Caring Ambassadors Lung Cancer Program
Literature Review, May 2018

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

Inhibition of MALAT1 sensitizes liver cancer cells to 5-flurouracil by regulating apoptosis through IKKα/NF-κB pathway. Ji DG1, Guan LY1, Luo X2, Ma F3, Yang B4, Liu HY1. Biochem Biophys Res Commun. 2018 Jun 18;501(1):33-40. doi: 10.1016/j.bbrc.2018.04.116. Epub 2018 May 7.
Metastasis associated lung adenocarcinoma transcript 1 (MALAT1) is involved in tumor cell growth process. However, its role and molecular mechanism in liver cancer is still not fully understood. In this study, we found that MALAT1 was significantly expressed in liver cancer cell lines. And knockdown of MALAT1 suppressed proliferation, migration and invasion of HepG2 cells, accompanied with decrease of Rho-associated coiled-coil-forming protein kinase 1 (ROCK1), α-smooth muscle actin (α-SMA), N-cadherin, Vimentin and TWIST. Significantly, MALAT1 deletion sensitized HepG2 cells to 5-FU-induced cell cycle arrest in G1 phase, as evidenced by the significant reduction in Cyclin D1 and CDK4 and increase in p53, p21 and p27 protein levels. In addition, MALAT1 knockdown triggered 5-FU induced apoptosis in HepG2 cells by inducing intrinsic apoptosis-related signals, including Cyto-c, Apaf-1, cleaved Caspase-9/-7/-3 and poly (ADP-ribose) polymerase (PARP). Furthermore, phosphorylated nuclear factor-κB (p-NF-κB) was also down-regulated by MALAT1 silence. Importantly, suppression of IKKα/NF-κB significantly elevated apoptosis and reduced liver cancer cell viability in MALAT1-knockdown cells with 5-FU incubation. The nude mice transplantation model also confirmed the promoted sensitivity of MALAT1-silenced HepG2 cells to 5-FU by blocking tumor cell proliferation and inducing apoptosis. Therefore, our data supplied a potential mechanism by which knockdown of MALAT1 might play an important role in augmenting sensitivity of HepG2 cells to 5-FU in therapeutic approaches, demonstrating suppressing of MALAT1 may serve as a combination with chemotherapeutic agents in liver cancer treatment.

Increased infiltration of macrophages to radioresistant lung cancer cells contributes to the development of the additional resistance of tumor cells to the cytotoxic effects of NK cells.
Shen M1, Chen Y2, Xu L2, Zhu R2, Xue X2, Tsai Y1, Keng PC1, Lee SO1, Chen Y1. Int J Oncol. 2018 Jul;53(1):317-328. doi: 10.3892/ijo.2018.4394. Epub 2018 May 4.

In this study, in order to investigate the effects of increased macrophage infiltration to radioresistant lung tumors in regulating natural killer (NK) cell-mediated immunity, we examined whether the treatment of radioresistant cells with conditioned medium (CM) from phorbol myristate acetate (PMA)/interleukin (IL)-4 treated THP-1 cells (used as a tumor-associated macrophage source) leads to the development of the additional resistance of tumor cells to NK cell cytotoxicity. We found that the susceptibility of THP-1 CM-treated radioresistant cells to NK cell cytotoxicity was decreased compared to the non-treated cells. In addition, it was found that such a decreased susceptibility was associated with increased programmed death receptor ligand 1 (PD-L1) and decreased natural killer group 2D (NKG2D) ligand levels in tumor cells. We further discovered that the THP-1 cells secreted a high level of IL-6, and that blocking IL-6 action by the addition of a neutralizing antibody (Ab) for IL-6 into the THP-1 CM decreased the resistance of THP-1 CM-treated radioresistant cells to NK cell cytotoxicity. Moreover, we discovered that MEK/Erk was the most critical IL-6 downstream signaling pathway in triggering the THP-1 CM effect; thus, the addition of MEK/Erk inhibitor to THP-1 CM enhanced the susceptibility of the THP-1 CM-treated radioresistant cells to NK cell cytotoxicity. On the whole, the findings of this study suggest the existence of a malignant loop characterized by increased macrophage infiltration into radioresistant cells which, in turn, promotes the development of the additional resistance of these cells to NK cell cytotoxicity.

[Radiation followed by OX40 stimulation drives local and abscopal antitumor effects in an anti-PD1-resistant lung tumor model.](#) Niknam S1, Barsoumian HB2, Schoenhals JE1, et al. Clin Cancer Res. 2018 May 21. pii: clincanres.3279.2017. doi: 10.1158/1078-0432.CCR-17-3279. [Epub ahead of print] **PURPOSE:** Radiation is used extensively to treat localized cancer, but improved understanding of its effects on the immune system have increased interest in its potential systemic (abscopal) effects, particularly in combination with checkpoint inhibitors such as anti-PD1. The majority of patients either do not respond or develop resistance to monotherapy over time. Here, we investigated the efficacy of OX40 (CD134) stimulation as an alternative immunotherapeutic approach in combination with radiotherapy (XRT) in a murine model of anti-PD1-resistant lung tumors. **EXPERIMENTAL DESIGN:** We established a bilateral tumor model in 129Sv/Ev mice using an anti-PD1 resistant lung tumor cell line. Primary tumors were treated with intratumoral injection of an OX40 agonist antibody, given as adjuvant therapy after XRT (36 Gy in three 12-Gy fractions), while secondary tumors were left untreated to investigate abscopal outcomes. Results: The combination of XRT followed by OX40 stimulation effectively inhibited local and systemic antitumor growth, limited lung metastases, and improved survival rates. This treatment regimen augmented CD4+ and CD8+ T cell expansion. XRT induced the expression of OX40 on T cells in tumors and spleens and increased the percentages of splenic CD103+ dendritic cells. **CONCLUSION:** Our data extends the benefits of radiation to systemic disease control, especially when combined with anti-OX40 agonist to promote immunologically mediated abscopal effects. Moreover, this study provides a rational treatment approach and sequence to overcome anti-PD1 resistant poorly immunogenic tumors.

[Combined treatment with apatinib and docetaxel in A549 xenograft mice and its cellular pharma-cokinetic basis.](#) Feng SQ1, Wang GJ1, Zhang JW1, Xie Y1, Sun RB1, Fei F1, Huang JQ1, Wang Y1, Aa JY1, Zhou F1. Acta Pharmacol Sin. 2018 May 17. doi: 10.1038/aps.2018.16. [Epub ahead of print] Apatinib, a small-molecule inhibitor of VEGFR-2, has attracted much attention due to its encouraging anticancer activity in third-line clinical treatment for many malignancies, including non-small cell lung cancer (NSCLC). Its usage in second-line therapy with chemotherapeutic drugs is still under exploration. In this study we investigated the antitumor effect of apatinib combined with docetaxel against NSCLC and its cellular pharmacokinetic basis. A549 xenograft nude mice were treated with apatinib (100 mg/kg every day for 20 days) combined with docetaxel (8 mg/kg, ip, every four days for 5 times). Apatinib

significantly enhanced the antitumor effect of docetaxel and alleviated docetaxel-induced liver damage as well as decreased serum transaminases (ALT and AST). LC-MS/MS analysis revealed that apatinib treatment significantly increased the docetaxel concentration in tumors (up to 1.77 times) without enhancing the docetaxel concentration in the serum, heart, liver, lung and kidney. Furthermore, apatinib decreased docetaxel-induced upregulation of P-glycoprotein in tumors. The effects of apatinib on the uptake, efflux and subcellular distribution of docetaxel were investigated in A549 and A549/DTX (docetaxel-resistant) cells in vitro. A cellular pharmacokinetic study revealed that apatinib significantly increased cellular/subcellular accumulation (especially in the cytosol) and decreased the efflux of docetaxel in A549/DTX cells through P-gp, while apatinib exerted no significant effect on the cellular pharmacokinetics of docetaxel in A549 cells. Consequently, the IC50 value of docetaxel in A549/DTX cells was more significantly decreased by apatinib than that in A549 cells. These results demonstrate that apatinib has potential for application in second-line therapy combined with docetaxel for NSCLC patients, especially for docetaxel-resistant or multidrug-resistant patients.

[Anti-Epidermal Growth Factor Vaccine Antibodies Enhance the Efficacy of Tyrosine Kinase Inhibitors and Delay the Emergence of Resistance in EGFR Mutant Lung Cancer Cells.](#)
Codony-Servat J1, García-Roman S1, Molina-Vila MÁ2, et al. J Thorac Oncol. 2018 May 8. pii: S1556-0864(18)30592-6. doi: 10.1016/j.jtho.2018.04.030. [Epub ahead of print]
INTRODUCTION: Mutations in EGFR correlate with impaired response to immune checkpoint inhibitors and the development of novel immunotherapeutic approaches for EGFR mutant NSCLC is of particular interest. Immunization against epidermal growth factor (EGF) has shown efficacy in a phase III trial including unselected NSCLC patients, but little was known about the mechanisms involved in the effects of the anti-EGF antibodies generated by vaccination (anti-EGF VacAbs) or their activity in tumor cells with EGFR mutations. **METHODS:** The EGFR-mutant, NSCLC cell lines H1975, and PC9, together with several gefitinib and osimertinib-resistant cells derived from PC9, were treated with anti-EGF VacAbs and/or EGFR tyrosine kinase inhibitors (TKIs). Cell viability was analyzed by proliferation assays, cell cycle by fluorescence-activated cell sorting analysis, and levels of RNA and proteins by quantitative retro-transcription polymerase chain reaction and Western blotting. **RESULTS:** Anti-EGF VacAbs generated in rabbits suppressed EGF-induced cell proliferation and cycle progression and inhibited downstream EGFR signaling in EGFR-mutant cells. Sera from patients immunized with an EGF vaccine were also able to block activation of EGFR effectors. In combination, the anti-EGF VacAbs significantly enhanced the antitumor activity of all TKIs tested, suppressed Erk1/2 phosphorylation, blocked the activation of signal transducer and activator of transcription 3 (STAT3) and downregulated the expression of AXL receptor tyrosine kinase (AXL). Finally, anti-EGF VacAbs significantly delayed the emergence in vitro of EGFR TKI resistant clones. **CONCLUSIONS:** EGFR-mutant patients can derive benefit from immunization against EGF, particularly if combined with EGFR TKIs. A phase I trial of an EGF vaccine in combination with afatinib has been initiated.

SCREENING, DIAGNOSIS AND STAGING

[Regional lymph node sampling in lung carcinoma: a single institutional and national database comparison.](#) Bosch DE1, Farjah F2, Wood DE2, Schmidt RA3. Hum Pathol. 2018 May;75:55-62. doi: 10.1016/j.humpath.2018.02.002. Epub 2018 Feb 13.
Assessing regional lymph node metastasis is a key component of lung carcinoma staging and prognostication. Recent guidelines have suggested a quality metric of 10 total regional lymph nodes sampled with each stage I-II primary lung carcinoma resection. However, the extent of mediastinal lymph node sampling remains controversial. We assessed factors contributing to regional lymph node counts and effect on overall patient survival in an institutional cohort of 888 cases and the Surveillance,

Epidemiology, and End Results national cancer registry (10 856 cases). The distribution of total lymph node counts in lobectomy and pneumonectomy cases was variable with a median of 10 and an interquartile range of 7 to 14. Multiple clinical and pathologic factors correlated with total regional node counts. Total lymph node counts of at least 10 in the institutional cohort did not correlate with significant differences in overall survival as compared with node counts of less than 10 (P = .38). In the Surveillance, Epidemiology, and End Results database, although 0 regional lymph nodes were correlated with reduced overall survival (hazard ratio, 1.47; P < .01), no significant difference was detected for 1 to 9 versus at least 10 nodes (P = .8). In conclusion, lymph node counts for primary lung carcinoma are driven by surgical, pathologic, and biologic variability. We find no evidence for a meaningful quality metric of 10 total regional lymph nodes at the institutional and national registry levels.

[Use of circulating tumor cells in prospective clinical trials for NSCLC patients - standardization of the pre-analytical conditions.](#) Ilie M1,2,3, Hofman V1,2,3, Leroy S4, et al. Clin Chem Lab Med. 2018 May 24;56(6):980-989. doi: 10.1515/cclm-2017-0764.
BACKGROUND: Circulating tumor cells (CTCs) hold potential for noninvasive diagnosis, prognosis and prediction testing in non-small cell lung cancer (NSCLC) patients. Minimizing degradation or loss of CTCs is pivotal for detection and profiling of the low abundance and fragile CTCs, particularly in clinical trials. We prospectively investigated (NCT02372448) whether a new blood collection device performed better compared to commonly used K3EDTA tubes, when subjected to long-term sample storage.
METHODS: Blood samples were drawn into K3EDTA and blood collection tubes (BCT) (Streck), and filtered by the Isolation by SizE of Tumor/Trophoblastic Cells (ISET® system), for CTC detection in two study populations of NSCLC patients; the training set of 14 patients with stage II/IV NSCLC, and the validation set of 36 patients with stage IV NSCLC). MET expression was evaluated by immunocytochemistry (ICC) and anaplastic lymphoma kinase (ALK) gene rearrangement by break-apart fluorescence in situ hybridization (FISH) on ISET-enriched CTCs. **RESULTS:** Blood processed after 24 h and 48 h in BCT tubes showed stable CTCs counts and integrity, whereas CTCs in K3EDTA tubes showed an altered morphology in all patients. CTCs recovered in BCT or K3EDTA tubes at 24 and 48 h were evaluable by ICC for MET expression and by FISH for ALK rearrangement. **CONCLUSIONS:** The BCT tubes gave a high yield and preserved the integrity of CTCs after 24 and 48 h of storage at room temperature, which facilitate their molecular characterization in NSCLC patients entering clinical trials.

[PD-L1 immunohistochemistry comparability study in real-life clinical samples: results of Blueprint phase 2 project.](#) Tsao MS1, Kerr KM2, Kockx M3, et al. J Thorac Oncol. 2018 May 22. pii: S1556-0864(18)30626-9. doi: 10.1016/j.jtho.2018.05.013. [Epub ahead of print]
The Blueprint (BP) PD-L1 immunohistochemistry (IHC) comparability project is a pivotal academic/professional society and industrial collaboration to assess the feasibility of harmonizing the clinical use of five independently developed commercial PD-L1 IHC assays. The goals of BP phase 2 (BP2) were to validate the results obtained in BP1, using real world clinical lung cancer samples (n=81) of various histological and sample types, with all five trial-validated PD-L1 assays (22C3, 28-8, SP142, SP263, and 73-10), by an international panel of pathologists. BP2 also assessed the reliability of PD-L1 scoring by digital images, and on samples prepared for cytology examination. PD-L1 expression was assessed for percentage (tumor proportional scoring or TPS) tumor cells (TC) and immune cell (IC) areas showing PD-L1 staining, with TC scored continuously or categorically with cut-offs used in checkpoint inhibitor trials. The results showed highly comparable staining by 22C3, 28-8 and SP263 assays, less sensitivity with SP142 assay, and higher sensitivity with 73-10 assay to detect PD-L1 expression on TC. Glass slide and digital image scorings were highly concordant (Pearson correlation >0.96). There was very strong reliability among pathologists in TC PD-L1 scoring with all assays (overall intraclass correlation coefficient/ICC 0.86-0.93), poor reliability in IC PD-L1 scoring (overall ICC 0.18-0.19), and

good agreement in assessing PD-L1 status on cytology cell blocks materials (ICC 0.78-0.85). BP2 consolidates the analytical evidence for interchangeability of 22C3, 28-8, and SP263 assays and lower sensitivity of SP142 assay for scoring TPS on TC, and demonstrates greater sensitivity of 73-10 compared to other assays.

MEDIASTinal staging of non-small cell lung cancer by endobronchial and endoscopic ultrasonography with or without additional surgical mediastinoscopy (MEDIASTrial): study protocol of a multicenter randomised controlled trial. Bousema JE1,2, Dijkgraaf MGW2,3, Papen-Botterhuis NE1, et al. BMC Surg. 2018 May 18;18(1):27. doi: 10.1186/s12893-018-0359-6.
BACKGROUND: In case of suspicious lymph nodes on computed tomography (CT) or fluorodeoxyglucose positron emission tomography (FDG-PET), advanced tumour size or central tumour location in patients with suspected non-small cell lung cancer (NSCLC), Dutch and European guidelines recommend mediastinal staging by endosonography (endobronchial ultrasound (EBUS) and endoscopic ultrasound (EUS)) with sampling of mediastinal lymph nodes. If biopsy results from endosonography turn out negative, additional surgical staging of the mediastinum by mediastinoscopy is advised to prevent unnecessary lung resection due to false negative endosonography findings. We hypothesize that omitting mediastinoscopy after negative endosonography in mediastinal staging of NSCLC does not result in an unacceptable percentage of unforeseen N2 disease at surgical resection. In addition, omitting mediastinoscopy comprises no extra waiting time until definite surgery, omits one extra general anaesthesia and hospital admission, and may be associated with lower morbidity and comparable survival. Therefore, this strategy may reduce health care costs and increase quality of life. The aim of this study is to compare the cost-effectiveness and cost-utility of mediastinal staging strategies including and excluding mediastinoscopy. **METHODS/DESIGN:** This study is a multicenter parallel randomized non-inferiority trial comparing two diagnostic strategies (with or without mediastinoscopy) for mediastinal staging in 360 patients with suspected resectable NSCLC. Patients are eligible for inclusion when they underwent systematic endosonography to evaluate mediastinal lymph nodes including tissue sampling with negative endosonography results. Patients will not be eligible for inclusion when PET/CT demonstrates 'bulky N2-N3' disease or the combination of a highly suspicious as well as irresectable mediastinal lymph node. Primary outcome measure for non-inferiority is the proportion of patients with unforeseen N2 disease at surgery. Secondary outcome measures are hospitalization, morbidity, overall 2-year survival, quality of life, cost-effectiveness and cost-utility. Patients will be followed up 2 years after start of treatment. **DISCUSSION:** Results of the MEDIASTrial will have immediate impact on national and international guidelines, which are accessible to public, possibly reducing mediastinoscopy as a commonly performed invasive procedure for NSCLC staging and diminishing variation in clinical practice. **TRIAL REGISTRATION:** The trial is registered at the Netherlands Trial Register on July 6th, 2017 (NTR 6528).

Feasibility of re-biopsy and EGFR mutation analysis in patients with non-small cell lung cancer. Kim TO1, Oh IJ1,2, Kho BG1, et al. Thorac Cancer. 2018 May 14. doi: 10.1111/1759-7714.12762. [Epub ahead of print]
BACKGROUND: In cases of EGFR-tyrosine kinase inhibitor (TKI) failure, re-biopsy may be useful to understand resistance mechanisms and guide further treatment decisions. However, performing re-biopsy is challenging because of several hurdles. We assessed the feasibility of re-biopsy in advanced non-small cell lung cancer (NSCLC) patients in real-world clinical practice. **METHODS:** We retrospectively reviewed the clinical and pathologic data of advanced NSCLC patients who experienced disease progression after previous treatment with EGFR-TKIs at a single tertiary hospital in Korea between January 2014 and December 2016. Re-biopsy specimens included small biopsy, surgical tissue, or liquid-based cytology. EGFR mutation was tested using peptide nucleic acid-mediated clamping PCR.

RESULTS: Of the 230 NSCLC patients that experienced progression after EGFR-TKI therapy, 105 (45.7%) underwent re-biopsy. Re-biopsy was successfully performed in 94 (89.5%) patients, and 11 patients were diagnosed with no malignancy. The complication rate was 8.6%, including seven cases of pneumothorax. EGFR mutation testing was performed on 75 patients using re-biopsy specimens. Of the 57 patients who had sensitizing mutations at diagnosis, T790M mutations were found in 19 (33.3%), while 38 (66.7%) had no T790M mutation. Multivariate analysis showed that the re-biopsy group was younger (P = 0.002) and exhibited a previous response to EGFR-TKIs (P < 0.001). **CONCLUSION:** Re-biopsy in advanced NSCLC is feasible in real world clinical practice, particularly in younger patients and those who achieved a previous response to EGFR-TKIs.

[Medical Care Costs Were Similar Across the Low-dose Computed Tomography and Chest X-Ray Arms of the National Lung Screening Trial Despite Different Rates of Significant Incidental Findings.](#) Gareen IF1, Black WC2, Tosteson TD3, Wang Q4, Sicks JD5, Tosteson ANA6. Med Care. 2018 May;56(5):403-409. doi: 10.1097/MLR.0000000000000900.

BACKGROUND: The National Lung Screening Trial (NLST) reported lung cancer and all-cause mortality reductions for low-dose computed tomography (LDCT) versus chest x-ray (CXR) screening. Although LDCT lung screening has received a grade B from the United States Preventive Services Task Force and is a covered service under most health plans, concerns remain on the costs engendered by screening, and the impact of the high rate of significant incidental finding (SIF) detection on those costs. **METHODS:** We linked American College of Radiology Imaging Network NLST and Medicare fee-for-service claims data for participants from 23 sites for 2002-2009. We performed participant-level analyses using generalized linear regression models to estimate the adjusted annual mean of the 3-year total medical costs per person in each study arm and within screen outcome categories (ever positive with abnormalities suspicious for lung cancer, always negative for abnormalities suspicious for lung cancer, but with SIFs, and always negative without SIFs). **RESULTS:** The adjusted annual mean total per person costs were not significantly different between screening arms [LDCT, $11,029 (95% confidence interval, $10,107-$11,951); CXR, $10,905 (95% confidence interval, $10,059-$11,751)], despite higher proportions of individuals with SIFs in the LDCT versus the CXR arm (18% vs. 4%; P<0.0001). **CONCLUSIONS:** We found little difference in total annual per person costs between LDCT-screened and CXR-screened Medicare participants, despite the higher number of SIFs in the LDCT arm of the study.

[Impact of Staging With Positron-emission Tomography (PET) and Comorbidities on Management and Survival of American Veterans With Stage I-III Non-Small Cell Lung Cancer.](#) Raghunathan R1, Cease K1, Troeschel S1, Zhao L2, Gross M3, Chen G4, Chopra V1, Ramnath N1. Am J Clin Oncol. 2018 May;41(5):513-518. doi: 10.1097/COC.0000000000000316.

OBJECTIVES: The extent of whether staging by fluorodeoxyglucose positron-emission tomography (PET) impacts outcomes in American Veterans with stage I-III non-small-cell lung cancer (NSCLC) is unknown. We investigated impact of fluorodeoxyglucose PET staging and age-adjusted comorbidities (AACs) on management and survival of NSCLC in this group. **MATERIALS AND METHODS:** We performed a retrospective review to identify with NSCLC who underwent initial PET scan and received care at the Ann Arbor Veterans Hospital between 2005 and 2010. Survival outcomes were estimated by Kaplan-Meier methods, quantile regressions, and Cox proportional hazards models, after accounting for age at diagnosis, sex, AAC, and initial treatment. **RESULTS:** The number of PET scans increased from 0 in 2005 to 66 in 2010. There were 170 men, 4 women, median age 64 years. Median AAC score was 4. In CS I (n=54), initial PET upstaged 5 patients. Median survival for no change in PET stage was 27.43 versus 67 months for upstaged patients (P=0.034). For CS II (n=15), initial PET scan upstaged 1 patient. Median survival for no change in PET stage was 16.53 versus 2.8 months for upstaged patient (P=0.335).

For CS III (n=104), PET scan upstaged 20 patients. Median survival for no change in PET stage was 13.3 versus 3.8 months for upstaged patients (P=0.016). **CONCLUSIONS:** PET scans resulted in upstaging in 15% in CS I-III NSCLC. AAC scores dictated therapy decisions and outcomes more than PET staging. Veterans had lower 5-year survival rates (26.3%, 15.8%/13.4%) compared with 53% and 27% in age/sex/time-period matched SEER data for stage I-II/III NSCLC.

[New subsolid pulmonary nodules in lung cancer screening: a brief report of the NELSON trial.](#)
Walter JE1, Heuvelmans MA2, Yousaf-Khan U3, et al. J Thorac Oncol. 2018 May 15. pii: S1556-0864(18)30605-1. doi: 10.1016/j.jtho.2018.05.006. [Epub ahead of print]
INTRODUCTION: Low-dose computed tomography (LDCT) lung cancer screening is recommended in the United States. While new solid nodules after baseline screening have a high lung cancer probability at small size and require lower size cutoff values than baseline nodules, there only is limited evidence on management of new subsolid nodules. **METHODS:** Within the Dutch-Belgian randomized controlled LDCT lung cancer screening trial (NELSON), 7557 participants underwent baseline screening between April 2004 and December 2006. Participants with new subsolid nodules detected after the baseline screening round were included. **RESULTS:** In the three incidence screening rounds, 60 new subsolid nodules (43 [72%] part-solid, 17 [28%] nonsolid) not visible in retrospect were detected in 51 participants, representing 0.7% (51/7295) of participants with at least one incidence screening. Eventually, 6% (3/51) of participants with a new subsolid nodule were diagnosed with a (pre-)malignancy in such a nodule. All (pre-)malignancies were adenocarcinoma (in situ) and diagnostic work-up (referral 950, 364, and 366 days after first detection respectively) showed favorable staging (stage I). Overall, 65% (33/49) of subsolid nodules with an additional follow-up screening were resolving. **CONCLUSIONS:** Less than 1% of participants in LDCT lung cancer screening presents with a new subsolid nodule after baseline. Contrary to new solid nodules, data suggest that new subsolid nodules may not require a more aggressive follow-up.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

[The Feasibility of Thoracoscopic Left Pneumonectomy.](#) Xu H1, Zhang L1. Thorac Cardiovasc Surg. 2018 May 1. doi: 10.1055/s-0038-1642618. [Epub ahead of print]
OBJECTIVE: In this study, we describe our experience with video-assisted thoracoscopic surgery (VATS) left pneumonectomy as a treatment for advanced malignant and benign diseases.
METHODS: Patients who underwent VATS left pneumonectomy in our clinic between October 2013 and August 2017 were retrospectively evaluated. VATS pneumonectomy was successfully completed in 46 patients. We reviewed and analyzed the characteristics of the patients in addition to intraoperative parameters, chest tube duration, length of hospital stay, morbidity, and mortality. **RESULTS:** A total of 46 patients underwent VATS left pneumonectomy. Of these, 43 patients had malignant tumors and 3 patients had destroyed lung. The histologic types were squamous cell carcinoma in 24 patients, adenocarcinoma in 11, large cell carcinoma in 2, sarcomatoid carcinoma in 1, follicular dendritic cell sarcoma in 1, and small cell carcinoma in 4. Primary lung cancers were classified as stage IA1 in 2 patients, IA2 in 2, IA3 in 1, IB in 3, IIA in 3, IIB in 11, IIIA in 18, and IIIB in 3. The mean operation time was 160.54 ± 43.44 minutes, and the mean blood loss was 401.09 ± 284.32 mL. There was no perioperative mortality and no secretion retention and bronchopleural fistula. Arrhythmia was found in three patients. Pneumonia was found in four patients. The median follow-up time in this cohort was 25 months. A total of 15 patients (34.8%) developed recurrent diseases, 12 developed distant or multiple

metastasis, and 3 developed locoregional recurrence. **CONCLUSION:** VATS pneumonectomy is a safe, feasible treatment for complicated diseases that induces acceptable damage and has lower morbidity.

[Risk Factors of Recurrence in Patients With Clinical Stage IA Adenocarcinoma Presented as Ground-Glass Nodule.](#) Su H1, Dai C1, Xie H2, Ren Y1, She Y1, Kadeer X1, Xie D1, Zheng H1, Jiang G1, Chen C3. Clin Lung Cancer. 2018 May 5. pii: S1525-7304(18)30102-5. doi: 10.1016/j.cllc.2018.04.020. [Epub ahead of print]
BACKGROUND: In this study we aimed to identify the risk factors of recurrence in patients with clinical stage IA adenocarcinoma presented as ground glass nodule (GGN) on computed tomography scans. **PATIENTS AND METHODS:** The study included 254 patients with clinical stage IA adenocarcinoma presented as GGN who underwent surgery during 2010 to 2013. All patients were divided into 2 subgroups on the basis of consolidation diameter to tumor diameter (C/T) ratio on lung window: (1) ground-glass opacity (GGO)-dominant subgroup (C/T ≤ 0.5; n = 179); (2) solid-dominant subgroup (C/T > 0.5; n = 66). Recurrence-free survival (RFS) was analyzed to identify independent risk factors of recurrence using the Kaplan-Meier approach and multivariable Cox models. **RESULTS:** Patients in the GGO-dominant subgroup had a better prognosis than those in the solid-dominant subgroup (5-year RFS: 98% vs. 87%; P < .001). Multivariate analysis confirmed that C/T ratio was an independent risk factor for RFS in patients with clinical stage IA adenocarcinoma presented as GGN (hazard ratio [HR], 9.47; 95% confidence interval [CI], 1.75-51.1; P = .009). In the analysis of the solid-dominant group, multivariate analysis showed that limited resection was an independent risk factor of recurrence in this subgroup (HR, 6.86; 95% CI, 1.50-31.42; P = .013). Regarding the GGO-dominant subgroup, surgical type was not a risk factor of recurrence. **CONCLUSION:** Patients with clinical stage IA solid-dominant adenocarcinoma (C/T ratio > 0.5) had a higher rate of recurrence after limited resection than lobectomy. Thus, limited resection should be performed cautiously in these patients (C/T ratio > 0.5).

[American Society of Anesthesiologists physical status facilitates risk stratification of elderly patients undergoing thoracoscopic lobectomy.](#) Zhang R1, Kyriss T1, Dippon J2, Hansen M3, Boedeker E1, Friedel G1. Eur J Cardiothorac Surg. 2018 May 1;53(5):973-979. doi: 10.1093/ejcts/ezx436.
OBJECTIVES: Accurate risk assessments are particularly important for elderly patients being considered for lobectomy. Considering the positive effects of the thoracoscopic approach on postoperative outcomes, we sought to review the reliability of the established risk factors for elderly patients undergoing thoracoscopic lobectomy. **METHODS:** From January 2009 to March 2016, 441 patients in our institution underwent thoracoscopic lobectomy for early-stage lung cancer. Clinical outcomes were compared between elderly (>70 years, n = 176) and younger patients (n = 265). **RESULTS:** There was no significant difference in postoperative mortality and morbidity between elderly and younger patients. In the regression analyses restricted to elderly patients, American Society of Anesthesiologists physical status (ASA-PS) was the single strong predictor of postoperative morbidity. The odds of pulmonary and cardiopulmonary complications increased nearly 6- and 3-fold, respectively, in those with ASA-PS Grade 3 compared with patients with ASA-PS Grade <3. Additionally, male gender was found to have a possible causal effect of pulmonary complication in elderly patients. After confounder adjustment using propensity score matching, the generalized linear mixed model revealed more than an 8-fold increase in the odds of pulmonary complications in elderly men compared with elderly women. To check the robustness of the above-mentioned finding, inverse probability of treatment weighting was used as an alternative analysis indicating a weaker but still substantively significant effect of male gender, with an odds ratio >3. **CONCLUSIONS:** Our results suggest that ASA-PS is a strong predictor of morbidity among elderly patients considered for thoracoscopic lobectomy. Compared with elderly women, elderly men are particularly prone to postoperative pulmonary complications.

Real-World Use and Outcomes of ALK-Positive Crizotinib-Treated Metastatic NSCLC in US Community Oncology Practices: A Retrospective Observational Study. Reynolds C1,2, Masters ET3, Black-Shinn J4, Boyd M5, Mardekian J6, Espirito JL7, Chioda M8. J Clin Med. 2018 May 29;7(6). pii: E129. doi: 10.3390/jcm7060129.

INTRODUCTION: Around 3⁻5% of non-small cell lung cancers (NSCLC) are ALK-positive. Crizotinib was the first approved ALK inhibitor from clinical trials. However, there are less data on the utilization and patient outcomes associated with crizotinib in real-world clinical practice. **METHODS:** This was a retrospective, observational study of adult crizotinib-treated ALK-positive metastatic NSCLC patients who received treatment between 1 September 2011 and 31 October 2014, with follow up through 31 December 2015. Data were obtained via programmatic queries of the US Oncology Network/McKesson Specialty Health electronic health record database, supplemented with chart abstraction. Overall survival (OS) and time to treatment failure (TTF) were estimated from crizotinib initiation using the Kaplan⁻Meier (KM) method. **RESULTS:** Of the n = 199 ALK-positive crizotinib-treated patients meeting eligibility criteria, crizotinib was prescribed as first line (1 L) in n = 123 (61.8%). The majority (88.9%) had confirmed adenocarcinoma histology and 32.2% had brain metastases at initial diagnosis. Median age at crizotinib initiation was 60.2 years (range 27.1⁻88.2); 54.8% were never smokers, 33.7% were former smokers. Treatment of 250 mg, twice daily, was most commonly prescribed (89.5%) with the dose unchanged from an initial dose in 79.4% of patients. The primary discontinuation reason was progression (n = 91, 58.7%). Patients (3.2%) were identified as discontinuing crizotinib as a result of treatment-related toxicity. With median follow-up time of 13.0 months (min⁻max = 0.03⁻46.6), median OS from crizotinib initiation was 33.8 months (95% CI = 24.3⁻38.8). Median TTF was 10.4 months. **CONCLUSIONS:** Crizotinib usage evaluated within the real-world setting is consistent with prior phase III clinical trial data, and illustrates the real-world effectiveness of crizotinib.

Current landscape and future of dual anti-CTLA4 and PD-1/PD-L1 blockade immunotherapy in cancer; lessons learned from clinical trials with melanoma and non-small cell lung cancer (NSCLC). Chae YK1,2,3, Arya A4, Iams W5, Cruz MR4, Chandra S4,6,5, Choi J6,5, Giles F4,6,5. J Immunother Cancer. 2018 May 16;6(1):39. doi: 10.1186/s40425-018-0349-3.

Immunotherapy is among the most rapidly evolving treatment strategies in oncology. The therapeutic potential of immune-checkpoint inhibitors is exemplified by the recent hail of Food and Drug Administration (FDA) approvals for their use in various malignancies. Continued efforts to enhance outcomes with immunotherapy agents have led to the formulation of advanced treatment strategies. Recent evidence from pre-clinical studies evaluating immune-checkpoint inhibitors in various cancer cell-lines has suggested that combinatorial approaches may have superior survival outcomes compared to single-agent immunotherapy regimens. Preliminary trials assessing combination therapy with anti-PD-1/PD-L1 plus anti-CTLA-4 immune-checkpoint inhibitors have documented considerable advantages in survival indices over single-agent immunotherapy. The therapeutic potential of combinatorial approaches is highlighted by the recent FDA approval of nivolumab plus ipilimumab for patients with advanced melanoma. Presently, dual-immune checkpoint inhibition with anti-programmed death receptor-1/programmed cell death receptor- ligand-1 (anti-PD-1/PD-L1) plus anti-cytotoxic T lymphocyte associated antigen-4 (anti-CTLA-4) monoclonal antibodies (MoAbs) is being evaluated for a wide range of tumor histologies. Furthermore, several ongoing clinical trials are investigating combination checkpoint inhibition in association with traditional treatment modalities such as chemotherapy, surgery, and radiation. In this review, we summarize the current landscape of combination therapy with anti-PD-1/PD-L1 plus anti-CTLA-4 MoAbs for patients with melanoma and non-small cell lung cancer (NSCLC).

We present a synopsis of the prospects for expanding the indications of dual immune-checkpoint inhibition therapy to a more diverse set of tumor histologies.

[Nivolumab Plus Erlotinib in Patients with Epidermal Growth Factor Receptor-Mutant Advanced Non-Squamous Non-Small Cell Lung Cancer.](#) Gettinger S1, Hellmann MD2, Chow LQM3, et al. J Thorac Oncol. 2018 May 23. pii: S1556-0864(18)30628-2. doi: 10.1016/j.jtho.2018.05.015. [Epub ahead of print]

INTRODUCTION: This phase I study evaluated nivolumab combined with erlotinib in patients with advanced EGFR-mutant non-small cell lung cancer (NSCLC). **METHODS:** Patients with advanced EGFR-mutant NSCLC who were EGFR tyrosine kinase inhibitor (TKI)-naive or TKI-treated but had not received chemotherapy were treated with nivolumab 3 mg/kg every 2 weeks and erlotinib 150 mg/day until disease progression or unacceptable toxicity. The primary objective was safety and tolerability. **RESULTS:** Twenty patients with TKI-treated and one with TKI-naive EGFR-mutant NSCLC were treated with nivolumab plus erlotinib. Treatment-related grade 3 toxicities occurred in five patients (liver enzyme elevations, n = 2; diarrhea, n = 2; weight loss, n = 1), with no grade ≥4 toxicities. In the TKI-treated population, the objective response rate was 15% (3/20, including one complete response), and the 24-week progression-free survival rate was 48%. Responses lasted 13.8, 17.6, and 38.2 months per investigator records. A fourth patient had a non-conventional immune-related response lasting 12.5 months. Among these four patients, two were never-smokers and one each had 35- and <1-pack-year histories. Post-EGFR TKI pre-trial tumor biopsies from these patients detected EGFR T790M mutations in two patients and MET amplification in a third; two patients each had primary EGFR exon 19 deletions or L858R mutations. The TKI-naive patient, who had compound EGFR mutations (L858R and S768I) and ultimately achieved a complete response, had an ongoing response lasting more than 5 years based on investigator records. **CONCLUSION:** Nivolumab plus erlotinib was tolerable, with durable responses in patients with EGFR-mutant, TKI-treated NSCLC. Copyright © 2018. Published by Elsevier Inc.

[Safety of Programmed Death-1 Pathway Inhibitors Among Patients With Non-Small-Cell Lung Cancer and Preexisting Autoimmune Disorders.](#) Leonardi GC1, Gainor JF1, Altan M1, et al. J Clin Oncol. 2018 May 10:JCO2017770305. doi: 10.1200/JCO.2017.77.0305. [Epub ahead of print]

PURPOSE: Although programmed death (PD)-1 pathway inhibitors are now used in nearly all patients with advanced non-small-cell lung cancer (NSCLC), the large number of patients with NSCLC and concurrent autoimmune disease (AID) have been universally excluded from immunotherapy clinical trials. Therefore, the safety of PD-1 and PD-ligand 1 (PD-L1) inhibitors in patients with NSCLC and underlying AID is currently unknown. **METHODS:** As part of a multi-institutional effort, we retrospectively collected clinicopathologic data from patients with NSCLC and a history of AID who received monotherapy with either a PD-1 or a PD-L1 (herein referred to as PD-[L]1) inhibitor. Qualifying AIDs included but were not limited to: rheumatologic, neurologic, endocrine, GI, and dermatologic conditions. **RESULTS:** We identified 56 patients with NSCLC and an AID who received a PD-(L)1 inhibitor. At the time of treatment initiation, 18% of patients had active AID symptoms and 20% were receiving immunomodulatory agents for their AID. A total of 55% of patients developed an AID flare and/or an immune-related adverse event (irAE). Exacerbation of the AID occurred in 13 patients (23% of the whole cohort), four of whom required systemic corticosteroids. Immune-related adverse events occurred in 21 patients (38%). Among irAEs, 74% were grade 1 or 2 and 26% were grade 3 or 4; eight patients required corticosteroids for irAE management. PD-(L)1 therapy was permanently discontinued in eight patients (14%) because of irAEs. The overall response rate to immunotherapy in this population was 22%. **CONCLUSION:** In patients with NSCLC with AID treated with a PD-(L)1 inhibitor, exacerbation of AID occurred in a minority of patients. The incidence of irAEs was similar to reported rates in clinical

trials where patients with AID were excluded. Adverse events were generally manageable and infrequently led to permanent discontinuation of immunotherapy.

Final Overall Survival Analysis From a Study Comparing First-Line Crizotinib Versus Chemotherapy in ALK-Mutation-Positive Non-Small-Cell Lung Cancer. Solomon BJ1, Kim DW1, Wu YL1, et al. J Clin Oncol. 2018 May 16:JCO2017774794. doi: 10.1200/JCO.2017.77.4794. [Epub ahead of print]

PURPOSE: The phase III PROFILE 1014 trial compared crizotinib with chemotherapy as first-line treatment in patients with anaplastic lymphoma kinase (ALK) -positive advanced nonsquamous non-small-cell lung cancer. Here, we report the final overall survival (OS) results. **PATIENTS AND METHODS:** Patients were randomly assigned to receive oral crizotinib 250 mg twice daily (n = 172) or intravenous pemetrexed 500 mg/m2 plus cisplatin 75 mg/m2 or carboplatin (area under the concentration-time curve of 5 to 6 mg·mL/min) every 3 weeks for a maximum of six cycles (n = 171). Crossover to crizotinib was permitted after disease progression. OS was analyzed using a stratified log-rank test and a prespecified rank-preserving structural failure time model to account for crossover. **RESULTS:** Median follow-up duration for OS was approximately 46 months for both arms. In the chemotherapy arm, 144 patients (84.2%) received crizotinib in subsequent lines. Hazard ratio for OS was 0.760 (95% CI, 0.548 to 1.053; two-sided P = .0978). Median OS was not reached (NR) with crizotinib (95% CI, 45.8 months to NR) and 47.5 months with chemotherapy (95% CI, 32.2 months to NR). Survival probability at 4 years was 56.6% (95% CI, 48.3% to 64.1%) with crizotinib and 49.1% (95% CI, 40.5% to 57.1%) with chemotherapy. After crossover adjustment, there was an improvement in OS that favored crizotinib (hazard ratio, 0.346; 95% bootstrap CI, 0.081 to 0.718). The longest OS was observed in crizotinib-treated patients who received a subsequent ALK tyrosine kinase inhibitor. No new safety signals were identified. **CONCLUSION:** The final analysis of the PROFILE 1014 study provides a new benchmark for OS in patients with ALK-rearranged non-small-cell lung cancer and highlights the benefit of crizotinib for prolonging survival in this patient population.

Exposure-response analysis of alectinib in crizotinib-resistant ALK-positive non-small cell lung cancer. Morcos PN1, Nueesch E2, Jaminion F3, Guerini E3, Hsu JC4, Bordogna W2, Balas B2, Mercier F3. Cancer Chemother Pharmacol. 2018 May 10. doi: 10.1007/s00280-018-3597-5. [Epub ahead of print]

PURPOSE: Alectinib is a selective and potent anaplastic lymphoma kinase (ALK) inhibitor that is active in the central nervous system (CNS). Alectinib demonstrated robust efficacy in a pooled analysis of two single-arm, open-label phase II studies (NP28673, NCT01801111; NP28761, NCT01871805) in crizotinib-resistant ALK-positive non-small-cell lung cancer (NSCLC): median overall survival (OS) 29.1 months (95% confidence interval [CI]: 21.3-39.0) for alectinib 600 mg twice daily (BID). We investigated exposure-response relationships from final pooled phase II OS and safety data to assess alectinib dose selection. **METHODS:** A semi-parametric Cox proportional hazards model analyzed relationships between individual median observed steady-state trough concentrations ($C_{trough,ss}$) for combined exposure of alectinib and its major metabolite (M4), baseline covariates (demographics and disease characteristics) and OS. Univariate logistic regression analysis analyzed relationships between $C_{trough,ss}$ and incidence of adverse events (AEs: serious and Grade ≥ 3). **RESULTS:** Overall, 92% of patients (n = 207/225) had $C_{trough,ss}$ data and were included in the analysis. No statistically significant relationship was found between $C_{trough,ss}$ and OS following alectinib treatment. The only baseline covariates that statistically influenced OS were baseline tumor size and prior crizotinib treatment duration. Larger baseline tumor size and shorter prior crizotinib treatment were both associated with shorter OS. Logistic regression confirmed no significant relationship between $C_{trough,ss}$ and AEs. **CONCLUSION:**

Alectinib 600 mg BID provides systemic exposures at plateau of response for OS while maintaining a well-tolerated safety profile. This analysis confirms alectinib 600 mg BID as the recommended global dose for patients with crizotinib-resistant ALK-positive NSCLC.

[Speed of Adoption of Immune Checkpoint Inhibitors of Programmed Cell Death 1 Protein and Comparison of Patient Ages in Clinical Practice vs Pivotal Clinical Trials.](#) O'Connor JM1,2, Fessele KL3, Steiner J3, et al. JAMA Oncol. 2018 May 10:e180798. doi: 10.1001/jamaoncol.2018.0798. [Epub ahead of print]

The US Food and Drug Administration (FDA) is increasing its pace of approvals for novel cancer therapeutics, including for immune checkpoint inhibitors of programmed cell death 1 protein (anti-PD-1 agents). However, little is known about how quickly anti-PD-1 agents reach eligible patients in practice or whether such patients differ from those studied in clinical trials that lead to FDA approval (pivotal clinical trials).

OBJECTIVES: To assess the speed with which anti-PD-1 agents reached eligible patients in practice and to compare the ages of patients treated in clinical practice with the ages of those treated in pivotal clinical trials. **DESIGN, SETTING, AND PARTICIPANTS:** This retrospective cohort study, performed from January 1, 2011, through August 31, 2016, included patients from the Flatiron Health Network who were eligible for anti-PD-1 treatment of selected cancer types, which included melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC). **MAIN OUTCOMES AND MEASURES:** Cumulative proportions of eligible patients receiving anti-PD-1 treatment and their age distributions. **RESULTS:** The study identified 3089 patients who were eligible for anti-PD-1 treatment (median age, 66 [interquartile range, 56-75] years for patients with melanoma, 66 [interquartile range, 58-72] years for patients with RCC, and 67 [interquartile range, 59-74] years for patients with NSCLC; 1742 male [56.4%] and 1347 [43.6%] female; 2066 [66.9%] white). Of these patients, 2123 (68.7%) received anti-PD-1 treatment, including 439 eligible patients with melanoma (79.1%), 1417 eligible patients with NSCLC (65.6%), and 267 eligible patients with RCC (71.2%). Within 4 months after FDA approval, greater than 60% of eligible patients in each cohort had received anti-PD-1 treatment. Overall, similar proportions of older and younger patients received anti-PD-1 treatment during the first 9 months after FDA approval. However, there were significant differences in age between clinical trial participants and patients receiving anti-PD-1 treatment in clinical practice, with more patients being older than 65 years in clinical practice (range, 327 of 1365 [60.6%] to 46 of 72 [63.9%]) than in pivotal clinical trials (range, 38 of 120 [31.7%] to 223 of 544 [41.0%]; all P < .001). **CONCLUSIONS AND RELEVANCE:** Anti-PD-1 agents rapidly reached patients in clinical practice, and patients treated in clinical practice differed significantly from patients treated in pivotal clinical trials. Future actions are needed to ensure that rapid adoption occurs on the basis of representative trial evidence.

[FIR: Efficacy, Safety, and Biomarker Analysis of a Phase II Open-Label Study of Atezolizumab in PD-L1-Selected Patients with Non-Small-Cell Lung Cancer.](#) Spigel DR1, Chaft JE2, Gettinger S3, et al. J Thorac Oncol. 2018 May 15. pii: S1556-0864(18)30603-8. doi: 10.1016/j.jtho.2018.05.004. [Epub ahead of print]

INTRODUCTION: The FIR phase II study (NCT01846416) evaluated the efficacy and safety of anti-programmed death-ligand 1 (PD-L1) atezolizumab in advanced non-small-cell lung cancer (NSCLC) selected by tumor cell (TC) or tumor-infiltrating immune cell (IC) PD-L1 expression. **METHODS:** Patients with PD-L1 TC2/3 (PD-L1 staining on ≥5% of TC) or IC2/3 tumors (PD-L1 staining on ≥5% of IC; determined by SP142 PD-L1 immunohistochemistry assay) with paired fresh and archival histology samples were recruited into Cohort 1 (chemotherapy-naïve/>6 months between adjuvant chemotherapy and recurrence), Cohort 2 (≥ second-line without brain metastases), or Cohort 3 (≥ second-line with treated brain metastases). Patients received 1200 mg atezolizumab, Day 1 (21-day cycles). Primary

endpoint: investigator-assessed modified Response Evaluation Criteria in Solid Tumors (mRECIST), objective response rate (ORR; RECIST v1.1). Secondary endpoints: overall survival, progression-free survival, duration of response, safety. **RESULTS:** Patients (n=138) were enrolled (137 evaluable for response: Cohort 1, n=31; Cohort 2, n=93; Cohort 3, n=13). Investigator-assessed ORR was 32%, 21%, and 23% for Cohorts 1, 2, and 3, respectively. Treatment-related adverse events (TRAEs) were reported in 81%, 67%, and 69% of patients, respectively, including grade 3-4 TRAEs in 16%, 19%, and 15%. Moreover, 88.6% (n=86/97) paired baseline tumor samples had <5% change in TC/IC PD-L1 expression over time. **CONCLUSIONS:** Atezolizumab monotherapy showed clinical activity in patients with NSCLC, including those with brain metastases; safety was consistent with previous trials. Atezolizumab has completed phase III monotherapy studies in second-line; front-line trials are ongoing, confirming these favorable results.

[**Nab-paclitaxel maintenance therapy following carboplatin + nab-paclitaxel combination therapy in chemotherapy naïve patients with advanced non-small cell lung cancer: multicenter, open-label, single-arm phase II trial.**](#) Nakao A1, Uchino J2, Igata F1, et al. Invest New Drugs. 2018 May 30. doi: 10.1007/s10637-018-0617-6. [Epub ahead of print]
BACKGROUND: A global multicenter study demonstrated superiority of carboplatin + nab-paclitaxel (PTX) therapy compared to carboplatin + PTX in terms of response rate (RR) and non-inferiority in terms of progression free survival (PFS) and overall survival (OS) in untreated patients with stage IIIB/IV non-small cell lung cancer; no clinical findings have so far been reported on maintenance therapies with nab-PTX. The aim of this study was to determine the efficacy and safety of maintenance therapy with nab-PTX following carboplatin + nab-PTX combination therapy. **METHODS:** Carboplatin (AUC 6) was administered on Day 1; and nab-PTX 100 mg/m2 on Days 1, 8, and 15, and dosing was repeated in 4 courses of 4 weeks each. In patients with clinical response was observed at the end of the 4th course, nab-PTX maintenance therapy was repeated. **RESULTS:** Out of 39 patients included in the efficacy analysis, 19 (48.7%) patients completed the induction therapy and 15 (38.5%) were transitioned to maintenance therapy. The median PFS in the maintenance phase was 6.5 (90%CI 1.4-11.4) months. The median OS in 15 patients was 12.6 (95%CI: 7.4-not reached). Grade ≥ 3 toxicities observed in more than 5% of patients were neutropenia (55.0%), anemia (15.0%), and febrile neutropenia (5.0%), with no increase during the maintenance phase. **CONCLUSIONS:** Although statistically significance was not demonstrated presumably due to a limited transition rate from induction to maintenance phase, nab-PTX was suggested to be a useful treatment option following the induction therapy with nab-PTX in patients with advanced NSCLC.

[**nab-Paclitaxel/carboplatin in elderly patients with advanced squamous non-small cell lung cancer: a retrospective analysis of a Phase III trial.**](#) Gridelli C1, Chen T2, Ko A2, O'Brien ME3, Ong TJ4, Socinski MA5, Postmus PE6. Drug Des Devel Ther. 2018 May 24;12:1445-1451. doi: 10.2147/DDDT.S155750. eCollection 2018.
BACKGROUND: Limited data on elderly patients with squamous advanced non-small cell lung cancer (NSCLC) preclude optimal treatment. Here, we report the outcomes of a retrospective analysis of a subset of patients ≥70 years with squamous histology from the Phase III trial that evaluated nab-paclitaxel/carboplatin vs paclitaxel/carboplatin. **PATIENTS AND METHODS:** Patients with stage IIIB/IV NSCLC received (1:1) nab-paclitaxel 100 mg/m2 on days 1, 8, and 15 or paclitaxel 200 mg/m2 on day 1, both with carboplatin area under the curve 6 mg×min/mL on day 1 every 3 weeks. The primary endpoint was independently assessed overall response rate as per the Response Evaluation Criteria in Solid Tumors v1.0. Secondary endpoints included progression-free survival, overall survival, and safety. **RESULTS:** Sixty-five patients ≥70 years with squamous histology were included (nab-paclitaxel/carboplatin, n=35; paclitaxel/carboplatin, n=30). nab-Paclitaxel/carboplatin vs

paclitaxel/carboplatin, respectively, resulted in an overall response rate of 46% vs 20% (response rate ratio, 2.29, P=0.029) and a median overall survival of 16.9 vs 8.6 months (hazard ratio, 0.50, P=0.018). No difference was observed in median progression-free survival (5.7 months for both). Incidences of grade 3/4 neutropenia (50% vs 63%), leukopenia (29% vs 37%), fatigue (3% vs 13%), and peripheral neuropathy (3% vs 13%) were lower, but those of thrombocytopenia (21% vs 10%) and anemia (21% vs 7%) were higher with nab-paclitaxel/carboplatin vs paclitaxel/carboplatin. **CONCLUSION:** nab-Paclitaxel/carboplatin was efficacious and tolerable in patients ≥70 years with squamous NSCLC. These results build upon prior analyses, indicating that nab-paclitaxel/carboplatin is effective for this difficult-to-treat patient subgroup.

[Concomitant driver mutations in advanced EGFR-mutated non-small-cell lung cancer and their impact on erlotinib treatment.](#) Jakobsen JN1, Santoni-Rugiu E2, Grauslund M2, Melchior L2, Sørensen JB1. Oncotarget. 2018 May 25;9(40):26195-26208. doi: 10.18632/oncotarget.25490. eCollection 2018 May 25.
BACKGROUND: Patients with EGFR-mutated non-small-cell lung cancer benefit from EGFR tyrosine kinase inhibitors (TKIs) like erlotinib. However, the efficacy may be impaired by driver mutations in other genes. **METHODS:** Five hundred and fourteen consecutive patients with NSCLC of all stages were tested for EGFR-mutations by cobas® EGFR Mutation Test. Fluorescent in situ hybridization (FISH) for MET-amplification, immunohistochemistry (IHC) for MET- and ALK-expression, and Next Generation Sequencing (NGS) for concomitant driver mutations were performed on EGFR-mutated tumor samples from erlotinib-treated patients. **RESULTS:** Thirty-six patients (7%) had EGFR-mutations, including 2 with intrinsic resistance mutation p.T790M together with the p.L858R sensitizing mutation and 1 harboring the p.G719C/S768I double-mutation. Twenty-three patients had either locally advanced or advanced disease and received first-line erlotinib-treatment. Concomitant driver mutations were found in 15/21 (71%) of NGS-analyzed TKI-treated NSCLCs, involving in 67% of cases TP53, in 13% CTNNB1, and in 7% KRAS, MET, SMAD4, PIK3CA, FGFR1, FGFR3, NRAS, DDR2, and ERBB4. No ALK-expression was found, whereas MET-overexpression and MET-amplification were observed in 5 and 4 patients, respectively. Objective responses occurred in 17/23 patients (74%), 4 did not respond (17%), and 2 harboring a SMAD4-mutation (p.R135*(stop)) and a FGFR3-mutation (p.D785fs*31), respectively, displayed mixed response with simultaneously progressing and responding tumors (8.7%). Thus, EGFR-mutated tumors harboring co-mutations were not less likely to respond. **CONCLUSION:** Co-mutations in other cancer-driver genes (oncogenes or tumor suppressor genes) were frequent in EGFR-mutated NSCLCs and few cases harbored concomitant activating and resistance EGFR-mutations before TKI-treatment. Most co-mutations did not impact the response to first-line erlotinib-treatment, but may represent potential additional therapeutic targets.

[Quality-adjusted Outcomes Stratified by Response in Patients With Advanced Non-Small-cell Lung Cancer Receiving First-line nab-Paclitaxel/Carboplatin or Paclitaxel/Carboplatin.](#) Hirsh V1, Wan Y2, Lin FJ2, Margunato-Debay S3, Ong TJ3, Botteman M2, Langer C4. Clin Lung Cancer. 2018 May 7. pii: S1525-7304(18)30105-0. doi: 10.1016/j.cllc.2018.04.023. [Epub ahead of print]
BACKGROUND: First-line nab-paclitaxel/carboplatin was associated with a significantly improved overall response rate (primary endpoint) versus paclitaxel/carboplatin in a phase III trial of advanced non-small-cell lung cancer (NSCLC). We report the results of an analysis evaluating the correlation of response and the time to response with survival and quality-adjusted outcomes. **PATIENTS AND METHODS:** Using a landmark approach, progression-free survival (PFS), overall survival (OS), and quality-adjusted time without symptoms or toxicity (Q-TWiST) were compared between patients with a confirmed partial or complete response at or before 6 weeks (≤ 6-week responders) and those without (≤ 6-week nonresponders). The outcomes were also analyzed in two 12-week landmark analyses: ≤ 12-week

responders versus ≤ 12-week nonresponders and early responders (≤ 6 weeks) versus late responders (6-12 weeks) versus ≤ 12-week nonresponders. **RESULTS:** The median OS and PFS for the ≤ 6-week responders versus ≤ 6-week nonresponders were 14.5 versus 10.3 months (P < .001) and 5.5 versus 4.5 months (P = .002), respectively. The ≤ 6-week responders gained 2.1 months of mean Q-TWiST. The median OS and PFS for the ≤ 12-week responders versus ≤ 12-week nonresponders were 16.3 versus 8.4 months and 5.3 versus 2.8 months (both P < .001), respectively, and the ≤ 12-week responders gained 3.2 months of mean Q-TWiST. The median OS was 13.1, 16.6, and 8.4 months (P < .001), the median PFS was 4.1, 6.7, and 2.8 months (P < .001), and the mean Q-TWiST was 10.2, 11.7, and 7.8 months for the early responders, late responders, and ≤ 12-week nonresponders, respectively. Both early and late responders had significantly longer Q-TWiST compared with the ≤ 12-week nonresponders (difference, +2.4 and +3.9 months, respectively; P < .05). **CONCLUSION:** These results underscore response as an important surrogate for assessment of long-term treatment outcomes in advanced NSCLC.

[Combination Immunotherapy in Non-small Cell Lung Cancer.](#) Marmarelis ME1, Aggarwal C2,3. Curr Oncol Rep. 2018 May 8;20(7):55. doi: 10.1007/s11912-018-0697-7.
PURPOSE OF REVIEW: Checkpoint blockade has changed the treatment landscape in non-small cell lung cancer (NSCLC), but single-agent approaches are effective for only a select subset of patients. Here, we will review the evidence for combination immunotherapies in NSCLC and the clinical data evaluating the efficacy of this approach. **RECENT FINDINGS:** Clinical trials evaluating combination PD-1 and CTLA-4 blockade as well as PD-1 in combination with agents targeting IDO1, B7-H3, VEGF, and EGFR show promising results. Additional studies targeting other immune pathways like TIGIT, LAG-3, and cellular therapies are ongoing. Combination immunotherapy has the potential to improve outcomes in NSCLC. Data from early clinical trials is promising and reveals that these agents can be administered together safely without a significant increase in toxicity. Further studies are needed to evaluate their long-term safety and efficacy and to determine appropriate patient selection.

[Phase II trial of induction chemotherapy of pemetrexed plus split-dose cisplatin followed by pemetrexed maintenance for untreated non-squamous non-small-cell lung cancer.](#) Koba T1,2, Minami S1, Nishijima-Futami Y1,2, et al. Cancer Chemother Pharmacol. 2018 May 4. doi: 10.1007/s00280-018-3598-4. [Epub ahead of print]
PURPOSE: We conducted a phase II trial to evaluate the efficacy and safety of induction chemotherapy of pemetrexed plus split-dose cisplatin followed by pemetrexed maintenance for advanced non-squamous non-small-cell lung cancer (NSCLC). **METHODS:** Patients with advanced or recurrent untreated non-squamous NSCLC received split-dose cisplatin (40 mg/m2, days 1 and 8) plus pemetrexed (500 mg/m2, day 1) tri-weekly. After four cycles of induction, patients without disease progression received pemetrexed maintenance until disease progression or unacceptable toxicity. The primary endpoint was the 1-year survival rate. The secondary endpoints were progression-free survival (PFS), overall survival (OS), response in induction phase, and safety. **RESULTS:** From February 2012 to September 2014, 53 assessable patients were enrolled in this study. Thirty-eight (71.7%) patients completed induction therapy, while 35 (66.0%) received maintenance therapy. The 1-year survival rate was 67.7%. The median PFS and OS were 5.3 and 18.6 months, respectively. The response rate and disease control rate (DCR) during the induction phase were 37.7 and 86.8%, respectively. Eight patients (15.1%) discontinued the therapy due to adverse events (AEs) during the induction phase, but both hematological and non-hematological AEs were infrequent. **CONCLUSIONS:** Treatment with induction chemotherapy of pemetrexed plus split-dose cisplatin showed a promising 1-year survival rate, DCR, and transition rate into maintenance phase. This regimen is feasible and well-tolerated. A phase III study comparing this regimen with conventional tri-weekly regimen is warranted.

Prophylactic Cranial Irradiation Versus Observation in Radically Treated Stage III Non-Small-Cell Lung Cancer: A Randomized Phase III NVALT-11/DLCRG-02 Study. De Ruysscher D1, Dingemans AC1, Praag J1, et al. J Clin Oncol. 2018 May 22:JCO2017775817. doi: 10.1200/JCO.2017.77.5817. [Epub ahead of print]

PURPOSE: The purpose of the current study was to investigate whether prophylactic cranial irradiation (PCI) reduces the incidence of symptomatic brain metastases in patients with stage III non-small-cell lung cancer (NSCLC) treated with curative intention. **PATIENTS AND METHODS:** Patients with stage III NSCLC-staged with a contrast-enhanced brain computed tomography or magnetic resonance imaging-were randomly assigned to either observation or PCI after concurrent/sequential chemoradiotherapy with or without surgery. The primary end point-development of symptomatic brain metastases at 24 months-was defined as one or a combination of key symptoms that suggest brain metastases-signs of increased intracranial pressure, headache, nausea and vomiting, cognitive or affective disturbances, seizures, and focal neurologic symptoms-and magnetic resonance imaging or computed tomography demonstrating the existence of brain metastasis. Adverse effects, survival, quality of life, quality-adjusted survival, and health care costs were secondary end points. **RESULTS:** Between 2009 and 2015, 175 patients were randomly assigned: 87 received PCI and 88 underwent observation only. Median follow-up was 48.5 months (95% CI, 39 to 54 months). Six (7.0%) of 86 patients in the PCI group and 24 (27.2%) of 88 patients in the control group had symptomatic brain metastases ($P = .001$). PCI significantly increased the time to develop symptomatic brain metastases (hazard ratio, 0.23; [95% CI, 0.09 to 0.56]; $P = .0012$). Median time to develop brain metastases was not reached in either arm. Overall survival was not significantly different between both arms. Grade 1 and 2 memory impairment (26 of 86 v seven of 88 patients) and cognitive disturbance (16 of 86 v three of 88 patients) were significantly increased in the PCI arm. Quality of life was only decreased 3 months post-PCI and was similar to the observation arm thereafter. **CONCLUSION:** PCI significantly decreased the proportion of patients who developed symptomatic brain metastases with an increase of low-grade toxicity.

Changes in Regional Ventilation During Treatment and Dosimetric Advantages of CT Ventilation Image Guided Radiation Therapy for Locally Advanced Lung Cancer. Yamamoto T1, Kabus S2, Bal M3, Bzdusek K4, Keall PJ5, Wright C6, Benedict SH6, Daly ME6. Int J Radiat Oncol Biol Phys. 2018 May 4. pii: S0360-3016(18)30741-7. doi: 10.1016/j.ijrobp.2018.04.063. [Epub ahead of print]

PURPOSE: Lung functional image guided radiation therapy (RT) that avoids irradiating highly functional regions has potential to reduce pulmonary toxicity following RT. Tumor regression during RT is common, leading to recovery of lung function. We hypothesized that computed tomography (CT) ventilation image-guided treatment planning reduces the functional lung dose compared to standard anatomic image-guided planning in 2 different scenarios with or without plan adaptation. **METHODS AND MATERIALS:** CT scans were acquired before RT and during RT at 2 time points (16-20 Gy and 30-34 Gy) for 14 patients with locally advanced lung cancer. Ventilation images were calculated by deformable image registration of four-dimensional CT image data sets and image analysis. We created 4 treatment plans at each time point for each patient: functional adapted, anatomic adapted, functional unadapted, and anatomic unadapted plans. Adaptation was performed at 2 time points. Deformable image registration was used for accumulating dose and calculating a composite of dose-weighted ventilation used to quantify the lung accumulated dose-function metrics. The functional plans were compared with the anatomic plans for each scenario separately to investigate the hypothesis at a significance level of 0.05. **RESULTS:** Tumor volume was significantly reduced by 20% after 16 to 20 Gy ($P = .02$) and by 32% after 30 to 34 Gy ($P < .01$) on average. In both scenarios, the lung accumulated dose-function metrics were significantly lower in the functional plans than in the anatomic plans without compromising

target volume coverage and adherence to constraints to critical structures. For example, functional planning significantly reduced the functional mean lung dose by 5.0% (P < .01) compared to anatomic planning in the adapted scenario and by 3.6% (P = .03) in the unadapted scenario. **CONCLUSIONS:** This study demonstrated significant reductions in the accumulated dose to the functional lung with CT ventilation image-guided planning compared to anatomic image-guided planning for patients showing tumor regression and changes in regional ventilation during RT.

[Three- Versus Five-Fraction Regimens of Stereotactic Body Radiotherapy for Peripheral Early-Stage Non-Small-Cell Lung Cancer: A Two-Institution Propensity Score-Matched Analysis.](#) Ma SJ1, Cummings M2, Serra LM1, et al. Clin Lung Cancer. 2018 May;19(3):e297-e302. doi: 10.1016/j.cllc.2017.11.007. Epub 2017 Nov 26.
PURPOSE: To evaluate differences in outcomes of early-stage peripheral non-small-cell lung cancer (NSCLC) treated with either 3- or 5-fraction stereotactic body radiotherapy (SBRT) at 2 institutions. **PATIENTS AND METHODS:** Patients diagnosed with peripherally located early-stage NSCLC who received either a median dose of 60 Gy (interquartile range [IQR], 60-60, biologically effective dose, 151-151) in 3 fractions or a median dose of 50 Gy (IQR, 50-50, biologically effective dose, 94-94) in 5 fractions were included in this study. All data were retrospectively collected and reviewed in an institutional review board-approved database. **RESULTS:** A total of 192 lesions in 192 patients were identified: 94 received 3-fraction SBRT and 98 received 5-fraction SBRT. Patients in the 5-fraction cohort had significantly smaller tumors (P = .0021). Larger tumor size was associated with worse overall survival (hazard ratio, 1.40, P = .0013) for all patients. A single grade 3 toxicity was reported in each cohort. A propensity score-matched cohort of 94 patients was constructed with a median follow-up of 29.3 months (IQR, 17.3-44.6) for the 3-fraction cohort and 31.0 months (IQR, 17.0-48.5) for the 5-fraction cohort (P = .84). There were no statistically significant differences between these 2 cohorts in overall survival (P = .33), progression-free survival (P = .40), local failure (P = .86), and nodal or distant failure (P = .57) at 2 years. **CONCLUSION:** The 3- and 5-fraction SBRT regimens for early-stage peripheral NSCLC had comparable clinical outcomes. Both regimens were well tolerated. A large tumor size was an adverse prognostic factor for worse survival.

[Stereotactic Body Radiation Therapy for Operable Early-Stage Lung Cancer: Findings From the NRG Oncology RTOG 0618 Trial.](#) Timmerman RD1,2, Paulus R3, Pass HI4, et al. JAMA Oncol. 2018 May 31. doi: 10.1001/jamaoncol.2018.1251. [Epub ahead of print]
IMPORTANCE: Stereotactic body radiation therapy (SBRT) has become a standard treatment for patients with medically inoperable early-stage lung cancer. However, its effectiveness in patients medically suitable for surgery is unclear. **OBJECTIVE:** To evaluate whether noninvasive SBRT delivered on an outpatient basis can safely eradicate lung cancer and cure selected patients with operable lung cancer, obviating the need for surgical resection. **DESIGN, SETTING, AND PARTICIPANTS:** Single-arm phase 2 NRG Oncology Radiation Therapy Oncology Group 0618 study enrolled patients from December 2007 to May 2010 with median follow-up of 48.1 months (range, 15.4-73.7 months). The setting was a multicenter North American academic and community practice cancer center consortium. Patients had operable biopsy-proven peripheral T1 to T2, N0, M0 non-small cell tumors no more than 5 cm in diameter, forced expiratory volume in 1 second (FEV1) and diffusing capacity greater than 35% predicted, arterial oxygen tension greater than 60 mm Hg, arterial carbon dioxide tension less than 50 mm Hg, and no severe medical problems. The data analysis was performed in October 2014. **INTER-VENTIONS:** The SBRT prescription dose was 54 Gy delivered in 3 18-Gy fractions over 1.5 to 2.0 weeks. **MAIN OUTCOMES AND MEASURES:** Primary end point was primary tumor control, with survival, adverse events, and the incidence and outcome of surgical salvage as secondary end points.

RESULTS: Of 33 patients accrued, 26 were evaluable (23 T1 and 3 T2 tumors; 15 [58%] male; median age, 72.5 [range, 54-88] years). Median FEV1 and diffusing capacity of the lung for carbon monoxide at enrollment were 72.5% (range, 38%-136%) and 68% (range, 22%-96%) of predicted, respectively. Only 1 patient had a primary tumor recurrence. Involved lobe failure, the other component defining local failure, did not occur in any patient, so the estimated 4-year primary tumor control and local control rate were both 96% (95% CI, 83%-100%). As per protocol guidelines, the single patient with local recurrence underwent salvage lobectomy 1.2 years after SBRT, complicated by a grade 4 cardiac arrhythmia. The 4-year estimates of disease-free and overall survival were 57% (95% CI, 36%-74%) and 56% (95% CI, 35%-73%), respectively. Median overall survival was 55.2 months (95% CI, 37.7 months to not reached). Protocol-specified treatment-related grade 3, 4, and 5 adverse events were reported in 2 (8%; 95% CI, 0.1%-25%), 0, and 0 patients, respectively. **CONCLUSIONS AND RELEVANCE:** As given, SBRT appears to be associated with a high rate of primary tumor control, low treatment-related morbidity, and infrequent need for surgical salvage in patients with operable early-stage lung cancer. **TRIAL REGISTRATION:** Clinicaltrials.gov identifier: nct00551369.

[**Postoperative Radiotherapy for Surgically Resected ypN2 Non-Small Cell Lung Cancer.**](#) Brandt WS1, Yan W1, Leeman JE2, et al. Ann Thorac Surg. 2018 May 25. pii: S0003-4975(18)30709-4. doi: 10.1016/j.athoracsur.2018.04.064. [Epub ahead of print]
BACKGROUND: The role of postoperative radiotherapy (PORT) in patients with clinical stage III-N2 (cIII-N2) non-small cell lung cancer (NSCLC) treated with induction chemotherapy and surgical resection with persistent ypN2 disease is not well-established. **METHODS:** We retrospectively reviewed a prospectively maintained database for patients with cIII-N2 SCLC who underwent induction chemotherapy followed by resection (2004-2016). Exclusion criteria included induction radiotherapy, non-biopsy-confirmed cN2 disease, incomplete resection, ypN0/1, and nonanatomic resection. The primary outcome was locoregional recurrence (LR); secondary outcomes were disease-free survival (DFS), lung cancer-specific death (LCSD), and overall survival (OS). Associations between variables and outcomes were assessed using Fine and Gray competing risk regression for LR/LCSD and Cox proportional hazard models for survival. **RESULTS:** Of the 501 patients identified with cIII-N2 disease, 99 met the inclusion criteria. Median follow-up was 25 months (range, 3-137). Sixty-nine patients (70%) received PORT. Sixty (61%) developed a recurrence: 3 (5%) with an initial isolated LR and 57 (95%) with an initial distant recurrence. On multivariable analysis, PORT was not associated with LR (HR, 0.51 [95% CI, 0.22-1.21], P=0.13). PORT was also not associated with DFS (P=0.6) or LCSD (P=0.1). PORT was associated with improved 3-year OS (55% [95% CI, 42%-71%]) versus the no-PORT group (50% [95% CI, 34%-74%]) (P=0.04). **CONCLUSIONS:** PORT is not independently associated with decreased LR or improved DFS/LCSD in this patient population. Given that the predominant failure pattern was distant recurrence, future clinical trials should focus on adjuvant systemic therapies, which may decrease distant recurrences in ypN2 patients.

[**Nomograms incorporating genetic variants in BMP/Smad4/Hamp pathway to predict disease outcomes after definitive radiotherapy for non-small cell lung cancer.**](#) Yang J1,2, Xu T1, Gomez DR1, et al. Cancer Med. 2018 May 9. doi: 10.1002/cam4.1349. [Epub ahead of print]
Hepcidin is crucial in regulating iron metabolism, and increased serum levels were strongly linked with poor outcomes in various malignancies. Thus, we investigated if genetic variants in the BMP/Smad4/Hamp hepcidin-regulating pathway were associated with outcomes in patients receiving definitive radiotherapy for NSCLC. Subjects were 664 NSCLC patients who received ≥60 Gy radiotherapy for NSCLC retrospectively identified from a single-institution database. Potentially, functional and tagging single nucleotide polymorphisms (SNPs) of BMP2 (rs170986, rs1979855, rs1980499, rs235768, and rs3178250), BMP4 (rs17563, rs4898820, and rs762642), Smad4 (rs12456284),

and Hamp (rs1882694, rs10402233, rs10421768, and rs12971321) were genotyped by TaqMan real-time polymerase chain reaction. Cox proportional hazard's analyses were used to assess potential influences of SNPs on overall survival (OS), local-regional progression-free survival (LRPFS), progression-free survival (PFS), and distant metastasis-free survival (DMFS). Nomogram of each endpoint model was developed using R project. The median patient age was 66 years. Most (488 [73.2%]) had stage III NSCLC. Age, disease stage, receipt of concurrent chemotherapy, and gross tumor volume were independent factors of OS. Hamp rs1882694 AC/CC genotypes were associated with poor OS, LRPFS, PFS, and DMFS in multivariate analyses. Besides, BMP2 rs1979855, rs3178250, and rs1980499 associated with PFS; Hamp rs10402233 and BMP2 rs1979855 associated with LRPFS; BMP2 rs3178250 associated with DMFS after adjustment for clinical factors. After adding SNPs to each model, all the likelihood ratios were increased; the nomograms were improved significantly to predict LRPFS (P < 0.001) and PFS (P < 0.001), and marginally to predict OS (P = 0.056) and DM (P = 0.057). Our nomograms incorporating significant SNPs in the BMP/Smad4/Hamp hepcidin-regulating pathway could improve the prediction of outcomes in patients given definitive radiotherapy for NSCLC. Intensified follow-ups would be recommended for patients with unfavorable outcomes identified in nomograms. Due to the rapid developments of targeted therapies and immunotherapies for NSCLC, it is necessary to further validate our findings in patients receiving such treatments.

Virtual Bronchoscopy-Guided Treatment Planning to Map and Mitigate Radiation-Induced Airway Injury in Lung SAbR. Kazemzadeh N1, Modiri A1, Samanta S1, et al. Int J Radiat Oncol Biol Phys. 2018 May 2. pii: S0360-3016(18)30738-7. doi: 10.1016/j.ijrobp.2018.04.060. [Epub ahead of print] **PURPOSE:** Radiation injury to the bronchial tree is an important yet poorly understood potential side effect in lung stereotactic ablative radiation therapy (SAbR). We investigate the integration of virtual bronchoscopy in radiation therapy planning to quantify dosage to individual airways. We develop a risk model of airway collapse and develop treatment plans that reduce the risk of radiation-induced airway injury. **METHODS AND MATERIALS:** Pre- and post-SAbR diagnostic-quality computerized tomography (CT) scans were retrospectively collected from 26 lung cancer patients. From each scan, the bronchial tree was segmented using a virtual bronchoscopy system and registered deformably to the planning CT. Univariate and stepwise multivariate Cox regressions were performed, examining factors such as age, comorbidities, smoking pack years, airway diameter, and maximum point dosage (Dmax). Logistic regression was utilized to formulate a risk function of segmental collapse based on Dmax and diameter. The risk function was incorporated into the objective function along with clinical dosage volume constraints for planning target volume (PTV) and organs at risk (OARs). **RESULTS:** Univariate analysis showed that segmental diameter (P = .014) and Dmax (P = .007) were significantly correlated with airway segment collapse. Multivariate stepwise Cox regression showed that diameter (P = .015), Dmax (P < .0001), and pack/years of smoking (P = .02) were significant independent factors associated with collapse. Risk management-based plans enabled significant dosage reduction to individual airway segments while fulfilling clinical dosimetric objectives. **CONCLUSION:** To our knowledge, this is the first systematic investigation of functional avoidance in lung SAbR based on mapping and minimizing doses to individual bronchial segments. Our early results show that it is possible to substantially lower airway dosage. Such dosage reduction may potentially reduce the risk of radiation-induced airway injury, while satisfying clinically prescribed dosimetric objectives.

Adding Radiation to Adjuvant Chemotherapy Does Not Improve Survival of Patients with N2 Lung Cancer. Drake JA1, Portnoy DC2, Tauer K2, Weksler B3. Ann Thorac Surg. 2018 May 29. pii: S0003-4975(18)30720-3. doi: 10.1016/j.athoracsur.2018.04.074. [Epub ahead of print] **BACKGROUND:** The management of N2 non-small cell lung cancer (NSCLC) found at operation is controversial. Current guidelines recommend adjuvant chemotherapy (AC) or adjuvant chemo-radiation

therapy (CRT). We evaluated if adjuvant CRT was associated with improved survival as compared with AC in patients with N2 NSCLC after complete resection. **METHODS:** We queried the National Cancer Database for all patients with clinical N0, pathological N2 NSCLC who did not receive preoperative therapy and underwent complete (R0) surgical resection followed by AC or CRT. We performed propensity matching to create a well-balanced cohort of patients with respect to age, sex, race, comorbidities, treating facility, tumor size, year of diagnosis, and number of positive nodes. Survival was examined using the Kaplan-Meier method with log-rank analysis. **RESULTS:** We identified 2,031 eligible patients; 1149 (56.6%) received AC and 882 (43.4%) received CRT. In the unmatched cohort, patients who received CRT tended to be younger (64.2 vs 65.4), and to have a comorbidity score of 0 (57.5% vs 52.1%). There was no difference in median survival (3.9 years with CRT vs 3.8 years with AC, p=0.518). We then identified 848 well-matched pairs and again did not detect differences in median survival (3.9 years with CRT vs 3.8 years with AC, p=0.705). **CONCLUSIONS:** In a large database study, the addition of radiation to adjuvant chemotherapy after resection of N2 NSCLC was not associated with improved survival. Until more definitive data is available, consideration should be given to treating patients with N2 disease detected at surgery with AC only.

[**Evaluation of functionally weighted dose-volume parameters for thoracic stereotactic ablative radiotherapy (SABR) using CT ventilation.**](#) Kanai T1, Kadoya N2, Nakajima Y3, et al. Phys Med. 2018 May;49:47-51. doi: 10.1016/j.ejmp.2018.05.001. Epub 2018 May 8.
For the purpose of reducing radiation pneumontisis (RP), four-dimensional CT (4DCT)-based ventilation can be used to reduce functionally weighted lung dose. This study aimed to evaluate the functionally weighted dose-volume parameters and to investigate an optimal weighting method to realize effective planning optimization in thoracic stereotactic ablative radiotherapy (SABR). Forty patients treated with SABR were analyzed. Ventilation images were obtained from 4DCT using deformable registration and Hounsfield unit-based calculation. Functionally-weighted mean lung dose (fMLD) and functional lung fraction receiving at least x Gy (fVx) were calculated by two weighting methods: thresholding and linear weighting. Various ventilation thresholds (5th-95th, every 5th percentile) were tested. The predictive accuracy for CTCAE grade $\geqq 2$ pneumonitis was evaluated by area under the curve (AUC) of receiver operating characteristic analysis. AUC values varied from 0.459 to 0.570 in accordance with threshold and dose-volume metrics. A combination of 25th percentile threshold and fV30 showed the best result (AUC: 0.570). AUC values with fMLD, fV10, fV20, and fV40 were 0.541, 0.487, 0.548 and 0.563 using a 25th percentile threshold. Although conventional MLD, V10, V20, V30 and V40 showed lower AUC values (0.516, 0.477, 0.534, 0.552 and 0.527), the differences were not statistically significant. fV30 with 25th percentile threshold was the best predictor of RP. Our results suggested that the appropriate weighting should be used for better treatment outcomes in thoracic SABR.

[**Pilot Study of the Safety and Efficacy of Dose Escalation in Stereotactic Body Radiotherapy for Peripheral Lung Tumors.**](#) Mitsuyoshi T1, Matsuo Y2, Shintani T1, Iizuka Y1, Ueki N3, Nakamura M1, Mizowaki T1. Clin Lung Cancer. 2018 May;19(3):e287-e296. doi: 10.1016/j.cllc.2017.11.008. Epub 2017 Nov 28.
BACKGROUND: This pilot study aimed to evaluate the safety and efficacy of a dose escalation method for the treatment of peripheral lung tumors by administrating steep dose gradients in the target volumes via stereotactic body radiotherapy (SBRT). **PATIENTS AND METHODS:** Patients with peripheral lung tumors were enrolled onto this study and treated with SBRT using a total dose of 70 Gy in 4 fractions at target isocenter, covering the planning target volume surface with 70% of the isodose. The primary end point was the rate of grade 2 or higher radiation pneumonitis (RP) within 1 year. **RESULTS:** A total of 35 patients were enrolled onto this study between September 2014 and January 2016. Thirty-two patients with primary lung cancers and 3 patients with lung metastases were treated with SBRT. Grade 2 RP was

observed in 4 patients within 1 year. No severe RP (grade 3 or higher) was observed within the follow-up period. The median follow-up period was 21.2 months (range, 4.2-31.7 months). Local recurrence was observed in a single patient with lung metastasis. No local recurrence was observed within the follow-up period in the 32 patients with primary lung cancer. The local control and overall survival rates at 2 years were 95.7% (95% confidence interval, 72.9-99.4) and 85.2% (95% confidence interval, 67.8-93.6), respectively. **CONCLUSION:** This dose escalation method with steep dose gradients using SBRT for peripheral lung tumors was safe in the subacute phases. These results also suggest that this method can obtain excellent local control rates.

SMALL CELL LUNG CANCER - SCLC

Immunohistochemical expression and prognostic value of PD-L1 in Extrapulmonary small cell carcinoma: a single institution experience. Salhab M1, Migdady Y2, Donahue M3, Xiong Y4, Dresser K4, Walsh W3, Chen BJ4, Liebmann J5. J Immunother Cancer. 2018 May 29;6(1):42. doi: 10.1186/s40425-018-0359-1.
BACKGROUND: Extrapulmonary small cell carcinomas (ESCC) are rare but aggressive tumors. Relapses are common despite treatment with chemotherapy and/or radiotherapy. Prospective data for treatment of ESCC are lacking; treatment of these cancers usually incorporates lung small cell carcinoma treatment recommendations. Cancer staging remains the most important prognostic factor. Cancer immunotherapy targeting the PD-1/PD-L1 pathway has shown efficacy in multiple tumor types, and could be an appealing treatment strategy for these rare tumors. **METHODS:** We investigated PD-L1 expression by immunochemistry (IHC) in ESCCs diagnosed at University of Massachusetts Medical Center, from 1999 to 2016. 34 cases with sufficient material were selected for PD-L1 IHC analysis using clone E1L3N. PD-L1 expression was evaluated using the combined positive score (CPS). Retrospective chart review was performed. We evaluated the incidence and prognostic value of PD-L1 expression in ESCC at our institution. **RESULTS:** Twelve out 34 cases (35%) had PD-L1 CPS scores ≥1. Ten cases had CPS scores ranging 1-5, whereas 2 cases had CPS scores > 80. The overall response rate to the standard chemotherapy with/without radiotherapy in the PD-L1 positive group was 80% versus 67% for the PDL-1 negative group (p-value 0.67). The median overall survival for the PD-L1 positive group, regardless of stage, was 11.5 months versus 7 months for PD-L1 negative group (p-value 0.34). Patients with limited stage disease with positive PD-L1 had a median survival of 53 months compared to 15 months for patients with PD-L1 negative limited stage (p-value 0.80). **CONCLUSIONS:** This study showed that at least one third of our ESCC tissue samples expressed PD-L1. There was a trend for higher response rates to the standard chemotherapy with/without radiotherapy and improved survival in PD-L1 positive patients. Further studies are required to understand the implications of immune dysregulation in these aggressive tumors. PD-L1/PD-1 inhibitors should be investigated in this group of patients.

Phase II study of maintenance pembrolizumab in patients with extensive-stage small cell lung cancer (SCLC). Gadgeel SM1, Pennell NA2, Fidler MJ3, et al. J Thorac Oncol. 2018 May 15. pii: S1556-0864(18)30600-2. doi: 10.1016/j.jtho.2018.05.002. [Epub ahead of print]
PURPOSE: To assess the efficacy of maintenance pembrolizumab in extensive-stage small cell lung cancer (SCLC) patients, after treatment with platinum/etoposide. **PATIENTS AND METHODS:** Extensive-stage SCLC patients with a response or stable disease following induction chemotherapy were eligible. Pembrolizumab at a dose of 200 mg IV every 3 weeks was initiated within 8 weeks of the last cycle of chemotherapy. The primary endpoint of the study was progression-free survival (PFS) from study registration, with overall survival (OS) as a key secondary endpoint. Available tumor tissue was assessed for PD-L1 expression both in the tumor cells and surrounding stroma. Blood for circulating tumor cells was collected before the first, second and third cycles of pembrolizumab. **RESULTS:** Of the 45 patients

enrolled, 56% were male and 22% had treated brain metastases. The median PFS was 1.4 months (95%CI- 1.3-2.8), with 1-year PFS of 13%. The median OS was 9.6 months (95%CI- 7.0-12), with 1-year OS of 37%. Of the 30 tumors that could be assessed, 3 had PD-L1 expression ($\geq$ 1%) in the tumor cells. Twenty tumors could be assessed for PD-L1 expression in the stroma. The median PFS in the 8 patients with tumors positive for stromal interface PD-L1 expression was 6.5 months (95% CI-1.1-12.8) compared to 1.3 months (95%CI- 0.6-2.5) in 12 patients with tumors negative for this marker. No unexpected toxicities were observed. **CONCLUSION:** Maintenance pembrolizumab did not appear to improve median PFS compared to historical data. However, 1-year PFS of 13% and OS of 37% suggest that a subset of patients did benefit from pembrolizumab.

[**Prophylactic Cranial Irradiation in Extensive Stage Small Cell Lung Cancer: Outcomes at a Comprehensive Cancer Centre.**](#) Bang A1, Kendal WS1, Laurie SA2, Cook G1, MacRae RM3. Int J Radiat Oncol Biol Phys. 2018 May 1. pii: S0360-3016(18)30736-3. doi: 10.1016/j.ijrobp.2018.04.058. [Epub ahead of print]
PURPOSE: The role of prophylactic cranial irradiation (PCI) remains controversial in extensive stage small cell lung cancer (ES-SCLC) with the publication of 2 randomized control trials demonstrating differing outcomes in overall survival. The aim of this study is to determine the impact of PCI on survival and the development of brain metastasis while addressing the disparate use of postchemotherapy brain imaging in the aforementioned trials. **METHODS AND MATERIALS:** The medical records of 397 consecutive patients with ES-SCLC between Jan. 1, 2005 and Dec. 31, 2011 were retrospectively reviewed. In those eligible patients (n = 155) without baseline brain metastases and who had at least a partial response to chemotherapy, overall survival and time to brain metastasis were estimated using the Kaplan-Meier method comparing patients receiving PCI or not, using both univariate and multivariate analyses. Patients were stratified by their receipt of initial postchemotherapy brain imaging. Follow-up did not include serial brain imaging, which was performed when clinically indicated. Differences between the groups with covariates were analyzed using χ2 statistics and Student's t-tests. **RESULTS:** By multivariate analysis, statistically significant predictors of overall survival were the presence of extrathoracic metastases, performance status and use of PCI. There was a statistically significant difference in overall survival (HR 0.55; 95% CI: 0.39-0.77; P = .0005) and time to brain metastasis (HR 0.40; 95% CI: 0.23-0.66; P = .0004) with the use of PCI. Median survival for the PCI and non-PCI groups was 13.5 and 8.5 months respectively. A survival difference with PCI was observed in both patients that received postchemotherapy brain imaging (HR 0.55; 95% CI: 0.35-0.88; P = .012) and those who did not (HR 0.48; 95% CI: 0.29-0.77; P = .0025). **CONCLUSIONS:** PCI in the setting of at least a partial response to chemotherapy was found to have a survival benefit and prolongation of the time to development of brain metastases, when factoring in the use of initial postchemotherapy but not routine surveillance brain imaging.

[**Timing of Thoracic Radiation Therapy With Chemotherapy in Limited-stage Small-cell Lung Cancer: Survey of US Radiation Oncologists on Current Practice Patterns.**](#)
Farrell MJ1, Yahya JB2, Degnin C2, et al. Clin Lung Cancer. 2018 May 5. pii: S1525-7304(18)30089-5. doi: 10.1016/j.cllc.2018.04.007. [Epub ahead of print]
INTRODUCTION: For limited-stage small-cell lung cancer (LS-SCLC), National Comprehensive Cancer Network guidelines recommend that thoracic radiotherapy (TRT) be delivered concurrently with chemotherapy and early in the regimen, with cycle 1 or 2. Evidence is conflicting regarding the benefit of early timing of TRT. A Korean randomized trial did not see a survival difference between early (cycle 1) and late (cycle 3) TRT. Current United States (US) practice patterns are unknown. **MATERIALS AND METHODS:** We surveyed US radiation oncologists using an institutional review board-approved online questionnaire. Questions covered treatment recommendations, self-rated knowledge of trials, and

demographics. **RESULTS:** We received 309 responses from radiation oncologists. Ninety-eight percent recommend concurrent chemoradiotherapy over sequential. Seventy-one percent recommend starting TRT in cycle 1 of chemotherapy, and 25% recommend starting in cycle 2. In actual practice, TRT is started most commonly in cycle 2 (48%) and cycle 1 (44%). One-half of respondents (54%) believe starting in cycle 1 improves survival compared with starting in cycle 3. Knowledge of the Korean trial was associated with flexibility in delaying TRT to cycle 2 or 3 (P = .02). Over one-third (38%) treat based on pre-chemotherapy volume. **CONCLUSION:** US radiation oncologists strongly align with National Comprehensive Cancer Network guidelines, which recommend early concurrent chemoradiotherapy. Nearly three-quarters of respondents prefer starting TRT with cycle 1 of chemotherapy. However, knowledge of a trial supporting a later start was associated with flexibility in delaying TRT. Treating based on pre-chemotherapy volume-endorsed by over one-third of respondents-may add unnecessary toxicity. This survey can inform development of future trials.

[Early versus late prophylactic cranial irradiation in patients with extensive small cell lung cancer.](#)
Chen Y1, Li J2, Zhang Y3, Hu Y2, Zhang G2, Yan X2, Lin Z2, Zhao Z4, Jiao S5,6. Strahlenther Onkol. 2018 May 17. doi: 10.1007/s00066-018-1307-1. [Epub ahead of print]
OBJECTIVE: Previous studies demonstrated that prophylactic cranial irradiation (PCI) significantly reduced the incidence of brain metastases in patients with extensive disease small cell lung cancer (ED-SCLC). However, the appropriate timing for PCI in treating ED-SCLC is still unclear. This study aimed to compare the effect and safety of early versus late PCI. **METHODS:** Between November 2011 and July 2016, 103 patients with ED-SCLC were reviewed, receiving appropriate imaging tests to exclude brain metastases prior to cranial irradiation. Of these 103 patients, early PCI was performed in 47 patients and the other 56 patients received late PCI. The primary endpoint was the incidence of brain metastases. The progression-free survival (PFS), overall survival (OS), and adverse events (AEs) were also assessed. **RESULTS:** Early PCI significantly lowered the risk of brain metastases, as compared to late PCI (p = 0.024). Additionally, multivariate analyses demonstrated that early PCI was a favorable independent predictor of the incidence of brain metastases. The PFS and OS of patients in the early and late PCI groups were comparable (PFS: 8.4 months vs. 7.5 months, p = 0.234; OS: 16.1 months vs. 15.2 months, p = 0.753). The AEs were generally acceptable in both groups. **CONCLUSION:** To reduce the incidence of brain metastases, early PCI is more effective than late PCI for ED-SCLC patients.

[Identification of candidate biomarkers and pathways associated with SCLC by bioinformatics analysis.](#) Wen P1, Chidanguro T1, Shi Z2, Gu H1, Wang N1, Wang T1, Li Y3, Gao J3. Mol Med Rep. 2018 May 29. doi: 10.3892/mmr.2018.9095. [Epub ahead of print]
Small cell lung cancer (SCLC) is one of the highly malignant tumors and a serious threat to human health. The aim of the present study was to explore the underlying molecular mechanisms of SCLC. mRNA microarray datasets GSE6044 and GSE11969 were downloaded from Gene Expression Omnibus database, and the differentially expressed genes (DEGs) between normal lung and SCLC samples were screened using GEO2R tool. Functional and pathway enrichment analyses were performed for common DEGs using the DAVID database, and the protein protein interaction (PPI) network of common DEGs was constructed by the STRING database and visualized with Cytoscape software. In addition, the hub genes in the network and module analysis of the PPI network were performed using CentiScaPe and plugin Molecular Complex Detection. Finally, the mRNA expression levels of hub genes were validated in the Oncomine database. A total of 150 common DEGs with absolute fold change >0.5, including 66 significantly downregulated DEGs and 84 upregulated DEGs were obtained. The Gene Ontology term enrichment analysis suggested that common upregulated DEGs were primarily enriched in biological processes (BPs), including 'cell cycle', 'cell cycle phase', 'M phase', 'cell cycle process' and 'DNA metabolic process'. The common downregulated genes were significantly enriched in BPs, including

'response to wounding', 'positive regulation of immune system process', 'immune response', 'acute inflammatory response' and 'inflammatory response'. Kyoto Encyclopedia of Genes and Genomes pathway analysis identified that the common downregulated DEGs were primarily enriched in the 'complement and coagulation cascades' signaling pathway; the common upregulated DEGs were mainly enriched in 'cell cycle', 'DNA replication', 'oocyte meiosis' and the 'mismatch repair' signaling pathways. From the PPI network, the top 10 hub genes in SCLC were selected, including topoisomerase IIα, proliferating cell nuclear antigen, replication factor C subunit 4, checkpoint kinase 1, thymidylate synthase, minichromosome maintenance protein (MCM) 2, cell division cycle (CDC) 20, cyclin dependent kinase inhibitor 3, MCM3 and CDC6, the mRNA levels of which are upregulated in Oncomine SCLC datasets with the exception of MCM2. Furthermore, the genes in the significant module were enriched in 'cell cycle', 'DNA replication' and 'oocyte meiosis' signaling pathways. Therefore, the present study can shed new light on the understanding of molecular mechanisms of SCLC and may provide molecular targets and diagnostic biomarkers for the treatment and early diagnosis of SCLC.

Development of targeted therapy and immunotherapy for treatment of small cell lung cancer.
Saito M1,2,3, Shiraishi K1, Goto A4, Suzuki H3, Kohno T1, Kono K2. Jpn J Clin Oncol. 2018 May 14. doi: 10.1093/jjco/hyy068. [Epub ahead of print]
Targeted therapy against druggable genetic aberrations has shown a significantly positive response rate and longer survival in various cancers, including lung cancer. In lung adenocarcinoma (LADC), specific thyroxin kinase inhibitors against EGFR mutations and ALK fusions are used as a standard treatment regimen and show significant positive efficacy. On the other hand, targeted therapy against driver gene aberrations has not been adapted yet in small cell lung cancer (SCLC). This is because driver genes and druggable aberrations are rarely identified by next generation sequencing in SCLC. Recent advances in the understanding of molecular biology have revealed several candidate therapeutic targets. To date, poly [ADP-ribose] polymerase (PARP), enhancer of zeste homologue 2 (EZH2) or delta-like canonical Notch ligand 3 (DLL3) are considered to be druggable targets in SCLC. In addition, another candidate of personalized therapy for SCLC is immune blockade therapy of programmed death-1 (PD-1) and its ligand, PD-L1. PD-1/PD-L1 blockade therapy is not a standard therapy for SCLC, so many clinical trials have been performed to investigate its efficacy. Herein, we review gene aberrations exploring the utility of targeted therapy and discuss blockade of immune checkpoints therapy in SCLC.

PALLIATIVE AND SUPPORTIVE CARE

The effect of early versus delayed radiation therapy on length of hospital stay in the palliative setting.
Cushman TR1, Shirvani S2, Khan M2, Kumar R3. Ann Palliat Med. 2018 May 28. pii: apm.2018.05.07. doi: 10.21037/apm.2018.05.07. [Epub ahead of print]
BACKGROUND: Radiation therapy (RT) can offer timely and effective treatment to oncology patients in the palliative setting. To date, there is sparse evidence investigating temporal relationships regarding the initiation of RT and subsequent hospital stay in the inpatient palliative setting. We aimed to assess whether times between admission, consultation, and initiation of treatment effected the length of hospital stay for patients receiving palliative radiation therapy (PRT). **METHODS:** This was a retrospective chart review of patients who received a consult for PRT from August 2014 to October 2016. All data was collected from a single community cancer center. Data including demographics, radiation treatment details, and temporal data (e.g., length of stay, time from admission to consult, etc.) were recorded. **RESULTS:** Of the 135 patients that received PRT, 60 of them were treated in the inpatient setting. The most common indications for PRT were pain (37%) and non-pain related neurologic symptoms (37%). The most common treatment sites were bone (58%), brain (22%), and lung (17%). There was a significant difference in duration of hospital stay between patients who were seen by palliative radiation oncology

within two days versus greater than 2 days (P=0.02); and patients who were treated within 2 days of admission versus greater than 2 days (P=0.03). **CONCLUSIONS:** Further research is needed to establish causal temporal relationships in palliative radiation oncology. However, this data suggests that early involvement of the radiation oncology team is associated with a reduced length of hospital stay.

Using patient-reported outcome measures to deliver enhanced supportive care to people with lung cancer: feasibility and acceptability of a nurse-led consultation model. Kotronoulas G1, Papadopoulou C2, Simpson MF3, McPhelim J3, Mack L3, Maguire R4. Support Care Cancer. 2018 May 19. doi: 10.1007/s00520-018-4234-x. [Epub ahead of print]
PURPOSE: Developing new supportive/palliative care services for lung cancer should encompass effective ways to promptly identify and address patients' healthcare needs. We examined whether an in-clinic, nurse-led consultation model, which was driven by use of a patient-reported outcomes (PRO) measure, was feasible and acceptable in the identification of unmet needs in patients with lung cancer. **METHODS:** A two-part, repeated-measures, mixed-methods study was conducted. Part 1 employed literature reviews and stakeholder focus group interviews to inform selection of a population-appropriate needs assessment PRO measure. In Part 2, lung cancer nurse specialists (CNS) conducted three consecutive monthly consultations with patients. Recruitment/retention data, PRO data, and exit interview data were analysed. **RESULTS:** The Sheffield Profile for Assessment and Referral to Care was the PRO measure selected based on Part 1 data. Twenty patients (response rate: 26%) participated in Part 2; 13 (65%) participated in all three consultations/assessments. The PRO measure helped patients to structure their thinking and prompted them to discuss previously underreported and/or sensitive issues, including such topics as family concerns, or death and dying. Lung CNS highlighted how PRO-measures-driven consultations differed from previous ones, in that their scope was broadened to allow nurses to offer personalised care. Small-to-moderate reductions in all domains of need were noted over time. **CONCLUSIONS:** Nurse-led PRO-measures-driven consultations are acceptable and conditionally feasible to holistically identify and effectively manage patient needs in modern lung cancer care. PRO data should be systematically collected and audited to assist in the provision of supportive care to people with lung cancer.

Healthcare experience among older cancer survivors: Analysis of the SEER-CAHPS dataset.
Halpern MT1, Urato MP2, Lines LM3, Cohen JB2, Arora NK4, Kent EE5. J Geriatr Oncol. 2018 May;9(3):194-203. doi: 10.1016/j.jgo.2017.11.005. Epub 2017 Dec 15.
OBJECTIVE: Little is known about factors affecting medical care experiences of cancer survivors. This study examined experience of care among cancer survivors and assessed associations of survivors' characteristics with their experience. **MATERIALS AND METHODS:** We used a newly-developed, unique data resource, SEER-CAHPS (NCI's Surveillance Epidemiology and End Results [SEER] data linked to Medicare Consumer Assessment of Healthcare Providers and Systems [CAHPS] survey responses), to examine experiences of care among breast, colorectal, lung, and prostate cancer survivors age >66years who completed CAHPS >1year after cancer diagnosis and survived ≥1year after survey completion. Experience of care was assessed by survivor-provided scores for overall care, health plan, physicians, customer service, doctor communication, and aspects of care. Multivariable logistic regression models assessed associations of survivors' sociodemographic and clinical characteristics with care experience. **RESULTS:** Among 19,455 cancer survivors with SEER-CAHPS data, higher self-reported general-health status was significantly associated with better care experiences for breast, colorectal, and prostate cancer survivors. In contrast, better mental-health status was associated with better care experience for lung cancer survivors. College-educated and Asian survivors were less likely to indicate high scores for care experiences. Few differences in survivors' experiences were observed by sex or years since diagnosis. **CONCLUSIONS:** The SEER-CAHPS data resources allows assessment of factors

influencing experience of cancer among U.S. cancer survivors. Higher self-reported health status was associated with better experiences of care; other survivors' characteristics also predicted care experience. Interventions to improve cancer survivors' health status, such as increased access to supportive care services, may improve experience of care.

Stress and Quality of Life in Cancer Patients: Medical and Psychological Intervention. Barre PV1, Padmaja G2, Rana S2, Tiamongla2. Indian J Psychol Med. 2018 May-Jun;40(3):232-238. doi: 10.4103/IJPSYM.IJPSYM_512_17.
BACKGROUND: Cancer pervades many dimensions of an individual's life - demanding a holistic treatment approach. However, studies with combined medical and psychological interventions (MPIs) are sparse. High-level stress and poor quality of life (QoL) can hinder patients' prognosis. The study thus aimed to analyze the impact of combined medical and psychological (psychoeducation, relaxation technique-guided imagery, and cognitive therapy) interventions on stress and QoL of cancer patients - head and neck, breast, and lung cancers. **METHODS:** The study was conducted in cancer hospitals employing one-group pretest-posttest-preexperimental design. Descriptive statistics, paired t-test, Cohen's d, and bar graphs were used to analyze the data. **RESULTS:** Findings showed high impact of the combined MPIs in reducing both the overall stress as well as the various components of the stress scale-fear, psychosomatic complaints, information deficit, and everyday life restrictions. Significant changes were also seen in QoL and its domains - global health status, besides functional and symptom scales. Results showed a significant improvement in physical, role and emotional functioning scale, while decrement in fatigue, pain, insomnia, appetite loss, diarrhea, and constipation of symptoms scales. **CONCLUSIONS:** It can be concluded that combined MPI has a positive impact - decreasing stress and improving QoL in cancer patients, which can further enhance their prognosis.

Long-term low-dose morphine for patients with moderate cancer pain is predominant factor effecting clinically meaningful pain reduction. Zheng RJ1, Fu Y2, Zhu J2, Xu JP3, Xiang QF2, Chen L4, Zhong H2, Li JY5, Yu CH6. Support Care Cancer. 2018 May 31. doi: 10.1007/s00520-018-4282-2. [Epub ahead of print]
PURPOSE: Patients with cancer often experience pain that affects their daily activities and quality of life. The analgesic ladder recommended by the World Health Organization has proved insufficient for many, and its scientific basis has been questioned. This retrospective study investigated factors related to adherence to long-term opioid therapy for patients with moderate cancer pain, including an evaluation of low-dose morphine relative to tramadol. **METHODS:** Clinical data were collected of patients with moderate cancer pain (n = 353) who received either low-dose morphine or tramadol and were followed for ≥ 27 weeks. Factors related to regime adherence were investigated, including the analgesia type, cancer therapy (antitumor therapy or palliative care), pain type (nociceptive, neuropathic, or mixed), and living distance to the hospital. Factors related to clinically meaningful pain reduction (≥ 30% reduction in pain from baseline) were also investigated. **RESULTS:** Patients taking tramadol, receiving antitumor therapy, experiencing neuropathic pain, and living far from the hospital were more likely to change analgesic strategy compared with, respectively, patients receiving low-dose morphine, palliative care, experiencing nociceptive pain, and living nearby. Factors that increased the likelihood of adherence to the analgesic regime were also associated with the likelihood of clinically meaningful pain reduction. Among adverse effects, a significantly higher percentage of patients experienced constipation in the tramadol group compared with those given morphine. **CONCLUSIONS:** Among patients with moderate cancer pain, long-term low-dose morphine was safe and more effective than tramadol for clinically meaningful pain reduction, and patients were less likely to change the analgesic strategy.

[**Association between patient-reported hearing and visual impairments and functional, psychological, and cognitive status among older adults with cancer.**](#) Soto-Perez-de-Celis E1,2, Sun CL1, Tew WP3, et al. Cancer. 2018 May 24. doi: 10.1002/cncr.31540. [Epub ahead of print]
BACKGROUND: Hearing and visual impairments are common among community-dwelling older adults, and are associated with psychological, functional, and cognitive deficits. However, to the authors' knowledge, little is known regarding their prevalence among older patients with cancer. **METHODS:** The current study was a secondary analysis combining 2 prospective cohorts of adults aged ≥65 years with solid tumors who were receiving chemotherapy. The authors assessed the association between patient-reported hearing and/or visual impairment (defined as fair/poor grading by self-report) and physical function, instrumental activities of daily living (IADLs), anxiety, depression, and cognition. Descriptive analyses were conducted to summarize patient and treatment characteristics. One-way analysis of variance and chi-square tests were conducted as appropriate to examine differences between patients with and without sensory impairments. Logistic regression was used to analyze associations between sensory impairments and outcomes. **RESULTS:** Among 750 patients with a median age of 72 years who had solid tumors (29% with breast/gynecological tumors, 28% with lung tumors, and 27% with gastrointestinal tumors), approximately 18% reported hearing impairment alone, 11% reported visual impairment alone, and 7% reported dual sensory impairment. Hearing impairment was associated with IADL dependence (odds ratio [OR], 1.9), depression (OR, 1.6), and anxiety (OR, 1.6). Visual impairment was associated with IADL dependence (OR, 1.9), poor physical function (OR, 1.9), and depression (OR, 2.5). Dual impairment was associated with IADL dependence (OR, 2.8), anxiety (OR, 2.3), depression (OR, 2.5), and cognitive impairment (OR, 3.2). **CONCLUSIONS:** Sensory impairment is common among older adults with cancer. Patients with sensory impairment are more likely to have functional, psychological, and cognitive deficits. Interventions aimed at improving the vision and hearing of older adults with cancer should be studied.

COMPLEMENTARY & ALTERNATIVE THERAPY

[**Oral administration of herbal medicines for radiation pneumonitis in lung cancer patients: A systematic review and meta-analysis.**](#) Kim KI1,2, Jun JH3,4, Baek H2,5, Kim JH2,5, Lee BJ2, Jung HJ2. PLoS One. 2018 May 30;13(5):e0198015. doi: 10.1371/journal.pone.0198015. eCollection 2018.
BACKGROUND: Radiation pneumonitis is a common and serious complication of radiotherapy. Many published randomized controlled studies (RCTs) reveal a growing trend of using herbal medicines as adjuvant therapy to prevent radiation pneumonitis; however, their efficacy and safety remain unexplored. **OBJECTIVE:** The aim of this systematic review is to evaluate the efficacy and safety of herbal medicines as adjunctive therapy for the prevention of radiation pneumonitis in patients with lung cancer who undergo radiotherapy. **METHODS:** We searched the following 11 databases: three English medical databases [MEDLINE (PubMed), EMBASE, The Cochrane Central Register of Controlled Trials (CENTRAL)], five Korean medical databases (Korean Studies Information, Research information Service System, KoreaMed, DBPIA, National Digital Science Library), and three Chinese medical databases [the China National Knowledge Database (CNKI), Journal Integration Platform (VIP), and WanFang Database]. The primary outcome was the incidence of radiation pneumonitis. The risk of bias was assessed using the Cochrane risk-of-bias tool. **RESULTS:** Twenty-two RCTs involving 1819 participants were included. The methodological quality was poor for most of the studies. Meta-analysis showed that herbal medicines combined with radiotherapy significantly reduced the incidence of radiation pneumonitis (n = 1819; RR 0.53, 95% CI 0.45-0.63, I2 = 8%) and the incidence of severe radiation pneumonitis (n = 903; RR 0.22, 95% CI 0.11-0.41, I2 = 0%). Combined therapy also improved the Karnofsky performance score (n = 420; WMD 4.62, 95% CI 1.05-8.18, I2 = 82%). **CONCLUSION:**

There is some encouraging evidence that oral administration of herbal medicines combined with radiotherapy may benefit patients with lung cancer by preventing or minimizing radiation pneumonitis. However, due to the poor methodological quality of the identified studies, definitive conclusion could not be drawn. To confirm the merits of this approach, further rigorously designed large scale trials are warranted.

MISCELLANEOUS WORKS

The landscape of actionable genomic alterations in cell-free circulating tumor DNA from 21,807 advanced cancer patients. Zill OA1, Banks KC2, Fairclough SR3, et al. Clin Cancer Res. 2018 May 18. pii: clincanres.3837.2017. doi: 10.1158/1078-0432.CCR-17-3837. [Epub ahead of print] **PURPOSE:** Cell-free DNA (cfDNA) sequencing provides a non-invasive method for obtaining actionable genomic information to guide personalized cancer treatment, but the presence of multiple alterations in circulation related to treatment and tumor heterogeneity complicate the interpretation of the observed variants. Experimental Design: We describe the somatic mutation landscape of 70 cancer genes from cfDNA deep-sequencing analysis of 21,807 patients with treated, late-stage cancers across >50 cancer types. To facilitate interpretation of the genomic complexity of circulating tumor DNA in advanced, treated cancer patients, we developed methods to identify cfDNA copy-number driver alterations and cfDNA clonality. **RESULTS:** Patterns and prevalence of cfDNA alterations in major driver genes for non-small cell lung, breast, and colorectal cancer largely recapitulated those from tumor tissue sequencing compendia (TCGA and COSMIC; r=0.90-0.99), with the principle differences in alteration prevalence being due to patient treatment. This highly sensitive cfDNA sequencing assay revealed numerous subclonal tumor-derived alterations, expected as a result of clonal evolution, but leading to an apparent departure from mutual exclusivity in treatment-naïve tumors. Upon applying novel cfDNA clonality and copy-number driver identification methods, robust mutual exclusivity was observed among predicted truncal driver cfDNA alterations (FDR=5x10-7 for EGFR and ERBB2), in effect distinguishing tumor-initiating alterations from secondary alterations. Treatment-associated resistance, including both novel alterations and parallel evolution, was common in the cfDNA cohort and was enriched in patients with targetable driver alterations (>18.6% patients). **CONCLUSIONS:** Together these retrospective analyses of a large cfDNA sequencing data set reveal subclonal structures and emerging resistance in advanced solid tumors. Copyright ©2018, American Association for Cancer Research.

Racial-Ethnic Disparities in End-of-Life Care Quality among Lung Cancer Patients: A SEER-Medicare-Based Study. Karanth S1, Rajan SS2, Sharma G3, Yamal JM4, Morgan RO1. J Thorac Oncol. 2018 May 10. pii: S1556-0864(18)30540-9. doi: 10.1016/j.jtho.2018.04.014. [Epub ahead of print] **INTRODUCTION:** Cancer end-of-life care and associated racial-ethnic disparities have been in focus during the last few years due to concerns regarding subjective care variations and poor quality of care. Given the high mortality rate and disease burden of lung cancer, end-of-life care quality is particularly crucial for this disease. This study uses previously validated measures and examines racial-ethnic disparities in lung cancer end-of-life care quality. **METHODS:** This study involves retrospective analysis of patients ≥66 years, who were diagnosed with stage I-IV lung cancer, and who died on or before December 31, 2013, using the Surveillance Epidemiology and End Result-Medicare data from 1991-2013. Poor quality of care was measured using three themes: (1) potentially preventable medical encounters, (2) delayed hospice referral, and (3) aggressive chemotherapy provision during end-of-life. The patients were analyzed as two separate cohorts of NSCLC and SCLC patients. Logistic regression analyses were performed to estimate racial-ethnic disparities in the adjusted odds of receiving poor quality end-of-life care. **RESULTS:** The study found considerable racial-ethnic disparities in end-of-life care quality. The

racial-ethnic minorities had higher odds of experiencing potentially preventable medical encounters in the last month of life as compared with non-Hispanic whites. Odds of delayed hospice referral and aggressive chemotherapy provision during end-of-life were lower in non-Hispanic blacks as compared with non-Hispanic whites. **CONCLUSIONS:** The study findings highlight the continued lack of access and care disparity among the minorities, which could precipitate potentially preventable utilizations, and limit access to hospice care during end-of-life. The study suggests the need to develop educational, patient navigational and other interventions that could potentially reduce aggressive utilizations and improve appropriate hospice care provision during end-of-life.

[**Real-World Treatment Patterns, Overall Survival, and Occurrence and Costs of Adverse Events Associated With First-line Therapies for Medicare Patients 65 Years and Older With Advanced Non-small-cell Lung Cancer: A Retrospective Study.**](#) Bittoni MA1, Arunachalam A2, Li H3, Camacho R3, He J3, Zhong Y3, Lubiniecki GM3, Carbone DP1. Clin Lung Cancer. 2018 May 7. pii: S1525-7304(18)30099-8. doi: 10.1016/j.cllc.2018.04.017. [Epub ahead of print]
PURPOSE: This study sought to better understand real-world treatment patterns, overall and non-small-cell lung cancer (NSCLC)-specific survival, adverse event (AE) occurrence, and economic impact of first-line cancer therapies in Medicare patients. **PATIENTS AND METHODS:** This retrospective cohort study identified patients ≥ 65 years in the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database who received a first-time advanced (stage IV) NSCLC diagnosis from 2007 to 2011, and who received first-line platinum-based chemotherapy from 2007 through mid-2013. First-line regimens, healthcare resource use, occurrence of AEs, and associated costs (2013 US dollars) were analyzed. Median survival was determined using the Kaplan-Meier method. **RESULTS:** Surprisingly, only 46% of patients (n = 13,472) with stage IIIB/IV NSCLC received systemic therapy, and 5931 received platinum-based therapy. The mean age was 73 years, with 3354 (57%) males; 1489 (25%) had squamous and 4442 (75%) nonsquamous histology. The most common regimens were carboplatin doublets (70%), including carboplatin/paclitaxel (38%), carboplatin/pemetrexed (12%), carboplatin/gemcitabine (11%), and carboplatin/docetaxel (7%). The median overall survival from first-line therapy initiation was 7.2 months (95% confidence interval, 7.0-7.5 months). Dyspnea and anemia were the most common AEs of interest, whereas atypical pneumonia was associated with the greatest AE-related costs (mean, $5044). The mean total per-patient-per-month cost was $11,909, with AE-related costs comprising 9% of total costs. The highest costs and survival were observed for patients treated with carboplatin/pemetrexed and bevacizumab/carboplatin/paclitaxel. **CONCLUSIONS:** These real-world data illustrate the most common first-line regimens by histology, overall survival, AEs, and some of the high AE-related costs of therapy for advanced NSCLC, and provides extremely useful information for clinicians. Copyright © 2018 The Author(s). Published by Elsevier Inc.

[**Insurance Coverage Policies for Pharmacogenomic and Multi-Gene Testing for Cancer.**](#) Lu CY1, Loomer S2, Ceccarelli R3, Mazor KM4, Sabin J5, Clayton EW6, Ginsburg GS7, Wu AC8. J Pers Med. 2018 May 16;8(2). pii: E19. doi: 10.3390/jpm8020019.
Insurance coverage policies are a major determinant of patient access to genomic tests. The objective of this study was to examine differences in coverage policies for guideline-recommended pharmacogenomic tests that inform cancer treatment. We analyzed coverage policies from eight Medicare contractors and 10 private payers for 23 biomarkers (e.g., HER2 and EGFR) and multi-gene tests. We extracted policy coverage and criteria, prior authorization requirements, and an evidence basis for coverage. We reviewed professional society guidelines and their recommendations for use of pharmacogenomic tests. Coverage for KRAS, EGFR, and BRAF tests were common across Medicare contractors and private payers, but few policies covered PML/RARA, CD25, or G6PD. Thirteen payers cover multi-gene tests for nonsmall lung cancer, citing emerging clinical recommendations. Coverage policies for single and multi-gene tests for

cancer treatments are consistent among Medicare contractors despite the lack of national coverage determinations. In contrast, coverage for these tests varied across private payers. Patient access to tests is governed by prior authorization among eight private payers. Substantial variations in how payers address guideline-recommended pharmacogenomic tests and the common use of prior authorization underscore the need for additional studies of the effects of coverage variation on cancer care and patient outcomes.

Closing Knowledge Gaps to Optimize Patient Outcomes and Advance Precision Medicine. Giusti K, Young AQ, Lehrhaupt K1. Cancer J. 2018 May/Jun;24(3):140-147. doi: 10.1097/PPO.0000000000000319.

Realizing the promise of precision medicine requires patient engagement at the key decision points throughout the cancer journey. Previous research has shown that patients who make the "right" decisions, such as being treated at a high-volume academic medical center, for example, have better outcomes. An online survey was conducted to understand awareness of and barriers to these decision points among patients with multiple myeloma and pancreatic, lung, prostate, and metastatic breast cancers. Survey respondents were identified by 5 participating foundations (multiple myeloma: n = 86, pancreatic: n = 108, lung: n = 56, prostate: n = 50, metastatic breast: n = 86) and recruited by an e-mail or social media invitation. Descriptive analyses were calculated, and the proportion of patients from each of the 5 groups was compared for each response category for each survey item. Consistent gaps in knowledge and actions were identified across all cancers evaluated in terms of finding the right doctors/team at the right center; getting the right diagnostic testing done before beginning treatment; engaging in the right course of treatment, including clinical trials; and in sharing data. Improving awareness of and changing behavior around these 4 decision points will allow patients to receive better care and contribute to the advancement of precision medicine.

The impact of self- and physician-administered cancer treatment on work productivity and healthcare utilization. Seabury SA1, Frasco MA2, van Eijndhoven E2, Sison S2, Zacker C3. Res Social Adm Pharm. 2018 May;14(5):434-440. doi: 10.1016/j.sapharm.2017.05.009. Epub 2017 May 22.

BACKGROUND: Lost productivity in the workplace represents a significant portion of the economic burden of cancer in the United States. Cancer treatments have historically been physician-administered, while recent innovations have led to the development of self-administered, usually oral, agents. Self-administered treatments have the potential to reduce healthcare utilization and time away from work, but the magnitude of these effects is unknown. **OBJECTIVE:** To compare the effects of self- and physician-administered cancer treatment on work productivity and health care utilization. **METHODS:** Cancer subtypes with self- and physician-administered treatment options were selected. Patients with female breast, or lung or bronchus cancer diagnosed in 2004-2013 were identified in the Truven Health Analytics Commercial Claims and Encounters and Health and Productivity Management databases. Using multivariate regression models, work productivity and healthcare utilization were compared for patients receiving self- versus physician-administered treatment in the 12 months after initial diagnosis. Work productivity outcomes included the number of sick days and short-term disability claims. **RESULTS:** One month of self- versus physician-administered treatment significantly reduced cancer-related outpatient services, doctor visits, and infusions in the 12 months after initial diagnosis for both cancers of interest. In addition, breast and lung or bronchus cancer patients who received self-administered treatment were less likely to have short-term disability claims, and breast cancer patients with non-metastatic disease who received self-administered treatment had significantly fewer sick days. **CONCLUSIONS:** Self-administered cancer treatment was associated with fewer cancer-related outpatient services and reduced time away from work compared to physician-administered cancer treatment.

[Annual Report to the Nation on the Status of Cancer, part I: National cancer statistics.](#) Cronin KA1, Lake AJ2, Scott S1, et al. Cancer. 2018 Jul 1;124(13):2785-2800. doi: 10.1002/cncr.31551. Epub 2018 May 22.
BACKGROUND: The American Cancer Society (ACS), the Centers for Disease Control and Prevention (CDC), the National Cancer Institute (NCI), and the North American Association of Central Cancer Registries (NAACCR) collaborate to provide annual updates on cancer occurrence and trends in the United States. **METHODS:** Incidence data were obtained from the CDC-funded and NCI-funded population-based cancer registry programs and compiled by NAACCR. Data on cancer deaths were obtained from the National Center for Health Statistics National Vital Statistics System. Trends in age-standardized incidence and death rates for all cancers combined and for the leading cancer types by sex, race, and ethnicity were estimated by joinpoint analysis and expressed as the annual percent change. Stage distribution and 5-year survival by stage at diagnosis were calculated for breast cancer, colon and rectum (colorectal) cancer, lung and bronchus cancer, and melanoma of the skin. **RESULTS:** Overall cancer incidence rates from 2008 to 2014 decreased by 2.2% per year among men but were stable among women. Overall cancer death rates from 1999 to 2015 decreased by 1.8% per year among men and by 1.4% per year among women. Among men, incidence rates during the most recent 5-year period (2010-2014) decreased for 7 of the 17 most common cancer types, and death rates (2011-2015) decreased for 11 of the 18 most common types. Among women, incidence rates declined for 7 of the 18 most common cancers, and death rates declined for 14 of the 20 most common cancers. Death rates decreased for cancer sites, including lung and bronchus (men and women), colorectal (men and women), female breast, and prostate. Death rates increased for cancers of the liver (men and women); pancreas (men and women); brain and other nervous system (men and women); oral cavity and pharynx (men only); soft tissue, including heart (men only); nonmelanoma skin (men only); and uterus. Incidence and death rates were higher among men than among women for all racial and ethnic groups. For all cancer sites combined, black men and white women had the highest incidence rates compared with other racial groups, and black men and black women had the highest death rates compared with other racial groups. Non-Hispanic men and women had higher incidence and mortality rates than those of Hispanic ethnicity. Five-year survival for cases diagnosed from 2007 through 2013 ranged from 100% (stage I) to 26.5% (stage IV) for female breast cancer, from 88.1% (stage I) to 12.6% (stage IV) for colorectal cancer, from 55.1% (stage I) to 4.2% (stage IV) for lung and bronchus cancer, and from 99.5% (stage I) to 16% (stage IV) for melanoma of the skin. Among children, overall cancer incidence rates increased by 0.8% per year from 2010 to 2014, and overall cancer death rates decreased by 1.5% per year from 2011 to 2015. **CONCLUSIONS:** For all cancer sites combined, cancer incidence rates decreased among men but were stable among women. Overall, there continue to be significant declines in cancer death rates among both men and women. Differences in rates and trends by race and ethnic group remain. Progress in reducing cancer mortality has not occurred for all sites. Examining stage distribution and 5-year survival by stage highlights the potential benefits associated with early detection and treatment. Cancer 2018;124:2785-2800. © 2018 American Cancer Society.

[Associations between the smoking-relatedness of a cancer type, cessation attitudes and beliefs, and future abstinence among recent quitters.](#) Martínez Ú1, Brandon TH1,2,3, Sutton SK2,3,4, Simmons VN1,2,3. Psychooncology. 2018 May 21. doi: 10.1002/pon.4774. [Epub ahead of print]
OBJECTIVE: Smoking after a diagnosis of cancer can negatively impact treatment outcomes and quality of life. It is important that patients quit smoking and remain abstinent regardless of cancer type. Some cancer types (eg, lung) have stronger links to smoking as a cause than do others (eg, colorectal). The aims of this study were to (1) assess associations between smoking-relatedness of the cancer type with beliefs and attitudes concerning smoking abstinence (eg, confidence, self-efficacy), and (2) assess these variables as predictors of future abstinence. **METHODS:** In this secondary analysis, cancer patients (N = 357) who

quit smoking within the previous 90 days were assigned a code of 3, 2, or 1 according to the cancer type's level of smoking-relatedness: Very related (n = 134, thoracic and head and neck), Somewhat related (n = 93, acute myeloid leukemia, bladder, cervix, colorectal, esophageal, kidney, liver, pancreas, and stomach), and Unlikely related (n = 137, all other cancer types). **RESULTS:** Smoking-relatedness was positively associated with plan to stay smoke-free, maximum confidence in being smoke-free in 6 months, higher abstinence self-efficacy, and lower expected difficulty in staying smoke-free. Each of the 4 beliefs and attitude variables predicted abstinence 2 months later. Smoking-relatedness also predicted abstinence in a univariate model, but not in a multivariable model with the belief and attitude variables. Using backwards stepwise procedures, the final model included plan to stay smoke-free, confidence in being smoke-free, and abstinence self-efficacy. **CONCLUSION:** These results are consistent with our conceptualization of cessation motivation differing by smoking-relatedness of the cancer type and predicting future abstinence.

Measuring public knowledge, attitudes, and behaviors related to radon to inform cancer control activities and practices. Neri A1,2, McNaughton C3, Momin B2, Puckett M2, Gallaway MS2. Indoor Air. 2018 Jul;28(4):604-610. doi: 10.1111/ina.12468. Epub 2018 May 14.
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Radon exposure is the second leading risk factor for lung cancer among smokers and the leading risk factor among non-smokers. Radon concentrated in lower levels of homes/buildings can be reduced if found, thus lowering lung cancer risk. The objective of this study was to measure radon knowledge in diverse populations, with varying radon-related laws, to inform radon-related cancer control practices and activities. A survey was mailed to 3000 homebuyers who purchased single-family homes; 995 responses (33%) were received. Overall, 86% of respondents heard of radon-related health issues. Real estate agents (69%) or home inspectors (65%) were the most common sources of information. Respondents were more likely to test their home for radon if they reported previously hearing of radon-related health issues or understanding of how radon-related health issues affect the home-buying process. Respondents in states with notification policies were twice as likely as those without policies to have heard about radon-related health issues (OR 2.01, 95% CI: 1.27-3.17). This study provides useful information for cancer control activities including that education is positively associated with home testing for radon. It also suggests partnering with real estate agents to further radon education and testing efforts to reduce radon exposure and lung cancer risk.