



## Caring Ambassadors Lung Cancer Program Literature Review, April 2019

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### BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

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[Circulating Inflammation Proteins Associated With Lung Cancer in African Americans.](#) Meaney CL1, Mitchell KA1, Zingone A1, et al. J Thorac Oncol. 2019 Apr 3. pii: S1556-0864(19)30269-2. doi: 10.1016/j.jtho.2019.03.014. [Epub ahead of print]

**INTRODUCTION:** Lung cancer incidence is higher among African Americans (AAs) compared with European Americans (EAs) in the United States. We and others have previously shown a relationship between immune and inflammation proteins with lung cancer in EAs. Our aim was to investigate the etiologic relationship between inflammation and lung cancer in AAs. **METHODS:** We adopted a two-stage, independent study design (discovery cases, n = 316; control cases, n = 509) (validation cases, n = 399; control cases, n = 400 controls) and measured 30 inflammation proteins in blood using Meso Scale Discovery V- PLEX multiplex assays. **RESULTS:** We identified and validated 10 proteins associated with lung cancer in AAs, some that were common between EAs and AAs (C-reactive proteins [OR: 2.90; 95% confidence interval (CI): 1.99-4.22], interferon  $\gamma$  [OR: 1.55; 95% CI: 1.10-2.19], interleukin 6 [OR: 6.28; 95% CI: 4.10-9.63], interleukin 8 [OR: 2.76; 95% CI: 1.92-3.98]) and some that are only observed among AAs (interleukin 10 [OR: 1.69; 95% CI: 1.20-2.38], interleukin 15 [OR: 2.83; 95% CI: 1.96-4.07], interferon gamma-induced protein 10 [OR: 1.54; 95% CI: 1.09-2.18], monocyte chemoattractant protein-1 [OR: 0.54; 95% CI: 0.38-0.76], macrophage inflammatory protein-1 alpha [OR: 1.57; 95% CI: 1.12-2.21], and tumor necrosis factor  $\beta$  [OR: 0.52; 95% CI: 0.37-0.74]). We did not find evidence that either menthol cigarette smoking or global genetic ancestry drove these population differences. **CONCLUSIONS:** Our results highlight a distinct inflammation profile associated with lung cancer in AAs compared with EAs. These data provide new insight into the etiology of lung cancer in AAs. Further work is needed to understand what drives this relationship with lung cancer and whether these proteins have utility in the setting of early diagnosis.

[Linc00221 modulates cisplatin resistance in non-small-cell lung cancer via sponging miR-519a.](#)

Tang H1, Han X2, Li M1, Li T1, Hao Y3. Biochimie. 2019 Apr 25;162:134-143. doi: 10.1016/j.biochi.2019.04.019. [Epub ahead of print]

Cisplatin resistance has been long considered an obstacle to the efficacy of chemotherapy in non-small-cell lung cancer (NSCLC). Long non-coding RNAs (lncRNAs) have been widely reported to participate in the various biological process including cancer. In the present study, we aim to explore the functions of Linc00221 and miR-519a in the sensitivity and the resistance of NSCLC to cisplatin. The levels of Linc00221, miR-519a, and zinc finger and BTB domain-containing five (ZBTB5) in NSCLC tissues were detected by qRT-PCR and Western blot. Colony formation and MTT assays were applied to detect the viability of cells after cisplatin treatment. Dual luciferase reporter assays were used to detect the inhibitory effect of miR-519a on ZBTB5 and Linc00221, and pull down experiments were employed to determine the direct interaction between Linc00221 and miR-519a. Our results showed that Linc00221 was highly expressed in cisplatin-resistant NSCLC tissues and cells and closely associated with poor prognosis. Linc00221 promoted the cisplatin resistance of NSCLC and miR-519a was a direct target of Linc00221. In addition, miR-519a could promote cisplatin sensitivity in NSCLC cells by targeting ZBTB5. Linc00221 could mediate the cisplatin sensitivity in NSCLC by adsorbing miR-519a to prevent its down-regulation of ZBTB5. In conclusion, Linc00221 promotes cisplatin resistance in NSCLC through the downstream miR-519a/ZBTB5 signaling axis, which could be used as a potential diagnostic and therapeutic target for clinical cisplatin-resistant NSCLC patients.

**[Plakophilin 1 is methylated and has a tumor suppressive activity in human lung cancer.](#)** Haase D1, Cui T1, Yang L1, Ma Y1, Liu H2, Theis B1, Petersen I1, Chen Y3. *Exp Mol Pathol.* 2019 Apr 1;108:73-79. doi: 10.1016/j.yexmp.2019.04.001. [Epub ahead of print]

**BACKGROUND:** Plakophilin 1 (PKP1) is an important plaque component of desmosomes, major intercellular adhesive junctions that act as anchorage points for intermediate filaments. Abnormal expression of PKP1 was observed in various types of cancer, however so far its function in lung cancer has not yet been elucidated. **METHODS:** The expression of PKP1 was analyzed by RT-PCR and western blotting in lung cancer cell lines. The protein expression of PKP1 was evaluated by immunohistochemistry in tissue microarray. The epigenetic mechanism of PKP1 was explored by demethylation test, bisulfite sequencing and Methylation-Specific-PCR. The function of PKP1 was investigated by stable transfection with an expression vector. **RESULTS:** We found that PKP1 was downregulated in 6 out of 8 lung cancer cell lines, and downregulation of PKP1 was associated with DNA hypermethylation. In advanced primary lung tumor samples, higher expression of PKP1 was significantly associated with favorable clinical outcome ( $p = .003$ ). Ectopic expression of PKP1 inhibited cell proliferation, colony formation, migration/invasion and enhanced apoptosis. These phenomena are accompanied by increased caspase 3/7 activities and cleaved PARP-1 as well as decreased extracellular signal-regulated kinase (ERK) activity. **CONCLUSION:** Taken together, our data suggest that PKP1 is a novel tumor suppressor and its protein expression might be a potential prognostic marker for patients with advanced lung cancer.

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## BIOMARKER TESTING, SCREENING, DIAGNOSIS AND STAGING

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**[Re-biopsy and liquid biopsy for patients with non-small cell lung cancer after EGFR-tyrosine kinase inhibitor failure.](#)** Zhou J1, Zhao C2, et al. *Thorac Cancer.* 2019 Apr;10(4):957-965. doi: 10.1111/1759-7714.13035. Epub 2019 Mar 18.

**BACKGROUND:** Re-biopsy is important for exploring resistance mechanisms, especially for non-small cell lung cancer (NSCLC) patients who develop resistance to EGFR-tyrosine kinase inhibitors (TKIs). Liquid biopsy using circulating tumor DNA has come into use for this purpose. This retrospective study investigated the status of re-biopsy and liquid biopsy in NSCLC patients with EGFR mutations and evaluated their effect on clinical strategies and prognosis. **METHODS:** Five hundred fifty-five NSCLC patients with resistance to EGFR-TKIs were included and divided into three groups: re-biopsy, liquid

biopsy, and no re-biopsy. Amplification refractory mutation system (ARMS) PCR or super ARMS PCR was used to detect EGFR mutations. **RESULTS:** Three hundred eight (55.5%) patients underwent re-biopsy; 45.5% (140/308) were positive for T790M. The most common re-biopsy procedure was computed tomography-guided percutaneous core needle biopsy (60.1%), followed by effusion drainage (29.5%) and superficial lymph node biopsy (6.5%). One hundred eighteen (21.3%) patients underwent liquid biopsy; the T790M detection rate was 41.5% (49/118.) Of the 308 patients who underwent re-biopsy, 69 were examined for EGFR mutations with plasma. The concordance rate of T790M detection between tissue and plasma was 66.7%. A statistical difference in further treatment after EGFR-TKI failure was observed among all groups ( $P = 0.014$ ). Patients in the biopsy groups were more likely to receive third-generation EGFR-TKIs. Multivariate analysis showed that re-biopsy had a significant impact on overall survival ( $P < 0.001$ ). **CONCLUSION:** Re-biopsy plays a pivotal role in the management of patients with NSCLC and resistance to EGFR-TKIs. Liquid biopsy may be an alternative if difficulties performing re-biopsy exist.

[Improving Lung Cancer Screening Access for Individuals With Serious Mental Illness.](#) Flores EJ1, Park ER2, Irwin KE2. *J Am Coll Radiol.* 2019 Apr;16(4 Pt B):596-600. doi: 10.1016/j.jacr.2018.12.045. Lung cancer continues to be the leading cause of cancer mortality in the United States across all races and ethnicities, but it does not affect everyone equally. Individuals with serious mental illness (SMI), including schizophrenia and bipolar disorder, experience two to four times greater lung cancer mortality in part due to high rates of smoking, delays in cancer diagnosis, and inequities in cancer treatment. Additionally, adults with SMI experience patient, clinician, and health care system-level barriers to accessing cancer screening, such as cognitive deficits that impact understanding of cancer risk, higher rates of poverty and social isolation, patient-provider communication challenges, decreased access to tobacco cessation, and the fragmentation of primary care and mental health care. Despite the proven benefits and mandated coverage by public and private payers, lung cancer screening participation rates remain low among eligible patients, below 4% a year. Given disparities in other cancer screening modalities, these rates are likely to be even lower among individuals with SMI. This article provides a brief overview of current challenges in lung cancer screening and describes a pilot collaboration between radiology and psychiatry that has potential to improve access to lung cancer screening for individuals with serious mental illness.

[Molecular and Morphological Profiling of Lung Cancer: A Foundation for "Next-Generation" Pathologists and Oncologists.](#) Kashima J1,2, Kitadai R3, Okuma Y4,5. *Cancers (Basel).* 2019 Apr 29;11(5). pii: E599. doi: 10.3390/cancers11050599.

The pathological diagnosis of lung cancer has largely been based on the morphological features observed microscopically. Recent innovations in molecular and genetic technology enable us to compare conventional histological classifications, protein expression status, and gene abnormalities. The introduction of The Cancer Genome Atlas (TCGA) project along with the widespread use of the next-generation sequencer (NGS) have facilitated access to enormous data regarding the molecular profiles of lung cancer. The World Health Organization classification of lung cancer, which was revised in 2015, is based on this progress in molecular pathology; moreover, immunohistochemistry has come to play a larger role in diagnosis. In this article, we focused on genetic and epigenetic abnormalities in non-small cell carcinoma (adenocarcinoma and squamous cell carcinoma), neuroendocrine tumor (including carcinoids, small cell carcinoma, and large cell neuroendocrine carcinoma), and carcinoma with rare histological subtypes. In addition, we summarize the therapeutic targeted reagents that are currently available and undergoing clinical trials. A good understanding of the morphological and molecular profiles will be necessary in routine practice when the NGS platform is widely used.

[The Patient Perspective on Lung Cancer Screening and Health Disparities.](#) Borondy Kitts AK1. J Am Coll Radiol. 2019 Apr;16(4 Pt B):601-606. doi: 10.1016/j.jacr.2018.12.028.

Lung cancer screening is just starting to be implemented across the United States. Challenges to screening include access to care, awareness of the option for screening, stigma and implicit bias that are due to stigmatization of smoking, stigma of race, nihilism with lung cancer diagnosis viewed as a "death sentence," shared decision making, and underestimation of lung cancer risk. African Americans (AA) have the highest lung cancer mortality rate in the United States despite similar smoking rates as whites. AAs are diagnosed at a later stage, and there is a greater likelihood they will refuse treatment options when diagnosed. Additionally, fewer AAs were found to meet lung cancer screening eligibility criteria compared with whites because of lower tobacco exposure and younger age at time of diagnosis. Outreach and access for lung cancer screening in the AA community and other subpopulations at risk are critical to avoid further increasing disparities in lung cancer morbidity and mortality as lung cancer screening is implemented across the United States. The path forward requires implementing outreach programs and providing lung cancer screening in underserved communities at high risk for lung cancer; consideration of using National Comprehensive Cancer Network guidelines for screening selection criteria, including risk model screening selection; and developing interventions to address stigma, clinician implicit bias, and nihilism.

[Improved False-Positive Rates and the Overestimation of Unintended Harm from Lung Cancer Screening.](#) Karush J1,2, Arndt A3, Shah P4, et al. Lung. 2019 Apr 12. doi: 10.1007/s00408-019-00217-4. [Epub ahead of print]

**BACKGROUND:** Concern over high false-positive rates and the potential for unintended harm to patients is a critical component of the lack of widespread adoption of lung cancer screening.

**METHODS:** An institutional database was used to identify patients who underwent lung cancer screening between 2/2015 and 2/2018 at Rush University Medical Center and Rush Oak Park Hospital. Reads were executed by dedicated thoracic radiologists and communicated using the Lung Imaging Reporting and Data System (Lung-RADS V.1). **RESULTS:** Six hundred and four patients were screened over the study period. We identified 21 primary lung cancers and 8 incidental cancers. We identified a false-positive rate of 17.5%. Only 9 patients underwent further investigative workup for benign disease (5.3%); however, only 4 (2.9%) of those patients were found to have inflammatory or infectious lesions, which are common mimickers of lung cancer. Excluding Lung-RADS category 3 for the purpose of quantifying risk of unintended harm from unnecessary procedures, we found a 6.9% false-positive rate, while diagnosing 25% of all Lung-RADS category 4 patients with primary lung cancer. **CONCLUSION:** False-positive rates in lung cancer screening programs continue to decline with improved radiologic expertise. Additionally, false-positive reporting overestimates the risk of unintended harm from further investigative procedures as only a percentage of positive findings are generally considered for tissue diagnosis (i.e., Lung-RADS category 4).

[Using a Dedicated Interventional Pulmonology Practice Decreases Wait Time Before Treatment Initiation for New Lung Cancer Diagnoses.](#) Benn BS1, Parikh M2, Tsau PH3, Seeley E4, Krishna G4,5. Lung. 2019 Apr;197(2):249-255. doi: 10.1007/s00408-019-00207-6. Epub 2019 Feb 19.

**PURPOSE:** While there is significant mortality and morbidity with lung cancer, early stage diagnoses carry a better prognosis. As lung cancer screening programs increase with more pulmonary nodules detected, expediting definitive treatment initiation for newly diagnosed patients is imperative. The objective of our analysis was to determine if the use of a dedicated interventional pulmonology practice decreases time delay from new diagnosis of lung cancer or metastatic disease to the chest to treatment initiation. **METHODS:** Retrospective chart analysis was done of 87 consecutive patients with a new diagnosis of primary lung cancer or metastatic cancer to the chest from our interventional pulmonology

procedures. Demographic information and time intervals from abnormal imaging to procedure and to treatment initiation were recorded. **RESULTS:** Patients were older (mean age 69) and former or current smokers (72%). A median of 27 days (1-127 days) passed from our diagnostic biopsy to treatment initiation. A median of 53 total days (2-449 days) passed from abnormal imaging to definitive treatment. Endobronchial ultrasound-guided transbronchial needle aspiration was the most commonly used diagnostic procedure (59%), with non-small cell lung cancer the majority diagnosis (64%). For surgical patients, all biopsy-negative lymph nodes from our procedures were cancer-free at surgical excision. **CONCLUSIONS:** Compared to prior reports from international and United States cohorts, obtaining a tissue biopsy diagnosis through a gatekeeper interventional pulmonology practice decreases median delay from abnormal imaging to treatment initiation. This finding has the potential to positively impact patient outcomes and requires further evaluation.

[Current knowledge of Ipilimumab and its use in treating non-small cell lung cancer.](#) Pinto JA1, Raez LE2, Oliveres H3, Rolfo CC4. *Expert Opin Biol Ther.* 2019 Apr 19:1-7. doi: 10.1080/14712598.2019.1610380. [Epub ahead of print]

The systemic treatment of non-small cell lung cancer (NSCLC) has changed dramatically with the identification of actionable mutations and the use of targeted agents. Unfortunately, many tumors will acquire resistance and >75% of NSCLC cases lack for an actionable gene aberration. In this setting, immunotherapy rises as effective therapeutic where immune checkpoint inhibitors have entered or are entering the market in many neoplasms, including NSCLC. Ipilimumab is a monoclonal antibody targeting CTLA-4, promoting T-cell activation and its subsequent anti-tumoral immune effect. Ipilimumab might have a very important role in NSCLC as it does in melanoma because of its synergistic effect with PD-1/PDL-1 inhibitors. Areas covered: We summarize current results of clinical studies of ipilimumab for efficacy and safety in NSCLC and also the current knowledge about potential biomarkers for its efficacy. Expert Opinion: Combined use of PD-1/PDL-1 and anti-CTLA4 inhibitors increases the efficacy against NSCLC and it is a very promising approach not only in NSCLC but also in small cell lung cancer (SCLC) for first or second-line therapy. It's very important to identify biomarkers that can better select the population of patients that benefit the most with these checkpoint inhibitors.

[Disparities in Lung Cancer Screening Availability: Lessons from Southwest, Virginia.](#) Martin AN1, Kozower BD2, Camacho F3, Hassinger T4, Anderson RT3, Yao N3. *Ann Thorac Surg.* 2019 Apr 2. pii: S0003-4975(19)30429-1. doi: 10.1016/j.athoracsur.2019.03.003. [Epub ahead of print]

**BACKGROUND:** Little is known about health disparities in access to low-dose computed tomography (LDCT) screening. We hypothesized the current capacity for LDCT screening would be exceeded by the number of at-risk individuals in Virginia. **METHODS:** Cancer incidence data and adult smoking rates for Virginia were obtained from public sources between 2006-2012. The American College of Radiology website was queried in 2015 to identify lung cancer screening facilities in Virginia, which were surveyed. Spatial exploratory data analysis was used to examine secondary data and descriptive analysis was used to examine primary survey data. **RESULTS:** Rural counties have higher lung cancer death rates and smoking rates than metropolitan counties. Despite tremendous burden for LDCT screening in rural counties, particularly in Southwest, VA, there were only two LDCT facilities. In total, 37 accredited LDCT facilities were identified in Virginia. On average, facilities had been screening for 14.6 months and screened an average of 76 patients. **CONCLUSIONS:** At-risk smokers in Virginia, particularly those living in rural areas with high smoking rates, do not have adequate recommended LDCT coverage. More screening centers are needed to care for the high number of rural smokers at-risk for lung cancer.

[Challenges and Opportunities for Lung Cancer Screening in Rural America.](#) Odahowski CL1, Zahnd WE2, Eberth JM3. J Am Coll Radiol. 2019 Apr;16(4 Pt B):590-595. doi: 10.1016/j.jacr.2019.01.001. Rural populations have higher rates of smoking and both lung cancer incidence and mortality compared with their urban peers. As such, it is imperative that high-risk, rural populations have access to recommended low-dose CT (LDCT) screening, which can detect lung cancer at an earlier, more treatable stage. Data from the 2015 National Health Interview Survey, a nationally representative survey, were analyzed to assess nonmetropolitan-metropolitan and geographic differences in LDCT utilization among screening-eligible individuals. Screening uptake did not differ by nonmetropolitan vs. metropolitan status (3.72% and 3.83%, respectively). Regional uptake varied from 1.58% in the West to 10.11% in the Northeast. Additionally, nonmetropolitan populations represent a disproportionately high 23% of the screening-eligible population despite accounting for only 15% of the US population. There are two key challenges to high-quality LDCT screening experienced by rural populations: (1) geographic access to LDCT screening programs and (2) provider-patient communication. Despite the increased availability of LDCT screening centers since 2015, which is when most insurance plans began to cover the costs of screening, centers are geographically maldistributed relative to the rural-urban and regional need. Although decision aids can facilitate discussion between providers and patients regarding the risks and benefits of LDCT screening, research on the uptake and utility of these tools in rural areas is very limited. Analyses of population-based surveys and administrative and clinical data are needed to continue to surveil screening utilization, elucidate predictors of screening use, and inform shared decision-making tools and interventions for at-risk rural populations.

## CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

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### NSCLC - SURGERY

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[No drain after thoracoscopic major lung resection for cancer helps preserve the physical function.](#) Ueda K1, Haruki T2, Murakami J2, Tanaka T2, Hayashi M2, Hamano K2. Ann Thorac Surg. 2019 Apr 5. pii: S0003-4975(19)30493-X. doi: 10.1016/j.athoracsur.2019.03.018. [Epub ahead of print]

**BACKGROUND:** We previously proved that omitting chest tube drainage in select patients undergoing thoracoscopic major lung resection for cancer was safe. The aim of the present study was to clarify the impact of omitting postoperative chest tube drainage on preserving the early-postoperative ventilatory capacity and exercise capacity. **METHODS:** The subjects of this retrospective study were 116 patients undergoing either thoracoscopic radical segmentectomy (n=18) or lobectomy (n=98). Whether or not chest tube drainage was to be performed was determined based on the predefined criteria. We routinely measured the vital capacity and 6-minute walking distance preoperatively, at postoperative day 1 and at postoperative day 7. Postoperative pain was assessed daily by the visual analog scale, and the number of analgesics used until postoperative day 7 was recorded. **RESULTS:** Postoperative chest tube drainage was omitted in 53 (46%) patients. Omitting chest tube drainage was associated with a significant reduction in both the postoperative pain and the number of analgesics used on postoperative day 0 and 1. In addition, omitting chest tube drainage was associated with a preservation of vital capacity and the 6-minute walking capacity on postoperative day 1. The vital capacity, the 6-minute walking distance and the pain as measured on postoperative day 1 were significantly correlated with each other. **CONCLUSIONS:** Omitting chest tube drainage results in reducing the pain, preservation of the ventilatory capacity, and preservation of exercise capacity in the early-postoperative period in patients undergoing thoracoscopic major lung resection for cancer.

[Surgical outcome of pulmonary artery reconstruction using the expanded polytetrafluoroethylene patch in patients with lung cancer.](#) Yoshino M1, Saitoh Y2, Chiyo M2, Hoshino H3, Sekine Y3, Wada H4, Suzuki H4, Yoshino I4. *Surg Today*. 2019 Apr 1. doi: 10.1007/s00595-019-01803-y. [Epub ahead of print]

**PURPOSE:** Pulmonary artery reconstruction is sometimes utilized as an alternative to pneumonectomy in lung cancer surgery. We herein report our experience of pulmonary artery reconstruction using an expanded polytetrafluoroethylene (ePTFE) patch based on the surgical results and long-term outcome. **METHODS:** Clinical records of lung cancer patients who underwent patch plasty were reviewed retrospectively. **RESULTS:** Between 2003 and 2017, pulmonary artery patch plasty were performed in 21 patients [18 males, 3 females; mean age 65 (range 47-79) years]. Induction chemoradiotherapy was performed in three patients. Bronchoplasty was performed in five patients. The pathologic stages were stage I in 3 patients, stage II in 6 and stage III in 12. Pneumonectomy, lobectomy and segmentectomy were performed in 2, 18 and 1 patient, respectively. The left upper lobe was the most frequent origin of lung cancer (15 patients). There was no reconstruction-related morbidity or mortality. The overall survival rate at 5 years was 64.1% with a mean follow-up of 39.5 months, and the survival rates for N0-1 and N2-3 were 80.8% and 28.6%, respectively. **CONCLUSION:** Patch angioplasty using the ePTFE sheet is a reliable procedure in radical surgery for lung cancer.

[Competing Risk Analysis in Lung Cancer Patients Over 80 Years Old Undergoing Surgery.](#) Hino H1, Karasaki T2, Yoshida Y3, et al. *World J Surg*. 2019 Apr 1. doi: 10.1007/s00268-019-04982-4. [Epub ahead of print]

**BACKGROUND:** This study aimed to analyze cause-specific mortality in lung cancer patients over 80 years old undergoing surgery. **METHODS:** This retrospective, multi-institutional analysis included patients aged  $\geq 80$  years who underwent radical surgery for primary lung cancer from January 1998 to December 2015. Preoperative clinical data, surgical results, survival, and cause of death were evaluated. Competing risk analysis for cause-specific mortality was performed. **RESULTS:** Of the 337 patients (median age 82 years) enrolled and analyzed, 68.1% were male. There were 52 and 44 cancer-specific and non-cancer-specific deaths, respectively. On competing risk regression analysis, non-cancer-specific deaths were significantly associated with male sex (hazard ratio [HR]: 3.06, 95% confidence interval [CI]: 1.02-9.12,  $p = 0.046$ ), coronary artery disease (HR: 2.49, 95% CI: 2.49 [1.14-5.47],  $p = 0.02$ ), interstitial pneumonia (HR: 3.58, 95% CI: 1.73-7.40,  $p < 0.001$ ), and pathological stage III (HR: 3.83, 95% CI: 1.44-10.13,  $p = 0.007$ ). In contrast, cancer-specific deaths were significantly associated with limited resection (HR: 1.99, 95% CI: 1.02-3.89,  $p = 0.04$ ) and pathological stage III (HR: 3.13, 95% CI: 1.44-6.80,  $p = 0.004$ ). The 5-year cumulative incidences of lung cancer-specific and non-cancer-specific deaths were 18.0% and 15.9%, respectively. **CONCLUSIONS:** Prognostic factors for non-cancer-specific death were different from those of cancer-specific death, except for pathological stage. Each prognostic factor should be considered when deciding surgical indication and procedure and monitoring for pulmonary events during outpatient follow-up.

[The impact of emphysema on surgical outcomes of early-stage lung cancer: a retrospective study.](#) Sato S1, Nakamura M2, Shimizu Y2, Goto T2, Koike T2, Ishikawa H3, Tsuchida M2. *BMC Pulm Med*. 2019 Apr 4;19(1):73. doi: 10.1186/s12890-019-0839-1.

**BACKGROUND:** The presence of emphysema on computed tomography (CT) is associated with an increased frequency of lung cancer, but the postoperative outcomes of patients with pulmonary emphysema are not well known. The objective of this study was to investigate the association between the extent of emphysema and long-term outcomes, as well as mortality and postoperative complications, in early-stage lung cancer patients after pulmonary resection. **METHODS:** The clinical records of 566 consecutive lung cancer patients who underwent pulmonary resection in our department were

retrospectively reviewed. Among these, the data sets of 364 pathological stage I patients were available. The associations between the extent of lung emphysema and long-term outcomes and postoperative complications were investigated. Emphysema was assessed on the basis of semiquantitative CT. Surgery-related complications of Grade  $\geq$  II according to the Clavien-Dindo classification were included in this study. **RESULTS:** Emphysema was present in 63 patients. The overall survival and relapse-free survival of the non-emphysema and emphysema groups at 5 years were 89.0 and 61.3% ( $P < 0.001$ ), respectively, and 81.0 and 51.7%, respectively ( $P < 0.001$ ). On multivariate analysis, significant prognostic factors were emphysema, higher smoking index, and higher histologic grade ( $p < 0.05$ ). Significant risk factors for poor recurrence-free survival were emphysema, higher smoking index, higher histologic grade, and presence of pleural invasion ( $P < 0.05$ ). Regarding Grade  $\geq$  II postoperative complications, pneumonia and supraventricular tachycardia were more frequent in the emphysema group than in the non-emphysema group ( $P = 0.003$  and  $P = 0.021$ , respectively). **CONCLUSION:** The presence of emphysema affects the long-term outcomes and the development of postoperative complications in early-stage lung cancer patients.

**[Preoperative thoracic muscle area on computed tomography predicts long-term survival following pneumonectomy for lung cancer.](#)** Troschel FM1, Kuklinski MW1, Knoll SJ2, Best TD1,3, Muniappan A2, Gaissert HA2, Fintelmann FJ1. *Interact Cardiovasc Thorac Surg.* 2019 Apr 1;28(4):542-549. doi: 10.1093/icvts/ivy280.

**OBJECTIVES:** To assess the prognostic role of thoracic muscle as quantified on preoperative computed tomography (CT) for the estimation of overall survival (OS) following pneumonectomy. **METHODS:** Muscle cross-sectional area (CSA) at the level of the fifth (T5) and eighth (T8) thoracic vertebra was measured on CT scans of consecutive patients with lung cancer prior to pneumonectomy. We stratified patients into high and low muscle groups using the gender-specific median of muscle CSA as separator and estimated associations of muscle CSA and OS using the Kaplan-Meier analysis. Multivariable logistic regression adjusted for body mass index, Charlson comorbidity index (includes age), forced expiratory volume in the first second as a % of predicted, sex, race, smoking status, tumour stage and prior lung cancer treatment was performed. **RESULTS:** A total of 128 patients were included ( $61.0 \pm 10.6$  years of age, mean body mass index of  $26.9 \text{ kg/m}^2$ , 55.5% men). The T8 level showed fewer artefacts and strong correlation with the T5 level (Pearson's  $\rho = 0.904$ ). T8 CSA was therefore used for subsequent analyses. Mean T8 CSA was  $118.5 \text{ cm}^2$  (median  $115.3 \text{ cm}^2$ ) in men and  $75.2 \text{ cm}^2$  (median  $74.0 \text{ cm}^2$ ) in women. During a median follow-up of 23.6 months (interquartile range 39.3), 65 patients (50.8%) died, of whom 41 were in the low muscle group. The Kaplan-Meier analysis showed significantly longer OS in the high muscle group (log-rank  $P = 0.02$ ). Multivariable analysis showed an independent association of muscle CSA and OS ( $P = 0.02$ ) with a hazard ratio of 0.80 (confidence interval 0.67-0.98) per  $10\text{-cm}^2$  increment. **CONCLUSIONS:** Thoracic muscle is independently associated with long-term overall survival following pneumonectomy for lung cancer and may contribute to refined survival estimates in this population.

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

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**[Efficacy and long-term survival of advanced lung adenocarcinoma patients with uncommon EGFR mutations treated with 1st generation EGFR-TKIs compared with chemotherapy as first-line therapy.](#)** Li H1, Wang C2, Wang Z1, et al. *Lung Cancer.* 2019 Apr;130:42-49. doi: 10.1016/j.lungcan.2019.02.001. Epub 2019 Feb 2.

**PURPOSE:** This study aims to understand the effects and long-term survival of 1st generation epithelial growth factor receptor tyrosine kinase inhibitors(EGFR-TKI)or platinum-based chemotherapy as first-line therapy in advanced lung adenocarcinoma patients with uncommon EGFR mutations. **PATIENTS AND**



**METHODS:** Specimens from 4276 advanced (IIIB/IV) patients were diagnosed with lung adenocarcinoma and underwent EGFR gene detection at the Affiliated Cancer Hospital of Zhengzhou University. The clinic characteristics, survival outcomes data, treatment outcomes and data of subsequent therapies after first-line treatment were collected of patients with uncommon EGFR mutations. The results were compared with common EGFR mutations. **RESULTS:** For patients with uncommon EGFR mutations, EGFR-TKIs or platinum-based chemotherapy as first-line therapy, showed no difference in objective response rate (ORR 33% vs 27.1% P = 0.499) and disease control rate (DCR 76.5% vs 87.5%, P = 0.194). EGFR-TKIs showed a superior progression-free survival than chemotherapy (median PFS, 7.2 vs 4.9 mt, HR = 0.604; P = 0.0088). Interestingly, compared with chemotherapy, we found that overall survival (median OS, 14.3 vs 20.7 mts, HR = 1.759; P = 0.0336) was significantly worse in patients with EGFR-TKIs. Multivariate analysis showed that extra metastases (HR = 2.240, P = 0.001) and smoking history (HR = 2.048, P = 0.013) were independent prognostic factors for OS in lung adenocarcinoma patients with EGFR uncommon mutations. **CONCLUSIONS:** Compared with chemotherapy, use of the 1st generation of EGFR-TKIs as first-line therapy can improve the short-term efficacy of patients with EGFR uncommon mutations advanced lung adenocarcinoma, but platinum-based chemotherapy showed a longer overall survival.

**[Low-Dose Apatinib Optimizes Tumor Microenvironment and Potentiates Antitumor Effect of PD-1/PD-L1 Blockade in Lung Cancer.](#)** Zhao S#1, Ren S#1, Jiang T#1, et al. Cancer Immunol Res. 2019 Apr;7(4):630-643. doi: 10.1158/2326-6066.CIR-17-0640. Epub 2019 Feb 12.

The lack of response to treatment in most lung cancer patients suggests the value of broadening the benefit of anti-PD-1/PD-L1 monotherapy. Judicious dosing of antiangiogenic agents such as apatinib (VEGFR2-TKI) can modulate the tumor immunosuppressive microenvironment, which contributes to resistance to anti-PD-1/PD-L1 treatment. We therefore hypothesized that inhibiting angiogenesis could enhance the therapeutic efficacy of PD-1/PD-L1 blockade. Here, using a syngeneic lung cancer mouse model, we demonstrated that low-dose apatinib alleviated hypoxia, increased infiltration of CD8+ T cells, reduced recruitment of tumor-associated macrophages in tumor and decreased TGF $\beta$  amounts in both tumor and serum. Combining low-dose apatinib with anti-PD-L1 significantly retarded tumor growth, reduced the number of metastases, and prolonged survival in mouse models. Anticancer activity was evident after coadministration of low-dose apatinib and anti-PD-1 in a small cohort of patients with pretreated advanced non-small cell lung cancer. Overall, our work shows the rationale for the treatment of lung cancer with a combination of PD-1/PD-L1 blockade and low-dose apatinib.

**[Application of time-dependent modeling for the exposure-efficacy analysis of ceritinib in untreated ALK-rearranged advanced NSCLC patients.](#)** Lau YY1, Gu W2, Ho YY2, Hong Y2, Zhang X2, Urban P3. Cancer Chemother Pharmacol. 2019 Apr 24. doi: 10.1007/s00280-019-03830-5. [Epub ahead of print]

**PURPOSE:** Ceritinib 750 mg/day was approved for the treatment of patients with untreated anaplastic lymphoma kinase (ALK)-rearranged non-small cell lung cancer (NSCLC) based on ASCEND-4 study. The objective of this article is to introduce the use of time-dependent modeling approach in the updated exposure-efficacy analysis of ceritinib for the first-line indication. **METHODS:** Exposure-efficacy analyses, including data from 156 patients, were first conducted using time-independent logistic regression model for response of complete or partial response and Cox regression model for progression-free survival (PFS). The exposure measure used was average C<sub>trough</sub>, which is defined as the geometric mean of all evaluable C<sub>trough</sub> for each patient. To further investigate the impact of exposure measure on exposure-efficacy analyses, a time-dependent modeling approach was used, where exposure at different time intervals was associated with the corresponding response endpoints in a longitudinal manner.

**RESULTS:** With exposure measure being average C<sub>trough</sub>, it was observed that higher exposure was associated with reduced efficacy in terms of response (odds ratio = 0.77) and PFS [hazard ratio

(HR) = 1.12]. These time-independent models do not account for the impact of time-varying concentration due to dose modifications. Subsequently, a new time-dependent modeling approach was used, where exposure and efficacy were associated longitudinally in the analyses. The results showed that the odds ratio of response became 1.07, and the HR of PFS became 1.04, indicating no apparent reverse relationship between exposure and efficacy across the exposure range studied. **CONCLUSION:** The drug effect on efficacy in clinical trials could be better characterized using time-dependent exposure-response models.

**Clinical features and outcomes of ALK rearranged non-small cell lung cancer with primary resistance to crizotinib.**

Ma D1, Zhang Y2, Xing P1, et al. Thorac Cancer. 2019 May;10(5):1213-1219. doi: 10.1111/1759-7714.13071. Epub 2019 Apr 16.

**BACKGROUND:** Crizotinib is associated with a favorable survival benefit in patients with ALK-positive non-small cell lung cancer (NSCLC); however, a subset of patients harboring ALK rearrangement shows a poor response. **METHODS:** We collected the clinical features and survival outcomes of 28 primary-resistant responders (PRR) with progression-free survival (PFS) of < 3 months on crizotinib and compared these with 78 long-term responders (LTR) that achieved > 24 months PFS (control). **RESULTS:** Primary resistance was observed in 6.5% of the patients. The median PFS of the PRR and LTR groups was 1.2 months (95% confidence interval [CI] 0.70-1.73) and 47.0 months (95% CI 34.39-59.64), respectively. A better Eastern Cooperative Oncology Group performance status score was significantly associated with longer PFS (odds ratio 0.06, 95% CI 0.01-0.33; P = 0.001). The median overall survival (OS) of the PRR group was 8.4 months (95% CI 3.47-13.42) and crizotinib as first-line treatment was an independent predictive factor for survival outcome (P = 0.005). Patients administered ALK-tyrosine kinase inhibitors after crizotinib progression had significantly longer survival than the PRR group treated with best supportive care (P = 0.007), but no significant difference was found between ALK-tyrosine kinase inhibitor treatment and single chemotherapy (P = 0.944). **CONCLUSION:** Patients with primary resistance to crizotinib displayed unfavorable survival outcomes and the underlying mechanism cannot be identified in clinical features. Nevertheless, next-generation ALK inhibitors and chemotherapy after crizotinib progression could confer a therapeutic and survival benefit in this population.

**Clinical analysis of EGFR-positive non-small cell lung cancer patients treated with first-line afatinib: A Nagano Lung Cancer Research Group.**

Sonehara K1, Kobayashi T2, Tateishi K1, et al. Thorac Cancer. 2019 May;10(5):1078-1085. doi: 10.1111/1759-7714.13047. Epub 2019 Apr 20.

**BACKGROUND:** In the LUX-Lung 3 and LUX-Lung 6 trials, afatinib improved overall survival in previously untreated patients with EGFR 19del mutated non-small cell lung cancer (NSCLC) compared to chemotherapy. The appropriate management of adverse events and dose reduction of afatinib are important for EGFR-positive NSCLC patients. We conducted a retrospective and observational study of patients treated with first-line afatinib for EGFR-positive NSCLC in Nagano prefecture, Japan, focusing on efficacy and toxicities. **METHODS:** We retrospectively collected the medical records of NSCLC patients initially treated with afatinib between May 2014 and March 2018. **RESULTS:** A total of 62 patients with a median age of 67 years and a median body surface area (BSA) of 1.57 m<sup>2</sup> were included. The overall response rate was 87.7% and median progression-free survival (PFS) was 15.7 months. The median PFS was similar between standard initial dose (40 mg) and reduced initial doses (30 and 20 mg) (15.7 vs. 14.2 months; P = 0.978). The frequency of dose reduction and the discontinuation rate in the 40 mg daily dose group was higher in patients with BSA < 1.58 m<sup>2</sup> (100%) compared to BSA ≥ 1.58 m<sup>2</sup> (68.2%) (P = 0.014). The frequency of diarrhea was higher in patients with BSA < 1.58 m<sup>2</sup> (93.5%) compared to BSA ≥ 1.58 m<sup>2</sup> (71.0%) (P = 0.02). **CONCLUSION:** In real-world clinical practice, first-

line afatinib was well managed and was equally as effective as in previous clinical trials of EGFR-positive NSCLC. BSA is considered a predictive marker for appropriate afatinib dose reduction.

**Exceptional responders with invasive mucinous adenocarcinomas: a phase 2 trial of bortezomib in patients with KRAS G12D-mutant lung cancers.** Drilon A#1,2, Schoenfeld AJ#1, Arbour KC1, et al. Cold Spring Harb Mol Case Stud. 2019 Apr 1;5(2). pii: a003665. doi: 10.1101/mcs.a003665. Print 2019 Apr.

KRAS G12D-mutant/p53-deficient non-small-cell lung cancer (NSCLC) models are dependent on the NF- $\kappa$ B pathway that can be down-regulated by the proteasome inhibitor bortezomib. Two exceptional responders were observed on prior clinical trials of bortezomib, both of whom had KRAS G12D-mutant NSCLC, prompting the initiation of this single-center phase 2 trial. Patients with advanced KRAS G12D-mutant NSCLC were eligible. Bortezomib was administered at 1.3 mg/m<sup>2</sup> subcutaneously (days 1, 4, 8, 11; 21-d cycle) until progression or unacceptable toxicity. The primary objective was best objective response (RECIST v1.1). Sixteen patients with KRAS G12D-mutant lung adenocarcinomas were treated. Patients had a median pack year smoking history of 4 (range 0-45). A partial response (PR) was observed in one patient (-66% from baseline) and stable disease in five patients on the first stage of this study (overall response rate of 6%, 95% CI: 0.2-30.2), and further patients were not accrued. The median progression-free survival was 1 mo (95% CI: 1-6). The median overall survival was 13 mo (95% CI: 6-NA). The most common treatment-related adverse events were fatigue (38%) and diarrhea (26%). TP53 status did not predict response on exploratory testing. Of note, the patient with a PR had a unique subtype of lung adenocarcinoma-invasive mucinous adenocarcinomas (IMA)-and had rapid clinical improvement and substantial disease regression, which was also previously observed in two other patients with advanced KRAS G12D-mutant lung cancer with IMAs who received bortezomib on separate clinical trials. Exceptional responses to bortezomib can be achieved in KRAS G12D-mutant NSCLCs. KRAS G12D mutation alone, however, is not a robust predictor of response. Further evaluation should only be performed after further elucidation of other factors such as co-occurring alterations and histologic subtype such as IMA that may predict sensitivity to therapy.

**Peripheral Blood Markers Identify Risk of Immune-Related Toxicity in Advanced Non-Small Cell Lung Cancer Treated with Immune-Checkpoint Inhibitors.** Pavan A1,2, Calvetti L3, Dal Maso A1,2, et al. Oncologist. 2019 Apr 23. pii: theoncologist.2018-0563. doi: 10.1634/theoncologist.2018-0563. [Epub ahead of print]

**BACKGROUND:** Immune-checkpoint inhibitors (ICIs) are now standard of care for advanced non-small cell lung cancer (NSCLC). Unfortunately, many patients experience immune-related adverse events (irAEs), which are usually mild and reversible, but they require timely management and may be life threatening. No predictive markers of irAEs are available. **MATERIALS AND METHODS:** The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were evaluated in patients with NSCLC consecutively treated with ICIs. Prespecified cutoff values of NLR and PLR were used and related to outcome and onset of irAEs. A control group of patients with advanced NSCLC not receiving ICIs was included. **RESULTS:** The study included 184 patients: 26 (14.1%) received pembrolizumab upfront, and 142 (77%) received ICIs (pembrolizumab, nivolumab or atezolizumab) after one or more lines of chemotherapy. The median number of ICIs cycles was six (range, 1-61). The median progression-free survival and overall survival were 4.8 (95% CI, 3.4-6.3) and 20.6 (95% CI, 14.7-26.5) months, respectively. Sixty patients (32.6%) developed irAEs, mainly grade 1-2 (65.0%), causing ICI interruption in 46 cases (25.0%). Low NLR and low PLR at baseline were significantly associated with the development of irAEs (odds ratio [OR], 2.2; p = .018 and OR, 2.8; p = .003, respectively). Multivariate analyses confirmed PLR as independent predictive marker of irAEs (OR, 2.3; p = .020). **CONCLUSION:**

NLR and PLR may predict the appearance of irAEs in non-oncogene-addicted aNSCLC, although this conclusion warrants prospective validation. **IMPLICATIONS FOR PRACTICE:** This study was designed to investigate the role of blood biomarkers in predicting the occurrence of immune-related adverse events (irAEs) in patients with advanced non-small cell lung cancer receiving immunotherapy. The results of the study suggest a potential predictive role of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as markers for irAE development in this category of patients. These data provide rationale for an easy and feasible application to be validated in clinical practice.

**[Comparison of a combination of chemotherapy and immune checkpoint inhibitors and immune checkpoint inhibitors alone for the treatment of advanced and metastatic non-small cell lung cancer.](#)** Kuo CS<sup>1,2</sup>, Wang CC<sup>3</sup>, Huang YC<sup>4</sup>, et al. Thorac Cancer. 2019 May;10(5):1158-1166. doi: 10.1111/1759-7714.13057. Epub 2019 Apr 5.

**BACKGROUND:** Single agent immune checkpoint inhibitors (ICIs) improve survival outcomes compared to chemotherapy for advanced non-small cell lung cancer (NSCLC), but treatment efficacy widely varies. The combination of ICIs with chemotherapy has shown promising efficacy over chemotherapy alone; however, whether this strategy is superior to single agent ICIs for the treatment of advanced NSCLC remains unknown. **METHODS:** The records of 109 patients with advanced NSCLC who were administered at least one cycle of ICIs were retrospectively reviewed. Patients were grouped based on the presence or absence of a chemotherapy treatment combination. Efficacy and survival outcomes were analyzed. **RESULT:** Sixty-nine (58.0%) patients received single agent ICIs (ICI group) and 50 (42.0%) received ICIs and chemotherapy (ICC group). The median (3.2 vs. 3.0 months;  $P = 0.025$ ) and one-year (34.5 vs. 9.6%;  $P = 0.026$ ) progression-free survival (PFS) rates were significantly better in the ICC than in the ICI group. The superior efficacy of ICC remained in the propensity score matched pairs (median PFS 3.2 vs. 2.6 months,  $P = 0.032$ ; 1-year PFS 35.2 vs. 7.6%;  $P = 0.035$ ). Eastern Cooperative Oncology Group performance status 0-1 (HR 0.37, 95% CI 0.22-0.62;  $P < 0.001$ ) and the ICC group (HR 0.56, 95% CI 0.34-0.94;  $P = 0.028$ ) were predictive of PFS. Subgroup-to-chemotherapy interaction revealed improved risk reduction for adenocarcinoma and EGFR mutation. **CONCLUSION:** Combining chemotherapy with ICIs improved treatment efficacy over ICIs alone. The additional efficacy of chemotherapy may differ between histological subtypes and EGFR mutation status.

**[Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer \(KEYNOTE-042\): a randomised, open-label, controlled, phase 3 trial.](#)** Mok TSK<sup>1</sup>, Wu YL<sup>2</sup>, Kudaba I<sup>3</sup>, et al. Lancet. 2019 May 4;393(10183):1819-1830. doi: 10.1016/S0140-6736(18)32409-7. Epub 2019 Apr 4.

**BACKGROUND:** First-line pembrolizumab monotherapy improves overall and progression-free survival in patients with untreated metastatic non-small-cell lung cancer with a programmed death ligand 1 (PD-L1) tumour proportion score (TPS) of 50% or greater. We investigated overall survival after treatment with pembrolizumab monotherapy in patients with a PD-L1 TPS of 1% or greater. **METHODS:** This randomised, open-label, phase 3 study was done in 213 medical centres in 32 countries. Eligible patients were adults ( $\geq 18$  years) with previously untreated locally advanced or metastatic non-small-cell lung cancer without a sensitising EGFR mutation or ALK translocation and with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, life expectancy 3 months or longer, and a PD-L1 TPS of 1% or greater. Randomisation was computer generated, accessed via an interactive voice-response and integrated web-response system, and stratified by region of enrolment (east Asia vs rest of world), ECOG performance status score (0 vs 1), histology (squamous vs non-squamous), and PD-L1 TPS ( $\geq 50\%$  vs 1-49%). Enrolled patients were randomly assigned 1:1 in blocks of four per stratum to receive pembrolizumab 200 mg every 3 weeks for up to 35 cycles or the investigator's choice of platinum-based chemotherapy for four to six cycles. Primary endpoints were

overall survival in patients with a TPS of 50% or greater, 20% or greater, and 1% or greater (one-sided significance thresholds,  $p=0.0122$ ,  $p=0.0120$ , and  $p=0.0124$ , respectively) in the intention-to-treat population, assessed sequentially if the previous findings were significant. This study is registered at ClinicalTrials.gov, number NCT02220894. **FINDINGS:** From Dec 19, 2014, to March 6, 2017, 1274 patients (902 men, 372 women, median age 63 years [IQR 57-69]) with a PD-L1 TPS of 1% or greater were allocated to pembrolizumab ( $n=637$ ) or chemotherapy ( $n=637$ ) and included in the intention-to-treat population. 599 (47%) had a TPS of 50% or greater and 818 patients (64%) had a TPS of 20% or greater. As of Feb 26, 2018, median follow-up was 12.8 months. Overall survival was significantly longer in the pembrolizumab group than in the chemotherapy group in all three TPS populations ( $\geq 50\%$  hazard ratio 0.69, 95% CI 0.56-0.85,  $p=0.0003$ ;  $\geq 20\%$  0.77, 0.64-0.92,  $p=0.0020$ , and  $\geq 1\%$  0.81, 0.71-0.93,  $p=0.0018$ ). The median survival values by TPS population were 20.0 months (95% CI 15.4-24.9) for pembrolizumab versus 12.2 months (10.4-14.2) for chemotherapy, 17.7 months (15.3-22.1) versus 13.0 months (11.6-15.3), and 16.7 months (13.9-19.7) versus 12.1 months (11.3-13.3), respectively. Treatment-related adverse events of grade 3 or worse occurred in 113 (18%) of 636 treated patients in the pembrolizumab group and in 252 (41%) of 615 in the chemotherapy group and led to death in 13 (2%) and 14 (2%) patients, respectively. **INTERPRETATION:** The benefit-to-risk profile suggests that pembrolizumab monotherapy can be extended as first-line therapy to patients with locally advanced or metastatic non-small-cell lung cancer without sensitising EGFR or ALK alterations and with low PD-L1 TPS.

[Malignant pleural effusion as a predictor of the efficacy of anti-PD-1 antibody in patients with non-small cell lung cancer.](#) Shibaki R1, Murakami S1, Shinno Y1, et al. Thorac Cancer. 2019 Apr;10(4):815-822. doi: 10.1111/1759-7714.13004. Epub 2019 Feb 14.

**BACKGROUND:** The aim of this study was to evaluate the usefulness of the presence of malignant pleural effusion (MPE) as a negative predictor of anti-PD-1 antibody efficacy. **METHODS:** A retrospective review of patients with advanced or recurrent non-small cell lung cancer treated with an anti-PD-1 antibody between December 2015 and March 2018 at the National Cancer Center Hospital, Japan, was conducted. Progression-free survival (PFS) and overall survival (OS) were compared between patients with and without MPE. Additional survival analysis according to PD-L1 expression status was conducted. Univariate and multivariate analyses were performed. **RESULTS:** A total of 252 patients were identified before the commencement of anti-PD-1 antibody treatment: 33 with MPE and 219 without MPE. PFS and OS were significantly shorter in patients with MPE than in patients without MPE (median PFS 3.0 vs. 5.8 months, hazard ratio [HR] 1.7,  $P = 0.014$ ; median OS 7.9 vs. 15.8 months, HR 2.1,  $P = 0.001$ ). In patients with PD-L1 expression in  $\geq 1\%$  of their tumor cells, the PFS of patients with MPE was significantly shorter than of patients without MPE (median PFS 3.1 vs. 6.5 months, HR 2.0, 95% confidence interval 1.0-3.5;  $P = 0.021$ ). The presence of MPE was independently associated with a shorter PFS and OS in multivariate analysis. **CONCLUSION:** The presence of MPE in patients administered an anti-PD-1 antibody is associated with shorter PFS and OS, regardless of the presence of PD-L1 expression  $\geq 1\%$  of tumor cells.

[Cannabis Impacts Tumor Response Rate to Nivolumab in Patients with Advanced Malignancies.](#)

Taha T1, Meiri D2,3, Talhamy S3, Wollner M1, Peer A1, Bar-Sela G4,3. Oncologist. 2019 Apr;24(4):549-554. doi: 10.1634/theoncologist.2018-0383. Epub 2019 Jan 22.

**BACKGROUND:** There has been a significant increase in the use of immunotherapy and cannabis recently, two modalities that have immunomodulatory effects and may have possible interaction. We evaluated the influence of cannabis use during immunotherapy treatment on response rate (RR), progression-free survival (PFS), and overall survival (OS). **SUBJECTS, MATERIALS, AND METHODS:** In this retrospective, observational study, data were collected from the files of patients

treated with nivolumab in the years 2015-2016 at our hospital, and cannabis from six cannabis-supplying companies. Included were 140 patients (89 nivolumab alone, 51 nivolumab plus cannabis) with advanced melanoma, non-small cell lung cancer, and renal clear cell carcinoma. The groups were homogenous regarding demographic and disease characteristics. A comparison between the two arms was made.

**RESULTS:** In a multivariate model, cannabis was the only significant factor that reduced RR to immunotherapy (37.5% RR in nivolumab alone compared with 15.9% in the nivolumab-cannabis group ( $p = .016$ , odds ratio = 3.13, 95% confidence interval 1.24-8.1). Cannabis use was not a significant factor for PFS or OS. Factors affecting PFS and OS were smoking (adjusted hazard ratio [HR] = 2.41 and 2.41, respectively) (and brain metastases (adjusted HR = 2.04 and 2.83, respectively). Low performance status (adjusted HR = 2.83) affected OS alone. Tetrahydrocannabinol and cannabidiol percentages did not affect RR in any group ( $p = .393$  and  $.116$ , respectively). **CONCLUSION:** In this retrospective analysis, the use of cannabis during immunotherapy treatment decreased RR, without affecting PFS or OS and without relation to cannabis composition. Considering the limitations of the study, further prospective clinical study is needed to investigate possible interaction. **IMPLICATIONS FOR PRACTICE:** Although the data are retrospective and a relation to cannabis composition was not detected, this information can be critical for cannabis users and indicates that caution is required when starting immunotherapy.

[Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer \(NSCLC\): updated results, including overall survival, from PROFILE 1001.](#) Shaw AT1, Riely GJ2, Bang YJ3, et al. *Ann Oncol.* 2019 Apr 13. pii: mdz131. doi: 10.1093/annonc/mdz131. [Epub ahead of print]

**BACKGROUND:** In the ongoing phase 1 PROFILE 1001 study, crizotinib showed antitumor activity in patients with ROS1-rearranged advanced non-small-cell lung cancer (NSCLC). Here, we present updated antitumor activity, overall survival (OS) and safety data (additional 46.2 months follow-up) for patients with ROS1-rearranged advanced NSCLC from PROFILE 1001. **PATIENTS AND METHODS:** ROS1 status was determined by fluorescence in situ hybridization or reverse transcriptase-polymerase chain reaction. All patients received crizotinib at a starting dose of 250 mg twice daily. **RESULTS:** Fifty-three patients received crizotinib, with a median duration of treatment of 22.4 months. At data cut-off, treatment was ongoing in 12 patients (23%). The objective response rate (ORR) was 72% (95% CI, 58-83), including 6 confirmed complete responses and 32 confirmed partial responses; 10 patients had stable disease. Responses were durable (median duration of response 24.7 months; 95% CI, 15.2-45.3). ORRs were consistent across different patient subgroups. Median progression-free survival was 19.3 months (95% CI, 15.2-39.1). A total of 26 deaths (49%) occurred (median follow-up period of 62.6 months), and of the remaining 27 patients (51%), 14 (26%) were in follow-up at data cut-off. Median OS was 51.4 months (95% CI, 29.3-not reached) and survival probabilities at 12, 24, 36, and 48 months were 79%, 67%, 53%, and 51%, respectively. No correlation was observed between overall survival and specific ROS1 fusion partner. Treatment-related adverse events (TRAEs) were mainly grade 1 or 2. There were no grade  $\geq 4$  TRAEs and no TRAEs associated with permanent discontinuation. No new safety signals were reported with long-term crizotinib treatment. **CONCLUSIONS:** These findings serve as a new benchmark for OS in ROS1-rearranged advanced NSCLC, and continue to show the clinically meaningful benefit and safety of crizotinib in this molecular subgroup.

[Safety and efficacy of crizotinib in patients with advanced or metastatic ROS1-rearranged lung cancer \(EUCROSS\): A European phase 2 clinical trial.](#) Michels S1, Massutí B2, Schildhaus HU3, et al. *J Thorac Oncol.* 2019 Apr 9. pii: S1556-0864(19)30276-X. doi: 10.1016/j.jtho.2019.03.020. [Epub ahead of print]

**INTRODUCTION:** ROS1 rearrangements are found in 1% of lung cancer patients. Therapeutic efficacy of crizotinib in this subset has been demonstrated in early phase trials in the US and East Asia. Here we present data on efficacy and safety of a prospective phase 2 trial evaluating crizotinib in European ROS1-

positive patients (EUCROSS). **PATIENTS AND METHODS:** Trial design: multi-centre, single arm phase 2 trial (Clinicaltrial.gov identifier: NCT02183870). Key eligibility criteria:  $\geq 18$  years of age, advanced/metastatic lung cancer, centrally confirmed ROS1-rearranged (fluorescence-in situ hybridisation). **TREATMENT:** 250 mg crizotinib twice daily. Primary endpoint: investigator-assessed objective response rate (ORR, Response Evaluation Criteria in Solid Tumors, version 1.1). Key secondary endpoints: progression-free survival (PFS), overall survival, efficacy by independent radiologic review (IRR), safety, health-related quality of life, molecular characterization of tumour tissue. **RESULTS:** Thirty-four patients received treatment. Four patients were excluded from efficacy analysis. Investigator ORR was 70% (95% CI, 51-85; 21 of 30 patients) and median PFS was 20.0 months (95% CI, 10.1-not reached). Two patients with ROS1 wild-type sequences assessed by DNA sequencing had progression as best response. CD74-ROS1-positive patients had a trend towards a higher ORR and longer median PFS. TP53-co-mutant patients had a significantly shorter median PFS than wild-type patients (7.0 months, 95% CI, 1.7-20.0 vs 24.1 months, 95% CI, 10.1-not reached;  $P=0.022$ ). Treatment-related adverse events were documented in 33 of 34 patients (97%). **CONCLUSION:** Crizotinib is highly effective and safe in ROS1-rearranged lung cancer patients. ROS1-/TP53-co-aberrant patients had a significantly worse outcome compared to TP53 wild-type patients.

[Analysis of resistance mechanisms to abivertinib, a third-generation EGFR tyrosine kinase inhibitor, in patients with EGFR T790M-positive non-small cell lung cancer from a phase I trial.](#)

Zhang YC1, Chen ZH1, Zhang XC1, et al. EBioMedicine. 2019 Apr 23. pii: S2352-3964(19)30269-5. doi: 10.1016/j.ebiom.2019.04.030. [Epub ahead of print]

**BACKGROUND:** Resistance to third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) presents a major clinical challenge in advanced non-small cell lung cancer (NSCLC). Here, we report resistance mechanisms to abivertinib, a novel third-generation EGFR TKI, from a phase I dose-escalation/expansion study (NCT02330367). **METHODS:** Patients with EGFR T790M-positive advanced NSCLC and progression on prior EGFR TKIs received abivertinib in dose escalation (50-350 mg twice daily [BID]) or expansion (300 mg BID) cohorts. Patients enrolled at Guangdong Lung Cancer Institute who underwent next-generation sequencing (NGS)-based genomic profiling upon abivertinib progression (prior to October 30, 2018) were enrolled in this exploratory analysis. **FINDINGS:** Thirty of 73 patients enrolled were eligible for resistance analysis. Upon abivertinib progression, 27 patients provided plasma samples (six patients also provided paired samples from the progression sites) and three patients only provided tissue samples from the progression sites for NGS. A heterogeneous landscape of resistance to abivertinib was observed: 15% (4/27) experienced EGFR T790M loss and 13% (4/30) developing EGFR tertiary mutations including C797S. EGFR amplification was observed in 11 patients (37%), and considered a putative resistance mechanism in seven (23%) patients. Other EGFR-independent resistance mechanisms involved CDKN2A, MET, PIK3CA, HER2, TP53, Rb1 and small-cell lung cancer transformation. **INTERPRETATION:** Our findings reveal a heterogeneous pattern of resistance mechanisms to abivertinib which is distinct from that previously reported with osimertinib. EGFR amplification was the most common resistance mechanism in this cohort. **FUND:** The National Key R&D Program of China (Grant No. 2016YFC1303800), Key Lab System Project of Guangdong Science and Technology Department - Guangdong Provincial Key Lab of Translational Medicine in Lung Cancer (Grant No. 2012A061400006/2017B030314120).

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## NSCLC - RADIOTHERAPY

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[Fiducial marker placement with electromagnetic navigation bronchoscopy: a subgroup analysis of the prospective, multicenter NAVIGATE study.](#) Bowling MR1, Folch EE2, Khandhar SJ3, et al. Ther Adv Respir Dis. 2019 Jan-Dec;13:1753466619841234. doi: 10.1177/1753466619841234.

**BACKGROUND:** Fiducial markers (FMs) help direct stereotactic body radiation therapy (SBRT) and localization for surgical resection in lung cancer management. We report the safety, accuracy, and practice patterns of FM placement utilizing electromagnetic navigation bronchoscopy (ENB).

**METHODS:** NAVIGATE is a global, prospective, multicenter, observational cohort study of ENB using the superDimension™ navigation system. This prospectively collected subgroup analysis presents the patient demographics, procedural characteristics, and 1-month outcomes in patients undergoing ENB-guided FM placement. Follow up through 24 months is ongoing. **RESULTS:** Two-hundred fifty-eight patients from 21 centers in the United States were included. General anesthesia was used in 68.2%. Lesion location was confirmed by radial endobronchial ultrasound in 34.5% of procedures. The median ENB procedure time was 31.0 min. Concurrent lung lesion biopsy was conducted in 82.6% (213/258) of patients. A mean of  $2.2 \pm 1.7$  FMs (median 1.0 FMs) were placed per patient and 99.2% were accurately positioned based on subjective operator assessment. Follow-up imaging showed that 94.1% (239/254) of markers remained in place. The procedure-related pneumothorax rate was 5.4% (14/258) overall and 3.1% (8/258) grade  $\geq 2$  based on the Common Terminology Criteria for Adverse Events scale. The procedure-related grade  $\geq 4$  respiratory failure rate was 1.6% (4/258). There were no bronchopulmonary hemorrhages. **CONCLUSION:** ENB is an accurate and versatile tool to place FMs for SBRT and localization for surgical resection with low complication rates. The ability to perform a biopsy safely in the same procedure can also increase efficiency. The impact of practice pattern variations on therapeutic effectiveness requires further study.

[Radiotherapy for oligometastatic tumor improved the prognosis of patients with non-small cell lung cancer \(NSCLC\).](#) Gong HY1, Wang Y1, Han G1, Song QB1. Thorac Cancer. 2019 May;10(5):1136-1140. doi: 10.1111/1759-7714.13054. Epub 2019 Apr 7.

**BACKGROUND:** This study was conducted to investigate if radiotherapy improved the overall survival (OS) of patients with oligometastatic non-small cell lung cancer (NSCLC). **METHODS:** From January 2012 to August 2015, 323 NSCLC patients with distant metastasis were administered radiotherapy. Ninety-five patients with oligometastatic NSCLC who were sensitive to the initial chemotherapy were treated with radiotherapy for the residual lesions. Initial treatment consisted of four to six cycles of induction chemotherapy. If the patients responded to the initial treatment without developing new metastases, the residual sites were radiated at a total dose of 56-66 Gy, including the primary and metastatic sites. OS, progression-free survival, and sites of progression were assessed. The Kaplan-Meier method was used to estimate the OS and progression-free survival probabilities. **RESULTS:** The median survival of the whole cohort was 15 months (95% confidence interval 6-40) and the median time to progression was 11 months (95% confidence interval 4-24). Sixty-seven patients had died by the end of follow-up. The one-year and two-year OS rates were 58% and 23%, respectively. Patients progressed either with brain (n = 14), bone (n = 11), lung (n = 10), liver (n = 7), adrenal gland (n = 5), or seven other sites of metastases (n = 3). Acute grade III esophageal toxicity was observed in 17 patients (18%) and grade III pulmonary toxicity in seven patients (7%). **CONCLUSION:** Oligometastatic non-progressive NSCLC patients may benefit from aggressive radiotherapy to the residual lesions with acceptable toxicity after systemic chemotherapy.

[Stereotactic body radiation therapy with higher biologically effective dose is associated with improved survival in stage II non-small cell lung cancer.](#) Yan SX1, Qureshi MM2, Dyer M2, Truong MT2, Mak KS3. Lung Cancer. 2019 May;131:147-153. doi: 10.1016/j.lungcan.2019.03.031. Epub 2019 Apr 1.

**OBJECTIVES:** The role of stereotactic body radiation therapy (SBRT) in treating stage II non-small cell lung cancer (NSCLC) remains unclear. This study evaluates SBRT dose prescription patterns and survival outcomes in Stage II NSCLC using the National Cancer Database (NCDB). **MATERIALS AND**



**METHODS:** Patients diagnosed with Stage II NSCLC and treated with SBRT between 2004-2013 were identified in NCDB. The biologically effective dose with  $\alpha/\beta = 10$  Gy (BED10) was calculated. Overall survival (OS) was analyzed using the Kaplan-Meier method and Cox regression models. **RESULTS:** Of 56,543 patients with Stage II NSCLC, 451 (0.8%) received SBRT. There were 360 patients (79.8%) with node-negative and 91 patients (20.2%) with node-positive disease. The most common prescriptions were 10 Gy x 5 (35.9%) and 12 Gy x 4 (19.3%). The mean and median BED10 were 114.9 Gy and 105.6 Gy, respectively. With median follow-up of 19.3 months, overall median survival was 23.7 months. Median survival was 22.4 months for those treated with BED10 < 114.9 Gy versus 31.5 months for BED10  $\geq$  114.9 Gy ( $p = 0.036$ ). On multivariate analysis, BED10 as a continuous variable (hazard ratio [HR] 0.991,  $p = 0.009$ ) and  $\geq 114.9$  Gy (HR 0.63,  $p = 0.015$ ) were associated with improved survival in node-negative patients. BED10 as a continuous variable (HR 0.997,  $p = 0.465$ ) and  $\geq 114.9$  Gy (HR 0.81,  $p = 0.546$ ) were not significant factors for predicting survival in node-positive patients. **CONCLUSION:** SBRT is infrequently utilized to treat Stage II NSCLC in the United States. Treatment with higher BED10 was associated with improved survival, and the benefit was limited to patients with node-negative disease.

[Comparative effectiveness of intensity modulated radiation therapy to 3-dimensional conformal radiation in locally advanced lung cancer: pathological and clinical outcomes.](#) Appel S1, Bar J2,3, Ben-Nun A3,4, et al. Br J Radiol. 2019 May;92(1097):20180960. doi: 10.1259/bjr.20180960. Epub 2019 Apr 1.

**OBJECTIVE:** Intensity-modulated radiotherapy (IMRT) has better normal-tissue sparing compared with 3-dimensional conformal radiation (3DCRT). We sought to assess the impact of radiation technique on pathological and clinical outcomes in locally advanced non-small cell lung cancer (LANSCCL) treated with a trimodality strategy. **METHODS:** Retrospective review of LANSCCL patients treated from August 2012 to August 2018 at Sheba Medical Center, Israel. The trimodality strategy consisted of concomitant chemoradiation to 60 Gray (Gy) followed by completion surgery. The planning target volume (PTV) was defined by co-registered PET/CT. Here we compare the pathological regression, surgical margin status, local control rates (LC), disease free (DFS) and overall survival (OS) between 3DCRT and IMRT. **RESULTS:** Our cohort consisted of 74 patients with mean age 62.9 years, male in 51/74 (69%), adenocarcinoma in 46/74 (62.1%), stage 3 in 59/74 (79.7%) and chemotherapy in 72/74 (97.3%). Radiation mean dose: 59.2 Gy (SD  $\pm$  3.8). Radiation technique : 3DCRT in 51/74 (68.9%), IMRT in 23/74 (31%). Other variables were similar between groups. Major pathological response (including pathological complete response or less than 10% residual tumor cells) was similar: 32/51 (62.7%) in 3DCRT and 15/23 (65.2%) in IMRT,  $p=0.83$ . Pathological complete response (pCR) rates were similar: 17/51 (33.3%) in 3DCRT and 8/23 (34.8%) in IMRT,  $p=0.9$ . Surgical margins were negative in 46/51 (90.1%) in 3DCRT vs. 17/19 (89.4%) in IMRT ( $p=1.0$ ). The 2-year LC rates were 81.6% (95% CI 69-89.4%); DFS 58.3% (95% CI 45.5-69%) and 3-year OS 70% (95% CI 57-80%). Comparing radiation techniques, there were no significant differences in LC ( $p=0.94$ ), DFS ( $p=0.33$ ) and OS ( $p=0.72$ ). **CONCLUSION:** When used to treat LANSCCL in the neoadjuvant setting, both IMRT and 3DCRT produce comparable pathological and clinical outcomes.

[Use of Crowd Innovation to Develop an Artificial Intelligence-Based Solution for Radiation Therapy Targeting.](#) Mak RH1, Endres MG2,3, Paik JH2,4, et al. JAMA Oncol. 2019 Apr 18. doi: 10.1001/jamaoncol.2019.0159. [Epub ahead of print]

**IMPORTANCE:** Radiation therapy (RT) is a critical cancer treatment, but the existing radiation oncologist work force does not meet growing global demand. One key physician task in RT planning involves tumor segmentation for targeting, which requires substantial training and is subject to significant interobserver variation. **OBJECTIVE:** To determine whether crowd innovation could be used to rapidly produce artificial intelligence (AI) solutions that replicate the accuracy of an expert radiation oncologist in

segmenting lung tumors for RT targeting. **DESIGN, SETTING, AND PARTICIPANTS:** We conducted a 10-week, prize-based, online, 3-phase challenge (prizes totaled \$55 000). A well-curated data set, including computed tomographic (CT) scans and lung tumor segmentations generated by an expert for clinical care, was used for the contest (CT scans from 461 patients; median 157 images per scan; 77 942 images in total; 8144 images with tumor present). Contestants were provided a training set of 229 CT scans with accompanying expert contours to develop their algorithms and given feedback on their performance throughout the contest, including from the expert clinician. **MAIN OUTCOMES AND MEASURES:** The AI algorithms generated by contestants were automatically scored on an independent data set that was withheld from contestants, and performance ranked using quantitative metrics that evaluated overlap of each algorithm's automated segmentations with the expert's segmentations. Performance was further benchmarked against human expert interobserver and intraobserver variation. **RESULTS:** A total of 564 contestants from 62 countries registered for this challenge, and 34 (6%) submitted algorithms. The automated segmentations produced by the top 5 AI algorithms, when combined using an ensemble model, had an accuracy (Dice coefficient = 0.79) that was within the benchmark of mean interobserver variation measured between 6 human experts. For phase 1, the top 7 algorithms had average custom segmentation scores (S scores) on the holdout data set ranging from 0.15 to 0.38, and suboptimal performance using relative measures of error. The average S scores for phase 2 increased to 0.53 to 0.57, with a similar improvement in other performance metrics. In phase 3, performance of the top algorithm increased by an additional 9%. Combining the top 5 algorithms from phase 2 and phase 3 using an ensemble model, yielded an additional 9% to 12% improvement in performance with a final S score reaching 0.68. **CONCLUSIONS AND RELEVANCE:** A combined crowd innovation and AI approach rapidly produced automated algorithms that replicated the skills of a highly trained physician for a critical task in radiation therapy. These AI algorithms could improve cancer care globally by transferring the skills of expert clinicians to under-resourced health care settings.

[Clinical outcomes after intensity-modulated proton therapy with concurrent chemotherapy for inoperable non-small cell lung cancer.](#) Elhammali A1, Blanchard P2, Yoder A1, Liao Z1, Zhang X3, Ronald Zhu X3, Allen PK1, Jeter M1, Welsh J1, Nguyen QN4. *Radiother Oncol.* 2019 Apr 17;136:136-142. doi: 10.1016/j.radonc.2019.03.029. [Epub ahead of print]

**BACKGROUND & PURPOSE:** We report disease control, survival, and toxicity in patients with advanced inoperable non-small cell lung cancer (NSCLC) receiving concurrent chemotherapy and intensity-modulated proton therapy (IMPT) at a single institution. **MATERIAL AND METHODS:** All patients were treated with IMPT with concurrent chemotherapy. Endpoints assessed were local, regional, and distant control, disease-free survival (DFS), and overall survival (OS). **RESULTS:** Fifty-one patients were enrolled with a median follow-up time of 23.0 months; 39 (76%) were treated with a simultaneous integrated boost to the gross tumor volume (GTV). The median GTV dose was 67.3 CGE and the median CTV dose was 60.0 CGE. Median OS and DFS times were 33.9 months and 12.6 months. The 3-year local control rate was 78.3%. Treatment was well tolerated, with a grade 3 toxicity rate of 18% (9 events: 4 esophagitis, 3 dermatitis, 1 esophageal stricture, and 1 fatigue) and no grade 4 or 5 toxicity. The most common grade 2 toxic effects were esophagitis (22 [43%]), dermatitis (16 [31%]), pain (15 [29%]), and fatigue (14 [27%]). **CONCLUSIONS:** Treatment of inoperable NSCLC with IMPT and concurrent chemotherapy achieves excellent disease control with tolerable toxicity.

[Re-irradiation in locally recurrent lung cancer patients.](#) Schlampff I1,2,3, Rieber J4,5,6, Adeberg S4,5,6, et al. *Strahlenther Onkol.* 2019 Apr 1. doi: 10.1007/s00066-019-01457-2. [Epub ahead of print]

**PURPOSE:** Lung cancer remains one of the tumour diagnoses with high lethality, although innovative treatment approaches have yielded improvements in local control and survival rates. There is still no consensus on how to treat local relapse in patients after first-line treatments. Radiotherapy may be

considered in this situation; however, data supporting its effectiveness are rare. The purpose of this retrospective analysis was to evaluate outcomes of patients re-irradiated for thoracic tumours in terms of overall survival (OS), local progression-free survival (LPFS), toxicity and dose-volume parameters. **PATIENTS AND METHODS:** Sixty-two patients with locally recurrent previously irradiated lung cancer were analysed retrospectively (NSCLC n = 52, SCLC n = 10). Target volumes both in lung and mediastinum were re-irradiated with conventional three-dimensional or intensity-modulated radiotherapy techniques. Median overall dose of re-irradiation was 38.5 Gy (range 20-60 Gy) with a median single dose per fraction of 2 Gy (1.8-3.0 Gy). Clinical documents and treatment plans were evaluated. **RESULTS:** Median follow-up was 8.2 months (range 0-27 months). OS following re-irradiation was 9.3 months (range: 0-27 months) and LPFS was 6.5 months (range: 0-24 months). OS and LPFS were not affected by histology, total dose or patient age and gender. OS was improved in patients whose re-irradiation volumes included less than two mediastinal lymph node stations ( $p = 0.016$ ). Twelve patients suffered from pneumonitis  $\geq$  grade II (19%) and two from pneumonitis grade III. One patient presumably died from pneumonitis grade V. A slight decline in forced expiratory volume (FEV1) was detected in post-re-irradiation lung function testing. **CONCLUSIONS:** Re-irradiation is an option for patients with tumour recurrence to control local progression and lower the symptom burden. Oncological outcome appears to be affected by size, location of mediastinal target volumes and lung function. Prospective clinical trials are warranted to substantiate the role of re-irradiation in recurrent lung cancer.

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## SMALL CELL LUNG CANCER - SCLC

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[Apatinib for chemotherapy-refractory extensive-stage SCLC: a retrospective study.](#) Li H1, Zeng J2, Jin X1, Yu X1, Zhou G3, Hong W4. *Cancer Chemother Pharmacol.* 2019 Jun;83(6):1083-1090. doi: 10.1007/s00280-019-03823-4. Epub 2019 Apr 1.

**PURPOSE:** There is no standard treatment strategy for patients with extensive-stage small cell lung cancer (SCLC) who have failed two or more prior chemotherapeutic regimens. In this study, we retrospectively evaluated the efficacy and safety of apatinib in patients with extensive-stage SCLC after failure of more than second-line chemotherapy. **METHODS:** A study group comprised of 22 patients with extensive-stage SCLC after failure of more than two prior chemotherapeutic regimens was given apatinib orally at an initial dose of 500 mg daily until disease progression or unacceptable toxicity. This study was analyzed according to the National Cancer Institute Common Toxicity Criteria for adverse events (AEs) and Response Evaluation Criteria in Solid Tumors (RECIST) for response assessment. **RESULTS:** Between August 30, 2015, and May 26, 2017, 22 patients were enrolled for evaluating the efficacy and safety of apatinib. Among them, 12/22 (54.5%) underwent dose reduction during treatment. Up to July 31, 2018, the median progression-free survival rate was 135.0 days [95% confidence interval (CI) 63.8-206.2]. According to the RECIST criteria, the disease control rate (DCR) was 86.4%, 19/22 [comprised of partial response (PR) 18.2%, 4/22; and stable disease (SD) 68.2%, 15/22 patients]. The most frequent AEs were hand-foot syndrome (45.5%, 10/22), secondary hypertension (45.5%, 10/22) and fatigue (40.9%, 9/22). The primary grade 3 or 4 toxicities were hypertension (22.7%, 5/22), hand-foot syndrome (13.6%, 3/22), and proteinuria (9.1%, 2/22). **CONCLUSIONS:** Apatinib exhibits modest activity and acceptable toxicity for patients with heavily pretreated extensive-stage SCLC.

[Salvage surgery for small cell lung cancer after chemoradiotherapy.](#) Nakanishi K1, Mizuno T1, Sakakura N1, Kuroda H1, Shimizu J2, Hida T2, Yatabe Y3, Sakao Y1. *Jpn J Clin Oncol.* 2019 Apr 1;49(4):389-392. doi: 10.1093/jjco/hyz010.

There are few reports on the use of salvage surgery for small cell lung cancer (SCLC). Five patients who underwent resection of post-chemoradiotherapy residual lesion/local reprogression of SCLC between 2005 and 2017 were included in the study. We retrospectively reviewed their surgical outcomes and

prognosis to assess the feasibility and potential efficacy of salvage surgery. Indications for salvage surgery were local reprogression (four patients) and residual lesion (one patient) with ycN0 disease. Complete pathological resection was achieved in four patients; however, malignant pleural effusion was diagnosed in one patient after the surgery. Morbidity and mortality rates were 0%. Estimated 5-year survival rate was 67%. Recurrence and death after surgery occurred only in the patient with malignant pleural effusion. We demonstrate the feasibility of salvage surgery in SCLC. In carefully-selected patients, especially those without lymph node involvement, salvage surgery may provide effective local control and favorable survival outcomes.

**Pharmacokinetics and safety of lobaplatin plus etoposide in Chinese men older than 65 years with extensive-stage small cell lung cancer: a phase II clinical trial.** Chen J1, Liu B2, Zhang F2, Cui W2, Zhang P3. *Cancer Chemother Pharmacol.* 2019 Apr 30. doi: 10.1007/s00280-019-03828-z. [Epub ahead of print]

**PURPOSE:** This phase II, multicenter, single arm clinical study was first performed to evaluate the therapeutic efficacy and safety of the regimen—a combination of lobaplatin (LBP) and etoposide (VP-16)—and investigate the pharmacokinetics of LBP in Chinese men older than 65 years with extensive-stage small cell lung cancer (SCLC). **METHODS:** Patients older than 65 were treated with the combination of LBP and VP-16 for 4-6 cycles through intravenous drip. The initial dose of VP-16 was 100 mg/m<sup>2</sup>/day for d1-d3 in each 21-day cycle, while LBP was administered for d1 in each cycle based on creatinine clearance (Ccr), 20 mg/m<sup>2</sup> for Ccr < 60 mL/min; 25 mg/m<sup>2</sup> for 60 ≤ Ccr < 80 mL/min and 30 mg/m<sup>2</sup> for Ccr ≥ 80 mL/min. Efficacy, safety and pharmacokinetics were evaluated to confirm the therapeutic effect. **RESULTS:** Thirteen elderly patients were enrolled and three patients were discontinued. The median progress-free survival was 129 days and the median overall survival was 238 days, which caused a significantly prolonged survival rate of 38.5% and a higher disease control rate of 80%. Most frequent adverse events were mild to moderate containing leukopenia, neutropenia, anemia, nausea and anorexia. Pharmacokinetic analysis revealed that there is no significant difference between LP-D1 and LP-D2 at the same dosage level. With the dosage increasing, the elimination clearance showed a slowing tendency, especially for 30 mg/m<sup>2</sup> group. **CONCLUSIONS:** LBP (20, 25, 30 mg/m<sup>2</sup>) in combination with VP-16 (100 mg/m<sup>2</sup>) could inhibit the elderly SCLC disease process, prolong their survival time and reduce adverse reactions via preliminary assessment and provide guidance for further investigation.

**Prognostic value of circulating tumour cells in limited-stage small cell lung cancer: analysis of the concurrent ONce-daily versus twice-daily RadioTherapy (CONVERT) randomised controlled trial.**

Tay RY1, Fernández-Gutiérrez F2, Foy V2, et al. *Ann Oncol.* 2019 Apr 24. pii: mdz122. doi: 10.1093/annonc/mdz122. [Epub ahead of print]

**BACKGROUND:** The clinical significance of circulating tumour cells (CTCs) in limited-stage small cell lung cancer (LS-SCLC) is not well defined. We report a planned exploratory analysis of the prevalence and prognostic value of CTCs in LS-SCLC patients enrolled within the phase 3 randomised CONVERT trial. **PATIENTS AND METHODS:** Baseline blood samples were enumerated for CTCs using CellSearch in 75 patients with LS-SCLC who were enrolled in the CONVERT trial and randomised between twice- and once-daily concurrent chemoradiation. Standard statistical methods were used for correlations of CTCs with clinical factors. Log-rank test and Cox regression analyses were applied to establish the associations of 2, 15 and 50 CTC thresholds with progression-free (PFS) and overall survival (OS). An optimal CTC count threshold for LS-SCLC was established. **RESULTS:** CTCs were detected in 60% (45/75) of patients (range 0-3750). CTC count thresholds of 2, 15 and 50 CTCs all significantly correlate with PFS and OS. An optimal CTC count threshold in LS-SCLC was established at 15 CTCs, defining 'favourable' and 'unfavourable' prognostic risk groups. The median OS in < 15 vs ≥ 15 CTCs was 26.7 m vs 5.9 m (p = 0.001). The presence of ≥ 15 CTCs at baseline independently predicted ≤ 1 year

survival in 70% and  $\leq 2$  years survival in 100% of patients. **CONCLUSION:** We report the prognostic value of baseline CTC count in an exclusive LS-SCLC population at thresholds of 2, 15 and 50 CTCs. Specific to LS-SCLC,  $\geq 15$  CTCs was associated with worse PFS and OS independent of all other factors and predicted  $\leq 2$  years survival. These results may improve disease stratification in future clinical trial designs and aid clinical decision-making.

[Timing of treatment in small-cell lung cancer.](#) Bhandari S1, Pham D2, Pinkston C3, Oechsli M2, Kloecker G2. *Med Oncol.* 2019 Apr 25;36(6):47. doi: 10.1007/s12032-019-1271-3.

Small-cell lung cancer (SCLC) is an aggressive disease with poor survival and rapid doubling time. Current practice is to treat SCLC as soon as possible but evidence on appropriate timing of treatment from diagnosis (TTD) is lacking. This is a retrospective analysis of SCLC patients from the 2012 to 2015 Kentucky Cancer Registry. Data collected included age at diagnosis, stage, gender, race, insurance and treatment. Factors and survival associated with TTD were identified with logistic regression analyses and Cox proportional hazards models. Among the 2992 SCLC patients, 2371 (79%) of SCLC patients were treated with one or more treatment modalities. Among treated patients, 93% received chemotherapy  $\pm$  radiation with the mean TTD of 18 days. Most patients (80%) have TTD of  $\leq 4$  weeks with 33% treated within 1 week, 20% 1-2 weeks, and 27% 2-4 weeks from diagnosis. Delay in treatment (TTD  $> 4$  weeks) was less in stage III and IV disease (odds ratio: 0.33 and 0.27 respectively,  $p < 0.01$ ) but not significantly associated with age, race, gender, and insurance. One and two-year survival of patients with TTD  $\leq 4$  weeks was significantly worse when compared to  $> 4$  weeks (hazard ratio = 1.43, 95% CI 1.2-1.6,  $p < 0.01$ ; HR = 1.45, 95% CI 1.3-1.6,  $p < 0.01$  respectively). These results show a trend toward better survival with late treatment of SCLC. Therefore, a general urgency to treat SCLC needs to be re-evaluated with consideration of patients needing more optimization before treatment. Further studies are needed to better clarify the appropriate timing of treatment from diagnosis in SCLC and who will benefit from early versus late treatment.

[Comparison of hyper- and hypofractionated radiation schemes with IMRT technique in small cell lung cancer: Clinical outcomes and the introduction of extended LQ and TCP models.](#) Li QW1, Qiu B1, Wang B1, et al. *Radiother Oncol.* 2019 Apr 15;136:98-105. doi: 10.1016/j.radonc.2019.03.035. [Epub ahead of print]

**PURPOSE:** To evaluate the outcomes of 45 Gy/15 fractions/once-daily and 45 Gy/30 fractions/twice-daily radiation schemes utilizing intensity-modulated radiation therapy (IMRT) in extensive stage small cell lung cancer (SCLC), and to build up a new radiobiological model for tumor control probability (TCP) considering multiple biological effects. **METHODS:** Fifty-eight consecutive patients diagnosed with extensive stage SCLC, treated with chemotherapy and chest irradiation, were retrospectively reviewed. Thirty-seven received hyperfractionated IMRT (Hyper-IMRT, 45 Gy/30 fractions/twice-daily) and 21 received hypofractionated IMRT (Hypo-IMRT, 45 Gy/15 fractions/once-daily). Local progression-free survival (LPFS) and overall survival (OS) were calculated and compared. An extended linear-quadratic (LQ) model, LQRG, incorporating cell repair, redistribution, reoxygenation, regrowth and Gompertzian tumor growth was created based on the clinical data. The TCP model was reformulated to predict LPFS. The classical LQ and TCP models were compared with the new models. Akaike information criterion (AIC) was used to assess the quality of the models. **RESULTS:** The 2-year LPFS (34.1% vs 27.9%,  $p = 0.44$ ) and OS (76.9% vs 76.9%,  $p = 0.26$ ) were similar between Hyper- and Hypo-IMRT patients. According to the LQRG model, the  $\alpha/\beta$  calculated was 9.2 (95% confidence interval: 8.7-9.9) Gy after optimization. The average absolute and relative fitting errors for LPFS were 9.1% and 18.7% for Hyper-IMRT, and 8.8% and 16.2% for Hypo-IMRT of the new TCP model, compared with 29.1% and 62.3% for Hyper-IMRT, and 30.7% and 65.3% for Hypo-IMRT of the classical model. **CONCLUSIONS:** Hypo-

and Hyper-IMRT resulted in comparable local control in the chest irradiation of extensive stage SCLC. The LQRG model has better performance in predicting the TCP (or LPFS) of the two schemes.

### [Multigene Mutation Profiling and Clinical Characteristics of Small-Cell Lung Cancer in Never-Smokers vs. Heavy Smokers \(Geno1.3-CLICaP\).](#)

Cardona AF1,2,3, Rojas L1,2,4, Zatarain-Barrón ZL5, et al. *Front Oncol.* 2019 Apr 17;9:254. doi: 10.3389/fonc.2019.00254. eCollection 2019.

**OBJECTIVES:** Lung cancer is a heterogeneous disease. Presentation and prognosis are known to vary according to several factors, such as genetic and demographic characteristics. Small-cell lung cancer incidence is increasing in never-smokers. However, the disease phenotype in this population is different compared with patients who have a smoking history. **MATERIAL AND METHODS:** To further investigate the clinical and genetic characteristics of this patient subgroup, a cohort of small cell lung cancer patients was divided into smokers (n = 10) and never/ever-smokers (n = 10). A somatic mutation profile was obtained using a comprehensive NGS assay. Clinical outcomes were compared using the Kaplan-Meier method and Cox proportional models. **RESULTS:** Median age was 63 years (46-81), 40% were men, and 90% had extended disease. Smoker patients had significantly more cerebral metastases (p = 0.04) and were older (p = 0.03) compared to their non-smoker counterparts. For never/ever smokers, the main genetic mutations were TP53 (80%), RB1 (40%), CYLD (30%), and EGFR (30%). Smoker patients had more RB1 (80%, p = 0.04), CDKN2A (30%, p = 0.05), and CEBPA (30%, p = 0.05) mutations. Response rates to first-line therapy with etoposide plus cisplatin/carboplatin were 50% in smokers and 90% in never/ever smokers (p = 0.141). Median overall survival was significantly longer in never smokers compared with smokers (29.1 months [23.5-34.6] vs. 17.3 months [4.8-29.7]; p = 0.0054). Never/ever smoking history (HR 0.543, 95% CI 0.41-0.80), limited-stage disease (HR 0.56, 95% CI 0.40-0.91) and response to first-line platinum-based chemotherapy (HR 0.63, 95% CI 0.60-0.92) were independently associated with good prognosis. **CONCLUSION:** Our data supports that never/ever smoker patients with small-cell lung cancer have better prognosis compared to their smoker counterparts. Further, patients with never/ever smoking history who present with small-cell lung cancer have a different mutation profile compared with smokers, including a high frequency of EGFR, MET, and SMAD4 mutations. Further studies are required to assess whether the differential mutation profile is a consequence of a diverse pathological mechanism for disease onset.

### [Delta-like Protein 3 Prevalence in Small Cell Lung Cancer and DLL3 \(SP347\) Assay](#)

**Characteristics.** Huang RSP, Holmes BF, Powell C, Marati RV, Tyree D, Admire B, Streator A, Newell AEH, Perez J, Dalvi D, ElGabry EA1. *Arch Pathol Lab Med.* 2019 Apr 8. doi: 10.5858/arpa.2018-0497-OA. [Epub ahead of print]

**CONTEXT:** Delta-like protein 3 (DLL3) is a protein that is implicated in the Notch pathway.

**OBJECTIVE:** To present data on DLL3 prevalence in small cell lung cancer and staining characteristics of the VENTANA DLL3 (SP347) Assay. In addition, the assay's immunoreactivity with other neoplastic and nonneoplastic tissues is outlined. **DESIGN:** Individual formalin-fixed, paraffin-embedded specimens of small cell lung cancer and tissue microarrays comprising neoplastic and nonneoplastic tissues were procured. Sections were cut and stained with DLL3 (SP347) assay. The slides were examined to determine prevalence, staining characteristics, and immunoreactivity. **RESULTS:** Cytoplasmic and/or membranous staining was observed in 1040 of 1362 specimens of small cell lung cancer (76.4%). Homogenous and/or heterogeneous and partial and/or circumferential granular staining with varied intensities was noted. Immunoreactivity was also observed in other neoplastic and nonneoplastic tissues. **CONCLUSIONS:** Our study findings provided the profile of DLL3 staining characteristics that can be used for determining the level of DLL3 expression in small cell lung cancer.

[Integrating early palliative care into routine practice for patients with cancer: A mixed methods evaluation of the INTEGRATE Project.](#) Evans JM1,2, Mackinnon M1, Pereira J3,4,5,6,7, et al.

Psychooncology. 2019 Apr 4. doi: 10.1002/pon.5076. [Epub ahead of print]

**OBJECTIVE:** With increasing evidence from controlled trials on benefits of early palliative care, there is a need for studies examining implementation in real-world settings. The INTEGRATE Project was a 3-year real-world project that promoted early identification and support of patients with cancer who may benefit from palliative care. This study assesses feasibility, stakeholder experiences, and early impact of the **INTEGRATE Project** **METHODS:** The INTEGRATE Project was implemented in four cancer centers in Ontario, Canada, and consisted of interdisciplinary provider education and an integrated care model. Providers used the Surprise Question to identify patients for inclusion. A mixed methods evaluation of INTEGRATE was conducted using descriptive data, interviews with providers and managers, and provider surveys. **RESULTS:** A total of 760 patients with cancer (lung, glioblastoma, head and neck, gastrointestinal) were included. Results suggest improvement in provider confidence to deliver palliative care and to initiate the Advanced Care Planning (ACP) conversation. The majority of patients (85%) had an ACP or goals of care (GOC) conversation initiated within a mean time to conversation of 5-46 days (SD 20-93) across centers. A primary care report was transmitted to family doctors 48-100% of the time within a mean time to transmission of 7-54 days (SD 9-27) across centers. Enablers and barriers influencing success of the model were also identified. **CONCLUSIONS:** A standardized model for the early introduction of palliative care for patients with cancer can be integrated into the routine practice of oncology providers, with appropriate education, integration into existing clinical workflows, and administrative support.

[Loneliness as a mediator of the relationship of social cognitive variables with depressive symptoms and quality of life in lung cancer patients beginning treatment.](#) Hyland KA1,2, Small BJ1,2, Gray JE1, et al.

Psychooncology. 2019 Apr 1. doi: 10.1002/pon.5072. [Epub ahead of print]

**OBJECTIVE:** Loneliness, or the discrepancy between perceived and desired level of social connectedness, is an understudied but important psychosocial factor in cancer patients. The current study investigated the relationship between loneliness, depressive symptoms, quality of life, and social cognitive variables (eg, stigma, social constraint, and cancer-related negative social expectations), and explored loneliness as a mediator of the relationship between social cognitive variables and depressive symptoms and quality of life in lung cancer patients beginning treatment. **METHODS:** Patients within 3 months of beginning treatment for lung cancer completed measures of loneliness, depressive symptoms, quality of life, and social cognitive variables. Correlational, chi-square, and hierarchical regression analyses evaluated relationships among variables. Bias-corrected bootstrapping methods estimated the indirect effect and 95% confidence interval for mediation models. **RESULTS:** Participants (n = 105, M = 65.5 years, 55% female) endorsed low to moderate levels of loneliness. Greater loneliness was associated with greater depressive symptoms and worse quality of life (P's < .001), and loneliness explained unique variance in depressive symptoms (F = 10.18, P < .001,  $\Delta R^2 = .06$ , Total R<sup>2</sup> = .35) and quality of life (F = 19.55, P < .001,  $\Delta R^2 = .05$ , Total R<sup>2</sup> = .52) after controlling for significant covariates. Greater stigma, social constraint, and cancer-related negative social expectations were associated with greater loneliness and depressive symptoms and worse quality of life (P's < .001). Loneliness partially mediated the relationship of social cognitive variables with depressive symptoms and quality of life. **CONCLUSIONS:** Beyond its direct impact on clinically relevant outcomes, the experience of loneliness may be a mechanism by which social cognitive factors influence depressive symptoms and quality of life in lung cancer patients.

[New lung cancer treatments \(immunotherapy and targeted therapies\) and their associations with depression and other psychological side effects as compared to chemotherapy.](#) McFarland DC1. Gen Hosp Psychiatry. 2019 Apr 18. pii: S0163-8343(18)30503-6. doi: 10.1016/j.genhosppsy.2019.04.001. [Epub ahead of print]

**OBJECTIVE:** Lung cancer carries a high prevalence of distress, anxiety and depression. New treatments, targeted therapy and immunotherapy have changed the disease course for subsets of patients and confer longer survival, but their psychological associations and possible mechanisms (e.g., inflammation and physical symptoms) are not well described. **METHOD:** Patients with metastatic lung cancer undergoing systemic treatment (n = 109) were evaluated for distress, self-endorsed problems using the Distress Thermometer and Problem List, and depression and anxiety using the Hospital Anxiety and Depression Scale. Demography, cancer-related information, and inflammation were evaluated for their associations with chemotherapy, targeted therapy, and immunotherapy. Inflammation was measured by C-reactive protein, albumin, and neutrophil to lymphocyte ratio. **RESULTS:** Chemotherapies were given most often followed by immunotherapy and targeted therapies. Depression and anxiety were endorsed by 23.9%, respectively, and 41.1% had significant distress. Chemotherapy was associated with depression (p = .006) and inflammation (p < .001). Physical symptoms were the same among treatment types. Targeted therapy and immunotherapy predicted for less depression (p = .04, p = .04 respectively) than chemotherapy when controlling for age, sex, and performance status however these predictors were not significant when controlled for inflammation. **CONCLUSION:** New immunotherapy and targeted therapies are associated with less depression and inflammation among patients who are living longer while their physical symptoms are the same.

[A qualitative study of healthcare-related experiences of non-smoking women with lung cancer.](#)

Dao D1, O'Connor JM2, Jatoi A3, Ridgeway J4, Deering E2, Schwecke A2, Breitkopf CR4, Huston O2, Le-Rademacher JG5. Support Care Cancer. 2019 Apr 15. doi: 10.1007/s00520-019-04759-4. [Epub ahead of print]

**PURPOSE:** Lung cancer in non-smoking women is a distinct entity, but few studies have examined these patients' healthcare-related experiences. **METHODS:** Women with lung cancer and with no smoking history underwent a face-to-face semi-structured, audio-recorded interview that was analyzed with a qualitative inductive approach. **RESULTS:** Twenty-three patients were interviewed, and three themes emerged. The first theme centered on a delay in cancer diagnosis. One patient described, "The whole initial diagnostic process just fills me with rage... I didn't actually get my Tarceva® until the last week in April." Second, the diagnosis of lung cancer seemed especially challenging in view of patients' non-smoking history and otherwise good health; these factors seem to have contributed to the diagnostic delay. One patient explained, "Well, I was just so adamant that I didn't like smoking... maybe if I had been a smoker, they [the healthcare providers] would've been more resourceful." Finally, the stigma of a smoking-induced malignancy was clearly articulated, "Yeah. Because it's a stigma, and I had read that, too -- people go, 'Well, it's your own damn fault because you were a smoker.'" **CONCLUSIONS:** Non-smoking women with lung cancer appear to endure a long trajectory from symptoms to cancer diagnosis to the initiation of cancer therapy. An awareness and acknowledgement of this long trajectory might help healthcare providers render more compassionate cancer care to these patients.

[Beliefs About Advanced Cancer Curability in Older Patients, Their Caregivers, and Oncologists.](#)

Loh KP1, Mohile SG2, Lund JL3, et al. Oncologist. 2019 Apr 23. pii: theoncologist.2018-0890. doi: 10.1634/theoncologist.2018-0890. [Epub ahead of print]

**BACKGROUND:** Ensuring older patients with advanced cancer and their oncologists have similar beliefs about curability is important. We investigated discordance in beliefs about curability in patient-oncologist and caregiver-oncologist dyads. **MATERIALS AND METHODS:** We used baseline data



from a cluster randomized trial assessing whether geriatric assessment improves communication and quality of life in older patients with advanced cancer and their caregivers. Patients were aged  $\geq 70$  years with incurable cancer from community oncology practices. Patients, caregivers, and oncologists were asked: "What do you believe are the chances the cancer will go away and never come back with treatment?" Options were 100%, >50%, 50/50, <50%, and 0% (5-point scale). Discordance in beliefs about curability was defined as any difference in scale scores ( $\geq 3$  points were severe). We used multivariate logistic regressions to describe correlates of discordance. **RESULTS:** Discordance was present in 60% (15% severe) of the 336 patient-oncologist dyads and 52% (16% severe) of the 245 caregiver-oncologist dyads. Discordance was less common in patient-oncologist dyads when oncologists practiced longer (adjusted odds ratio [AOR] 0.90, 95% confidence interval [CI] 0.84-0.97) and more common in non-Hispanic white patients (AOR 5.77, CI 1.90-17.50) and when patients had lung (AOR 1.95, CI 1.29-2.94) or gastrointestinal (AOR 1.55, CI 1.09-2.21) compared with breast cancer. Severe discordance was more common when patients were non-Hispanic white, had lower income, and had impaired social support. Caregiver-oncologist discordance was more common when caregivers were non-Hispanic white (AOR 3.32, CI 1.01-10.94) and reported lower physical health (AOR 0.88, CI 0.78-1.00). Severe discordance was more common when caregivers had lower income and lower anxiety level. **CONCLUSION:** Discordance in beliefs about curability is common, occasionally severe, and correlated with patient, caregiver, and oncologist characteristics. **IMPLICATIONS FOR PRACTICE:** Ensuring older patients with advanced cancer and their caregivers have similar beliefs about curability as the oncologist is important. This study investigated discordance in beliefs about curability in patient-oncologist (PO) and caregiver-oncologist (CO) dyads. It found that discordance was present in 60% (15% severe) of PO dyads and 52% (16% severe) of CO dyads, raising serious questions about the process by which patients consent to treatment. This study supports the need for interventions targeted at the oncologist, patient, caregiver, and societal levels to improve the delivery of prognostic information and patients'/caregivers' understanding and acceptance of prognosis.

**Understanding Underuse of Advance Care Planning Among a Cohort of African American Patients With Advanced Cancer: Formative Research That Examines Gaps in Intent to Discuss Options for Care.**

Rhodes RL<sup>1,2</sup>, Ukoha NCE<sup>3</sup>, Williams KA<sup>4</sup>, et al. *Am J Hosp Palliat Care*. 2019 Apr 21:1049909119843276. doi: 10.1177/1049909119843276. [Epub ahead of print]

**BACKGROUND:** Advance care planning (ACP), palliative care (PC), and hospice are often underutilized by African Americans (AAs). This study assessed the impact of stage of intent to discuss ACP options as key potential barriers. **METHODS:** We examined intent to discuss completion of ACP, PC, and hospice among 22 AA patients with cancer admitted to a local safety net hospital. Participants were asked about intent to discuss an advanced directive or living will (AD/LW), medical power of attorney (MPOA), PC, and hospice with their doctors. Intent to discuss these ACP components was based on the transtheoretical model. Electronic health records were reviewed at various intervals to assess completion of ACP behaviors and survival. **RESULTS:** Participants had colorectal (33%), breast (44%), and lung (23%) cancer, and 82% had stage III/IV disease. Low percentages of patients were in the precontemplation stage for AD/LW completion (4.6%), MPOA completion (13.6%), and PC discussions (27.2%), but 77.2% were in the precontemplation stage for hospice discussions. At 1 year, only 5% completed an AD/LW, 36.4% appointed an MPOA, 42.9% were referred to PC, and 12.5% were referred to hospice. More than half (54.6%) were deceased by the study's conclusion. Most (81%) of these died within 6 months of their baseline study assessment. **CONCLUSIONS:** Despite being hospitalized with advanced cancer and having poor prognosis, intent to discuss ACP options, PC, and hospice in this population was variable, and completion of these activities was low. This formative research is needed to develop education and counseling interventions for this high-risk, vulnerable population.

**[Honokiol for cancer therapeutics: A traditional medicine that can modulate multiple oncogenic targets.](#)** Banik K1, Ranaware AM2, Deshpande V2, et al. *Pharmacol Res.* 2019 Apr 17;144:192-209. doi: 10.1016/j.phrs.2019.04.004. [Epub ahead of print]

In spite of billions of dollars expended on cancer research every year, the incidence rate and the mortality rate due to this widespread disease has increased drastically over the last few decades. Recent reports from the World Health Organization advocate that overall global cancer burden and deaths due to cancer are expected to double by the next decade. Synthetic drugs developed as chemotherapeutics have repeatedly shown adverse side effects and development of chemoresistance. Cancer is basically a multifactorial disease that necessitates the modulation of multiple targets and oncogenic signaling pathways. Honokiol (C<sub>18</sub>H<sub>18</sub>O<sub>2</sub>) is a biphenolic natural compound isolated from the leaves and barks of Magnolia plant species and has been extensively studied for its beneficial effects against several chronic diseases. Honokiol is capable of efficiently preventing the growth of wide variety of tumors such as those of brain, breast, cervical, colon, liver, lung, prostate, skin, and hematological malignancies. Recent work has shown that this phytochemical can modulate various molecular targets such as activation of pro-apoptotic factors, suppression of anti-apoptotic proteins and different transcription factors, downregulation of various enzymes, chemokines, cell surface adhesion molecules, and cell cycle proteins, and inhibition of activity of protein tyrosine kinases and serine/threonine kinases. Because of its pharmacological safety, honokiol can either be used alone or in combination with other chemotherapeutic drugs for the prevention and treatment of cancer. The current review describes in detail the various reports supporting these anti-cancer studies documented with this promising agent.

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**MISCELLANEOUS WORKS**

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**[Impact of the Hydraulic Fracturing on Indoor Radon Concentrations in Ohio: A Multilevel Modeling Approach.](#)** Xu Y1, Sajja M2, Kumar A2. *Front Public Health.* 2019 Apr 10;7:76. doi: 10.3389/fpubh.2019.00076. eCollection 2019.

According to the United States Environmental Protection Agency (U.S. EPA), exposure to radon gas is the second leading cause of lung cancer after smoking. Extant research that has reported that fracking activity increases the radon levels. "Fracking" also known as hydraulic fracturing, which is a technology that is used to extract naturally occurring shale gas from the Marcellus and the Utica shales. Based on the data from the Ohio Radon Information System (ORIS) from 2007 to 2014 in Ohio, this research uses multilevel modeling (MLM) to examine the association between the incidences of hydraulic fracturing and elevated airborne radon levels. The ORIS data include information on 118,421 individual records of households geocoded to zip code areas. Individual records include radon concentrations, device types of the test, and seasons. Euclidean distances between zip code centroid to the 1,162 fracking wells are measured at the zip code level. Two additional zip code variables, namely the population density and urbanicity, are also included as control variables. Multilevel modeling results show that at the zip code level, distance to fracking wells and population density are significant and negative covariate of the radon concentration. By comparing with urban areas, urban clusters, and rural areas are significant which linked to higher radon concentrations. These findings lend support to the effect of hydraulic fracturing in influencing radon concentrations, and promote public policies that need to be geographically adaptable.

**[Lung cancer stigma and depression: Validation of the Lung Cancer Stigma Inventory.](#)** Ostroff JS1, Riley KE1, Shen MJ2, Atkinson TM1, Williamson TJ1, Hamann HA3. *Psychooncology.* 2019 Feb 19. doi: 10.1002/pon.5033. [Epub ahead of print]

**OBJECTIVE:** In an effort to provide further evidence for the validity of the Lung Cancer Stigma Inventory (LCSI), this paper examined group differences in lung cancer stigma for patients who report clinically significant depressive symptoms and established a suggested scoring benchmark to identify patients with clinically meaningful levels of lung cancer stigma. **METHODS:** Patients (N = 231) who were diagnosed with lung cancer and treated within the past 12 months at one of two National Cancer Institute (NCI)-designated Cancer Centers located in the northeast and southern parts of the United States completed a single battery of questionnaires examining lung cancer stigma and depressed mood. Group differences, bivariate correlations, and receiver operating characteristic (ROC) analyses were conducted. **RESULTS:** Slightly more than a third of patients (35.9%) reported an elevated level of depression. There was a significant correlation ( $r = 0.44$ ) between lung cancer stigma and depressive mood. The ROC curve analysis indicated an area under curve (AUC) of 0.71. A LCSI cutoff score of 37.5 yielded the optimal ratio of sensitivity (0.93) to specificity (0.70) for identifying patients with clinically meaningful lung cancer stigma. **CONCLUSIONS:** Consistent with prior work, lung cancer stigma, as measured by the LCSI, was found to be moderately associated with depressed mood. Clinical investigators may use an LCSI total score above 37.5 (ie, greater than or equal to 38 on the LCSI scale of integer scores) as a clinical threshold for identifying patients who may be experiencing clinically meaningful stigma and may benefit from stigma-reducing interventions.

[Advanced Stage Non-Small Cell Lung Cancer: Advances in Thoracic Oncology 2018.](#) Remon J1, Ahn MJ2, Girard N3, Johnson M4, Kim DW5, Lopes G6, Pillai RN7, Solomon B8, Villacampa G9, Zhou Q10. *J Thorac Oncol.* 2019 Apr 16. pii: S1556-0864(19)30280-1. doi: 10.1016/j.jtho.2019.03.022. [Epub ahead of print]

In 2018 research in the field of advanced non-small cell lung cancers (NSCLC) led to an expanded reach and impact of immune-checkpoint inhibitors (ICIs) as part of frontline treatment strategy, regardless of histology subtype, while ICI use was extended to include stage III disease, shifting the prognosis of all these patients. This new standard first-line approach opens a gap in standard second-line treatment, and older combinations may again become standard care after progression on ICIs. The characterization of predictive biomarkers, patient selection, the definition of strategies with ICI combinations upon progression on ICIs, as well as prospective evaluation of the efficacy of ICIs in subpopulations (such as patients with poor performance status or brain metastases) represent upcoming challenges in advanced thoracic malignancies. In oncogenic-addicted NSCLC three major steps were taken during 2018: next-generation tyrosine kinase inhibitors (TKIs) have overtaken more established agents as the new standard of care in EGFR and ALK-positive tumors. Mechanisms of acquired resistance have been reported among patients treated with next-generation EGFR TKIs reflecting the diversity of the landscape. One major step forward was the approval of personalized treatment in very uncommon genomic alterations, mainly fusions. This raises a new question about the challenge of next generation sequencing implementation in daily clinical practice for detecting new and uncommon genomic alterations as well as to capture the heterogeneity of the mechanisms of acquired resistance while on treatment, as well as the need to extend research into new therapeutic strategies to overcome them.

[Indoor radon exposure increases tumor mutation burden in never-smoker patients with lung adenocarcinoma.](#) Lim SM1, Choi JW2, Hong MH3, et al. *Lung Cancer.* 2019 May;131:139-146. doi: 10.1016/j.lungcan.2019.04.002. Epub 2019 Apr 3.

**OBJECTIVES:** Radon, a natural radiation, is the leading environmental cause of lung cancer in never-smokers. However, the radon exposure impact on the mutational landscape and tumor mutation burden (TMB) of lung cancer in never-smokers has not been explored. The aim of this study was to investigate the mutational landscape of lung adenocarcinoma in never-smokers who were exposed to various degrees of residential radon. **MATERIALS AND METHODS:** To investigate the effect of indoor radon

exposure, we estimated the cumulative exposure to indoor radon in each house of patients with lung cancer with a never-smoking history. Patients with at least 2 year-duration of residence before the diagnosis of lung adenocarcinoma were included. Patients were subgrouped based on the median radon exposure level (48 Bq/m<sup>3</sup>): radon-high vs. radon-low and targeted sequencing of tumor and matched blood were performed in all patients. **RESULTS:** Among 41 patients with lung adenocarcinoma, the TMB was significantly higher in the radon-high group than it was in the radon-low group (mean 4.94 vs. 2.6 mutations/Mb, P = 0.01). The recurrence rates between radon-high and radon-low group did not differ significantly. Mutational signatures of radon-high tumors showed features associated with inactivity of the base excision repair and DNA replication machineries. The analysis of tumor evolutionary trajectories also suggested a series of mutagenesis induced by radon exposure. In addition, radon-high tumors revealed a significant protein-protein interaction of genes involved in DNA damage and repair (P < 0.001). **CONCLUSIONS:** Indoor radon exposure increased the TMB in never-smoker patients with lung adenocarcinoma and their mutational signature was associated with defective DNA mismatch repair.