Caring Ambassadors Lung Cancer Program
Literature Review, September 2016

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

A threshold of systemic MAGE-A gene expression predicting survival in resected non-small cell lung cancer. Mecklenburg I1, Sienel W2, Schmid S3, Passlick B4, Kufer P5. Clin Cancer Res. 2016 Aug 19. pii: clincanres.0557.2016. [Epub ahead of print]

PURPOSE: Quantitative measurement of minimal residual disease (MRD) predicting recurrence in individual cancer patients is available only in very few indications such as acute lymphoblastic leukemia but is still missing in most solid tumors including non-small cell lung cancer (NSCLC).
EXPERIMENTAL DESIGN: MAGE-A expression levels in blood and bone marrow determined as calibrator normalized relative ratios by quantitative multimarker real-time RT-PCR for transcript amplification of MAGE-A1, -A2, -A3/6, -A4, -A10 and -A12 in 94 patients with completely resected NSCLC were correlated with survival in a clinical study. **RESULTS:** Patients with MAGE-A expression levels {greater than or equal to} 0.2 in at least one sample of bone marrow or blood at tumor surgery had a significantly reduced overall ($p = 0.007$), cancer-free ($p = 0.002$), and distant-metastasis-free survival ($p < 0.001$) versus patients below 0.2 in all samples without significant difference in locoregional-recurrence-free survival. The corresponding hazard ratios ({greater than or equal to} 0.2 vs. < 0.2) for death, cancer-related death and development of distant metastasis were 2.56 (95% CI, 1.42 - 4.63), 3.32 (95% CI, 1.66 - 6.61), and 4.03 (95% CI, 1.77 - 9.18), respectively. Five-year Kaplan-Meier estimates of distant-metastasis-free survival were 43% (MAGE-A {greater than or equal to} 0.2) versus 87% (MAGE-A < 0.2). **CONCLUSIONS:** MAGE-A expression in blood or bone marrow at tumor surgery is an independent predictor of survival in resected NSCLC. The reliable prediction of distant metastasis in individual patients with a statistically proven impact on overall survival may help to refine patient selection for adjuvant therapy urgently needed especially in the clinical management of elderly patients.

Programmed Cell Death Ligand 1 (PD-L1) Expression in Resected Lung Adenocarcinomas: Association with Immune Microenvironment. Huynh TG1, Morales-Oyarvide V2, Campo MJ3, et al. J Thorac Oncol. 2016 Aug 24. pii: S1556-0864(16)30900-5. doi: 10.1016/j.jtho.2016.08.134. [Epub ahead of print]

INTRODUCTION: PD-L1 expression on tumor cells can be upregulated via activation of CD8+ cytotoxic T lymphocytes (CTLs) and/or Th1 pathway, counterbalancing the CTL/Th1 microenvironment. However, PD-L1 expression in association with subtypes of tumor-associated lymphocytes and molecular alterations has not been well characterized in lung adenocarcinomas. **METHODS:** PD-L1 expression was evaluated in 261 resected lung adenocarcinomas using tissue microarrays and various scoring systems, and was correlated with clinicopathologic/molecular features including the extent/subtype of tumor-associated lymphocytes (CD8, T-bet [Th1 transcription factor] and GATA3 [Th2 transcription factor]), and patient outcomes. **RESULTS:** PD-L1 expression was present in 129 (49%), 95 (36.5%) and 62 (24%) cases using cutoffs of ≥1%, ≥5% and ≥50%, respectively, 98 (38%) by H score and 72 (28%) by Immune score. PD-L1 expression was associated with abundant CD8+ and/or T-bet+ tumor-infiltrating lymphocytes as well as EGFR wild-type, significant smoking history, and aggressive pathologic features. Furthermore, concurrent PD-L1 expression and abundant CD8+ tumor-associated lymphocytes were seen in 1/4 of KRAS mutants or cases with no alterations by clinical molecular testing as opposed to only 7.4% of EGFR mutants. PD-L1 expression was significantly associated with decreased progression-free and overall survivals by univariate analysis, but not by multivariate analysis. **CONCLUSION:** PD-L1 expression in resected lung adenocarcinomas is frequently observed in the presence of CTL/Th1 microenvironment, in particular in those with KRAS mutations or no common molecular alterations, suggesting that blockade of the PD-1/PD-L1 axis may be a promising treatment strategy to reinstitute active immune response for at least a subset of such patient populations.

Human Leukocyte Antigen G Polymorphism and Expression Are Associated with an Increased Risk of Non-Small-Cell Lung Cancer and Advanced Disease Stage. Ben Amor A1, Beauchemin K2, Faucher MC2, Hamzaoui A1,3, Hamzaoui K1,3, Roger M2,4. PLoS One. 2016 Aug 12;11(8):e0161210. doi: 10.1371/journal.pone.0161210. eCollection 2016.

Human leukocyte antigen (HLA)-G acts as negative regulator of the immune responses and its expression may enable tumor cells to escape immunosurveillance. The purpose of this study was to investigate the influence of HLA-G allelic variants and serum soluble HLA-G (sHLA-G) levels on risk of non-small-cell lung cancer (NSCLC). We analyzed 191 Caucasian adults with NSCLC and 191 healthy subjects recruited between January 2009 and March 2014 in Ariana (Tunisia). Serum sHLA-G levels were measured by immunoassay and HLA-G alleles were determined using a direct DNA sequencing procedures. The heterozygous genotypes of HLA-G 010101 and -G 010401 were associated with increased risks of both NSCLC and advanced disease stages. In contrast, the heterozygous genotypes of HLA-G 0105N and -G 0106 were associated with decreased risks of NSCC and clinical disease stage IV, respectively. Serum sHLA-G levels were significantly higher in patients with NSCLC and particularly in those with advanced disease stages compared to healthy subjects. The area under the receiver-operating characteristic (ROC) curves was 0.82 for controls vs patients. Given 100% specificity, the highest sensitivity achieved to detect NSCLC was 52.8% at a cutoff value of 24.9 U/ml. Patients with the sHLA-G above median level (≥ 50 U/ml) had a significantly shorter survival time. This study demonstrates that HLA-G allelic variants are independent risk factors for NSCLC. Serum sHLA-G levels in NSCLC patients could be useful biomarkers for the diagnostic and prognosis of NSCLC.

Leveraging Hypoxia-Activated Prodrugs to Prevent Drug Resistance in Solid Tumors. Lindsay D1, Garvey CM2, Mumenthaler SM2, Foo J1. PLoS Comput Biol. 2016 Aug 25;12(8):e1005077. doi: 10.1371/journal.pcbi.1005077. eCollection 2016.

Experimental studies have shown that one key factor in driving the emergence of drug resistance in solid tumors is tumor hypoxia, which leads to the formation of localized environmental niches where drug-resistant cell populations can evolve and survive. Hypoxia-activated prodrugs (HAPs) are compounds

designed to penetrate to hypoxic regions of a tumor and release cytotoxic or cytostatic agents; several of these HAPs are currently in clinical trial. However, preliminary results have not shown a survival benefit in several of these trials. We hypothesize that the efficacy of treatments involving these prodrugs depends heavily on identifying the correct treatment schedule, and that mathematical modeling can be used to help design potential therapeutic strategies combining HAPs with standard therapies to achieve long-term tumor control or eradication. We develop this framework in the specific context of EGFR-driven non-small cell lung cancer, which is commonly treated with the tyrosine kinase inhibitor erlotinib. We develop a stochastic mathematical model, parametrized using clinical and experimental data, to explore a spectrum of treatment regimens combining a HAP, evofosfamide, with erlotinib. We design combination toxicity constraint models and optimize treatment strategies over the space of tolerated schedules to identify specific combination schedules that lead to optimal tumor control. We find that (i) combining these therapies delays resistance longer than any monotherapy schedule with either evofosfamide or erlotinib alone, (ii) sequentially alternating single doses of each drug leads to minimal tumor burden and maximal reduction in probability of developing resistance, and (iii) strategies minimizing the length of time after an evofosfamide dose and before erlotinib confer further benefits in reduction of tumor burden. These results provide insights into how hypoxia-activated prodrugs may be used to enhance therapeutic effectiveness in the clinic.

A Quantitative Comparison of Antibodies to Programmed Cell Death 1 Ligand 1. Gaule P1, Smithy JW1, Toki M1, et al. JAMA Oncol. 2016 Aug 18. doi: 10.1001/jamaoncol.2016.3015. [Epub ahead of print]

IMPORTANCE: Assessment of PD-L1 (programmed cell death 1 ligand 1) expression by immunohistochemical analysis has been used as a predictive diagnostic test to identify responders and guide treatment in trials of the PD-1 (programmed cell death 1) axis inhibitors. The definition of PD-L1 positive lacks standardization, and prediction of response by immunohistochemical analysis is additionally limited by the subjective nature of this technique. **OBJECTIVE:** To examine whether PD-L1 antibody reagents are interchangeable by quantitatively comparing the expression of the PD-L1 protein. **DESIGN, SETTING, AND PARTICIPANTS:** In this immunohistochemistry standardization study, 30 randomly selected cases of lung cancer resected from January 1, 2008, through December 31, 2009, were obtained from Yale Pathology Archives with a range of expression of PD-L1. To test for protein measurement, rather than clinical utility, a PD-L1 index tissue microarray, including cell line and tissue controls, was used. The results were then validated on a commercially available, genetically defined PD-L1 engineered cell line array with a range of controlled protein-expressing cell lines using 6 monoclonal antibodies (SP142, E1L3N, 9A11, SP263, 22c3, and 28-8). Protein levels were measured by quantitative immunofluorescence and quantitative chromogenic assessment. Data analysis was performed from September 2015 through May 2016. **RESULTS:** Concordance between 4 antibodies revealed regression for tumor tissue cores ($R2 = 0.42$-0.91) and cell line cores ($R2 = 0.83$-0.97) by quantitative immunofluorescence in the PD-L1 index tissue microarray. All 6 antibodies had high levels of concordance ($R2 = 0.76$-0.99) when using chromogenic staining in isogenic cell lines. **CONCLUSIONS AND RELEVANCE:** Because the antibodies are highly concordant, these results suggest that assays based on the use of these antibodies could yield concordant results. They further suggest that previously described differences in PD-L1 expression in tissue are independent of the antibody used and likely attributable to tumor heterogeneity, assay- or platform-specific variables, or other factors.

Strategies to inhibit ABCB1- and ABCG2-mediated efflux transport of erlotinib at the blood-brain barrier: a PET study in non-human primates. Tournier N1, Goutal S1, Auvity S1, et al. J Nucl Med. 2016 Aug 4. pii: jnumed.116.178665. [Epub ahead of print]

The tyrosine kinase inhibitor erlotinib poorly penetrates the blood-brain barrier (BBB) due to efflux transport by P-glycoprotein (ABCB1) and breast cancer resistance protein (ABCG2) thereby limiting its utility in the treatment of non-small cell lung cancer brain metastases. Pharmacological strategies to inhibit ABCB1/ABCG2-mediated efflux transport at the BBB have been successfully developed in rodents, but it remains unclear if these can be translated to humans given pronounced species differences in ABCG2/ABCB1 expression ratios at the BBB. We assessed the efficacy of two different ABCB1/ABCG2 inhibitors to enhance brain distribution of 11C-erlotinib in non-human primates as a model of the human BBB. **METHODS:** Papio anubis baboons underwent PET scans of the brain following i.v. injection of 11C-erlotinib under baseline conditions (n = 4) and during i.v. infusion of high-dose erlotinib (10 mg/kg/h, n = 4) or elacridar (12 mg/kg/h, n = 3). **RESULTS:** Under baseline conditions, 11C-erlotinib distribution to the brain (total volume of distribution, VT = 0.22 ± 0.015 mL/cm3) was markedly lower than its distribution to muscle tissue surrounding the skull (VT = 0.86 ± 0.10 mL/cm3). Elacridar infusion resulted in a 3.5 ± 0.9-fold increase in 11C-erlotinib distribution to the brain (VT = 0.81 ± 0.21 mL/cm3, $P < 0.01$), reaching comparable levels as in muscle tissue, without changing 11C-erlotinib plasma pharmacokinetics. During high-dose erlotinib infusion 11C-erlotinib brain distribution was also significantly (1.7 ± 0.2-fold) increased (VT = 0.38 ± 0.033 mL/cm3, $P < 0.05$) with a concomitant increase in 11C-erlotinib plasma exposure. **CONCLUSION:** We successfully implemented ABCB1/ABCG2 inhibition protocols in non-human primates resulting in pronounced increases in brain distribution of 11C-erlotinib. Such inhibition protocols may ultimately find application for a more effective treatment of patients with brain tumors using drugs that undergo efflux transport at the BBB.

SCREENING, DIAGNOSIS AND STAGING

Patient Perspectives on Low-Dose Computed Tomography for Lung Cancer Screening, New Mexico, 2014. Mishra SI1, Sussman AL2, Murrietta AM3, et al. Prev Chronic Dis. 2016 Aug 18;13:E108. doi: 10.5888/pcd13.160093.

INTRODUCTION: National guidelines call for annual lung cancer screening for high-risk smokers using low-dose computed tomography (LDCT). The objective of our study was to characterize patient knowledge and attitudes about lung cancer screening, smoking cessation, and shared decision making by patient and health care provider. **METHODS:** We conducted semistructured qualitative interviews with patients with histories of heavy smoking who received care at a Federally Qualified Health Center (FQHC Clinic) and at a comprehensive cancer center-affiliated chest clinic (Chest Clinic) in Albuquerque, New Mexico. The interviews, conducted from February through September 2014, focused on perceptions about health screening, knowledge and attitudes about LDCT screening, and preferences regarding decision aids. We used a systematic iterative analytic process to identify preliminary and emergent themes and to create a coding structure. **RESULTS:** We reached thematic saturation after 22 interviews (10 at the FQHC Clinic, 12 at the Chest Clinic). Most patients were unaware of LDCT screening for lung cancer but were receptive to the test. Some smokers said they would consider quitting smoking if their screening result were positive. Concerns regarding screening were cost, radiation exposure, and transportation issues. To support decision making, most patients said they preferred one-on-one discussions with a provider. They also valued decision support tools (print materials, videos), but raised concerns about readability and Internet access. **CONCLUSION:** Implementing lung cancer screening in sociodemographically diverse populations poses significant challenges. The value of tobacco cessation counseling cannot be overemphasized. Effective interventions for shared decision making to undergo lung

cancer screening will need the active engagement of health care providers and will require the use of accessible decision aids designed for people with low health literacy.

Differences in Patient Outcomes of Prevalence, Interval, and Screen-Detected Lung Cancers in the CT Arm of the National Lung Screening Trial. Schabath MB1, Massion PP2, Thompson ZJ3, Eschrich SA4, Balagurunathan Y5, Goldof D6, Aberle DR7, Gillies RJ5. PLoS One. 2016 Aug 10;11(8):e0159880. doi: 10.1371/journal.pone.0159880. eCollection 2016.
Lung cancer screening identifies cancers with heterogeneous behaviors. Some lung cancers will be identified among patients who had prior negative CT screens and upon follow-up scans develop a de novo nodule that was determined to be cancerous. Other lung cancers will be identified among patients who had one or more prior stable positive scans that were not determined to be lung cancer (indeterminate pulmonary nodules), but in follow-up scans was diagnosed with an incidence lung cancer. Using data from the CT arm of the National Lung Screening Trial, this analysis investigated differences in patient characteristics and survival endpoints between prevalence-, interval-, and screen-detected lung cancers, characterized based on sequence of screening results. Lung cancers immediately following a positive baseline (T0), and prior to the T1 screen, formed the prevalence cohort. Interval cancers were diagnosed following a negative screen at any time point prior to the next screening round. Two cohorts of screen-detected lung cancers (SDLC) were identified that had a baseline positive screen that was that was not determined to be lung cancer (i.e., an indeterminate pulmonary nodule), but in follow-up scans was diagnosed with an incidence lung cancer 12 (SDLC1) or 24 (SDLC2) months later. Two other incidence cohorts had screen-detected lung cancers that had baseline negative screen and upon follow-up scans developed a de novo nodule determined to be cancerous at 12 (SDLC3) or 24 (SDLC4) months later. Differences in patient characteristics, progression-free survival (PFS), and overall survival (OS) were assessed. The lung cancer-specific death rate was higher for SDLC3/SDLC4 compared to SDLC1/SDLC2 lung cancers (136.6/1,000 person-years vs. 71.3/1,000 person-years, $P < 0.001$). Moreover, PFS and OS were significantly lower for SDLC3/SDLC4 compared to SDLC1/SDLC2 ($P < 0.004$; $P < 0.002$, respectively). The findings were consistent when stratified by stage and histology. Multivariable Cox proportional models revealed that the SDLC3/SDLC4 case groups were associated with significantly poorer PFS (HR = 1.89; 95% CI 1.31-2.74) and OS (HR = 1.80; 95% CI 1.21-2.67) compared to SDLC1/SDLC2 lung cancers (HR = 1.00). Lung cancer patients who develop a de novo nodule that determined to be cancerous (i.e., at least one negative CT screen prior to cancer diagnosis) had poorer survival outcomes compared to patients who had at least one positive screen prior to cancer diagnosis. As such, the observation that de novo screen-detected are associated with poorer survival could be attributed to faster growing, more aggressive cancers that arose from a lung environment previously lacking focal abnormalities.

Sociocultural Barriers to Lung Cancer Screening Among Korean Immigrant Men. Sin MK1, Ha A2, Taylor V3. J Community Health. 2016 Aug;41(4):790-7. doi: 10.1007/s10900-016-0154-1.
Lung cancer is a commonly occurring cancer among Korean American men. Korean Americans have lower rates of cancer screening participation than other Asian American sub-groups. However, little is known about factors that influence the cancer screening behavior of Korean immigrants. The purpose of this study was to explore facilitators of and barriers to lung cancer screening (i.e., low dose CT of the chest) among Korean immigrant men, using qualitative individual interviews and focus groups. A convenience sample of 24 Korean men who were immigrants, Washington State residents, able to speak Korean, aged 55-79, and eligible for lung cancer screening (based on current guidelines) were recruited from Korean churches and senior centers. Five focus groups (that included between two and five men) and nine individual interviews were conducted. Content analysis was used to analyze the qualitative data. Facilitators of lung cancer screening included perceptions about positive aspects of the health care system

in South Korea, recommendations from others (physicians, family members, and community organizations), existing health problems and respiratory symptoms, interest in health, and the health consequences of aging. Barriers included costs of health care in the US, lack of time, lack of knowledge (about lung cancer and screening), attitudes about prevention, and lack of physician recommendation. This study adds new knowledge to a field where little information is available. It also lays the groundwork for developing culturally relevant lung cancer screening interventions for Korean Americans and the health care providers who serve them.

FDG-PET/CT Limited to the Thorax and Upper Abdomen for Staging and Management of Lung Cancer. Arens AI1, Postema JW2, Schreurs WM3, Lafeber A4, Hendrickx BW5, Oyen WJ2, Vogel WV4. PLoS One. 2016 Aug 24;11(8):e0160539. doi: 10.1371/journal.pone.0160539. eCollection 2016. **PURPOSE:** This study evaluates the diagnostic accuracy of [F-18]-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) of the chest/upper abdomen compared to the generally performed scan from head to upper thighs, for staging and management of (suspected) lung cancer in patients with no history of malignancy or complaints outside the thorax. **METHODS:** FDG-PET/CT scans of 1059 patients with suspected or recently proven lung cancer, with no history of malignancy or complaints outside the thorax, were analysed in a retrospective multi-centre trial. Suspect FDG-avid lesions in the chest and upper abdomen, the head and neck area above the shoulder line and in the abdomen and pelvis below the caudal tip of the liver were noted. The impact of lesions detected in the head and neck area and abdomen and pelvis on additional diagnostic procedures, staging and treatment decisions was evaluated. **RESULTS:** The head and neck area revealed additional suspect lesions in 7.2%, and the abdomen and pelvis in 15.8% of patients. Imaging of the head and neck area and the abdomen and pelvic area showed additional lesions in 19.5%, inducing additional diagnostic procedures in 7.8%. This resulted in discovery of additional lesions considered malignant in 10.7%, changing patient management for lung cancer in 1.2%. In (suspected) lung cancer, PET/CT limited to the chest and upper abdomen resulted in correct staging in 98.7% of patients, which led to the identical management as full field of view PET in 98.8% of patients. **CONCLUSION:** High value of FDG-PET/CT for staging and correct patient management is already achieved with chest and upper abdomen. Findings in head and neck area and abdomen and pelvis generally induce investigations with limited or no impact on staging and treatment of NSCLC, and can be interpreted accordingly.

A Comparison of Lung Nodule Segmentation Algorithms: Methods and Results from a Multi-institutional Study. Kalpathy-Cramer J1, Zhao B2, Goldgof D3, Gu Y4, Wang X5, Yang H2, Tan Y2, Gillies R4, Napel S6. J Digit Imaging. 2016 Aug;29(4):476-87. doi: 10.1007/s10278-016-9859-z. Tumor volume estimation, as well as accurate and reproducible borders segmentation in medical images, are important in the diagnosis, staging, and assessment of response to cancer therapy. The goal of this study was to demonstrate the feasibility of a multi-institutional effort to assess the repeatability and reproducibility of nodule borders and volume estimate bias of computerized segmentation algorithms in CT images of lung cancer, and to provide results from such a study. The dataset used for this evaluation consisted of 52 tumors in 41 CT volumes (40 patient datasets and 1 dataset containing scans of 12 phantom nodules of known volume) from five collections available in The Cancer Imaging Archive. Three academic institutions developing lung nodule segmentation algorithms submitted results for three repeat runs for each of the nodules. We compared the performance of lung nodule segmentation algorithms by assessing several measurements of spatial overlap and volume measurement. Nodule sizes varied from 29 μl to 66 ml and demonstrated a diversity of shapes. Agreement in spatial overlap of segmentations was significantly higher for multiple runs of the same algorithm than between segmentations generated by different algorithms ($p < 0.05$) and was significantly higher on the phantom dataset compared to the other datasets ($p < 0.05$). Algorithms differed significantly in the bias of the

measured volumes of the phantom nodules ($p < 0.05$) underscoring the need for assessing performance on clinical data in addition to phantoms. Algorithms that most accurately estimated nodule volumes were not the most repeatable, emphasizing the need to evaluate both their accuracy and precision. There were considerable differences between algorithms, especially in a subset of heterogeneous nodules, underscoring the recommendation that the same software be used at all time points in longitudinal studies.

Rationale for a Minimum Number of Lymph Nodes Removed with Non-Small Cell Lung Cancer Resection: Correlating the Number of Nodes Removed with Survival in 98,970 Patients. Samayoa AX1, Pezzi TA2, Pezzi CM3, et al. Ann Surg Oncol. 2016 Aug 16. [Epub ahead of print]
BACKGROUND: The benefit of thoracic lymphadenectomy in the treatment of resectable non-small cell lung cancer (NSCLC) continues to be debated. We hypothesized that the number of lymph nodes (LNs) removed for patients with pathologic node-negative NSCLC would correlate with survival. **METHODS:** The National Cancer Data Base (NCDB) was queried for resected, node-negative, NSCLC patients treated between 2004 and 2014. Patients were grouped according to the number of LNs removed (1-4, 5-8, 9-12, 13-16, and ≥17). Patients with <10 LNs removed were also compared with those with ≥10 LNs removed. A Cox regression analysis was performed and hazard ratios (HRs) calculated, with 95 % confidence intervals (CIs). **RESULTS:** Of 1,089,880 patients with NSCLC reported to the NCDB during the study period, 98,970 (9.0 %) underwent resection without evidence of pathologic nodal involvement. Lobectomy was performed in 83.9 %, sublobar resection was performed in 12.7 % and pneumonectomy was performed in 2.8 % of patients. The number of LNs removed correlated with increasing tumor size and extent of resection. On multivariate analysis, increasing age, male sex, white ethnicity, high tumor grade, larger tumor size, pneumonectomy, and positive surgical margins were all negatively correlated with overall survival. The number of LNs removed and lobectomy/bi-lobectomy correlated with improved survival. The removal of <10 LNs was associated with a 12 % increased risk of death (HR: 1.12, 95 % CI 1.09-1.14; $p < 0.001$). **CONCLUSION:** Survival of early-stage NSCLC patients is associated with the number of LNs removed. The surgical management of early-stage NSCLC should include thoracic lymphadenectomy of at least 10 nodes.

Comparison of detection methods and follow-up study on the tyrosine kinase inhibitors therapy in non-small cell lung cancer patients with ROS1 fusion rearrangement. Wu J1, Lin Y1, He X1, Yang H2, He P1, Fu X1, Li G1, Gu X3. BMC Cancer. 2016 Aug 4;16:599. doi: 10.1186/s12885-016-2582-9.
BACKGROUND: The screening of ROS proto-oncogene 1, receptor tyrosine kinase(ROS1) fusion rearrangement might be potentially beneficial for an effective therapy against non-small cell lung cancer (NSCLC). However, the three main ROS1 rearrangement detection methods have limitations, and no routine protocol for the detection of ROS1 rearrangement in NSCLC is available. In this study, our aims were to compare immunohistochemistry (IHC), fluorescent in situ hybridization (FISH) and quantitative real-time polymerase chain reaction (qRT-PCR) in their ability to detect ROS1 rearrangement in NSCLC, and discuss the clinical characteristics and histopathology of the patients with ROS1 rearrangement. Moreover, the effects of tyrosine kinase inhibitors (TKIs) therapy on the patients with ROS1 rearrangement and advanced stage disease (III b-IV) were investigated. **METHODS:** Patients with a previously diagnosed NSCLC were recruited in this study from November 2013 to October 2015. IHC was performed using the D4D6 monoclonal antibody (mAb) in an automatic IHC instrument, while FISH and qRT-PCR were carried out to confirm the IHC results. FISH and qRT-PCR positive cases underwent direct sequencing. After detection, patients with advanced ROS1 rearranged NSCLC had received TKI therapy. **RESULTS:** Two hundred and thirty-eight patients were included in this study. ROS1 rearrangement was detected in 10 patients. The concordant rate of FISH and qRT-PCR results was 100 %, while in the FISH and IHC results high congruence was present when IHC showed a diffusely (≥60 % tumor cells) 2-3+ cytoplasmic reactivity pattern. Patients harboring ROS1 rearrangement were mostly

young (8/10), females (7/10) and non-smokers (7/10) with adenocarcinoma (10/10) and acinar pattern. Most of their tumor were in intermediate grade (6/8). Among these 10 patients, three of them in stage IV with ROS1 rearrangement gained benefits from ROS1 TKI therapy. **CONCLUSIONS:** IHC, FISH and qRT-PCR can reliably detect ROS1 rearrangement in NSCLC, while IHC can be used as a preliminary screening tool. These results supported the efficacy of ROS1 TKI therapy in treating advanced NSCLC patients with ROS1 rearrangement.

Effects of Implementation of Lung Cancer Screening at One Veterans Affairs Medical Center. Okereke IC1, Bates MF2, Jankowich MD3, Rounds SI3, Kimble BA3, Baptiste JV3, Ng TT2, Nici LL3. Chest. 2016 Aug 24. pii: S0012-3692(16)57740-X. doi: 10.1016/j.chest.2016.08.1431. [Epub ahead of print]
BACKGROUND: Lung cancer screening recommendations have been developed, but none has focused on veterans. We report the results of the lung cancer screening program at our Veterans Affairs Medical Center and compare them to historic results. **METHODS:** All veterans between 55 and 74 years who were current smokers or quit within the past 15 years and had at least a 30 pack year smoking history were invited to receive an annual low-dose chest computerized tomography (CT) scan beginning in December 2013. Demographics, CT results, and pathologic data of screened patients were recorded retrospectively. Overall results during the screening period were compared to results in veterans diagnosed from January 2011 to December 2013 (pre-screening period). **RESULTS:** From December 2013 through December 2014 (screening period) 1,832 patients obtained a screening CT scan. Mean age was 65. A lung nodule was present in 24% (439/1832) of patients. Lung cancer was diagnosed in 3.0% (55/1832) of screened patients. During the pre-screening period, 37% (30/82) of every lung cancer detected at our center was Stage I or Stage II. After implementation of the screening program that percentage rose to 60% (52/87, $p < 0.01$). During the screening period 63% (55/87) of all diagnosed lung cancers were detected through the screening program. The number of lung cancers detected per month rose from 2.4 to 6.7 after implementation of the screening program ($p < 0.01$). **CONCLUSIONS:** Implementation of lung cancer screening in the veteran population leads to detection of increased number and proportion of early stage lung cancers. Lung cancer screening in veterans may also increase the rate of lung cancer diagnoses in the immediate post-implementation period.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

Lobe-specific lymph node dissection as a standard procedure in surgery for non-small-cell lung cancer: A propensity score matching study. Adachi H1, Sakamaki K2, Nishii T3, et al. J Thorac Oncol. 2016 Aug 20. pii: S1556-0864(16)30847-4. doi: 10.1016/j.jtho.2016.08.127. [Epub ahead of print]
INTRODUCTION: Systematic lymph node dissection is the standard procedure in surgical treatment for non-small-cell lung cancer (NSCLC), but the value of this approach for survival and nodal staging is still uncertain. In this study, we evaluated the potential of lobe-specific lymph node dissection in surgery for NSCLC, using a propensity score matching method. **METHODS:** From 2005 to 2007, 565 patients with cT1a-2bN0-1M0 NSCLC underwent lobectomy with lymph node dissection at our 10 affiliated hospitals. Patients were classified into groups that underwent nodal sampling (NS), lobe-specific dissection (L-SND) and systematic dissection (SND) based on pathological data for the number and extent of nodal resection. A total of 77 patients with insufficient pathological data were excluded from the study. **RESULTS:** Overall survival did not differ significantly among the groups ($p = 0.552$), but the rate of detection of pN2 in the SND group (13.1%) was significantly higher than those in the NS (3.3%) and L-SND (9.0%) groups ($p = 0.010$). However, given the many confounding factors in the patient

characteristics in each group, outcomes were re-evaluated using a propensity score matching method for the L-SND and SND groups. After matching, the two groups had no significant differences in 5-year overall survival (73.5% for L-SND vs. 75.3% for SND, p = 0.977) and pN2 detection (8.2% in both groups, p = 0.779). **CONCLUSIONS:** These results suggest that lobe-specific lymph node dissection has the potential to be a standard procedure in surgical treatment for non-small-cell lung cancer.

Anatomical segmentectomy and wedge resections are associated with comparable outcomes for small cT1N0 non-small cell lung cancer. Altorki NK1, Kamel MK2, Narula N3, et al. J Thorac Oncol. 2016 Aug 2. pii: S1556-0864(16)30695-5. doi: 10.1016/j.jtho.2016.06.031. [Epub ahead of print]
OBJECTIVE: Sublobar resection is advocated for non-small cell lung cancer (NSCLC) patients with compromised cardiopulmonary reserve, as well as for selected patients with early stage disease. Anatomic segmentectomy (AS) has traditionally been considered superior to wedge resection (WR), however well balanced, comparative studies are lacking. We hypothesize that for cT1N0-NSCLC, WR and AS are associated with comparable oncologic outcomes. **METHODS:** A retrospective review of a prospective database was performed (2000-2014) for cT1N0 patients, excluding patients with multiple primaries, carcinoid tumors, adenocarcinoma in-situ and minimally invasive adenocarcinoma. Demographic, clinical, and pathological data were reviewed. Overall (OS) and Disease free survival (DFS) were estimated using the Kaplan-Meier method and differences compared using log-rank test. Multivariable analysis (MVA) of factors affecting DFS was performed by Cox regression analysis. For further comparison of the effect of resection type on survival, propensity score matching (age, gender, Charlson comorbidity index, FEV1%, clinical tumor size, and tumor SUVmax) was done to obtain balanced cohorts of patients undergoing WR and AS (n=76 per group). **RESULTS:** 289 patients met our selection criteria, including WR in 160, and AS in 129. Poor performance status, and limited cardiopulmonary reserve were the primary indications for sublobar resection in 76% of WR patients and in 62% of AS patients (P=0.011). Thirteen patients (4.5%) had pN1/2 disease. Patients undergoing AS were more likely to have nodal sampling/dissection [123 (95%) vs. 112 (70%), P<0.001], more stations sampled (3 vs. 2, P<0.001), and more total nodes resected (7 vs. 4, P=0.001). However, there was no difference between patients undergoing WR vs. AS in local recurrence [15 vs. 14, p=0.68] or 5 year DFS (51% vs. 53%, p=0.7, median follow up 34 months). Univariate analysis showed no effect of extent of resection on DFS (HR 1.07, CI: 0.74 - 1.56, p=0.696). MVA showed that only tumor SUVmax was associated with worse DFS (HR 1.07, CI: 1.01 - 1.13, P=0.016). In the propensity matched analysis of balanced subgroups, there was also no difference (p=0.950) in 3- or 5-year DFS in cT1N0 patients undergoing WR (65% and 49%) or AS (68% and 49%). **CONCLUSIONS:** Our data show that WR and AS are comparable oncologic procedures for carefully staged cT1N0-NSCLC patients. Although AS is associated with a more thorough lymph node dissection, this did not translate to a survival benefit in this patient population with a low rate of nodal metastases.

Re-Assessment of Intentional Extended Segmentectomy for Clinical T1aN0 Non-Small Cell Lung Cancer. Nishio W1, Yoshimura M2, Maniwa Y3, Kitamura Y2, Tane K2, Takenaka D4, Adachi S4. Ann Thorac Surg. 2016 Aug 12. pii: S0003-4975(16)30566-5. doi: 10.1016/j.athoracsur.2016.05.071. [Epub ahead of print]
BACKGROUND: This study compares long-term prognosis of intentional extended segmentectomy and lobectomy of clinical T1aN0M0 non-small cell lung cancer (NSCLC). Risk factors of local-regional recurrence are identified and segmentectomy outcomes are examined per segment. **METHODS:** 164 intentional extended segmentectomies were compared with 73 lobectomies subcategorized by consolidation to maximum tumor diameter ratio (C/T) measured by computed tomographies. Preoperative characteristics were propensity score matched to evaluate local-regional recurrence-free survival using the log-rank test. Preoperative factors and surgical procedure were analyzed with the Cox proportional

hazards regression model to identify independent predictor of local-regional recurrence. Local-regional recurrence per segment were assessed by Kaplan-Meier estimates between both groups. **RESULTS:** No recurrences were observed for 46 C/T ≤0.5 segmentectomies. In 59 C/T >0.5 propensity score-matched pairs, 5-year local-regional recurrence-free survival rates of segmentectomies were 76.3%, versus 91.5% for lobectomies (p = 0.082). Multivariate analysis confirmed segmentectomies to be the only independent risk factor for local-regional recurrence-free probability (p = 0.020). Subset analysis reveals superior segmentectomies have significantly less local-regional recurrence (p = 0.029) than other segments and comparable prognosis to lower lobectomies. Left upper lobe segmentectomies also showed comparable prognosis to lobectomies. Segmentectomies in the right upper lobe and of basal segments showed significantly higher local recurrence (p = 0.001) than other segments. Basal segmentectomies showed significantly poor prognosis versus lower lobectomies (p = 0.005). **CONCLUSIONS:** For radiographically invasive right upper lobe or basal segment clinical T1a NSCLC, strict inclusion criteria is necessary for intentional segmentectomy. For superior and left upper lobe segments, however, segmentectomies may be preferred with prognosis comparable to lobectomies.

The Influence of Reconstructive Technique on Perioperative Pulmonary and Infectious Outcomes Following Chest Wall Resection. Spicer JD1, Shewale JB2, Antonoff MB2, et al. Ann Thorac Surg. 2016 Aug 12. pii: S0003-4975(16)30567-7. doi: 10.1016/j.athoracsur.2016.05.072. [Epub ahead of print] **BACKGROUND:** Emerging technologies for prosthetic reconstruction after chest wall resection have yielded a wide variety of reconstructive options for thoracic surgeons. The ideal chest wall reconstruction and its impact on perioperative outcomes has not been well defined. Our goal was to determine whether mesh characteristics such as rigidity or absorbability altered perioperative pulmonary and infectious outcomes. **METHODS:** Our institutional database was queried for patients who underwent chest wall resection and reconstruction for primary or secondary chest wall tumors between the years 1998 and 2013. A focused chart review supplied clinical and perioperative variables. The main study outcomes focused on perioperative pulmonary and wound/implant infectious complications. Univariate and multivariate analyses were performed to identify variables associated with outcome. **RESULTS:** We identified 1,096 patients who underwent chest wall resection during the study period, of which 427 required chest wall reconstruction. Pulmonary complications occurred in 24% (n = 102 of 427) of patients. We observed no significant difference in pulmonary complications between those that had a rigid versus flexible chest wall reconstruction (p = 0.401; OR, 1.43; 95% CI, 0.83-2.43). The odds of pulmonary complications increased with each additional resected rib (OR, 1.43; 95% CI, 1.2-1.71). Multivariable analysis identified the number of resected ribs (OR, 1.26; 95% CI, 1.00-1.59) and concomitant lobectomy (OR, 3.59; 95% CI, 1.62-7.92) as variables associated with perioperative pulmonary morbidity. Infectious complications occurred in 13 patients and were not predicted by the use of permanent versus absorbable prosthetic materials (p = 0.575). **CONCLUSIONS:** The type of reconstructive material, whether with rigid, flexible, permanent, or biologic characteristics, does not appear to influence perioperative pulmonary or infectious wound complications. Rather, the number of resected ribs and the concomitant lung parenchymal resection predict pulmonary morbidity following chest wall resection. Depending on the circumstances, an effective chest wall reconstruction can be achieved with either rigid or flexible prosthetic material.

"Even if I Don't Remember, I Feel Better". A Qualitative Study of Patients with Early-Stage Non-Small Cell Lung Cancer Undergoing Stereotactic Body Radiotherapy or Surgery.
Golden SE1, Thomas CR Jr2, Deffebach ME3,4, Sukumar MS5, Schipper PH5, Tieu BH5, Kee AY6, Ann Am Thorac Soc. 2016 Aug;13(8):1361-9. doi: 10.1513/AnnalsATS.201602-130OC.
RATIONALE: While surgical resection is recommended for most patients with early stage lung cancer according to the National Comprehensive Cancer Network guidelines, stereotactic body radiotherapy is increasingly being used. Provider-patient communication regarding the risks and benefits of each approach may be a modifiable factor leading to improved patient-centered outcomes. **OBJECTIVES:** To qualitatively describe the experiences of patients undergoing either surgery or stereotactic body radiotherapy for early stage non-small cell lung cancer. **METHODS:** We qualitatively evaluated and used content analysis to describe the experiences of 13 patients with early clinical stage non-small cell lung cancer before undergoing treatment in three health care systems in the Pacific Northwest, with a focus on knowledge obtained, communication, and feelings of distress. **MEASUREMENTS AND MAIN RESULTS:** Although most participants reported rarely having been told about other options for treatment and could not readily recall many details about specific risks of recommended treatment, they were satisfied with their care. The patients paradoxically described clinicians as displaying caring and empathy despite not explicitly addressing their concerns and worries. We found that the communication domains that underlie shared decision making occurred infrequently, but that participants were still pleased with their role in the decision-making process. We did not find substantially different themes based on where the participant received care or the treatment selected. **CONCLUSIONS:** Patients were satisfied with all aspects of their care, despite reporting little knowledge about risks or other treatment options, no direct elicitation of worries from providers, and a lack of shared decision making. While the development of effective communication strategies to address these gaps is warranted, their effect on patient-centered outcomes, such as distress and decisional conflict, is unclear.

NSCLC - CHEMOTHERAPY

Dermatological adverse events with taxane chemotherapy. Sibaud V1, Lebœuf NR2, Roche H3, et al. Eur J Dermatol. 2016 Aug 22. [Epub ahead of print]
Taxanes (docetaxel and paclitaxel) are among the most commonly prescribed anticancer drugs approved for the treatment of metastatic or locally advanced breast, non-small cell lung, prostate, gastric, head and neck, and ovarian cancers, as well as in the adjuvant setting for operable node-positive breast cancers. Although the true incidence of dermatological adverse events (AEs) in patients receiving taxanes is not known, and has never been prospectively analysed, they clearly represent one of the major AEs associated with these agents. With an increase in the occurrence of cutaneous AEs during treatment with novel targeted and immunological therapies when used in combination with taxanes, a thorough understanding of reactions attributable to this class is imperative. Moreover, identification and management of dermatological AEs is critical for maintaining the quality of life in cancer patients and for minimizing dose modifications of their antineoplastic regimen. This analysis represents a systematic review of the dermatological conditions reported with the use of these drugs, complemented by experience at comprehensive cancer centres. The conditions reported herein include skin, hair, and nail toxicities. Lastly, we describe the dermatological data available for the new, recently FDA-and EMA- approved, solvent-free nab-paclitaxel.

Weekly vinorelbine and paclitaxel in older patients with advanced non-small cell lung cancer: A phase II Fred and Pamela Buffet Cancer Center Clinical Trials Network study. Huerter MM1, Meza JL2, Copur MS3, et al. J Geriatr Oncol. 2016 Aug 1. pii: S1879-4068(16)30095-9. doi: 10.1016/j.jgo.2016.07.006. [Epub ahead of print]

OBJECTIVE: Platinum-based doublet chemotherapy is the standard for most patients with advanced non-small cell lung cancer (NSCLC). Toxicity concerns limit chemotherapy for patients over 70years. Vinorelbine and paclitaxel are effective as single agents in advanced NSCLC. This phase II study evaluates safety and efficacy of a combination of these two agents in patients >70years with advanced NSCLC. **MATERIALS AND METHODS:** Patients with treatment naïve metastatic NSCLC received two cycles comprising 6 weekly doses of vinorelbine and paclitaxel, with restaging scans at week 8. Patients with radiographic progression came off study. The estimated sample size was 29. Toxicity analyses were conducted after 10 patients and again after 19 patients were enrolled. Outcomes were safety and efficacy, progression free (PFS) and overall survival (OS) and quality of life (QOL). **RESULTS:** The study closed at second interim analysis as 6/19 patients had ≥grade 4 non-hematologic toxicity (respiratory failure, sepsis, ischemic encephalopathy, pneumonia, hypoxemia, cardiopulmonary arrest, neutropenic fever, death). Of the 16 evaluable patients, 7 completed the study. Disease control rate (partial response+stable disease) was 47% (n=9); 37% (n=7) progressed. No complete responses were seen. Median PFS was 3.5months (95% CI: 1.4, 5.5) and OS 7.8months (95% CI: 1.9, 13.6). QOL did not change compared to baseline, at week 9, but increased at week 17. **CONCLUSIONS:** Although the combination met its response end points, increased toxicity makes this combination unsuitable for older patients. While QOL improved over the study, the small sample hinders interpretation.

The BATTLE-2 Study: A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients With Advanced Non-Small-Cell Lung Cancer. Papadimitrakopoulou V1, Lee JJ2, Wistuba II2, et al. J Clin Oncol. 2016 Aug 1. pii: JCO660084. [Epub ahead of print]
PURPOSE: By applying the principles of real-time biopsy, biomarker-based, adaptively randomized studies in non-small-cell lung cancer (NSCLC) established by the Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) trial, we conducted BATTLE-2 (BATTLE-2 Program: A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients With Advanced Non-Small Cell Lung Cancer), an umbrella study to evaluate the effects of targeted therapies focusing on KRAS-mutated cancers. **PATIENTS AND METHODS:** Patients with advanced NSCLC (excluding sensitizing EGFR mutations and ALK gene fusions) refractory to more than one prior therapy were randomly assigned, stratified by KRAS status, to four arms: (1) erlotinib, (2) erlotinib plus MK-2206, (3) MK-2206 plus AZD6244, or (4) sorafenib. Tumor gene expression profiling-targeted next-generation sequencing was performed to evaluate predictive and prognostic biomarkers. **RESULTS:** Two hundred patients, 27% with KRAS-mutated (KRAS mut+) tumors, were adaptively randomly assigned to erlotinib (n = 22), erlotinib plus MK-2206 (n = 42), MK-2206 plus AZD6244 (n = 75), or sorafenib (n = 61). In all, 186 patients were evaluable, and the primary end point of an 8-week disease control rate (DCR) was 48% (arm 1, 32%; arm 2, 50%; arm 3, 53%; and arm 4, 46%). For KRAS mut+ patients, DCR was 20%, 25%, 62%, and 44% whereas for KRAS wild-type patients, DCR was 36%, 57%, 49%, and 47% for arms 1, 2, 3, and 4, respectively. Median progression-free survival was 2.0 months, not different by KRAS status, 1.8 months for arm 1, and 2.5 months for arms 2 versus arms 3 and 4 in KRAS mut+ patients (P = .04). Median overall survival was 6.5 months, 9.0 and 5.1 months for arms 1 and 2 versus arms 3 and 4 in KRAS wild-type patients (P = .03). Median overall survival was 7.5 months in mesenchymal versus 5 months in epithelial tumors (P = .02). **CONCLUSION:** Despite improved progression-free survival on therapy that did not contain erlotinib for KRAS mut+ patients and improved prognosis for mesenchymal tumors, better biomarker-driven treatment strategies are still needed.

Salvage treatment with irinotecan/cisplatin versus pemetrexed/cisplatin in patients with non-small cell lung cancer pre-treated with a non-platinum-based regimen in the first-line setting: a randomized phase II study of the Hellenic Oncology Research Group (HORG).
Kentepozidis N1, Economopoulou P1, Christofyllakis C1, et al. Clin Transl Oncol. 2016 Aug 4. [Epub ahead of print]
BACKGROUND: Platinum-based chemotherapy is the standard front-line treatment for patients with advanced non-small cell lung cancer (NSCLC). However, non-platinum combinations of third-generation chemotherapeutic agents are considered an alternative therapeutic option for patients who cannot tolerate the toxic effects of platinum compounds. In this study, the efficacy and toxicity of the combination of irinotecan plus cisplatin (IC) was compared to pemetrexed plus cisplatin (PC) regimen, in platinum-naïve patients with advanced NSCLC, who had been previously treated with the combination of a taxane plus gemcitabine. **PATIENTS AND METHODS:** A total of 124 patients with locally advanced or metastatic NSCLC were randomly assigned to either irinotecan 110 mg/m2 on day 1 and 100 mg/m2 on day 8 plus cisplatin 80 mg/m2 on day 8 every 3 weeks (IC arm) or pemetrexed 500 mg/m2 plus cisplatin 80 mg/m2 on day 1 every 3 weeks (PC arm). The primary endpoint of the study was the overall response rate (ORR). **RESULTS:** The ORR and median progression-free survival (PFS) in the IC arm were 18 % and 3.3 months, respectively, while in the PC arm were 19 % and 4.2 months (p = ns). Median overall survival (OS) was significantly higher in patients with PC (6.9 vs. 10.9; p = 0.013). PC regimen had a better toxicity profile compared to IC, with a statistically significant lower incidence of grade 3/4 neutropenia (3 vs. 31 %; p = 0.0001) and diarrhea (1.6 vs. 14.7 %, p = 0.018). **CONCLUSIONS:** In patients with advanced NSCLC pretreated with docetaxel/gemcitabine, the combination of pemetrexed/cisplatin is associated with increased OS and is better tolerated than the combination of irinotecan/cisplatin and should be considered as a valid therapeutic option for platinum-naive, previously treated patients.

Randomized Phase II Trial of Gefitinib With and Without Pemetrexed as First-Line Therapy in Patients With Advanced Nonsquamous Non-Small-Cell Lung Cancer With Activating Epidermal Growth Factor Receptor Mutations. Cheng Y1, Murakami H1, Yang PC1, et al. J Clin Oncol. 2016 Aug 9. pii: JCO669218. [Epub ahead of print]
PURPOSE: To determine whether the addition of pemetrexed to gefitinib (P+G) provides clinical benefit, compared with gefitinib monotherapy, in patients with advanced nonsquamous (NS) non-small-cell lung cancer (NSCLC) and activating epidermal growth factor receptor (EGFR) mutations.
PATIENTS AND METHODS: Chemotherapy-naïve for advanced NSCLC patients from China, Japan, Korea, and Taiwan (35 sites) with advanced, EGFR-mutant, NS NSCLC were randomly assigned (2:1; computer-generated, interactive voice response) to open-label pemetrexed (500 mg/m2 on day 1 of every 21-day cycle) plus gefitinib (250 mg/d [n = 129]) or gefitinib alone (n = 66). The primary end point was progression-free-survival (PFS); secondary end points were time to progressive disease, overall survival, tumor response rates, duration of response, and safety. All end points were assessed in the intent-to-treat and safety population (P+G, n = 126; gefitinib alone, n = 65). **RESULTS:** PFS was significantly longer with P+G (median, 15.8 months; 95% CI, 12.6 to 18.3 months) than with gefitinib (median, 10.9 months; 95% CI, 9.7 to 13.8 months; adjusted hazard ratio [HR], 0.68; 95% CI, 0.48 to 0.96; one-sided P = .014; two-sided P = .029). Results of EGFR exon 19 deletion and EGFR exon 21 L858R point mutation subgroup analyses were consistent with the intent-to-treat result. P+G, compared with gefitinib alone, resulted in significantly longer time to progressive disease (median, 16.2 v 10.9 months, respectively; HR, 0.66; 95% CI, 0.47 to 0.93) and numerically longer duration of response (median, 15.4 v 11.3 months, respectively; HR, 0.74; 95% CI, 0.50 to 1.08). Tumor response rates did not differ. Overall survival data are immature. Drug-related grade 3 or 4 adverse events were more common with P+G, but toxicities were manageable. **CONCLUSION:** P+G improved PFS compared with gefitinib alone in East Asian patients with advanced NS NSCLC and activating EGFR mutations. This combination may offer EGFR mutation-

positive patients new treatment options and improved clinical outcomes compared with the current standard of care.

Patients with ROS1 rearrangement-positive non-small-cell lung cancer benefit from pemetrexed-based chemotherapy. Song Z1,2, Su H3, Zhang Y1,2. Cancer Med. 2016 Aug 20. doi: 10.1002/cam4.809. [Epub ahead of print]
ROS1 gene-rearrangement in non-small-cell lung cancer (NSCLC) patients has recently been identified as a driver gene and benefited from crizotinib treatment. However, no data are available for ROS1-positive NSCLC about chemotherapeutic options and prognostic data. We investigated pemetrexed-based treatment efficacy in ROS1 translocation NSCLC patients and determined the expression of thymidylate synthetase (TS) to provide a rationale for the efficacy results. We determined the ROS1 status of 1750 patients with lung adenocarcinoma. Patients' clinical and therapeutic profiles were assessed. In positive cases, thymidylate synthetase (TS) mRNA level was performed by RT-PCR. For comparison, we evaluated the TS mRNA status and pemetrexed-based treatment efficacy from 170 NSCLC patients with anaplastic lymphoma kinase (ALK) translocation (n = 46), EGFR mutation (n = 50), KRAS mutation (n = 32), and wild-type of EGFR/ALK/ROS1/KRAS (n = 42). Thirty-four ROS1 translocation patients were identified at two institutions. Among the 34 patients, 12 with advanced stage or recurrence were treated with pemetrexed-based first-line chemotherapy. The median progression-free survivals of pemetrexed-based first-line chemotherapy in ROS1 translocation, ALK translocation, EGFR mutation, KRAS mutation, and EGFR/ALK/ROS1/KRAS wild-type patients were 6.8, 6.7, 5.2, 4.2, and 4.5 months, respectively (P = 0.003). The TS mRNA level was lower in patients with ROS1-positive than ROS1-negative patients (264 ± 469 × 10-4 vs. 469 ± 615 × 10-4 , P = 0.03), but similar with ALK-positive patients (264 ± 469 × 10-4 vs. 317 ± 524 × 10-4 , P = 0.64). Patients diagnosed with ROS1 translocation lung adenocarcinoma may benefit from pemetrexed-based chemotherapy. TS mRNA level enables the selection of therapeutic options for ROS1 translocation patients.

Open-label, randomized study of individualized, pharmacokinetically (PK)-guided dosing of paclitaxel combined with carboplatin or cisplatin in patients with advanced non-small-cell lung cancer (NSCLC). Joerger M1, von Pawel J2, Kraff S3, et al. Ann Oncol. 2016 Aug 8. pii: mdw290. [Epub ahead of print]
BACKGROUND: Variable chemotherapy exposure may cause toxicity or lack of efficacy. This study was initiated to validate pharmacokinetically (PK)-guided paclitaxel dosing in patients with advanced non-small-cell lung cancer (NSCLC) to avoid supra- or subtherapeutic exposure. **PATIENTS AND METHODS:** Patients with newly diagnosed, advanced NSCLC were randomly assigned to receive up to 6 cycles of 3-weekly carboplatin AUC 6 or cisplatin 80 mg/m2 either with standard paclitaxel at 200 mg/m2 (arm A) or PK-guided dosing of paclitaxel (arm B). In arm B, initial paclitaxel dose was adjusted to body surface area, age, sex, and subsequent doses were guided by neutropenia and previous-cycle paclitaxel exposure [time above a plasma concentration of 0.05 μM (Tc>0.05)] determined from a single blood sample on day 2. The primary end point was grade 4 neutropenia; secondary end points included neuropathy, radiological response, progression-free survival (PFS) and overall survival (OS). **RESULTS:** Among 365 patients randomly assigned, grade 4 neutropenia was similar in both arms (19% versus 16%; P = 0.10). Neuropathy grade ≥2 (38% versus 23%, P < 0.001) and grade ≥3 (9% versus 2%, P < 0.001) was significantly lower in arm B, independent of the platinum drug used. The median final paclitaxel dose was significantly lower in arm B (199 versus 150 mg/m2, P < 0.001). Response rate was similar in arms A and B (31% versus 27%, P = 0.405), as was adjusted median PFS [5.5 versus 4.9 months, hazard ratio (HR) 1.16, 95% confidence interval (CI) 0.91-1.49, P = 0.228] and OS (10.1 versus 9.5 months, HR 1.05, 95% CI 0.81-1.37, P = 0.682). **CONCLUSION:** PK-guided dosing of paclitaxel does not improve severe

neutropenia, but reduces paclitaxel-associated neuropathy and thereby improves the benefit-risk profile in patients with advanced NSCLC.

Cost-effectiveness of pembrolizumab versus docetaxel for the treatment of previously treated PD-L1 positive advanced NSCLC patients in the United States. Huang M1, Lou Y2, Pellissier J1, Burke T1, Liu FX1, Xu R1, Velcheti V3. J Med Econ. 2016 Aug 29:1-28. [Epub ahead of print]
OBJECTIVES: This analysis aimed to evaluate the cost-effectiveness of pembrolizumab compared with docetaxel in patients with previously treated advanced non-squamous cell lung cancer (NSCLC) with PD-L1 positive tumors (total proportion score [TPS]> =50%). The analysis was conducted from a US third-party payer perspective. **METHODS:** A partitioned-survival model was developed using data from patients from the KEYNOTE 010 clinical trial. The model used Kaplan-Meier (KM) estimates of progression-free survival (PFS) and overall survival (OS) from the trial for patients treated with either pembrolizumab 2mg/kg or docetaxel 75mg/m2 with extrapolation based on fitted parametric functions and long-term registry data. Quality-adjusted life years (QALYs) were derived based on EQ-5D data from KEYNOTE 010 using a time to death approach. Costs of drug acquisition/administration, adverse event management, and clinical management of advanced NSCLC were included in the model. The base-case analysis used a time horizon of 20 years. Costs and health outcomes were discounted at a rate of 3% per year. A series of one-way and probabilistic sensitivity analyses were performed to test the robustness of the results. **RESULTS:** Base case results project for PD-L1 positive (TPS> =50%) patients treated with pembrolizumab a mean survival of 2.25 years. For docetaxel, a mean survival time of 1.07 years was estimated. Expected QALYs were 1.71 and 0.76 for pembrolizumab and docetaxel, respectively. The incremental cost per QALY gained with pembrolizumab versus docetaxel is $168,619/QALY, which is cost-effective in the US using a threshold of three times GDP per capita. Sensitivity analyses showed the results to be robust over plausible values of the majority of inputs. Results were most sensitive to extrapolation of overall survival. **CONCLUSIONS:** Pembrolizumab improves survival, increases QALYs and can be considered as a cost-effective option compared to docetaxel in PD-L1 positive (TPS> =50%) pre-treated advanced NSCLC patients in the US.

NSCLC - RADIOTHERAPY

Decreased Risk of Radiation Pneumonitis With Coincident Concurrent Use of Angiotensin-converting Enzyme Inhibitors in Patients Receiving Lung Stereotactic Body Radiation Therapy. Alite F1, Balasubramanian N, Adams W, Surucu M, Mescioglu I, Harkenrider MM. Am J Clin Oncol. 2016 Aug 24. [Epub ahead of print]
OBJECTIVES: Angiotensin-converting enzyme inhibitors (ACEi) have demonstrated decreased rates of radiation-induced lung injury in animal models and clinical reports have demonstrated decreased pneumonitis in the setting of conventionally fractionated radiation to the lung. We tested the role of ACEi in diminishing rates of symptomatic (grade ≥2) pneumonitis in the setting of lung stereotactic body radiation therapy (SBRT). **METHODS:** We analyzed patients treated with thoracic SBRT to 48 to 60 Gy in 4 to 5 fractions from 2006 to 2014. We reviewed pretreatment and posttreatment medication profiles to document use of ACEi, angiotensin receptor blockers, bronchodilators, aspirin, PDE-5 inhibitors, nitrates, and endothelin receptor antagonists. Pneumonitis was graded posttreatment based on Common Terminology Criteria for Adverse Events Version 4.0. Univariate and multivariate analysis was performed and time to development of pneumonitis was evaluated by the Kaplan-Meier method. **RESULTS:** A total of 189 patients were evaluated with a median follow-up of 24.8 months. The overall 1-year rate of symptomatic pneumonitis was 13.2%. The 1-year rate of symptomatic pneumonitis was 4.2% for ACEi users versus 16.3% in nonusers (P=0.03). On univariate analysis, the odds of developing grade 2 or greater pneumonitis were significantly lower for patients on ACEi (P=0.03). On multivariate analysis,

after controlling for clinicopathologic characteristics and dosimetric endpoints, there was a significant association between ACEi use and decreased risk of clinical pneumonitis (P=0.04). Angiotensin receptor blockers or other bronchoactive medications did not show significant associations with development of pneumonitis. **CONCLUSIONS:** Incidental concurrent use of ACEi demonstrated efficacy in diminishing rates of symptomatic pneumonitis in the setting of lung SBRT.

Stereotactic Ablative Radiotherapy and immunotherapy combinations: turning the future into systemic therapy? Walshaw RC1, Honeychurch J1, Illidge TM1. Br J Radiol. 2016 Aug 24:20160472. [Epub ahead of print]
Radiotherapy (RT) is effective at cytoreducing tumours and until relatively recently the focus in radiobiology has been on the direct effects of RT on the tumour. Increasingly however the effect of RT on the tumour vasculature, tumour stroma and immune system are recognised as important to the overall outcome. RT is known to lead to the induction of immunogenic cell death (ICD) which can generate tumour-specific immunity. However, systemic immunity leading to "abscopal effects" resulting in tumour shrinkage outside of the RT treatment field are rare, which is thought to be caused by the immunosuppressive nature of the tumour microenvironment. Recent advances in understanding the nature of this immunosuppression and therapeutics targeting immune checkpoints such as Programmed Death-1 (PD-1) has led to durable clinical responses in a range of cancer types including malignant melanoma and non small cell lung cancer (NSCLC). The effects of RT dose and fraction on the generation of ICD and systemic immunity are largely unknown and currently under investigation. Stereotactic ablative radiotherapy (SABR) provides an opportunity to deliver single or hypofractionated large doses of RT and potentially increase the amount of ICD tumour cell death and the generation of systemic immunity. Here we review the interplay of RT and the tumour microenvironment and the rationale for combining SABR with immunomodulatory agents to generate systemic immunity and improve outcomes.

Comparison of the Effectiveness of Radiofrequency Ablation With Stereotactic Body Radiation Therapy in Inoperable Stage I Non-Small Cell Lung Cancer: A Systemic Review and Pooled Analysis. Bi N1, Shedden K2, Zheng X3, Kong FM4. Int J Radiat Oncol Biol Phys. 2016 Aug 1;95(5):1378-90. doi: 10.1016/j.ijrobp.2016.04.016.
PURPOSE: To performed a systematic review and pooled analysis to compare clinical outcomes of stereotactic body radiation therapy (SBRT) and radiofrequency ablation (RFA) for the treatment of medically inoperable stage I non-small cell lung cancer. **METHODS AND MATERIALS:** A comprehensive literature search for published trials from 2001 to 2012 was undertaken. Pooled analyses were performed to obtain overall survival (OS) and local tumor control rates (LCRs) and adverse events. Regression analysis was conducted considering each study's proportions of stage IA and age. **RESULTS:** Thirty-one studies on SBRT (2767 patients) and 13 studies on RFA (328 patients) were eligible. The LCR (95% confidence interval) at 1, 2, 3, and 5 years for RFA was 77% (70%-85%), 48% (37%-58%), 55% (47%-62%), and 42% (30%-54%) respectively, which was significantly lower than that for SBRT: 97% (96%-98%), 92% (91%-94%), 88% (86%-90%), and 86% (85%-88%) (P<.001). These differences remained significant after correcting for stage IA and age (P<.001 at 1 year, 2 years, and 3 years; P=.04 at 5 years). The effect of RFA was not different from that of SBRT on OS (P>.05). The most frequent complication of RFA was pneumothorax, occurring in 31% of patients, whereas that for SBRT (grade ≥3) was radiation pneumonitis, occurring in 2% of patients. **CONCLUSIONS:** Compared with RFA, SBRT seems to have a higher LCR but similar OS. More studies with larger sample sizes are warranted to validate such findings.

Accelerated hypofractionated radiation therapy (AHRT) for non-small-cell lung cancer: can we leave standard fractionation?

de Dios NR1,2,3, Sanz X4,5,6, Foro P4,5,6, Membrive I4,5, Reig A4,5, Ortiz A4,5, Jiménez R4,5, Algara M4,5,6. Clin Transl Oncol. 2016 Aug 23. [Epub ahead of print]

PURPOSE: To report interim results from a single-institution study conducted to assess accelerated hypofractionated radiotherapy (AHRT) delivered with 3D conformal radiotherapy in two groups of patients with non-small cell lung cancer: (1) patients with early stage disease unable to tolerate surgery and ineligible for stereotactic body radiation therapy, and (2) patients with locally advanced disease unsuitable for concurrent chemoradiotherapy. **METHODS/PATIENTS:** A total of 83 patients (51 stage I-II, 32 stage III) were included. Radiotherapy targets included the primary tumor and positive mediastinal areas identified on the pre-treatment PET-CT. Mean age was 77.8 ± 7.8 years. ECOG performance status (PS) was ≥2 in 50.6 % of cases. Radiotherapy was delivered in daily fractions of 2.75 Gy to a total dose of 66 Gy (BED10 84 Gy). Acute and late toxicities were evaluated according to NCI CTC criteria. **RESULTS:** At a median follow-up of 42 months, median overall survival (OS) and cause-specific survival (CSS) were 23 and 36 months, respectively. On the multivariate analysis, PS [HR 4.14, p = 0.0001)], stage [HR 2.51, p = 0.005)], and maximum standardized uptake values (SUVmax) [HR 1.04, p = 0.04)] were independent risk factors for OS. PS [HR 5.2, p = 0.0001)] and stage [HR 6.3, p = 0.0001)] were also associated with CSS. No cases of severe acute or late treatment-related toxicities were observed. **CONCLUSIONS:** OS and CSS rates in patients treated with AHRT for stage I-II and stage III NSCLC were good. Treatment was well tolerated with no grade three or higher treatment-related toxicity. PS, stage, and SUV max were predictive for OS and CSS.

IMMUNOTHERAPY

The safety and efficacy of nivolumab in advanced (metastatic) non-small cell lung cancer.

Tanvetyanon T1, Creelan BC1, Antonia SJ1. Expert Rev Anticancer Ther. 2016 Aug 22:1-8. [Epub ahead of print]

INTRODUCTION: Advanced non-small cell lung cancer (NSCLC) is a challenging oncological problem. Following standard initial therapy, disease progression will typically develop. Patients with relapsed or refractory disease are left with limited treatment options. The advent of nivolumab, a monoclonal antibody against Program Death-1 (PD-1), has substantially changed the outlook for such patients. **AREA COVERED:** Nivolumab is the first checkpoint immunotherapeutic agent to gain regulatory approval for NSCLC. By enabling host immune-mediated cytotoxic activity against tumor cells, nivolumab induces a partial or complete tumor response in 15-20% of patients, regardless of number of previous lines of anti-cancer therapy. Nivolumab-related adverse effects are generally milder and less frequent than those observed with conventional cytotoxic chemotherapy. Although immune-related adverse events such as fatal pneumonitis have been reported with nivolumab therapy, most adverse events are reversible with a prompt immunosuppression. Studies investigating nivolumab in combination with other agents are ongoing. Expert commentary: Nivolumab represents a significant breakthrough in the treatment of advanced NSCLC. Its therapeutic role for NSCLC may soon expand to include consolidation or maintenance setting. Furthermore, several clinical trials investigating the combination of nivolumab with other immunologic or non-immunologic treatments are ongoing and these will likely result in additional roles of nivolumab in NSCLC.

A phase II study of topotecan and cisplatin with sequential thoracic radiotherapy in elderly patients with small-cell lung cancer: Okayama Lung Cancer Study Group 0102. Kubo T1, Fujiwara K2, Hotta K3,4, et al. . Cancer Chemother Pharmacol. 2016 Aug 20. [Epub ahead of print]
PURPOSE: The treatment outcome in elderly patients with limited-disease small-cell lung cancer (LD-SCLC) remains poor. We carried out a phase II trial of split topotecan and cisplatin (TP) therapy and sequential thoracic radiotherapy for elderly LD-SCLC patients as a follow-up to our previous phase I trial. **METHODS:** In total, 30 patients aged 76 years or older, with untreated LD-SCLC were enrolled. Four courses of topotecan (1.0 mg/m2, days 1-3) and cisplatin (20 mg/m2, days 1-3) were administered, followed by thoracic radiotherapy (1.8 Gy/day, total of 45 Gy). The primary end point was the overall response rate (ORR). **RESULTS:** The trial was terminated early with 22 patients because of slow accrual. Their median age was 79 years. The median number of courses of chemotherapy administered was three, and the actual completion rate of the entire treatment course was 41 %. The ORR was 68 % with a 95 % confidence interval of 47-89 % (15/22 cases). The median progression-free survival and overall survival were 9.1 and 22.2 months, respectively. The main toxicity was myelosuppression, with grades 3-4 neutropenia (96 %), thrombocytopenia (50 %), and febrile neutropenia (32 %). **CONCLUSIONS:** This regimen produced a favorable survival outcome, despite moderate-to-severe toxicity profiles. Further efforts are necessary to define an optimal regimen for elderly patients with limited SCLC.

Karnofsky Performance Score, Radiation Dose and Nodal Status Predict Survival of Elderly Patients Irradiated for Limited-disease Small-cell Lung Cancer. Käsmann L1, Janssen S2, Rades D3. Anticancer Res. 2016 Aug;36(8):4177-80.
AIM: Elderly patients require special consideration in oncology treatment. Small-cell lung cancer (SCLC) is a highly aggressive tumour with dismal prognosis. The present study focused on prognostic factors in elderly patients irradiated for limited-disease SCLC. **PATIENTS AND METHODS:** In 36 patients aged ≥65 years, 11 factors were evaluated for the impact on survival, namely gender, Karnofsky performance score, body mass index, T-category, N-category, tobacco consumption, time from SCLC diagnosis to irradiation, smoking during irradiation, simultaneous chemotherapy, radiation dose and prophylactic cranial irradiation. **RESULTS:** On multivariate analysis, Karnofsky performance score of >70 ($p<0.001$), N-category 0-2 ($p\leq0.001$) and total radiation dose of >52 Gy ($p=0.011$) were significantly associated with better survival. **CONCLUSION:** Significant predictors of survival in elderly patients irradiated for limited-disease SCLC were identified. A radiation dose of >52 Gy resulted in improved survival when compared to lower doses.

Favorable Disease-free Survival Associated with Programmed Death Ligand 1 Expression in Patients with Surgically Resected Small-cell Lung Cancer.
Toyokawa G1, Takada K2, Haratake N3, Takamori S3, Akamine T3, Katsura M3, Fujishita T3, Shoji F3, Okamoto T3, Oda Y4, Maehara Y3. Anticancer Res. 2016 Aug;36(8):4329-36.
BACKGROUND: The prognostic significance of programmed death ligand 1 (PD-L1) has been reported in non-small cell lung cancer; however, the significance of PD-L1 expression in patients with resected small-cell lung cancer (SCLC) remains to be clarified. **MATERIALS AND METHODS:** Forty patients with SCLC whose resected specimens were available for immunohistochemistry for PD-L1 were evaluated to determine the association between its expression and the clinicopathological factors and prognosis. **RESULTS:** Among 40 patients, PD-L1 was expressed in tumor cells (TCs) of six (15%), tumor-infiltrating cells (ICs) of 16 (40%), and TCs and/or ICs cells of 18 (45%) patients. Patients with PD-L1-positve ICs and TCs and/or ICs exhibited significantly longer disease-free survival than those without PD-L1-expression (hazard ratio (HR)=0.268; 95% confidence interval (CI)=0.100-0.645; p=0.003

and HR=0.301; 95% CI=0.118-0.702; p=0.005, respectively). **CONCLUSION:** This study provides important evidence on the prognostic value of the PD-L1 expression in resected SCLC patients.

Comorbidity and outcomes of concurrent chemo- and radiotherapy in limited disease small cell lung cancer. Halvorsen TO1,2, Sundstrøm S2, Fløtten Ø3, et al. Acta Oncol. 2016 Aug 23:1-9. [Epub ahead of print]
BACKGROUND: Many patients with limited disease small cell lung cancer (LD SCLC) suffer from comorbidity. Not all patients with comorbidity are offered standard treatment, though there is little evidence for such a policy. The aim of this study was to investigate whether patients with comorbidity had inferior outcomes in a LD SCLC cohort. **MATERIAL AND METHODS:** We analyzed patients from a randomized study comparing two three-week schedules of thoracic radiotherapy (TRT) plus standard chemotherapy in LD SCLC. Patients were to receive four courses of cisplatin/etoposide and TRT of 45 Gy/30 fractions (twice daily) or 42 Gy/15 fractions (once daily). Responders received prophylactic cranial irradiation (PCI). Comorbidity was assessed using the Charlson Comorbidity Index (CCI), which rates conditions with increased one-year mortality. **RESULTS:** In total 157 patients were enrolled between May 2005 and January 2011. Median age was 63 years, 52% were men, 16% had performance status 2, and 72% stage III disease. Forty percent had no comorbidity; 34% had CCI-score 1; 15% CCI 2; and 11% CCI 3-5. There were no significant differences in completion rates of chemotherapy, TRT or PCI across CCI-scores; or any significant differences in the frequency of grade 3-5 toxicity ($p = 0.49$), treatment-related deaths ($p = 0.36$), response rates ($p = 0.20$), progression-free survival ($p = 0.18$) or overall survival ($p = 0.09$) between the CCI categories. **CONCLUSION:** Patients with comorbidity completed and tolerated chemo-radiotherapy as well as other patients. There were no significant differences in response rates, progression-free survival or overall survival - suggesting that comorbidity alone is not a reason to withhold standard therapy in LD SCLC.

Barasertib,(AZD1152)a small molecule Aurora B inhibitor, inhibits the growth of SCLC cell lines in vitro and in vivo. Helfrich BA1, Kim J1, Gao D2, Chan DC1, Zhang Z1, Tan AC1, Bunn PA3. Mol Cancer Ther. 2016 Aug 5. pii: molcanther.0298.2016. [Epub ahead of print]
Small cell lung cancer (SCLC) cells have rapid proliferation, universal Rb inactivation and high rates of MYC family amplification, making aurora kinase inhibition a natural target. Preclinical studies have demonstrated activity for Aurora A and pan Aurora inhibitors with some relationship to MYC family expression. A clinical trial showed activity for an Aurora kinase A inhibitor but no biomarkers were evaluated. We screened a panel of 23 SCLC lines with and without MYC family gene amplification or high MYC family gene expression for growth inhibition by the highly potent, selective aurora kinase B inhibitor barasertib. Nine of the SCLC lines were very sensitive to growth inhibition by barasertib with IC50 values of < 50 nM and $> 75\%$ growth inhibition at 100 nM. Growth inhibition correlated with cMYC amplification ($p = 0.018$) and cMYC gene expression ($p = 0.026$). Sensitive cell lines were also enriched in a published MYC gene signature ($p = 0.042$). In vivo the barasertib inhibited the growth of xenografts established from a SCLC line which had high cMYC gene expression, no cMYC amplification and was positive for the core MYC gene signature. Our studies suggest that SCLC tumors with cMYC amplification/high gene expression will frequently respond to Aurora B inhibitors and that clinical studies coupled with predictive biomarkers are indicated.

Belotecan/cisplatin versus etoposide/cisplatin in previously untreated patients with extensive-stage small cell lung carcinoma: a multi-center randomized phase III trial. Oh IJ1, Kim KS1, Park CK1, et al. BMC Cancer. 2016 Aug 26;16:690. doi: 10.1186/s12885-016-2741-z.
BACKGROUND: No novel chemotherapeutic combinations have demonstrated superior efficacy to etoposide/cisplatin (EP), a standard treatment regimen for extensive-stage small cell lung carcinoma (ES-

SCLC) over the past decade. We aimed to compare the efficacy and safety of belotecan/cisplatin (BP) and EP regimens in chemotherapy- and radiotherapy-naïve patients with previously untreated ES-SCLC. **METHODS:** We conducted a multi-center, randomized, open-label, parallel-group, phase III clinical study. A total of 157 patients were recruited at 14 centers with 147 patients meeting the inclusion/exclusion criteria and randomized to either BP (n = 71) or EP (n = 76) treatment arms. A non-inferior response rate (RR) in the BP arm, analyzed by intent-to-treat analysis according to Response Evaluation Criteria in Solid Tumors version 1.0 criteria, was used as the primary endpoint. The secondary endpoints were progression-free survival (PFS) and overall survival (OS). **RESULTS:** In the BP arm, one patient had a complete response, 41 had a partial response (PR), and 17 had stable disease (SD). In the EP arm, 35 patients had PR and 28 had SD. The RR in the BP arm was non-inferior to the EP regimen in patients with ES-SCLC (BP: 59.2 %, EP: 46.1 %, difference: 13.1 %, 90 % two-sided confidence interval: -0.3-26.5, meeting the predefined non-inferiority criterion of -15.0 %). No significant differences in OS or PFS were observed between the treatment arms. Hematologic toxicities, including grade 3/4 anemia and thrombocytopenia, were significantly more prevalent in the BP arm than the EP arm. **CONCLUSIONS:** The RR to the BP regimen was non-inferior to the EP regimen in chemotherapy- and radiotherapy-naïve patients with previously untreated ES-SCLC. Hematologic toxicities were significantly more prevalent in the BP group, indicating that BP should be used with care, particularly in patients with a poor performance status. Further studies assessing PFS and OS are required to validate the superiority of the BP regimen.

PALLIATIVE AND SUPPORTIVE CARE

Preparing Cancer Patients and Family Caregivers for Lung Surgery: Development of a Multimedia Self-Management Intervention.
Sun V1, Kim JY2, Raz DJ2, et al. J Cancer Educ. 2016 Aug 20. [Epub ahead of print]
The surgical treatment of lung malignancies often results in persistent symptoms, psychosocial distress, and decrements in quality of life (QOL) for cancer patients and their family caregivers (FCGs). The potential benefits of providing patients and FCGs with preparatory education that begins in the preoperative setting have been explored in multiple medical conditions, with positive impact observed on postoperative recovery, psychological distress, and QOL. However, few studies have explored the benefits of preparatory educational interventions to promote self-management in cancer surgery, including lung surgery. This paper describes the systematic approach used in the development of a multimedia self-management intervention to prepare cancer patients and their FCGs for lung surgery. Intervention development was informed by (1) contemporary published evidence on the impact of lung surgery on patients and FCG, (2) our previous research that explored QOL, symptoms, and caregiver burden after lung surgery, (3) the use of the chronic care self-management model (CCM) to guide intervention design, and (4) written comments and feedback from patients and FCGs that informed intervention development and refinement. Pilot-testing of the intervention is in process, and a future randomized trial will determine the efficacy of the intervention to improve patient, FCG, and system outcomes.

The prevalence and nature of supportive care needs in lung cancer patients. Giuliani ME1, Milne RA1, Puts M2, et al. Curr Oncol. 2016 Aug;23(4):258-65. doi: 10.3747/co.23.3012. Epub 2016 Aug 12.
PURPOSE: In the present work, we set out to comprehensively describe the unmet supportive care and information needs of lung cancer patients. **METHODS:** This cross-sectional study used the Supportive Care Needs Survey Short Form 34 (34 items) and an informational needs survey (8 items). Patients with primary lung cancer in any phase of survivorship were included. Demographic data and treatment details were collected from the medical charts of participants. The unmet needs were determined overall and by domain. Univariable and multivariable regression analyses were performed to determine factors

associated with greater unmet needs. **RESULTS:** From August 2013 to February 2014, 89 patients [44 (49%) men; median age: 71 years (range: 44-89 years)] were recruited. The mean number of unmet needs was 8 (range: 0-34), and 69 patients (78%) reported at least 1 unmet need. The need proportions by domain were 52% health system and information, 66% psychological, 58% physical, 24% patient care, and 20% sexuality. The top 2 unmet needs were "fears of the cancer spreading" [n = 44 of 84 (52%)] and "lack of energy/tiredness" [n = 42 of 88 (48%)]. On multivariable analysis, more advanced disease and higher MD Anderson Symptom Inventory scores were associated with increased unmet needs. Patients reported that the most desired information needs were those for information on managing symptoms such as fatigue (78%), shortness of breath (77%), and cough (63%). **CONCLUSIONS:** Unmet supportive care needs are common in lung cancer patients, with some patients experiencing a very high number of unmet needs. Further work is needed to develop resources to address those needs.

The Impact of Hospice Services in the Care of Patients with Advanced Stage Nonsmall Cell Lung Cancer. Duggan KT1, Duffus SH1, D'Agostino RB Jr1, Petty WJ1, Streer NP1, Stephenson RC1. J Palliat Med. 2016 Aug 25. [Epub ahead of print]
INTRODUCTION: Prior research has shown that advanced stage nonsmall cell lung cancer (NSCLC) patients enrolled in hospice care receive less aggressive treatment at the end of life (EOL) without compromising survival. Our purpose was to profile the continuum of care of these patients, exploring the connection between hospice enrollment and quality indicators for excellence in EOL cancer care. **METHODS:** One hundred ninety-seven deceased stage IV NSCLC patients diagnosed between 2008 and 2010 at two separate tertiary care centers within the same county were identified. A retrospective review was conducted, collecting data from electronic medical records regarding antitumor treatment, postdiagnosis hospital visits and admissions, hospice referrals and enrollments, and circumstances surrounding the patient's death. Patients were grouped by their status of hospice enrollment, and the remainder of the measures compared accordingly. **RESULTS:** There was no significant difference found in total number of postdiagnosis hospital admissions between the patients who were enrolled in hospice and those who were not. However, the group who received hospice services had a significantly lower number of hospitalizations ($p < 0.001$), emergency department visits ($p < 0.01$), and intensive care unit admissions in the last 30 days of life ($p < 0.001$). The number of lines of chemotherapy received did not differ significantly between the groups. Median survival, measured by the length of time between diagnosis and death, was significantly longer for hospice patients ($p = 0.02$). **CONCLUSIONS:** This study demonstrates that, among patients with metastatic NSCLC, hospice enrollment was associated with optimized EOL oncological care and a significantly longer median survival.

Sharing bad news of a lung cancer diagnosis: understanding through communication privacy management theory. Ngwenya N1, Farquhar M2, Ewing G1. Psychooncology. 2016 Aug;25(8):913-8. doi: 10.1002/pon.4024. Epub 2015 Nov 25.
BACKGROUND: The aim of this paper is to understand the process of information disclosure and privacy as patients share their news of lung cancer with significant others. **METHODS:** Twenty patients with lung cancer and 17 family members/friends accompanying them at diagnosis-giving completed either individual or dyad semi-structured interviews. Initial thematic analysis, then Petronio's Communication Privacy Management theory was used to inform interpretation. **RESULTS:** Patients described a sense of ownership of the news of their cancer and sought control of how, when and with whom it was shared. Family members expressed a need to follow the patients' rules in sharing this news, which limited their own support systems. Patients and family members had to live within the relational communication boundaries in order to maintain their trusting relationship and avoid potential disruptions.
CONCLUSION: Patients as individuals are strongly interlinked with significant others, which impacts on their experience of disclosing private information. This shapes their psychological processes and

outcomes impacting on their illness experience. This should be considered when developing interventions to support patients with sharing bad news.

Efficacy and safety of lipegfilgrastim compared with placebo in patients with non-small cell lung cancer receiving chemotherapy: post hoc analysis of elderly versus younger patients.
Volovat C1, Bondarenko I2, Gladkov O3, et al. Support Care Cancer. 2016 Aug 8. [Epub ahead of print]
PURPOSE: Lipegfilgrastim, a glycoPEGylated recombinant granulocyte colony-stimulating factor (G-CSF), reduces neutropenia duration and febrile neutropenia (FN) incidence in patients with cancer receiving myelosuppressive chemotherapy. A phase 3 trial of lipegfilgrastim was conducted in patients with advanced non-small cell lung cancer (NSCLC) receiving cisplatin/etoposide (which produces mild-to-moderate myelosuppression). Because patients aged >65 years are at higher risk for FN versus younger patients, this post hoc analysis compared outcomes in elderly (>65 years) versus younger participants in this trial. **METHODS:** Patients were randomized 2:1 to receive a once-per-cycle single subcutaneous injection of lipegfilgrastim 6 mg or placebo, with up to 4 cycles of every-3-week cisplatin (day 1) and etoposide (days 1-3). The primary end point was FN incidence during cycle 1. Outcomes were compared across treatment groups and by age groups (≤65 and >65 years). **RESULTS:** For patients aged ≤65 years, FN incidence during cycle 1 was similar in the lipegfilgrastim and placebo groups (3.0 vs 3.2 %, respectively), whereas for elderly patients, there was a reduction in FN incidence with lipegfilgrastim (0 vs 13.3 %, respectively). In both age subgroups, lipegfilgrastim showed a propensity to reduce the incidence and duration of severe neutropenia, time to absolute neutrophil count (ANC) recovery, and depth of ANC nadir. Adverse events were generally similar between groups. **CONCLUSIONS:** This analysis suggests that in patients with a higher FN risk, such as the elderly patients of this study, lipegfilgrastim reduces not only the duration of severe neutropenia but also the incidence of FN.

Patient-reported symptom interference as a measure of postsurgery functional recovery in lung cancer. Shi Q1, Wang XS2, Vaporciyan AA3, Rice DC3, Popat KU4, Cleeland CS1. J Pain Symptom Manage. 2016 Aug 10. pii: S0885-3924(16)30223-8. doi: 10.1016/j.jpainsymman.2016.07.005. [Epub ahead of print]
CONTEXT: Few empirical studies have combined the patient's perspective (patient-reported outcomes, or PROs) with clinical outcomes (risk for complications, length of hospital stay, return to planned treatment) to assess the effectiveness of treatment after thoracic surgery for early-stage non-small cell lung cancer (NSCLC). **OBJECTIVES:** Quantitatively measure PROs to assess functional recovery postsurgery. **METHODS:** Treatment-naïve patients (N=72) with NSCLC who underwent either open thoracotomy or video-assisted thoracoscopic surgery (VATS) used the MD Anderson Symptom Inventory (MDASI) to report symptom interference with general activity, work, walking, mood, relations with others, and enjoyment of life for 3 months postsurgery. Functional recovery was defined as interference scores returning to presurgery levels. The MDASI's sensitivity to change in functional recovery over time was evaluated via its ability to distinguish between surgical techniques. **RESULTS:** Interference scores increased sharply by day 3 postsurgery (all $P<0.001$), then returned to baseline levels via different trajectories. Patients who had unscheduled clinic visits during the study period reported higher scores on all 6 MDASI interference items (all $P<0.05$). Compared with the open-thoracotomy group, the VATS group returned more quickly to baseline interference levels for walking (18 vs 43 days), mood (8 vs 19 days), relations with others (4 vs 16 days) and enjoyment of life (15 vs 41 days) (all $P<0.05$).
CONCLUSION: Repeated measurement of MDASI interference characterized functional recovery after thoracic surgery for NSCLC and was sensitive to VATS' ability to enhance postoperative recovery. Further study of the clinical applicability of measuring recovery outcomes using PRO-based functional assessment is warranted.

Predictors of responses to corticosteroids for anorexia in advanced cancer patients: a multicenter prospective observational study. Matsuo N1, Morita T2, Matsuda Y3, et al. Support Care Cancer. 2016 Aug 18. [Epub ahead of print]
PURPOSE: Although corticosteroids are widely used to relieve anorexia, information regarding the factors predicting responses to corticosteroids remains limited. The purpose of the study is to identify potential factors predicting responses to corticosteroids for anorexia in advanced cancer patients. **METHODS:** Inclusion criteria for this multicenter prospective observational study were patients who had metastatic or locally advanced cancer and had an anorexia intensity score of 4 or more on a 0-10 Numerical Rating Scale (NRS). Univariate and multivariate analyses were conducted to identify the factors predicting ≥2-point reduction in NRS on day 3. **RESULTS:** Among 180 patients who received corticosteroids, 99 (55 %; 95 % confidence interval [CI], 47-62 %) had a response with ≥2-point reduction. Factors that significantly predicted responses were Palliative Performance Scale (PPS) > 40 and absence of drowsiness. In addition, factors that tended to be associated with ≥2-point reduction in NRS included PS 0-3, absence of diabetes mellitus, absence of peripheral edema, presence of lung metastasis, absence of peritoneal metastasis, baseline anorexia NRS of >6, presence of pain, and presence of constipation. A multivariate analysis showed that the independent factors predicting responses were PPS of >40 (odds ratio = 2.7 [95 % CI = 1.4-5.2]), absence of drowsiness (2.6 [1.3-5.0]), and baseline NRS of >6 (2.4 [1.1-4.8]). **CONCLUSIONS:** Treatment responses to corticosteroids for anorexia may be predicted by PPS, drowsiness, and baseline symptom intensity. Larger prospective studies are needed to confirm these results.

How Does Caregiver Well-Being Relate to Perceived Quality of Care in Patients With Cancer? Exploring Associations and Pathways. Litzelman K1, Kent EE2, Mollica M2, Rowland JH2. J Clin Oncol. 2016 Aug 29. pii: JCO673434. [Epub ahead of print]
PURPOSE: Perceived quality of care (QOC) is an increasingly important metric of care quality and can be affected by such factors among patients with cancer as quality of life and physician trust. This study sought to evaluate whether informal caregiver well-being was also associated with perceived QOC among patients with cancer and assessed potential pathways that link these factors. **METHODS:** This study used data from the Cancer Care Outcomes Research and Surveillance (CanCORS) consortium. Patients with lung and colorectal cancer enrolled in CanCORS (N = 689) nominated an informal caregiver to participate in a caregiving survey. Both groups self-reported sociodemographic, psychosocial, and caregiving characteristics; cancer characteristics were obtained from the CanCORS core data set. Multivariable logistic regression was used to assess the association between caregiver psychosocial factors and subsequent patient-perceived QOC, controlling for earlier patient-perceived QOC and covariates. Secondary analysis examined potential pathways that link these factors. **RESULTS:** Patients whose informal caregiver had higher levels of depressive symptoms were significantly more likely to report fair or poor QOC (odds ratio, 1.06; 95% CI, 1.01 to 1.13). When caregivers reported fair or poor self-rated health, patients were more than three times more likely to report fair or poor perceived QOC (odds ratio, 3.76; 95% CI, 1.76 to 9.55). Controlling for patient psychosocial factors and physician communication and coordination of medical care reduced the effect size and/or statistical significance of these relationships. **CONCLUSION:** Informal caregivers are an important part of the care team and their well-being is associated with patient-perceived QOC. Engaging informal cancer caregivers as part of the care team and conducting ongoing risk stratification screening and intervention to optimize their health may improve patient-reported outcomes and QOC.

A preliminary randomised controlled study of short-term Antrodia cinnamomea treatment combined with chemotherapy for patients with advanced cancer. Tsai MY1,2,3, Hung YC4,5, Chen YH6, Chen YH7, Huang YC8, Kao CW4, Su YL6, Chiu HH5, Rau KM9. BMC Complement Altern Med. 2016 Aug 26;16(1):322. doi: 10.1186/s12906-016-1312-9.

BACKGROUND: Antrodia cinnamomea (AC) is a popular medicinal mushroom in Taiwan that has been widely used for treatment of various cancers. Few clinical studies have reported its application and efficiency in therapeutic chemotherapy strategies. We performed a double-blind, randomized clinical study to investigate whether AC given for 30 days had acceptable safety and efficacy in advanced cancer patients receiving chemotherapy. **METHODS:** Patients with advanced and/or metastatic adenocarcinoma, performance status (PS) 0-2, and adequate organ function who had previously been treated with standard chemotherapy were randomly assigned to receive routine chemotherapy regimens with AC (20 ml twice daily) orally for 30 days or placebo. The primary endpoint was 6-month overall survival (OS); the secondary endpoints were disease control rate (DCR), quality of life (QoL), adverse event (AE), and biochemical features within 30 days of treatment. **RESULTS:** From August 2010 to July 2012, 37 subjects with gastric, lung, liver, breast, and colorectal cancer (17 in the AC group, 20 in the placebo group) were enrolled in the study. Disease progression was the primary cause of death in 4 (33.3 %) AC and 8 (66.7 %) placebo recipients. Mean OSs were 5.4 months for the AC group and 5.0 months for the placebo group ($p = 0.340$), and the DCRs were 41.2 and 55 %, respectively ($p = 0.33$). Most hematologic, liver, or kidney functions did not differ significantly between the two groups, but platelet counts were lower in the AC group than in the placebo group ($p = 0.02$). QoL assessments were similar in the two groups, except that the AC group showed significant improvements in quality of sleep ($p = 0.04$). **CONCLUSIONS:** Although we found a lower mortality rate and longer mean OS in the AC group than in the control group, A. cinnamomea combined with chemotherapy was not shown to improve the outcome of advanced cancer patients, possibly due to the small sample size. In fact, the combination may present a potential risk of lowered platelet counts. Adequately powered clinical trials will be necessary to address this question.

Yu Ping Feng San reverses cisplatin-induced multi-drug resistance in lung cancer cells via regulating drug transporters and p62/TRAF6 signalling.
Lou JS1,2, Yan L1, Bi CW1,2, Chan GK1, Wu QY1, Liu YL1, Huang Y1, Yao P1, Du CY3, Dong TT1, Tsim KW1. Sci Rep. 2016 Aug 25;6:31926. doi: 10.1038/srep31926.

Yu Ping Feng San (YPFS), an ancient Chinese herbal decoction composed of Astragali Radix, Atractylodis Macrocephalae Rhizoma and Saposhnikoviae Radix, has been used in the clinic for treating immune deficiency. In cancer therapy, YPFS is being combined with chemotherapy drugs to achieve improved efficacy; however, scientific evidence to illustrate this combination effect is lacking. The present study aims to demonstrate the anti-drug resistance of YPFS in cisplatin (DDP)-resistant non-small cell lung cancer cells (A549/DDP). The application of YPFS exhibited a synergistic enhancement of DDP-induced cytotoxicity as well as of the apoptotic signalling molecules. DDP-induced expression of the multi-drug-resistance efflux transporters was markedly reduced in the presence of YPFS, resulting in a higher intracellular concentration of DDP. In addition, the application of YPFS increased DDP-induced ROS accumulation and MMP depletion, decreased p62/TRAF6 signalling in DDP-treated A549/DDP cells. The co-treatment of DDP and YPFS in tumour-bearing mice reduced the tumour size robustly (by more than 80%), which was much better than the effect of DDP alone. These results indicate that YPFS can notably improve the DDP-suppressed cancer effect, which may be a consequence of the elevation of intracellular DDP via the drug transporters as well as the down regulation of p62/TRAF6 signalling.

MISCELLANEOUS WORKS

Identifying Subsequent Therapies in Patients with Advanced Non-Small-Cell Lung Cancer and Factors Associated with Overall-Survival. Afanasjeva J1,2, Hui RL3, Spence MM3, et al. Pharmacotherapy. 2016 Aug 13. doi: 10.1002/phar.1826. [Epub ahead of print]
STUDY OBJECTIVES: Identify subsequent therapies used after first-line therapies in patients with advanced non-small-cell lung cancer (NSCLC; compare overall survival (OS) associated with subsequent therapies, and evaluate factors associated with OS in these patients. **METHODS:** The study was a retrospective cohort analysis of patients with advanced NSCLC (stage IIIB/IV) who were initiated on first-line therapy from January 1, 2008 through September 30, 2013 and afterwards given subsequent chemotherapy (index date). Patients had to be ≥ 18 years of age at time of diagnosis of advanced NSCLC. Patients were followed from the index date until one of the following end points: end of the study (September 30, 2014), disenrollment from the health plan, or death- whichever came the earliest. The primary outcome was OS. Kaplan-Meier curves and Cox proportional hazard models were used to analyze OS and evaluate the factors associated with OS. **RESULTS:** The analysis included 1,280 patients on subsequent therapies. The most common subsequent therapies were pemetrexed (n = 284, 22%), erlotinib (n = 216, 17%), and docetaxel (n = 139, 11%). Patients from the singlets group had a lower OS at 6.3 months compared to all other groups : -pemetrexed-based, combination of pemetrexed and bevacizumab-based, bevacizumab-based, doublets, and tyrosine kinase inhibitors ($p < 0.0001$). Factors associated with greater OS included age younger than 65, female gender, and a longer time between initiation of first and subsequent therapies. Factors associated with a reduction in OS were pemetrexed-based or singlet regimens for subsequent therapy, diagnosis of squamous histology, and a higher number of adverse events prior to subsequent therapy. **CONCLUSION:** In this study, we found that a subsequent therapy consisting of singlets is associated with reduced OS compared to other chemotherapy groups. Patient characteristics such as female gender, age less than 65, diagnosis of non-squamous histology, and/or longer timeframe between initiation of first-line and subsequent chemotherapy are associated with longer survival.

The Association between Ambient Fine Particulate Air Pollution and Lung Cancer Incidence: Results from the AHSMOG-2 Study. Gharibvand L1, Shavlik D2, Ghamsary M3, Beeson WL1,2, Soret S3, Knutsen R1,2, Knutsen SF1,2. Environ Health Perspect. 2016 Aug 12. [Epub ahead of print]
BACKGROUND: There is a positive association between ambient fine particulate matter (PM2.5) and incidence and mortality of lung cancer (LC), but few studies have assessed the relationship between ambient PM2.5 and LC among never smokers. **OBJECTIVES:** To assess the association between PM2.5 and risk of LC using the Adventist Health and Smog Study-2 (AHSMOG-2), a cohort of health conscious non-smokers where 81% have never smoked. **METHODS:** A total of 80,285 AHSMOG-2 subjects were followed for an average of 7.5 years with respect to incident LC identified through linkage with U.S. state cancer registries. Estimates of ambient air pollution levels at subjects' residences were obtained for 2000 and 2001, the years immediately prior to study start. **RESULTS:** A total of 250 incident LC cases occurred during 598,927 person-years of follow-up. For each 10-µg/m3 increment in PM2.5, adjusted hazard ratio (HR) with 95% confidence interval (CI) for LC incidence was 1.43 (95% CI: 1.11, 1.84) in the two-pollutant multivariable model with O3. Among those who spent more than 1 hr/day outdoors or who had lived 5 or more years at their enrollment address, the HR was 1.68 (95% CI: 1.28, 2.22) and 1.54 (95% CI: 1.17, 2.04), respectively. **CONCLUSION:** Increased risk estimates of LC were observed for each 10-µg/m3 increment in ambient PM2.5 concentration. The estimate was higher among those with longer residence at enrollment address and those who spent more than 1 hr/day outdoors.

Genetic Risk Can Be Decreased: Quitting Smoking Decreases and Delays Lung Cancer for Smokers With High and Low CHRNA5 Risk Genotypes - A Meta-analysis. Chen LS1, Baker T2, Hung RJ3, et al. EBioMedicine. 2016 Aug 10. pii: S2352-3964(16)30361-9. doi: 10.1016/j.ebiom.2016.08.012. [Epub ahead of print]

BACKGROUND: Recent meta-analyses show that individuals with high risk variants in CHRNA5 on chromosome 15q25 are likely to develop lung cancer earlier than those with low-risk genotypes. The same high-risk genetic variants also predict nicotine dependence and delayed smoking cessation. It is unclear whether smoking cessation confers the same benefits in terms of lung cancer risk reduction for those who possess CHRNA5 risk variants versus those who do not. **METHODS:** Meta-analyses examined the association between smoking cessation and lung cancer risk in 15 studies of individuals with European ancestry who possessed varying rs16969968 genotypes (N=12,690 ever smokers, including 6988 cases of lung cancer and 5702 controls) in the International Lung Cancer Consortium. **RESULTS:** Smoking cessation (former vs. current smokers) was associated with a lower likelihood of lung cancer (OR=0.48, 95%CI=0.30-0.75, p=0.0015). Among lung cancer patients, smoking cessation was associated with a 7-year delay in median age of lung cancer diagnosis (HR=0.68, 95%CI=0.61-0.77, p=4.9∗10-10). The CHRNA5 rs16969968 risk genotype (AA) was associated with increased risk and earlier diagnosis for lung cancer, but the beneficial effects of smoking cessation were very similar in those with and without the risk genotype. **CONCLUSION:** We demonstrate that quitting smoking is highly beneficial in reducing lung cancer risks for smokers regardless of their CHRNA5 rs16969968 genetic risk status. Smokers with high-risk CHRNA5 genotypes, on average, can largely eliminate their elevated genetic risk for lung cancer by quitting smoking- cutting their risk of lung cancer in half and delaying its onset by 7years for those who develop it. These results: 1) underscore the potential value of smoking cessation for all smokers, 2) suggest that CHRNA5 rs16969968 genotype affects lung cancer diagnosis through its effects on smoking, and 3) have potential value for framing preventive interventions for those who smoke.

Creating Virtual Integration and Improved Oncology Care Quality Through a Co-Management Services Agreement. Hartung NL1, Henschel RM2, Smith KB1, Gesme DH Jr1. J Oncol Pract. 2016 Aug 9. pii: JOPR010645. [Epub ahead of print]

PURPOSE: Implementation of a co-management services agreement (Co-MSA) creates agreed-upon cancer care delivery quality metrics, a forum for discussion of service line oversight, and virtually integrated care without institutional employment of oncologists. The goal of this project was to demonstrate that a Co-MSA improved predefined quality metrics and provided enhanced communications between a health system's oncology service line and a group of independent oncologists. **METHODS:** Iterative planning discussions were scheduled biweekly over an 18-month period. Contractual, quality, and clinical data with benchmarking were considered in the creation of the Co-MSA. Review of the first year's implementation occurred through examination of the metric achievements and qualitative themes that arose through committee meetings, clinical implementation processes, and cross-organizational discussions. **RESULTS:** Metrics designed for the Co-MSA included improved adherence to the breast cancer, colon cancer, and non-small-cell lung cancer level I pathways; improvement of the medical oncology physician communication component of the hospital system's Hospital Consumer Assessment of Healthcare Providers and Systems survey scores; and increased delivery of survivorship care plans to appropriate patients. Nonquantifiable themes from the first year of implementation included the need for technology to collect data, both organizations needing a wider understanding of quality improvement techniques, and a need for greater executive leadership involvement. **CONCLUSION:** In its first year, the Co-MSA resulted in improvement of the delivery of survivorship care plans and adherence to value pathways powered by the National Comprehensive Cancer Network. Improvement of Hospital Consumer Assessment of Healthcare Providers and Systems scores did not occur.

Damaging Effects of Cannabis Use on the Lungs. Yayan J1, Rasche K2. Adv Exp Med Biol. 2016 Aug 30. [Epub ahead of print]
Cannabis is the most widely smoked illicit substance in the world. It can be smoked alone in its plant form, marijuana, but it can also be mixed with tobacco. The specific effects of smoking cannabis are difficult to assess accurately and to distinguish from the effects of tobacco; however its use may produce severe consequences. Cannabis smoke affects the lungs similarly to tobacco smoke, causing symptoms such as increased cough, sputum, and hyperinflation. It can also cause serious lung diseases with increasing years of use. Cannabis can weaken the immune system, leading to pneumonia. Smoking cannabis has been further linked with symptoms of chronic bronchitis. Heavy use of cannabis on its own can cause airway obstruction. Based on immuno-histopathological and epidemiological evidence, smoking cannabis poses a potential risk for developing lung cancer. At present, however, the association between smoking cannabis and the development of lung cancer is not decisive.

Treatment patterns and cost-effectiveness of first line treatment of advanced nonsquamous non-small cell lung cancer in Medicare patients. Gilden DM1, Kubisiak JM1, Pohl GM2, Ball DE2, Gilden DE1, John WJ2, Wetmore S2, Winfree KB2. J Med Econ. 2016 Aug 30:1-23. [Epub ahead of print]
AIM: To assess the cost-effectiveness of first-line pemetrexed/platinum and other commonly administered regimens in a representative U.S. elderly population with advanced nonsquamous non-small cell lung cancer (NSCLC). **MATERIALS AND METHODS:** This study utilized the Surveillance Epidemiology and End Results (SEER) cancer registry linked to Medicare claims records. The study population included all SEER-Medicare patients diagnosed in 2008-2009 with advanced nonsquamous NSCLC (stages IIIB-IV) as their only primary cancer and who started chemotherapy within 90 days of diagnosis. The study evaluated the four most commonly observed first-line regimens: paclitaxel/ carboplatin, platinum monotherapy, pemetrexed/platinum and paclitaxel/carboplatin/bevacizumab. Overall survival and total healthcare cost comparisons as well as incremental cost-effectiveness ratios (ICERs) were calculated for pemetrexed/platinum versus each of the other three. Unstratified analyses and analyses stratified by initial disease stage were conducted. **RESULTS:** The final study population consisted of 2,461 patients. Greater administrative censorship of pemetrexed recipients at the end of the study period disproportionately reduced the observed mean survival for pemetrexed/platinum recipients. The disease stage-stratified ICER analysis found that the pemetrexed/platinum incurred total Medicare costs of $536,424 and $283,560 per observed additional year of life relative to platinum monotherapy and paclitaxel/carboplatin, respectively. The pemetrexed/platinum versus triplet comparator analysis indicated that pemetrexed/platinum was associated with considerably lower total Medicare costs, with no appreciable survival difference. **LIMITATIONS:** Limitations included differential censorship of the study regimen recipients and differential administration of radiotherapy. **CONCLUSIONS:** Pemetrexed/platinum yielded either improved survival at increased cost or similar survival at reduced cost relative to comparator regimens in the treatment of advanced nonsquamous NSCLC. Limitations in the study methodology suggest that the observed pemetrexed survival benefit was likely conservative.