



Caring Ambassadors Lung Cancer Program Literature Review, September 2017

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES	1-4
SCREENING, DIAGNOSIS AND STAGING	4-8
CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES	
NSCLC SURGERY	8-9
NSCLC CHEMOTHERAPY	10-18
NSCLC RADIOTHERAPY	18-21
SMALL CELL LUNG CANCER (SCLC)	21-25
PALLIATIVE AND SUPPORTIVE CARE	25-27
COMPLEMENTARY AND ALTERNATIVE THERAPY	28
MISCELLANEOUS WORKS	28-30

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

[Mitochondrial degeneration precedes the development of muscle atrophy in progression of cancer cachexia in tumour-bearing mice.](#)

Brown JL1, Rosa-Caldwell ME1, Lee DE1, et al. J Cachexia Sarcopenia Muscle. 2017 Aug 28. doi: 10.1002/jcsm.12232. [Epub ahead of print]

BACKGROUND: Cancer cachexia is largely irreversible, at least via nutritional means, and responsible for 20-40% of cancer-related deaths. Therefore, preventive measures are of primary importance; however, little is known about muscle perturbations prior to onset of cachexia. Cancer cachexia is associated with mitochondrial degeneration; yet, it remains to be determined if mitochondrial degeneration precedes muscle wasting in cancer cachexia. Therefore, our purpose was to determine if mitochondrial degeneration precedes cancer-induced muscle wasting in tumour-bearing mice. **METHODS:** First, weight-stable (MinStable) and cachectic (MinCC) ApcMin/+ mice were compared with C57Bl6/J controls for mRNA contents of mitochondrial quality regulators in quadriceps muscle. Next, Lewis lung carcinoma (LLC) cells or PBS (control) were injected into the hind flank of C57Bl6/J mice at 8 week age, and tumour allowed to develop for 1, 2, 3, or 4 weeks to examine time course of cachectic development. Succinate dehydrogenase stain was used to measure oxidative phenotype in tibialis anterior muscle. Mitochondrial quality and function were assessed using the reporter MitoTimer by transfection to flexor digitorum brevis and mitochondrial function/ROS emission in permeabilized adult myofibres from plantaris. RT-qPCR and immunoblot measured the expression of mitochondrial quality control and antioxidant proteins. Data were analysed by one-way ANOVA with Student-Newman-Kuels post hoc test. **RESULTS:** MinStable mice displayed ~50% lower Pgc-1 α , Ppar α , and Mfn2 compared with C57Bl6/J controls, whereas MinCC exhibited 10-fold greater Bnip3 content compared with C57Bl6/J controls. In LLC, cachectic muscle loss was evident only at 4 weeks post-tumour implantation. Oxidative capacity and mitochondrial content decreased by ~40% 4 weeks post-tumour implantation. Mitochondrial function decreased by ~25% by 3 weeks after tumour implantation. Mitochondrial degeneration was evident by 2 week LLC compared with PBS control, indicated by MitoTimer red/green ratio and number of pure red puncta. Mitochondrial ROS production was elevated by ~50 to ~100% when compared with PBS at 1-3 weeks post-tumour implantation. Mitochondrial quality control was dysregulated throughout the progression of cancer cachexia in tumour-bearing mice. In contrast, antioxidant proteins were not altered

in cachectic muscle wasting. **CONCLUSIONS:** Functional mitochondrial degeneration is evident in LLC tumour-bearing mice prior to muscle atrophy. Contents of mitochondrial quality regulators across ApcMin/+ and LLC mice suggest impaired mitochondrial quality control as a commonality among pre-clinical models of cancer cachexia. Our data provide novel evidence for impaired mitochondrial health prior to cachectic muscle loss and provide a potential therapeutic target to prevent cancer cachexia.

[Non-small cell lung cancer: miR-30d suppresses tumor invasion and migration by directly targeting NFIB.](#) Wu Y1, Zhang J2, Hou S1, Cheng Z1, Yuan M1. *Biotechnol Lett.* 2017 Aug 31. doi: 10.1007/s10529-017-2428-9. [Epub ahead of print]

OBJECTIVE: To evaluate the role and the molecular mechanism of miR-30d in non-small cell lung cancer (NSCLC). **RESULTS:** qRT-PCR was used to detect miR-30d expression in NSCLC tissues and cell lines. miR-30d was frequently down-regulated in NSCLC and its expression was associated with clinicopathological features of NSCLC patients. Over-expression of miR-30d notably inhibited cell migration and invasion in NSCLC cell lines. miR-30d could negatively regulate Nuclear factor I B (NFIB) by directly targeting its 3'-UTR, which was confirmed by luciferase assay. NFIB also reversed miR-30d-mediated suppression on the migration and invasion in NSCLC cell lines. **CONCLUSION:** miR-30d suppressed cell migration and invasion by directly targeting NFIB in NSCLC, and NFIB could partially abrogate the inhibition of biological functions by miR-30d.

[Activation of an AKT/FOXM1/STMN1 pathway drives resistance to tyrosine kinase inhibitors in lung cancer.](#) Li M1,2, Yang J1,2, Zhou W1,2, et al. *Br J Cancer.* 2017 Aug 29. doi: 10.1038/bjc.2017.292. [Epub ahead of print]

BACKGROUND: Tyrosine kinase inhibitors (TKIs) have demonstrated clinical benefits in the treatment of several tumour types. However, the emergence of TKI resistance restricts the therapeutic effect. This study uses non-small cell lung cancer (NSCLC) to explore the mechanisms contributing to TKI resistance in tumours. **METHODS:** Biological phenotypes and RNA microarray expression data were analysed in NSCLC cells with and without TKI pretreatment. Specific inhibitors and siRNAs were used to validate the direct involvement of an AKT/FOXM1/STMN1 pathway in TKI resistance. Patients' tissues were analysed to explore the clinical importance of FOXM1 and STMN1. **RESULTS:** In vitro and in vivo studies showed that TKIs induced the enrichment of cancer stem cells (CSC), promoted epithelial to mesenchymal transition (EMT), and conferred multidrug resistance on NSCLC cells in a cell type- and TKI class-dependent manner. Mechanistically, TKIs activated an AKT/FOXM1/STMN1 pathway. The crucial role of this pathway in TKI-induced enrichment of CSC and drug resistance was verified by silencing FOXM1 and STMN1 or blocking the AKT pathway. Additionally, overexpression of STMN1 was associated with upregulation of FOXM1 in advanced NSCLC patients, and STMN1/FOXM1 upregulation predicted a poor outcome. **CONCLUSIONS:** Our findings elucidate an additional common mechanism for TKI resistance and provide a promising therapeutic target for reversing TKI resistance in NSCLC. *British Journal of Cancer* advance online publication, 29 August 2017; doi:10.1038/bjc.2017.292 www.bjcancer.com.

[A Molecular-Targeted Immunotherapeutic Strategy for Melanoma via Dual-Targeting Nanoparticles Delivering Small Interfering RNA to Tumor-Associated Macrophages.](#)

Qian Y, Qiao S, Dai Y, Xu G, Dai B, Lu L, Yu X, Luo Q, Zhang Z. *ACS Nano.* 2017 Aug 31. doi: 10.1021/acsnano.7b05465. [Epub ahead of print]

Tumor-associated macrophages (TAMs) are a promising therapeutic target for cancer immunotherapy. Targeted delivery of therapeutic drugs to the tumor-promoting M2-like TAMs is challenging. Here, we developed excellent M2-like TAM dual-targeting nanoparticles (M2NPs), whose structure and function were controlled by α -peptide (a scavenger receptor B type 1 (SR-B1) targeting peptide) linked with

M2pep (an M2 macrophage binding peptide). By loading anti-colony stimulating factor-1 receptor (anti-CSF-1R) small interfering RNA (siRNA) on the M2NPs, we developed a molecular-targeted immunotherapeutic approach to specifically block the survival signal of M2-like TAMs and deplete them from melanoma tumors. We confirmed the validity of SR-B1 for M2-like TAM targeting and demonstrated the synergistic effect of the two targeting units (α -peptide and M2pep) in the fusion peptide (α -M2pep). After being administered to tumor-bearing mice, M2NPs had higher affinity to M2-like TAMs than to tissue-resident macrophages in liver, spleen and lung. Compared with control treatment groups, M2NP-based siRNA delivery resulted in a dramatic elimination of M2-like TAMs (52%), decreased tumor size (87%) and prolonged survival. Additionally, this molecular-targeted strategy inhibited immunosuppressive IL-10 and TGF- β production, increased immuno-stimulatory cytokines (IL-12 and IFN- γ) expression and CD8+ T cell infiltration (2.9-fold) in tumor microenvironment. Moreover, the siRNA-carrying M2NPs down-regulated expression of the exhaustion markers (PD-1 and Tim-3) on the infiltrating CD8+ T cells and stimulated their IFN- γ secretion (6.2-fold), indicating the restoration of T cell immune function. Thus, the dual-targeting property of M2NPs combined with RNA interference provide a potential strategy of molecular-targeted cancer immunotherapy for clinical application.

[The Tumor Microenvironment Regulates Sensitivity of Murine Lung Tumors to PD-1/PD-L1 Antibody Blockade.](#) Li HY^{1,2}, McSharry M², Bullock B², et al. *Cancer Immunol Res.* 2017

Sept;5(9):767-777. doi: 10.1158/2326-6066.CIR-16-0365. Epub 2017 Aug 17.

Immune checkpoint inhibitors targeting the interaction between programmed cell death-1 (PD-1) and its ligand PD-L1 induce tumor regression in a subset of non-small cell lung cancer patients. However, clinical response rates are less than 25%. Evaluation of combinations of immunotherapy with existing therapies requires appropriate preclinical animal models. In this study, murine lung cancer cells (CMT167 and LLC) were implanted either orthotopically in the lung or subcutaneously in syngeneic mice, and response to anti-PD-1/PD-L1 therapy was determined. Anti-PD-1/PD-L1 therapy inhibited CMT167 orthotopic lung tumors by 95%. The same treatments inhibited CMT167 subcutaneous tumors by only 30% and LLC orthotopic lung tumors by 35%. CMT167 subcutaneous tumors had more Foxp3+ CD4+ T cells and fewer PD-1+ CD4+ T cells compared with CMT167 orthotopic tumors. Flow cytometric analysis also demonstrated increased abundance of PD-L1^{high} cells in the tumor microenvironment in CMT167 tumor-bearing lungs compared with CMT167 subcutaneous tumors or LLC tumor-bearing lungs. Silencing PD-L1 expression in CMT167 cells resulted in smaller orthotopic tumors that remained sensitive to anti-PD-L1 therapy, whereas implantation of CMT167 cells into PD-L1⁻ mice blocked orthotopic tumor growth, indicating a role for PD-L1 in both the cancer cell and the microenvironment. These findings indicate that the response of cancer cells to immunotherapy will be determined by both intrinsic properties of the cancer cells and specific interactions with the microenvironment. Experimental models that accurately recapitulate the lung tumor microenvironment are useful for evaluation of immunotherapeutic agents. *Cancer Immunol Res*; 5(9); 767-77. ©2017 AACR.

SCREENING, DIAGNOSIS AND STAGING

[Clinical validation of a highly sensitive assay to detect EGFR mutations in plasma cell-free DNA from patients with advanced lung adenocarcinoma.](#) Li Y¹, Xu H¹, Su S¹, Ye J¹, Chen J¹, Jin X¹, Lin Q¹, Zhang D¹, Ye C², Chen C¹. *PLoS One.* 2017 Aug 22;12(8):e0183331. doi: 10.1371/journal.pone.0183331. eCollection 2017.

BACKGROUND: Circulating tumor DNA (ctDNA) is a promising biomarker for noninvasive epidermal growth factor receptor (EGFR) mutations detection in lung cancer patients, but the existing methods have limitations in sensitivity or in availability. In this study, we evaluated the performance of a novel assay called ADx-SuperARMS in detecting EGFR mutations in plasma cell-free DNA from patients with

advanced lung adenocarcinoma. **METHODS:** A total of 109 patients with metastatic advanced adenocarcinoma were recruited who provided both blood samples and matched tumor tissue samples. EGFR mutation status in plasma samples were tested with ADx-SuperARMS EGFR assay and tumor tissue samples were tested with ADx-ARMS EGFR assay. The clinical sensitivity, specificity, positive prediction value (PPV), and negative prediction value (NPV) of ADx-SuperARMS EGFR assay were calculated by using EGFR mutation status in tumor tissue as standard reference. A receiver operating characteristic (ROC) analysis was implemented and an area under the curve (AUC) was calculated to evaluate sensitivity and specificity of exon 19 deletion (E19Del) and L858R mutation detection. The objective response rate (ORR) were calculated according to the EGFR mutation status determined by ADx-superARMS as well. **RESULTS:** 0.2% analytical sensitivity and 100% specificity of the ADx-SuperARMS EGFR assays for EGFR E19Del, L858R, and T790M mutants were confirmed by using a series of diluted cell line DNA. In the clinical study, EGFR mutations were detected in 45.9% (50/109) of the plasma samples and in 56.9% (62/109) of the matched tumor tissue samples. The sensitivity, specificity, PPV and NPV of the ADx-SuperARMS EGFR assay for plasma EGFR mutation detection were 82.0% (50/61), 100% (48/48), 100% (50/50), and 81.4% (48/59), respectively. In ROC analysis, ADx-SuperARMS achieved sensitivity and specificity of 88% and 99% in E19Dels as well as sensitivity and specificity of 89% and 100% in L858R, respectively. Among the 35 patients who were plasma EGFR mutation positive and treated with first generation of EGFR-tyrosine kinase inhibitors (TKIs), 23 (65.7%) achieved partial response, 11 (31.4%) sustained disease, and 1 (2.9%) progressive disease. The ORR and disease control rate (DCR) were 65.7% and 97.1%, respectively. **CONCLUSIONS:** ADx-SuperARMS EGFR assay is likely to be a highly sensitive and specific method to noninvasively detect plasma EGFR mutations of patients with advanced lung adenocarcinoma. The EGFR mutations detected by ADx-SuperARMS EGFR assay could predict the efficacy of the treatment with first generation of EGFR-TKIs. Hence, EGFR blood testing with ADx-SuperARMS could address the unmet clinical needs.

[ALK Status Assessment with Liquid Biopsies of Lung Cancer Patients.](#) Hofman P1,2. *Cancers* (Basel). 2017 Aug 12;9(8). pii: E106. doi: 10.3390/cancers9080106.

Patients with advanced stage non-small cell lung carcinoma (NSCLC) harboring an anaplastic lymphoma kinase ALK gene rearrangement, detected from a tissue sample, can benefit from targeted ALK inhibitor treatment. However, while treatment is initially effective in most cases, relapse or progression occurs due to different resistance mechanisms including mutations in the tyrosine kinase domain of echinoderm microtubule-associated protein-like 4 (EML4)-ALK. The liquid biopsy concept has recently radically changed the clinical care of NSCLC patients, in particular for those harboring an epidermal growth factor receptor (EGFR) gene mutation. Therefore, liquid biopsy is an alternative or complementary method to tissue biopsy for the detection of some resistance mutations in EGFR arising during tyrosine kinase inhibitor treatment. Moreover, in some frail patients, or if the tumor lesion is not accessible to a tissue biopsy, a liquid biopsy can also detect some activating mutations in EGFR on initial assessment. Recent studies have evaluated the possibility of also using a liquid biopsy approach to detect an ALK rearrangement and/or the emergence during inhibitor treatment of some resistance mutations in ALK. These assessments can be performed by studying circulating tumor cells by fluorescent in situ hybridization and by immunocytochemistry and/or after the isolation of RNA from plasma samples, free or associated with platelets. Thus, the liquid biopsy may be a complementary or sometimes alternative method for the assessment of the ALK status in certain NSCLC patients, as well as a non-invasive approach for early detection of ALK mutations. In this review, we highlight the current data concerning the role of the liquid biopsy for the ALK status assessment for NSCLC patients, and we compare the different approaches for this evaluation from blood samples.

[Comparative effectiveness: 18F-FDG-PET/CT versus CT for post-treatment follow-up of patients with lung cancer.](#) Sheikhabahaei S1, Ahn SJ, Young B, Taghipour M, Marcus C, Subramaniam RM. Nucl Med Commun. 2017 Aug;38(8):720-725. doi: 10.1097/MNM.0000000000000707.

PURPOSE: This study aimed to evaluate the comparative effectiveness of follow-up fluorine-18-fluorodeoxyglucose (F-FDG)-PET/CT and chest CT in the detection of local, regional, and distant metastatic diseases in lung cancer. **PATIENTS AND METHODS:** Follow-up F-FDG-PET/CT and chest-CT pairs of biopsy-proven lung cancer patients were reviewed retrospectively (May 2004-June 2013). Histopathological, clinical, or imaging follow-up data of at least 6 months was considered the reference standard. The κ statistics, the percentage agreement between the two techniques, and per-scan basis diagnostic performances were reported. **RESULTS:** A total of 270 patients with a total of 423 paired F-FDG-PET/CT and chest-CT scans were included (median time interval between two scans=2 days). The two imaging modalities showed concordance of 82.7% ($\kappa=0.71$) for local disease, 82% ($\kappa=0.65$) for regional disease, and 77.3% ($\kappa=0.55$) for distant metastasis. Overall, F-FDG-PET/CT identified more lesions compared with chest CT both in the regional lymph nodes (308 vs. 204 regional zone involvement) and in cases of distant metastasis (253 vs. 182 metastatic sites). In the evaluation of local disease, F-FDG-PET/CT appeared to have fairly similar sensitivity (96 vs. 95.4%) and specificity (82.1 vs. 83%) compared with chest CT. In the evaluation of regional lymph nodes and distant metastases, F-FDG-PET/CT showed higher sensitivity (regional nodes: 96 vs. 89.8%; distant metastases: 91.9 vs. 70.7%) and comparable specificity (regional nodes: 87.1 vs. 88.9%; distant metastases: 87.1 vs. 88.1%). **CONCLUSION:** The sensitivity of F-FDG-PET/CT is superior to that of chest CT in the detection of regional and distant metastasis, while having comparable specificity.

[Assessment of EGFR mutation status using cell-free DNA from bronchoalveolar lavage fluid.](#)

Park S1, Hur JY1, Lee KY1, Lee JC1, Rho JK1, Shin SH1, Choi CM1. Clin Chem Lab Med. 2017 Aug 28;55(10):1489-1495. doi: 10.1515/cclm-2016-0302.

BACKGROUND: Much attention has been focused on epidermal growth factor receptor (EGFR) mutation testing since the introduction of EGFR-tyrosine kinase inhibitors have improved survival in EGFR-positive lung cancer patients. Liquid biopsy using circulating tumor cells or cell-free DNA (cfDNA) has enabled less invasive testing, but requires a highly sensitive method. To date, liquid biopsy using bronchoalveolar lavage (BAL) fluid has rarely been used. **METHODS:** From 20 patients with lung adenocarcinoma, we isolated cfDNA from 20 samples of cell-free BAL fluid and 19 cell-free bronchial washing samples. cfDNA was examined for EGFR mutations using peptide nucleic acid (PNA)-mediated PCR clamping method. In cases where the results from the tumor biopsy and BAL-derived cfDNA test were not consistent, PANAMutyper™ R EGFR kit was used along with PNA clamping-assisted fluorescence melting curve analysis. **RESULTS:** We included 17 patients with advanced stage disease and three with non-advanced stage disease. Tumor biopsy detected EGFR mutations in 12 of the patients. One patient had a p.L858R mutation and a de novo p.T790M mutation. The results from PNA-mediated PCR clamping were 75.0% (9/12) concordant with the tumor biopsy results for EGFR mutation status. PANAMutyper with fluorescence melting curve analysis was performed in three cases, which detected EGFR mutations in two more patients (11/12, 91.7%). EGFR mutations were detected in the cfDNA extracted from two bronchial washing samples. **CONCLUSIONS:** cfDNA from BAL fluid could be used for molecular testing of EGFR mutations and identification of p.T790M mutations, with an easily applicable method.

[Diagnostic performance of endobronchial ultrasound-guided mediastinal lymph node sampling in early stage non-small cell lung cancer: A prospective study.](#) Vial MR1,2, O'Connell OJ1, Grosu HB1, et al. *Respirology*. 2017 Aug 30. doi: 10.1111/resp.13162. [Epub ahead of print]

BACKGROUND AND OBJECTIVE: Standard nodal staging of lung cancer consists of positron emission tomography/computed tomography (PET/CT), followed by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) if PET/CT shows mediastinal lymphadenopathy. Sensitivity of EBUS-TBNA in patients with N0/N1 disease by PET/CT is unclear and largely based on retrospective studies. We assessed the sensitivity of EBUS-TBNA in this setting. **METHODS:** We enrolled patients with proven or suspected lung cancer staged as N0/N1 by PET/CT and without metastatic disease (M0), who underwent staging EBUS-TBNA. Primary outcome was sensitivity of EBUS-TBNA compared with a composite reference standard of surgical stage or EBUS-TBNA stage if EBUS demonstrated N2/N3 disease. **RESULTS:** Seventy-five patients were included in the analysis. Mean tumour size was 3.52 cm (± 1.63). Fifteen of 75 patients (20%) had N2 disease. EBUS-TBNA identified six while nine were only identified at surgery. Sensitivity of EBUS-TBNA for N2 disease was 40% (95% CI: 16.3-67.7%). **CONCLUSION:** A significant proportion of patients with N0/N1 disease by PET/CT had N2 disease (20%) and EBUS-TBNA identified a substantial fraction of these patients, thus improving diagnostic accuracy compared with PET/CT alone. Sensitivity of EBUS-TBNA however appears lower compared with historical data from patients with larger volume mediastinal disease. Therefore, strategies to improve EBUS-TBNA accuracy in this population should be further explored.

[Diagnostic classification of solitary pulmonary nodules using dual time 18F-FDG PET/CT image texture features in granuloma-endemic regions.](#) Chen S1, Harmon S2, Perk T2, Li X1, Chen M1, Li Y3, Jeraj R4. *Sci Rep*. 2017 Aug 24;7(1):9370. doi: 10.1038/s41598-017-08764-7.

Lung cancer, the most commonly diagnosed cancer worldwide, usually presents as solid pulmonary nodules (SPNs) on early diagnostic images. Classification of malignant disease at this early timepoint is critical for improving the success of surgical resection and increasing 5-year survival rates. 18F-fluorodeoxyglucose (18F-FDG) PET/CT has demonstrated value for SPNs diagnosis with high sensitivity to detect malignant SPNs, but lower specificity in diagnosing malignant SPNs in populations with endemic infectious lung disease. This study aimed to determine whether quantitative heterogeneity derived from various texture features on dual time FDG PET/CT images (DTPI) can differentiate between malignant and benign SPNs in patients from granuloma-endemic regions. Machine learning methods were employed to find optimal discrimination between malignant and benign nodules. Machine learning models trained by texture features on DTPI images achieved significant improvements over standard clinical metrics and visual interpretation for discriminating benign from malignant SPNs, especially by texture features on delayed FDG PET/CT images.

[Retrospective analysis of technical success rate and procedure-related complications of 867 percutaneous CT-guided needle biopsies of lung lesions.](#) Mills M1, Choi J1, El-Haddad G1, Sweeney J1, Biebel B1, Robinson L2, Antonia S2, Kumar A3, Kis B4. *Clin Radiol*. 2017 Aug 26. pii: S0009-9260(17)30409-9. doi: 10.1016/j.crad.2017.07.023. [Epub ahead of print]

AIM: To investigate the technical success rate and procedure-related complications of computed tomography (CT)-guided needle biopsy of lung lesions and to identify the factors that are correlated with the occurrence of procedure-related complications. **MATERIALS AND METHODS:** This was a single-institution retrospective study of 867 consecutive CT-guided needle biopsies of lung lesions performed on 772 patients in a tertiary cancer centre. The technical success rate and complications were correlated with patient, lung lesion, and procedure-related variables. **RESULTS:** The technical success rate was 87.2% and the mortality rate was 0.12%. Of the 867 total biopsies 25.7% were associated with pneumothorax, and 6.5% required chest tube drainage. The haemothorax rate was 1.8%. There was positive correlation

between the development of pneumothorax and smaller lesion diameter ($p < 0.001$), longer transparenchymal distance ($p < 0.001$), and prone position ($p = 0.027$). There was positive correlation between the need for chest tube placement and longer transparenchymal distance ($p = 0.007$) and smaller lesion diameter ($p = 0.018$). Lesions in the left lower lobe had the lowest rates of pneumothorax ($p = 0.008$) and chest tube drainage ($p = 0.018$). Patients whose pneumothoraces were diagnosed on the follow-up chest X-ray, but not on the immediate post-procedural CT scan had significantly higher requirement for chest tube drainage ($p = 0.039$). **CONCLUSION:** CT-guided lung biopsy has a high rate of technical success and a low rate of major complications. The present study has revealed several variables that can be used to identify high-risk procedures. A post-procedural chest X-ray within hours after the procedure is highly recommended to identify high-risk patients who require chest tube placement.

[**A Prospective, Multi-institutional, Pathologist-Based Assessment of 4 Immunohistochemistry Assays for PD-L1 Expression in Non-Small Cell Lung Cancer.**](#) Rimm DL1, Han G2, Taube JM3, et al. JAMA Oncol. 2017 Aug 1;3(8):1051-1058. doi: 10.1001/jamaoncol.2017.0013.

IMPORTANCE: Four assays registered with the US Food and Drug Administration (FDA) detect programmed cell death ligand 1 (PD-L1) to enrich for patient response to anti-programmed cell death 1 and anti-PD-L1 therapies. The tests use 4 separate PD-L1 antibodies on 2 separate staining platforms and have their own scoring systems, which raises questions about their similarity and the potential interchangeability of the tests. **OBJECTIVE:** To compare the performance of 4 PD-L1 platforms, including 2 FDA-cleared assays, 1 test for investigational use only, and 1 laboratory-developed test. **DESIGN, SETTING, AND PARTICIPANTS:** Four serial histologic sections from 90 archival non-small cell lung cancers from January 1, 2008, to December 31, 2010, were distributed to 3 sites that performed the following immunohistochemical assays: 28-8 antibody on the Dako Link 48 platform, 22c3 antibody on the Dako Link 48 platform, SP142 antibody on the Ventana Benchmark platform, and E1L3N antibody on the Leica Bond platform. The slides were scanned and scored by 13 pathologists who estimated the percentage of malignant and immune cells expressing PD-L1. Statistical analyses were performed from December 1, 2015, to August 30, 2016, to compare antibodies and pathologists' scoring of tumor and immune cells. **MAIN OUTCOMES AND MEASURES:** Percentages of malignant and immune cells expressing PD-L1. **RESULTS:** Among the 90 samples, the SP142 assay was an outlier, with a significantly lower mean score of PD-L1 expression in both tumor and immune cells (tumor cells: 22c3, 2.96; 28-8, 3.26; SP142, 1.99; E1L3N, 3.20; overall mean, 2.85; and immune cells: 22c3, 2.15; 28-8, 2.28; SP142, 1.62; E1L3N, 2.28; overall mean, 2.08). Pairwise comparisons showed that the scores from the 28-8 and E1L3N tests were not significantly different but that the 22c3 test showed a slight (mean difference, 0.24-0.30) but statistically significant reduction in labeling of PD-L1 expression in tumor cells. Evaluation of intraclass correlation coefficients (ICCs) between antibodies to quantify interassay variability for PD-L1 expression in tumor cells showed high concordance between antibodies for tumor cell scoring (0.813; 95% CI, 0.815-0.839) and lower levels of concordance for immune cell scoring (0.277; 95% CI, 0.222-0.334). When examining variability between pathologists for any single assay, the concordance between pathologists' scoring for PD-L1 expression in tumor cells ranged from ICCs of 0.832 (95% CI, 0.820-0.844) to 0.882 (95% CI, 0.873-0.891) for each assay, while the ICCs from immune cells for each assay ranged from 0.172 (95% CI, 0.156-0.189) to 0.229 (95% CI, 0.211-0.248). **CONCLUSIONS AND RELEVANCE:** The assay using the SP142 antibody is an outlier that detected significantly less PD-L1 expression in tumor cells and immune cells. The assay for antibody 22c3 showed slight yet statistically significantly lower staining than either 28-8 or E1L3N, but this significance was detected only when using the mean of 13 pathologists' scores. The pathologists showed excellent concordance when scoring tumor cells stained with any antibody but poor concordance for scoring immune cells stained with any antibody. Thus, for tumor cell assessment of PD-L1, 3 of the 4 tests are concordant and reproducible as read by pathologists.

[Mid-radiotherapy PET/CT for prognostication and detection of early progression in patients with stage III non-small cell lung cancer.](#) Gensheimer MF1, Hong JC2, Chang-Halpenny C3, et al. *Radiation Oncology*. 2017 Aug 19. pii: S0167-8140(17)32514-8. doi: 10.1016/j.radonc.2017.08.007. [Epub ahead of print]

BACKGROUND AND PURPOSE: Pre- and mid-radiotherapy FDG-PET metrics have been proposed as biomarkers of recurrence and survival in patients treated for stage III non-small cell lung cancer. We evaluated these metrics in patients treated with definitive radiation therapy (RT). We also evaluated outcomes after progression on mid-radiotherapy PET/CT. **MATERIAL AND METHODS:** Seventy-seven patients treated with RT with or without chemotherapy were included in this retrospective study. Primary tumor and involved nodes were delineated. PET metrics included metabolic tumor volume (MTV), total lesion glycolysis (TLG), and SUVmax. For mid-radiotherapy PET, both absolute value of these metrics and percentage decrease were analyzed. The influence of PET metrics on time to death, local recurrence, and regional/distant recurrence was assessed using Cox regression. **RESULTS:** 91% of patients had concurrent chemotherapy. Median follow-up was 14 months. None of the PET metrics were associated with overall survival. Several were positively associated with local recurrence: pre-radiotherapy MTV, and mid-radiotherapy MTV and TLG ($p=0.03-0.05$). Ratio of mid- to pre-treatment SUVmax was associated with regional/distant recurrence ($p=0.02$). 5/77 mid-radiotherapy scans showed early out-of-field progression. All of these patients died. **CONCLUSIONS:** Several PET metrics were associated with risk of recurrence. Progression on mid-radiotherapy PET/CT was a poor prognostic factor.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

[The Role of Thoracic Surgery in the Therapeutic Management of Metastatic Non-small Cell Lung Cancer.](#) David EA1, Clark JM2, Cooke DT2, Melnikow J3, Kelly K4, Canter RJ5. *J Thorac Oncol*. 2017 Aug 23. pii: S1556-0864(17)30683-4. doi: 10.1016/j.jtho.2017.08.008. [Epub ahead of print]

INTRODUCTION: The majority of non-small cell lung cancer (NSCLC) patients are diagnosed with advanced stage disease for whom the prognosis is poor and survival is typically measured in months. Standard therapeutic treatment regimens for patients with stage IV NSCLC typically include chemotherapy and palliative radiation. Despite newer regimens that may include molecularly targeted therapy and immunotherapy, the overall 5-year survival for stage IV disease remains low at 4-6%. Although therapeutic surgery is performed in a minority of cases, accumulating data suggest that thoracic surgery may play several beneficial roles for these patients. **METHODS:** In this narrative review, we summarize the literature on surgical intervention in the multimodality management of stage IV NSCLC; focusing on the potential evidence for and against therapeutic/curative intent procedures to impact outcomes for patients with oligometastatic disease and pleural metastasis. **RESULTS:** In selected patients, surgical resection can result in a 5-year survival of 30-50%, but this is heavily influenced by the presence of mediastinal nodal disease, which should be evaluated before therapeutic surgical procedures are undertaken. Additionally, diagnostic or palliative surgical procedures can play an important role in the personalized management of stage IV disease. These data suggest that for carefully selected patients with advanced stage NSCLC, surgical intervention can be an important component of combined modality treatment. **CONCLUSIONS:** Given advances in molecular targeted therapy and immunotherapy, further studies should focus on the possible use of surgery as a strategy of therapeutic "consolidation" for appropriately selected patients with stage IV NSCLC receiving combined modality care.

[Impact of Timing of Lobectomy on Survival for Clinical Stage IA Lung Squamous Cell Carcinoma.](#)

Yang CJ1, Wang H1, Kumar A1, Wang X2, Hartwig MG1, D'Amico TA1, Berry MF3. Chest. 2017 Aug 8. pii: S0012-3692(17)31330-2. doi: 10.1016/j.chest.2017.07.032. [Epub ahead of print]

BACKGROUND: Because the relationship between timing of surgery following diagnosis of lung cancer and survival has not been precisely described, guidelines on what constitutes a clinically meaningful delay of resection of early-stage lung cancer do not exist. This study tested the hypothesis that increasing time between diagnosis and lobectomy for stage IA squamous cell carcinoma (SCC) was associated with worse survival. **METHODS:** The association between timing of lobectomy and survival for patients with clinical stage IA SCC in the National Cancer Data Base (2006-2011) was assessed using multivariable Cox proportional hazards analysis and restricted cubic spline (RCS) functions. **RESULTS:** The 5-year overall survival of 4,984 patients who met study inclusion criteria was 58.3% (95% CI, 56.3-60.2). Surgery was performed within 30 days of diagnosis in 1,811 (36%) patients, whereas the median time to surgery was 38 days (interquartile range, 23, 58). In multivariable analysis, patients who had surgery 38 days or more after diagnosis had significantly worse 5-year survival than patients who had surgery earlier (hazard ratio, 1.13 [95% CI, 1.02-1.25]; $P = .02$). Multivariable RCS analysis demonstrated the hazard ratio associated with time to surgery increased steadily the longer resection was delayed; the threshold time associated with statistically significant worse survival was ~ 90 days or greater. **CONCLUSIONS:** Longer intervals between diagnosis of early-stage lung SCC and surgery are associated with worse survival. Although factors other than the timing of treatment may contribute to this finding, these results suggest that efforts to minimize delays beyond those needed to perform a complete preoperative evaluation may improve survival.

[A National Analysis of Long-term Survival Following Thoracoscopic Versus Open Lobectomy for Stage I Non-small-cell Lung Cancer.](#)

Yang CJ1, Kumar A, Klapper JA, et al. Ann Surg. 2017 Aug 9. doi: 10.1097/SLA.0000000000002342. [Epub ahead of print]

OBJECTIVE: The objective of this study was to compare the long-term survival of open versus thoracoscopic (VATS) lobectomy for early stage non-small-cell lung cancer (NSCLC).

BACKGROUND: Data from national studies on long-term survival for VATS versus open lobectomy are limited. **METHODS:** Outcomes of patients who underwent open versus VATS lobectomy for clinical T1-2, N0, M0 NSCLC in the National Cancer Data Base were evaluated using propensity score matching. **RESULTS:** The median follow-up of 7114 lobectomies (5566 open and 1548 VATS) was 52.0 months. Propensity score matching resulted in 1464 open and 1464 VATS patients who were well-matched by 14 common prognostic covariates including tumor size and comorbidities. The VATS approach was associated with a shorter median length of stay (5 vs. 6 days, $P < 0.001$) and better 5-year survival (66.0% vs. 62.5%, $P = 0.026$), and was not significantly different compared with the open approach with regard to nodal upstaging (11.2% vs. 12.5%, $P = 0.46$), and 30-day mortality (1.7% vs. 2.5%, $P = 0.14$). In the propensity-matched analysis of 2928 patients, there were no significant differences in 5-year survival between the VATS and open groups (66.3% vs. 65.8%, $P = 0.92$). **CONCLUSIONS:** In this national analysis, VATS lobectomy was used in the minority of patients with stage I NSCLC. VATS lobectomy was associated with shorter length of stay and noninferior long-term survival when compared with open lobectomy. These results support previous findings from smaller single- and multi-institutional studies that suggest that VATS does not compromise oncologic outcomes when used for early-stage lung cancer and suggest the need for broader implementation of VATS techniques.

[Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update.](#)

Hanna N1, Johnson D1, Temin S1, et al. J Clin Oncol. 2017 Aug 14;JCO2017746065. doi: 10.1200/JCO.2017.74.6065. [Epub ahead of print]

PURPOSE: Provide evidence-based recommendations updating the 2015 ASCO guideline on systemic therapy for patients with stage IV non-small-cell lung cancer (NSCLC). **METHODS:** The ASCO NSCLC Expert Panel made recommendations based on a systematic review of randomized controlled trials from February 2014 to December 2016 plus the Cancer Care Ontario Program in Evidence-Based Care's update of a previous ASCO search. **RESULTS:** This guideline update reflects changes in evidence since the previous guideline update. Fourteen randomized controlled trials provide the evidence base; earlier phase trials also informed recommendation development. **RECOMMENDATIONS:** New or revised recommendations include the following. Regarding first-line treatment for patients with non-squamous cell carcinoma or squamous cell carcinoma (without positive markers, eg, EGFR/ALK /ROS1), if the patient has high programmed death ligand 1 (PD-L1) expression, pembrolizumab should be used alone; if the patient has low PD-L1 expression, clinicians should offer standard chemotherapy. All other clinical scenarios follow 2015 recommendations. Regarding second-line treatment in patients who received first-line chemotherapy, without prior immune checkpoint therapy, if NSCLC tumor is positive for PD-L1 expression, clinicians should use single-agent nivolumab, pembrolizumab, or atezolizumab; if tumor has negative or unknown PD-L1 expression, clinicians should use nivolumab or atezolizumab. All immune checkpoint therapy is recommended alone plus in the absence of contraindications. For patients who received a prior first-line immune checkpoint inhibitor, clinicians should offer standard chemotherapy. For patients who cannot receive immune checkpoint inhibitor after chemotherapy, docetaxel is recommended; in patients with nonsquamous NSCLC, pemetrexed is recommended. In patients with a sensitizing EGFR mutation, disease progression after first-line epidermal growth factor receptor tyrosine kinase inhibitor therapy, and T790M mutation, osimertinib is recommended; if NSCLC lacks the T790M mutation, then chemotherapy is recommended. Patients with ROS1 gene rearrangement without prior crizotinib may be offered crizotinib, or if they previously received crizotinib, they may be offered chemotherapy.

[Acquired Resistance to Erlotinib in EGFR Mutation-Positive Lung Adenocarcinoma among Hispanics \(CLICaP\).](#)

Cardona AF1,2,3, Arrieta O4, Zapata MI5, et al. Target Oncol. 2017 Aug;12(4):513-523. doi: 10.1007/s11523-017-0497-2.

BACKGROUND: Lung cancer harboring epidermal growth factor receptor (EGFR) mutations and treated with EGFR tyrosine kinase inhibitors (TKIs) all eventually develop acquired resistance to the treatment, with half of the patients developing EGFR T790M resistance mutations. **OBJECTIVE:** The purpose of this study was to assess histological and clinical characteristics and survival outcomes in Hispanic EGFR mutated lung cancer patients after disease progression. **PATIENTS AND METHODS:** EGFR mutation-positive lung cancer patients (n = 34) with acquired resistance to the EGFR-TKI erlotinib were identified from 2011 to 2015. Post-progression tumor specimens were collected for molecular analysis. Post-progression interventions, response to treatment, and survival were assessed and compared among all patients and those with and without T790M mutations. **RESULTS:** Mean age was 59.4 ± 13.9 years, 65% were never-smokers, and 53% had a performance status 0-1. All patients received erlotinib as first-line treatment. Identified mutations included: 60% DelE19 (Del746-750) and 40% L858R. First-line erlotinib overall response rate (ORR) was 61.8% and progression free survival (PFS) was 16.8 months (95% CI: 13.7-19.9). Acquired resistance mutations identified were T790M mutation (47.1%); PI3K mutations (14.7%); EGFR amplification (14.7%); KRAS mutation (5.9%); MET amplification (8.8%); HER2 alterations (5.9%, deletions/insertions in e20); and SCLC transformation (2.9%). Of patients,

79.4% received treatment after progression. ORR for post-erlotinib treatment was 47.1% (CR 2/PR 14) and median PFS was 8.3 months (95% CI: 2.2-36.6). Median overall survival (OS) from treatment initiation was 32.9 months (95% CI: 30.4-35.3), and only the use of post-progression therapy affected OS in a multivariate analysis ($p = 0.05$). **CONCLUSIONS:** Hispanic patients with acquired resistance to erlotinib continued to be sensitive to other treatments after progression. The proportion of T790M+ patients appears to be similar to that previously reported in Caucasians.

Osimertinib: A Review in T790M-Positive Advanced Non-Small Cell Lung Cancer. Lamb YN1, Scott LJ2. *Target Oncol.* 2017 Aug;12(4):555-562. doi: 10.1007/s11523-017-0519-0.

Osimertinib (Tagrisso™) is an oral, CNS-active, third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that targets EGFR TKI-sensitizing mutations and, crucially, the T790M mutation that often underlies acquired resistance to EGFR TKI therapy. Osimertinib has been approved in numerous countries for use in patients with T790M-positive advanced NSCLC. In the pivotal, international AURA3 trial in patients with T790M-positive advanced NSCLC who had disease progression after EGFR TKI therapy, osimertinib treatment significantly prolonged progression-free survival (PFS; primary endpoint) compared with platinum-pemetrexed therapy at the time of the primary analysis. PFS results were consistent across predefined subgroups of patients, including those with CNS metastases at baseline. There was no difference between treatment groups in overall survival at 26% maturity. Objective response rates (ORRs) and patient-reported outcomes for prespecified symptoms were also significantly improved with osimertinib relative to platinum-pemetrexed, with CNS ORRs in patients with CNS metastases more than twofold higher in the osimertinib than in the platinum-pemetrexed group. Osimertinib had a manageable tolerability profile, with relatively few patients permanently discontinuing treatment because of adverse events (AEs). With limited treatment options available in this setting, osimertinib is an important option in adult patients with advanced EGFR T790M-positive NSCLC.

Efficacy and Safety of Nintedanib Plus Docetaxel in Patients with Advanced Lung Adenocarcinoma: Complementary and Exploratory Analyses of the Phase III LUME-Lung 1 Study.

Gottfried M1, Bennouna J2, Bondarenko I3, et al. *Target Oncol.* 2017 Aug;12(4):475-485. doi: 10.1007/s11523-017-0517-2.

BACKGROUND: Nintedanib is a triple angiokinase inhibitor approved with docetaxel for adenocarcinoma non-small cell lung cancer after first-line chemotherapy (FLT). In the phase III LUME-Lung 1 study, overall survival (OS) was significantly longer with nintedanib/docetaxel than with placebo/docetaxel in all adenocarcinoma patients and those with time from start of FLT (TSFLT) <9 months. **OBJECTIVE:** This study sought to extend analyses from the LUME-Lung 1 study, specifically for adenocarcinoma patients, to explore the impact of clinically relevant characteristics on outcomes such as time to progression after FLT. **PATIENTS AND METHODS:** Exploratory analyses were conducted of the overall and European LUME-Lung 1 adenocarcinoma population according to age, prior therapy, and tumor dynamics. Analyses also used TSFLT and time from end of FLT (TEFLT). **RESULTS:** Treatment with nintedanib/docetaxel significantly improved OS in European patients independently of age or prior therapy. Analyses of several patient subgroups showed improvements in median OS: TSFLT <6 months, 9.5 versus 7.5 months (hazard ratio [HR] 0.73, 95% confidence interval [CI] 0.55-0.98); chemorefractory to FLT, 9.1 versus 6.9 months (HR 0.72, 95% CI 0.52-0.99); progressive disease (PD) as best response to FLT, 9.8 versus 6.3 months (HR 0.62, 95% CI 0.41-0.94); TEFLT ≤6 months, 11.3 versus 8.2 months (HR 0.75, 95% CI 0.61-0.92); and TEFLT <3 months, 11.0 versus 8.0 months (HR 0.74, 95% CI 0.58-0.94). **CONCLUSIONS:** Nintedanib/docetaxel demonstrated significant OS benefits in adenocarcinoma patients, which were more pronounced in patients with shorter TSFLT or TEFLT, or with PD as best response to FLT. This study was registered at ClinicalTrials.gov: NCT00805194.

[Metabolic activity by 18F-FDG-PET/CT is predictive of early response after nivolumab in previously treated NSCLC.](#) Kaira K1, Higuchi T2, Naruse I3, et al. Eur J Nucl Med Mol Imaging. 2017 Aug 21. doi: 10.1007/s00259-017-3806-1. [Epub ahead of print]

BACKGROUND: Nivolumab, an anti-programmed death-1 (PD-1) antibody, is administered in patients with previously treated non-small cell lung cancer. However, little is known about the established biomarker predicting the efficacy of nivolumab. Here, we conducted a preliminary study to investigate whether 18F-FDG-PET/CT could predict the therapeutic response of nivolumab at the early phase.

METHODS: Twenty-four patients were enrolled in this study. 18F-FDG-PET/CT was carried out before and 1 month after nivolumab therapy. SUVmax, metabolic tumour volume (MTV), and total lesion glycolysis (TLG) were calculated. Immunohistochemical analysis of PD-L1 expression and tumour-infiltrating lymphocytes was conducted. **RESULTS:** Among all patients, a partial metabolic response to nivolumab was observed in 29% on SUVmax, 25% on MTV, and 33% on TLG, whereas seven (29%) patients achieved a partial response (PR) based on RECIST v1.1. The predictive probability of PR (100% vs. 29%, $p = 0.021$) and progressive disease (100% vs. 22.2%, $p = 0.002$) at 1 month after nivolumab initiation was significantly higher in 18F-FDG on PET/CT than in CT scans. Multivariate analysis confirmed that 18F-FDG uptake after administration of nivolumab was an independent prognostic factor. PD-L1 expression and nivolumab plasma concentration could not precisely predict the early therapeutic efficacy of nivolumab. **CONCLUSION:** Metabolic response by 18F-FDG was effective in predicting efficacy and survival at 1 month after nivolumab treatment.

[Randomised Phase 2 study of maintenance linsitinib \(OSI-906\) in combination with erlotinib compared with placebo plus erlotinib after platinum-based chemotherapy in patients with advanced non-small cell lung cancer.](#) Ciuleanu TE1, Ahmed S2, Kim JH3, et al. Br J Cancer. 2017 Sep 5;117(6):757-766. doi: 10.1038/bjc.2017.226. Epub 2017 Aug 3.

BACKGROUND: Maintenance therapy is important in advanced/metastatic non-small cell lung cancer (NSCLC). Erlotinib as switch maintenance following platinum-based chemotherapy increases survival. Cross-talk between the epidermal growth factor receptor and insulin-like growth factor receptor (IGFR) pathways mediate resistance to individual receptor blockade. This study compared maintenance linsitinib plus erlotinib vs erlotinib plus placebo in patients with NSCLC. **METHODS:** In this Phase II randomised trial, patients without progression following four cycles of first-line platinum-based chemotherapy (N=205) received continuous schedule maintenance oral linsitinib 150 mg or placebo BID combined with erlotinib 150 mg QD for 21-day cycles. The primary endpoint was progression-free survival (PFS). **RESULTS:** The study was unblinded early due to linsitinib non-superiority. No difference was found between the two treatment groups in median PFS of 125 days linsitinib vs 129 days placebo ($P=0.601$); no difference in overall survival (OS) was observed. Tolerability was similar, although in the linsitinib group, treatment-related adverse events and discontinuations were more frequent. No drug-drug interaction was implicated. **CONCLUSIONS:** Linsitinib maintenance therapy added to erlotinib did not improve PFS or OS in non-progressing NSCLC patients. This highlights the need for robust biomarkers of response for combinations that incorporate IGFR-targeted therapies in maintenance or other therapeutic settings.

[Glesatinib Exhibits Antitumor Activity in Lung Cancer Models and Patients Harboring MET Exon 14 Mutations and Overcomes Mutation-Mediated Resistance to Type I MET Inhibitors in Nonclinical Models.](#) Engstrom L1, Aranda R1, Lee M1, et al. Clin Cancer Res. 2017 Aug 1. pii: clincanres.1192.2017. doi: 10.1158/1078-0432.CCR-17-1192. [Epub ahead of print]

PURPOSE:

MET exon 14 deletion (METex14 del) mutations represent a novel class of non-small cell lung cancer (NSCLC) driver mutations. We evaluated glesatinib, a spectrum-selective MET inhibitor exhibiting a

type II binding mode, in METex14 del-positive nonclinical models and NSCLC patients and assessed its ability to overcome resistance to type I MET Inhibitors. **EXPERIMENTAL DESIGN:** As most MET inhibitors in clinical development bind the active site with a type I binding mode, we investigated mechanisms of acquired resistance to each MET inhibitor class utilizing in vitro and in vivo models and in glesatinib clinical trials. **RESULTS:** Glesatinib inhibited MET signaling, demonstrated marked regression of METex14 del-driven patient-derived xenografts, and demonstrated a durable RECIST partial response in a METex14 del mutation-positive patient enrolled on a glesatinib clinical trial. Prolonged treatment of nonclinical models with selected MET inhibitors resulted in differences in resistance kinetics and mutations within the MET activation loop (i.e., D1228N, Y1230C/H) that conferred resistance to type I MET inhibitors, but remained sensitive to glesatinib. In vivo models exhibiting METex14 del/A-loop double mutations and resistance to type I inhibitors exhibited a marked response to glesatinib. Finally, a METex14 del mutation-positive NSCLC patient who responded to crizotinib but later relapsed, demonstrated a mixed response to glesatinib including reduction in size of a MET Y1230H mutation-positive liver metastasis and concurrent loss of detection of this mutation in plasma DNA. **CONCLUSIONS:** Together, these data demonstrate glesatinib exhibits a distinct mechanism of target inhibition and can overcome resistance to type I MET inhibitors.

[Osimertinib As First-Line Treatment of EGFR Mutation-Positive Advanced Non-Small-Cell Lung Cancer.](#) Ramalingam SS1, Yang JC1, Lee CK1, et al. J Clin Oncol. 2017 Aug 25;JCO2017747576. doi: 10.1200/JCO.2017.74.7576. [Epub ahead of print]

PURPOSE: The Osimertinib First Time in Patients Ascending Dose (AURA) study (ClinicalTrials.gov identifier: NCT01802632) included two cohorts of treatment-naïve patients to examine clinical activity and safety of osimertinib (an epidermal growth factor receptor [EGFR] -tyrosine kinase inhibitor selective for EGFR-tyrosine kinase inhibitor sensitizing [EGFRm] and EGFR T790M resistance mutations) as first-line treatment of EGFR-mutated advanced non-small-cell lung cancer (NSCLC). **Patients and Methods** Sixty treatment-naïve patients with locally advanced or metastatic EGFRm NSCLC received osimertinib 80 or 160 mg once daily (30 patients per cohort). End points included investigator-assessed objective response rate (ORR), progression-free survival (PFS), and safety evaluation. Plasma samples were collected at or after patients experienced disease progression, as defined by Response Evaluation Criteria in Solid Tumors (RECIST), to investigate osimertinib resistance mechanisms. **Results** At data cutoff (November 1, 2016), median follow-up was 19.1 months. Overall ORR was 67% (95% CI, 47% to 83%) in the 80-mg group, 87% (95% CI, 69% to 96%) in the 160-mg group, and 77% (95% CI, 64% to 87%) across doses. Median PFS time was 22.1 months (95% CI, 13.7 to 30.2 months) in the 80-mg group, 19.3 months (95% CI, 13.7 to 26.0 months) in the 160-mg group, and 20.5 months (95% CI, 15.0 to 26.1 months) across doses. Of 38 patients with postprogression plasma samples, 50% had no detectable circulating tumor DNA. Nine of 19 patients had putative resistance mechanisms, including amplification of MET (n = 1); amplification of EGFR and KRAS (n = 1); MEK1, KRAS, or PIK3CA mutation (n = 1 each); EGFR C797S mutation (n = 2); JAK2 mutation (n = 1); and HER2 exon 20 insertion (n = 1). Acquired EGFR T790M was not detected. **CONCLUSION:** Osimertinib demonstrated a robust ORR and prolonged PFS in treatment-naïve patients with EGFRm advanced NSCLC. There was no evidence of acquired EGFR T790M mutation in postprogression plasma samples.

[Induction chemotherapy for T3N0M0 non-small-cell lung cancer increases the rate of complete resection but does not confer improved survival.](#) Anderson KL Jr1, Mulvihill MS2, Yerokun BA2, Speicher PJ2, D'Amico TA3, Tong BC3, Berry MF4, Hartwig MG3. Eur J Cardiothorac Surg. 2017 Aug 1;52(2):370-377. doi: 10.1093/ejcts/ezx091.

OBJECTIVES: The objective of this study was to evaluate outcomes of induction therapy prior to an operation in patients with cT3 non-small-cell lung cancer (NSCLC). **METHODS:** Patients diagnosed

with cT3N0M0 NSCLC from 2006 to 2011 in the National Cancer Database who were treated with lobectomy or pneumonectomy were stratified by treatment strategy: an operation first versus induction chemotherapy. Propensity scores were developed and matched cohorts were generated. Short-term outcomes included margin status, 30- and 90-day mortality rates, readmission and length of stay. Survival analyses using Kaplan-Meier methods were performed on both the unadjusted and propensity matched cohorts. **RESULTS:** A total of 3791 cT3N0M0 patients were identified for inclusion, of which 580 (15%) were treated with induction chemotherapy. Prior to adjustment, patients treated with induction chemotherapy were younger, had a higher comorbidity burden and were more likely to have private insurance (all $P < 0.001$). Following matching, patients receiving induction chemotherapy were more likely to subsequently undergo an open procedure (87.3 vs 77.8%, $P = 0.005$). These patients were more likely to obtain R0 resection (93.1% vs 90.0%, $P = 0.04$) and were thereby less likely to have positive margins at the time of resection (6.9% vs 10.0%, $P = 0.03$). Patients who received induction therapy had higher rates of 90-day mortality (6.6% vs 3.4%) but there was no difference in long-term survival between the groups. **CONCLUSIONS:** Despite yielding increased rates of R0 resection, induction chemotherapy for cT3N0M0 NSCLC is not associated with improved survival and should not be considered routinely. Further studies are warranted to elucidate cohorts that may benefit from induction therapy.

[Comparison of Concurrent Use of Thoracic Radiation With Either Carboplatin-Paclitaxel or Cisplatin-Etoposide for Patients With Stage III Non-Small-Cell Lung Cancer: A Systematic Review.](#)

Steuer CE1,2, Behera M1,2, Ernani V1,2, et al. JAMA Oncol. 2017 Aug 1;3(8):1120-1129. doi: 10.1001/jamaoncol.2016.4280.

IMPORTANCE: The 2 most common chemotherapy regimens used concurrently with thoracic radiation for patients with unresectable IIIA and IIIB non-small-cell lung cancer (NSCLC) are carboplatin-paclitaxel and cisplatin-etoposide. There are no prospective comparisons of these 2 regimens in this setting. **OBJECTIVE:** To conduct a systematic review of published trials to compare outcomes and toxic effects between cisplatin-etoposide and carboplatin-paclitaxel in patients with non-small-cell lung cancer receiving thoracic radiation. **EVIDENCE REVIEW:** Studies that enrolled patients with stage III disease receiving radiotherapy (RT) with carboplatin-paclitaxel or cisplatin-etoposide were identified using electronic databases (MEDLINE, EMBASE, and Cochrane library) and meeting abstracts. Trials were excluded if they were phase 1, enrolled less than 10 patients, or included surgical resection. A systematic analysis of extracted data was performed with software using random and fixed effect models. Clinical outcomes were compared using point estimates for weighted values of median overall survival, progression-free survival, response rate, and toxic effects. A 2-tailed t test with a significance level of .05 was used for all comparisons. **FINDINGS:** Overall, 3090 patients were included from 31 studies in the cisplatin-etoposide groups (median age, 61 years; 65% male; 40% squamous histology; median radiation dose, 63.0 Gy), and 3728 patients from 48 studies in carboplatin-paclitaxel groups (median age, 63 years; 65% male; 40% squamous histology; median radiation dose, 64.6 Gy). There was no significant difference in response rates between cisplatin-etoposide and carboplatin-paclitaxel (58% vs 56%; $P = .26$), respectively. For cisplatin-etoposide vs carboplatin-paclitaxel, there was no significant difference in median progression free survival (12 months vs 9.3 months; $P = .20$), overall survival (19.6 months vs 18.4 months; $P = .40$), or 3-year survival rate (31% vs 25%; $P = .50$). Cisplatin-etoposide was associated with higher grade 3 to 4 hematological toxic effects compared with carboplatin-paclitaxel (eg, neutropenia [54% vs 23%; $P < .001$] and grade 3/4 nausea/vomiting [20% vs 11%; $P = .03$]), while rates of grade 3 to 4 pneumonitis (12% vs 9%; $P = .12$) and esophagitis (23% vs 21%; $P = .27$) were similar. **CONCLUSIONS AND RELEVANCE:** Cisplatin-etoposide and carboplatin-paclitaxel regimens were associated with comparable efficacy when used with concurrent definitive radiotherapy for patients with stage III unresectable NSCLC. The toxic effect profiles favored the carboplatin-paclitaxel regimen.

[Intercalating and maintenance gefitinib plus chemotherapy versus chemotherapy alone in selected advanced non-small cell lung cancer with unknown EGFR status.](#) Jian H1, Li W2, Ma Z3, et al. *Sci Rep.* 2017 Aug 16;7(1):8483. doi: 10.1038/s41598-017-08399-8.

Epidermal growth factor receptor tyrosine-kinase inhibitors (EGFR-TKIs) are standard treatment for advanced non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) mutation. However, EGFR mutation testing is not attainable in approximately 20% of patients. The current study examined intercalating and maintaining gefitinib treatment in stage IIIB/IV non-squamous NSCLC, never or former light smoking patients with unknown EGFR mutation status. Briefly, 219 patients who achieved stable disease (SD) with gemcitabine (1250 mg/m²) plus carboplatin (5 AUC) were randomized at 1:1 ratio to continue chemotherapy (n = 110) or intercalating gefitinib (250 mg/day on days 15-25 of each cycle until disease progress (n = 109). Progression-free survival (PFS) was 9.7 vs. 4.2 month in the gefitinib vs. control arm (HR: 0.41, 95% CI: 0.31-0.56; P < 0.001). Overall survival (OS) was also longer in the gefitinib arm (20.1 vs. 15.4 months; HR: 0.68; 95% CI 0.48-0.97; P = 0.0323). Adverse events, including diarrhea, dermal reaction and thrombocytopenia, were more common in the gefitinib arm. In conclusion, intercalating and maintenance gefitinib treatment is a viable option for advanced NSCLC patients with unknown EGFR mutation status in subpopulations with high EGFR mutation rate.

[Everolimus with paclitaxel and carboplatin as first-line treatment for metastatic large-cell neuroendocrine lung carcinoma: a multicenter phase II trial.](#) Christopoulos P1, Engel-Riedel W2, Grohé C3, Kropf-Sanchen C4, et al. *Ann Oncol.* 2017 Aug 1;28(8):1898-1902. doi: 10.1093/annonc/mdx268.

BACKGROUND: Large-cell neuroendocrine carcinoma of the lung (LCNEC) is a rare disease with poor prognosis and limited treatment options. Neuroendocrine tumors frequently show overactivation of the mTOR pathway. Based on the good activity of the mTOR inhibitor everolimus in different types of neuroendocrine tumors and the results of a previous phase I trial, we evaluated the efficacy and safety of everolimus in combination with carboplatin and paclitaxel as upfront treatment for patients with advanced LCNEC. **PATIENTS AND METHODS:** In this prospective, multicenter phase II trial chemotherapy-naive patients with stage IV LCNEC received 5 mg everolimus daily combined with paclitaxel 175 mg/m² and carboplatin AUC 5 every 3 weeks for a maximum of four cycles followed by maintenance everolimus 5 mg daily until progression. Efficacy parameters were determined based on central radiologic assessment. **RESULTS:** Forty-nine patients with a mean age of 62 ±9 years and a predominance of male (71%) smokers (98%) were enrolled in 10 German centers. The overall response rate was 45% (95% confidence interval [CI] 31%-60%), the disease control rate 74% (CI 59%-85%), the median progression-free survival 4.4 (CI 3.2-6) months and the median overall survival 9.9 (CI 6.9-11.7) months. The progression-free survival rate at 3 months (primary end point) was 76% (CI 64%-88%) according to Kaplan-Meier. Grade-3/4 toxicities occurred in 51% of patients and mainly consisted of general physical health deterioration (8%), cytopenias (24%), infections (10%) and gastrointestinal problems (8%). Typical everolimus-related adverse events, like stomatitis, rash and ocular problems occurred only in a minority of patients (<15%) and were exclusively of grade 1-2. **CONCLUSION:** Everolimus in combination with carboplatin and paclitaxel is an effective and well-tolerated first-line treatment for patients with metastatic LCNEC.

[The association of genetic variations in DNA repair pathways with severe toxicities in NSCLC patients undergoing platinum-based chemotherapy.](#)

Zheng Y1,2,3, Deng Z4, Yin J1,2, et al. *Int J Cancer.* 2017 Aug 9. doi: 10.1002/ijc.30921. [Epub ahead of print]

Genetic variations in genes involved in repairing platinum-induced DNA lesions may contribute to the toxicity of platinum-based chemotherapy. The role of single-nucleotide polymorphisms (SNPs) within DNA repair pathways in the occurrence of severe toxicity is not yet understood. Current studies prefer to do original works rather than analyze previously published data. Our study aimed to replicate associations between previously investigated SNPs and toxicities and to identify new genetic makers. We systematically examined the relevance of 97 SNPs in 54 candidate genes responsible for repairing DNA interstrand and intrastrand cross-links to severe toxicity in a discovery cohort of 437 NSCLC patients receiving platinum-based chemotherapy. Statistically significant SNPs were then assessed for replication in an independent validation cohort of 781 NSCLC patients. We found that 7 SNPs were significant at $p < 0.01$ (RRM1 rs12806698, XPC rs2228000, XPF rs1799801, hMLH1 rs1800734, PMS2 rs1062372, REV3L rs462779 and FANCC rs4647554) in the discovery cohort. Among them, two SNPs (RRM1 rs12806698 and hMLH1 rs1800734) remained significant after Bonferroni correction. XPC rs2228000 showed a significant relationship with severe gastrointestinal toxicity in the validation cohort. When the two cohorts were combined, XPC rs2228000 presented better tolerance of severe hematologic toxicity, gastrointestinal toxicity and leukopenia (OR = 0.677, 95% CI: 0.510-0.899, $p = 0.007$; OR = 0.565, 95% CI: 0.368-0.869, $p = 0.009$; OR = 0.628, 95% CI: 0.439-0.899, $p = 0.011$, respectively). Our findings can offer comprehensive pharmacogenetic information for platinum-induced toxicities.

[Phase III Trial of Ipilimumab Combined With Paclitaxel and Carboplatin in Advanced Squamous Non-Small-Cell Lung Cancer.](#) Govindan R1, Szczesna A1, Ahn MJ1, et al. J Clin Oncol. 2017 Aug 30;JCO2016717629. doi: 10.1200/JCO.2016.71.7629. [Epub ahead of print]

PURPOSE: Patients with squamous non-small-cell lung cancer (NSCLC) have poor prognosis and limited treatment options. This randomized, double-blind, phase III study investigated the efficacy and safety of first-line ipilimumab or placebo plus paclitaxel and carboplatin in advanced squamous NSCLC. **PATIENTS AND METHODS:** Patients with stage IV or recurrent chemotherapy-naïve squamous NSCLC were randomly assigned (1:1) to receive paclitaxel and carboplatin plus blinded ipilimumab 10 mg/kg or placebo every 3 weeks on a phased induction schedule comprising six chemotherapy cycles, with ipilimumab or placebo from cycles 3 to 6 and then, after induction treatment, ipilimumab or placebo maintenance every 12 weeks for patients with stable disease or better. The primary end point was overall survival (OS) in patients receiving at least one dose of blinded study therapy. **RESULTS:** Of 956 randomly assigned patients, 749 received at least one dose of blinded study therapy (chemotherapy plus ipilimumab, $n = 388$; chemotherapy plus placebo, $n = 361$). Median OS was 13.4 months for chemotherapy plus ipilimumab and 12.4 months for chemotherapy plus placebo (hazard ratio, 0.91; 95% CI, 0.77 to 1.07; $P = .25$). Median progression-free survival was 5.6 months for both groups (hazard ratio, 0.87; 95% CI, 0.75 to 1.01). Rates of grade 3 or 4 treatment-related adverse events (TRAEs), any-grade serious TRAEs, and TRAEs leading to discontinuation were numerically higher with chemotherapy plus ipilimumab (51%, 33%, and 28%, respectively) than with chemotherapy plus placebo (35%, 10%, and 7%, respectively). Seven treatment-related deaths occurred with chemotherapy plus ipilimumab, and one occurred with chemotherapy plus placebo. **CONCLUSION:** The addition of ipilimumab to first-line chemotherapy did not prolong OS compared with chemotherapy alone in patients with advanced squamous NSCLC. The safety profile of chemotherapy plus ipilimumab was consistent with that observed in previous lung and melanoma studies. Ongoing studies are evaluating ipilimumab in combination with nivolumab in this population.

[Apatinib enhances antitumour activity of EGFR-TKIs in non-small cell lung cancer with EGFR-TKI resistance.](#) Li F1, Zhu T2, Cao B3, Wang J4, Liang L5. Eur J Cancer. 2017 Aug 17;84:184-192. doi: 10.1016/j.ejca.2017.07.037. [Epub ahead of print]

BACKGROUND: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs)-rechallenged therapy for EGFR-mutant non-small cell lung cancer (NSCLC) patients who acquired resistance showed moderate efficacy. Considering the high interrelation between EGFR and vascular endothelial growth factor/vascular endothelial growth factor receptor (VEGF/VEGFR) pathways, we firstly evaluated EGFR-TKI combined with apatinib (a highly selective VEGFR2 inhibitor) in EGFR-TKI-resistant model and patients. **METHODS:** Effects of apatinib, gefitinib and gefitinib plus apatinib were assessed on four NSCLC cell lines (A549 with wild-type EGFR, H1975 harbouring L858R and T790M, H1650 and HCC827 harbouring E746_A750 deletion) and xenograft model of acquired resistance that was established by injecting H1975 cells. Furthermore, we retrospectively evaluated EGFR-TKI rechallenge with apatinib in 16 patients. **RESULTS:** Gefitinib plus apatinib strengthened the effect of gefitinib and apatinib alone on the four NSCLC cell lines, and H1975 was the most susceptible one. Co-administration delayed the tumour growth than mono-therapy in the xenograft model and had better effect on inhibiting the activation of EGFR and VEGFR2 and expression of CD31 (an angiogenesis marker) and vascular endothelial growth factor A (an important pro-angiogenesis factor in the tumour microenvironment). Changes in protein expression of protein kinase B/mammalian target of rapamycin and extracellular signal-regulated kinase pathways demonstrated the potent inhibitory effect on the pro-survival signalling pathways by combined therapy. EGFR-TKI rechallenge with apatinib achieved a median progression-free survival of 4.60 months (95% confidence interval, 2.23-12.52 months) in the patients. **CONCLUSIONS:** Apatinib significantly potentiated the antitumour effect of gefitinib in NSCLC with T790M-related EGFR-TKI resistance both in vivo and vitro. EGFR-TKI rechallenge with apatinib might represent a new option for NSCLC with T790M or unknown resistance mechanism.

Proton Beam Radiotherapy and Concurrent Chemotherapy for Unresectable Stage III Non-Small Cell Lung Cancer: Final Results of a Phase 2 Study. Chang JY1, Verma V2, Li M1, et al. JAMA

Oncol. 2017 Aug 10;3(8):e172032. doi: 10.1001/jamaoncol.2017.2032. Epub 2017 Aug 10.

IMPORTANCE: Proton beam radiotherapy (PBT) has the potential to reduce toxic effects in the definitive management of locally advanced non-small cell lung cancer (NSCLC), but long-term

prospective data are lacking. **OBJECTIVE:** To report the final (5-year) results of a prospective study evaluating concurrent chemotherapy and high-dose PBT to treat unresectable stage III NSCLC.

DESIGN, SETTING, AND PARTICIPANTS: In this open-label, single-group assignment study, with median follow-up of 27.3 months for all patients and 79.6 months for survivors, 64 patients were enrolled and analyzed; inclusion criteria were unresectable IIIA/IIIB histologically confirmed NSCLC, Karnofsky performance status 70 to 100, and 6-month prediagnosis weight loss of no more than 10%. Staging used positron emission tomography and/or computed tomography. Induction chemotherapy was allowed.

INTERVENTIONS: Concurrent chemotherapy (carboplatin-paclitaxel) and passively scattered PBT (74-Gy relative biological effectiveness) in all patients. **MAIN OUTCOMES AND MEASURES:** Kaplan-Meier analysis of overall survival (OS), progression-free survival (PFS), actuarial distant metastasis, and locoregional recurrence. Patterns of treatment failure were categorized as local/regional or distant. Acute and late toxic effects were prospectively assigned using Common Terminology Criteria for Adverse Events, v3.0. **RESULTS:** Of 64 patients (22 [34%] female; median [range] age, 70 [37-78] years; stage IIIA, 30 [47%]; IIIB, 34 [53%]), 17 (27%) were alive at last follow-up. Median OS was 26.5 months (5-year OS, 29%; 95% CI, 18%-41%). Five-year PFS was 22% (95% CI, 12%-32%); 5-year actuarial distant metastasis and locoregional recurrence were 54% (n = 36) and 28% (n = 22), respectively. Treatment failures were largely (31 [48%] patients) distant, with low rates of crude local (10 [16%]) and regional (9 [14%]) recurrences. Rates of grade 2 and 3 acute esophagitis were 18 (28%) and 5 (8%), respectively. Acute grade 2 pneumonitis occurred in 1 (2%) patient. Late toxic effects were uncommon: 1 (2%) patient developed an esophageal stricture (grade 2) and 1 (2%) grade 4 esophagitis. Late grades 2 and 3 pneumonitis occurred in 10 (16%) and 8 (12%), respectively. Two (3%) patients developed a bronchial

stricture (grade 2), and 1 (2%) a grade 4 bronchial fistula. There were no acute or late grade 5 toxic effects. **CONCLUSIONS AND RELEVANCE:** Concurrent chemotherapy and PBT to treat unresectable NSCLC afford promising clinical outcomes and rates of toxic effects compared with historical photon therapy data. Further optimization of proton therapy, particularly intensity-modulated proton therapy, is still needed.

The Era of Checkpoint Blockade in Lung Cancer: Taking the Brakes Off the Immune System.

Moon EK1, Langer CJ1, Albelda SM1. Ann Am Thorac Soc. 2017 Aug;14(8):1248-1260. doi: 10.1513/AnnalsATS.201702-152FR.

Despite recent advances with targeted kinase inhibitors and better-tolerated chemotherapy, the treatment of metastatic non-small-cell lung cancer remains suboptimal. One recent advance that holds great promise is immunotherapy—an approach that enhances a patient's immune system to better recognize and react to abnormal cells. The most successful immunotherapeutic strategy to date uses antibodies to block inhibitory receptors (also called "checkpoints") that are up-regulated on the T cells that infiltrate the tumor. Two examples of such molecules are programmed cell death-1 (PD1) and cytotoxic T lymphocyte-associated protein-4. With more than a dozen clinical trials in non-small-cell lung cancer completed, checkpoint blockade targeting PD1 has demonstrated durable responses and superior survival compared with traditional chemotherapy agents when used as first-line therapy in individuals with more than 50% PD1 ligand (PDL1) expression by immunohistochemical staining and as second-line therapy independent of PDL1 status. Antibodies to PDL1 have shown similar activity. Combinations of anti-PD1 and anti-PDL1 with anti-cytotoxic T lymphocyte-associated protein-4 and chemotherapy are being actively tested. These agents have generally tolerable safety profiles; pneumonitis, although rare, remains the most feared adverse effect. PDL1 expression on tumors has been identified as a biomarker predictive of response. Although PDL1 expression has traditionally been measured on resected tumor specimens, the pulmonologist has a growing role in obtaining samples for testing via minimally invasive means.

NSCLC - RADIOTHERAPY

Oligometastatic cancer: stereotactic ablative radiotherapy for patients affected by isolated body metastasis.

Lancia A1, Ingrosso G1, Carosi A1, et al. Acta Oncol. 2017 Aug 18:1-5. doi: 10.1080/0284186X.2017.1346383. [Epub ahead of print]

BACKGROUND: To evaluate the outcome of patients affected by a single isolated body metastasis treated with stereotactic body radiotherapy (SBRT). **MATERIAL AND METHODS:** Seven-eight patients were treated with SBRT for isolated body metastasis. The most frequent primary tumor was prostate cancer (28.2%), followed by colorectal cancer (23.1%) and lung cancer (20.5%). Median age at diagnosis of oligometastatic disease was 70 years (range 47-88). Median Karnofsky Performance Status (KPS) was 90 (range 70-100). The most common SBRT fractionation scheme was 5 × 7 Gy (total dose 35 Gy). Response to radiotherapy was determined according to RECIST criteria v1.1. Toxicity was registered according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0. The survival analysis was performed with the Kaplan-Meier method. The correlation between time actuarial incidence and clinical parameters was studied, and the Kaplan-Meier method of log-rank test was applied.

RESULTS: With a median follow-up of 22.68 months, local control was achieved in 89.7% of the cases. The two-year overall survival (OS) and progression-free survival (PFS) were 68% and 42%, respectively. On univariate analysis, KPS ≥80 is predictive for improved OS (p = .001) and PFS (p = .001). Acute toxicity of grade ≥2 occurred in eight (10.2%) patients and late grade ≥2 toxicity in five (6.4%) patients.

CONCLUSIONS: Ablative radiotherapy in 'early oligometastatic state' is a safe, effective and minimally invasive treatment modality. A good performance status (KPS ≥80) seems to influence the clinical outcome.

[Assessment of per endoscopic guided placement of fiducial gold markers for small peripheral lung nodules of less than 20 mm before stereotactic radiation therapy.](#) Lachkar S1, Guisier F2, Roger M1, et al. Chest. 2017 Aug 25. pii: S0012-3692(17)31433-2. doi: 10.1016/j.chest.2017.08.016. [Epub ahead of print]

BACKGROUND: Stereotactic radiotherapy is used to treat peripheral lung cancer in inoperable patients. Placement of fiducial gold markers (FMs) is crucial for tracking small lesions that are not visible on chest X-ray. Our objective was to assess endoscopic FM placement in small peripheral lung nodules (PLN) that are not trackable using automated tracking software. **MATERIALS AND METHODS:** All patients benefiting from virtual bronchoscopy and radial endobronchial ultrasound (r-EBUS) guided placement of FM for PLN of less than 20mm were included. After confirmation by biopsy sampling, a gold-seed FM was inserted into the nodule using a bronchial brush, without use of fluoroscopy. The performances and complications of the procedure were recorded. **RESULTS:** From May 2010 to June 2015, FMs were placed in the PLN of 54 consecutive patients, 34 of whom presented with a nodule of less than 20mm. 76% of procedures were performed under local anesthesia, on an outpatient basis. Median long and short axis diameters of nodules were 15mm (9-20mm) and 11mm (6-20mm), respectively, with 31 of 34 nodules exhibiting a short axis of less than 15mm. In 23 cases (79%), histology was obtained during the procedure that allowed FM placement. Migration occurred in 6 cases, including 2 in the hours following the procedure. FMs were in place and visible in 80% of cases on CT scan performed 3 months after radiation therapy. No complications were reported. **CONCLUSION:** Diagnosis of peripheral nodules of less than 20mm and FM placement using r-EBUS are efficient and safe in a single procedure.

[Patient preference for stereotactic radiosurgery plus or minus whole brain radiotherapy for the treatment of brain metastases.](#) Zeng KL1, Raman S1, Sahgal A1, Soliman H1, Tsao M1, Wendzicki C2, Chow E1, Lo SS3. Ann Palliat Med. 2017 Aug 8. pii: apm.2017.06.11. doi: 10.21037/apm.2017.06.11. [Epub ahead of print]

BACKGROUND: Optimal management for limited, non-resectable brain metastases is an evolving area in radiation oncology. Previous data show no difference in survival between stereotactic radiosurgery (SRS) and SRS plus whole-brain radiotherapy (WBRT). Neurocognitive toxicities, treatment duration and tumor recurrence differ and therefore patient values play an important role in decision making. We aim to elicit patient preferences and understand factors important in deciding which treatment to pursue.

METHODS: Patients were recruited from 2 centers in North America. Eligibility criteria included ≤ 4 intracranial lesions and physician judgment that either treatment was appropriate. Those with prior treatment for brain metastases were excluded. A decision board presented the treatments and summarized evidence regarding disease control and toxicity. An option to either take an active or passive role was offered. If taking a passive role, treatment was left to the clinician. If an active role was taken, patients made a decision about whether to receive SRS alone, or in combination with WBRT. A debriefing questionnaire to rank important factors in decision making was then completed. Descriptive statistics summarized findings. **RESULTS:** A total of 23 patients were enrolled. The majority of patients were male (15/23; 65.2%), had primary lung cancer (15/23; 65.2%) and the mean age was 65.5 years. All patients took an active role in deciding their treatment. The majority of patients (21/23) chose to receive SRS alone. The highest ranked factors were quality of life (9.4/10), ability to maintain functional independence (9.3/10) and influence of treatment on survival (9.2/10). The least important factor was number of trips required to the cancer center (5.0/10). **CONCLUSIONS:** A patient centered approach to decision making in brain metastases is feasible. Most patients will take an active role in management if relevant information is presented in a clear, understandable manner. When informed, most patients prefer SRS alone rather than SRS + WBRT and identify quality of life, ability to maintain functional independence and influence of treatment on survival as highly important factors in making their decision.

[Results from a clinical trial evaluating the efficacy of real-time body surface visual feedback in reducing patient motion during lung cancer radiotherapy.](#) Price GJ1, Faivre-Finn C1, Stratford J1, Chauhan S2, Bewley M2, Clarke L2, Johnson CN1, Moore CJ1. Acta Oncol. 2017 Aug 7:1-8. doi: 10.1080/0284186X.2017.1360511. [Epub ahead of print]

INTRODUCTION: Optical surface measurement devices are a maturing technology in radiotherapy. The challenge for such devices is to demonstrate how they can improve clinical care. We present results from a phase 1 clinical trial designed to test the hypothesis that if presented with live data from a novel optical measurement device, showing their deviation from an ideal radiotherapy treatment position, patients will be able to better control their motion and increase their geometrical conformance. **METHOD AND**

MATERIALS: Fourteen lung cancer patients were enrolled in a prospective clinical study and asked to use a variety of visual feedback schema from a novel in-house developed optical surface measurement device. The magnitude and regularity of their body surface motion using the different schema was compared to that when free-breathing at three time-points throughout their radiotherapy treatment schedule. Additionally, 4D Cone Beam CT data, acquired simultaneously with the optical measurements, was used to test if improvements in external motion are reflected in changes in internal tumor motion.

RESULTS: The primary endpoint of the trial, device tolerability assessed by the fraction of participants completing all study sessions, was 86%. Secondary endpoints showed that use of the visual feedback device was found to statistically significantly decrease body surface motion magnitude by an average of 17% over the study cohort, although not universally. Similarly body surface motion variability was decreased by 18% on average. Internal tumor motion magnitude was also found to be statistically significantly decreased by an average of 14% when using the feedback device. Reduction in external motion was predictive of reduced internal motion but no evidence of a simple correlation between changes in internal and external motion magnitude was found. **CONCLUSIONS:** Visual feedback of live motion is well tolerated by lung cancer patients and can reduce both body surface and tumor motion.

[Dose-escalated radiation therapy is associated with better overall survival in patients with bone metastases from solid tumors: a propensity score-matched study.](#) Chou YC1, Lin CY1, et al. Cancer Med. 2017 Aug 15. doi: 10.1002/cam4.1150. [Epub ahead of print]

We aimed to compare the overall survival (OS) of patients with bone metastases (BM) from solid tumors after standard-dose radiotherapy ([RT]; 30 Gy administered in 10 fractions; EQD2Gy = 32.5 Gy) and dose-escalated RT (EQD2Gy > 32.5 Gy). We retrospectively reviewed the clinical charts of 1795 patients (median age, 62.3 years; age range, 18-96 years) with BM from solid tumors who were referred for RT to our institute between 2000 and 2013. These patients were assigned to the standard-dose (n = 1125; 63%) and dose-escalated (n = 670; 37%) RT groups. OS, estimated as the duration between the first RT session and death, served as the main outcome measure. The dose-escalated RT group had a significantly better OS than the standard-dose RT group (P = 0.000). After allowing potential confounders in multivariate analysis, the RT dose retained its independent association with OS (hazard ratio [HR], 0.837; 95% confidence interval [CI], 0.753-0.929, P = 0.001). After propensity score matching of the baseline characteristics of both groups, RT dose retained its independent association with OS (HR, 0.887; 95% CI, 0.737-0.951; P = 0.011) on multivariate analysis. Dose-escalated RT exerted more favorable effects on OS in patients with non-lung cancer, those without multiple metastases, those without symptoms, and those with favorable prognosis. Dose-escalated RT was significantly associated with better OS in patients with BM from solid malignancies, particularly among those with non-lung cancer, those without multiple metastases, those without symptoms, and those with favorable prognosis.

[National trends in radiotherapy for brain metastases at time of diagnosis of non-small cell lung cancer.](#) Trifiletti DM1, Sheehan JP2, Grover S3, Dutta SW4, Rusthoven CG5, Kavanagh BD5, Sahgal A6, Showalter TN4. *J Clin Neurosci.* 2017 Aug 30. pii: S0967-5868(17)30874-3. doi: 10.1016/j.jocn.2017.08.028. [Epub ahead of print]

BACKGROUND: To analyze the national trends of patients treated radiotherapy for brain metastases from non-small cell lung cancer (NSCLC) that were found at diagnosis. **METHODS:** The National Cancer Database was queried for patients with NSCLC diagnosed from 2004 to 2013 that received brain irradiation for metastases and patients grouped into having had received fractionated brain radiotherapy (5-15 fractions with or without radiosurgery) or intracranial radiosurgery alone (1-5 fractions). Univariable and multivariable (MVA) analyses were performed to investigate factors associated with the receipt of SRS alone, and temporal/regional trends. **RESULTS:** 47,746 patients met inclusion criteria, of which 42,148 received fractionated brain irradiation (88%) and 5,598 received radiosurgery (12%). 345 patients received fractionated brain irradiation with a radiosurgical boost (0.8%). The utilization of radiosurgery-alone increased over time owing to increases in each radiosurgery modality. On MVA, several factors were associated with increased odds of receiving intracranial radiosurgery-alone over fractionated brain radiotherapy including more recent year of diagnosis, increased median income, eastern U.S. regions, further distance to the hospital, and the receipt of chemotherapy (each $p < 0.001$). Patients of Asian descent were less likely to receive radiosurgery alone ($p = 0.044$). **CONCLUSIONS:** In the management of brain metastases from NSCLC, overall utilization of an intracranial radiosurgery alone treatment strategy has increased over the past decade. Despite this, there appear to be significant geographic variations and disparities remain based on patient income level and race. Further study is needed to define the reasons for these disparities and appropriate actions to mitigate them. Copyright © 2017 Elsevier Ltd. All rights reserved.

SMALL CELL LUNG CANCER - SCLC

[The effect of brassinolide, a plant steroid hormone, on drug resistant small-cell lung carcinoma cells.](#) Sadava D1, Kane SE2. *Biochem Biophys Res Commun.* 2017 Aug 25. pii: S0006-291X(17)31653-4. doi: 10.1016/j.bbrc.2017.08.094. [Epub ahead of print]

Small-cell lung carcinoma (SCLC) has a dismal prognosis in part because of multidrug resistance (MDR). Epibrassinolide (EB) is a steroid hormone in plants, with many physiological effects. It acts via a membrane receptor and GSK3 pathway, resulting in stabilization of a transcription factor. The parallels to the Wnt signaling pathway, which is activated in SCLC and results in increased β -catenin, prompted investigations of the effects of EB on drug-resistant (VPA17) and drug-sensitive (H69) SCLC cells. EB was cytotoxic to both cell lines ($IC_{50} = 2 \mu M$), indicating a lack of cross-resistance in the VPA17 cell line. EB was pro-apoptotic after 24 h as measured by ELISA of BUdR-labeled DNA fragments and caspase-3 specific activity (2.5 enzyme units/mg protein vs. 0.01 units/mg protein for untreated controls). Matrigel assays showed that EB reduced the SCLC cell invasion phenotype by 80%. Pre-incubation of VPA17 cells in 1 μM EB for 96 h reversed resistance to etoposide ($IC_{50} = 6.0 \mu M$, reduced to 1.8 μM with EB) and doxorubicin ($IC_{50} = 0.37 \mu M$, reduced to 0.09 μM). Synergism between EB and chemotherapy drugs was investigated by exposure of VPA17 cells to 1:1 ratios at the respective IC_{50} values, with serial dilutions at 0.25 to 2.0 $\times IC_{50}$ and determination of the combination index (CI). EB and etoposide showed synergism (CI = 0.80 at ED50); EB and doxorubicin also showed synergism (CI = 0.65 at ED50). Incubation of SCLC cells in EB led to a time- and dose dependent reduction of β -catenin (maximum 80% reduction). Gene expression analyses of SCLC cells showed EB incubation resulted in significant reduction in expression of β -catenin-dependent genes that are anti-apoptotic (e.g., c-Jun, survivin), cell division-related (e.g., CCND1 cyclin, sox9), and metastasis-related (e.g., MMP7, uPAR). WIKI4, a known inhibitor of Wnt signaling, was cytotoxic to SCLC cells ($IC_{50} = 0.02 \mu M$). Synergism

between EB and WIKI4 was determined by the CI method and showed antagonism (CI = 1.09 at ED50), suggesting that EB and WIKI4 act on the same pathway. Taken together, these data indicate that EB, a natural product with widespread occurrence in plants, is pharmacologically active in both drug-sensitive and drug-resistant SCLC cells and acts through the Wnt signaling pathway.

[Pembrolizumab in Patients With Extensive-Stage Small-Cell Lung Cancer: Results From the Phase Ib KEYNOTE-028 Study.](#) Ott PA1, Elez E1, Hirt S1, Kim DW1, Morosky A1, Saraf S1, Piperdi B1, Mehnert JM1. *J Clin Oncol.* 2017 Aug 16;JCO2017725069. doi: 10.1200/JCO.2017.72.5069. [Epub ahead of print]

PURPOSE: The safety and efficacy of pembrolizumab, a humanized monoclonal antibody against programmed death 1 (PD-1), were assessed in patients with programmed death ligand 1 (PD-L1)-expressing extensive-stage small-cell lung cancer (SCLC) in the multicohort, phase Ib open-label KEYNOTE-028 study (ClinicalTrials.gov identifier: NCT02054806). **METHODS PATIENTS:** with SCLC received pembrolizumab 10 mg/kg every 2 weeks for 24 months or until disease progression or intolerable toxicity occurred. PD-L1 expression was assessed by immunohistochemistry. PD-L1-positive patients had membranous PD-L1 expression in $\geq 1\%$ of tumor and associated inflammatory cells or positive staining in stroma. Response was assessed by investigator per Response Evaluation Criteria in Solid Tumors version 1.1 every 8 weeks for the first 6 months and every 12 weeks thereafter. Adverse events (AEs) were reported per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Primary end points were safety, tolerability, and objective response rate (ORR). Secondary end points included progression-free survival, overall survival, and duration of response.

RESULTS: Twenty-four patients with PD-L1-expressing SCLC were enrolled and received at least one pembrolizumab dose. At the data cutoff date (June 20, 2016), the median follow-up duration was 9.8 months (range, 0.5 to 24 months). All 24 patients experienced AEs; the most common were asthenia (n = 7), fatigue (n = 7), and cough (n = 6). Two patients experienced grade 3 to 5 treatment-related AEs: one patient had elevated bilirubin, and one patient had asthenia, grade 5 colitis, and intestinal ischemia. One patient had a complete response, and seven patients had partial responses, resulting in an ORR of 33% (95% CI, 16% to 55%). **CONCLUSION:** The safety of pembrolizumab was consistent with the known safety profile in other tumor types. Pembrolizumab demonstrated promising antitumor activity in patients with pretreated, PD-L1-expressing SCLC.

[Patterns of failure in limited-stage small cell lung cancer: Implications of TNM stage for prophylactic cranial irradiation.](#) Wu AJ1, Gillis A2, Foster A2, et al. *Radiother Oncol.* 2017 Aug 1. pii: S0167-8140(17)32478-7. doi: 10.1016/j.radonc.2017.07.019. [Epub ahead of print]

BACKGROUND AND PURPOSE: The relationship between tumor-node-metastasis (TNM) stage and patterns of failure in limited-stage small cell lung cancer (LS-SCLC) remains unclear. We hypothesized that TNM stage predicts brain metastasis risk, and could inform the use of prophylactic cranial irradiation. **MATERIAL AND METHODS:** We reviewed 283 patients with stage I-III SCLC. Competing-risks regression was used to analyze local, distant, and brain failure. Multivariate analysis was used to evaluate the effect of treatment and clinical factors on failure and OS. **RESULTS:** Patients with stage I or II SCLC (35% of cohort) had significantly better survival and lower risk of distant and brain metastasis, compared with stage III patients. The 5-year cumulative incidence of brain metastasis for stage I/II and III were 12% and 26%, respectively. Stage had no correlation with local failure. On multivariate analysis, stage was independently prognostic for survival, distant metastasis risk, and brain metastasis risk. **CONCLUSIONS:** TNM staging predicts likelihood of distant metastasis, brain metastasis, and survival in LS-SCLC. This supports the routine use of TNM staging in clinical practice. The lower risk of brain metastasis in stage I and II SCLC suggests that prophylactic cranial irradiation could play a more limited role in treatment of early-stage disease.

[Small cell lung carcinoma cell line screen of etoposide/carboplatin plus a third agent.](#) Teicher BA1, Silvers T2, Selby M2, et al. *Cancer Med.* 2017 Aug;6(8):1952-1964. doi: 10.1002/cam4.1131. Epub 2017 Aug 1.

The SCLC combination screen examined a 9-point concentration response of 180 third agents, alone and in combination with etoposide/carboplatin. The predominant effect of adding a third agent to etoposide/carboplatin was additivity. Less than additive effects occurred frequently in SCLC lines sensitive to etoposide/carboplatin. In SCLC lines with little or no response to etoposide/carboplatin, greater than additive SCLC killing occurred over the entire spectrum of SCLC lines but never occurred in all SCLC lines. Exposing SCLC lines to tubulin-targeted agents (paclitaxel or vinorelbine) simultaneously with etoposide/carboplatin resulted primarily in less than additive cell killing. As single agents, nuclear kinase inhibitors including Aurora kinase inhibitors, Kinesin Spindle Protein/EG5 inhibitors, and Polo-like kinase-1 inhibitors were potent cytotoxic agents in SCLC lines; however, simultaneous exposure of the SCLC lines to these agents along with etoposide/carboplatin, generally, resulted in less than additive cell killing. Several classes of agents enhanced the cytotoxicity of etoposide/carboplatin toward the SCLC lines. Exposure of the SCLC lines to the MDM2 inhibitor JNJ-27291199 produced enhanced killing in 80% of the SCLC lines. Chk-1 inhibitors such as rabeprazole increased the cytotoxicity of etoposide/carboplatin to the SCLC lines in an additive to greater than additive manner. The combination of GSK-3 β inhibitor LY-2090314 with etoposide/carboplatin increased killing in approximately 40% of the SCLC lines. Exposure to the BET bromodomain inhibitor MK-8628 increased the SCLC cell killing by etoposide/carboplatin in 20-25% of the SCLC lines. Only 10-15% of the SCLC lines had an increased response to etoposide/carboplatin when simultaneously exposed to the PARP inhibitor talazoparib.

[Current Treatments for Surgically Resectable, Limited-Stage, and Extensive-Stage Small Cell Lung Cancer.](#) Stinchcombe TE1. *Oncologist.* 2017 Aug 4. pii: theoncologist.2017-0204. doi: 10.1634/theoncologist.2017-0204. [Epub ahead of print]

The prevalence of small cell lung cancer (SCLC) has declined in the U.S. as the prevalence of tobacco use has declined. However, a significant number of people in the U.S. are current or former smokers and are at risk of developing SCLC. Routine histological or cytological evaluation can reliably make the diagnosis of SCLC, and immunohistochemistry stains (thyroid transcription factor-1, chromogranin, synaptophysin, and CD56) can be used if there is uncertainty about the diagnosis. Rarely do patients present with SCLC amenable to surgical resection, and evaluation requires a meticulous workup for extra-thoracic metastases and invasive staging of the mediastinum. Resected patients require adjuvant chemotherapy and/or thoracic radiation therapy (TRT), and prophylactic cranial radiation (PCI) should be considered depending on the stage. For limited-stage disease, concurrent platinum-etoposide and TRT followed by PCI is the standard. Thoracic radiation therapy should be started early in treatment, and can be given twice daily to 45 Gy or once daily to 60-70 Gy. For extensive-stage disease, platinum-etoposide remains the standard first-line therapy, and the standard second-line therapy is topotecan. Preliminary studies have demonstrated the activity of immunotherapy, and the response rate is approximately 10-30% with some durable responses observed. Rovalpituzumab tesirine, an antibody drug conjugate, has shown promising activity in patients with high delta-like protein 3 tumor expression (approximately 70% of patients with SCLC). The emergence of these and other promising agents has rekindled interest in drug development in SCLC. Several ongoing trials are investigating novel agents in the first-line, maintenance, and second-line settings.

[Second-line treatments of small-cell lung cancers.](#) Baize N1, Monnet I2, Greillier L3, Quere G4, Kerjouan M5, Janicot H6, Vergnenegre A7, Auliac JB8, Chouaid C2. *Expert Rev Anticancer Ther.* 2017 Aug 29. doi: 10.1080/14737140.2017.1372198. [Epub ahead of print]

INTRODUCTION: Second-line therapies for relapsed small cell lung cancer (SCLC) patients remain a challenge, with limited clinical benefit because of rapid tumor growth, early dissemination and the development of drug resistance during the disease. Recent developments in genomic sequencing have provided further insight into the biology of the disease, identifying new targets and new pathways. Areas covered: This review details chemotherapy, targeted therapies and immune-checkpoint blockades that have been investigated as second-line treatments for SCLC patients using a PubMed search (period 1990 - 2016, terms used: SCLC, treatments, second line, therapy). **EXPERT COMMENTARY:** Recent genomic, proteomic and preclinical studies have identified novel therapeutic strategies currently being evaluated in clinical trials. Promising approaches for SCLC management include delta-like ligand-3 (DLL3)-targeted antibody-drug conjugate, combination targeted therapies, or targeted therapy-chemotherapy with an additive effect superior to the efficacy of single agents. The blockade of immune checkpoints has yielded promising preliminary results and is being investigated in ongoing trials. The inclusion of SCLC patients relapsing after platin-doublet induction in well-designed clinical trials remains a major challenge.

[Thoracic radiotherapy \(TRT\) improved survival in both oligo- and polymetastatic extensive stage small cell lung cancer.](#) Xu LM1, Cheng C2, Kang M2,3, Luo J1, Gong LL1, Pang QS1, Wang J1, Yuan ZY1, Zhao LJ4, Wang P5. *Sci Rep.* 2017 Aug 23;7(1):9255. doi: 10.1038/s41598-017-09775-0.

There has been no previous study on the efficacy of the thoracic radiotherapy (TRT) in oligometastatic or polymetastatic extensive stage small-cell lung cancer (ES-SCLC) to the overall survival (OS). In a group of 270 ES-SCLC cases retrospective study, 78 patients (28.9%) had oligometastases and 192 (71.1%) had polymetastases, among which 51 oligometastatic patients (65.4%) and 93 polymetastatic patients (51.6%) received TRT. Propensity score matching (PSM) was utilized. The 2-year OS, progression free survival (PFS) and local control (LC) in oligometastatic and polymetastatic patients were 22.8% and 4.5% ($p < 0.001$), 12.0% and 3.8% ($p < 0.001$), and 36.7% and 6.1% ($p < 0.001$), respectively. The 2-year OS in oligometastatic patients with the chemotherapy + radiotherapy and chemotherapy alone were 25.2% and 12.7% ($p = 0.002$), in contrast to 10.0% and 6.8% ($p = 0.030$) in polymetastatic patients. The estimated hazard ratios for survival were 2.9 and 1.7 for both oligometastatic and polymetastatic patients with radiotherapy. The polymetastatic group has a lower LC (6.1% v.s. 36.7%, ($p < 0.001$)), due to polymetastases patients receiving involved-sites radiotherapy with low dose schemas. TRT improved OS of patients with oligometastases and polymetastases. Our study demonstrated that aggressive TRT might be a suitable addition of chemotherapy when treating ES-SCLC patients with oligometastases and polymetastases.

[Incidence of Second Malignancy after Successful Treatment of Limited-Stage Small-Cell Lung Cancer and Its Effects on Survival.](#) Kono M1, Allen PK2, Lin SH2, Wei X2, Jeter M2, Welsh JW2, Cox JD2, Komaki R3. *J Thorac Oncol.* 2017 Aug 10. pii: S1556-0864(17)30661-5. doi: 10.1016/j.jtho.2017.07.030. [Epub ahead of print]

INTRODUCTION: Extended survival outcomes from improved treatments for patients with cancer come with an increased risk of developing a metachronous second malignancy (MSM). We evaluated the incidence of MSM after successful treatment of SCLC and compared survival between SCLC patients who developed MSM and those who did not. **METHODS:** Selection criteria were a diagnosis of limited-stage SCLC and receipt of ≥ 45 Gy radiotherapy and chemotherapy at a single institution in 1985-2012. MSM was defined as a tumor of a different histologic type than the primary that appeared more than 2 years after the diagnosis of SCLC. **RESULTS:** Of 704 patients identified, 32 were excluded for lack of follow-up, 48 for having SCLC as MSM after treatment of another type of cancer, 37 for non-melanoma skin cancer as MSM, and 46 for MSM within 2 years after SCLC diagnosis; of the remaining 541 patients, 346 had recurrent SCLC, 180 had no second malignancy and no recurrence, and 15 (2.8%) had

MSM (13 in lung [8 adenocarcinoma, 5 squamous cell carcinoma], 1 sarcoma, 1 acute myeloid leukemia). All 15 patients with MSM achieved complete response to the SCLC treatment. Overall survival was longer for patients with MSM than for patients with no other malignancies and no recurrence, with 10-year rates of 61.9% (95% confidence interval [CI] 30.0%-82.6%) and 29.9% (95% CI 21.5%-38.6%), respectively (p=0.03). **CONCLUSIONS:** Long-time survivors after treatment for SCLC should be made aware of the risk of MSM and the necessity of follow-up.

PALLIATIVE AND SUPPORTIVE CARE

[Psychological distress associated with cancer screening: A systematic review.](#) Chad-Friedman E1,2, Coleman S3, Traeger LN2,4, Pirl WF2,4, Goldman R1, Atlas SJ5, Park ER1,2,4,6. Cancer. 2017 Aug 22. doi: 10.1002/cncr.30904. [Epub ahead of print]

BACKGROUND: Current national cancer screening recommendations include the potential risk of psychological harm related to screening. However, data on the relation of psychological distress to cancer screening is limited. The authors conducted a systematic review to assess psychological distress associated with cancer screening procedures. **METHODS:** Studies that administered measures of psychological distress between 2 weeks before and 1 month after the screening procedure were included. **RESULTS:** In total, 22 eligible studies met criteria for review, including 13 observational trials and 9 randomized controlled trials. Eligible studies used a broad range of validated and unvalidated measures. Anxiety was the most commonly assessed construct and was measured using the State Trait Anxiety Inventory. Studies included breast, colorectal, prostate, lung, and cervical screening procedures. Distress was low across procedures, with the exception of colorectal screening. Distress did not vary according to the time at which distress was measured. None of the studies were conducted exclusively with the intention of assessing distress at the time of screening. **CONCLUSIONS:** Evidence of low distress during the time of cancer screening suggests that distress might not be a widespread barrier to screening among adults who undergo screening. However, more studies are needed using validated measures of distress to further understand the extent to which screening may elicit psychological distress and impede adherence to national screening recommendations. Cancer 2017. © 2017 American Cancer Society.

[The Yale Fitness Intervention Trial in female cancer survivors: Cardiovascular and physiological outcomes.](#) Knobf MT1, Jeon S2, Smith B3, Harris L4, Thompson S5, Stacy MR6, Insogna K7, Sinusas AJ8. Heart Lung. 2017 Sep - Oct;46(5):375-381. doi: 10.1016/j.hrtlng.2017.06.001. Epub 2017 Aug 10.

BACKGROUND: Induced premature menopause and cardio-toxic therapy increase cardiovascular disease risk in female cancer survivors. **OBJECTIVE:** To compare the effects of a 12 month aerobic-resistance fitness center intervention to home based physical activity on cardiovascular function and metabolic risk factors. **METHODS:** Subjects (N = 154) who had completed primary and/or adjuvant chemotherapy (past 3 years) were randomized to a fitness center intervention or a home based group. The fitness center intervention was a structured thrice weekly aerobic (30 min brisk walking treadmill in target heart range) combined with resistance (30 min of lower body strength training) exercise program, supervised for the first 6 months. The home based group received national guidelines for 30 min moderate intensity exercise most days of the week. Fasting serum samples were collected at baseline, 6 and 12 months for insulin, glucose, lipids and hemoglobin A-1C. A graded exercise stress test was also performed at baseline and 6 months. **RESULTS:** The majority of subjects were white (85.7%), had breast cancer (83.1%) and the average age was 51.9 years. Subjects in the fitness center intervention had significantly improved time on treadmill (p = .039), improved heart rate recovery at 1 min (p = .028), greater MET minutes/week (p ≤ .0001), a trend for improved insulin resistance (p = .067) and stable insulin levels (p = .045) compared to the home based physical activity group. **CONCLUSIONS:** Exercise represents a potential cardiac risk reduction intervention for cancer survivors.

Quality Improvement Initiatives to Optimize the Management of Chronic Obstructive Pulmonary Disease in Patients With Lung Cancer. Digby GC1, Robinson A1. J Oncol Pract. 2017 Aug

25:JOP2017022228. doi: 10.1200/JOP.2017.022228. [Epub ahead of print]

PURPOSE: Patients with lung cancer (LC) frequently have chronic obstructive pulmonary disease (COPD), the optimization of which improves outcomes. A 2014 Queen's University Hospitals audit demonstrated that COPD was underdiagnosed and undertreated in outpatients with LC. We sought to improve the diagnosis and management of COPD in this population. **METHODS:** We implemented change using a Define/Measure/Analyze/Improve/Control (DMAIC) improvement cycle. Data were obtained by chart review from the Cancer Care Ontario database and e-Patient System for patients with newly diagnosed LC, including patient characteristics, pulmonary function test (PFT) data, and bronchodilator therapies. Improvement cycle 1 included engaging stakeholders and prioritizing COPD management by respirologists in the Lung Diagnostic Assessment Program. Improvement cycle 2 included physician restructuring and developing a standard work protocol. Data were analyzed monthly and presented on statistical process control P-charts, which assessed differences over time. The χ^2 and McNemar tests assessed for significance between independent and dependent groups, respectively. **RESULTS:** A total of 477 patients were studied (165 patients at baseline, 166 patients in cycle 1, and 127 patients in cycle 2). There was no change in PFT completion over time, although respirology-managed patients were significantly more likely to undergo a PFT than patients who were not managed by respirology (56.7% v 96.1%; $P < .00001$). The proportion of respirology-managed patients with LC with airflow obstruction receiving inhaled bronchodilator significantly increased (baseline, 46.3%; cycle 1, 51.0%; and cycle 2, 74.3%). By cycle 2, patients with airflow obstruction were more likely to receive a long-acting bronchodilator if managed by respirology (74.3% v 44.8%; $P = .0009$). **CONCLUSION:** COPD is underdiagnosed and undertreated in outpatients with LC. A DMAIC quality improvement strategy emphasizing COPD treatment during LC evaluation in the Lung Diagnostic Assessment Program significantly improved COPD management.

Clinical decision-making and health-related quality of life during first-line and maintenance therapy in patients with advanced non-small cell lung cancer (NSCLC): findings from a real-world setting. Sztankay M1,2, Giesinger JM3, Zabernigg A4, et al. BMC Cancer. 2017 Aug 23;17(1):565. doi:

10.1186/s12885-017-3543-7.

BACKGROUND: Maintenance therapy (MT) with pemetrexed has been shown to improve overall and progression-free survival of patients with non-squamous non-small cell lung cancer (NSCLC), without impairing patients' health-related quality of life (HRQOL) substantially. Comprehensive data on HRQOL under real-life conditions are necessary to enable informed decision-making. This study aims to (1) assess HRQOL during first-line chemotherapy and subsequent MT and (2) record patients' and physicians' reasons leading to clinical decisions on MT. **METHODS:** Patients treated for NSCLC at three Austrian medical centres were included. HRQOL was assessed at every chemotherapy cycle using the EORTC QLQ-C30/+LC13 questionnaire. Semi-structured interviews were conducted before MT initiation and at the time of discontinuation to evaluate patients' and physicians' reasons for treatment decisions. Longitudinal QOL analysis was based on linear mixed models. **RESULTS:** Sixty-one (73%) out of 84 patients were considered for MT. Thirty-six patients (43%) received MT and 29 (35%) discontinued therapy. Decisions on MT initiation (in 20 cases by the physician vs 4 by the patient) and discontinuation (19 vs 10) were mainly voiced by the physician. Treatment toxicity of first-line chemotherapy was the main reason for rejection of MT in patients with stable disease and was more often indicated by patients than clinicians. HRQOL data were collected from 83 patients at 422 assessment time points and indicated significantly lower symptom severity during MT compared with first-line therapy for nausea and vomiting ($p = 0.006$), sleep disturbances ($p < 0.001$), appetite loss ($p = 0.043$), constipation ($p = 0.017$)

and chest pain ($p = 0.022$), and a deterioration in emotional functioning ($p = 0.023$) and cognitive functioning ($p = 0.044$) during MT. **CONCLUSIONS:** Our results indicate that HRQOL and symptom burden improve between first-line treatment to MT in some respects, although some late toxicity persists. Discrepancies between patients' and physicians' perception of reasons for rejecting MT were evident. Thus, the integration of patient-reported outcomes, such as HRQOL, is required to enable shared decision-making and personalised healthcare based on mutual understanding of treatment objectives.

[Risk factors for falls in older patients with cancer.](#) Zhang X1, Sun M1, Liu S2, et al. *BMJ Support Palliat Care*. 2017 Aug 31. pii: bmjpcare-2017-001388. doi: 10.1136/bmjpcare-2017-001388. [Epub ahead of print]

OBJECTIVES: A rising number of patients with cancer are older adults (65 years of age and older), and this proportion will increase to 70% by the year 2020. Falls are a common condition in older adults. We sought to assess the prevalence and risk factors for falls in older patients with cancer. **METHODS:** This is a single-site, retrospective cohort study. Patients who were receiving cancer care underwent a comprehensive geriatric assessments, including cognitive, functional, nutritional, physical, falls in the prior 6 months and comorbidity assessment. Vitamin D and bone densitometry were performed. **ANALYSIS:** Descriptive statistics and multivariable logistic regression. **RESULTS:** A total of 304 patients aged 65 or above were enrolled in this study. The mean age was 78.4 ± 6.9 years. They had haematological, gastrointestinal, urological, breast, lung and gynaecological cancers. A total of 215 patients with available information about falls within the past 6 months were included for final analysis. Seventy-seven (35.8%) patients had at least one fall in the preceding 6 months. Functional impairment ($p=0.048$), frailty ($p<0.001$), dementia ($p=0.021$), major depression ($p=0.010$) and low social support ($p=0.045$) were significantly associated with the fall status in the univariate analysis. Multivariate logistic regression analysis identified frailty and functional impairment to be independent risk factors for falls. **CONCLUSIONS:** Falls are common in older patients with cancer and lead to adverse clinical outcomes. Major depression, functional impairment, frailty, dementia and low social support were risk factors for falls. Heightened awareness and targeted interventions can prevent falls in older patients with cancer.

[Effect of Palliative Care on Aggressiveness of End-of-Life Care Among Patients With Advanced Cancer.](#) Triplett DP1, LeBrett WG1, Bryant AK1, et al. *J Oncol Pract*. 2017 Aug 22;JOP2017020883. doi: 10.1200/JOP.2017.020883. [Epub ahead of print]

PURPOSE: Palliative care's role in oncology has expanded, but its effect on aggressiveness of care at the end of life has not been characterized at the population level. **METHODS:** This matched retrospective cohort study examined the effect of an encounter with palliative care on health-care use at the end of life among 6,580 Medicare beneficiaries with advanced prostate, breast, lung, or colorectal cancer. We compared health-care use before and after palliative care consultation to a matched nonpalliative care cohort. **RESULTS:** The palliative care cohort had higher rates of health-care use in the 30 days before palliative care consultation compared with the nonpalliative cohort, with higher rates of hospitalization (risk ratio [RR], 3.33; 95% CI, 2.87 to 3.85), invasive procedures (RR, 1.75; 95% CI, 1.62 to 1.88), and chemotherapy administration (RR, 1.61; 95% CI, 1.45 to 1.78). The opposite pattern emerged in the interval from palliative care consultation through death, where the palliative care cohort had lower rates of hospitalization (RR, 0.53; 95% CI, 0.44-0.65), invasive procedures (RR, 0.52; 95% CI, 0.45 to 0.59), and chemotherapy administration (RR, 0.46; 95% CI, 0.39 to 0.53). Patients with earlier palliative care consultation in their disease course had larger absolute reductions in health-care use compared with those with palliative care consultation closer to the end of life. **CONCLUSION:** This population-based study found that palliative care substantially decreased health-care use among Medicare beneficiaries with advanced cancer. Given the increasing number of elderly patients with advanced cancer, this study emphasizes the importance of early integration of palliative care alongside standard oncologic care.

[A new method based on supercritical fluid extraction for polyacetylenes and polyenes from Echinacea pallida \(Nutt.\) Nutt. roots.](#)

Tacchini M1, Spagnoletti A1, Brighenti V2, et al. J Pharm Biomed Anal. 2017 Aug 12;146:1-6. doi: 10.1016/j.jpba.2017.07.053. [Epub ahead of print]

The genus Echinacea (Asteraceae) includes species traditionally used in phytotherapy. Among them, Echinacea pallida (Nutt.) Nutt. root extracts are characterized by a representative antiproliferative activity, due to the presence of acetylenic compounds. In this study, supercritical fluid extraction (SFE) was applied and compared with conventional Soxhlet extraction (SE) in order to obtain a bioactive extract highly rich in polyacetylenes and polyenes from E. pallida roots. The composition of the extracts was monitored by means of HPLC-UV/DAD and HPLC-ESI-MSn by using an Ascentis Express C18 column (150mm×3.0mm I.D., 2.7µm, Supelco, Bellefonte, PA, USA) with a mobile phase composed of (A) water and (B) acetonitrile, under gradient elution. By keeping SFE time at the threshold of 1h (15min static and 45min dynamic for 1 cycle) with the oven temperature set at 40-45°C and 90bar of pressure, an overall extraction yield of 1.18-1.21% (w/w) was obtained, with a high selectivity for not oxidized lipophilic compounds. The biological activity of the extracts was evaluated against human non-small lung A549 and breast carcinoma MCF-7 cancer cell lines. The cytotoxic effect of the SFE extract was more pronounced towards the MCF-7 than the A549 cancer cells, with IC50 values ranging from 21.01±2.89 to 31.11±2.14µg/mL; cell viability was affected mainly between 24 and 48h of exposure. The results show the possibility of a new "green" approach to obtain extracts highly rich in genuine polyacetylenes and polyenes from E. pallida roots. The bioactivity evaluation confirmed the cytotoxicity of E. pallida extracts against the considered cancer cell lines, especially against MCF-7 cells, thus suggesting to represent a valuable tool for applicative purposes in cancer prevention.

MISCELLANEOUS WORKS

[Germline mutations in DNA repair genes in lung adenocarcinoma.](#) Parry EM1, Gable DL2, Stanley SE2, Khalil SE3, Antonescu V4, Florea L4, Armanios M5. J Thorac Oncol. 2017 Aug 23. pii: S1556-0864(17)30686-X. doi: 10.1016/j.jtho.2017.08.011. [Epub ahead of print]

INTRODUCTION: While lung cancer is generally thought to be environmentally provoked, anecdotal familial clustering has been reported suggesting there may be genetic susceptibility factors. We systematically tested whether germline mutations in eight candidate genes may be risk factors for lung adenocarcinoma. **METHODS:** We studied lung adenocarcinoma cases for whom germline sequence data had been generated as part of The Cancer Genome Atlas (TCGA) project, but that had not been previously analyzed. We selected eight genes, ATM, BRCA2, CHEK2, EGFR, PARK2, TERT, TP53, and YAP1, based on prior anecdotal association with lung cancer or genome wide association studies. **RESULTS:** Among 555 lung adenocarcinoma cases, we detected 14 pathogenic mutations in five genes; they occurred at a frequency of 2.5% and represented an odds ratio of 66 (95 confidence interval, 33 to 125, P<0.0001, chi-square test). The mutations fell most commonly in ATM (50%), followed by TP53, BRCA2, EGFR and PARK2. The majority (86%) of these variants had been reported in other familial cancer syndromes. Another 12 cases (2%) carried ultra-rare variants that were predicted to be deleterious by three protein prediction programs; these most frequently involved ATM and BRCA2.

CONCLUSIONS: A subset of lung adenocarcinoma patients, at least 2.5% to 4.5%, carries germline variants that have been linked to cancer risk in Mendelian syndromes. The genes fall most frequently in DNA repair pathways. Our data indicate that lung adenocarcinoma, similar to other solid tumors, contains a subset of patients with inherited susceptibility.

[Trends in Adult Cancer-Related Emergency Department Utilization: An Analysis of Data From the Nationwide Emergency Department Sample.](#) Rivera DR1, Gallicchio L1, Brown J2, Liu B1, Kyriacou DN3, Shelburne N1. JAMA Oncol. 2017 Aug 31:e172450. doi: 10.1001/jamaoncol.2017.2450. [Epub ahead of print]

IMPORTANCE: The emergency department (ED) is used to manage cancer-related complications among the 15.5 million people living with cancer in the United States. However, ED utilization patterns by the population of US adults with cancer have not been previously evaluated or described in published literature. **OBJECTIVE:** To estimate the proportion of US ED visits made by adults with a cancer diagnosis, understand the clinical presentation of adult patients with cancer in the ED, and examine factors related to inpatient admission within this population. **DESIGN, SETTING, AND PARTICIPANTS:** Nationally representative data comprised of 7 survey cycles (January 2006-December 2012) from the Nationwide Emergency Department Sample were analyzed. Identification of adult (age ≥ 18 years) cancer-related visits was based on Clinical Classifications Software diagnoses documented during the ED visit. Weighted frequencies and proportions of ED visits among adult patients with cancer by demographic, geographic, and clinical characteristics were calculated. Weighted multivariable logistic regression was used to examine the associations between inpatient admission and key demographic and clinical variables for adult cancer-related ED visits. **MAIN OUTCOMES AND MEASURES:** Adult cancer-related ED utilization patterns; identification of primary reason for ED visit; patient-related factors associated with inpatient admission from the ED. **RESULTS:** Among an estimated 696 million weighted adult ED visits from January 2006 to December 2012, 29.5 million (4.2%) were made by a patient with a cancer diagnosis. The most common cancers associated with an ED visit were breast, prostate, and lung cancer, and most common primary reasons for visit were pneumonia (4.5%), nonspecific chest pain (3.7%), and urinary tract infection (3.2%). Adult cancer-related ED visits resulted in inpatient admissions more frequently (59.7%) than non-cancer-related visits (16.3%) ($P < .001$). Septicemia (odds ratio [OR], 91.2; 95% CI, 81.2-102.3) and intestinal obstruction (OR, 10.94; 95% CI, 10.6-11.4) were associated with the highest odds of inpatient admission. **CONCLUSIONS AND RELEVANCE:** Consistent with national prevalence statistics among adults, breast, prostate, and lung cancer were the most common cancer diagnoses presenting to the ED. Pneumonia was the most common reason for adult cancer-related ED visits with an associated high inpatient admission rate. This analysis highlights cancer-specific ED clinical presentations and the opportunity to inform patient and system-directed prevention and management strategies.

[National Cancer Data Base Report on Pneumonectomy Versus Lung-Sparing Surgery for Malignant Pleural Mesothelioma.](#) Verma V1, Ahern CA2, Berlind CG2, et al. J Thorac Oncol. 2017 Aug 23. pii: S1556-0864(17)30687-1. doi: 10.1016/j.jtho.2017.08.012. [Epub ahead of print]

INTRODUCTION: Controversy exists regarding the optimal surgical technique for malignant pleural mesothelioma (MPM). We evaluated national practice patterns and outcomes of MPM treated with extrapleural pneumonectomy (EPP) versus lung-sparing extended pleurectomy/decortication (P/D). **METHODS:** The National Cancer Data Base was queried for newly-diagnosed MPM patients undergoing EPP or P/D. Multivariable logistic regression ascertained clinical factors independently associated with P/D receipt. Kaplan-Meier analysis evaluated overall survival (OS) between cohorts; multivariable Cox proportional hazards modeling evaluated factors associated with OS. Survival was then evaluated between propensity-matched populations. **RESULTS:** Overall, 1,307 patients (n=271 (21%) EPP, n=1,036 (79%) P/D) met criteria. Patients receiving P/D were older ($p=0.028$), whereas those undergoing EPP more likely lived in rural areas ($p=0.044$), farther from the treating facility ($p=0.039$), and treated at academic centers ($p=0.050$). There were no differences between cohorts in 30-day readmission or mortality (all $p>0.05$). Median OS in the EPP and P/D groups was 19 versus 16 months ($p=0.120$); no differences were observed after propensity-matching ($p=0.540$). **CONCLUSIONS:** In the

largest such analysis to date, findings from this contemporary cohort demonstrate that P/D comprised the majority of surgical procedures for MPM. Procedure type was influenced by sociodemographic and geographical factors, without observed differences in survival or postoperative mortality/readmission rates between techniques.