), and safety and toxicity profiles. **RESULTS:** A total of 96 patients were randomized, and 91 patients were treated at 14 centers in Korea. The ORR was 34.8% (16/46) for the PC arm and 17.8% (8/45) for the P arm (p=0.066). With 23.4 months of follow-up, the median PFS was 5.4 months in the PC arm and 6.4 months in the P arm (p=0.114). The median OS was 17.9 months and 15.7 months in PC and P arms, respectively (p=0.787). Adverse events ≥ grade 3 were reported in 12 patients (26.1%) in the PC arm and 9 patients (20.0%) in the P arm (p=0.491). The overall time trends of HRQOL were not significantly different between the two arms. **CONCLUSION:** The outcomes of pemetrexed therapy in NSCLC patients with disease progression after first-line EGFR-TKI might not be improved by adding cisplatin.

[Treatment effectiveness and tolerability of afatinib at different doses in patients with EGFR-mutated lung adenocarcinoma: How low can we go?](#) Lim CK1, Wei YF2, Tsai MS3, Chen KY4, Shih JY5, Yu CJ5. Eur J Cancer. 2018 Sep 7;103:32-40. doi: 10.1016/j.ejca.2018.07.128. [Epub ahead of print]
INTRODUCTION: Afatinib is commonly used as the first-line treatment for EGFR-mutated lung adenocarcinoma. However, dose adjustments are frequently required. This study aimed to investigate the treatment effectiveness of afatinib administered at different doses to patients with EGFR-mutated lung adenocarcinoma. **METHODS:** Treatment-naïve patients with advanced EGFR-mutated lung adenocarcinoma who received afatinib therapy between May 2014 and September 2016 were enrolled retrospectively. Collected clinical data included age, sex, smoking history, performance status, disease stages, EGFR mutation status, initial doses of afatinib, dose adjustments, treatment responses, progression-free survival and treatment-associated adverse events. The average daily dose was calculated by dividing the summation of all doses of prescribed tablets during the treatment period by the total days of afatinib use. The patients were classified into five treatment groups based on average daily doses: 40 mg, <40 and >30 mg, 30 mg, <30 and ≥ 20 mg and <20 mg. **RESULTS:** A total of 254 patients were included. No significant differences were found among these five treatment groups with respect to response rates (69.3%, 68.3%, 70.5%, 77.8% and 66.7%, respectively, p = 0.920) and disease control

rates (97.4%, 95.2%, 97.7%, 100% and 100%, respectively, p = 0.749). However, the treatment group with an average daily dose of <20 mg had a significant shorter progression-free survival as compared with the other groups (16.8, 12.4, 13.9, 17.0 and 5.3 months, respectively, p = 0.049). **CONCLUSIONS:** Dose reduction may not affect the treatment effectiveness until the average daily dose is below 20 mg. Further prospective studies of afatinib therapy at different daily doses are warranted.

NSCLC - RADIOTHERAPY

Defining Optimal Comorbidity Measures for Patients with Early Stage Non-small Cell Lung Cancer (NSCLC) Treated with Stereotactic Body Radiation Therapy (SBRT). DeWees TA1, Nikitas J2, Rehman S3, Bradley JD2, Robinson CG2, Roach MC4. Pract Radiat Oncol. 2018 Sep 19. pii: S1879-8500(18)30264-9. doi: 10.1016/j.prro.2018.09.001. [Epub ahead of print]
INTRODUCTION: Comparison of overall survival (OS) between SBRT and other treatments for early stage NSCLC is confounded by differences in age, performance status, and medical comorbidity. We sought to define the most robust measurement for this population amongst five indices: age, Eastern Cooperative Oncology Group (ECOG) performance status, Adult Comorbidity Evaluation-27 (ACE-27), Charlson Comorbidity Index (CCI), and age adjusted CCI (CCIa). **METHODS:** 548 patients with stage I NSCLC treated with SBRT were analyzed. Patients were divided into "high" and "low" risk groups for OS for each index using the log-rank test. Continuous and dichotomized models were compared via Akaike Information Criterion (AIC) and the Vuong test. Multivariate Cox regression modelling was used with demographic information to determine the independent prognostic value of the continuous and dichotomized versions of the indices. The best was used to stratify the patients into as many significantly different cohorts as possible. **RESULTS:** Optimal cut-points between "high-risk" and "low-risk" OS groups for age, ECOG, ACE-27, CCI, and CCIa were ≥75 years, ≥1, ≥3, ≥3, and ≥6 with HRs for death of 1.23 (95% CI: 1.00-1.50), 1.66 (1.28-2.15), 1.37 (1.12-1.67), 1.43 (1.17-1.76), and 1.47 (1.20-1.80) respectively. Dichotomizing did not result in a significant loss in prognostic power. While there was not a significant difference in prognostic power between the indices, CCIa best predicted OS. CCIa divided the patients into 3 cohorts with median OS of 42 months, 33 months, and 23 months for scores of ≤5, 6-7, and ≥8 respectively. **CONCLUSIONS:** CCIa was the best indicator of OS in every model employed with no loss of prognostic power with dichotomization. Dichotomization of CCIa (≥6) could be implemented in future comparisons of SBRT with OS. No cohort could be identified with a median survival of less than a year where treatment could be deemed futile.

Stereotactic Body Radiation Therapy for Operable Early-Stage Lung Cancer: Findings From the NRG Oncology RTOG 0618 Trial. Timmerman RD1,2, Paulus R3, Pass HI4, et al. JAMA Oncol. 2018 Sep 1;4(9):1263-1266. doi: 10.1001/jamaoncol.2018.1251.
IMPORTANCE: Stereotactic body radiation therapy (SBRT) has become a standard treatment for patients with medically inoperable early-stage lung cancer. However, its effectiveness in patients medically suitable for surgery is unclear. **OBJECTIVE:** To evaluate whether noninvasive SBRT delivered on an outpatient basis can safely eradicate lung cancer and cure selected patients with operable lung cancer, obviating the need for surgical resection. **DESIGN, SETTING, AND PARTICIPANTS:** Single-arm phase 2 NRG Oncology Radiation Therapy Oncology Group 0618 study enrolled patients from December 2007 to May 2010 with median follow-up of 48.1 months (range, 15.4-73.7 months). The setting was a multicenter North American academic and community practice cancer center consortium. Patients had operable biopsy-proven peripheral T1 to T2, N0, M0 non-small cell tumors no more than 5 cm in diameter, forced expiratory volume in 1 second (FEV1) and diffusing capacity greater than 35% predicted, arterial oxygen tension greater than 60 mm Hg, arterial carbon dioxide tension less than 50 mm Hg, and no severe medical problems. The data analysis was performed in October 2014.

INTERVENTIONS: The SBRT prescription dose was 54 Gy delivered in 3 18-Gy fractions over 1.5 to 2.0 weeks. **MAIN OUTCOMES AND MEASURES:** Primary end point was primary tumor control, with survival, adverse events, and the incidence and outcome of surgical salvage as secondary end points. **RESULTS:** Of 33 patients accrued, 26 were evaluable (23 T1 and 3 T2 tumors; 15 [58%] male; median age, 72.5 [range, 54-88] years). Median FEV1 and diffusing capacity of the lung for carbon monoxide at enrollment were 72.5% (range, 38%-136%) and 68% (range, 22%-96%) of predicted, respectively. Only 1 patient had a primary tumor recurrence. Involved lobe failure, the other component defining local failure, did not occur in any patient, so the estimated 4-year primary tumor control and local control rate were both 96% (95% CI, 83%-100%). As per protocol guidelines, the single patient with local recurrence underwent salvage lobectomy 1.2 years after SBRT, complicated by a grade 4 cardiac arrhythmia. The 4-year estimates of disease-free and overall survival were 57% (95% CI, 36%-74%) and 56% (95% CI, 35%-73%), respectively. Median overall survival was 55.2 months (95% CI, 37.7 months to not reached). Protocol-specified treatment-related grade 3, 4, and 5 adverse events were reported in 2 (8%; 95% CI, 0.1%-25%), 0, and 0 patients, respectively. **CONCLUSIONS AND RELEVANCE:** As given, SBRT appears to be associated with a high rate of primary tumor control, low treatment-related morbidity, and infrequent need for surgical salvage in patients with operable early-stage lung cancer.

[**The impact of radiation therapy on lymphocyte count and survival in metastatic cancer patients receiving PD-1 immune checkpoint inhibitors.**](#) Pike LRG1, Bang A2, Mahal BA3, et al. Int J Radiat Oncol Biol Phys. 2018 Sep 15. pii: S0360-3016(18)33755-6. doi: 10.1016/j.ijrobp.2018.09.010. [Epub ahead of print]
PURPOSE: Therapeutic radiation has conflicting immune effects: radiation (RT)-induced immunogenic cell death can contribute to immune response, but lymphocytes are also sensitive to RT. It is unknown whether palliative RT leads to lymphopenia in patients treated with immune checkpoint inhibitors (ICI) and whether this impacts outcomes. As such, we sought to assess the impact of palliative RT on circulating lymphocyte count and neutrophil-lymphocyte-ratio (NTL) in patients being treated with PD-1 directed ICI and associations with survival. **MATERIALS AND METHODS:** We identified patients from five radiation oncology centers, treated with palliative RT and either pembrolizumab or nivolumab with non-small cell lung cancer (NSCLC), metastatic melanoma (MM), and renal cell carcinoma (RCC). Patients who received intervening cytotoxic chemotherapy were excluded. We recorded absolute lymphocyte count (ALC) and neutrophil to lymphocyte ratio (NTL) before and after palliative RT, and at the start of ICI. Survival was analyzed using the Kaplan-Meier method and Cox proportional hazard models. **RESULTS:** One hundred ten patients received 225 courses of palliative RT. Median change in ALC (dALC) after RT was -161 cells/mL. Decreases in ALC were greater with RT to the spine, lung/mediastinum, and chest wall compared with the brain, extremity, or abdomen/pelvis (p=0.002), and after courses >5 fractions (p=0.003). Extracranial and >5 fraction radiation was associated with increased odds of severe lymphopenia (ALC<500) at the end of RT (OR 3.7, p=0.001, and OR 3.9 p=0.001, respectively). Patients who developed RT-induced severe lymphopenia were more likely to have severe lymphopenia when ICI was initiated (OR 6.4, p=0.0001), particularly when RT was administered in the previous 3 months (OR 189, p<0.0001). Severe lymphopenia at onset of ICI therapy was associated with increased mortality on multivariable analysis (HR 2.1, p=0.03). **CONCLUSIONS:** Extracranial or prolonged courses of RT increase the risk of severe lymphopenia, which is associated with poorer survival in patients treated with ICI.

[**A prospective study of the feasibility of FDG-PET/CT imaging to quantify radiation-induced lung inflammation in locally advanced non-small cell lung cancer patients receiving proton or photon**](#)

radiotherapy. Jahangiri P1, Pournazari K1, Torigian DA1, Werner TJ1, Swisher-McClure S2, Simone CB 2nd3, Alavi A1. Eur J Nucl Med Mol Imaging. 2018 Sep 18. doi: 10.1007/s00259-018-4154-5. [Epub ahead of print]

PURPOSE: This prospective study assessed the feasibility of 18F-2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography/computed tomography (PET/CT) to quantify radiation-induced lung inflammation in patients with locally advanced non-small cell lung cancer (NSCLC) who received radiotherapy (RT), and compared the differences in inflammation in the ipsilateral and contralateral lungs following proton and photon RT. **METHODS:** Thirty-nine consecutive patients with NSCLC underwent FDG-PET/CT imaging before and after RT on a prospective study. A novel quantitative approach utilized regions of interest placed around the anatomical boundaries of the lung parenchyma and provided lung mean standardized uptake value (SUVmean), global lung glycolysis (GLG), global lung parenchymal glycolysis (GLPG) and total lung volume (LV). To quantify primary tumor metabolic response to RT, an adaptive contrast-oriented thresholding algorithm was applied to measure metabolically active tumor volume (MTV), tumor uncorrected SUVmean, tumor partial volume corrected SUVmean (tumor-PVC-SUVmean), and total lesion glycolysis (TLG). Parameters of FDG-PET/CT scans before and after RT were compared using two-tailed paired t-tests. **RESULTS:** All tumor parameters after either proton or photon RT decreased significantly (p < 0.001). Among the 21 patients treated exclusively with proton RT, no significant increase in PVC-SUVmean or PVC-GLPG was observed in ipsilateral lungs after the PVC parameters of primary tumor were subtracted (p = 0.114 and p = 0.453, respectively). Also, there were no significant increases in SUVmean or GLG of contralateral lungs of patients who received proton RT (p = 0.841, p = 0.241, respectively). In contrast, among the nine patients who received photon RT, there was a statistically significant increase in PVC-GLPG of ipsilateral lung (p < 0.001) and in GLG of contralateral (p = 0.036) lung. In the subset of nine patients who received a combined proton and photon RT, there was a statistically significant increase in PVC-GLPG of ipsilateral lung (p < 0.001). **CONCLUSION:** Our data suggest less induction of inflammatory response in both the ipsilateral and contralateral lungs of patients treated with proton compared to photon or combined proton-photon RT.

SMALL CELL LUNG CANCER - SCLC

Clinical value of carcinoembryonic antigen for predicting the incidence of brain metastases and survival in small cell lung cancer patients treated with prophylactic cranial irradiation. Guo D#1,2, Jing W#2,3, Zhu H2, Li M2, Zou B2, Zhang Y2, Fu L2, Kong L2, Yue J2,4, Yu J2,4. Cancer Manag Res. 2018 Sep 4;10:3199-3205. doi: 10.2147/CMAR.S175043. eCollection 2018.

BACKGROUND: Although the role of prophylactic cranial irradiation (PCI) in the treatment of small cell lung cancer (SCLC) has been confirmed, the occurrence of brain metastases (BM) in patients remains a major problem. We designed this study to evaluate the clinical value of carcinoembryonic antigen (CEA) for predicting the incidence of BM and survival in SCLC patients who received PCI. **MATERIALS AND METHODS:** The records of 128 consecutive SCLC patients, who underwent PCI in our institute between 2005 and 2015, were analyzed. The collected data included clinicopathological features and the levels of CEA, neuron-specific enolase (NSE), cytokeratin 19 fragments (CYFRA21-1), and albumin. Kaplan-Meier and Cox regression analyses were used to determine the factors that affect BM and survival in SCLC patients after PCI. **RESULTS:** In total, 128 patients were identified, with a median (range) age of 62 (30-83) years. Thirty-two patients developed BM at some time during follow-up. The median levels of CEA, NSE, CYFRA21-1, and albumin were 7.6 ng/mL, 44 ng/mL, 4.6 ng/mL, and 42.1 g/L, respectively. In the multivariate analysis, CEA level (HR: 2.479, 95% CI: 1.101-5.581; P=0.028), advanced clinical stage (HR: 2.929, 95% CI: 1.338-6.413; P=0.007), and NSE level (HR: 3.021, 95% CI: 1.226-7.442; P=0.016) were significantly correlated with BM. CEA (HR: 1.903, 95% CI: 1.133-3.195; P=0.015) and advanced clinical stage (HR: 2.002, 95% CI: 1.227-3.267; P=0.005) were

independently associated with worse overall survival in SCLC patients. **CONCLUSION:** CEA is an independent predictive factor for the incidence of BM after PCI in SCLC and can be used as a predictor of BM in SCLC. In addition, a high level of CEA indicates a poor prognosis in SCLC patients after PCI. Prospective randomized clinical studies are required to confirm these findings.

[Will liquid biopsies improve outcomes for patients with small-cell lung cancer?](#) Blackhall F1, Frese KK2, Simpson K2, Kilgour E2, Brady G2, Dive C3. Lancet Oncol. 2018 Sep;19(9):e470-e481. doi: 10.1016/S1470-2045(18)30455-8.
Small-cell lung cancer (SCLC) is an aggressive tumour that seeds metastases early with dismal outcomes. As expected from a disease that is closely associated with smoking, mutation burden in SCLC is high. Intratumoral and intertumoral heterogeneity is a substantial obstacle to successful treatment and the SCLC genomic landscape reveals few targets that are readily druggable. Chemotherapy elicits responses in most patients with SCLC, but their effects are short lived. Multiple clinical trials have been unsuccessful in showing positive survival outcomes and biomarkers to select patients and monitor responses to novel targeted treatments have been lacking, not least because acquisition of tumour biopsies, especially during relapse after chemotherapy, is a substantial challenge. Liquid biopsies via blood sampling in SCLC, notably circulating tumour cells and circulating free tumour DNA can be readily and repeatedly accessed, and are beginning to yield promising data to inform SCLC biology and patient treatment. Primary cell cultures and preclinical mouse models can also be derived from the relatively plentiful SCLC circulating tumour cells providing a tractable platform for SCLC translational research and drug development.

[BLACAT1 predicts poor prognosis and serves as oncogenic lncRNA in small-cell lung cancer.](#)
Chen W1, Hang Y1, Xu W1, Wu J2, Chen L1, Chen J1, Mao Y1, Song J1, Song J2, Wang H1. J Cell Biochem. 2018 Sep 11. doi: 10.1002/jcb.27548. [Epub ahead of print]
Bladder cancer-associated transcript 1 (BLACAT1) is a novel identified long noncoding RNA (lncRNA) in bladder cancer, and has been suggested to function as an oncogenic lncRNA in several types of human cancer. However, its involvement in the progression of small-cell lung cancer (SCLC) remained unknown. The aim of our study was to investigate the clinical value and biological function in SCLC. In our results, BLACAT1 expression was increased in SCLC tissues and cell lines compared with paired adjacent normal tissues and bronchial epithelial cell lines, respectively. In addition, BLACAT1 high-expression was obviously associated with advanced clinical stage, large tumor size, more lymph node metastasis, present distant metastasis, and poor prognosis. Furthermore, multivariate analysis indicated that high-expression of BLACAT1 acted as an independent poor prognostic factor for overall survival in SCLC cases. The loss-of-function studies suggested that of BLACAT1 suppressed SCLC cell proliferation, migration, and invasion, and induced G0/G1 phase arrest. In conclusion, BLACAT1 is associated with the malignant status and prognosis in patients with SCLC, and functions as an oncogenic lncRNA in regulating cell proliferation and motility, suggesting BLACAT1 may act as a potential target for SCLC prevention and treatment.

[Targeted Therapy and Immune Therapy for Small Cell Lung Cancer.](#) Gadgeel SM1. Curr Treat Options Oncol. 2018 Sep 10;19(11):53. doi: 10.1007/s11864-018-0568-3.
Approximately 15% of the over 220,000 new lung cancers diagnosed each year in the USA are small cell lung cancer (SCLC). The standard of care for SCLC patients has not changed for many years. Therefore, there remains a need to evaluate novel drugs for the management of SCLC patients. In recent years, there is a greater understanding of the molecular alterations that occur in SCLC. There is an expectation that targeting these molecular alterations could provide clinical benefit. Targeting angiogenesis by inhibiting the vascular endothelial growth factor (VEGF) pathway has been evaluated in SCLC patients and has shown only limited clinical benefit. Alterations in DNA repair make these tumors susceptible to DNA

repair pathway inhibitors and formed the basis for PARP inhibitor trials. Initial trials with PARP inhibitors have shown promising activity in some SCLC patients. Due to increased expression of anti-apoptotic Bcl-2 proteins, drugs targeting these proteins may also provide clinical benefit. Pre-clinical studies have shown that pathways of self-renewal such as the hedgehog and NOTCH pathways may be altered in SCLCs and could be targeted for therapeutic benefit. Initial trials with drugs targeting these pathways, including drugs-targeting DLL3, a NOTCH ligand, suggest the need for appropriate biomarkers to identify SCLC patients most likely to benefit from these strategies. Trials of immune checkpoint inhibitors have shown that these agents may have therapeutic role in SCLC. As is true in other tumor types, these agents benefit only a proportion of patients but the benefit when observed can be sustained. Tumor mutational burden and PD-L1 expression may predict for clinical benefit with these agents. Ongoing trials will define the role of these agents in management of SCLC patients.

[Risk factors for brain metastasis in patients with small cell lung cancer without prophylactic cranial irradiation.](#) Zheng Y1,2,3, Wang L2,3, Zhao W1, Dou Y1, Lv W1, Yang H1, Sun Y1, Xing L4,5. Strahlenther Onkol. 2018 Sep 14. doi: 10.1007/s00066-018-1362-7. [Epub ahead of print] **BACKGROUND:** This study aimed to determine the risk factors for brain metastasis (BM) and the prognostic factors for overall survival (OS) in patients with small cell lung cancer without prophylactic cranial irradiation (PCI). **PATIENTS AND METHODS:** Limited stage small cell lung cancer (LS-SCLC) patients achieving a complete response (CR) or partial response (PR) were enrolled into this study between January 2010 and December 2016. We retrospectively evaluated the influencing factors for time to BM and overall survival (OS). **RESULTS:** A total of 153 patients were enrolled into this study. Sixty-eight developed BM during the follow-up period. For the whole cohort, the 1- and 2-year BM rates were 29.4 and 41.2%, respectively. Multivariate analysis showed that T stage (hazard ratio [HR] = 2.27, P = 0.024), neutrophil-to-lymphocyte ratio (NLR; HR = 2.07, P = 0.029), time to thoracic radiotherapy (HR = 0.34, P = 0.002) and chemotherapy cycles (HR = 0.49, P = 0.036) were the independent influencing factors of time to BM. Only NLR (HR = 2.11, P = 0.005) and time to thoracic radiotherapy (HR = 1.95, P = 0.011) were independent prognostic factors of OS. Of the 68 patients developing BM, those with BM occurring as the first relapse (42/68) had better OS than the others (39.5 months vs 23.0 months, P = 0.016). **CONCLUSION:** LS-SCLC patients without PCI had a high risk of BM. High T stage, high NLR, early thoracic radiotherapy and fewer chemotherapy cycles were the risk factors of BM. Further research is needed to confirm the results.

[Recurrent WNT pathway alterations are frequent in relapsed small cell lung cancer.](#) Wagner AH1, Devarakonda S2,3, Skidmore ZL1, et al. Nat Commun. 2018 Sep 17;9(1):3787. doi: 10.1038/s41467-018-06162-9.
Nearly all patients with small cell lung cancer (SCLC) eventually relapse with chemoresistant disease. The molecular mechanisms driving chemoresistance in SCLC remain un-characterized. Here, we describe whole-exome sequencing of paired SCLC tumor samples procured at diagnosis and relapse from 12 patients, and unpaired relapse samples from 18 additional patients. Multiple somatic copy number alterations, including gains in ABCC1 and deletions in MYCL, MSH2, and MSH6, are identifiable in relapsed samples. Relapse samples also exhibit recurrent mutations and loss of heterozygosity in regulators of WNT signaling, including CHD8 and APC. Analysis of RNA-sequencing data shows enrichment for an ASCL1-low expression subtype and WNT activation in relapse samples. Activation of WNT signaling in chemosensitive human SCLC cell lines through APC knockdown induces chemoresistance. Additionally, in vitro-derived chemoresistant cell lines demonstrate increased WNT activity. Overall, our results suggest WNT signaling activation as a mechanism of chemoresistance in relapsed SCLC.

Use of Dietary Supplements at a Comprehensive Cancer Center. Luo Q1, Asher GN2,3. J Altern Complement Med. 2018 Sep/Oct;24(9-10):981-987. doi: 10.1089/acm.2018.0183.
OBJECTIVES: The objectives of this study were to define dietary supplement (DS) use by cancer patients and to investigate factors associated with DS use during cancer treatment. **METHODS:** A cross-sectional survey of adults diagnosed with breast, colorectal, lung, or prostate cancer in 2010-2012 at the University of North Carolina Comprehensive Cancer Center was conducted. Questionnaires were sent to 1794 patients. Phone calls were made to nonrespondents. The authors described type of DS use before, during, and after initial cancer treatment, source of advice on DS use, and used logistic regression to investigate the association of DS use during or after cancer treatment with clinical/sociodemographic characteristics and source of advice. **RESULTS:** Six hundred and three (34%) patients completed the questionnaires. Nonvitamin nonmineral DS use during initial cancer treatments was common: any cancer treatment (49%), chemotherapy (52%), and radiation therapy (51%). Among patients seeking advice on DS use, 75% reported professional sources, 44% reported media sources, and 47% reported lay sources. DS use during cancer treatment was strongly predicted by prior DS use, followed by prior complementary therapies' use, receiving DS advice from a cancer care provider, being female, and higher education level. **CONCLUSION:** DS use is common and persists during cancer treatment. Among DS users during treatment, 18% used an herbal supplement, which are likely to carry greater risk of interaction with chemotherapy agents compared with vitamin, mineral, and other supplements. Although many respondents sought DS advice from professional sources, the use of nonprofessional sources remains high.

Self-efficacy, cancer-related fatigue, and quality of life in patients with resected lung cancer.
Chen HL1, Liu K2, You QS2. Eur J Cancer Care (Engl). 2018 Sep 25:e12934. doi: 10.1111/ecc.12934.
[Epub ahead of print]
We aim to investigate the relationship between self-efficacy, cancer-related fatigue, and quality of life in patients with resected lung cancer. A prospective cohort among 452 patients with resected NSCLC was conducted in 2014 to 2015. The self-efficacy, cancer-related fatigue, and quality of life assessments were investigated in the 3-month follow-up by General Self-Efficacy Scale (GSES), Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF), and Short Form Health Survey (SF-36), respectively. Structural equation modelling was used to evaluate the relationships between the latent variables. Structural equation modelling analysis showed that both GSES ($\beta = 0.69$, $p < 0.05$) and MFSI-SF ($\beta = -0.46$, $p < 0.01$) had direct effect on SF-36; GSES also can indirect effect on SF-36 though MFSI-SF ($\beta = -0.42$, $p < 0.01$). The model fit indices demonstrated a reasonable fit ($\chi2 = 27.221$, CFI = 0.911, GFI = 0.962, RMSEA = 0.051). The results showed self-efficacy has direct and indirect effect on quality of life in patients with resected lung cancer. Furthermore, cancer-related fatigue, as mediated variables, can mediate the relationship between self-efficacy and quality of life. In the future, self-efficacy interventions are need for improving quality of life in patients with resected lung cancer.

Sleep Disordered Breathing Is Highly Prevalent in Patients with Lung Cancer: Results of the Sleep Apnea in Lung Cancer Study. Cabezas E1, Pérez-Warnisher MT2, Troncoso MF1, et al. Respiration. 2018 Sep 27:1-6. doi: 10.1159/000492273. [Epub ahead of print]
BACKGROUND: Obstructive sleep apnea (OSA) has been linked to tumorigenesis and tumor progression. **OBJECTIVES:** The Sleep Apnea in Lung Cancer (SAIL) study (NCT02764866) was designed to determine the prevalence of OSA in patients with lung cancer. **METHODS:** Cross-sectional study including consecutive patients with newly diagnosed lung cancer. All patients were offered home

sleep apnea testing (HSAT) and administered a sleep-specific questionnaire prior to initiating oncologic treatment. Sleep study-related variables, symptoms, and epidemiologic data as well as cancer related variables were recorded. **RESULTS:** Eighty-three patients were enrolled in the SAIL study. Sixty-six completed HSAT. The mean age was 68 ± 11 years and 58% were male with a mean body mass index of 28.1 ± 5.4. Forty-seven percent were current smokers, 42% former smokers, and 11% never smokers with a median tobacco consumption of 51 pack-years. Fifty percent had COPD with a mean FEV1 of $83 \pm 22.6\%$ of predicted and a mean DLCO of $85.5 \pm 20.1\%$. Adenocarcinoma was the most common histologic type (46.7%), followed by squamous cell (16.7%) and small cell (16.7%). Most patients were diagnosed at an advanced stage (65% in stages III-IV). The vast majority (80%) had OSA (apnea-hypopnea index [AHI] > 5), and 50% had moderate to severe OSA (AHI > 15) with a mean Epworth Sleepiness Score of 7.43 ± 3.85. Significant nocturnal hypoxemia was common (Median T90: 10.9% interquartile range 2.4-42.2). **CONCLUSIONS:** Sleep apnea and nocturnal hypoxemia are highly prevalent in patients with lung cancer.

[**A Patient-Centered Activity Regimen Improves Participation in Physical Activity Interventions in Advanced-Stage Lung Cancer.**](#) Bade BC1, Hyer JM2, Bevill BT2, Pastis A3, Rojewski AM2, Toll BA2, Silvestri GA2. Integr Cancer Ther. 2018 Sep;17(3):921-927. doi: 10.1177/1534735418781739. Epub 2018 Jun 14.

INTRODUCTION: Physical activity (PA) is a potential therapy to improve quality of life in patients with advanced-stage lung cancer (LC), but no PA regimen has been shown to be beneficial, clinically practical, and sustainable. We sought to test the hypothesis that a patient-centered activity regimen (PCAR) will improve patient participation and PA more effectively than weekly phone calls. **METHODS:** In patients with advanced-stage LC, we implemented a walking-based activity regimen and motivated patients via either weekly phone calls (n = 29; FitBit Zip accelerometer) or PCAR (n = 15; FitBit Flex, an educational session, and twice-daily gain-framed text messages). Data collection over a 4-week period was compared, and a repeated-measures, mixed-effects model for activity level was constructed. **RESULTS:** Subjects receiving PCAR more frequently used the device (100% vs 79%) and less frequently had missing data (11% vs 38%). "More active" and "less active" groups were created based on mean step count in the first week. "Less active" patients in the PCAR group increased their PA level, whereas PA level fell in the "more active" group. Most subjects found PCAR helpful (92%) and would participate in another activity study (85%). **DISCUSSION:** Compared with weekly phone calls, PCAR has higher patient participation, is more likely to improve PA in "less active" subjects, and has high patient satisfaction. A multifaceted PA regimen may be a more efficacious mechanism to study PA in advanced LC. PCAR should be used in a randomized controlled trial to evaluate for improvements in symptom burden, quality of life, and mood.

COMPLEMENTARY & ALTERNATIVE THERAPY

[**Complementary and Integrative Medicine to Reduce Adverse Effects of Anticancer Therapy.**](#) Rossi E1, Noberasco C1, Picchi M1, Stefano MD1, Rossi A1, Nurra L1, Ventura L2. J Altern Complement Med. 2018 Sep/Oct;24(9-10):933-941. doi: 10.1089/acm.2018.0143.

BACKGROUND: To address the side effects of anticancer treatments, the Clinic for Complementary Medicine and Diet in Oncology was opened, in collaboration with the oncology department, at the Hospital of Lucca (Italy) in 2013. **AIM:** To present the results of complementary medicine treatment targeted toward reducing the adverse effects of anticancer therapy and cancer symptoms, and improving patient quality of life. Dietary advice was aimed at the reduction of foods that promote inflammation in favor of those with antioxidant and anti-inflammatory properties. **METHODS:** This is a retrospective observational study on 357 patients consecutively visited from September 2013 to December 2017. The

intensity of symptoms was evaluated according to a grading system from G0 (absent) to G1 (slight), G2 (moderate), and G3 (strong). The severity of radiodermatitis was evaluated with the Radiation Therapy Oncology Group (RTOG) scale. Almost all the patients (91.6%) were receiving or had just finished some form of conventional anticancer therapy. **RESULTS:** The main types of cancer were breast (57.1%), colon (7.3%), lung (5.0%), ovary (3.9%), stomach (2.5%), prostate (2.2%), and uterus (2.5%). Comparison of clinical conditions before and after treatment showed a significant amelioration of nausea, insomnia, depression, anxiety, fatigue, mucositis, hot flashes, joint pain, dysgeusia, neuropathy, and all symptoms. Moreover, in a subgroup of 17 patients in radiotherapy undergoing integrative treatment, the level of toxicities and the severity of radiodermatitis were much lower than in the 13 patients without integrative treatment. Twenty-one cancer patients (6.2%) either refused (18) or discontinued (3) conventional anticancer treatment against the recommendation of their oncologist; after the integrative oncology (IO) visit, 7 (41.2%) out of 17 patients with follow-up decided to accept standard oncologic treatments. **CONCLUSIONS:** An IO clinic may contribute to reducing the adverse effects of anticancer therapy and improving the quality of life of cancer patients.

[**Complementary and Integrative Medicine in Lung Cancer: Questions and Challenges.**](#) Frenkel M1,2, Slater R1, Sapire K3, Sierpina V1. J Altern Complement Med. 2018 Sep/Oct;24(9-10):862-871. doi: 10.1089/acm.2018.0175.
Lung cancer represents 13% of all cancers, making it the second most common type of malignancy in the United States. Lung cancer is the leading cause of cancer death in men and women in the United States and accounts for nearly 18% of all deaths from cancer. Because of its high mortality rate, lung cancer is associated with an increased rate of distress. Patients use various strategies to cope with this distress during and after cancer treatments, and complementary and integrative medicine (CIM) has become a common coping strategy. This review covers major questions and challenges of incorporating CIM during and beyond treatment for lung cancer. The questions revolve around determining the value of nutrition and nutritional supplements, assessing the role of exercise, addressing the mind-body connection, enhancing the benefit of immunotherapy, and determining the benefit of incorporating complementary therapies such as acupuncture and homeopathy. This review may provide a basis for discussion that can enhance patient-doctor dialogue regarding the use of CIM during and after treatment for lung cancer.

[**Shenmai injection for the treatment of cancer-related fatigue in advanced non-small cell lung cancer patients undergoing chemotherapy: study protocol for a randomized controlled trial.**](#) Zhou Y1, Zhao B2, Wu W1, Yang X3, Long S1, Deng H1, He W1, Liao G1, Li Q1, Xie Z1. Trials. 2018 Sep 4;19(1):474. doi: 10.1186/s13063-018-2845-7.
BACKGROUND: Cancer-related fatigue (CRF) is the most common symptom in patients with advanced non-small cell lung cancer (NSCLC) undergoing treatment with chemotherapy. However, evidence upon which to base management strategies is scarce. Traditional Chinese Medicine (TCM) has been shown to be beneficial to patients with CRF. Chinese herbal injections should be administered under an evidence-based approach. This trial aims to assess the efficacy and safety of the addition of the Shenmai injection (SMI) to conventional therapy for CRF in NSCLC patients undergoing chemotherapy.
METHODS/DESIGN: The study is a two-group, prospective, randomized controlled trial (RCT) designed to evaluate the efficacy and safety of SMI for CRF NSCLC patients undergoing chemotherapy. Eligible participants will be randomized to either a treatment group receiving a 5-day Shenmai injection regimen plus conventional therapy or a control group receiving only conventional therapy. The primary outcome is fatigue, assessed using severity scores from the Functional Assessment for Chronic Illness Therapy-Fatigue (FACIT-F) measurement system. Secondary outcomes include symptom distress scores, depression, sleep disorders, quality of life, and levels of immunologic indicators. Assessments will be carried out at baseline and on day 5 (the end of the intervention). **DISCUSSION:** This study can provide

evidence to support clinical decision-making in the management of CRF in NSCLC patients undergoing chemotherapy in a way that can be scaled up and used throughout China.

MISCELLANEOUS WORKS

[Genome-wide association study of familial lung cancer.](#) Byun J1, Schwartz AG2, Lusk C2, et al. Carcinogenesis. 2018 Sep 21;39(9):1135-1140. doi: 10.1093/carcin/bgy080.
To identify genetic variation associated with lung cancer risk, we performed a genome-wide association analysis of 685 lung cancer cases that had a family history of two or more first or second degree relatives compared with 744 controls without lung cancer that were genotyped on an Illumina Human OmniExpressExome-8v1 array. To ensure robust results, we further evaluated these findings using data from six additional studies that were assembled through the Transdisciplinary Research on Cancer of the Lung Consortium comprising 1993 familial cases and 33 690 controls. We performed a meta-analysis after imputation of all variants using the 1000 Genomes Project Phase 1 (version 3 release date September 2013). Analyses were conducted for 9 327 222 SNPs integrating data from the two sources. A novel variant on chromosome 4p15.31 near the LCORL gene and an imputed rare variant intergenic between CDKN2A and IFNA8 on chromosome 9p21.3 were identified at a genome-wide level of significance for squamous cell carcinomas. Additionally, associations of CHRNA3 and CHRNA5 on chromosome 15q25.1 in sporadic lung cancer were confirmed at a genome-wide level of significance in familial lung cancer. Previously identified variants in or near CHRNA2, BRCA2, CYP2A6 for overall lung cancer, TERT, SECISPB2L and RTEL1 for adenocarcinoma and RAD52 and MHC for squamous carcinoma were significantly associated with lung cancer.

[Survival trends among non-small-cell lung cancer patients over a decade: impact of initial therapy at academic centers.](#) Lou Y1, Dholaria B1, Soyano A1, et al. Cancer Med. 2018 Sep 2. doi: 10.1002/cam4.1749. [Epub ahead of print]
BACKGROUND: Treatment of non-small-cell lung cancer (NSCLC) has been rapidly advancing over the last decade. Academic centers are considered equipped with better expertise. NSCLC outcome trends in novel therapeutic era and impact of initial treatment at academic centers have not been reported.
METHODS: The National Cancer Database (NCDB) was used to identify NSCLC incident cases from 2004 to 2013. Overall survival (OS) was plotted by year of diagnosis and type of initial treatment center, accounting for several factors available in NCDB. **RESULTS:** A total of 1 150 722 NSCLC patients were included and separated by initial treatment center type (academic: 31.5%; nonacademic: 68.5%). Median follow-up and OS for all patients were 11.8 months (range: 0-133.6 months) and 13.1 months (95% CI: 13.08-13.17), respectively. Median OS improved significantly for those diagnosed in 2010-2013 (14.8 months [95% CI: 14.7-14.9]) as compared to 2004-2009 (12.4 months [95% CI: 12.3-12.5]) (P < 0.001). Treatment at academic centers was associated with improved OS (multivariate HR for OS = 0.929 [95% CI: 0.92-0.94], P < 0.0010). Four-year OS for academic and nonacademic cohorts was 28.5%% and 22.1%, respectively (P < 0.001), and the difference was more pronounced in stage I to III NSCLC.
CONCLUSION: In this largest analysis, thus far, NSCLC survival has improved over time, and type of initial treatment center significantly influences survival. Identifying and removing barriers to obtaining initial treatment of NSCLC at academic medical centers could improve OS.