Caring Ambassadors Lung Cancer Program
Literature Review, December 2018

Basic and Applied Science, Pre-Clinical Studies

Tumor-derived exosomal proteins as diagnostic biomarkers in non-small cell lung cancer. Niu L1,2, Song X3, Wang N4, Xue L2, Song X2, Xie L2. Cancer Sci. 2019 Jan;110(1):433-442. doi: 10.1111/cas.13862. Epub 2018 Dec 6.

Accumulating evidence supports a role for exosomal protein in diagnosis. The purpose of this study was to identify the tumor-derived exosomal biomarkers in the serum that improve the diagnostic value in Chinese non-small cell lung cancer (NSCLC) patients. Serum exosomes were isolated from healthy donors (n = 46) and NSCLC patients (n = 125) by ultracentrifugation and were characterized using transmission electron microscopy, qNano, and immunoblotting. Proteomic profiles (by mass spectrometry) revealed multiple differentially expressed proteins in the healthy and NSCLC groups. The exosomal expression levels of alpha-2-HS-glycoprotein (AHSG) and extracellular matrix protein 1 (ECM1) increased significantly in the NSCLC patients compared to the healthy group. Alpha-2-HS-glycoprotein showed diagnostic values with a maximum area under the receiver operating characteristic curve (AUC) as 0.736 for NSCLC vs healthy individuals ($P < .0001$) and 0.682 for early stage NSCLC vs healthy individuals ($P < .01$). Extracellular matrix protein 1 showed the diagnostic capacity with AUC values of 0.683 ($P < .001$) and 0.656 ($P < .05$) in cancer and early stage NSCLC compared to healthy individuals. When AHSG was combined with ECM1, the AUCs were 0.795 and 0.739 in NSCLC and early stage patients, respectively. Taken together, the combination of AHSG, ECM1, and carcinoembryonic antigen improved the diagnostic potential of NSCLC. The diagnosis values were AUC of 0.938 for NSCLC and 0.911 for early stage NSCLC vs healthy individuals. Our results suggest that novel proteomic signatures found in serum exosomes of NSCLC patients show potential usefulness as diagnostic tools.

DCUN1D1 facilitates tumor metastasis by activating FAK signaling and up-regulates PD-L1 in non-small-cell lung cancer. Li J1, Yu T1, Yan M1, Zhang X1, Liao L2, Zhu M1, Lin H1, Pan H3, Yao M4. Exp Cell Res. 2019 Jan 15;374(2):304-314. doi: 10.1016/j.yexcr.2018.12.001. Epub 2018 Dec 4.
E3 ubiquitin ligases, which are key enzymes in the ubiquitin proteasome system, catalyze the ubiquitination of proteins to target them for proteasomal degradation. Emerging evidence suggests that E3 ubiquitin ligases play important roles in the development and progression of lung cancer. In our study, we characterized the gene expression landscape of lung cancer using data obtained from TCGA to explore the changes in E3 ubiquitin ligase containing the regulators of E3 ubiquitin ligase activity. Overall, most gene expression changes occurred in NSCLC tissues compared with adjacent normal ones. In total, 48 E3 ubiquitin ligases containing the regulators were up-regulated in NSCLC tissues compared with their levels in normal tissues. We analyzed the expression of up-regulated E3 ubiquitin ligases containing the regulators in two publicly available transcriptome data sets (GSE13213 and GSE30219). We found that four E3 ubiquitin ligases (UHRF1, BRCA1, TRAIP and HLTF) and one regulator of ubiquitin E3 activity DCUN1D1 that were dramatically up-regulated in cancer were significantly associated with tumor metastasis and patient's poor prognosis both in two transcriptome data sets. Next, clinical analysis indicated that the expression levels of DCUN1D1 correlated with clinical stage and lymph node metastasis in NSCLC patients as determined by quantitative reverse transcription-PCR. Furthermore, functional assays showed that DCUN1D1 promoted NSCLC cell invasion and migration as determined by transwell assay in vitro. Mechanistically, we found that the C-terminal Cullin binding domain leads to oncogenic activity and the UBA domain acts as a negative regulator of DCUN1D1 function in NSCLC. Moreover, DCUN1D1 activated the FAK oncogenic signaling pathway and up-regulated PD-L1. Taken together, our results demonstrate that DCUN1D1 is a metastasis regulator and suggest a new therapeutic option for NSCLC metastasis.

CircPUM1 promotes the malignant behavior of lung adenocarcinoma by regulating miR-326. Chen J1, Xu S2, Chen S3, Zong Z4, Han X1, Zhao Y3, Shang H5. Biochem Biophys Res Commun. 2019 Jan 15;508(3):844-849. doi: 10.1016/j.bbrc.2018.11.176. Epub 2018 Dec 7.
CircRNAs are reported to be implicated in the development of lung cancer. This study focused on assessing the expression, functions and molecular mechanism of circPUM1 in lung adenocarcinoma. Here, it showed that circPUM1 is significantly upregulated in both lung adenocarcinoma cell lines and tissues. Furthermore, silencing of circPUM1 impaired the proliferation, migration and invasion ability, and increased apoptosis in A549 cells. Nevertheless, overexpression of circPUM1 in SPC-A1 cells has the opposite effect. Silencing of circPUM1 inhibits the tumorigenesis in nude mice. Mechanistically, circPUM1 could sponge miR-326 and promote the expression of its downstream proteins Cyclin D1 and Bcl-2. In summary, this present study revealed that circPUM1 functions as an oncogene to promote the tumorigenesis of lung adenocarcinoma through circPUM1/miR-326/Cyclin D1 and Bcl-2 axis. This indicates that circPUM1 may act as a potential therapeutic target for lung adenocarcinoma.

PGAM5 expression and macrophage signatures in non-small cell lung cancer associated with chronic obstructive pulmonary disease (COPD). Ng Kee Kwong F1,2,3, Nicholson AG4,5, Pavlidis S4, Adcock IM4, Chung KF4. BMC Cancer. 2018 Dec 10;18(1):1238. doi: 10.1186/s12885-018-5140-9.
BACKGROUND: COPD patients are at increased risk of developing non-small cell lung carcinoma that has a worse prognosis. Oxidative stress contributes to carcinogenesis and is increased in COPD patients due to mitochondrial dysfunction. We determined whether mitochondrial dysfunction is a contributing factor to the reduced survival of COPD patients with non-small cell lung carcinoma (NSCLC).
METHODS: Using a transcriptomic database and outcome data of 3553 NSCLC samples, we selected mitochondrial-related genes whose levels in the tumour correlated with patient mortality. We further selected those genes showing a ≥ 2 fold expression in cancer compared to normal tissue. Cell-type specific

expression of these proteins in lung tissue from NSCLC patients who were non-smokers or smokers with or without COPD (healthy smokers) was determined by immunohistochemistry. Gene set variation analysis was used in additional NSCLC datasets to determine the relative expression of specific macrophage transcriptomic signatures within lung cancer tissue. **RESULTS:** The expression of 14 mitochondrial-related genes was correlated with patient mortality and these were differentially expressed between cancer and normal lung tissue. We studied further the expression of one of these genes, PGAM5 which is a regulator of mitochondrial degradation by mitophagy. In background lung tissue, PGAM5 was only expressed in alveolar macrophages, with the highest expression in smokers with COPD compared to healthy smokers and non-smokers. In cancerous tissue, only the malignant epithelial cells and associated macrophages at the periphery of the cancer expressed PGAM5. Pre-neoplastic epithelium also showed the expression of PGAM5. There was no difference in expression in cancer tissue between COPD, healthy smoker and non-smoker groups. Macrophages at the edge of the cancer from COPD patients showed a trend towards higher expression of PGAM5 compared to those from the other groups. There was a significant correlation between PGAM5 expression in cancer tissue and the level of expression of 9 out of 49 previously-defined macrophage transcriptomic signatures with a particular one associated with patient mortality ($p < 0.05$). **CONCLUSION:** PGAM5 is expressed in pre-neoplastic tissue and NSCLC, but not in normal epithelium. The association between PGAM5 expression and patient mortality may be mediated through the induction of specific macrophage phenotypes.

The genomic alterations of lung adenocarcinoma and lung squamous cell carcinoma can explain the differences of their overall survival rates. Meng F1, Zhang L1, Ren Y1, Ma Q1. J Cell Physiol. 2018 Dec 13. doi: 10.1002/jcp.27917. [Epub ahead of print]
In the US, lung carcinoma accounted for over 150,000 deaths in 2018 and the advances in increasing survival rates are still limited. In this study, we investigated the cohorts with lung adenocarcinoma (LUAD) or lung squamous cell carcinoma (LUSC) from The Cancer Genome Atlas to figure out the risk factors and genomic alterations that affected their prognosis. The histoclinical factors that differed between LUAD and LUSC were identified and the risk factors affecting the overall survival were figured out for both LUAD and LUSC. Next, the patterns of nucleotides substitutions and the mutational signatures were extracted to illustrate whether different mutational processes performed for them. Finally, the genes that had different frequencies of mutation were identified. LUAD and LUSC presented differences in histoclinical factors including age at the time of diagnosis, sex, smoking history, pathological T classification, and overall survival. This was caused by the distinct genomic alterations including the transition-to-transversion ratios, mutational signatures, and the frequently mutated genes. We proposed that the mutational signature associated with aging could be used to predict the prognosis of patients with LUAD. On the other hand, the AID/APOBEC family was associated with the prognosis of LUSC. Finally, SNTG1 and LRRK2 might be important in LUAD and LUSC, respectively.

SCREENING, DIAGNOSIS AND STAGING

Impact of low-dose computed tomography screening on lung cancer mortality among asbestos-exposed workers. Barbone F1,2, Barbiero F1,3, Belvedere O4, et al. Int J Epidemiol. 2018 Dec 1;47(6):1981-1991. doi: 10.1093/ije/dyy212.
BACKGROUND: We previously showed that low-dose computed tomography (LDCT) screening in asbestos-exposed workers is effective in detecting lung cancer (LC) at an early stage. Here, we evaluate whether LDCT screening could reduce mortality from LC in such a high-risk population. **METHODS:** Within a cohort of 2433 asbestos-exposed men enrolled in an Occupational Health surveillance programme, we compared mortality between the participants in the ATOM002 study (LDCT-P, N = 926)

and contemporary non-participants (LDCT-NP, N = 1507). We estimated standardized mortality ratios for the LDCT-P and LDCT-NP populations using regional and national rates (SMR_FVG and SMR_ITA, respectively). We compared survival for all causes, all neoplasms, LC and malignant neoplasm of pleura (MNP) between LDCT-P and LDCT-NP using Cox proportional hazard models adjusted for age, smoking history, asbestos exposure level and comorbidities. **RESULTS:** A reduction in mortality from LC was observed in the LDCT-P group compared with regional and national figures (SMR_FVG = 0.55, 95% confidence interval (CI) 0.24-1.09; SMR_ITA = 0.51, 95% CI 0.22-1.01); this was not the case for the LDCT-NP group (SMR_FVG = 2.07, 95% CI 1.53-2.73; SMR_ITA = 1.98, 95% CI 1.47-2.61). A strong reduction in LC mortality was observed for the LDCT-P compared with the LDCT-NP [hazard ratio (HR) = 0.41, 95% CI 0.17-0.96]. Mortality was also reduced for all causes (HR = 0.61, 95% CI 0.44-0.84), but not for all neoplasms (HR = 0.97, 95% CI 0.62-1.50) and MNP (HR = 0.86, 95% CI 0.31-2.41) within the LDCT-P population. **CONCLUSIONS:** In our cohort, participation in the LDCT screening study was associated with reduced mortality from LC. This finding supports the use of LDCT in surveillance programmes for asbestos-exposed workers.

Liquid Biopsy and Lung Cancer. Pisapia P, Malapelle U, Troncone G. Acta Cytol. 2018 Dec 19:1-8. doi: 10.1159/000492710. [Epub ahead of print]
The identification of non-small cell lung cancer (NSCLC) patients potentially responsive to targeted therapies relies on a number of relevant biomarkers, including EGFR, ALK, ROS-1, and PD-L1. Biomarker identification is most commonly based on surgical sample collection. However, when tissues are difficult to reach or when multiple analyses are necessary to monitor tumor progression and treatment response, liquid biopsy is a valid noninvasive alternative. This analysis, which is preferentially performed on circulating tumor DNA (ctDNA) extracted from plasma samples, has the major advantage of reducing the inherent risks and discomfort of tissue biopsy. However, a major disadvantage is that it yields only a low number of ctDNA targets. Thus, to avoid false-positive and false-negative results, it is important to adopt and validate technologies with high sensitivity and specificity in the pre-analytical phase of sampling. This review succinctly addresses the principal methodologies for analyzing plasma-derived ctDNA in NSCLC patients.

Tumor mutational burden in non-small cell lung cancer-the pathologist's point of view. Penault-Llorca F1, Radosevic-Robin N1. Transl Lung Cancer Res. 2018 Dec;7(6):716-721. doi: 10.21037/tlcr.2018.09.26.
In non-small cell lung cancer (NSCLC), the pathologist has contributed to the development of personalized medicine from the determination of the right histological type to EGFR and ALK/ROS1 molecular screening for targeted therapies. With the development of immunotherapies, pathologists intervene forefront with programmed death-ligand 1 (PD-L1) immunohistochemical testing, companion test for pembrolizumab monotherapy, first line and complementary test to the other programmed cell death-1 (PD-1) PD-L1 inhibitors. Recently, tumor mutational burden has emerged as a promising tool to evaluate sensitivity to immunotherapy (IO). The pathologist has a crucial role in the setting of tumor mutational burden (TMB) testing for the selection and the preparation of the sample for high throughput molecular analysis, and in the first steps of the next-generation sequencing (NGS) workflow.

Implementing tumor mutational burden (TMB) analysis in routine diagnostics-a primer for molecular pathologists and clinicians. Allgäuer M1, Budczies J1,2, Christopoulos P3,4, Transl Lung Cancer Res. 2018 Dec;7(6):703-715. doi: 10.21037/tlcr.2018.08.14.
Tumor mutational burden (TMB) is a new biomarker for prediction of response to PD-(L)1 treatment. Comprehensive sequencing approaches (i.e., whole exome and whole genome sequencing) are ideally suited to measure TMB directly. However, as their applicability in routine diagnostics is currently limited

by high costs, long turnaround times and poor availability of fresh tissue, targeted next-generation sequencing (NGS) of formalin-fixed and paraffin-embedded (FFPE) samples appears to be a more feasible and straight-forward approach for TMB approximation, which can be seamlessly integrated in already existing diagnostic workflows and pipelines. In this work, we provide an overview of the clinical implications of TMB testing and highlight key parameters including pre-analysis, analysis and post-analytical steps that influence and shape TMB approximation by panel sequencing. Collectively, the data will not only serve as a field guide and state of the art knowledge source for molecular pathologists who consider implementation of TMB measurement in their lab, but also enable clinicians in understanding the specific parameters influencing TMB test results and reporting.

Demographic, Social, and Behavioral Determinants of Lung Cancer Perceived Risk and Worries in a National Sample of American Adults; Does Lung Cancer Risk Matter? Chalian H1, Khoshpouri P2, Assari S3,4. Medicina (Kaunas). 2018 Dec 3;54(6). pii: E97. doi: 10.3390/medicina54060097.
BACKGROUND: Perceived risk and worries of developing cancer are important constructs for cancer prevention. Many studies have investigated the relationship between health behaviors and subjective risk perception. However, factors correlated with lung cancer risk perception and worries in individuals more susceptible to lung cancer have rarely been investigated. Objective: To determine demographic, social, and behavioral determinants of cancer perceived risk and worries and to explore heterogeneities in these associations by the level of lung cancer risk in a nationally representative sample of American adults. **METHODS:** For this cross-sectional study, data came from the Health Information National Trends Survey (HINTS) 2017, which included a 2277 representative sample of American adults. Smoking status, cancer perceived risk, cancer worries, age, gender, race, education, income, and insurance status were measured. We ran structural equation models (SEMs) for data analysis. **RESULTS:** "Ever smoker" status was associated with higher cancer perceived risk ($b = 0.25$; 95% CI = 0.05–0.44, $p = 0.013$) and worries ($b = 0.34$, 95% CI = 0.18–0.50, $p < 0.001$), suggesting that "ever smokers" experience higher levels of cancer perceived risk and worries regarding cancer, compared to "never smokers". Other factors that correlate with cancer perceived risk and worries were race, age, income, and insurance status. Blacks demonstrated less cancer perceived risk and worry ($b = -0.98$, 95% CI = -1.37–0.60, $p < 0.001$) in both low and high risk lung cancer groups. However, the effects of social determinants (income and insurance status) and age were observed in low but not high risk group. **CONCLUSIONS:** Determinants of cancer perceived risk and worries vary in individuals depending on the level of lung cancer risk. These differences should be considered in clinical practice and policy makings with the goal of improving participation rates in lung cancer screening programs.

Molecular Testing in EBUS-TBNA Specimens of Lung Adenocarcinoma: A Study of Concordance Between Cell Block Method and Liquid-Based Cytology in Appraising Sample Cellularity and EGFR Mutations. Magnini D1, Fuso L2, Varone F2, et al. Mol Diagn Ther. 2018 Dec;22(6):723-728. doi: 10.1007/s40291-018-0359-3.
PURPOSE: Cytological endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) specimens of mediastinal lymph node metastasis are frequently used to perform concomitant diagnosis, staging and genetic testing in non-small-cell lung cancer (NSCLC). The purposes of this single-center retrospective study were to evaluate EBUS-TBNA samples' adequacy for molecular testing of epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK), and to analyze the concordance between the cell block method and liquid-based cytology (LBC) in appraising the sample cellularity and in detecting EGFR mutation. **MATERIALS AND METHODS:** We retrospectively examined 82 patients who underwent EBUS-TBNA from October 2012 to September 2015 and received a confirmed diagnosis of lymph node metastasis of lung adenocarcinoma. Each sample was processed using both cell block and LBC to carry out DNA analysis (adequacy criterion: tumor cell percentage > 25%)

and EGFR mutation testing. **RESULTS:** Fifty-four patients were male, 66 were current or former-smokers, and the median age was 67 years. The median size of sampled lymph nodes was 14.8 mm. Seventy-one and 66 samples were adequate to perform cell block and LBC, respectively. The κ-statistic (0.78) showed an excellent concordance. EGFR mutation was detected in eight patients using cell block and in seven using LBC, with a simple percentage agreement of 87.5%. ALK translocation was found in two patients. **CONCLUSIONS:** This study demonstrates the feasibility of EGFR mutation analysis with both cell block and LBC, with an excellent concordance between the two methods. Considering that the majority of advanced NSCLCs are diagnosed on cytology specimens, LBC is feasible and needs to be implemented for ancillary tests (immunocytochemistry, molecular analysis).

CT screening for lung cancer: comparison of three baseline screening protocols. Henschke CI1,2,3, Yip R4, Ma T4,5, Aguayo SM6, Zulueta J7, Yankelevitz DF4; Writing Committee for the I-ELCAP Investigators. Eur Radiol. 2018 Dec 3. doi: 10.1007/s00330-018-5857-5. [Epub ahead of print]
PURPOSE: Clinical management decisions arising from the baseline round for lung cancer screening are the most challenging, as findings have accumulated over a lifetime and may be of no clinical concern. To minimize unnecessary harms and costs of workup prior to the first, annual repeat screening, workup should be limited to participants with the highest suspicion of lung cancer while still aiming to identify small, early lung cancers. **METHODS:** We compared recommendations for immediate, delayed (by 3 or 6 months) workup to assess growth at a malignant rate, and the resulting overall and potential biopsies of three baseline screening protocols: I-ELCAP, the two scenarios of ACR-LungRADS, and the European Consortium. For each protocol, the efficiency ratio (ER) of each recommendation was calculated by dividing the number of participants recommended for that workup by the number of resulting lung cancer diagnoses. The ER for potential biopsies was calculated, assuming that biopsies were performed on all participants recommended for immediate workup as well as those diagnosed with lung cancer after delayed workup. **RESULTS:** For I-ELCAP, ACR-LungRADS Scenario 1, ACR-LungRADS Scenario 2, and the European consortium, the overall ER was 13.9, 18.3, 18.3, and 31.9, respectively, and for potential biopsies, it was 2.2, 8.1, 3.2, and 4.4, respectively. ER for immediate workup was 2.9, 8.6, 3.9, and 5.6, respectively, and for delayed workup was 36.1, 160.3, 57.8, and 111.9, respectively.
CONCLUSIONS: I-ELCAP recommendations had the lowest ER values for overall, immediate, and delayed workup, and for potential biopsies. **KEY POINTS:** • Small differences in protocol thresholds can lead to many unnecessary diagnostic workups. • I-ELCAP recommendations were the most efficient for immediate and overall workup, and potential biopsies. • Definition of a "positive result" and recommendations for further workup in the baseline round needs to be continually reevaluated and updated.

Lung cancer screening: assessment of health literacy and readability of online educational resources. Haas K1, Brillante C2, Sharp L3, Elzokaky AK2, et al. BMC Public Health. 2018 Dec 7;18(1):1356. doi: 10.1186/s12889-018-6278-8.
BACKGROUND: Lung cancer screening can reduce mortality but can be a complex, multi-step process. Poor health literacy is associated with unfavorable outcomes and decreased use of preventative services, so it is important to address barriers to care through efficient and practical education. The readability of lung cancer screening materials for patients is unknown and may not be at the recommended 6th grade reading level set by the American Medical Association. Our goals were to: (1) measure the health literacy of a lung cancer screening population from an urban academic medical center, and (2) examine the readability of online educational materials for lung cancer screening. **METHODS:** We performed a retrospective cross sectional study at a single urban academic center. Health literacy was assessed using three validated screening questions. To assess the readability of educational materials, we performed a Google search using the phrase, "What is lung cancer screening?" and the Flesch-Kincaid Grade Level

(FKGL) formula was used to estimate the grade level required to understand the text. **RESULTS:** There were 404 patients who underwent lung cancer screening during the study period. The prevalence of inadequate/marginal health literacy was 26.7-38.0%. Fifty websites were reviewed and four were excluded from analysis because they were intended for medical providers. The mean FKGL for the 46 websites combined was 10.6 ± 2.2. **CONCLUSIONS:** Low health literacy was common and is likely a barrier to appropriate education for lung cancer screening. The current online educational materials regarding lung cancer screening are written above the recommended reading level set by the American Medical Association.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

Long-term outcomes of video-assisted thoracoscopic surgery lobectomy vs. thoracotomy lobectomy for stage IA non-small cell lung cancer. Oda R1, Okuda K2, Osaga S3, Watanabe T1, Sakane T1, Tatematsu T1, Yokota K1, Haneda H1, Nakanishi R1. Surg Today. 2018 Dec 3. doi: 10.1007/s00595-018-1746-4. [Epub ahead of print]

OBJECTIVES: Video-assisted thoracoscopic surgery (VATS) lobectomy is performed widely for patients with clinical stage I non-small cell lung cancer (NSCLC) because of its superior short-term outcomes to those of thoracotomy lobectomy. However, the long-term outcomes of VATS lobectomy vs. thoracotomy lobectomy remain controversial. **METHODS:** We reviewed the clinical data of 202 consecutive patients who underwent lobectomy for clinical stage IA NSCLC at our institution between January, 2008 and December, 2013. Stage IA NSCLC was confirmed pathologically in 162 of these patients, 60 of whom underwent VATS lobectomy and 102 of whom underwent thoracotomy lobectomy. We compared the perioperative clinical factors and outcomes of these two groups, using a propensity score-matched analysis. **RESULTS:** In an analysis of 58 matched cases, the VATS group showed less blood loss, a shorter duration of chest tube placement, a shorter postoperative hospital stay, and a lower peak C-reactive protein value, despite a longer operative time. The VATS group also had significantly longer survival than the thoracotomy group [5-year overall survival, 100% vs. 87%, respectively ($p = 0.01$); 5-year disease-free survival, 100% vs. 86% ($p = 0.03$)]. **CONCLUSIONS:** These findings suggest that VATS may have better long-term as well as short-term outcomes than thoracotomy for patients with early-stage NSCLC.

Long-term survival in patients with advanced non-small-cell lung cancer treated with atezolizumab versus docetaxel: Results from the randomised phase III OAK study. von Pawel J1, Bordoni R2, Satouchi M3, et al. Eur J Cancer. 2019 Jan;107:124-132. doi: 10.1016/j.ejca.2018.11.020. Epub 2018 Dec 17.

BACKGROUND: Atezolizumab (anti-programmed death-ligand 1 [PD-L1]) received approval from the US Food and Drug Administration and European Medicines Agency for previously treated advanced non-small-cell lung cancer based on OAK-a randomised, phase III trial that showed significantly improved survival with atezolizumab versus docetaxel regardless of PD-L1 expression. With longer follow-up, we summarised the characteristics of long-term survivors (LTSs). **METHODS:** In OAK (NCT02008227), patients were randomised 1:1 to receive atezolizumab or docetaxel until loss of clinical benefit or disease progression, respectively. Overall survival was evaluated after a 26-month minimum follow-up, including in patient subgroups defined by best overall response (BOR). LTSs were defined as patients who lived ≥24 months since randomisation. Non-LTSs died within 24 months, and patients censored before 24 months were excluded from the analysis. The baseline characteristics, including biomarkers, BOR,

subsequent non-protocol therapy (NPT) and safety, are reported. **RESULTS:** Survival benefit with atezolizumab was observed across all patient subgroups defined by BOR. More atezolizumab-treated patients were LTSs versus those treated with docetaxel (28% versus 18%). Most atezolizumab responders were LTSs (77%) versus only 48% of docetaxel responders. However, 21% of atezolizumab-arm LTSs had progressive disease (PD) as BOR, and more atezolizumab-arm LTSs than non-LTSs continued treatment post-PD. Fifty-two percent of docetaxel-arm LTSs received immunotherapy as subsequent NPT. Despite extended treatment duration in atezolizumab-arm LTSs (median, 18 months), atezolizumab was well tolerated. **CONCLUSIONS:** After >2 years of follow-up, atezolizumab continued to provide durable survival benefit versus docetaxel, with tolerable safety. Atezolizumab-arm LTSs were enriched for patients with high PD-L1 expression and included PD-L1-negative patients. Long-term survival was not limited to responders.

Prognostic Factors of Pathological N1 Non-small Cell Lung Cancer After Curative Resection Without Adjuvant Chemotherapy. Moon Y1, Sung SW2, Park JK2, Lee KY3, Ahn S2. World J Surg. 2018 Dec 7. doi: 10.1007/s00268-018-04875-y. [Epub ahead of print]
BACKGROUND: The aim of this study was to evaluate the outcomes of patients with pathological N1 non-small cell lung cancer who did not receive adjuvant chemotherapy. We attempted to identify those patients for whom adjuvant chemotherapy would be indispensable. **METHODS:** Among 132 patients who were diagnosed with pathological N1 lung cancer at a single institution from January 2010 to December 2016 were 32 patients who did not receive adjuvant treatment after curative surgical resection. The surgical and oncological outcomes of these patients were analyzed. Candidate factors for predicting recurrence were analyzed to identify patients at high risk of recurrence. **RESULTS:** The median follow-up time for all 32 patients was 1044 days. The 5-year recurrence-free survival (RFS) and disease-specific survival rates of the patients without adjuvant therapy were 50.3% and 77.6%, respectively. By multivariate analysis, tumors with a lepidic growth pattern [hazard ratio (HR) 0.119, $p = 0.024$] and extralobar lymph node metastasis (HR 6.848, $p = 0.015$) were significant factors predicting recurrence. The difference between the 5-year RFS rates of patients with tumors with or without a lepidic growth pattern was statistically significant (63.5% vs 40.0%, respectively; $p = 0.050$). The 5-year RFS rates of patients with intralobar lymph node metastasis versus those with extralobar lymph node metastasis were 63.3% and 18.8%, respectively ($p = 0.002$). **CONCLUSIONS:** Patients with tumors without a lepidic growth pattern or with extralobar lymph node metastasis who do not receive adjuvant chemotherapy have a high recurrence rate after surgery. Therefore, these patients should be encouraged to undergo adjuvant chemotherapy if their overall condition is not a contraindication for chemotherapy.

Surgical Outcomes of Complex versus Simple Segmentectomy for Stage I Non-Small Cell Lung Cancer. Handa Y1, Tsutani Y1, Mimae T1, Tasaki T1, Miyata Y1, Okada M2. Ann Thorac Surg. 2018 Dec 11. pii: S0003-4975(18)31801-0. doi: 10.1016/j.athoracsur.2018.11.018. [Epub ahead of print]
BACKGROUND: As segmentectomy becomes widely used for lung cancer treatment, "complex segmentectomy," which makes several, intricate intersegmental planes, remains controversial because of procedural complexity and risk of increased complications and incurability. Questions remain regarding mortality, morbidity, surgical margin, lymph nodes dissection, and postoperative pulmonary function. We evaluated operative and postoperative outcomes of complex compared to simple segmentectomy. **METHODS:** We retrospectively reviewed clinical stage I lung cancer patients who could tolerate lobectomy and underwent complex or simple segmentectomy between April 2007 and March 2017. Clinicopathologic, operative, and postoperative results of the complex ($n = 117$) and simple ($n = 92$) segmentectomy groups were compared. **RESULTS:** No significant differences were detected in age, sex, comorbidities, preoperative pulmonary function, tumor histology, and size. Although only median operative time (180 vs. 143.5 minutes; $P < 0.0001$) was significantly longer in the complex group, 30-day

mortality (0% vs. 0%), overall complications (24.8% vs. 22.8%), and prolonged air leakage (11.9% vs. 10.9%) were nearly equivalent between the two groups, respectively. The complex group showed comparable results in median surgical margin distance (16.0 vs. 17.5 mm) and number of dissected lymph nodes (6.0 vs. 7.0 nodes). Margin relapse occurred in two patients in the simple group but none occurred in the complex group. Both groups also showed similar postoperative pulmonary functions. **CONCLUSIONS:** Complex segmentectomy is a safe option in the treatment of lung cancers with adequate operative outcomes.

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

Low Baseline Serum Sodium Concentration Is Associated with Poor Clinical Outcomes in Metastatic Non-Small Cell Lung Cancer Patients Treated with Immunotherapy. Fucà G1, Galli G2, Poggi M2, et al. Target Oncol. 2018 Dec;13(6):795-800. doi: 10.1007/s11523-018-0599-5.
BACKGROUND: A consistent percentage of patients with metastatic non-small cell lung cancer (NSCLC) derives no or only marginal benefit from immunotherapy (IO). **OBJECTIVE:** Since serum sodium has been linked to both prognosis in NSCLC and modulation of immune cells activity, we aimed to assess the association between low baseline serum sodium concentration (≤ 135 mEq/L) and clinical outcomes of patients with metastatic NSCLC treated with IO. **PATIENTS AND METHODS:** We included metastatic NSCLC patients treated with checkpoint inhibitors in our department from April 2013 to April 2018 with available baseline serum sodium concentration. Demographics, clinical and pathological characteristics were collected. Survival analyses were performed using the Kaplan-Meier method and the Cox proportional-hazards model. **RESULTS:** Of 197 patients included, 26 (13%) presented low baseline serum sodium concentration. Patients in the low sodium cohort experienced a poorer disease control rate (OR 0.36; 95% CI, 0.15-0.86; Wald test P = .02), median overall survival (OS) (2.8 vs. 11.6 months; HR 3.00; 95% CI, 1.80-4.80; P < .001) and progression-free survival (PFS) (1.8 vs. 3.3 months; HR 2.60; 95% CI, 1.70-3.90; P < .001) compared to patients in the control cohort. At multivariate analyses, low baseline serum sodium concentration was independently associated with disease control and OS, but not with PFS. **CONCLUSIONS:** Our study showed for the first time that low baseline serum sodium concentration is associated with impaired clinical outcomes in patients with metastatic NSCLC treated with IO. The role of serum sodium concentration in this setting warrants further pre-clinical and clinical investigation.

Value of adjuvant chemotherapy in patients with resected stage IB solid predominant and solid non-predominant lung adenocarcinoma. Cao S1, Teng J1, Xu J1, Han B1, Zhong H1. Thorac Cancer. 2018 Dec 18. doi: 10.1111/1759-7714.12942. [Epub ahead of print]
BACKGROUND: The use of adjuvant chemotherapy (ACT) for stage IB lung adenocarcinoma remains controversial. We examined the benefits of ACT in stage IB patients with tumors composed of solid material. **METHODS:** The records of 309 patients with stage IB lung adenocarcinoma who had undergone complete resection between 2006 and 2015 were reviewed. All pathological slides were evaluated for the composition of solid material. **RESULTS:** Our data showed that although disease-free survival (DFS) and overall survival (OS) were not significantly different (P = 0.306 and P = 0.061, respectively) between patients displaying a solid pattern of tumor growth and treated with or without ACT, patients with a solid predominant pattern of tumor growth treated with ACT had longer DFS (hazard ratio 0.359; P = 0.033) and OS (hazard ratio 0.205; P = 0.003). In patients with solid non-predominant patterns, treatment with ACT had no effect on DFS (P = 0.326) or OS (P = 0.508). **CONCLUSIONS:** Postoperative patients with the solid predominant pattern of stage IB lung adenocarcinoma may benefit from ACT, while those with the solid non-predominant pattern will not.

Biomarkers in lung cancer screening: achievements, promises and challenges. Seijo LM1, Peled N2, Ajona D3, et al. J Thorac Oncol. 2018 Dec 4. pii: S1556-0864(18)33501-9. doi: 10.1016/j.jtho.2018.11.023. [Epub ahead of print]
The present review is an update of the research and development efforts regarding the use of molecular biomarkers in the lung cancer screening setting. The two main unmet clinical needs, namely, the refinement of risk in order to improve the selection of individuals undergoing screening and the characterization of undetermined nodules found during the CT-based screening process are the object of the biomarkers described in the present review. We first propose some principles to optimize lung cancer biomarker discovery projects. Then, we summarize the discovery and developmental status of currently promising molecular candidates such as autoantibodies, complement fragments, miRNAs, circulating tumor DNA, DNA methylation, blood protein profiling, or RNA airway or nasal signatures. We also mention other emerging biomarkers or new technologies to follow such as exhaled breath biomarkers, metabolomics, sputum cell imaging, genetic predisposition studies or the integration of NGS in circulating DNA. We also underline the importance of integrating different molecular technologies together with imaging, radiomics and artificial intelligence. We list a number of completed ongoing or planned trials to show clinical utility of molecular biomarkers. Finally, we comment on the future research challenges in the field of biomarkers in the context of lung cancer screening and propose a design of a trial to test clinical utility of one or several biomarker candidates.

Different mutational characteristics of the subsets of EGFR-tyrosine kinase inhibitor sensitizing mutation-positive lung adenocarcinoma. Kim EY1, Kim A1, Lee G2, Lee H2, Chang YS3. BMC Cancer. 2018 Dec 6;18(1):1221. doi: 10.1186/s12885-018-5116-9.
BACKGROUND: A subset of lung adenocarcinoma with EGFR-tyrosine kinase inhibitor sensitizing mutations (mEGFR) is common in non-smokers and women, suggesting that mutational stressors other than smoking are involved. **METHODS:** Targeted sequencing using a custom panel containing 70 cancer-related genes were performed from 73 cases of lung adenocarcinoma with mEGFR (study cohort). In parallel, publicly available data of 47 TCGA-LUAD cases with mEGFR (LUAD cohort) were extracted from the GDC data portal and analyzed by non-negative matrix factorization using the Maftools package. **RESULTS:** In the study cohort, the C > A transversions accounted for 12.9% of all single nucleotide variations (SNVs), comprising the second smallest proportion among SNVs. The E19del-subgroup had a significantly lower mutational burden with significantly higher Ti/Tv ratio than the SNV-subgroup, which includes cases with L858R and other EGFR-TKI sensitizing SNVs. (P = 0.0326 and 0.0002, respectively, Mann-Whitney U test). In the LUAD cohort, the mutational burden was substantially lower than in other TCGA cancer cohorts, and the frequency of C > A transversions was 30.3%, occupying the second frequency. The E19del-subgroup had a lower mutational burden overall and a higher Ti/Tv ratio than the SNV-subgroup (P = 0.0497 and P = 0.0055, respectively, Mann-Whitney U test). Smoking-related signature 4 was observed only in the L858R-subgroup, while ignature 30 and 5 was observed in both groups. **CONCLUSIONS:** Lung adenocarcinoma with mEGFR(+) has a lower mutational burden and does not show a characteristic mutation pattern influenced by smoking. E19del and L858R, which are representative subtypes of mEGFR(+) lung adenocarcinoma, differ in terms of mutational spectrum, as the E19del-subgroup has a lower mutation burden and a higher Ti/Tv ratio than the SNV-subgroup. These findings could help explain the differences in the responses to EGFR-TKIs and in the clinical courses between the two lung adenocarcinoma subgroups.

Liquid-Biopsy-Based Identification of EGFR T790M Mutation-Mediated Resistance to Afatinib Treatment in Patients with Advanced EGFR Mutation-Positive NSCLC, and Subsequent Response to Osimertinib. Hochmair MJ1, Buder A2, Schwab S3, Burghuber OC3,4, Prosch H5, Hilbe W6, Cseh

A7, Fritz R7, Filipits M2. Target Oncol. 2018 Dec 12. doi: 10.1007/s11523-018-0612-z. [Epub ahead of print]
BACKGROUND: Acquired epidermal growth factor receptor (EGFR) T790M mutation is the primary resistance mechanism to first-generation EGFR tyrosine kinase inhibitors (TKIs) used in advanced, EGFR mutation-positive non-small-cell lung cancer (NSCLC). Available data, predominantly in Asian patients, suggest that this mutation is also the major cause of resistance to the irreversible ErbB family blocker, afatinib. For EGFR T790M-positive patients who progress on EGFR TKI therapy, osimertinib is an effective treatment option. However, data on osimertinib use after afatinib are, to date, scarce.
OBJECTIVE: To identify the prevalence of EGFR T790M mutations in predominantly Caucasian patients with stage IV EGFR mutation-positive NSCLC who progressed on afatinib, and to investigate the subsequent response to osimertinib. **PATIENTS AND METHODS:** In this single-center, retrospective analysis, EGFR T790M mutation status after afatinib failure was assessed using liquid biopsy and tissue rebiopsy. EGFR T790M-positive patients subsequently received osimertinib. **RESULTS:** Sixty-seven patients received afatinib in the first-, second-, or third-line (80.6%, 14.9%, and 4.5%, respectively). After afatinib failure, the T790M mutation was identified in 49 patients (73.1%). Liquid biopsy and tissue rebiopsy were concordant in 79.4% of cases. All patients with T790M-positive tumors received osimertinib (73.5% after first-line afatinib); 37 (75.5%) of these had an objective response (complete response: 22.4%; partial response: 53.1%). Response rate was independent of T790M copy number.
CONCLUSION: EGFR T790M mutation is a major mechanism of acquired resistance to afatinib. Osimertinib confers high response rates after afatinib failure in EGFR T790M-positive patients and its use in sequence potentially allows extended chemotherapy-free treatment.

Multicenter phase II study on cisplatin, pemetrexed, and bevacizumab followed by maintenance with pemetrexed and bevacizumab for patients with advanced or recurrent nonsquamous non-small cell lung cancer: MAP study. Tsutani Y1, Miyata Y1, Masuda T2, et al. BMC Cancer. 2018 Dec 10;18(1):1231. doi: 10.1186/s12885-018-5146-3.
BACKGROUND: We evaluated the safety and efficacy of induction chemotherapy with bevacizumab followed by maintenance chemotherapy with bevacizumab for advanced non-small cell lung cancer (NSCLC) in this multicenter phase II study. **METHODS:** Chemotherapy-naïve patient with stage IIIB-IV or recurrent nonsquamous NSCLC were eligible. We planned approximately four cycles of induction cisplatin (75 mg/m2), pemetrexed (500 mg/m2), and bevacizumab (15 mg/kg) followed by maintenance with pemetrexed (500 mg/m2) and bevacizumab (15 mg/kg) until disease progression. Progression-free survival (PFS) was the primary endpoint. **RESULTS:** Forty patients received a median of four induction chemotherapy cycles. Of them, 35 (87.5%) patients received a median of nine maintenance chemotherapy cycles. The objective response was 70.6%, and the disease control rate was 97.1%. The median PFS was 10.8 (95% CI, 9.0-12.6), and overall survival was 48.0 (95% CI, 32.9-63.1) months. Median PFS of 23 patients with epidermal growth factor receptor (EGFR) mutations and of 16 patients without EGFR mutations were 12.9 (95% CI, 9.4-16.3) and 7.9 (95% CI, 1.1-14.7) months, respectively. Toxicities graded ≥3 included neutropenia (15%), anemia (15%), hypertension (7.5%), anorexia (7.5%), fatigue (7.5%), thromboembolic events (5%), jaw osteonecrosis (5%), nausea (2.5%), oral mucositis (2.5%), tumor pain (2.5%), hyponatremia (2.5%), and gastrointestinal perforation (2.5%). Treatment-related deaths were not found. **CONCLUSIONS:** In patients with advanced or recurrent nonsquamous NSCLC, induction chemotherapy with cisplatin, pemetrexed, and bevacizumab followed by maintenance chemotherapy with pemetrexed and bevacizumab is safe and effective regardless of their EGFR mutation status.

Which is the optimal immunotherapy for advanced squamous non-small-cell lung cancer in combination with chemotherapy: anti-PD-1 or anti-PD-L1? Zhang Y1,2,3, Zhou H1,2,3, Zhang L4,5,6. J Immunother Cancer. 2018 Dec 3;6(1):135. doi: 10.1186/s40425-018-0427-6.
Recent randomized phase III trials (KEYNOTE-407 and IMpower131) reported that adding anti-programmed death (ligand) 1 (anti-PD-(L)1) antibodies in combination with taxane-platinum improve the therapeutic efficacy for advanced squamous non-small-cell lung cancer (NSCLC). However, there is no head-to-head comparison of pembrolizumab (anti-PD-1) plus chemotherapy vs. atezolizumab (anti-PD-L1) plus chemotherapy. Therefore, we performed an indirect comparison to explore the optimal choice of anti-PD-(L)1 treatment for advanced squamous NSCLC in combination with chemotherapy. The clinical outcomes were overall survival (OS), progression-free survival (PFS), objective response rate (ORR) and adverse event (AE). For overall patients, pembrolizumab had significantly superior OS (hazard ratio (HR) with 95% confidence interval, 0.67, 0.47-0.94; P = 0.02) and numerically better PFS (HR, 0.79, 0.60-1.04; P = 0.10) than atezolizumab, while they had similar ORR, all cause AE and grade 3-5 AE. For PD-L1 high patients, pembrolizumab and atezolizumab showed similar OS and PFS. However, for PD-L1 low/negative patients, pembrolizumab had superior OS (HR, 0.43, 0.24-0.76; P < 0.01/ HR, 0.74, 0.40-1.38; P = 0.35) and better PFS (HR, 0.80, 0.51-1.26; P = 0.33/ HR, 0.46, 0.28-0.75; P <0.01) than atezolizumab. Our analysis raises the hypothesis that anti-PD-1 antibody therapy in combination with chemotherapy may have superior efficacy compared to anti-PD-L1 antibody combination for patients with PD-L1 low/negative advanced squamous NSCLC.

Influence of afatinib dose on outcomes of advanced EGFR-mutant NSCLC patients with brain metastases. Tan WL1, Ng QS1, Lim C2, et al. BMC Cancer. 2018 Dec 3;18(1):1198. doi: 10.1186/s12885-018-5110-2.
BACKGROUND: Afatinib is an oral irreversible epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor (TKI) indicated in first-line treatment of advanced EGFR-mutant (EGFRm+) non-small cell lung cancer (NSCLC). Dose dependent side effects can limit drug exposure, which may impact on extracranial and central nervous system (CNS) disease control. **METHODS:** We performed a retrospective study of 125 patients diagnosed with advanced EGFRm+ NSCLC treated with first-line afatinib at a tertiary Asian cancer center, exploring clinicopathological factors that may influence survival outcomes. Median progression free survival (PFS) was estimated using the Kaplan-Meier method. Comparison of PFS between subgroups of patients was done using log-rank tests and Cox proportional hazards models. **RESULTS:** Out of 125 patients, 62 (49.6%) started on 40 mg once daily (OD) afatinib, 61 (48.8%) on 30 mg OD and 1 (0.8%) on 20 mg OD. After median follow-up of 13.8 months from afatinib initiation, the observed response rate was 70.4% and median PFS 11.9 months (95% CI 10.3-19.3). 42 (33.6%) patients had baseline brain metastases (BM) and PFS of those who started on 40 mg OD (n = 17) vs. 30 mg OD (n = 25) was 13.3 months vs. 5.3 months (HR 0.39, 95% CI 0.15-0.99). BM+ patients who started on 40 mg had similar PFS to patients with no BM (13.3 months vs. 15.0 months; HR 0.79, 95% CI 0.34-1.80). **CONCLUSION:** In patients with advanced EGFRm+ NSCLC with BM+, initiating patients on afatinib 40 mg OD was associated with improved PFS compared to 30 mg OD, underscoring the potential importance of dose intensity in control of CNS disease.

Prognostic modeling of the immune-centric transcriptome reveals interleukin signaling candidates contributing to differential patient outcomes. Watza D1,2, Lusk CM1,2, et al. Carcinogenesis. 2018 Dec 31;39(12):1447-1454. doi: 10.1093/carcin/bgy119.
Immunotherapy is a promising advancement in the treatment of non-small-cell lung carcinoma (NSCLC), although much of how lung tumors interact with the immune system in the natural course of disease remains unknown. We investigated the impact of the expression of immune-centric genes and pathways in tumors on patient survival to reveal novel candidates for immunotherapeutic research. Tumor

transcriptomes and detailed clinical characteristics were obtained from patients with NSCLC who were participants of either the Inflammation, Health and Lung Epidemiology (INHALE) (discovery, N = 280) or The Cancer Genome Atlas (TCGA) Lung (replication, N = 1026) studies. Expressions of 2253 genes derived from 48 major immune pathways were assessed for association with patient prognosis using a multivariable Cox model and pathway effects were assessed with an in-house implementation of the Gene Set Enrichment Analysis (GSEA) algorithm. Prognosis-guided gene and pathway analysis of immune-centric expression in tumors revealed significant survival enrichments across both cohorts. The 'Interleukin Signaling' pathway, containing 430 genes, was found to be statistically and significantly enriched with prognostic signal in both the INHALE (P = 0.008) and TCGA (P = 0.039) datasets. Subsequent leading-edge analysis identified a subset of genes (N = 23) shared between both cohorts, driving the pathway enrichment. Cumulative expression of this leading-edge gene signature was a strong predictor of patient survival [discovery: hazard ratio (HR) = 1.59, P = 3.0 × 10-8; replication: HR = 1.29, P = 7.4 × 10-7]. **These data demonstrate** the impact of immune-centric expression on patient outcomes in NSCLC. Furthermore, prognostic gene effects were localized to discrete immune pathways, of which Interleukin Signaling had the greatest impact on overall survival and the subset of genes driving these effects have promise for future therapeutic intervention.

Safety and Efficacy of Bevacizumab Plus Standard-of-Care Treatment Beyond Disease Progression in Patients With Advanced Non-Small Cell Lung Cancer: The AvaALL Randomized Clinical Trial.
Gridelli C1, de Castro Carpeno J2, Dingemans AC3, et al. JAMA Oncol. 2018 Dec 1;4(12):e183486. doi: 10.1001/jamaoncol.2018.3486. Epub 2018 Dec 13.
IMPORTANCE: Bevacizumab treatment beyond progression has been investigated in breast and metastatic colorectal cancers. Avastin in All Lines Lung (AvaALL) is the first randomized phase 3 study of bevacizumab across multiple lines of treatment beyond progression in non-small cell lung cancer (NSCLC). **OBJECTIVE:** To assess the efficacy and safety of continuous bevacizumab treatment beyond first progression in NSCLC. **DESIGN, SETTING, AND PARTICIPANTS:** AvaALL was a randomized, open-label, phase 3b trial, conducted from 2011 to 2015 in 123 centers worldwide. Patients with nonsquamous NSCLC previously treated with first-line bevacizumab plus platinum-doublet chemotherapy and at least 2 cycles of bevacizumab maintenance were randomized (1:1) at first progression to receive bevacizumab plus standard of care (SOC) or SOC alone. **INTERVENTIONS:** Patients received bevacizumab (7.5 or 15 mg/kg intravenously every 21 days) and/or investigator's choice of SOC. For subsequent lines, patients treated with bevacizumab received SOC with or without bevacizumab; the SOC arm received SOC only. **MAIN OUTCOMES AND MEASURES:** The primary outcome was overall survival (OS). Secondary outcomes included progression-free survival from first to second (PFS2) and third progression (PFS3), time to second (TTP2) and third progression (TTP3), and safety. **RESULTS:** Between June 2011 and January 2015, 485 patients (median age, 63.0 years [range, 26-84 years]; 293 [60.4%] male) were randomized. Median OS was not significantly longer with bevacizumab plus SOC vs SOC alone: 11.9 (90% CI, 10.2-13.7) vs 10.2 (90% CI, 8.6-11.9) months (hazard ratio [HR], 0.84; 90% CI, 0.71-1.00; P = .104). Median PFS2 was numerically longer with bevacizumab plus SOC vs SOC alone: 5.5 (90% CI, 4.2-5.7) vs 4.0 (90% CI, 3.4-4.3) months (HR, 0.83; 90% CI, 0.70-0.98; P = .06). Median PFS3 appeared longer with bevacizumab plus SOC vs SOC alone: 4.0 (90% CI, 2.9-4.5) vs 2.6 (90% CI, 2.3-2.9) months (HR, 0.63; 90% CI, 0.49-0.83), as did TTP2 and TTP3. Grade 3/4 adverse events were more frequent with bevacizumab plus SOC (186 [76.5%]) vs SOC alone (140 [60.3%]). No new safety signals were observed. **CONCLUSIONS AND RELEVANCE:** The primary end point was not met; however, OS was underpowered according to initial statistical assumptions. Continued therapy beyond first progression led to improved PFS3 (but not PFS2), TTP2, and TTP3. Although a result with P = .06 for PFS2 would conventionally be considered significant at a

specified 2-sided α of .10, in the absence of adjustments for multiplicity, this result could be a chance finding. No new safety signals were identified with bevacizumab treatment beyond progression.

Osimertinib in patients with T790M mutation-positive, advanced non-small cell lung cancer: Long-Term follow-up from a pooled analysis of 2 phase 2 studies. Ahn MJ1, Tsai CM2, Shepherd FA3, et al. Cancer. 2018 Dec 4. doi: 10.1002/cncr.31891. [Epub ahead of print]
BACKGROUND: Osimertinib is a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that is selective for both EGFR-TKI-sensitizing and T790M (threonine-to-methionine substitution at codon 790)-resistance mutations. The authors present long-term follow-up data from a preplanned, pooled analysis of phase 2 studies, the AZD9291 First Time in Patients Ascending Dose Study (AURA) extension trial (clincialtrials.gov identifier NCT01802632) and the AURA2 trial (NCT02094261). **METHODS:** Patients with centrally confirmed, T790M mutation-positive, advanced non-small cell lung cancer received osimertinib 80 mg once daily until disease progression or study discontinuation. Response was assessed by a blinded, independent, central review using Response Evaluation Criteria in Solid Tumors, version 1.1. The primary endpoint was the objective response rate. **RESULTS:** In total, 411 patients received osimertinib (second line, 129 patients; third line or later, 282 patients). At the data cutoff date of November 1, 2016, the median treatment exposure was 16.4 months (range, 0-29.7 months), the objective response rate was 66% (95% confidence interval [CI], 61%-70%), the median response duration was 12.3 months (95% CI, 11.1-13.8 months), and the median progression-free survival was 9.9 months (95% CI, 9.5-12.3 months). At the data cutoff date of May 1, 2018, 271 patients (66%) had died, and 140 patients (34%) had discontinued before death. The median overall survival was 26.8 months (95% CI, 24.0-29.1 months); and the 12-month, 24-month, and 36-month survival rates were 80%, 55%, and 37%, respectively. Grade ≥3 possibly causally related (investigator assessed) adverse events were reported in 65 patients (16%), and the most common were rash (grouped terms; 42%; grade ≥3, 1%) and diarrhea (39%; <1%). **CONCLUSIONS:** This pooled analysis represents the most mature clinical trial data for osimertinib in patients with pretreated, T790M-positive, advanced non-small cell lung cancer, further establishing osimertinib as a standard of care for this patient population.

Efficacy of Alectinib in Patients with ALK-Positive NSCLC and Symptomatic or Large CNS Metastases. Lin JJ1, Jiang GY1, Joshipura N2, et al. J Thorac Oncol. 2018 Dec 7. pii: S1556-0864(18)33510-X. doi: 10.1016/j.jtho.2018.12.002. [Epub ahead of print]
BACKGROUND: Central nervous system (CNS) metastases represent a significant source of morbidity and mortality for patients with ALK-positive non-small cell lung cancer (NSCLC). Alectinib has demonstrated robust CNS activity in both crizotinib-naïve and crizotinib-resistant settings. However, the CNS efficacy of alectinib has not been established in patients with untreated symptomatic, large CNS metastases. **METHODS:** In this retrospective study, patients were eligible if they had advanced ALK-positive NSCLC with large (defined as ≥1 cm) or symptomatic CNS metastases and received alectinib. Medical records and radiographic imaging were reviewed to determine treatment outcomes. CNS efficacy was assessed per the modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. **RESULTS:** Of 19 patients, 15 (79%) had measurable CNS disease at baseline and were evaluable for response. CNS objective response rate (CORR) in these patients was 73.3% (95% CI, 44.9% to 92.2%), CNS disease control rate (CDCR) was 100.0% (95% CI, 78.2% to 100.0%), and median CNS duration of response (CDOR) was 19.3 months (95% CI, 14.3 months to not evaluable). In 18 evaluable patients with measurable and/or nonmeasurable baseline CNS disease, CORR was 72.2% (95% CI, 46.5% to 90.3%), CDCR was 100.0% (95% CI, 81.5% to 100.0%), and median CDOR was 17.1 months (95% CI, 14.3 to not evaluable). All eight patients with symptoms attributable to CNS metastases had clinical improvement upon starting alectinib. Six patients (32%) eventually required salvage brain radiotherapy.

CONCLUSIONS: Alectinib demonstrated meaningful CNS efficacy in ALK-positive NSCLC patients with untreated, symptomatic or large brain metastases.

Natural history and factors associated with overall survival in stage IV ALK rearranged non-small-cell lung cancer. Pacheco JM1, Gao D2, Smith D2, et al. J Thorac Oncol. 2018 Dec 29. pii: S1556-0864(18)33533-0. doi: 10.1016/j.jtho.2018.12.014. [Epub ahead of print]
BACKGROUND: Clinical variables describing the natural history and longitudinal therapy outcomes of stage IV anaplastic lymphoma kinase (ALK) positive non-small-cell lung cancer (NSCLC), and their relationship with long-term overall survival (OS) have not previously been described in detail.
METHODS: Stage IV patients treated with an ALK inhibitor at University of Colorado Cancer Center from 2009 through November 2017 were identified retrospectively. OS curves were constructed using Kaplan Meier methods. Multivariate cox proportional hazard analysis was used to determine relationship of variables with OS. **RESULTS:** 110 ALK+ NSCLC patients were identified, 105 received crizotinib as their initial ALK inhibitor. With a median follow-up of 47 months, the median OS from diagnosis of stage IV disease was 81 months (6.8 years). Brain metastasis at diagnosis of stage IV disease (HR 1.01, p=0.971) and year of stage IV presentation (p=0.887) did not influence OS. More organs with tumor at diagnosis of stage IV disease associated with worse OS (HR 1.49 for each additional organ with disease including the CNS, p=0.002). Each additional month of pemetrexed based therapy associated with a 7% relative decrease in risk of death. **CONCLUSION:** Stage IV ALK+ NSCLC patients can have prolonged OS. Brain metastasis at diagnosis of stage IV disease does not influence OS. More organs involved with tumor at stage IV presentation is associated with worse outcomes. Prolonged benefit from pemetrexed was associated with better outcomes.

Adverse Event Management in Patients with BRAF V600E-Mutant Non-Small Cell Lung Cancer Treated with Dabrafenib plus Trametinib. Chalmers A1, Cannon L2, Akerley W2. Oncologist. 2018 Dec 31. pii: theoncologist.2018-0296. doi: 10.1634/theoncologist.2018-0296. [Epub ahead of print]
Therapies for advanced non-small cell lung cancer (NSCLC) continue to become more sophisticated. Chemotherapeutics are giving way to newer approaches such as immune checkpoint inhibitors and targeted therapies for greater efficacy and improved outcomes. Dabrafenib plus trametinib combination therapy was first approved for the treatment of metastatic melanoma harboring the BRAF V600-mutation in 2014. In 2017, the U.S. Food and Drug Administration approved the combination for patients with NSCLC with the same mutation based on an ≈ 65% response rate and median progression-free survival of 10-11 months. BRAF mutations are a high-frequency event in melanoma (≈ 50%), whereas the overall incidence in lung cancer is ≈ 2%, but similar in number, because of the high incidence of the disease. As a new approach in NSCLC treatment, dabrafenib plus trametinib has a unique toxicity profile that is likely unfamiliar to care providers in thoracic and general oncology who have not used the combination to treat patients with melanoma. Common adverse events such as pyrexia, fatigue, and nausea, as well as a range of less frequent cutaneous, ocular, and hemorrhagic events, can be observed during treatment with dabrafenib plus trametinib. Previous experience in metastatic melanoma revealed that these events can be effectively managed to improve patient quality of life and reduce unnecessary drug discontinuation. The aim of this review is to summarize treatment guidelines, along with key insights obtained from previous clinical-trial and real-world experience in patients with metastatic melanoma, to properly manage toxicities associated with dabrafenib plus trametinib for NSCLC. **IMPLICATIONS FOR PRACTICE:** The combination of dabrafenib plus trametinib has demonstrated substantial clinical activity in patients with BRAF V600E-mutant non-small cell lung cancer, leading to U.S. Food and Drug Administration approval. Although the combination has a manageable safety profile, many toxicities associated with the regimen may not be familiar to thoracic specialists or general oncologists. Extensive clinical experience with the combination in patients with metastatic melanoma has provided a wealth of strategies to identify

and manage adverse events associated with dabrafenib plus trametinib. These can be used by medical oncologists to enhance early recognition of toxicities and facilitate effective management, thereby improving quality of treatment for patients.

NSCLC - RADIOTHERAPY

Final report of survival and late toxicities in the Phase I study of stereotactic body radiation therapy for peripheral T2N0M0 non-small cell lung cancer (JCOG0702). Onimaru R1, Onishi H2, Ogawa G3, et al. Jpn J Clin Oncol. 2018 Dec 1;48(12):1076-1082. doi: 10.1093/jjco/hyy141.
PURPOSE: A dose escalation study to determine the recommended dose with stereotactic body radiation therapy (SBRT) for peripheral T2N0M0 non-small cell carcinomas (JCOG0702) was conducted. The purpose of this paper is to report the survival and the late toxicities of JCOG0702. **MATERIALS AND METHODS:** The continual reassessment method was used to determine the dose level that patients hould be assigned to and to estimate the maximum tolerated dose. The starting dose was 40 Gy in four fractions at D95 of PTV. **RESULTS:** Twenty-eight patients were enrolled. Ten patients were treated with 40 Gy at D95 of PTV, four patients with 45 Gy, eight patients with 50 Gy, one patient with 55 Gy and five patients with 60 Gy. Ten patients were alive at the last follow-up. Overall survival (OS) for all patients was 67.9% (95% CI 47.3-81.8%) at 3 years and 40.8% (95% CI 22.4-58.5%) at 5 years. No Grade 3 or higher toxicity was observed after 181 days from the beginning of the SBRT. Compared to the toxicities up to 180 days, chest wall related toxicities were more frequent after 181 days. **CONCLUSIONS:** The 5-year OS of 40.8% indicates the possibility that SBRT for peripheral T2N0M0 non-small cell lung cancer is superior to conventional radiotherapy. The effect of the SBRT dose escalation on OS is unclear and further studies are warranted.

Early impact of pulmonary stereotactic fractionated body radiotherapy (SBRT) on Quality of Life (QoL): Benefit for patients with low initial scores (STRIPE trial). Adebahr S1, Hechtner M2, Schräder N3, et al. J Thorac Oncol. 2018 Dec 3. pii: S1556-0864(18)33496-8. doi: 10.1016/j.jtho.2018.10.170. [Epub ahead of print]
INTRODUCTION: Quality of life (QoL) of comorbid patients with pulmonary malignancies is a key issue in considering stereotactic fractionated body radiotherapy (SBRT) indication. This study investigates the early impact of SBRT on QoL. **METHODS:** 100 patients with pulmonary lesions were treated with SBRT from 02/2011 to 11/2014 within the prospective, monocenter, phase II STRIPE trial. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core module (EORTC QLQ-C30) and the QLQ-LC13 lung cancer-specific questionnaire were used to evaluate QoL before and 2, 7 weeks after SBRT, then 3-monthly for 2 years. We report on the analysis of early changes from baseline to 7 week-Follow up (FU). Impact of patient- and treatment-related factors on the change in QoL was analyzed. **RESULTS:** QoL was assessed in 97 patients; compliance was 92% and 85% at baseline and 7 weeks after SBRT. No clinically relevant changes ≥10 in QoL/Global health status (GHS), function scores and inquired symptoms were observed. Patients with baseline QoL below the median showed clinically relevant improvement in QoL/GHS ($\Delta 16.7 \pm 25.3$, $p=0.003$), Emotional Function ($\Delta 14.4 \pm 25.4$, $p=0.013$), and fatigue ($\Delta -10.1 \pm 26.5$, $p=0.089$), in contrast to patients with high initial scores. No changes were observed in the dichotomized subgroups of initial Karnofsky Index, Charlson Comorbidity Index, age, diagnosis and tumor localization. **CONCLUSIONS:** In short-term FU QoL is well maintained after pulmonary SBRT. Especially patients with low initial QoL/GHS scores show benefit from SBRT with respect to QoL.

Effect of Tumor Location and Dosimetric Predictors for Chest Wall Toxicity in Single Fraction SBRT for Stage I Non-Small Cell Lung Cancer. Manyam BV1, Videtic GM2, Verdecchia K2, Reddy CA2, Woody NM2, Stephans KL2. Pract Radiat Oncol. 2018 Dec 7. pii: S1879-8500(18)30348-5. doi: 10.1016/j.prro.2018.11.011. [Epub ahead of print]

PURPOSE/OBJECTIVE(S): Dosimetric parameters to limit CWT are not well defined in single-fraction stereotactic body radiation therapy (SF-SBRT) phase II trials. We sought to determine the relationship of tumor location and dosimetric parameters with CWT for SF-SBRT. **MATERIALS/METHODS:** From a prospective registry of 1,462 patients, we identified patients treated with 30 Gy or 34 Gy. Gross tumor volume was measured as abutting, ≤ 1 cm, 1-2 cm or > 2 cm from CW. CWT was prospectively graded according to CTCAE 3.0, with Grade 2 requiring medical therapy, Grade 3 requiring procedural intervention, and Grade 4 being disabling pain. Grade 1 CWT or radiographic rib fracture was not included. Logistic regression analysis was used to identify parameters associated with CWT and to calculate probability of CWT with dose. **RESULTS:** This study included 146 lesions. Median follow-up was 23.8 months. Five-year local control, distant metastasis, and overall survival were 91.8%, 19.2%, and 28.7%, respectively. Grade 2-4 CWT was 30.6% for lesions abutting CW, 8.2% ≤ 1 cm from CW, 3.8% 1-2 cm from CW, and 5.7% >2 cm from CW. Grade ≥ 3 CWT was 1.4%. Tumor abutment (OR 6.5; p=0.0005), BMI (OR 1.1; p= 0.02), rib D1cc (OR 1.01 per Gy; p= 0.03), CW D1cc (OR= 1.08 per Gy; p=0.03), and CW D5cc (OR 1.10 per Gy; p= 0.01) were significant predictors for CWT on UVA. Tumor abutment was significant for CWT (OR 7.5; p= 0.007) on MVA. Probability of CWT was 15% with CW D5cc=27.2 Gy and rib D1cc=30.2 Gy. **CONCLUSION:** Rate of CWT with SF-SBRT is similar to rates published for fractionated SBRT, with most CWT being low grade. Tumor location relative to CW is not a contraindication to SF-SBRT, though rates rise significantly with abutment. Rib D1cc and CW D1cc and D5cc may be used as predictors of CWT.

Long term follow-up on NRG Oncology RTOG 0915 (NCCTG N0927): A randomized phase II study comparing 2 stereotactic body radiation therapy schedules for medically inoperable patients with stage I peripheral non-small cell lung cancer. Videtic GM1, Paulus R2, Singh AK3, et al. Int J Radiat Oncol Biol Phys. 2018 Dec 1. pii: S0360-3016(18)34048-3. doi: 10.1016/j.ijrobp.2018.11.051. [Epub ahead of print]

PURPOSE/OBJECTIVE(S): To present long-term results of XXXX, a randomized lung stereotactic body radiotherapy (SBRT) trial of 34 Gy in 1 fraction versus 48 Gy in 4 fractions. **MATERIALS/METHODS:** This was a phase II multicenter study of medically inoperable non-small cell lung cancer patients with biopsy-proven peripheral T1 or T2 N0M0 tumors, with 1-year toxicity rates as primary endpoint and selected failure and survival outcomes as secondary endpoints. The study opened in September 2009 and closed in March 2011. Final data were analyzed through May 17, 2018. **RESULTS:** Eighty-four of 94 patients accrued were eligible for analysis: 39 in arm 1 and 45 in arm 2. Median follow-up time was 4.0 years for all patients, and 6.0 years for those alive at analysis. Rates of grade 3 and higher toxicity were 2.6% in arm 1 and 11.1% in arm 2. Median survival times (in years) for 34 Gy and 48 Gy were 4.1 vs. 4.6, respectively. Five-year outcomes as % (95% CI) for 34 Gy and 48 Gy were: primary tumor failure rate of 10.6 (3.3, 23.1) vs. 6.8 (1.7, 16.9); overall survival of 29.6 (16.2, 44.4) vs. 41.1 (26.6, 55.1); and progression-free survival of 19.1 (8.5, 33.0) vs. 33.3 (20.2, 47.0); respectively. Distant failure as the sole failure or a component of first failure occurred in 6 patients (37.5%) in the 34 Gy arm and in 7 (41.2%) in the 48 Gy arm. **CONCLUSIONS:** No excess in late-appearing toxicity was seen in either arm. Primary tumor control rates at 5 years were similar by arm. Median survival times of 4 years for each arm suggest similar efficacy pending any larger studies appropriately powered to detect survival differences.

Radiofrequency Ablation and Radiation Therapy Improve Local Control in Spinal Metastases Compared to Radiofrequency Ablation Alone. Prezzano KM1, Prasad D1, Hermann GM1, Belal AN2, Alberico RA2. Am J Hosp Palliat Care. 2018 Dec 13:1049909118819460. doi: 10.1177/1049909118819460. [Epub ahead of print]

PURPOSE: The spinal column is the most common location for osseous metastases and is associated with pain and decreased quality of life. This study evaluated combined radiofrequency ablation (RFA) with radiation therapy (RT) compared to RFA alone for improving pain and local control. **METHODS:** This was a single-institution retrospective review of patients who underwent RFA of spinal metastases between 2016 and 2017, with or without RT to the same vertebral level. Pain was measured with visual analog scale at initial presentation and at 3 and 12 weeks of follow-up. Local failure (LF), distant failure, and overall survival (OS) were compared and Kaplan-Meier statistics were calculated. **RESULTS:** Twenty-six patients with 28 spinal metastases were treated with RFA. Ten patients with 11 metastases were treated with RFA + RT. More patients with lung primaries were treated with RFA alone and more patients with breast primaries were treated with combination RFA+RT. There was no significant difference in pain scores between groups (P = .96). At a median follow-up of 8.2 months, LF was noted in 8 of 17 metastases treated with RFA alone compared to 1 of 11 metastases treated with RFA+RT (P = .049). There was a significant benefit in time to LF favoring RFA+RT (P = .02) and a significant benefit in OS (P = .0045). **CONCLUSION:** This study demonstrates a benefit in local control with RFA+RT versus RFA alone. Palliation of pain was effective using both regimens. This study was limited by a nearly unequal distribution of primary tumor histologies between groups. Literature regarding combined treatment of RFA and RT for spinal metastases is scarce and prospective protocols are warranted.

SMALL CELL LUNG CANCER - SCLC

EGFR-mutant SCLC exhibits heterogeneous phenotypes and resistance to common antineoplastic drugs. Lin CA1, Yu SL1, Chen HY2, Chen HW3, Lin SU4, Chang CC1, Yu CJ5, Yang PC5, Ho CC6. J Thorac Oncol. 2018 Dec 3. pii: S1556-0864(18)33499-3. doi: 10.1016/j.jtho.2018.11.021. [Epub ahead of print]

INTRODUCTION: Approximately 5% of patients with EGFR-activating mutations acquire EGFR-TKIs resistance through SCLC transformation. However, the reason for the poor outcome and the molecular basis of EGFR-mutant SCLC that has transformed from adenocarcinoma remain unclear.

METHODS: In this study, we established 2 EGFR-mutant SCLC cell lines from lung adenocarcinoma patients after failed EGFR-TKI treatment to investigate their molecular basis and potential therapeutic strategies in the hope of improving patient outcome. **RESULTS:** These 2 EGFR-mutant SCLC cell lines displayed 2 different phenotypes: suspensive and adherent. Both phenotypes shared the same genomic alterations analyzed by array-based comparative genomic hybridization (aCGH) assay. Increased expression of EGFR and mesenchymal markers and decreased expression of neuroendocrine markers were observed in adherent cells. Principal component analysis (PCA) and hierarchical clustering analysis of RNA microarray revealed that these 2 cell lines displayed a unique gene expression pattern that was distinctly different from that in NSCLC and classical SCLC cells. Combined treatment using an EGFR-TKI and an AKT inhibitor attenuated cell viabilities in our 2 cell lines. Moreover, the use of a histone deacetylase (HDAC) inhibitor significantly inhibited the cell viabilities of both cell lines in vitro and in vivo. **CONCLUSION:** Our findings suggest that EGFR-mutant SCLC may be a distinct subclass of SCLC that exhibits epithelial-mesenchymal transition (EMT) phenotypes, and adding an AKT or HDAC inhibitor to pre-existing therapies may be one of the therapeutic choices for transformed EGFR-mutant SCLC.

Prospects of targeted and immune therapies in SCLC. Hendriks LEL1,2, Menis J3, Reck M4. Expert Rev Anticancer Ther. 2018 Dec 28:1-17. doi: 10.1080/14737140.2019.1559057. [Epub ahead of print]
Small cell lung cancer (SCLC) is a tumor with a poor prognosis, often diagnosed in an advanced stage. Despite aggressive treatment of early and locally advanced disease, SCLC often relapses. First line chemotherapy provides good response rates in advanced disease, but progression free and overall survival are limited. New drugs such as some targeted therapies and immune therapies are promising in SCLC. Areas covered: In this review, we discuss the preclinical rationale and trial data for targeted therapies and immune therapies in SCLC, with a specific focus on clinical trials. Expert commentary: Lack of identification of clear prognostic and predictive biomarkers has limited the advances in treatment efficacy. This has most likely been the main cause of failure for compounds tested so far. Due to the highly mutational profile and the rapid growth pattern of SCLC, immunotherapy combined with chemotherapy seems the most promising treatment option. Concerning targeted agents, achievements made so far are small, but DLL3-antibodies or combinations of PARPi and immunotherapy could be very promising. These promising strategies also need testing in limited disease.

Randomized-controlled phase II trial of salvage chemotherapy after immunization with a TP53-transfected dendritic cell-based vaccine (Ad.p53-DC) in patients with recurrent small cell lung cancer. Chiappori AA1, Williams CC2, Gray JE2, et al. Cancer Immunol Immunother. 2018 Dec 27. doi: 10.1007/s00262-018-2287-9. [Epub ahead of print]
Small cell lung cancer TP53 mutations lead to expression of tumor antigens that elicits specific cytotoxic T-cell immune responses. In this phase II study, dendritic cells transfected with wild-type TP53 (vaccine) were administered to patients with extensive-stage small cell lung cancer after chemotherapy. Patients were randomized 1:1:1 to arm A (observation), arm B (vaccine alone), or arm C (vaccine plus all-trans-retinoic acid). Vaccine was administered every 2 weeks (3 times), and all patients were to receive paclitaxel at progression. Our primary endpoint was overall response rate (ORR) to paclitaxel. The study was not designed to detect overall response rate differences between arms. Of 69 patients enrolled (performance status 0/1, median age 62 years), 55 were treated in stage 1 (18 in arm A, 20 in arm B, and 17 in arm C) and 14 in stage 2 (arm C only), per 2-stage Simon Minimax design. The vaccine was safe, with mostly grade 1/2 toxicities, although 1 arm-B patient experienced grade 3 fatigue and 8 arm-C patients experienced grade 3 toxicities. Positive immune responses were obtained in 20% of arm B (95% confidence interval [CI], 5.3-48.6) and 43.3% of arm C (95% CI 23.9-65.1). The ORRs to the second-line chemotherapy (including paclitaxel) were 15.4% (95% CI 2.7-46.3), 16.7% (95% CI 2.9-49.1), and 23.8% (95% CI 9.1-47.5) for arms A, B, and C, with no survival differences between arms. Although our vaccine failed to improve ORRs to the second-line chemotherapy, its safety profile and therapeutic immune potential remain. Combinations with the other immunotherapeutic agents are reasonable options.

Irinotecan plus cisplatin compared with etoposide plus cisplatin in patients with previously untreated extensive-stage small cell lung cancer: A meta-analysis. Liu ZL1, Wang B1, Liu JZ1, Liu WW1. J Cancer Res Ther. 2018 Dec;14(Supplement):S1076-S1083. doi: 10.4103/0973-1482.199387.
OBJECTIVE: To systematically review the effect and safety of irinotecan plus cisplatin (IP) compared with etoposide plus cisplatin (EP) in patients with previously untreated extensive-stage small cell lung cancer (E-SCLC). **MATERIALS AND METHODS:** Databases including PubMed, The Cochrane Library, EMBASE, China National Knowledge Infrastructure, VIP, and WanFang Data were searched for the randomized controlled trials (RCTs) about IP compared with EP in patients with previously untreated E-SCLC from the establishment to June 2016. Two reviewers independently screened literature, extracted data and assessed the methodological quality of included studies. Then meta-analysis was performed using RevMan 5.3 software (Cochrane Collaboration, Oxford, UK). **RESULTS:** A total of 12 RCTs involving 2030 patients were finally included. Meta-analysis showed that compared with EP regimen, IP

regimen significantly improved the 1- and 2-year survival rates of the patients with previously untreated E-SCLC (risk ratio [RR] = 1.16, 95% confidence interval [CI] [1.03-1.31], P = 0.02; RR = 1.79, 95% CI [1.22-2.61], P = 0.003, respectively). However, there was no significant difference between IP regimen and EP regimen in the objective response rate (ORR) (RR = 1.07, 95% CI [0.99-1.15], P = 0.10) and disease control rate (DCR) (RR = 1.03, 95% CI [0.96-1.10], P = 0.38). The incidence of Grade 3/4 leukopenia, neutropenia, anemia, and thrombocytopenia of IP regimen was sigificantly lower than EP regimen (all P < 0.05), the incidence of Grade 3/4 nausea/vomiting and diarrhea of IP regimen was sigificantly higher than EP regimen (all P < 0.05). **CONCLUSION:** IP regimen significantly improves the 1- and 2-year survival rates, but not significantly improves the ORR and DCR, compared with EP regimen in patients with previously untreated E-SCLC. IP regimen has less Grade 3 or 4 hematological adverse events. IP regimen is an alternative of EP regimen in patients with previously untreated E-SCLC.

Randomized Phase II Trial of Cisplatin and Etoposide in Combination With Veliparib or Placebo for Extensive-Stage Small-Cell Lung Cancer: ECOG-ACRIN 2511 Study. Owonikoko TK1, Dahlberg SE1, Sica GL1, et al. J Clin Oncol. 2018 Dec 5:JCO1800264. doi: 10.1200/JCO.18.00264. [Epub ahead of print]

PURPOSE: Veliparib, a poly (ADP ribose) polymerase inhibitor, potentiated standard chemotherapy against small-cell lung cancer (SCLC) in preclinical studies. We evaluated the combination of veliparib with cisplatin and etoposide (CE; CE+V) doublet in untreated, extensive-stage SCLC (ES-SCLC). **MATERIALS AND METHODS:** Patients with ES-SCLC, stratified by sex and serum lactate dehydrogenase levels, were randomly assigned to receive four 3-week cycles of CE (75 mg/m2 intravenously on day 1 and 100 mg/m2 on days 1 through 3) along with veliparib (100 mg orally twice per day on days 1 through 7) or placebo (CE+P). The primary end point was progression-free survival (PFS). Using an overall one-sided 0.10-level log-rank test, the study had 88% power to demonstrate a 37.5% reduction in the PFS hazard rate. **RESULTS:** A total of 128 eligible patients received treatment on protocol. The median age was 66 years, 52% of patients were men, and Eastern Cooperative Oncology Group performance status was 0 for 29% of patients and 1 for 71%. The respective median PFS for the CE+V arm versus the CE+P arm was 6.1 versus 5.5 months (unstratified hazard ratio [HR], 0.75 [one-sided P = .06]; stratified HR, 0.63 [one-sided P = .01]), favoring CE+V. The median overall survival was 10.3 versus 8.9 months (stratified HR, 0.83; 80% CI, 0.64 to 1.07; one-sided P = .17) for the CE+V and CE+P arms, respectively. The overall response rate was 71.9% versus 65.6% (two-sided P = .57) for CE+V and CE+P, respectively. There was a significant treatment-by-strata interaction in PFS: Male patients with high lactate dehydrogenase levels derived significant benefit (PFS HR, 0.34; 80% CI, 0.22 to 0.51) but there was no evidence of benefit among patients in other strata (PFS HR, 0.81; 80% CI, 0.60 to 1.09). The following grade ≥ 3 hematology toxicities were more frequent in the CE+V arm than the CE+P arm: CD4 lymphopenia (8% v 0%; P = .06) and neutropenia (49% v 32%; P = .08), but treatment delivery was comparable. **CONCLUSION:** The addition of veliparib to frontline chemotherapy showed signal of efficacy in patients with ES-SCLC and the study met its prespecified end point.

Adoption of prophylactic cranial irradiation (PCI) for extensive stage small cell lung cancer (ES-SCLC): a population based outcome study. Soon YY1,2,3,4, Zheng H5, Ho SZ6, Koh WY7, et al. Radiat Oncol. 2018 Dec 14;13(1):247. doi: 10.1186/s13014-018-1184-x.

BACKGROUND: The survival benefit of PCI in ES-SCLC reported by a European randomized trial (RCT) in 2007 was not replicated by a Japanese RCT published in 2017. This study aimed to evaluate the uptake of PCI before and after publication of the European RCT and its association with survival in ES-SCLC. **METHODS:** We identified eligible patients in the only two Singapore national cancer centres from 2003 to 2010. We linked their electronic medical records to the national death registry. We described the utilization of PCI in patients diagnosed from 2003 to 2006 (pre-adoption cohort) with

patients diagnosed from 2007 to 2010 (post-adoption cohort). We performed univariable and multivariable Cox regression analysis to assess the association between PCI and survival. **RESULTS:** We identified 224 patients with ES-SCLC with no brain metastases. Among the 71 patients who had at least stable disease after first line chemotherapy, there was an increase in the use of PCI from the period 2007 to 2010 compared with 2003 to 2006 (32% versus 10%, P = 0.044). PCI was associated with improved OS (hazard ratio 0.22, 95% CI 0.10 to 0.47, P < 0.001) compared to no PCI in the multivariable analysis. **CONCLUSION:** There was an increase in the adoption of PCI for ES-SCLC since 2007. PCI was associated with improved survival in patients who did not have mandatory MRI brain imaging prior to PCI and had stable disease or better after first line chemotherapy, suggesting that the results of the European RCT are reproducible in the real-world practice.

Additional radiation boost to whole brain radiation therapy may improve the survival of patients with brain metastases in small cell lung cancer. Sun H1, Xu L1, Wang Y1, Zhao J1, Xu K1, Qi J1, Yuan Z1, Zhao L2, Wang P1. Radiat Oncol. 2018 Dec 18;13(1):250. doi: 10.1186/s13014-018-1198-4.
BACKGROUND: The role of the dose escalation strategy in brain radiotherapy for small cell lung cancer (SCLC) patients with brain metastases (BMs) has not been identified. This study aims to determine whether an additional radiation boost to whole brain radiation therapy (WBRT) has beneficial effects on overall survival (OS) compared with WBRT-alone. **METHODS:** A total of 82 SCLC patients who were found to have BMs treated with WBRT plus a radiation boost (n = 33) or WBRT-alone (n = 49) from January 2008 to December 2015 were retrospectively analyzed. All patients were limited-stage (LS) SCLC at the time of the initial diagnosis, and none of them had extracranial metastases prior to detection of BMs. The primary end point was OS. **RESULTS:** The median OS for all of the patients was 9.6 months and the 6-, 12- and 24-months OS rates were 69.1, 42.2 and 12.8%, respectively. At baseline, the proportion of more than 3 BMs was significantly higher in the WBRT group than in the WBRT plus boost group (p = 0.0001). WBRT plus a radiation boost was significantly associated with improved OS in these patients when compared with WBRT-alone (13.4 vs. 8.5 months; p = 0.004). Further, the survival benefit still remained significant in WBRT plus boost group among patients with 1 to 3 BMs (13.4 vs. 9.6 months; p = 0.022). **CONCLUSION:** Compared with WBRT-alone, the use of WBRT plus a radiation boost may prolong survival in SCLC patients with BMs. The dose escalation strategy in brain radiotherapy for selected BMs patients with SCLC should be considered.

PALLIATIVE AND SUPPORTIVE CARE

The relationship between comorbidity medication adherence and health related quality of life among patients with cancer. Drzayich Antol D1, Waldman Casebeer A1, et al. J Patient Rep Outcomes. 2018 Jul 4;2:29. doi: 10.1186/s41687-018-0057-2. eCollection 2018 Dec.
BACKGROUND: Studies have demonstrated that comorbidities compound the adverse influence of cancer on health-related quality of life (HRQoL). Comorbidities adversely impact adherence to cancer treatment. Additionally, adherence to medications for comorbidities is positively associated with HRQoL for various diseases. This study used the Center for Disease Control and Prevention's Healthy Days measure of HRQoL to explore the association between HRQoL and adherence to comorbidity medication for elderly patients with cancer and at least one comorbid condition. **METHODS:** We conducted a cross-sectional survey combined with retrospective claims data. Patients with metastatic breast, lung or colorectal cancer were surveyed regarding their HRQoL, comorbidity medication adherence and cancer-related symptoms. Patients reported the number of physical, mental and total unhealthy days in the prior month. The Morisky Medication Adherence 8-point scale was differentiated into moderate/high (> 6) and low (≤ 6) comorbidity medication adherence. **RESULTS:** Of the 1847 respondents, the mean age was

69.2 years, most were female (66.8%) and the majority of the sample had Medicare coverage (88.2%). Low comorbidity medication adherence was associated with significantly more total, mental and physical unhealthy days. Low comorbidity medication adherence was associated with the presence of patient-reported cancer-related symptoms. Patients reporting low, as compared to moderate/high, comorbidity medication adherence had 23.4% more unhealthy days in adjusted analysis, P = 0.007. **CONCLUSION:** The positive association between low comorbidity medication adherence and the number of unhealthy days suggests that addressing barriers to comorbidity medication adherence during cancer treatment may be an avenue for improving or maintaining HRQoL for older patients with cancer and comorbid conditions.

Precision-Exercise-Prescription in patients with lung cancer undergoing surgery: rationale and design of the PEP study trial. Ulrich CM1,2, Himbert C1,2, et al. BMJ Open. 2018 Dec 16;8(12):e024672. doi: 10.1136/bmjopen-2018-024672.
INTRODUCTION: Lung cancer is a significant burden on societies worldwide, and the most common cause of death in patients with cancer overall. Exercise intervention studies in patients with lung cancer have consistently shown benefits with respect to physical and emotional functioning. However, to date, exercise training has not been consistently implemented into clinical practice given that interventions have been costly and not aligned with clinical care. **METHODS/DESIGN:** The Precision-Exercise-Prescription (PEP) study is a prospective randomised controlled trial comparing the effectiveness and feasibility of a personalised intervention exercise programme among patients with lung cancer undergoing surgery. Two-hundred patients who are diagnosed with stage primary or secondary lung cancer and are eligible to undergo surgical treatment at Huntsman Cancer Institute comprise the target population. Patients are randomised to either the (1) outpatient precision-exercise intervention group or (2) delayed intervention group. The intervention approach uses Motivation and Problem Solving, a hybrid behavioural treatment based on motivational interviewing and practical problem solving. The dosage of the exercise intervention is personalised based on the individual's Activity Measure for Post-Acute-Care outpatient basic mobility score, and incorporates four exercise modes: mobility, callisthenics, aerobic and resistance. Exercise is implemented by physical therapists at study visits from presurgery until 6 months postsurgery. The primary endpoint is the level of physical function assessed by 6 min walk distance at 2 months postsurgery. Secondary outcomes include patient-reported outcomes (eg, quality of life, fatigue and self-efficacy) and other clinical outcomes, including length of stay, complications, readmission, pulmonary function and treatment-related costs up to 6 months postsurgery. **THICS/DISSEMINATION:** The PEP study will test the clinical effectiveness and feasibility of a personalised exercise intervention in patients with lung cancer undergoing surgery. Outcomes of this clinical trial will be presented at national and international conferences and symposia and will be published in international, peer-reviewed journals. Ethics approval was obtained at the University of Utah (IRB 00104671). **TRIAL REGISTRATION NUMBER:** NCT03306992.

Factors associated with self-reported falls, balance or walking difficulty in older survivors of breast, colorectal, lung, or prostate cancer: Results from Surveillance, Epidemiology, and End Results-Medicare Health Outcomes Survey linkage. Huang MH1, Blackwood J1, Godoshian M2, Pfalzer L1. PLoS One. 2018 Dec 19;13(12):e0208573. doi: 10.1371/journal.pone.0208573. eCollection 2018.
BACKGROUND: Cancer and its treatment affect body systems that are important in preventing falls and controlling balance/walking. This study examined factors associated with self-reported falls and balance/walking difficulty in the past 12 months in older survivors of four major cancers. **METHODS:** This was a cross-sectional study analyzing population-based data from Surveillance, Epidemiology, and End Results-Medicare Health Outcomes Survey (SEER-MHOS). Data from cohorts 9 to 14 (January 2006

to December 2013) were extracted. Inclusion criteria were: age ≥65 years at cancer diagnosis, first MHOS completed during years 1-5 post-cancer diagnosis, first primary breast (n = 2725), colorectal (n = 1646), lung (n = 752), and prostate (n = 4245) cancer, and availability of cancer staging information. Primary outcomes were self-reported falls and balance/walking difficulty in the past 12 months. Multivariable logistic regression was constructed for each cancer type to examine independent factors associated with falls and balance/walking difficulty. **RESULTS:** In all cancer types, advancing age at cancer diagnosis and dependence in activities of daily living were significant independent factors associated with increased odds of reporting falls and balance/walking difficulty in the past 12 months. Additionally, depression was independently associated with falls and sensory impairment in feet was independently linked to balance/walking difficulty in all cancer types. Other independent factors of falls and balance/walking difficulty varied across cancer types. In breast cancer only, localized or regional cancer stage was significantly associated with increased odds of reporting falls and balance/walking difficulty, whereas treatment with radiation decreased the odds of falling. No association between falls and balance/walking difficulty with time since cancer diagnosis, cancer stage, or cancer treatment was found in colorectal, lung, and prostate cancer. **CONCLUSION:** There exists some heterogeneity in factors associated with self-reported falls and balance/walking difficulty between different cancer types. Future research is necessary to ascertain factors predictive of falls and balance/walking difficulty in older cancer survivors, particularly factors related to cancer diagnosis and treatment.

Prevalence of psychosocial distress in cancer patients across 55 North American cancer centers. Carlson LE1, Zelinski EL1, Toivonen KI2, Sundstrom L3, Jobin CT3, Damaskos P4, Zebrack B3. J Psychosoc Oncol. 2018 Dec 28:1-17. doi: 10.1080/07347332.2018.1521490. [Epub ahead of print]
Routine distress screening in United States oncology clinics has been mandatory since 2015. **OBJECTIVE:** This study was the first to assess distress in a geographically diverse sample of cancer patients following mandated distress screening implementation by oncology social workers. **METHODS:** Sites were self-selected via social workers who applied to participate in the Association of Oncology Social Work's Project to Assure Quality Cancer Care, advertised through their social media outlets and conference. Electronic screening records were collected from 55 cancer treatment centers in the United States and Canada. Cases required cancer diagnoses and Distress Thermometer (DT) scores to be included. Distress rates and rates by age, sex, cancer type, and ethnicity were examined. **RESULTS:** Of 4664 cases, 46% (2157) experienced significant distress (DT score ≥ 4). Being female, age 40-59, and having diagnoses of pancreatic or lung cancer was associated with increased likelihood of distress. Half of cases experience clinically-significant distress, though this need was not evenly distributed across patient or cancer types. **CONCLUSION:** Identifying those at risk for distress may help inform optimal resource allocation. Methods to address needs of distressed patients in cases of limited resources are discussed.

Efficacy of nebulized acetylcysteine for relieving symptoms and reducing usage of expectorants in patients with radiation pneumonitis. Han DW1, Ji W2, Lee JC1,3, Song SY4, Choi CM1,2,3. Thorac Cancer. 2018 Dec 26. doi: 10.1111/1759-7714.12938. [Epub ahead of print]
BACKGROUND: Radiation pneumonitis is one of the most harmful and clinically significant complications of radiotherapy. This study investigated the benefits of nebulized acetylcysteine for lung cancer patients diagnosed with radiation pneumonitis after radiotherapy. **METHODS:** We prospectively enrolled and followed 25 patients with radiation pneumonitis who used nebulized acetylcysteine three times a day for 12 weeks. We also reviewed the medical records of 106 control patients who had undergone radiotherapy for lung cancer but had not used acetylcysteine. We evaluated the effects of nebulized acetylcysteine by comparing visits 1 and 4 among nebulizer users and by comparing the acetylcysteine group with the control group. **RESULTS:**

Twenty-five acetylcysteine group patients and 101 control group patients were included in the analyses. The mean patient-rated severity score associated with sputum production decreased in the acetylcysteine group between visits 1 and 4 (from 1.10 to 0.95; P = 0.08). None of the patients used additional expectorant agents after using nebulized acetylcysteine and critical adverse events were not reported. The acetylcysteine group had a shorter mean duration of expectorant use among patients whose radiation pneumonitis required steroid therapy and covered > 10% of a single lung field on computed tomography (37.2 vs. 78.1 days, respectively; P = 0.07). **CONCLUSIONS:** The beneficial effects of nebulized acetylcysteine for patients with radiation pneumonitis included relieving sputum severity and minimizing expectorant use, especially in severe cases. Further investigation is required to clarify and expand on the benefits of nebulized acetylcysteine for patients with radiation pneumonitis.

Care coordination for complex cancer survivors in an integrated safety-net system: a study protocol. Lee SJC1,2, Jetelina KK3, Marks E4, Shaw E5, Oeffinger K6, Cohen D7, Santini NO8, Cox JV4,8, Balasubramanian BA9,3. BMC Cancer. 2018 Dec 4;18(1):1204. doi: 10.1186/s12885-018-5118-7.
BACKGROUND: The growing numbers of cancer survivors challenge delivery of high-quality survivorship care by healthcare systems. Innovative ways to improve care coordination for patients with cancer and multiple chronic conditions ("complex cancer survivors") are needed to achieve better care outcomes, improve patient experience of care, and lower cost. Our study, Project CONNECT, will adapt and implement three evidence-based care coordination strategies, shown to be effective for primary care conditions, among complex cancer survivors. Specifically, the purpose of this study is to: 1) Implement a system-level EHR-driven intervention for 500 complex cancer survivors at Parkland; 2) Test effectiveness of the strategies on system- and patient-level outcomes measured before and after implementation; and 3) Elucidate system and patient factors that facilitate or hinder implementation and result in differences in experiences of care coordination between complex patients with and without cancer. **METHODS:** Project CONNECT is a quasi-experimental implementation study among 500 breast and colorectal cancer survivors with at least one of the following chronic conditions: diabetes, hypertension, chronic lung disease, chronic kidney disease, or heart disease. We will implement three evidence-based care coordination strategies in a large, county integrated safety-net health system: 1) an EHR-driven registry to facilitate patient transitions between primary and oncology care; 2) co-locating a nurse practitioner trained in care coordination within a complex care team; 3) and enhancing teamwork through coaching. Segmented regression analysis will evaluate change in system-level (i.e. composite care quality score) and patient-level outcomes (i.e. self-reported care coordination). To evaluate implementation, we will merge quantitative findings with structured observations and physician and patient interviews. **DISCUSSION:** This study will result in an evaluation toolkit identifying key model elements, barriers, and facilitators that can be used to guide care coordination interventions in other safety-net settings. Because Parkland is a vanguard of safety-net healthcare nationally, findings will be widely applicable as other safety-nets move toward increased integration, enhanced EHR capability, and experience with growing patient diversity. Our proposal recognizes the complexity of interventions and scaffolds evidence-based strategies together to meet the needs of complex patients, systems of care, and service integration. **TRIAL REGISTRATION:** ClinicalTrials.gov, NCT02943265 . Registered 24 October 2016.

C-reactive protein and its association with depression in patients receiving treatment for metastatic lung cancer. McFarland DC1, Shaffer K2, Breitbart W2, Rosenfeld B3, Miller AH4. Cancer. 2018 Dec 6. doi: 10.1002/cncr.31859. [Epub ahead of print]
BACKGROUND: Depression is highly prevalent in lung cancer. Although there is a known association between inflammation and depression, this relationship has not been examined in patients with lung cancer who undergo treatment with immune and other targeted drug therapies. Peripheral blood C-reactive protein (CRP), a marker of systemic inflammation, may help identify metastatic lung cancer

patients with inflammation-associated depression. **METHOD:** Patients with metastatic lung cancer undergoing treatment were evaluated for depression using the Hospital Anxiety and Depression Scale (HADS). Inflammation (CRP and CRP cutoffs ≥1 and ≥3 mg/mL) and demographic and treatment variables were analyzed for association with depression. **RESULTS:** One hundred nine consecutive participants exhibited an average plasma CRP concentration of 1.79 mg/mL (median, 0.75 mg/mL [standard deviation, 2.5 mg/mL), and 20.7% had a CRP concentration of ≥3.0 mg/mL; 23.9% met depression screening criteria (HADS ≥8). A log transformation of CRP was significantly correlated with depression severity ($r = 0.47$, $P < .001$). CRP was the only covariate to predict depression severity ($P = .008$) in a multivariate model including lung cancer disease subtype and type of systemic treatment. Receiver operating characteristic analysis indicated that CRP had moderate predictive accuracy in identifying elevated depression (area under the curve = 0.74). A cutoff of CRP ≥3.0 generated high specificity (88%) but identified only 50% of those with elevated depression. **CONCLUSION:** Elevated CRP is associated with depression in patients with metastatic lung cancer. Thus, CRP may identify a subset of lung cancer patients with inflammation-induced depression and may be useful in predicting response to treatments that target inflammation or its downstream mediators on the brain.

COMPLEMENTARY & ALTERNATIVE THERAPY

Water extract of ginseng and astragalus regulates macrophage polarization and synergistically enhances DDP's anticancer effect. Chen Y1, Bi L2, Luo H1, Jiang Y1, Chen F1, Wang Y3, Wei G4, Chen W5. J Ethnopharmacol. 2018 Dec 5;232:11-20. doi: 10.1016/j.jep.2018.12.003. [Epub ahead of print]

ETHNOPHARMACOLOGICAL RELEVANCE: In traditional Chinese medicine, supplementing Qi and strengthening body resistance are an important principle of anticancer treatment. Panax ginseng C.A.Mey. (ginseng) and Astragalus membranaceus Bunge (astragalus) are the representative herbs for this therapeutic principle. **AIM OF THE STUDY:** This study aims to explore the effect of the water extract of ginseng and astragalus (WEGA) on regulating macrophage polarization and mediating anticancer in the tumor microenvironment. **MATERIALS AND METHODS:** A549 cells were cultured in tumor-associated macrophage (TAM) supernatant with various concentrations of WEGA (0, 5, 10, 20 mg/mL). A549 cell proliferation was determined through methyl thiazole tetrazolium (MTT) assay and real-time cell analysis (RTCA), respectively. In vivo experiments were performed with a Lewis lung cancer (LLC) xenograft mouse model. Forty-eight mice were divided into six groups and treated with saline, WEGA, or cis-diamine dichloro platinum (DDP) with dosage of WEGA (0, 30, 60, 120 mg/kg body weight/day). The different groups were administered with drugs via oral or intraperitoneal injection once a day for 21 consecutive days. Tumor inhibition rate, spleen index, thymus index, cytokine, protein, and mRNA expression levels were detected in mice. **RESULTS:** In a co-culture system, WEGA remarkably inhibited A549 cell proliferation, promoted the expression of M1 macrophage markers and inhibited M2 TAMs markers. Therefore, WEGA affected the biological behavior of cancer cells by regulating the expression of some markers relevant to macrophage polarization. In addition, the group of WEGA and DDP chemotherapy effectively inhibited the transplanted tumor growth in mice and improved weight loss and immunosuppressive with the cisplatin inducing. **CONCLUSIONS:** This study provides mechanistic insights into the anticancer effect of WEGA through the regulation of macrophage polarization and highlights that WEGA could be a novel option for integrative cancer therapies.

MISCELLANEOUS WORKS

Reduced Cancer Survival Among Adults With HIV and AIDS-Defining Illnesses Despite No Difference in Cancer Stage at Diagnosis. Grover S1, Desir F2, Jing Y2, et al. J Acquir Immune Defic Syndr. 2018 Dec 1;79(4):421-429. doi: 10.1097/QAI.0000000000001842.
BACKGROUND: It is not known whether immune dysfunction is associated with increased risk of death after cancer diagnosis in persons with HIV (PWH). AIDS-defining illness (ADI) can signal significant immunosuppression. Our objective was to determine differences in cancer stage and mortality rates in PWH with and without history of ADI. **METHODS:** PWH with anal, oropharynx, cervical, lung cancers, or Hodgkin lymphoma diagnoses from January 2000 to December 2009 in the North American AIDS Cohort Collaboration on Research and Design were included. **RESULTS:** Among 81,865 PWH, 814 had diagnoses included in the study; 341 (39%) had a history of ADI at time of cancer diagnosis. For each cancer type, stage at diagnosis did not differ by ADI ($P > 0.05$). Mortality and survival estimates for cervical cancer were limited by $n = 5$ diagnoses. Adjusted mortality rate ratios showed a 30%-70% increase in mortality among those with ADI for all cancer diagnoses, although only lung cancer was statistically significant. Survival after lung cancer diagnosis was poorer in PWH with ADI vs. without ($P = 0.0001$); the probability of survival was also poorer in those with ADI at, or before other cancers although not statistically significant. **CONCLUSIONS:** PWH with a history of ADI at lung cancer diagnosis had higher mortality and poorer survival after diagnosis compared to those without. Although not statistically significant, the findings of increased mortality and decreased survival among those with ADI (vs. without) were consistent for all other cancers, suggesting the need for further investigations into the role of HIV-related immune suppression and cancer outcomes.

Discrepancies Between FDA-Required Labeling and Evidence that Payers Cite in Drug Coverage Policies. Chambers JD1, Pope EF1, Wilkinson CL1, Neumann PJ1. J Manag Care Spec Pharm. 2018 Dec;24(12):1240-1246. doi: 10.18553/jmcp.2018.24.12.1240.
BACKGROUND: FDA-required labeling summarizes certain data that the FDA relies on in its drug approval process. However, when determining coverage of specialty drugs, health care payers may consider dissimilar evidence. **OBJECTIVE:** To compare evidence cited by the largest U.S. commercial payers in their specialty drug coverage policies with evidence featured in the labeling of the indicated drugs. **METHODS:** We used the Tufts Medical Center Specialty Drug Evidence and Coverage Database (SPEC)-a database of specialty drug coverage policies issued by 17 of the 20 largest U.S. commercial health care payers-to identify coverage policies for drugs indicated for multiple sclerosis, rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, and non-small cell lung cancer (NSCLC). These disease categories were selected because each was represented by multiple drugs. For each drug, we identified endpoints included in the clinical studies presented in the FDA-required labeling. Using SPEC, we identified randomized controlled trials (RCTs) and other clinical studies that at least 1 payer cited in its coverage policies for the included drugs. We reviewed the full text of each study to identify the endpoints reported. We categorized endpoints as identical to endpoints in the FDA-required labeling of the drugs; similar (e.g., a different measurement scale was used to evaluate the same endpoint); and different (the endpoint was not featured in the FDA-required labeling). **RESULTS:** We included 41 drugs and reviewed 348 studies (246 RCTs and 102 other clinical studies). Of 2,237 endpoints, 63% were categorized as identical, 26% as similar, and 12% as different. Rheumatoid arthritis was the indication with the largest proportion of endpoints categorized as identical (74% of endpoints in the RCTs cited by payers; 59% of endpoints in the other clinical studies cited by payers). NSCLC was the indication with the largest proportion of endpoints categorized as different (33% of end-points in the RCTs cited by

payers; 37% of endpoints in the other clinical studies cited by payers). **CONCLUSIONS:** Payers often report reviewing clinical evidence that goes beyond information included in FDA-required labeling. Our findings suggest that the FDA should continue engaging with the manufacturer and payer communities to appropriately facilitate communication of information necessary to allow for informed coverage decisions. **DISCLOSURES:** This study was funded by an unrestricted grant from the Pharmaceutical Research and Manufacturers of America. The authors work with The Center for the Evaluation of Value and Risk in Health, which is partially supported through the CEA Registry Sponsorship program; the CEA Registry has received funding from the National Science Foundation, National Library of Medicine, Agency for Healthcare Research and Quality, Centers for Disease Control and Prevention, and a variety of pharmaceutical and device companies that subscribe to the data. Chambers reports personal fees from Health Advances, Ernst & Young, Magellan Health, Summit Therapeutics, and Sanofi-Aventis, unrelated to this study. Neumann reports past advisory board work with Amgen, Avexis, Axovant, Bayer, Bluebird, Congressional Budget Office, Janssen, Merck, Novo Nordisk, Pacira, Paratek, and Sage; consulting work for Boston Health Economics, GSK, Precision Health Economics, Veritech, and Vertex; speaker fees from AbbVie, Celgene, and Roche; and grants from the Alzheimer's Association, Amgen, Gates, Lundbeck, NIH, NPC, and Sage, all unrelated to this study. The other authors have nothing to disclose.

Interprofessional Lung Cancer Tumor Board: The Role of the Oncology Nurse Navigator in Improving Adherence to National Guidelines and Streamlining Patient Care. Peckham J1, Mott-Coles S2. Clin J Oncol Nurs. 2018 Dec 1;22(6):656-662. doi: 10.1188/18.CJON.656-662.
BACKGROUND: Lung cancer traditionally has a high morbidity and mortality rate because of late diagnosis. Use of a tumor board has been noted as one way to improve patient care and quality of life. **OBJECTIVES:** This article aimed to determine the contributions of an oncology nurse navigator (ONN) related to physician adherence to guidelines and streamlined patient care in an interprofessional lung cancer tumor board. **METHODS:** Retrospective chart review was performed for 18 months prior to and following implementation of the lung cancer tumor board. **FINDINGS:** After implementation of the lung cancer tumor board and the creation of clinical pathways by the ONN, diagnosis of early-stage non-small cell lung cancer and the use of diagnostic workups increased.

Exposure to Secondhand Smoke Among Nonsmokers - United States, 1988-2014. Tsai J, Homa DM, Gentzke AS, Mahoney M, Sharapova SR, Sosnoff CS, Caron KT, Wang L, Melstrom PC, Trivers KF. MMWR Morb Mortal Wkly Rep. 2018 Dec 7;67(48):1342-1346. doi: 10.15585/mmwr.mm6748a3.
Exposure to secondhand smoke from burning tobacco products can cause sudden infant death syndrome, respiratory infections, ear infections, and asthma attacks in infants and children, and coronary heart disease, stroke, and lung cancer in adult nonsmokers (1). There is no risk-free level of secondhand smoke exposure (2). CDC analyzed questionnaire and laboratory data from the National Health and Nutrition Examination Survey (NHANES) to assess patterns of secondhand smoke exposure among U.S. nonsmokers. The prevalence of secondhand smoke exposure among U.S. nonsmokers declined substantially during 1988-2014, from 87.5% to 25.2%. However, no change in exposure occurred between 2011-2012 and 2013-2014, and an estimated one in four nonsmokers, or approximately 58 million persons, were still exposed to secondhand smoke during 2013-2014. Moreover, marked disparities persisted across population groups. Exposure prevalence was highest among nonsmokers aged 3-11 years (37.9%), non-Hispanic blacks (50.3%), and those who were living in poverty (47.9%), in rental housing (38.6%), or with someone who smoked inside the home (73.0%), or among persons who had less than a high school education (30.7%). Comprehensive smoke-free laws and policies for workplaces and public places and smoke-free rules for homes and vehicles can further reduce secondhand smoke exposure among all nonsmokers.

Practice Patterns for Older Adult Patients With Advanced Cancer: Physician Office Versus Hospital Outpatient Setting. Lipitz-Snyderman A1, Atoria CL1, Schleicher SM1, Bach PB1, Panageas KS1. J Oncol Pract. 2019 Jan;15(1):e30-e38. doi: 10.1200/JOP.18.00315. Epub 2018 Dec 13.
PURPOSE: A shift in outpatient oncology care from the physician's office to hospital outpatient settings has generated interest in the effect of practice setting on outcomes. Our objective was to examine whether medical oncologists' prescribing of drugs and services for older adult patients with advanced cancer is used more in physicians' offices compared with hospital outpatient departments. **METHODS:** This was a retrospective comparative study. SEER-Medicare data (2004 to 2011) were used to identify Medicare beneficiaries diagnosed with advanced breast, colon, esophagus, non-small-cell lung, pancreatic, or stomach cancer. Between physicians' offices and hospital outpatient departments, we compared use of selected likely low-value supportive drugs, low-value therapeutic drugs, chemotherapy-related hospitalizations, and hospice. We used hierarchical modeling to assess differences between settings to account for correlation within physicians. **RESULTS:** Compared with patients treated in a hospital outpatient department, those treated in a physician's office setting were more likely to receive erythropoiesis-stimulating agents (odds ratio, 1.72; 95% CI, 1.53 to 1.94) and granulocyte colony-stimulating factors (odds ratio, 1.28; 95% CI, 1.18 to 1.38). For combination chemotherapy and nanoparticle albumin-bound-paclitaxel in patients with breast cancer, there was a trend toward higher use in physicians' offices, although this was not statistically significant. Chemotherapy-related hospitalizations and hospice did not vary by setting. **CONCLUSION:** We found somewhat higher use of several drugs for patients with advanced cancer in physicians' office settings compared with hospital outpatient departments. Findings support research to dissect the mechanisms through which setting might influence physicians' behavior.

Patient-Centered Medical Homes in Community Oncology Practices: Changes in Spending and Care Quality Associated With the COME HOME Experience. Waters TM1,2, Kaplan CM2, Graetz I2, Price MM3, Stevens LA4,5, McAneny BL4,6,7. J Oncol Pract. 2019 Jan;15(1):e56-e64. doi: 10.1200/JOP.18.00479. Epub 2018 Dec 5.
PURPOSE: We examined whether the Community Oncology Medical Home (COME HOME) program, a medical home program implemented in seven community oncology practices, was associated with changes in spending and care quality. **PATIENTS AND METHODS:** We compared outcomes from elderly fee-for-service Medicare beneficiaries diagnosed between 2011 and 2015 with breast, lung, colorectal, thyroid, or pancreatic cancer, lymphoma, or melanoma and served by COME HOME practices before and after program implementation versus similar beneficiaries served by other geographically proximate oncologists. Difference-in-differences analysis compared changes in outcomes for COME HOME patients versus concurrent controls. Propensity score matching and regression methods were adjusted for clinical and sociodemographic differences. Our primary outcome was 6-month medical spending per beneficiary. Secondary outcomes included 6-month out-of-pocket spending, inpatient and ambulatory care-sensitive hospitalizations, readmissions, length of stay, and emergency department and evaluation and management visits. **RESULTS:** Before COME HOME, 6-month medical spending was $2,975 higher for the study group compared with controls (95% CI, $1,635 to $4,315; P < .001) and increasing at a similar rate. After intervention, this difference was reduced to $318 (95% CI, -$1,105 to $1,741; P = .661), a significant change of -$2,657 (95% CI, -$4,631 to -$683; P = .008) or 8.1% savings relative to 6-month average spending ($32,866). COME HOME was also associated with significantly reduced (10.2 %) emergency department visits per 1,000 patients per 6-month period (P = .024). There were no statistically significant differences in other outcomes. **CONCLUSION:** COME HOME was associated with reduced Medicare spending and improved emergency department use. The patient-centered medical home model holds promise for oncology practices, but improvements were not uniform.