Caring Ambassadors Lung Cancer Program
Literature Review, June 2017

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Triplet therapy with afatinib, cetuximab, and bevacizumab induces deep remission in lung cancer cells harboring EGFR T790M in vivo. Kudo K1, Ohashi K2, Makimoto G1, et al. Mol Oncol. 2017 Jun;11(6):670-681. doi: 10.1002/1878-0261.12063. Epub 2017 May 2.

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have changed the treatment strategy for EGFR-mutant lung cancers; however, resistance usually occurs due to a secondary mutation, T790M, in EGFR. Combination therapy using afatinib and cetuximab has had good results in lung tumors harboring EGFRT790M mutations in clinical trials. The effect of bevacizumab, an antivascular endothelial growth factor (VEGF) antibody, combined with EGFR-TKIs has also been investigated. We hypothesized that the dose of afatinib and cetuximab could be reduced by combination with bevacizumab and that the triplet therapy may result in better tumor inhibition with tolerable toxicity. Using a xenograft mouse model with H1975-harboring EGFRL858R+T790M and RPC-9-harboring EGFR19DEL+T790M , we tested the efficacy of the triplet therapy with a modified dose of afatinib, cetuximab, and bevacizumab, and compared this therapy to single and double therapies. Triplet therapy with afatinib, cetuximab, and bevacizumab induced pathological complete remission in xenograft tumors with H1975 and RPC-9 cells versus tumors treated with single or double therapies. We saw no body weight loss in the mice. The triple therapy induced a significant reduction in CD31-positive vascular endothelial cells and increased cleaved caspase-3-positive cells in the tumors. This suggests that one mechanism underlying the deep remission could be suppression of neovascularization and induction of apoptosis by intensive inhibition of driver oncoproteins and VEGF. These results highlight the potential of afatinib, cetuximab, and bevacizumab to induce deep remission in tumors harboring EGFRT790M mutations. Therefore, clinical trials of this combination therapy are warranted.

Exosomes derived from mesenchymal non-small cell lung cancer cells promote chemoresistance. Lobb RJ1,2, van Amerongen R1, Wiegmans A1, Ham S1, Larsen JE2,3, Möller A1,2. Int J Cancer. 2017 Aug 1;141(3):614-620. doi: 10.1002/ijc.30752. Epub 2017 May 12.

Non-small cell lung cancer (NSCLC) is the most common lung cancer type and the most common cause of mortality in lung cancer patients. NSCLC is often associated with resistance to chemotherapeutics and together with rapid metastatic spread, results in limited treatment options and poor patient survival. NSCLCs are heterogeneous, and consist of epithelial and mesenchymal NSCLC cells. Mesenchymal NSCLC cells are thought to be responsible for the chemoresistance phenotype, but if and how this phenotype can be transferred to other NSCLC cells is currently not known. We hypothesised that small extracellular vesicles, exosomes, secreted by mesenchymal NSCLC cells could potentially transfer the chemoresistance phenotype to surrounding epithelial NSCLC cells. To explore this possibility, we used a unique human bronchial epithelial cell (HBEC) model in which the parental cells were transformed from an epithelial to mesenchymal phenotype by introducing oncogenic alterations common in NSCLC. We found that exosomes derived from the oncogenically transformed, mesenchymal HBECs could transfer chemoresistance to the parental, epithelial HBECs and increase ZEB1 mRNA, a master EMT transcription factor, in the recipient cells. Additionally, we demonstrate that exosomes from mesenchymal, but not epithelial HBECs contain the ZEB1 mRNA, thereby providing a potential mechanism for the induction of a mesenchymal phenotype in recipient cells. Together, this work demonstrates for the first time that exosomes derived from mesenchymal, oncogenically transformed lung cells can transfer chemoresistance and mesenchymal phenotypes to recipient cells, likely via the transfer of ZEB1 mRNA in exosomes.

[**Genome-wide copy number variation pattern analysis and a classification signature for non-small cell lung cancer.**](url) Qiu ZW1, Bi JH1, Gazdar AF2,3, Song K1,2. Genes Chromosomes Cancer. 2017 Jul;56(7):559-569. doi: 10.1002/gcc.22460. Epub 2017 May 4.

The accurate classification of non-small cell lung carcinoma (NSCLC) into lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) is essential for both clinical practice and lung cancer research. Although the standard WHO diagnosis of NSCLC on biopsy material is rapid and economic, more than 13% of NSCLC tumors in the USA are not further classified. The purpose of this study was to analyze the genome-wide pattern differences in copy number variations (CNVs) and to develop a CNV signature as an adjunct test for the routine histopathologic classification of NSCLCs. We investigated the genome-wide CNV differences between these two tumor types using three independent patient datasets. Approximately half of the genes examined exhibited significant differences between LUAD and LUSC tumors and the corresponding non-malignant tissues. A new classifier was developed to identify signature genes out of 20 000 genes. Thirty-three genes were identified as a CNV signature of NSCLC. Using only their CNV values, the classification model separated the LUADs from the LUSCs with an accuracy of 0.88 and 0.84, respectively, in the training and validation datasets. The same signature also classified NSCLC tumors from their corresponding non-malignant samples with an accuracy of 0.96 and 0.98, respectively. We also compared the CNV patterns of NSCLC tumors with those of histologically similar tumors arising at other sites, such as the breast, head, and neck, and four additional tumors. Of greater importance, the significant differences between these tumors may offer the possibility of identifying the origin of tumors whose origin is unknown.

[**Circulating Tumor Cells with Aberrant ALK Copy Number Predict Progression-Free Survival during Crizotinib Treatment in ALK-Rearranged Non-Small Cell Lung Cancer Patients.**](url) Pailler E1,2,3, Oulhen M1,2, Borget I4,5, et al. Cancer Res. 2017 May 1;77(9):2222-2230. doi: 10.1158/0008-5472.CAN-16-3072.

The duration and magnitude of clinical response are unpredictable in ALK-rearranged non-small cell lung cancer (NSCLC) patients treated with crizotinib, although all patients invariably develop resistance. Here, we evaluated whether circulating tumor cells (CTC) with aberrant ALK-FISH patterns [ALK-rearrangement, ALK-copy number gain (ALK-CNG)] monitored on crizotinib could predict progression-

free survival (PFS) in a cohort of ALK-rearranged patients. Thirty-nine ALK-rearranged NSCLC patients treated with crizotinib as first ALK inhibitor were recruited prospectively. Blood samples were collected at baseline and at an early time-point (2 months) on crizotinib. Aberrant ALK-FISH patterns were examined in CTCs using immunofluorescence staining combined with filter-adapted FISH after filtration enrichment. CTCs were classified into distinct subsets according to the presence of ALK-rearrangement and/or ALK-CNG signals. No significant association between baseline numbers of ALK-rearranged or ALK-CNG CTCs and PFS was observed. However, we observed a significant association between the decrease in CTC number with ALK-CNG on crizotinib and a longer PFS (likelihood ratio test, P = 0.025). In multivariate analysis, the dynamic change of CTC with ALK-CNG was the strongest factor associated with PFS (HR, 4.485; 95% confidence interval, 1.543-13.030, P = 0.006). Although not dominant, ALK-CNG has been reported to be one of the mechanisms of acquired resistance to crizotinib in tumor biopsies. Our results suggest that the dynamic change in the numbers of CTCs with ALK-CNG may be a predictive biomarker for crizotinib efficacy in ALK-rearranged NSCLC patients. Serial molecular analysis of CTC shows promise for real-time patient monitoring and clinical outcome prediction in this population. Cancer Res; 77(9); 2222-30. ©2017 AACR.

[Silencing long non-coding RNA ROR improves sensitivity of non-small-cell lung cancer to cisplatin resistance by inhibiting PI3K/Akt/mTOR signaling pathway.](#) Shi H1, Pu J2, Zhou XL3, Ning YY1, Bai C1. Tumour Biol. 2017 May;39(5):1010428317697568. doi: 10.1177/1010428317697568.
This study aimed to investigate the effects of long non-coding RNA ROR (regulator of reprogramming) on cisplatin (DDP) resistance in patients with non-small-cell lung cancer by regulating PI3K/Akt/mTOR signaling pathway. Human cisplatin-resistant A549/DDP cell lines were selected and divided into control group, negative control group, si-ROR group, ROR over-expression group, Wortmannin group, and ROR over-expression + Wortmannin group. MTT assay was used to determine the optimum inhibitory concentration of DDP. Quantitative real-time polymerase chain reaction and western blotting were applied to detect expressions of long non-coding RNA ROR, PI3K, Akt, and mTOR. Colony-forming assay, scratch test, Transwell assay, and flow cytometry were conducted to detect cell proliferation, migration, invasion, and apoptosis, respectively. Tumor-formation assay was performed to detect the growth of transplanted tumors. Long non-coding RNA ROR expression was high in human A549/DDP cell lines. Compared with the control and negative control groups, the mRNA and protein expressions of PI3K, Akt, mTOR, and bcl-2 decreased, whereas the mRNA and protein expression of bax and the sensitivity of cells to DDP significantly increased. Cell proliferation, migration, and invasion abilities decreased in the si-ROR and Wortmannin groups. In comparison with control and negative control groups, the mRNA and protein expressions of PI3K, Akt, mTOR, and bcl-2 increased, whereas the mRNA and protein expressions of bax decreased, the sensitivity of cells to DDP significantly increased, and cell proliferation, migration, and invasion abilities decreased in the ROR over-expression group. For nude mice in tumor-formation assay, compared with control and negative control groups, the tumor weight was found to be lighter (1.03 ± 0.15) g, the protein expressions of PI3K, Akt, mTOR, and bcl-2 decreased, and the protein expression of bax increased in the si-ROR group. Long non-coding RNA ROR may affect the sensitivity of lung adenocarcinoma cells to DDP by targeting PI3K/Akt/mTOR signaling pathway.

[Clinical Significance and Tumor-Suppressive Function of miR-516b in Nonsmall Cell Lung Cancer.](#) Zhu J1, Zhang Y1, Yang X1, Jin L2. Cancer Biother Radiopharm. 2017 May;32(4):115-123. doi: 10.1089/cbr.2016.2163.
BACKGROUND: MicroRNA-516b (miR-516b) has been recently reported to be downregulated in nonsmall cell lung cancer (NSCLC). However, its clinical significance and biological function in NSCLC remain to be clarified. **MATERIALS AND METHODS:** Quantitative real-time polymerase chain

reaction (qRT-PCR) was used to detect the expression of miR-516b in 82 paired fresh primary tumor tissues and NSCLC cell lines. The association of miR-516b expression with clinicopathological factors and prognosis was statistically analyzed by SPSS 21.0 software, Kaplan-Meier method, and Cox regression analyses. Cell Counting Kit-8, colony formation, flow cytometric, Transwell migration, and invasion assays were used to evaluate the proliferation, cell cycle, apoptosis, migration, and invasion of NSCLC cells after miR-516b mimics or negative control of mimics transfection. **RESULTS:** The expression level of miR-516b was found to be significantly lower in NSCLC tissues and cell lines than in corresponding normal tissues and cells. Decreased miR-516b expression was significantly associated with tumor size (p = 0.004), Tumor Node Metastasis (TNM) stage (p = 0.016), and shorter overall survival (p = 0.0039). Multivariate analysis suggested that miR-516b was an independent risk factor for NSCLC (hazard ratio = 2.435, 95% confidence interval: 1.423-2.457; p = 0.003). Furthermore, overexpression of miR-516b could inhibit NSCLC cell proliferation, cell cycle progression, migration and invasion, and promoted cell apoptosis. The qRT-PCR results indicated that overexpressing miR-516b reduced the mRNA expression of CDK2, MMP-2, and MMP-9, whereas increased BAX mRNA expression in NSCLC cells. Their protein expression levels presented similar trends, as confirmed by Western blotting. **CONCLUSIONS:** Findings in this study demonstrated for the first time that miR-516b expression might be a novel diagnostic and prognostic factor, as well as a promising target for NSCLC.

SCREENING, DIAGNOSIS AND STAGING

[Computed Tomography Screening for Lung Cancer: Mediastinal Lymph Node Resection in Stage IA Nonsmall Cell Lung Cancer Manifesting as Subsolid and Solid Nodules.](#)
Flores RM1, Nicastri D, Bauer T, et al. Ann Surg. 2017 May;265(5):1025-1033. doi: 10.1097/SLA.0000000000001802.
OBJECTIVE: To compare long-term survival rates of patients with first, primary, clinical stage IA nonsmall cell lung cancer from a large cohort undergoing computed tomography screening with and without mediastinal lymph node resection (MLNR) under an Institutional Review Board-approved common protocol from 1992 to 2014. **BACKGROUND:** Assessing survival differences of patients with and without MLNR manifesting as solid and subsolid nodules. **METHODS:** Long-term Kaplan-Meier (K-M) survival rates for those with and without MLNR were compared and Cox regression analyses were used to adjust for demographic, computed tomography, and surgical covariates. **RESULTS:** The long-term K-M rates for 462 with and 145 without MLNR was 92% versus 96% (P = 0.19), respectively. For 203 patients with a subsolid nodule, 151 with and 52 without MLNR, the rate was 100%. For the 404 patients with a solid nodule, 311 with and 93 without MLNR, the rate was 87% versus 94% (P = 0.24) and Cox regression showed no statistically significant difference (P = 0.28) when adjusted for all covariates. Risk of dying increased significantly with increasing decades of age (hazard ratio [HR] 2.3, 95% confidence interval [CI] 1.4-3.8), centrally located tumor (HR 2.5, 95% CI 1.2-5.2), tumor size 21 to 30mm (HR 2.7, 95% CI 1.2-6.0), and invasion beyond the lung stroma (HR 3.0, 95% CI 1.4-6.1). For the 346 patients with MLNR, tumor size was 20mm or less; K-M rates for the 269 patients with and 169 patients without MLNR were also not significantly different (HR 2.1, P = 0.24). **CONCLUSIONS:** It is not mandatory to perform MLNR when screen-diagnosed nonsmall cell lung cancer manifests as a subsolid nodule.

[External Validation of the New International Association for the Study of Lung Cancer Tumor, Node, and Metastasis 8th Edition Staging System and Updated T Descriptors in Determining Prognosis for Patients With Non-Small Cell Lung Cancer Patients With N3 Disease.](#) Shin JY1, Yoon JK2, Marwaha G2. Clin Lung Cancer. 2017 May 10. pii: S1525-7304(17)30144-4. doi: 10.1016/j.cllc.2017.05.009. [Epub ahead of print]

OBJECTIVE: The objective of this study is to externally validate the 8th Edition of the Tumor, Node, and Metastasis staging system and its updated T descriptors in patients with non-small cell lung cancer with N3 disease. **METHODS:** Data were extracted from the Surveillance, Epidemiology, and End Results database. Chi-square test, Kaplan-Meier method, and Cox regression models were used in SPSS 23.0 (IBM Corp, Armonk, NY). **RESULTS:** A total of 7732 patients with non-small cell lung cancer with T1-4N3M0 disease from 1988 to 2013 were identified. A total of 1410 patients (18.2%) had T1N3 disease, 2491 patients (32.2%) had T2N3 disease, 1563 patients (20.2%) had T3N3 disease, and 2268 patients (29.3%) had T4N3 disease. The 5-year overall survival (OS) for the entire cohort was 8.4%. There was a significant difference in OS concerning T stage (T1N3: 10.8% vs. T2N3: 8.3% vs. T3N3: 8.1% vs. T4N3: 7.3%; $P < .001$). When stratified by the median age of patients (66 years), a significant difference in OS by stage of disease (IIIB vs. IIIC) was still observed in both the younger ($P < .001$) and older ($P < .001$) patient populations. A significant difference in disease-specific survival (DSS) was observed by T stage (T1N3: 14.7% vs. T2N3: 11.6% vs. T3N3: 11.3% vs. T4N3: 9.7%; $P < .001$). On multivariate analysis, T stage, year of diagnosis, age, gender, histology, and receipt of radiotherapy remained independent prognostic factors for both OS and DSS. **CONCLUSIONS:** The 8th Edition of the Tumor, Node, and Metastasis staging system significantly stratifies both overall and DSS between stages IIIB and IIIC among those with N3 disease. However, small absolute differences in 5-year outcomes between T stage may suggest limited clinical relevance.

Gene methylation as a powerful biomarker for detection and screening of non-small cell lung cancer in blood.
Wang BH1, Li YY2, Han JZ3, Zhou LY1, Lv YQ3, Zhang HL1, Zhao L3. Oncotarget. 2017 May 9;8(19):31692-31704. doi: 10.18632/oncotarget.15919.

DNA methylation has been reported to become a potential powerful tool for cancer detection and diagnosis. However, the possibilities for the application of blood-based gene methylation as a biomarker for non-small cell lung cancer (NSCLC) detection and screening remain unclear. Hence, we performed this meta-analysis to evaluate the value of gene methylation detected in blood samples as a noninvasive biomarker in NSCLC. A total of 28 genes were analyzed from 37 case-control studies. In the genes with more than three studies, we found that the methylation of P16, RASSF1A, APC, RARβ, DAPK, CDH13, and MGMT was significantly associated with risks of NSCLC. The methylation statuses of P16, RASSF1A, APC, RARβ, DAPK, CDH13, and MGMT were not linked to age, gender, smoking behavior, and tumor stage and histology in NSCLC. Therefore, the use of the methylation status of P16, RASSF1A, APC, RARβ, DAPK, CDH13, and MGMT could become a promising and powerful biomarker for the detection and screening of NSCLC in blood in clinical settings. Further large-scale studies with large sample sizes are necessary to confirm our findings in the future.

Development and Clinical Utility of a Blood-Based Test Service for the Rapid Identification of Actionable Mutations in Non-Small Cell Lung Carcinoma.
Mellert H1, Foreman T1, Jackson L1, et al. J Mol Diagn. 2017 May;19(3):404-416. doi: 10.1016/j.jmoldx.2016.11.004.

Nearly 80% of cancer patients do not have genetic mutation results available at initial oncology consultation; up to 25% of patients begin treatment before receiving their results. These factors hinder the ability to pursue optimal treatment strategies. This study validates a blood-based genome-testing service that provides accurate results within 72 hours. We focused on targetable variants in advanced non-small cell lung carcinoma-epidermal growth factor receptor gene (EGFR) variant L858R, exon 19 deletion (ΔE746-A750), and T790M; GTPase Kirsten ras gene (KRAS) variants G12C/D/V; and echinoderm microtubule associated protein like and 4 anaplastic lymphoma receptor tyrosine kinase fusion (EML4-ALK) transcripts 1/2/3. Test development included method and clinical validation using samples from donors with (n = 219) or without (n = 30) cancer. Clinical sensitivity and specificity for each variant ranged from 78.6% to 100% and 94.2% to 100%, respectively. We also report on 1643 non-small cell

lung carcinoma samples processed in our CLIA-certified laboratory. Mutation results were available within 72 hours for 94% of the tests evaluated. We detected 10.5% mutations for EGFR sensitizing (n = 2801 samples tested), 13.8% mutations for EGFR resistance (n = 1055), 13.2% mutations in KRAS (n = 3477), and 2% mutations for EML4-ALK fusion (n = 304). This rapid, highly sensitive, and actionable blood-based assay service expands testing options and supports faster treatment decisions.

[Clinical framework for next generation sequencing based analysis of treatment predictive mutations and multiplexed gene fusion detection in non-small cell lung cancer.](#) Lindquist KE1, Karlsson A2, Levéen P1, et al. Oncotarget. 2017 May 23;8(21):34796-34810. doi: 10.18632/oncotarget.16276.

Precision medicine requires accurate multi-gene clinical diagnostics. We describe the implementation of an Illumina TruSight Tumor (TST) clinical NGS diagnostic framework and parallel validation of a NanoString RNA-based ALK, RET, and ROS1 gene fusion assay for combined analysis of treatment predictive alterations in non-small cell lung cancer (NSCLC) in a regional healthcare region of Sweden (Scandinavia). The TST panel was clinically validated in 81 tumors (99% hotspot mutation concordance), after which 533 consecutive NSCLCs were collected during one-year of routine clinical analysis in the healthcare region (~90% advanced stage patients). The NanoString assay was evaluated in 169 of 533 cases. In the 533-sample cohort 79% had 1-2 variants, 12% >2 variants and 9% no detected variants. Ten gene fusions (five ALK, three RET, two ROS1) were detected in 135 successfully analyzed cases (80% analysis success rate). No ALK or ROS1 FISH fusion positive case was missed by the NanoString assay. Stratification of the 533-sample cohort based on actionable alterations in 11 oncogenes revealed that 66% of adenocarcinomas, 13% of squamous carcinoma (SqCC) and 56% of NSCLC not otherwise specified harbored ≥1 alteration. In adenocarcinoma, 10.6% of patients (50.3% if including KRAS) could potentially be eligible for emerging therapeutics, in addition to the 15.3% of patients eligible for standard EGFR or ALK inhibitors. For squamous carcinoma corresponding proportions were 4.4% (11.1% with KRAS) vs 2.2%. In conclusion, multiplexed NGS and gene fusion analyses are feasible in NSCLC for clinical diagnostics, identifying notable proportions of patients potentially eligible for emerging molecular therapeutics.

[What, When, and How of Biomarker Testing in Non-Small Cell Lung Cancer.](#) Riely GL1. J Natl Compr Canc Netw. 2017 May;15(5S):686-688.

Biomarker testing is recommended for all patients diagnosed with non-small cell lung cancer. At a minimum, testing should include the mutations/fusions EGFR, ALK, ROS1, and the protein programmed death ligand-1 (PD-L1), because FDA-approved therapies are available for these alterations. Other actionable molecular findings include RET rearrangements, BRAFV600E mutations, and MET exon 14 alterations. If adequate testing was not performed at treatment initiation, molecular testing should be performed before administration of subsequent lines of therapy. In patients with EGFR-mutant lung cancer, when resistance develops, physicians should seek to identify the T790M mutation using plasma and tissue assays, because osimertinib therapy is available for this mutation.

[Time and Effort Required for Tissue Acquisition and Submission in Lung Cancer Clinical Trials.](#) Garcia S1, Saltarski JM2, Yan J3, Xie XJ4, Gerber DE5. Clin Lung Cancer. 2017 May 8. pii: S1525-7304(17)30132-8. doi: 10.1016/j.cllc.2017.04.012. [Epub ahead of print]

BACKGROUND: Increasingly, analysis of tumor tissue samples for predictive and pharmacodynamic biomarkers is incorporated into lung cancer clinical trials. We determined the time and effort required for tissue acquisition and submission. **PATIENTS AND METHODS:** We analyzed data from patients enrolled from 2009 to 2016 at UT Southwestern onto lung cancer trials with mandatory or optional submission of tumor tissue. We collected dates of treatment-related events and staff communications;

nature of tissue requirement and biomarker analysis; and location of archival tissue. Associations between case characteristics, clinical intervals, and number of staff communications were analyzed by Fisher's exact test, Wilcoxon 2-sample test, and Kruskal-Wallis test. **RESULTS:** We identified 129 patients enrolled onto 19 clinical trials, of whom 108 (84%) ultimately received study therapy. For cases in which tissue submission was required if available or optional, 16% and 0%, respectively, had tissue sent. The median interval between consent and treatment was 28 (interquartile range, 11-43) days if tissue was requested and 7 (interquartile range, 6-13) days if tissue was not requested (P < .001). Among cases with requested tissue, the median number of related research staff communications was 3 (range, 0-10). Over time, the number of staff communications increased (P < .001). Location of archival tissue was not associated with number of staff communications or treatment intervals. **CONCLUSION:** Lung cancer clinical trial requirements for tissue acquisition and submission affect the time to treatment initiation and require increasing staff effort. Improved systems to expedite these processes, as well as use of blood- or imaging-based biomarkers, may help address these issues.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

Preoperative platelet to lymphocyte and neutrophil to lymphocyte ratios are independent prognostic factors for patients undergoing lung cancer radical surgery: A single institutional cohort study. Lan H1, Zhou L1, Chi D1, Zhou Q2, Tang X2, Zhu D2, Yue J1, Liu B1. Oncotarget. 2017 May 23;8(21):35301-35310. doi: 10.18632/oncotarget.13312.
BACKGROUND: The aim of this study was to assess the prognostic value for NSCLC patients who were scheduled to receive lung cancer radical resection. **METHODS:** In this cohort study (Dec.2014-Feb.2016), patients with non-small cell lung cancer (NSCLC) who underwent radical lung cancer thoracotomy were enrolled and accessed at postoperative complications, one-year overall survival (OS) and relapse-free survival (RFS). The preoperative PLR and NLR of all patients were calculated based on preoperative complete blood counts. Univariate and multivariate Cox regression analyses were performed to determine the associations of PLR and NLR with OS and RFS. **RESULTS:** A total of 174 NSCLC patients were studied. The results indicated that both high PLR (>148.6) and NLR (>2.9) were related to a high rate of postoperative pulmonary complications significantly (49.3%vs.29.1%, P = 0.007; 50.7% vs. 28.6%, P = 0.003). Moreover, NSCLC patients with a high PLR level (> 148.6) was significantly associated with a lower one-year OS (90.3% vs. 77.5%, P = 0.034). **CONCLUSIONS:** Preoperative PLR and NLR were good prognostic factors for postoperative pulmonary complications and OS in NSCLC patients undergoing radical lung cancer surgery. Thus, blood PLR and NLR would be helpful as a prognostic tool before radical lung cancer surgery.

Long-term pulmonary function after surgery for lung cancer. Kobayashi N1, Kobayashi K2, Kikuchi S1, Goto Y1, Ichimura H2, Endo K2, Sato Y1. Interact Cardiovasc Thorac Surg. 2017 May 1;24(5):727-732. doi: 10.1093/icvts/ivw414.
OBJECTIVES: Many patients with lung cancer have been cured by surgical intervention. However, the long-term effects of lung resection on pulmonary function are unclear. Therefore, we investigated long-term pulmonary function after surgery. **METHODS:** We retrospectively reviewed the medical records of patients who underwent surgery for lung cancer between 2001 and 2009. A total of 445 patients who had survived more than 5 years since the surgery were included. The patients were divided into lobectomy, segmentectomy and partial resection groups. The time-dependent changes in pulmonary function were investigated. **RESULTS:** The percentages of the vital capacity and forced expiratory volume in 1 second (FEV 1) at postoperative year (POY) 1 vs preoperative values were $92.9 \pm 11.1\%$ and $91.3 \pm 13.0\%$ in the

lobectomy group, $95.9 \pm 9.0\%$ and $93.8 \pm 10.5\%$ in the segmentectomy group and $97.8 \pm 7.3\%$ and $98.1 \pm 8.3\%$ in the partial resection group, respectively. The values in the lobectomy group were significantly lower than those in the segmentectomy and partial resection groups. The percentages of vital capacity and FEV 1 at POY 5 vs preoperative values were $90.0 \pm 11.5\%$ and $86.2 \pm 11.9\%$ in the lobectomy group, $93.4 \pm 9.8\%$ and $91.1 \pm 9.8\%$ in the segmentectomy group and $94.3 \pm 8.8\%$ and $94.0 \pm 8.0\%$ in the partial resection group, respectively. The decrease in the rates from POY 1 to POY 5 were not significantly different among the procedures. **CONCLUSIONS:** Pulmonary function declined with pulmonary resection. After the patient recovered from the operation, pulmonary function decreased with time regardless of the surgical procedure.

Prospective study of quality of life after lung cancer resection. Hopkins KG1, Ferson PF2, Shende MR3, Christie NA2, Schuchert MJ2, Pennathur A2,4. Ann Transl Med. 2017 May;5(10):204. doi: 10.21037/atm.2017.04.34.
BACKGROUND: Surgical resection with curative-intent remains the gold standard for clinically operable early-stage non-small cell lung cancer (NSCLC). This goal can be accomplished using a minimally invasive option, e.g., video assisted thoracic surgery (VATS) or standard thoracotomy. Surgical techniques continue to evolve and few studies have compared the QOL of patients managed with these procedures using current approaches. The primary goal of this study was to investigate differences between patients managed surgically via VATS compared to thoracotomy with respect to ratings of chronic pain, anxiety/depression and quality of life (QOL). The secondary goal was to investigate differences between patients converted from VATS to thoracotomy versus those managed with the originally with thoracotomy. **METHODS:** We conducted a prospective cross sectional design study comparing the QOL after surgical resection of NSCLC. Data were obtained between 3-12 months postoperatively, from patients with potentially resectable stage I-IIIa NSCLC, who underwent a thoracotomy or VATS resection. All patients were consented. Pain was evaluated with a 0 to 10 numeric pain assessment scale (NAS), mood with the Hospital Anxiety and Depression Scale (HADS) (mood disorders) and QOL with FACT-L (Functional Assessment of Cancer Therapy-Lung). **RESULTS:** A total of 97 patients with stage I-IIIa lung cancer were enrolled; of these 66 (68%) underwent a standard thoracotomy and 31 (32%) underwent VATS resection. The preferred surgical approach was a thoracotomy for patients with stage IIIa lung cancer, or patients requiring a pneumonectomy or a bi-lobectomy. There were no significant differences between VATS and thoracotomy patients in ratings of chronic pain, mood disorders, or QOL. Conversion from VATS to thoracotomy occurred in 22 (23%) of patients. There were no significant differences between VATS conversion to thoracotomy and those with initial thoracotomy procedures in ratings of chronic pain, mood disorders, or QOL. Conversion from VATS to standard thoracotomy occurred more commonly early in the series. **CONCLUSIONS:** While previous studies have shown that VATS offers an early advantage with regards to perioperative outcomes, our study demonstrated that VATS and thoracotomy patients had similar late QOL outcomes.

The Influence of Body Mass Index on Overall Survival Following Surgical Resection of Non-Small Cell Lung Cancer. Sepesi B1, Gold KA2, Correa AM1, Heymach JV3, Vaporciyan AA1, Roszik J4, Dmitrovsky E5, Liu X6.
J Thorac Oncol. 2017 May 25. pii: S1556-0864(17)30390-8. doi: 10.1016/j.jtho.2017.05.010. [Epub ahead of print]
BACKGROUND: Population studies suggest that high body mass index (BMI) correlates with a reduced risk of death from lung cancer. The aim of our study was to evaluate definitively the influence of BMI on long term overall survival (OS) in surgical patients with non-small cell lung cancer (NSCLC).
METHODS: Study population consisted of 1935 patients who underwent surgical resection for lung cancer at MD Anderson Cancer Center (2000-2014). Study variables included both patient and treatment

related characteristics. Univariate and multivariate Cox regression analyses were performed to identify variables associated with overall survival. **RESULTS:** On univariate analysis, significant predictors of improved survival were higher BMI, pathologic tumor stage (stage I vs II, III, or IV), type of surgery (lobectomy/pneumonectomy versus wedge resection/segmentectomy), younger age, female gender, and adenocarcinoma histology (versus squamous) (all $p<0.05$, Table 2 and 3). Morbidly obese patients (BMI$\geq$35) had a trend towards better outcomes than those classified as obese (BMI $\geq$30 and <35) ($p=0.05$), overweight (BMI $\geq$25 and <30) ($p=0.13$), or healthy weight (BMI <25) ($p=0.37$) (HR 0.727, 0.848, 0.926, and 1, respectively). On multivariate analysis, BMI remained an independent predictor of survival ($p=0.02$). Propensity matching analysis demonstrated significantly better OS ($p=0.003$) in patients with BMI$\geq$30 as compared to BMI 25. **CONCLUSIONS:** In this large, retrospective, single center series, after controlling for disease stage and other variables, higher BMI was associated with improved OS following surgical resection of NSCLC. Further studies are necessary to elucidate the precise relationship between BMI and treatment outcomes.

[Functional evaluation before lung resection: searching for a low technology test in a safer environment for the patient: a pilot study.](#) Novoa NM, Esteban P, Rodriguez M, Gomez MT, Varela G. Eur J Cardiothorac Surg. 2017 May 1;51(5):856-860. doi: 10.1093/ejcts/ezw403.

OBJECTIVES: Stair climbing is considered the first step for functional evaluation of patients requiring anatomical lung resection who have low-predicted postoperative forced expiratory volume in the first second of expiration (FEV1) or diffusing capacity of the lungs for carbon monoxide (DLCO) values. Nevertheless, stair climbing is not performed in many centres because of structural issues or patient safety concerns. We hypothesized that comparable exercise can be obtained on an ergometric bicycle in a safer environment where any adverse event can be treated. We tried to correlate the amount of exercise performed by stair climbing and by using an ergometric bicycle in a series of patients with non-small-cell lung cancer (NSCLC) evaluated prospectively. **METHODS:** Thirty-four consecutive patients with NSCLC who were scheduled for lung resection were prospectively enrolled to complete two low-technology exercise tests: The first one was stair climbing, and the second was a ramp test on an ergometric bicycle. For most patients (85%), both tests were performed on the same day, separated with at least 2 h of rest. The amount of exercise on the stair-climbing test (in watts: Watt 1) was calculated per patient weight, height reached on stairs and time spent. The bicycle test was performed on a Lode Corival ergometer with automatic calculation of the total work load (Watt 2). No estimation of VO 2 max was attempted. The bicycle test was conducted in an ad-hoc room fully equipped with oxygen, cardiac and blood pressure and PO 2 monitoring and resuscitation equipment. The Bland-Altman plot was used to evaluate the agreement between both tests. A linear regression model was constructed in which the power developed on the stairs was the dependent variable and the watts generated on the bicycle and patient age were the covariates. **RESULTS:** All patients (median age: 65.5 years; range: 41-84), completed both tests without any adverse events. The number of watts was greater on the stairs tests (mean 227 vs 64 on the ergometric bicycle). The Bland-Altman plot showed agreement between tests in most cases (Pitman-Morgan test: 0.96). Work load was more dependent on age in the stairs tests (Pearson coefficient -0.72 on stairs; -0.52 on ergometric bicycle). The logistic model was highly predictive when the workload on the bicycle was corrected by the patient's age ($R 2 = 0.80$; Wald test <0.001). **CONCLUSIONS:** This simple test on an ergometric bicycle shows a high correlation with the widely accepted stair-climbing test when workload results are corrected using the patient's age. It could replace the stair-climbing test and has the advantage of being conducted in an environment that is safer for the patient. Nevertheless, its reliability for risk prediction needs to be adequately evaluated.

Pazopanib or placebo in completely resected stage I NSCLC patients: results of the phase II IFCT-0703 trial. Besse B1, Mazières J2, Ribassin-Majed L3,4, et al. Ann Oncol. 2017 May 1;28(5):1078-1083. doi: 10.1093/annonc/mdx070.
BACKGROUND: Adjuvant treatment in resected stage I non-small-cell lung cancer (NSCLC) is generally not recommended. Pazopanib is an oral tyrosine kinase inhibitor of VEGFR-1/2/3 and PDGFR-α/β. We explored the feasibility and efficacy of adjuvant pazopanib in this population. **PATIENTS AND METHODS:** In this double-blind phase II/III trial, patients with resected stage I NSCLC were randomized to placebo or pazopanib 800 mg/day (P800) for 6 months with a two-step Fleming design. The primary endpoint was compliance (percentage of patients receiving ≥3 months pazopanib). From the interim analysis after 64 patients were included, the IDMC recommended reducing to pazopanib 400 mg/day (P400) due to insufficient compliance, with a one-step Fleming. Although unplanned, survival data were analyzed. **RESULTS:** A total of 71 patients were enrolled in each arm; 61% were male, 91% were smokers, median age was 60 years, 80% had pathological stage IA, and 16% had squamous cell carcinoma. Pazopanib compliance was 38% [95% confidence interval (CI) 23-55] with P800, increasing to 69% (95% CI 50-84; P = 0.027) with P400. Two patients had grade 4 toxicities with P800. The most common grade 3 toxicities were increased transaminases (16%), hypertension (13%), and diarrhea (9%) with P800, and gastrointestinal disorders (16%; 6% diarrhea) and hypertension (6%) with P400. Median follow-up was 47 months. Three-year recurrence-free survival was 76% (95% CI 65%-86%) with pazopanib and 83% (95% CI 74%-92%) with placebo [hazard ratio = 1.3 (95% CI 0.6-2.7), P = 0.53]. Five-year overall survival was 83% (95% CI 72-94) with pazopanib and 94% [95% CI 88-100] with placebo [hazard ratio = 1.8 (95% CI 0.6-5.5), P = 0.26]. **CONCLUSIONS:** In resected stage I NSCLC patients adjuvant 400 mg/day pazopanib but not 800 mg/day was feasible, although possibly infra-therapeutic and failed to improve relapse-free survival.

A diagnostic microdosing approach to investigate platinum sensitivity in non-small cell lung cancer. Wang SS1, Zimmermann M1,2, Zhang H1, et al. Int J Cancer. 2017 Aug 1;141(3):604-613. doi: 10.1002/ijc.30747. Epub 2017 May 15.
The platinum-based drugs cisplatin, carboplatin and oxaliplatin are often used for chemotherapy, but drug resistance is common. The prediction of resistance to these drugs via genomics is a challenging problem since hundreds of genes are involved. A possible alternative is to use mass spectrometry to determine the propensity for cells to form drug-DNA adducts-the pharmacodynamic drug-target complex for this class of drugs. The feasibility of predictive diagnostic microdosing was assessed in non-small cell lung cancer (NSCLC) cell culture and a pilot clinical trial. Accelerator mass spectrometry (AMS) was used to quantify [14 C]carboplatin-DNA monoadduct levels in the cell lines induced by microdoses and therapeutic doses of carboplatin, followed by correlation with carboplatin IC50 values for each cell line. The adduct levels in cell culture experiments were linearly proportional to dose (R2 = 0.95, p < 0.0001) and correlated with IC50 across all cell lines for microdose and therapeutically relevant carboplatin concentrations (p = 0.02 and p = 0.01, respectively). A pilot microdosing clinical trial was conducted to define protocols and gather preliminary data. Plasma pharmacokinetics (PK) and [14 C]carboplatin-DNA adducts in white blood cells and tumor tissues from six NSCLC patients were quantified via AMS. The blood plasma half-life of [14 C]carboplatin administered as a microdose was consistent with the known PK of therapeutic dosing. The optimal [14 C]carboplatin formulation for the microdose was 107 dpm/kg of body weight and 1% of the therapeutic dose for the total mass of carboplatin. No microdose-associated toxicity was observed in the patients. Additional accruals are required to significantly correlate adduct levels with response.

Evaluation of dosing strategy for pembrolizumab for oncology indications. Freshwater T1, Kondic A1, Ahamadi M1, Li CH1, de Greef R2, de Alwis D1, Stone JA1. J Immunother Cancer. 2017 May 16;5:43. doi: 10.1186/s40425-017-0242-5. eCollection 2017.

BACKGROUND: Traditionally, most monoclonal antibodies (mAbs) have been dosed based on body weight because of perceived contribution of body size in pharmacokinetic variability. The same approach was used in the initial pembrolizumab studies; however, following availability of PK data, the need for weight-based dosing for pembrolizumab was reassessed. **METHODS:** A previously established population PK (popPK) model as well as exposure-response results from patients with advanced melanoma or non-small cell lung cancer (NSCLC) were used to evaluate the potential application of a fixed dosing regimen with the aim of maintaining pembrolizumab exposures within the range demonstrated to provide near maximal efficacy and acceptable safety. Individual PK exposures for the selected fixed dosing regimen from recently completed trials with head and neck cancer, NSCLC, microsatellite instability high (MSI-H) in colorectal cancer (CRC) and urothelial cancer were used to confirm acceptability. To determine whether fixed dosing would maintain exposures within the range of clinical experience, the individual AUC distributions with fixed dosing were compared with the range of exposures from the pembrolizumab doses that were evaluated in early studies (2 mg/kg Q3W, 10 mg/kg Q3W/Q2W). **RESULTS:** Body-weight dependence of clearance was characterized by a power relationship with an exponent of 0.578, a value consistent with fixed- and weight-based dosing providing similar control of PK variability. A fixed dose of 200 mg Q3W was investigated in trials based on predicted exposures maintained within the established exposure range in all patients. Mean (% CV, n) AUCss, 6-weeks was 1.87 (37%, 830), 1.38 (38%, 760) and 7.63 (35%, 1405) mg*day/mL in patients receiving 200 mg, 2 mg/kg and 10 mg/kg Q3W pembrolizumab. High-weight patients had the lowest exposures with 200 mg Q3W; however, exposures in this group (>90 kg) were within the range of prior clinical experience at 2 mg/kg Q3W associated with near maximal efficacy. **CONCLUSIONS:** Doses of 200 mg and 2 mg/kg provide similar exposure distributions with no advantage to either dosing approach with respect to controlling PK variability. These findings suggest that weight-based and fixed-dose regimens are appropriate for pembrolizumab.

Immunotherapies for Lung Cancer. Gubens MA1. J Natl Compr Canc Netw. 2017 May;15(5S):692-695.

In 2017, immunotherapy is the standard of care for patients with non-small cell lung cancer (NSCLC) either in the first or second line depending on programmed death ligand-1 (PD-L1) and mutation status. For first-line therapy, pembrolizumab is currently the standard of care for patients whose tumors express PD-L1 >50%. All patients with NSCLC should undergo PD-L1 testing before initiating treatment on pembrolizumab. For patients not eligible in the first line, immunotherapy is the standard of care for most in the second line. Nivolumab and atezolizumab are approved in all patients as second-line therapies after platinum-based doublet failure regardless PD-L1 expression level, although pembrolizumab is approved as second-line therapy for those whose tumors express PD-L1 >1%.

Clinical efficacy of icotinib in lung cancer patients with different EGFR mutation status: a meta-analysis. Qu J1, Wang YN2, Xu P1, Xiang DX1, Yang R3, Wei W4, Qu Q3. Oncotarget. 2017 May 16;8(20):33961-33971. doi: 10.18632/oncotarget.15475.

Icotinib is a novel and the third listed epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), which exerts a good anti-tumor efficacy on non-small cell lung cancer (NSCLC). The efficacy of EGFR-TKIs has been shown to be associated with the EGFR mutation status, especially exon 19 deletion (19Del) and exon 21 L858R mutation. Therefore, a meta-analysis was performed to assess the efficacy of icotinib in NSCLC patients harboring EGFR mutations (19Del or L858R) and wild type (19Del and L858R loci wild type). A total of 24 studies were included for comparing the objective response rate

(ORR) in the EGFR wild type and mutant patients treated with icotinib. The ORRs of EGFR mutant patients (19Del or L858R) are better than those of EGFR wild type patients (OR = 7.03(5.09-9.71), P < 0.00001). The pooling ORs from 21 studies on the disease control rate (DCR) in EGFR mutant patients are better than those of EGFR wild type patients (OR = 10.54(5.72-19.43), P < 0.00001). Moreover, the ORRs of EGFR 19Del patients are better than those of EGFR L858R patients after pooling ORs of 12 studies (OR = 2.04(1.12-3.73), P = 0.019). However, there was no significant difference on DCRs of EGFR 19Del patients and those of EGFR L858R patients (OR = 2.01(0.94-4.32), P = 0.072). Our findings indicated that compared with EGFR wild type patients, EGFR mutant patients have better ORRs and DCRs after icotinib treatment; EGFR 19Del patients treated with icotinib have better ORRs than EGFR L858R patients. EGFR mutation status is a useful biomarker for the evaluation of icotinib efficacy in NSCLC patients.

Clinical features and treatment outcome of non-small cell lung cancer (NSCLC) patients with uncommon or complex epidermal growth factor receptor (EGFR) mutations. Frega S1,2, Lorenzi M1, Fassan M3, et al. Oncotarget. 2017 May 16;8(20):32626-32638. doi: 10.18632/oncotarget.15945.
INTRODUCTION: Tyrosine-kinase inhibitors (TKIs) represent the best treatment for advanced non-small cell lung cancer (NSCLC) with common exon 19 deletion or exon 21 epidermal growth factor receptor mutation (EGFRm). This is an observational study investigating epidemiology, clinical features and treatment outcome of NSCLC cases harbouring rare/complex EGFRm. **RESULTS:** Among 764 non-squamous NSCLC cases with known EGFRm status, 26(3.4%) harboured rare/complex EGFRm. Patients receiving first-line TKIs (N = 17) achieved median Progression Free Survival (PFS) and Overall Survival (OS) of 53 (IC 95%, 2-105) and 84 (CI 95%, 27-141) weeks respectively, without significant covariate impact. Response Rate and Disease Control Rate (DCR) were 47% and 65%, respectively. Uncommon exon 19 mutations achieved longer OS and PFS and higher DCR compared with exon 18 and 20 mutations. No additional gene mutation was discovered by MassARRAY analysis. TKIs were globally well tolerated. **MATERIALS AND METHODS:** A retrospective review of advanced non-squamous NSCLC harbouring rare/complex EGFRm referred to our Center between 2010 and 2015 was performed. Additional molecular pathways disregulation was explored in selected cases, through MassARRAY analysis. **CONCLUSIONS:** Peculiar clinical features and lower TKIs sensitivity of uncommon/complex compared with common EGFRm were shown. Exon 19 EGFRm achieved the best TKIs treatment outcome, while the optimal treatment of exon 18 and 20 mutations should be further clarified.

Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. Hida T1, Nokihara H2, Kondo M3, et al. Lancet. 2017 May 10. pii: S0140-6736(17)30565-2. doi: 10.1016/S0140-6736(17)30565-2. [Epub ahead of print]
BACKGROUND: Alectinib, a potent, highly selective, CNS-active inhibitor of anaplastic lymphoma kinase (ALK), showed promising efficacy and tolerability in the single-arm phase 1/2 AF-001JP trial in Japanese patients with ALK-positive non-small-cell lung cancer. Given those promising results, we did a phase 3 trial to directly compare the efficacy and safety of alectinib and crizotinib. **METHODS:** J-ALEX was a randomised, open-label, phase 3 trial that recruited ALK inhibitor-naive Japanese patients with ALK-positive non-small-cell lung cancer, who were chemotherapy-naive or had received one previous chemotherapy regimen, from 41 study sites in Japan. Patients were randomly assigned (1:1) via an interactive web response system using a permuted-block method stratified by Eastern Cooperative Oncology Group performance status, treatment line, and disease stage to receive oral alectinib 300 mg twice daily or crizotinib 250 mg twice daily until progressive disease, unacceptable toxicity, death, or withdrawal. The primary endpoint was progression-free survival assessed by an independent review facility. The efficacy analysis was done in the intention-to-treat population, and safety analyses were done in all patients who received at least one dose of the study drug. The study is ongoing and patient

recruitment is closed. This study is registered with the Japan Pharmaceutical Information Center (number JapicCTI-132316). **FINDINGS:** Between Nov 18, 2013, and Aug 4, 2015, 207 patients were recruited and assigned to the alectinib (n=103) or crizotinib (n=104) groups. At data cutoff for the second interim analysis, 24 patients in the alectinib group had discontinued treatment compared with 61 in the crizotinib group, mostly due to lack of efficacy or adverse events. At the second interim analysis (data cutoff date Dec 3, 2015), an independent data monitoring committee determined that the primary endpoint of the study had been met (hazard ratio 0·34 [99·7% CI 0·17-0·71], stratified log-rank p<0·0001) and recommended an immediate release of the data. Median progression-free survival had not yet been reached with alectinib (95% CI 20·3-not estimated) and was 10·2 months (8·2-12·0) with crizotinib. Grade 3 or 4 adverse events occurred at a greater frequency with crizotinib (54 [52%] of 104) than alectinib (27 [26%] of 103). Dose interruptions due to adverse events were also more prevalent with crizotinib (77 [74%] of 104) than with alectinib (30 [29%] of 103), and more patients receiving crizotinib (21 [20%]) than alectinib (nine [9%]) discontinued the study drug because of an adverse event. No adverse events with a fatal outcome occurred in either treatment group. **INTERPRETATION:** These results provide the first head-to-head comparison of alectinib and crizotinib and have the potential to change the standard of care for the first-line treatment of ALK-positive non-small-cell lung cancer. The dose of alectinib (300 mg twice daily) used in this study is lower than the approved dose in countries other than Japan; however, this limitation is being addressed in the ongoing ALEX study.

[Pooled Analysis of Individual Patient Data on Concurrent Chemoradiotherapy for Stage III Non-Small-Cell Lung Cancer in Elderly Patients Compared With Younger Patients Who Participated in US National Cancer Institute Cooperative Group Studies.](#) Stinchcombe TE1, Zhang Y1, Vokes EE1, et al. J Clin Oncol. 2017 May 11:JCO2016714758. doi: 10.1200/JCO.2016.71.4758. [Epub ahead of print] **PURPOSE:** Concurrent chemoradiotherapy is standard treatment for patients with stage III non-small-cell lung cancer. Elderly patients may experience increased rates of adverse events (AEs) or less benefit from concurrent chemoradiotherapy. **PATIENTS AND METHODS:** Individual patient data were collected from 16 phase II or III trials conducted by US National Cancer Institute-supported cooperative groups of concurrent chemoradiotherapy alone or with consolidation or induction chemotherapy for stage III non-small-cell lung cancer from 1990 to 2012. Overall survival (OS), progression-free survival, and AEs were compared between patients age ≥ 70 (elderly) and those younger than 70 years (younger). Unadjusted and adjusted hazard ratios (HRs) for survival time and CIs were estimated by single-predictor and multivariable frailty Cox models. Unadjusted and adjusted odds ratio (ORs) for AEs and CIs were obtained from single-predictor and multivariable generalized linear mixed-effect models. **RESULTS:** A total of 2,768 patients were classified as younger and 832 as elderly. In unadjusted and multivariable models, elderly patients had worse OS (HR, 1.20; 95% CI, 1.09 to 1.31 and HR, 1.17; 95% CI, 1.07 to 1.29, respectively). In unadjusted and multivariable models, elderly and younger patients had similar progression-free survival (HR, 1.01; 95% CI, 0.93 to 1.10 and HR, 1.00; 95% CI, 0.91 to 1.09, respectively). Elderly patients had a higher rate of grade ≥ 3 AEs in unadjusted and multivariable models (OR, 1.35; 95% CI, 1.07 to 1.70 and OR, 1.38; 95% CI, 1.10 to 1.74, respectively). Grade 5 AEs were significantly higher in elderly compared with younger patients (9% v 4%; P < .01). Fewer elderly compared with younger patients completed treatment (47% v 57%; P < .01), and more discontinued treatment because of AEs (20% v 13%; P < .01), died during treatment (7.8% v 2.9%; P < .01), and refused further treatment (5.8% v 3.9%; P = .02). **CONCLUSION:** Elderly patients in concurrent chemoradiotherapy trials experienced worse OS, more toxicity, and had a higher rate of death during treatment than younger patients.

Phase II Study of Modified Carboplatin Plus Weekly Nab-Paclitaxel in Elderly Patients with Non-Small Cell Lung Cancer: North Japan Lung Cancer Study Group Trial 1301. Miyauchi E1, Inoue A2, Usui K3, et al. Oncologist. 2017 May 19. pii: theoncologist.2017-0059. doi: 10.1634/theoncologist.2017-0059. [Epub ahead of print]
LESSONS LEARNED: Weekly nanoparticle albumin-bound-paclitaxel (75 mg/m2) in combination with carboplatin (area under the curve 6 mg/mL/min) in elderly patients with previously untreated, advanced non-small cell lung cancer showed favorable efficacy, was well tolerated, and showed less neuropathic toxicity.This modified regimen offers potential for the treatment of elderly patients. **BACKGROUND:** The CA031 trial suggested weekly nanoparticle albumin-bound-paclitaxel (nab-PTX) was superior in efficacy to paclitaxel (PTX) once every 3 weeks when combined with carboplatin (CBDCA) for advanced non-small cell lung cancer (NSCLC) patients; a subgroup analysis of elderly patients looked promising. In a multicenter phase II trial, we prospectively evaluated the efficacy and tolerability of modified CBDCA plus weekly nab-PTX for elderly patients with untreated advanced NSCLC. **METHODS:** Eligible patients received CBDCA (area under the curve [AUC] 6 mg/mL/min) on day 1 and nab-PTX (75 mg/m2) on days 1, 8, and 15 every 4 weeks. The primary endpoint was an overall response rate (ORR), and secondary endpoints were progression-free survival (PFS), overall survival (OS), and toxicity. **RESULTS:** Of 32 patients (median age of 78 years), 84% were male, 56% had stage IV NSCLC, and 56% had squamous cell carcinoma. ORR and disease control rates were 50% (95% confidence interval (CI): 33-67) and 94% (95% CI: 85-100), respectively. Median PFS and OS were 6.4 months (95% CI: 4.8-8.0) and 17.5 months (95% CI: 11.9-23.1), respectively. Grade ≥3 toxicities were neutropenia (47%), leukopenia (38%), anemia (34%), thrombocytopenia (25%), and anorexia (9%). Febrile neutropenia and treatment-related deaths were not observed. **CONCLUSION:** Modified CBDCA plus weekly nab-PTX demonstrated significant efficacy and acceptable toxicities in elderly patients with advanced NSCLC. The Oncologist 2017;22:1-5.

Targeted Therapy as an Alternative to Whole-Brain Radiotherapy in EGFR-Mutant or ALK-Positive Non-Small-Cell Lung Cancer With Brain Metastases. Martínez P1, Mak RH2, Oxnard GR1. JAMA Oncol. 2017 May 18. doi: 10.1001/jamaoncol.2017.1047. [Epub ahead of print]
CLINICAL QUESTION: Is up-front whole-brain radiotherapy required to treat multiple brain metastases from non-small-cell lung cancer when highly active targeted therapies are available?
CLINICAL APPLICATION: Patients with EGFR-mutant or ALK-positive non-small-cell lung cancer with brain metastases now have the potential to achieve a prolonged survival. Through use of highly active targeted therapies, whole-brain radiotherapy can be safely postponed, diminishing toxic effects that could impair quality of life.

Open-Label, Multicenter, Phase II Study of Ceritinib in Patients With Non-Small-Cell Lung Cancer Harboring ROS1 Rearrangement. Lim SM1, Kim HR1, Lee JS1, et al. J Clin Oncol. 2017 May 18:JCO2016713701. doi: 10.1200/JCO.2016.71.3701. [Epub ahead of print]
PURPOSE: ROS1 rearrangement is a distinct molecular subset of non-small-cell lung cancer (NSCLC). We investigated the efficacy and safety of ceritinib in patients with ROS1-rearranged NSCLC. Patients and Methods We enrolled 32 patients with advanced NSCLC who tested positive for ROS1 rearrangement by fluorescent in situ hybridization. Ceritinib 750 mg was administered once daily. The primary end point was objective response rate. The secondary end points were disease control rate; duration of response; progression-free survival; overall survival; toxicity; and concordance among fluorescent in situ hybridization, immunohistochemistry, and next-generation sequencing. Results Between June 7, 2013, and February 1, 2016, 404 patients underwent ROS1 prescreening, and 32 patients with ROS1 rearrangement were enrolled. All patients except two were crizotinib-naïve. At the time of data cutoff, the median follow-up was 14.0 months, and 18 patients (56%) had discontinued treatment. Of

the 32 patients enrolled, 28 were evaluable for response by independent radiologic review. Objective response rate was 62% (95% CI, 45% to 77%), with one complete response and 19 partial responses; duration of response was 21.0 months (95% CI, 17 to 25 months); and disease control rate was 81% (95% CI, 65% to 91%). The median progression-free survival was 9.3 months (95% CI, 0 to 22 months) for all patients and 19.3 months (95% CI, 1 to 37 months) for crizotinib-naïve patients. The median overall survival was 24 months (95% CI, 5 to 43 months). Of the eight patients with brain metastases, intracranial disease control was reported in five (63%; 95% CI, 31% to 86%). The most common adverse events (majority, grade 1 or 2) for all treated patients were diarrhea (78%), nausea (59%), and anorexia (56%). **CONCLUSION:** Ceritinib demonstrated potent clinical activity in patients with ROS1-rearranged NSCLC who were heavily treated previously with multiple lines of chemotherapy.

[Detection of ALK and KRAS Mutations in Circulating Tumor DNA of Patients With Advanced ALK-Positive NSCLC With Disease Progression During Crizotinib Treatment.](#) Bordi P1, Tiseo M2, Rofi E3, Petrini I4, Restante G3, Danesi R3, Del Re M3. Clin Lung Cancer. 2017 May 18. pii: S1525-7304(17)30133-X. doi: 10.1016/j.cllc.2017.04.013. [Epub ahead of print]
BACKGROUND: In patients with anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer (NSCLC), disease progression occurs after a median of 9 to 10 months of crizotinib treatment. Several mechanisms of resistance have been identified and include ALK mutations and amplification or the activation of bypassing signaling pathways. Rebiopsy in NSCLC patients represents a critical issue and the analysis of circulating cell-free DNA (cfDNA) has a promising role for the identification of resistance mechanisms. **PATIENTS AND METHODS:** Twenty patients with advanced ALK-positive NSCLC were enrolled after disease progression during crizotinib treatment; cfDNA was analyzed using digital droplet polymerase chain reaction (BioRad, Hercules, CA) for ALK (p.L1196M, p.G1269A, and p.F1174L) and Kirsten rat sarcoma (KRAS) (codons 12 and 13) mutations. **RESULTS:** ALK secondary mutations (p.L1196M, p.G1269A, and p.F1174L) were identified in 5 patients; 1 patient had 2 ALK mutations (p.L1196M and p.G1269A). Overall, 10 patients presented KRAS mutations (7 p.G12D, 2 p.G12V, and 1 p.G12C mutations, respectively). In 3 patients KRAS mutations were associated with ALK mutations. cfDNA was monitored during the treatment with second-generation ALK inhibitors and the amount of ALK as well as KRAS mutations decreased along with tumor regression. **CONCLUSION:** ALK and KRAS mutations are associated with acquired resistance to crizotinib in ALK-positive NSCLC. In particular, ALK acquired mutations can be detected in plasma and could represent a promising tumor marker for response monitoring.

[Clinical outcomes of platinum-based chemotherapy according to T790M mutation status in EGFR-positive non-small cell lung cancer patients after initial EGFR-TKI failure.](#) Yoshida T1, Kuroda H2, Oya Y3, et al. Lung Cancer. 2017 Jul;109:89-91. doi: 10.1016/j.lungcan.2017.05.001. Epub 2017 May 3.
BACKGROUND: Emergence of the T790M point mutation in exon 20 of epidermal growth factor receptor (EGFR) is the most common mechanism of resistance to EGFR tyrosine kinase inhibitors (EGFR-TKIs). It remains unclear whether the efficacy of platinum-doublet chemotherapy is impacted by the presence of the T790M mutation. The aim of this study is to evaluate the efficacy of platinum-doublet chemotherapy after initial EGFR-TKI failure according to the EGFR T790M in patients with advanced EGFR-mutation-positive non-small cell lung cancer (NSCLC). **PATIENTS AND METHODS:** We retrospectively reviewed 50 patients with advanced NSCLC harboring EGFR mutations who underwent rebiopsy to evaluate their T790M mutation status after development of resistance to first-line EGFR-TKIs (gefitinib, erlotinib, or afatinib) and were subsequently treated with second-line platinum-based chemotherapy. **RESULTS:** The median age of patients was 63 years (range, 35-77 years), and 15 (30%) patients were male. Histological examination revealed that all patients had adenocarcinoma, 39 (78%) had stage IV disease, and 11 (22%) patients had postoperative recurrence. Of all, 17 patients (34%) had the

T790M mutation by rebiopsy after initial EGFR-TKI failure. The overall response rate (ORR) of platinum-doublet chemotherapy was 24% for both T790M-positive and T790M-negative patients. There was no significant difference in the progression-free survival (PFS) in T790M-positive and T790M-negative patients (median PFS, 6.0 months vs. 5.1 months; 95% confidence interval [CI], 0.1-11.9 vs. 4.4-5.8; hazard ratio [HR], 0.90 [95%CI, 0.49-1.66]; P=0.7210). None of the factors were predictive of platinum-doublet chemotherapy efficacy by the multivariate analysis. **CONCLUSION:** There were no differences in clinical outcomes of platinum-based chemotherapy according to the T790M status of NSCLC patients.

[**Brigatinib in Patients With Crizotinib-Refractory Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer: A Randomized, Multicenter Phase II Trial.**](#) Kim DW1, Tiseo M1, Ahn MJ1, et al. J Clin Oncol. 2017 May 5:JCO2016715904. doi: 10.1200/JCO.2016.71.5904. [Epub ahead of print]
PURPOSE: Most crizotinib-treated patients with anaplastic lymphoma kinase gene (ALK)-rearranged non-small-cell lung cancer (ALK-positive NSCLC) eventually experience disease progression. We evaluated two regimens of brigatinib, an investigational next-generation ALK inhibitor, in crizotinib-refractory ALK-positive NSCLC. Patients and Methods Patients were stratified by brain metastases and best response to crizotinib. They were randomly assigned (1:1) to oral brigatinib 90 mg once daily (arm A) or 180 mg once daily with a 7-day lead-in at 90 mg (180 mg once daily [with lead-in]; arm B). Investigator-assessed confirmed objective response rate (ORR) was the primary end point. Results Of 222 patients enrolled (arm A: n = 112, 109 treated; arm B: n = 110, 110 treated), 154 (69%) had baseline brain metastases and 164 of 222 (74%) had received prior chemotherapy. With 8.0-month median follow-up, investigator-assessed confirmed ORR was 45% (97.5% CI, 34% to 56%) in arm A and 54% (97.5% CI, 43% to 65%) in arm B. Investigator-assessed median progression-free survival was 9.2 months (95% CI, 7.4 to 15.6) and 12.9 months (95% CI, 11.1 to not reached) in arms A and B, respectively. Independent review committee-assessed intracranial ORR in patients with measurable brain metastases at baseline was 42% (11 of 26 patients) in arm A and 67% (12 of 18 patients) in arm B. Common treatment-emergent adverse events were nausea (arm A/B, 33%/40%), diarrhea (arm A/B, 19%/38%), headache (arm A/B, 28%/27%), and cough (arm A/B, 18%/34%), and were mainly grades 1 to 2. A subset of pulmonary adverse events with early onset (median onset: day 2) occurred in 14 of 219 treated patients (all grades, 6%; grade ≥ 3, 3%); none occurred after escalation to 180 mg in arm B. Seven of 14 patients were successfully retreated with brigatinib. Conclusion: Brigatinib yielded substantial whole-body and intracranial responses as well as robust progression-free survival; 180 mg (with lead-in) showed consistently better efficacy than 90 mg, with acceptable safety.

NSCLC - RADIOTHERAPY

[**Efficacy of postoperative radiotherapy in patients with pathological stage N2 epidermal growth factor receptor wild type adenocarcinoma and squamous cell carcinoma lung cancer.**](#)
Lin YK1, Hsu HL2,3, Lin WC4, et al. Oncotarget. 2017 May 23;8(21):35280-35288. doi: 10.18632/oncotarget.13257.
PURPOSE: Few large, prospective, randomized studies have compared the effects of postoperative radiotherapy (PORT) in pathological N2 (pN2) with those of surgical resection alone. in terms of long-term survival in lung adenocarcinoma (adenoCA; wild-type [WT] epidermal growth factor receptor [EGFR]) and squamous cell carcinoma (squCA) settings. This nationwide cohort study clarifies the role of PORT in the survival of pN2 lung adenoCA (WT EGFR) and squCA patientsPatients and Methods: We analyzed data of patients with adenoCA (WT EGFR) and squCA collected from the Taiwan Cancer Registry database. The patients were categorized into five groups according to the treatment modality:

Group 1 (surgery alone), Group 2 (adjuvant chemotherapy [CT] alone), Group 3 (adjuvant radiotherapy [RT] alone), Group 4 (adjuvant concurrent chemoradiotherapy [CCRT]), and Group 5 (adjuvant sequential CT and intensity-modulated RT [IMRT]). **RESULTS:** We enrolled 588 lung adenoCA (WT EGFR) and squCA patients without distant metastasis. After adjustments for age at surgery, surgical years, and Charlson comorbidity index scores, the multivariate Cox regression analysis demonstrated that adjusted HRs (aHRs; 95% confidence intervals [CIs]) for the overall mortality of female lung adenoCA (WT EGFR) patients were 0.257 (0.111-0.594), 0.530 (0.226-1.243), 0.192 (0.069-0.534), and 0.399 (0.172-0.928) in Groups 2, 3, 4, and 5, respectively. For male lung squCA patients, the aHRs (95% CIs) for overall mortality were 0.269 (0.160-0.451), 0.802 (0.458-1.327), 0.597 (0.358-0.998), and 0.456 (0.265-0.783) in Groups 2, 3, 4, and 5, respectively. **CONCLUSIONS:** Adjuvant CCRT or sequential CT and IMRT at ≥5000 cGy significantly reduced the mortality rate of female lung adenoCA (WT EGFR) and male squCA pN2 patients.

Early postoperative radiotherapy is associated with improved outcomes over late postoperative radiotherapy in the management of completely resected (R0) Stage IIIA-N2 non-small cell lung cancer. Wang HH1, Deng L2, Wen QL3, et al. Oncotarget. 2017 May 23. doi: 10.18632/oncotarget.18071. [Epub ahead of print]
AIMS: The aim of this study was to evaluate the ideal timing of PORT in the management of completely resected (R0) Stage IIIA-N2 NSCLC. **PATIENTS AND METHODS:** Between January 2008 and December 2015, patients with known histologies of pathologic Stage IIIA-N2 NSCLC who underwent R0 resection and received PORT concurrent with or prior to two sequential cycles of chemotherapy ("early PORT") or with PORT administered after two cycles of chemotherapy ("late PORT") at multiple hospitals. The primary endpoint was OS; secondary end points included pattern of the first failure, LRRFS, and DMFS. Kaplan-Meier OS, LRRFS, and DMFS curves were compared with the log-rank test. Cox regression analysis was used to determine prognosticators for OS, LRRFS, and DMFS. **RESULTS:** Of 112 included patients, 41 (36.6%) and 71 (63.4%) patients received early PORT and late PORT, respectively. The median OS, LRRFS, and DMFS were longer for those who received early PORT than for those who received late PORT at the median follow-up of 29.6 months (all p < 0.05). Uni- and multi-variate analyses showed that number of POCT cycles and the combination schedule of PORT and POCT were independent prognostic factors for OS, LRRFS, and DMFS. **CONCLUSIONS:** Early PORT is associated with improved outcomes in pathologic Stage IIIA-N2 R0 NSCLC patients.

Imaging features from pre-treatment CT scans are associated with clinical outcomes in non-small-cell lung cancer patients treated with stereotactic body radiotherapy.
Li Q1,2, Kim J3, Balagurunathan Y2, et al. Med Phys. 2017 May 2. doi: 10.1002/mp.12309. [Epub ahead of print]
PURPOSE: To investigate whether imaging features from pre-treatment planning CT scans are associated with overall survival (OS), recurrence-free survival (RFS), and loco-regional recurrence-free survival (LR-RFS) after stereotactic body radiotherapy (SBRT) among non-small-cell lung cancer (NSCLC) patients. **PATIENTS AND METHODS:** A total of 92 patients (median age: 73 years) with stage I or IIA NSCLC were qualified for this study. A total dose of 50 Gy in 5 fractions was the standard treatment. Besides clinical characteristics, 24 "semantic" image features were manually scored based on a point scale (up to 5) and 219 computer-derived "radiomic" features were extracted based on whole tumor segmentation. Statistical analysis was performed using Cox proportional hazards model and Harrell's C-index, and the robustness of final prognostic model was assessed using ten-fold cross validation by dichotomizing patients according to the survival or recurrence status at 24 months. **RESULTS:** Two-year OS, RFS and LR-RFS were 69.95%, 41.3% and 51.85%, respectively. There was an improvement of Harrell's C-index when adding imaging features to a clinical model. The model for OS contained the

Eastern Cooperative Oncology Group (ECOG) performance status (Hazard Ratio [HR] = 2.78, 95% Confidence Interval [CI]: 1.37 - 5.65), pleural retraction (HR = 0.27, 95% CI: 0.08 - 0.92), F2 (short axis × longest diameter, HR = 1.72, 95% CI: 1.21 - 2.44) and F186 (Hist-Energy-L1, HR = 1.27, 95% CI: 1.00 - 1.61); The prognostic model for RFS contained vessel attachment (HR = 2.13, 95% CI: 1.24 - 3.64) and F2 (HR = 1.69, 95% CI: 1.33 - 2.15); and the model for LR-RFS contained the ECOG performance status (HR = 2.01, 95% CI: 1.12 - 3.60) and F2 (HR = 1.67, 95% CI: 1.29 - 2.18). **CONCLUSIONS:** Imaging features derived from planning CT demonstrate prognostic value for recurrence following SBRT treatment, and might be helpful in patient stratification. This article is protected by copyright. All rights reserved.

[Outcomes targeting the PD-1/PD-L1 axis in conjunction with stereotactic radiation for patients with non-small cell lung cancer brain metastases.](#) Ahmed KA1, Kim S1, Arrington J2, et al. J Neurooncol. 2017 May 2. doi: 10.1007/s11060-017-2437-5. [Epub ahead of print]

Anti-PD-1/PD-L1 therapies have demonstrated activity in patients with advanced stage non-small cell lung cancer (NSCLC). However, little is known about the safety and feasibility of patients receiving anti-PD-1/PD-L1 therapy and stereotactic radiation for the treatment of brain metastases. Data were analyzed retrospectively from NSCLC patients treated with stereotactic radiation either before, during or after anti-PD-1/PD-L1 therapy with nivolumab (anti-PD-1) or durvalumab (anti-PD-L1). Seventeen patients treated with stereotactic radiosurgery (SRS) or fractionated stereotactic radiation therapy (FSRT) to 49 brain metastases over 21 sessions were identified. Radiation was administered prior to, during and after anti-PD-1/PD-L1 therapy in 22 lesions (45%), 13 lesions (27%), and 14 lesions (29%), respectively. The 6 months Kaplan-Meier (KM) distant brain control rate was 48% following stereotactic radiation. Six and 12 month KM rates of OS from the date of stereotactic radiation and the date of cranial metastases diagnosis were 48/41% and 81/51%, respectively. The 6 month rate of distant brain control following stereotactic radiation for patients treated with stereotactic radiation during or prior to anti-PD-1/PD-L1 therapy was 57% compared to 0% among patients who received anti-PD-1/PD-L1 therapy before stereotactic radiation (p = 0.05). A Karnofsky Performance Status (KPS) of <90 was found to be predictive of worse OS following radiation treatment on both univariate and multivariate analyses (MVA, p = 0.01). In our series, stereotactic radiation to NSCLC brain metastases was well tolerated in patients who received anti-PD-1/PD-L1 therapy. Prospective evaluation to determine how these two modalities can be used synergistically to improve distant brain control and OS is warranted.

[Imaging features from pre-treatment CT scans are associated with clinical outcomes in non-small-cell lung cancer patients treated with stereotactic body radiotherapy.](#)

Li Q1,2, Kim J3, Balagurunathan Y2, Liu Y1, et al. Med Phys. 2017 May 2. doi: 10.1002/mp.12309. [Epub ahead of print]

PURPOSE: To investigate whether imaging features from pre-treatment planning CT scans are associated with overall survival (OS), recurrence-free survival (RFS), and loco-regional recurrence-free survival (LR-RFS) after stereotactic body radiotherapy (SBRT) among non-small-cell lung cancer (NSCLC) patients. **PATIENTS AND METHODS:** A total of 92 patients (median age: 73 years) with stage I or IIA NSCLC were qualified for this study. A total dose of 50 Gy in 5 fractions was the standard treatment. Besides clinical characteristics, 24 "semantic" image features were manually scored based on a point scale (up to 5) and 219 computer-derived "radiomic" features were extracted based on whole tumor segmentation. Statistical analysis was performed using Cox proportional hazards model and Harrell's C-index, and the robustness of final prognostic model was assessed using ten-fold cross validation by dichotomizing patients according to the survival or recurrence status at 24 months. **RESULTS:** Two-year OS, RFS and LR-RFS were 69.95%, 41.3% and 51.85%, respectively. There was an improvement of Harrell's C-index when adding imaging features to a clinical model. The model for OS contained the

Eastern Cooperative Oncology Group (ECOG) performance status (Hazard Ratio [HR] = 2.78, 95% Confidence Interval [CI]: 1.37 - 5.65), pleural retraction (HR = 0.27, 95% CI: 0.08 - 0.92), F2 (short axis × longest diameter, HR = 1.72, 95% CI: 1.21 - 2.44) and F186 (Hist-Energy-L1, HR = 1.27, 95% CI: 1.00 - 1.61); The prognostic model for RFS contained vessel attachment (HR = 2.13, 95% CI: 1.24 - 3.64) and F2 (HR = 1.69, 95% CI: 1.33 - 2.15); and the model for LR-RFS contained the ECOG performance status (HR = 2.01, 95% CI: 1.12 - 3.60) and F2 (HR = 1.67, 95% CI: 1.29 - 2.18). **CONCLUSIONS:** Imaging features derived from planning CT demonstrate prognostic value for recurrence following SBRT treatment, and might be helpful in patient stratification. This article is protected by copyright. All rights reserved.

[A Single-Institution Analysis of 126 Patients Treated with Stereotactic Radiosurgery for Brain Metastases.](#) Harris KB1, Corbett MR2, Mascarenhas H3, Lee KS3, Arastu H1, Leinweber C1, Ju AW1. Front Oncol. 2017 May 12;7:90. doi: 10.3389/fonc.2017.00090. eCollection 2017.
BACKGROUND: The objective of this study was to report our institutional experience with Gamma Knife® Radiosurgery (GKRS) in the treatment of patients with brain metastases. **METHODS:** Retrospectively collected demographic and clinical data on 126 patients with intracranial metastases were reviewed. The patients in our study underwent GKRS at Vidant Medical Center between 2009 and 2014. Kaplan-Meier curves were used to compare survival based on clinical characteristics for univariate analysis, and a Cox proportional hazards model was used for multivariate analysis. **RESULTS:** The median age of the patient population was 62 years. Medicare patients constituted 51% of our patient cohort and Medicaid patients 15%. The most common tumor histologies were non-small cell lung cancer (50%), breast cancer (12.7%), and melanoma (11.9%). The median overall survival time for all patients was 5.8 months. Patients with breast cancer had the longest median survival time of 9.15 months, while patients with melanoma had the shortest median survival time of 2.86 months. On univariate analysis, the following factors were predictors for improved overall survival, ECOG score 0 or 1 vs. 2 or greater (17.0 vs. 1.8 months, $p < 0.001$), controlled extracranial disease vs. progressive extracranial disease (17.4 vs. 4.6 months, $p = 0.0001$), recursive partitioning analysis Stage I vs. II-III (18.2 vs. 6.2 months, $p < 0.007$), multiple GKRS treatments ($p = 0.002$), prior brain metastasectomy ($p = 0.012$), and prior chemotherapy ($p = 0.021$). Age, ethnicity, gender, previous external beam radiation therapy, number of brain metastases, and hemorrhagic vs. non-hemorrhagic tumors were not predictors of longer median survival time. Number of metastatic brain lesions of 1-3 vs. ≥4 ($p = 0.051$) and insurance status of Medicare/Medicaid vs. commercial insurance approached significance (13.7 vs. 6.8 months, $p = 0.08$). On multivariate analysis, ECOG performance status 0-1 ($p < 0.001$), multiple GKRS treatments ($p = 0.003$), and control of extracranial disease ($p = 0.001$) remained significant predictors of survival. **CONCLUSION:** ECOG score, control of extracranial disease, and multiple GKRS treatments are predictors of longer median survival following GKRS in our patient population. GKRS is an effective treatment for brain metastases, but these factors may be considered in patient selection for GKRS.

[Phase I study of stereotactic body radiation therapy for centrally located stage IA non-small cell lung cancer (JROSG10-1).](#)
Kimura T1, Nagata Y2, Harada H3, et al. Int J Clin Oncol. 2017 May 2. doi: 10.1007/s10147-017-1125-y. [Epub ahead of print]
BACKGROUND: To investigate the maximum tolerated dose (MTD) and recommended dose (RD) of stereotactic body radiation therapy (SBRT) for centrally located stage IA non-small cell lung cancer (NSCLC). **METHODS:** Five dose levels, ranging from of 52 to 68 Gy in eight fractions, were determined; the treatment protocol began at 60 Gy (level 3). Each dose level included 10 patients. Levels 1-2 were indicated if more than four patients exhibited dose-limiting toxicity (DLT), which was defined as an occurrence of a grade 3 (or worse) adverse effect within 12 months after SBRT initiation. MTD was

defined as the lowest dose level at which more than four patients exhibited DLT. **RESULTS:** Ten patients were enrolled in the level 3 study. One patient was considered unsuitable because of severe emphysema. Therefore, nine patients were evaluated and no patient exhibited DLT. The level 3 results indicated that we should proceed to level 4 (64 Gy). However, due to the difficulty involved in meeting the dose constraints, further dose escalation was not feasible and the MTD was found to be 60 Gy. **CONCLUSIONS:** The RD of SBRT for centrally located stage IA NSCLC was 60 Gy in eight fractions.

SMALL CELL LUNG CANCER - SCLC

[**Vulnerability of small cell lung cancer to apoptosis induced by the combination of BET bromodomain proteins and BCL2 inhibitors.**](#) Lam LT1, Lin X2, Faivre EJ2, et al. Mol Cancer Ther. 2017 May 3. pii: molcanther.0459.2016. doi: 10.1158/1535-7163.MCT-16-0459. [Epub ahead of print] 10% to 15% of all lung cancers are small cell lung cancer (SCLC). SCLC usually grows and metastasizes before it is diagnosed and relapses rapidly upon treatment. Unfortunately, no new targeted agent has been approved in the past 30 years for patients with SCLC. The BET (bromodomain and extra-terminal) proteins bind acetylated histones and recruit protein complexes to promote transcription initiation and elongation. BET proteins have been shown to regulate expression of key genes in oncogenesis such as MYC, CCND2, and BCL2L1 Here, we demonstrate that ~50% of SCLC cell lines are exquisitely sensitive to growth inhibition by the BET inhibitor, ABBV-075. The majority of these SCLC cell lines underwent apoptosis in response to ABBV-075 treatment via induction of caspase 3/7 activity. ABBV-075 enhanced the expression of proapoptotic protein BIM and down-regulated antiapoptotic proteins BCL2 and BCLxl to a lesser extent. Furthermore, BET inhibition increased BCL2-BIM complex, thus priming the cells for apoptosis. Indeed strong synergy was observed both in vitro and in vivo when co-treating the cells with BET inhibitor and the BH3-mimetic, BCL2 inhibitor venetoclax (ABT-199). ABBV-075 interaction with venetoclax positively correlated with BCL2 expression. Taken together, our studies provide a rationale for treating SCLC with BET and BCL2 inhibitors in tumors with high BCL2 protein expression.

[**Surgery Versus Chemotherapy and Radiotherapy For Early and Locally Advanced Small Cell Lung Cancer: A Propensity-Matched Analysis of Survival.**](#) Wakeam E1, Acuna SA2, Leighl NB3, Giuliani ME4, Finlayson SRG5, Varghese TK6, Darling GE7. Lung Cancer. 2017 Jul;109:78-88. doi: 10.1016/j.lungcan.2017.04.021. Epub 2017 May 1.
BACKGROUND: The role of surgery in small cell lung cancer (SCLC) is controversial. Survival outcomes for resection of stage I-IIIA SCLC compared to chemotherapy-based non-surgical treatment (NST) were examined using propensity matching. **METHODS:** 29,994 clinical stage I-IIIA SCLC patients, including 2,619 undergoing surgery, were identified in the National Cancer Database. Stage-specific propensity scores for receipt of surgery were created. Resected patients were matched 1:1 to those undergoing NST. Overall survival (OS) was assessed using Kaplan-Meier and multivariable Cox models. A separate match was performed comparing Stage I/II patients aged <85 with a Charlson score of 0 who underwent lobectomy with adjuvant chemotherapy (and radiotherapy if node positive) to those treated with multiagent chemotherapy and concurrent chest radiotherapy (CRT) of at least 40 gray. **RESULTS:** 2,089 patients were matched, and cohorts were well balanced. Surgery was associated with longer survival for Stage I (median OS 38.6 months vs. 22.9 months, HR 0.62 95%CI 0.57-0.69, p<0.0001), but survival differences were attenuated for Stage II (median OS 23.4 months vs. 20.7 months, HR 0.84 95%CI 0.70-1.01, p=0.06) and IIIA (median OS 21.7 vs. 16.0 months, HR 0.71 95%CI 0.60-0.83, p <0.0001). In analyses by T and N stage, longer OS was observed in resected patients with stage T3/T4 N0 (median OS 33.0 vs. 16.8 months, p=0.008) and node positivity(N1+ 24.4 vs. 18.3 months p=0.03; N2+ 20.1 vs. 14.6 months p=0.007). In the subgroup analysis, 507 stage I/II patients receiving lobectomy and

adjuvant chemotherapy were matched to patients receiving concurrent CRT. In this cohort, lobectomy with adjuvant chemotherapy was associated with significantly longer survival (median OS 48.6 vs. 28.7 months, p<0.0001). **CONCLUSIONS:** Surgical resection is associated with significantly longer survival for early SCLC. New randomized trials should assess trimodality therapy in stages I/II, and in node negative disease.

[Trends, practice patterns and underuse of surgery in the treatment of early stage small cell lung cancer.](#) Wakeam E1, Varghese TK Jr2, Leighl NB3, Giuliani M4, Finlayson SRG5, Darling GE6. Lung Cancer. 2017 Jul;109:117-123. doi: 10.1016/j.lungcan.2017.05.004. Epub 2017 May 13.

BACKGROUND: Practice guidelines from the National Comprehensive Cancer Network and the American Society of Clinical Oncology recommend pathologic mediastinal staging and surgical resection for patients with clinically node-negative T1/T2 small cell lung cancer (SCLC), but the extent to which surgery is used is unknown. We sought to assess trends and practice patterns in the use of surgery for SCLC. **METHODS:** T1 or T2N0M0 SCLC cases were identified in the National Cancer Database (NCDB), 2004-2013. Characteristics of patients undergoing resection were analyzed. Hierarchical logistic regression was used to identify individual and hospital-level predictors of receipt of surgery, adjusting for clinical, demographic and facility characteristics. Trends in resection rates were analyzed over the study period. **FINDINGS:** 9740 patients were identified with clinical T1 or T2 N0M0 SCLC. Of these, 2210 underwent surgery (22.7%), with 1421 (64.3%) undergoing lobectomy, 739 (33.4%) sublobar resections and 50 (2.3%) pneumonectomies. After adjustment, Medicaid patients were less likely to receive surgery (OR0.65 95% CI 0.48-0.89, p=0.006), as were those with T2 tumors (OR0.25 CI0.22-0.29, p<0.0001). Academic facilities were more likely to resect eligible patients (OR 1.90 CI1.45-2.49, p<0.0001). Between 2004 and 2013, resection rates more than doubled from 9.1% to 21.7%. Overall, 68.7% of patients were not offered surgery despite having no identifiable contraindication. In patients not receiving surgery, only 7% underwent pathologic mediastinal staging. **INTERPRETATION:** Rates of resection are increasing, but two thirds of potentially eligible patients fail to undergo surgery. Further study is required to address the lack of concordance between guidelines and practice.

[Trastuzumab emtansine suppresses the growth of HER2-positive small-cell lung cancer in preclinical models.](#) Morimura O1, Minami T2, Kijima T3, et al. Biochem Biophys Res Commun. 2017 Jul 8;488(4):596-602. doi: 10.1016/j.bbrc.2017.05.090. Epub 2017 May 17.

Overcoming chemoresistance is essential for achieving better prognoses in SCLC. Previously, we reported that HER2 is upregulated when HER2-positive SCLC cells acquire chemoresistance. HER2-upregulated cisplatin- or etoposide-resistant SCLC cells were sensitive to trastuzumab-mediated ADCC. However, irinotecan-resistant SCLC cells, such as SBC-3/SN-38, were refractory to trastuzumab despite high HER2 expression. To address this issue, we examined the antitumor efficacy of trastuzumab emtansine (T-DM1) on trastuzumab-resistant HER2-positive SCLC. Treatment with T-DM1 significantly suppressed the growth of SBC-3/SN-38 xenografts in mice compared with trastuzumab (P < 0.05). Histological analysis of xenografts was performed to evaluate the therapeutic effect on apoptosis, proliferation and tumor vasculature. T-DM1 monotherapy induced apoptosis in SBC-3/SN-38 xenografts to a greater extent than trastuzumab monotherapy with the apoptotic index of 3.71 ± 1.56% vs. 0.60 ± 0.32% (P < 0.05), and also inhibited the proliferation of tumor cells compared with trastuzumab with the proliferative index of 74.30 ± 5.54% vs. 80.12 ± 4.81% (P < 0.05). On the other hand, no significant difference in micro vessel density was observed between the treatment groups. In vivo imaging using fluorescence-labeled T-DM1 showed that intravenously administered T-DM1 was rapidly delivered to xenografts and continued to accumulate for several days in a HER2-selective fashion. From these findings, delivery of the cytotoxic agent DM1 into cells via HER2-mediated internalization is expected to

exert antitumor effect in such ADCC-lacking SCLC cells. Collectively, T-DM1 will be a promising option for overcoming trastuzumab-resistance in HER2-upregulated SCLC.

[A Randomized, Placebo-Controlled, Phase 1b/2 Study of Rilotumumab or Ganitumab in Combination With Platinum-Based Chemotherapy as First-Line Treatment for Extensive-Stage Small-Cell Lung Cancer.](#) Glisson B1, Besse B2, Dols MC3, et al. Clin Lung Cancer. 2017 May 10. pii: S1525-7304(17)30142-0. doi: 10.1016/j.cllc.2017.05.007. [Epub ahead of print]
INTRODUCTION/BACKGROUND: In this randomized, double-blind, placebo-controlled phase 1b/2 study we assessed the efficacy/safety of rilotumumab or ganitumab combined with etoposide and carboplatin or cisplatin as first-line treatment in patients with extensive stage small-cell lung cancer (ES-SCLC). **PATIENTS AND METHODS:** In the phase 1b study, patients received rilotumumab 15 mg/kg or ganitumab 18 mg/kg with etoposide and carboplatin or cisplatin. In the phase 2 study, patients were randomly assigned 1:1:1 to receive placebo, rilotumumab, or ganitumab with etoposide and carboplatin or cisplatin. Chemotherapy was administered for ≤ 6 cycles; rilotumumab, ganitumab, or placebo was then continued as maintenance therapy. The primary end points were incidence of dose-limiting toxicities (DLTs; phase 1b) and overall survival (OS; phase 2). Secondary end points included progression-free survival (PFS) and safety. **RESULTS:** In the phase 1b study (n = 28), 1 patient treated with ganitumab experienced a DLT (Grade 4 neutropenia/thrombocytopenia lasting ≥ 7 days). In the phase 2 study, 185 patients were enrolled (placebo, n = 61; rilotumumab, n = 62; ganitumab, n = 62). Median OS was 10.8, 12.2 (hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.56-1.25; P = .384), and 10.7 (HR, 0.95; 95% CI, 0.63-1.41; P = .787) months, in placebo, rilotumumab, or ganitumumab arms, respectively. Median PFS was 5.4, 5.4 (HR, 1.05; 95% CI, 0.71-1.54; P = .797), and 5.5 (HR, 1.05; 95% CI, 0.72-1.55; P = .780) months, respectively. Adverse events resulting in treatment discontinuation occurred in 11 (19%), 10 (16%), and 7 (12%) patients, respectively. Serum biomarker analysis showed improved survival for patients with baseline hepatocyte growth factor levels below the median in the rilotumumab arm. **CONCLUSION:** Although the combination of rilotumumab or ganitumab with chemotherapy was tolerable, overall outcomes were not improved in patients with ES-SCLC.

[Survival changes in patients with small cell lung cancer and disparities between different sexes, socioeconomic statuses and ages.](#) Wang S1, Tang J2, Sun T3, et al. Sci Rep. 2017 May 2;7(1):1339. doi: 10.1038/s41598-017-01571-0.
Small cell lung cancer (SCLC), as a proportion, makes up only 15-17% of lung cancer cases. The development of treatments for SCLC has remained stagnant for decades, and SCLC is expected to persist as a threat to human health. To date, no publications based on large populations have been reported. We calculated survival changes in patients with SCLC during each decade between 1983 and 2012 to determine the roles of race, sex, age, and socioeconomic status (SES) on survival rates based on the Surveillance, Epidemiology, and End Results (SEER) registries. In total, 106,296 patients with SCLC were identified, with the overall incidence per 100,000 decreasing each decade from 9.6 to 7.8 to 5.8. The median survival for SCLC remained 7 months, and the 12-month relative survival rates (RSRs) remained relatively stable at 32.9%, 33.2% and 33.2% during each decade. The 5-year RSRs significantly improved from 4.9% to 5.9% to 6.4% during each decade, but remained extremely low. In addition, a narrowing of the survival gaps among SES groups and stable survival gaps between sexes were observed. Although the incidence of SCLC decreased during each decade, the overall survival remained relatively stable, highlighting the urgency of developing novel treatments and the importance of prevention and early detection.

Phase I/II study of induction chemotherapy using carboplatin plus irinotecan and sequential thoracic radiotherapy (TRT) for elderly patients with limited-disease small-cell lung cancer (LD-SCLC): TORG 0604. Misumi Y1, Okamoto H2, Sasaki J3, et al. BMC Cancer. 2017 May 26;17(1):377. doi: 10.1186/s12885-017-3353-y.

BACKGROUND: The role of irinotecan for elderly patients with LD-SCLC has been unclear, and the timing of TRT combined with chemotherapy has not been fully evaluated. **METHODS:** Patients aged > 70 years with untreated, measurable, LD-SCLC, performance status (PS) 0-2, and adequate organ function were eligible. Treatment consisted of induction with carboplatin on day 1 and irinotecan on days 1 and 8, every 21 days for 4 cycles, and sequential TRT (54Gy in 27 fractions). Carboplatin doses were based on AUC of 4 and 5 (levels 1 and 2, respectively), with a fixed irinotecan dose (50 mg/m2). Primary objective of the phase II study was overall responce rate. **RESULTS:** Forty-three patients were enrolled and forty-one were finally analyzed (median age: 75 years [range 70-86 years); males 31; PS 0/1/2, n = 22/18/1]. Two patients were excluded because of protocol violation (ascertained to be extensive disease). Twelve patients were accrued at phase I and the number of patients with carboplatin dose-limiting toxicities at levels-1 (n = 6) and -2 (n = 6) were 1(grade 3 hypertension) and 2 (grade 4 thrombocytopenia), respectively. The phase II trial was expanded to 29 additional patients receiving the level 1 carboplatin dose, total of 35 patients. The median number of chemotherapy cycles was 4 (range 1-4), and the median radiation dose was 54Gy (range 36-60). Toxicities were generally mild. There were 4 complete and 27 partial responses (response rate 88.6%). With a median follow-up of 52 months, the median progression-free and overall survival times of phase II were 11.2 and 27.1 months, respectively. **CONCLUSIONS:** Induction chemotherapy of carboplatin plus irinotecan and sequential TRT was well tolerated and effective for elderly patients with LD-SCLC. Additional confirmatory studies are warranted. **TRIAL REGISTRATION:** Trial registration number: UMIN000007352 Name of registry: UMIN. Date of registration: 1/Dec/2006. Date of enrolment of the first participant to the trial: 6/Feb/2007. Clinical trial registration date: 1/Feb/2006 (prospective).

Unravelling the biology of SCLC: implications for therapy. Sabari JK1, Lok BH2, Laird JH3, Poirier JT1,4, Rudin CM1,4,5. Nat Rev Clin Oncol. 2017 May 23. doi: 10.1038/nrclinonc.2017.71. [Epub ahead of print]

Small-cell lung cancer (SCLC) is an aggressive malignancy associated with a poor prognosis. First-line treatment has remained unchanged for decades, and a paucity of effective treatment options exists for recurrent disease. Nonetheless, advances in our understanding of SCLC biology have led to the development of novel experimental therapies. Poly [ADP-ribose] polymerase (PARP) inhibitors have shown promise in preclinical models, and are under clinical investigation in combination with cytotoxic therapies and inhibitors of cell-cycle checkpoints.Preclinical data indicate that targeting of histone-lysine N-methyltransferase EZH2, a regulator of chromatin remodelling implicated in acquired therapeutic resistance, might augment and prolong chemotherapy responses. High expression of the inhibitory Notch ligand Delta-like protein 3 (DLL3) in most SCLCs has been linked to expression of Achaete-scute homologue 1 (ASCL1; also known as ASH-1), a key transcription factor driving SCLC oncogenesis; encouraging preclinical and clinical activity has been demonstrated for an anti-DLL3-antibody-drug conjugate. The immune microenvironment of SCLC seems to be distinct from that of other solid tumours, with few tumour-infiltrating lymphocytes and low levels of the immune-checkpoint protein programmed cell death 1 ligand 1 (PD-L1). Nonetheless, immunotherapy with immune-checkpoint inhibitors holds promise for patients with this disease, independent of PD-L1 status. Herein, we review the progress made in uncovering aspects of the biology of SCLC and its microenvironment that are defining new therapeutic strategies and offering renewed hope for patients.

[Decreased sensory nerve excitation and bone pain associated with mouse Lewis lung cancer in TRPV1-deficient mice.](#) Wakabayashi H1,2, Wakisaka S3, Hiraga T1,4, Hata K1, Nishimura R1, Tominaga M5, Yoneda T6,7. J Bone Miner Metab. 2017 May 17. doi: 10.1007/s00774-017-0842-7. [Epub ahead of print]

Bone pain is one of the most common and life-limiting complications of cancer metastasis to bone. Although the mechanism of bone pain still remains poorly understood, bone pain is evoked as a consequence of sensitization and excitation of sensory nerves (SNs) innervating bone by noxious stimuli produced in the microenvironment of bone metastases. We showed that bone is innervated by calcitonin gene-related protein (CGRP)+ SNs extending from dorsal root ganglia (DRG), the cell body of SNs, in mice. Mice intratibially injected with Lewis lung cancer (LLC) cells showed progressive bone pain evaluated by mechanical allodynia and flinching with increased CGRP+ SNs in bone and augmented SN excitation in DRG as indicated by elevated numbers of pERK- and pCREB-immunoreactive neurons. Immunohistochemical examination of LLC-injected bone revealed that the tumor microenvironment is acidic. Bafilomycin A1, a selective inhibitor of H+ secretion from vacuolar proton pump, significantly alleviated bone pain, indicating that the acidic microenvironment contributes to bone pain. We then determined whether the transient receptor potential vanilloid 1 (TRPV1), a major acid-sensing nociceptor predominantly expressed on SNs, plays a role in bone pain by intratibially injecting LLC cells in TRPV1-deficient mice. Bone pain and SN excitation in the DRG and spinal dorsal horn were significantly decreased in TRPV1 -/- mice compared with wild-type mice. **Our results suggest** that TRPV1 activation on SNs innervating bone by the acidic cancer microenvironment in bone contributes to SN activation and bone pain. Targeting acid-activated TRPV1 is a potential therapeutic approach to cancer-induced bone pain.

[Work Experiences of Patients Receiving Palliative Care at a Comprehensive Cancer Center: Exploratory Analysis.](#) Glare PA1, Nikolova T1, Alickaj A1, Patil S2, Blinder V1,2. J Palliat Med. 2017 May 31. doi: 10.1089/jpm.2016.0478. [Epub ahead of print]

BACKGROUND: Employment-related issues have been largely overlooked in cancer patients needing palliative care. These issues may become more relevant as cancer evolves into more of a chronic illness and palliative care is provided independent of stage or prognosis. **OBJECTIVE:** To characterize the employment situations of working-age palliative care patients. **DESIGN:** Cross-sectional survey setting/subjects: Consecutive sample of 112 patients followed in palliative care outpatient clinics at a comprehensive cancer center. **MEASUREMENTS:** Thirty-seven-item self-report questionnaire covering demographics, clinical status, and work experiences since diagnosis. **RESULTS:** The commonest cancer diagnoses were breast, colorectal, gynecological, and lung. Eighty-one percent had active disease. Seventy-four percent were on treatment. Eighty percent recalled being employed at the time of diagnosis, with 65% working full time. At the time of the survey, 44% were employed and 26% were working full time. Most participants said work was important, made them feel normal, and helped them feel they were "beating the cancer". Factors associated with being employed included male gender, self-employed, and taking less than three months off work. Respondents with pain and/or other symptoms were significantly less likely to be working. On multivariate analysis, only pain (odds ratio [OR] 8.16, $p < 0.001$) and other physical symptoms (OR 5.90, $p = 0.012$) predicted work status; gender (OR 2.07), self-employed (OR 3.07), and current chemotherapy (OR 1.81) were included in the model, but were not statistically significant in this small sample. **CONCLUSION:** Work may be an important issue for some palliative care patients. Additional research is needed to facilitate ongoing employment for those who wish or need to continue working.

Cancer Survivors' Reported Discussions with Health Care Providers About Follow-Up Care and Receipt of Written Care Plans. Reed SC1, Walker R2, Ziebell R2, Rabin B3, Nutt S4, Chubak J2, Nekhlyudov L5. J Cancer Educ. 2017 May 8. doi: 10.1007/s13187-017-1228-1. [Epub ahead of print]
Prior studies reveal gaps in cancer survivors' discussions with health care providers about follow-up care and receipt of care plans; however, whether survivorship care planning may vary by cancer type is not known. We surveyed 615 survivors of breast, colorectal, prostate, lung cancer, and melanoma enrolled in three health plans to examine cancer survivors' self-reported discussions of follow-up care, including the need for surveillance, late and long-term effects, emotional needs, and health behaviors. We assessed whether cancer survivors received a written treatment summary and post-treatment care instructions. Most (92%) survivors reported having a discussion about the need for surveillance; 75%, late and long-term effects; 69%, lifestyle and health behaviors; and 53%, emotional and social needs. Most (88%) reported receiving post-treatment care instructions and 47%, a treatment summary. While there was little difference among survivors' receipt of surveillance or health behavior recommendations by cancer type (p = 0.85 and p = 0.66, respectively), discussions of late and long-term effects occurred among 82% of prostate, 78% of breast, 73% of melanoma, 72% of colorectal, and 67% of lung survivors (p = 0.06). Approximately half of survivors reported discussions of emotional needs, with modest differences by cancer type (p = 0.08). Our findings indicate that most patient-provider discussions cover information on surveillance, with less emphasis on late and long-term effects, lifestyle and health behaviors, and substantially less focusing on emotional and social needs. No or modest differences in discussions occurred by cancer type. Whether tailoring information to individual cancer survivor needs is beneficial should be examined.

Differences in Symptom Clusters Identified Using Ratings of Symptom Occurrence Versus Severity in Lung Cancer Patients Receiving Chemotherapy. Wong ML1, Cooper BA2, Paul SM2, Levine JD1, Conley YP3, Wright F4, Hammer M5, Miaskowski C6. J Pain Symptom Manage. 2017 May 19. pii: S0885-3924(17)30188-4. doi: 10.1016/j.jpainsymman.2017.04.005. [Epub ahead of print]
An important question in symptom clusters research is whether the number and types of symptom clusters vary based on the specific dimension of the symptom experience used to create the clusters.
OBJECTIVES: Given that lung cancer patients undergoing chemotherapy (CTX) report an average of 14 co-occurring symptoms and studies of symptom clusters in these patients are limited, the purpose of this study, in lung cancer patients undergoing CTX (n=145), was to identify whether the number and types of symptom clusters differed based on whether symptom occurrence rates or symptom severity ratings were used to create the clusters. **METHODS:** A modified version of the Memorial Symptom Assessment Scale was used to assess for the occurrence and severity of 38 symptoms, one week after the administration of CTX. Exploratory factor analysis was used to extract the symptom clusters. **RESULTS:** Both the number and types of symptom clusters were relatively similar using symptom occurrence rates or symptom severity ratings. Five symptom clusters were identified using both symptom occurrence rates and severity ratings (i.e., sickness behavior, lung cancer-specific, psychological, nutritional, epithelial). Across these two dimensions, the specific symptoms within each of the symptom clusters were relatively similar. **CONCLUSIONS:** Identification of symptom clusters in patients with lung cancer may assist with the development of more targeted symptom management interventions. Future studies are warranted to determine if symptom clusters change over a cycle of CTX in patients with lung cancer.

Muscle mass and association to quality of life in non-small cell lung cancer patients. Bye A1,2, Sjøblom B3,4,5, Wentzel-Larsen T6,7,8, et al. J Cachexia Sarcopenia Muscle. 2017 May 10. doi: 10.1002/jcsm.12206. [Epub ahead of print]
BACKGROUND: Cancer wasting is characterized by muscle loss and may contribute to fatigue and poor quality of life (QoL). Our aim was to investigate associations between skeletal muscle index (SMI) and

skeletal muscle radiodensity (SMD) and selected QoL outcomes in advanced non-small cell lung cancer (NSCLC) at diagnosis. **METHODS:** Baseline data from patients with stage IIIB/IV NSCLC and performance status 0-2 enrolled in three randomized trials of first-line chemotherapy (n = 1305) were analysed. Associations between SMI (cm2 /m2) and SMD (Hounsfield units) based on computed tomography-images at the third lumbar level and self-reported physical function (PF), role function (RF), global QoL, fatigue, and dyspnoea were investigated by linear regression using flexible non-linear modelling. **RESULTS:** Complete data were available for 734 patients, mean age 65 years. Mean SMI was 47.7 cm2 /m2 in men (n = 420) and 39.6 cm2 /m2 in women (n = 314). Low SMI values were non-linearly associated with low PF and RF (men P = 0.016/0.020, women P = 0.004/0.012) and with low global QoL (P = 0.001) in men. Low SMI was significantly associated with high fatigue (P = 0.002) and more pain (P = 0.015), in both genders, but not with dyspnoea. All regression analyses showed poorer physical outcomes below an SMI breakpoint of about 42-45 cm2 /m2 for men and 37-40 cm2 /m2 for women. In both genders, poor PF and more dyspnoea were significantly associated with low SMD. **CONCLUSIONS:** Low muscle mass in NSCLC negatively affects the patients' PF, RF, and global QoL, possibly more so in men than in women. However, muscle mass must be below a threshold value before this effect can be detected.

[**The effects of supportive care interventions on depressive symptoms among patients with lung cancer: A metaanalysis of randomized controlled studies.**](#) Hsieh CC1, Hsiao FH1. Palliat Support Care. 2017 May 16:1-14. doi: 10.1017/S1478951517000335. [Epub ahead of print]
OBJECTIVE: Our aim was to examine the effect of supportive care interventions on depressive symptoms in patients with lung cancer. **METHOD:** We searched the databases of the Cochrane Central Register of Controlled Trials (CENTRAL), Ovid EMBASE, PubMed, and the Chinese Electronic Periodical Services (CEPS) from their inception until September of 2015. We included randomized controlled trial studies that compared standard care with supportive care interventions. The standardized mean difference (SMD) (Cohen's d) was calculated to estimate the effect of interventions. Subgroup analysis was conducted to identify possible sources of heterogeneity. **RESULTS:** A total of 1,472 patients with lung cancer were identified. Compared with standard care, the overall effects of all supportive care interventions significantly reduced depressive symptoms (SMD = -0.74, CI 95% = -1.07 to -0.41), and the effects could be maintained at weeks 4, 8, and 12 of follow-up. Three types of supportive care interventions were identified: psychotherapy combined with psychoeducation, psychoeducation alone, and an exercise program. Both psychotherapy combined with psychoeducation and exercise significantly improved depressive symptoms, while psychoeducation alone did not yield significant effects. The moderating effects indicated that greater improvements in depressive symptoms were found in lung cancer patients with a severe level of depressive symptoms at baseline. **SIGNIFICANCE OF RESULTS:** Personalized supportive care interventions can be developed based on the main causes of depressive symptoms. Psychotherapy combined with psychoeducation can target the causes of depressive symptoms, including both physical distress and psychological trauma due to lung cancer, while exercise programs can effectively improve depressive symptoms for lung cancer patients with impaired respiratory function.

COMPLEMENTARY & ALTERNATIVE THERAPY

[**Anticancer potential of Thevetia peruviana fruit methanolic extract.**](#) Ramos-Silva A1, Tavares-Carreón F1, Figueroa M2, et al. BMC Complement Altern Med. 2017 May 2;17(1):241. doi: 10.1186/s12906-017-1727-y.
BACKGROUND: Thevetia peruviana (Pers.) K. Schum or Cascabela peruviana (L.) Lippold (commonly known as ayoyote, codo de fraile, lucky nut, or yellow oleander), native to Mexico and Central America,

is a medicinal plant used traditionally to cure diseases like ulcers, scabies, hemorrhoids and dissolve tumors. The purpose of this study was to evaluate the cytotoxic, antiproliferative and apoptotic activity of methanolic extract of T. peruviana fruits on human cancer cell lines. **METHODS:** The cytotoxic activity of T. peruviana methanolic extract was carried out on human breast, colorectal, prostate and lung cancer cell lines and non-tumorigenic control cells (fibroblast and Vero), using the MTT assay. For proliferation and motility, clonogenic and wound-healing assays were performed. Morphological alterations were monitored by trypan blue exclusion, as well as DNA fragmentation and AO/EB double staining was performed to evaluate apoptosis. The extract was separated using flash chromatography, and the resulting fractions were evaluated on colorectal cancer cells for their cytotoxic activity. The active fractions were further analyzed through mass spectrometry. **RESULTS:** The T. peruviana methanolic extract exhibited cytotoxic activity on four human cancer cell lines: prostate, breast, colorectal and lung, with values of IC50 1.91 ± 0.76, 5.78 ± 2.12, 6.30 ± 4.45 and 12.04 ± 3.43 μg/mL, respectively. The extract caused a significant reduction of cell motility and colony formation on all evaluated cancer cell lines. In addition, morphological examination displayed cell size reduction, membrane blebbing and detachment of cells, compared to non-treated cancer cell lines. The T. peruviana extract induced apoptotic cell death, which was confirmed by DNA fragmentation and AO/EB double staining. Fractions 4 and 5 showed the most effective cytotoxic activity and their MS analysis revealed the presence of the secondary metabolites: thevetiaflavone and cardiac glycosides. **CONCLUSION:** T. peruviana extract has potential as natural anti-cancer product with critical effects in the proliferation, motility, and adhesion of human breast and colorectal cancer cells, and apoptosis induction in human prostate and lung cancer cell lines, with minimal effects on non-tumorigenic cell lines.

[**Bu Fei Decoction attenuates the tumor associated macrophage stimulated proliferation, migration, invasion and immunosuppression of non-small cell lung cancer, partially via IL-10 and PD-L1 regulation.**](#) Pang L1, Han S1, Jiao Y1, Jiang S1, He X1, Li P1. Int J Oncol. 2017 May 19. doi: 10.3892/ijo.2017.4014. [Epub ahead of print]
Macrophages play a pivotal role in tumor microenvironment. Bu-Fei Decoction (BFD) is a classical formula of traditional Chinese medicine (TCM) to alleviate lung cancer related symptoms, whether it has antitumor effect or could influence cancer microenvironment deserves further study. The aim of the present study was to examine the antitumor effect of BFD on non-small cell lung cancer (NSCLC), and to investigate the underlying mechanisms through tumor associated macrophages (TAMs). M2-polarized TAMs were induced by Phorbol 12-myristate 13-acetate (PMA) and interleukin 4 (IL-4). The antitumor activity of BFD in vitro was investigated in A549 and H1975 cells using MTT assay. The in vivo anticancer effect of BFD was evaluated in athymic nude mouse xenograft model. The invasive and migration properties of NSCLC cells were measured using Transwell. The protein expression was assessed using western blotting, ELISA and immunohistochemistry. The gene expression was examined using RT-PCR. TAMs was successfully established. Conditioned medium from TAMs increased cell proliferation, migration and invasion in NSCLC cells (p<0.05). BFD showed dose-dependent inhibitory effect on cell proliferation, migration and invasion abilities induced by TAMs. TAMs and rhIL-10 promoted the mRNA and protein expression of PD-L1 in NSCLC cells (p<0.01). Anti IL 10 antibodies inhibited the elevated PD-L1 expression induced by TAMs. In vitro, the expression of PD-L1 and IL-10 was inhibited by BFD dose-dependently. In vivo, BFD suppressed A549 and H1975 tumor growth and decreased the expression of IL-10, PD-L1 and CD206. The results showed that TAMs play an important role in tumor progression of NSCLC, which was associated with tumor proliferation, migration, invasion and immunosuppression. Moreover, the antitumor mechanism of BFD is related to interruption of the link between TAMs and cancer cells by inhibiting the expression of IL-10 and PD-L1 in vitro and in vivo. Our results demonstrated BFD's potential as a novel treatment for NSCLC.

Yangfei Kongliu Formula, a compound Chinese herbal medicine, combined with cisplatin, inhibits growth of lung cancer cells through transforming growth factor-β1 signaling pathway. Shen SJ1,2, Zhang YH1, Gu XX2, Jiang SJ3, Xu LJ2. J Integr Med. 2017 May;15(3):242-251. doi: 10.1016/S2095-4964(17)60330-3.

OBJECTIVE: To investigate the tumor inhibition effect of Yangfei Kongliu Formula (YKF), a compound Chinese herbal medicine, combined with cisplatin (DDP) and its action mechanisms. **METHODS:** C57BL/6 mice with Lewis lung carcinoma were divided into six groups: control group (C), DDP group (2 mg/kg, DDP), low-dose YKF group (2.43 g/kg, L), high-dose YKF group (24.3 g/kg, H), low-dose YKF combined with DDP group (L + DDP) and high-dose YKF combined with DDP group (H + DDP). Transforming growth factor-β1 (TGF-β1), mothers against decapentaplegic homolog 3 (Smad3) and Smad7 levels were measured with quantitative real-time polymerase chain reaction (qPCR), Western blotting and immunohistochemistry. An enzyme-linked immunosorbent assay was used to analyze the expressions of interleukin-2 (IL-2) and tumor necrosis factor-α (TNF-α). **RESULTS:** YKF combined with DDP significantly inhibited the growth and metastasis of tumors relative to the control group, and YKF groups ($P < 0.05$). There was no significant difference between high-dose YKF group and low-dose YKF group ($P > 0.05$). We also found that the expression levels of TGF-β1 and Smad3 were both significantly decreased by YKF relative to the control group ($P < 0.05$). Furthermore, after treatment with YKF combined with DDP, the expression levels of TGF-β1 and Smad3 were decreased but the expression level of Smad7 was increased relative to the DDP group ($P < 0.05$). Compared to the DDP group, the combination of YKF and DDP enhanced the effect of tumor inhibition ($P < 0.05$), showing obvious synergy between YKF and DDP. Treatment with DDP or YKF decreased serum levels of IL-2 and TNF-α relative to the control group ($P < 0.05$). Furthermore, the expression levels of IL-2 and TNF-α were significantly decreased when treated with YKF in combination with DDP. Co-treatment with YKF and DDP significantly inhibited tumor growth, decreased the expressions of TGF-β1, Smad3, IL-2 and TNF-α and increased the expression of Smad7; these differences were significant relative to both YKF groups and the control group ($P < 0.05$). **CONCLUSION:** YKF can inhibit tumor growth synergistically with DDP, mainly through the TGF-β1 signaling pathway.

MISCELLANEOUS WORKS

Survival improvement in patients with non-small cell lung cancer between 1983 and 2012: Analysis of the Surveillance, Epidemiology, and End Results database. Wang S1, Sun T2, Sun H1, et al. Tumour Biol. 2017 May;39(5):1010428317691677. doi: 10.1177/1010428317691677.

Non-small cell lung cancer is the most common malignancy in males; it constitutes the majority of lung cancer cases and requires massive medical resources. Despite improvements in managing non-small cell lung cancer, long-term survival remains very low. This study evaluated survival improvement in patients with non-small cell lung cancer in each decade between 1983 and 2012 to determine the impact of race, sex, age, and socioeconomic status on the survival rates in these patients. We extracted data on non-small cell lung cancer cases in each decade between 1983 and 2012 from the Surveillance, Epidemiology, and End Results registries. In total, 573,987 patients with non-small cell lung cancer were identified in 18 Surveillance, Epidemiology, and End Results registry regions during this period. The 12-month relative survival rates improved slightly across three decades, from 39.7% to 40.9% to 45.5%, with larger improvement in the last two decades. However, the 5-year-relative survival rates were very low, with 14.3%, 15.5%, and 18.4%, respectively, in three decades, indicating the urgency for novel comprehensive cancer care. In addition, our data demonstrated superiority in survival time among non-small cell lung cancer patients of lower socioeconomic status and White race. Although survival rates of non-small cell lung cancer patients have improved across the three decades, the 5-year-relative survival rates remain very poor. In addition, widening survival disparities among the race, the sex, and various socioeconomic

status groups were confirmed. This study will help in predicting future tendencies of incidence and survival of non-small cell lung cancer, will contribute to better clinical trials by balancing survival disparities, and will eventually improve the clinical management of non-small cell lung cancer.

[Menstrual and reproductive factors and lung cancer risk: A pooled analysis from the international lung cancer consortium.](#) Ben Khedher S1, Neri M1, Papadopoulos A2, et al. Int J Cancer. 2017 Jul 15;141(2):309-323. doi: 10.1002/ijc.30750. Epub 2017 May 10.

Many clinical features of lung cancer are different in women and men. Sex steroid hormones exert effects in nonreproductive organs, such as the lungs. The association between menstrual and childbearing factors and the risk of lung cancer among women is still debated. We performed a pooled analysis of eight studies contributing to the International Lung Cancer Consortium (4,386 cases and 4,177 controls). Pooled associations between menstrual or reproductive factors and lung cancer were estimated using multivariable unconditional logistic regression. Subgroup analyses were done for menopause status, smoking habits and histology. We found no strong support for an association of age at menarche and at menopause with lung cancer, but peri/postmenopausal women were at higher risk compared to premenopausal (OR 1.47, 95% CI 1.11-1.93). Premenopausal women showed increased risks associated with parity (OR 1.74, 95% CI 1.03-2.93) and number of children (OR 2.88, 95% CI 1.21-6.93 for more than 3 children; p for trend 0.01) and decreased with breastfeeding (OR 0.54, 95% CI 0.30-0.98). In contrast, peri/postmenopausal subjects had ORs around unity for the same exposures. No major effect modification was exerted by smoking status or cancer histology. Menstrual and reproductive factors may play a role in the genesis of lung cancer, yet the mechanisms are unclear, and smoking remains the most important modifiable risk factor. More investigations in large well-designed studies are needed to confirm these findings and to clarify the underlying mechanisms of gender differences in lung cancer risk. © 2017 UICC.

[Analysis of the Use and Impact of Twitter During American Society of Clinical Oncology Annual Meetings From 2011 to 2016: Focus on Advanced Metrics and User Trends.](#) Pemmaraju N1, Thompson MA1, Mesa RA1, Desai T1. J Oncol Pract. 2017 May 17:JOP2017021634. doi: 10.1200/JOP.2017.021634. [Epub ahead of print]

PURPOSE: The use of social media, in particular Twitter, has substantially increased among health care stakeholders in the field of hematology and oncology, with an especially sharp increase in the use of Twitter during times of major national meetings. The most attended meeting in the oncology field is the ASCO annual meeting. Little is known about the detailed metrics involved in the use, volume, and impact of Twitter during the ASCO annual meeting. **METHODS:** We conducted a retrospective review of tweets during the ASCO annual meetings from 2011 to 2016. The total data set encompassed 190,732 tweets from 39,745 authors over six consecutive ASCO meetings from 2011 to 2016 (inclusive). Tweets, all publically available, were collected by Nephrology On-Demand Analytics. **RESULTS:** The number of individual authors increased from 1,429 during the 2011 ASCO meeting to 15,796 during the 2016 ASCO meeting, an 11-fold increase over the total 5-year period. There was a notable increase in tweets from the 2011 ASCO meeting (n = 7,746) to the 2016 ASCO meeting (n = 72,698), a nine-fold increase during the study period. The most commonly tweeted term or topic changed over time, generally reflecting the breakthroughs of each designated year; these terms were "melanoma" for both the 2011 and 2012 ASCO meetings; "breast cancer" for the 2013 ASCO meeting; "lung cancer" for the 2014 ASCO meeting; and "ImmunOnc" or "immunotherapy/immuno-oncology" for both the 2015 and 2016 ASCO meetings. **CONCLUSION:** The use of Twitter among health care stakeholders during the ASCO meeting has markedly increased over time, demonstrating the increasing role of social media in the dissemination of findings at the most highly attended hematology and oncology conference of the year.

Current status of research and treatment for non-small cell lung cancer in never-smoking females.
Saito S1, Espinoza-Mercado F2, Liu H3, Sata N1, Cui X4, Soukiasian HJ2. Cancer Biol Ther. 2017 May 11:0. doi: 10.1080/15384047.2017.1323580. [Epub ahead of print]
Lung cancer is the leading cause of cancer-related deaths worldwide with over 1 million deaths each year. The overall prognosis of lung cancer patients remains unsatisfactory, with a 5-year overall survival rate of less than 15%. Although most lung cancers are a result of smoking, approximately 25% of lung cancer cases worldwide are not attributable to tobacco use. Notably, more than half of the lung cancer cases in women occur in non-smokers. Among non-small-cell lung cancer (NSCLC) cases, cigarette-smokers have a greater association with squamous cell carcinoma than adenocarcinoma, which is more common in non-smokers. These findings imply that specific molecular and pathological features may associate with lung adenocarcinoma arising in non-smoker female patients. Over the past decade, whole genome sequencing and other '-omics' technologies led to the discovery of pathogenic mutations that drive tumor cell formation. These technological developments may enable tailored patient treatments throughout the course of their disease, potentially leading to improved patient outcomes. Some clinical and laboratory studies have shown success outcomes using epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKI) in patients with EGFR mutations and ALK rearrangements, respectively. In fact, these two mutations are predominantly present in female non-smokers with adenocarcinoma. Immunotherapy has also recently emerged as a major therapeutic modality in NSCLC. In this review, we summarize the current understanding of NSCLC biology and new therapeutic molecular targets, focusing on the pathogenesis of non-smoker female NSCLC patients.

Ibuprofen and fatal lung cancer: A brief report of the prospective results from the Third National Health and Nutrition Examination Survey (NHANES III). Bittoni MA1,2, Carbone DP1,2, Harris RE1,3. Mol Clin Oncol. 2017 Jun;6(6):917-920. doi: 10.3892/mco.2017.1239. Epub 2017 May 5.
Chronic inflammation appears to increase the risk of lung cancer and, reciprocally, agents that reduce inflammation have been found to reduce this risk. However, few prospective studies have assessed whether there exists an association between lung cancer and the use of non-steroidal anti-inflammatory drugs (NSAIDs). In the present study, the association between fatal lung cancer and NSAIDs was investigated using cohort data from the Third National Health and Nutrition Examination Study (NHANES III). Baseline data were collected on smoking, NSAID use and other lifestyle factors for 10,735 participants during 1988-1994, with cause-specific mortality status ascertained through probabilistic record matching based on the National Death Index until 2006. Cox proportional hazards regression models were conducted to estimate hazard ratios (HRs) and confidence intervals (CIs) for NSAID use and death from lung cancer, controlling for current smoking and other covariates. During the 18 years of follow-up, 269 participants succumbed to lung cancer, of whom 252 (93.6%) reported a history of cigarette smoking. Since all but 17 of the 269 fatal lung cancer cases occurred among current or former smokers, estimates of NSAID effects were ascertained from a sub-cohort of 5,882 individuals who reported a history of past or current cigarette smoking. Multivariate regression models revealed that regular use of ibuprofen resulted in a 48% reduced risk of lung cancer mortality (HR=0.52, 95% CI: 0.33-0.82, P<0.01). The main effects of other compounds tested, such as aspirin or acetaminophen, were not statistically significant. Our results suggest that high-risk subgroups of smokers may benefit from the regular use of specific NSAIDs, which may prove to be a useful strategy for lung cancer prevention.

Clinical decisions surrounding genomic and proteomic testing among United States veterans treated for lung cancer within the Veterans Health Administration.
Efimova O1, Berse B2,3,4, Denhalter DW1,5, DuVall SL1,5, Filipski KK6, Icardi M7,8, Kelley MJ9,10, Lynch JA11,12,13,14. BMC Med Inform Decis Mak. 2017 May 30;17(1):71. doi: 10.1186/s12911-017-0475-8.

BACKGROUND: Current clinical guidelines recommend epidermal growth factor receptor (EGFR) mutational testing in patients with metastatic non-small cell lung cancer (NSCLC) to predict the benefit of the tyrosine kinase inhibitor erlotinib as first-line treatment. Proteomic (VeriStrat) testing is recommended for patients with EGFR negative or unknown status when erlotinib is being considered. Departure from this clinical algorithm can increase costs and may result in worse outcomes. We examined EGFR and proteomic testing among patients with NSCLC within the Department of Veterans Affairs (VA). We explored adherence to guidelines and the impact of test results on treatment decisions and cost of care. **METHODS:** Proteomic and EGFR test results from 2013 to 2015 were merged with VA electronic health records and pharmacy data. Chart reviews were conducted. Cases were categorized based on the appropriateness of testing and treatment. **RESULTS:** Of the 69 patients with NSCLC who underwent proteomic testing, 33 (48%) were EGFR-negative and 36 (52%) did not have documented EGFR status. We analyzed 138 clinical decisions surrounding EGFR/proteomic testing and erlotinib treatment. Most decisions (105, or 76%) were concordant with clinical practice guidelines. However, for 24 (17%) decisions documentation of testing or justification of treatment was inadequate, and 9 (7%) decisions represented clear departures from guidelines. **CONCLUSION:** EGFR testing, the least expensive clinical intervention analyzed in this study, was significantly underutilized or undocumented. The records of more than half of the patients lacked information on EGFR status. Our analysis illustrated several clinical scenarios where the timing of proteomic testing and erlotinib diverged from the recommended algorithm, resulting in excessive costs of care with no documented improvements in health outcomes.

[**Decreasing Smoking but Increasing Stigma? Anti-tobacco Campaigns, Public Health, and Cancer Care.**](#) Riley KE1, Ulrich MR2, Hamann HA3, Ostroff JS4. AMA J Ethics. 2017 May 1;19(5):475-485. doi: 10.1001/journalofethics.2017.19.5.msoc1-1705.
Public health researchers, mental health clinicians, philosophers, and medical ethicists have questioned whether the public health benefits of large-scale anti-tobacco campaigns are justified in light of the potential for exacerbating stigma toward patients diagnosed with lung cancer. Although there is strong evidence for the public health benefits of anti-tobacco campaigns, there is a growing appreciation for the need to better attend to the unintended consequence of lung cancer stigma. We argue that there is an ethical burden for creators of public health campaigns to consider lung cancer stigma in the development and dissemination of hard-hitting anti-tobacco campaigns. We also contend that health care professionals have an ethical responsibility to try to mitigate stigmatizing messages of public health campaigns with empathic patient-clinician communication during clinical encounters.