



Caring Ambassadors Lung Cancer Program Literature Review, December 2021

SCREENING, COMPREHENSIVE BIOMARKER TESTING, DIAGNOSIS AND STAGING	1-8
CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES	
NSCLC SURGERY	8-13
NSCLC SYSTEMIC THERAPIES (CHEMOTHERAPY, TARGETED THERAPY, AND IMMUNOTHERAPY)	13-21
NSCLC RADIOTHERAPY	21-23
SMALL CELL LUNG CANCER (SCLC)	23-27
PALLIATIVE AND SUPPORTIVE CARE	27-30
COMPLEMENTARY AND ALTERNATIVE THERAPY	30-31
MISCELLANEOUS WORKS	31-34

SCREENING, COMPREHENSIVE BIOMARKER TESTING, DIAGNOSIS AND STAGING

[Comparative Analysis of Predictive Biomarkers for PD-1/PD-L1 Inhibitors in Cancers: Developments and Challenges](#)

Cancers (Basel). 2021 Dec 27;14(1):109. doi: 10.3390/cancers14010109. Fang Yang ¹, Jacqueline F Wang ², Yucai Wang ³, Baorui Liu ¹, Julian R Molina ⁴
Immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) have dramatically changed the landscape of cancer therapy. Both remarkable and durable responses have been observed in patients with melanoma, non-small-cell lung cancer (NSCLC), and other malignancies. However, the PD-1/PD-L1 blockade has demonstrated meaningful clinical responses and benefits in only a subset of patients. In addition, several severe and life-threatening adverse events were observed in these patients. Therefore, the identification of predictive biomarkers is urgently needed to select patients who are more likely to benefit from ICI therapy. PD-L1 expression level is the most commonly used biomarker in clinical practice for PD-1/PD-L1 inhibitors. However, negative PD-L1 expression cannot reliably exclude a response to a PD-1/PD-L1 blockade. Other factors, such as tumor microenvironment and other tumor genomic signatures, appear to impact the response to ICIs. In this review, we examine emerging data for novel biomarkers that may have a predictive value for optimizing the benefit from anti-PD-1/PD-L1 immunotherapy.

[A Cost-Effectiveness Analysis of Lung Cancer Screening With Low-Dose Computed Tomography and a Diagnostic Biomarker](#)

JNCI Cancer Spectr. 2021 Oct 6;5(6):pkab081. doi: 10.1093/jncics/pkab081. eCollection 2021 Dec. Iakovos Toumazis ¹, S Ayca Erdogan ², Mehrad Bastani ¹, Ann Leung ², Sylvia K Plevritis ¹

BACKGROUND: The Lung Computed Tomography Screening Reporting and Data System (Lung-RADS) reduces the false-positive rate of lung cancer screening but introduces prolonged periods of uncertainty for indeterminate findings. We assess the cost-effectiveness of a screening program that assesses indeterminate findings earlier via a hypothetical diagnostic biomarker introduced in place of Lung-RADS 3 and 4A guidelines. **METHODS:** We evaluated the performance of the US Preventive Services Task Force (USPSTF) recommendations on lung cancer screening with and without a

hypothetical noninvasive diagnostic biomarker using a validated microsimulation model. The diagnostic biomarker assesses the malignancy of indeterminate nodules, replacing Lung-RADS 3 and 4A guidelines, and is characterized by a varying sensitivity profile that depends on nodules' size, specificity, and cost. We tested the robustness of our findings through univariate sensitivity analyses. **RESULTS:** A lung cancer screening program per the USPSTF guidelines that incorporates a diagnostic biomarker with at least medium sensitivity profile and 90% specificity, that costs \$250 or less, is cost-effective with an incremental cost-effectiveness ratio lower than \$100 000 per quality-adjusted life year, and improves lung cancer-specific mortality reduction while requiring fewer screening exams than the USPSTF guidelines with Lung-RADS. A screening program with a biomarker costing \$750 or more is not cost-effective. The health benefits accrued and costs associated with the screening program are sensitive to the disutility of indeterminate findings and specificity of the biomarker, respectively. **CONCLUSIONS:** Lung cancer screening that incorporates a diagnostic biomarker, in place of Lung-RADS 3 and 4A guidelines, could improve the cost-effectiveness of the screening program and warrants further investigation.

[Patient navigation to promote lung cancer screening in a community health center for people experiencing homelessness: Protocol for a pragmatic randomized controlled trial](#)

Contemp Clin Trials. 2021 Dec 28;113:106666. doi: 10.1016/j.cct.2021.106666. Online ahead of print. Travis P Baggett 1 , Joana Barbosa Teixeira 2 , Elijah C Rodriguez 3 , Nillani Anandakugan 2 , Nora Sporn 2 , Yuchiao Chang 4 , Sanja Percac-Lima 4 , Elyse R Park 4 , Nancy A Rigotti 4

BACKGROUND: Lung cancer is a major cause of death among people experiencing homelessness, with mortality rates more than double those in the general population. Lung cancer screening (LCS) with low-dose computed tomography (LDCT) could reduce lung cancer deaths in this population, although the circumstances of homelessness present multiple barriers to LCS LDCT completion. Patient navigation is a promising strategy for overcoming these barriers. **METHODS:** The Investigating Navigation to Help Advance Lung Equity (INHALE) Study is a pragmatic randomized controlled trial of patient navigation for LCS among individuals receiving primary care at Boston Health Care for the Homeless Program (BHCHP). Three hundred BHCHP patients who meet Medicare/Medicaid criteria for LCS will be randomized 2:1 to usual care with (n = 200) or without (n = 100) LCS navigation. Following a structured, theory-based protocol, the patient navigator assists with each step in the LCS process, providing lung cancer education, facilitating shared decision-making visits with primary care providers (PCPs), assisting in making and attending LCS LDCT appointments, arranging follow-up when needed, and offering tobacco cessation support for smokers. The primary outcome is receipt of LCS LDCT at 6 months. Using a sequential explanatory mixed methods approach, qualitative interviews with participants and PCPs will aid in interpreting and contextualizing the trial results. **DISCUSSION:** This trial will produce the first experimental evidence on patient navigation for cancer screening in a homeless health care setting. Results could inform cancer health equity efforts at the 299 Health Care for the Homeless programs that serve over 900,000 patients annually in the US.

[A Lung Cancer Screening Education Program Impacts both Referral Rates and Provider and Medical Assistant Knowledge at Two Federally Qualified Health Centers](#)

Clin Lung Cancer. 2021 Dec 12;S1525-7304(21)00289-8. doi: 10.1016/j.clcc.2021.12.002. Online ahead of print. Aamna Akhtar 1 , Ernesto Sosa 2 , Samuel Castro 1 , et al.

BACKGROUND: Federally Qualified Health Centers (FQHCs) serve minority and low-socioeconomic populations and provide care to high-risk smokers. These centers frequently experience barriers, including low provider and medical assistant (MA) knowledge around lung cancer screening (LCS). Subsequent low LCS referral rates by providers at FQHCs limit utilization of LCS in eligible, high-risk, underserved patients. **METHODS:** Providers and MAs from two FQHCs participated in a LCS educational session. A pre-educational survey was administered at the start of the session and a post-educational survey at the

end. The intervention included a presentation with education around non-small cell lung cancer, LCS, tobacco cessation, and shared-decision making. Both surveys were used to evaluate changes in provider and MA ability to determine eligible patients for LCS. The Pearson's Chi-squared test with Yates' continuity correction was used to measure the impact. **RESULTS:** A total of 29 providers and 28 MAs enrolled in the study from two FQHCs. There was an improvement, $P < .009$ and $P < .015$ respectively, in provider and MA confidence in identifying patients for LCS. Additionally, one year prior to the program, 9 low-dose computed tomography (LDCTs) were ordered at one of the FQHCs and 0 at the other. After the program, over 100 LDCTs were ordered at each FQHC. **CONCLUSIONS:** A targeted LCS educational program improves provider and MAs' ability to identify eligible LCS patients and is associated with an increase in the number of patients referred to LDCT at FQHCs.

[Impact of the shared decision-making process on lung cancer screening decisions](#) Cancer Med. 2021 Dec 28. doi: 10.1002/cam4.4445. Online ahead of print. Naomi Q P Tan ¹, Shawn P E Nishi ², Lisa M Lowenstein ¹, Tito R Mendoza ³, Maria A Lopez-Olivo ¹, Laura C Crocker ¹, Karen R Sepucha ⁴, Robert J Volk ¹

BACKGROUND: Professional organizations recommend the use of shared decision-making (SDM) in supporting patients' decisions about lung cancer screening (LCS). The objective of this study was to assess the impact of the SDM process on patient knowledge about LCS, decisional conflict, intentions to adhere to screening recommendations, and its role in how the patient made the final decision.

METHODS: This study surveyed patients screened for lung cancer within 12 months of the survey, recruited from two academic tertiary care centers in the South Central Region of the U.S. (May to July 2018). **RESULTS:** Two hundred and sixty-four patients completed the survey (87.9% White, 52% male, and mean age of 64.81). Higher SDM process scores (which indicates a better SDM process reported by patients) were significantly associated with greater knowledge of LCS ($b = 0.17$ $p < 0.01$). Higher SDM process scores were associated with less decisional conflict about their screening choice ($b = 0.45$, $p < 0.001$), greater intentions to make the same decision again (OR = 1.42, 95% CI = [1.06-1.89]), and greater intentions to undergo LCS again (OR = 1.32, 95% CI = [1.08-1.62]). The SDM process score was not associated with patients' report of whether or not they shared the final decision with the healthcare provider (OR = 1.07, 95% CI = [0.85-1.35]). **CONCLUSION(S):** This study found that a better SDM process was associated with better affective-cognitive outcomes among patients screened for lung cancer.

[Prevalence of cigarette and e-cigarette use among U.S. adults eligible for lung cancer screening based on updated USPSTF guidelines](#) Cancer Epidemiol. 2022 Feb;76:102079. doi: 10.1016/j.canep.2021.102079. Epub 2021 Dec 8. Brendan T Heiden ¹, Kathryn E Engelhardt ², Chao Cao ³, Bryan F Meyers ⁴, Varun Puri ⁴, Yin Cao ⁵, Benjamin D Kozower ⁴

BACKGROUND: The United States Preventative Services Taskforce recently updated lung cancer screening guidelines for U.S. adults with high-risk smoking histories. This has generated a previously undescribed patient population in which the prevalence of cigarette and e-cigarette use has not been described. **METHODS:** We performed a cross-sectional study using population-based data from the Behavioral Risk Factor Surveillance System (2017-2018). We defined lung cancer screening eligibility as adults 50-80 years old with ≥ 20 pack-year smoking history who were currently smoking or quit within the last 15 years. We assessed several smoking-related outcomes including current cigarette use, ever e-cigarette use, and current e-cigarette use among respondents. **RESULTS:** Among 7541 screening-eligible adults, current cigarette use was reported by 3604 (47.8%) participants. Ever and current e-cigarette use were reported by 3003 (39.8%) and 670 (8.9%) participants, respectively. Compared to individuals who were previously eligible for screening, individuals newly eligible for screening (i.e., between 50 and 55 years old with a 20-30 pack-year smoking history) were more likely to currently smoke (aOR 1.828, 95% CI 1.649-2.026, $p < 0.001$). While newly eligible respondents were more likely to report a history of ever

using an e-cigarette (aOR 1.144, 95% CI 1.034-1.266, $p = 0.009$), current e-cigarette use was similar in this group compared to those individuals who were previously screening-eligible (aOR 1.014, 95% CI 0.844-1.219, $p = 0.88$). **CONCLUSIONS:** Cigarette and e-cigarette exposure are common among U.S. adults who are eligible for lung cancer screening. Expanded USPSTF criteria will capture a patient population with greater exposure to both of these products.

[Cost-effectiveness Evaluation of the 2021 US Preventive Services Task Force Recommendation for Lung Cancer Screening](#) JAMA Oncol. 2021 Dec 1;7(12):1833-1842. doi:

10.1001/jamaoncol.2021.4942. Iakovos Toumazis 1 , Koen de Nijs 2 , Pianpian Cao 3 , Mehrad Bastani 4 , Vidit Munshi 5 , Kevin Ten Haaf 2 , et al.

IMPORTANCE: The US Preventive Services Task Force (USPSTF) issued its 2021 recommendation on lung cancer screening, which lowered the starting age for screening from 55 to 50 years and the minimum cumulative smoking exposure from 30 to 20 pack-years relative to its 2013 recommendation. Although costs are expected to increase because of the expanded screening eligibility criteria, it is unknown whether the new guidelines for lung cancer screening are cost-effective. **OBJECTIVE:** To evaluate the cost-effectiveness of the 2021 USPSTF recommendation for lung cancer screening compared with the 2013 recommendation and to explore the cost-effectiveness of 6 alternative screening strategies that maintained a minimum cumulative smoking exposure of 20 pack-years and an ending age for screening of 80 years but varied the starting ages for screening (50 or 55 years) and the number of years since smoking cessation (≤ 15 , ≤ 20 , or ≤ 25). Design, setting, and participants: A comparative cost-effectiveness analysis using 4 independently developed microsimulation models that shared common inputs to assess the population-level health benefits and costs of the 2021 recommended screening strategy and 6 alternative screening strategies compared with the 2013 recommended screening strategy. The models simulated a 1960 US birth cohort. Simulated individuals entered the study at age 45 years and were followed up until death or age 90 years, corresponding to a study period from January 1, 2005, to December 31, 2050.

EXPOSURES: Low-dose computed tomography in lung cancer screening programs with a minimum cumulative smoking exposure of 20 pack-years. **MAIN OUTCOMES AND MEASURES:** Incremental cost-effectiveness ratio (ICER) per quality-adjusted life-year (QALY) of the 2021 vs 2013 USPSTF lung cancer screening recommendations as well as 6 alternative screening strategies vs the 2013 USPSTF screening strategy. Strategies with a mean ICER lower than \$100 000 per QALY were deemed cost-effective. **RESULTS:** The 2021 USPSTF recommendation was estimated to be cost-effective compared with the 2013 recommendation, with a mean ICER of \$72 564 (range across 4 models, \$59 493-\$85 837) per QALY gained. The 2021 recommendation was not cost-effective compared with 6 alternative strategies that used the 20 pack-year criterion. Strategies associated with the most cost-effectiveness included those that expanded screening eligibility to include a greater number of former smokers who had not smoked for a longer duration (ie, ≤ 20 years and ≤ 25 years since smoking cessation vs ≤ 15 years since smoking cessation). In particular, the strategy that screened former smokers who quit within the past 25 years and began screening at age 55 years was associated with screening coverage closest to that of the 2021 USPSTF recommendation yet yielded greater cost-effectiveness, with a mean ICER of \$66 533 (range across 4 models, \$55 693-\$80 539). **CONCLUSIONS AND RELEVANCE:** This economic evaluation found that the 2021 USPSTF recommendation for lung cancer screening was cost-effective; however, alternative screening strategies that maintained a minimum cumulative smoking exposure of 20 pack-years but included individuals who quit smoking within the past 25 years may be more cost-effective and warrant further evaluation.

[Factors Associated With Obtaining Lung Cancer Screening Among Persons Who Smoke](#) MDM Policy Pract. 2021 Dec 17;6(2):23814683211067810. doi: 10.1177/23814683211067810. eCollection Jul-

Dec 2021. Kristin G Maki¹, Kaiping Liao¹, Lisa M Lowenstein¹, M Angeles Lopez-Olivo¹, Robert J Volk¹

BACKGROUND: Screening with low-dose computed tomography scans can reduce lung cancer deaths but uptake remains low. This study examines psychosocial factors associated with obtaining lung cancer screening (LCS) among individuals. **METHODS:** This is a secondary analysis of a randomized clinical trial conducted with 13 state quitlines' clients. Participants who met age and smoking history criteria were enrolled and followed-up for 6 months. Only participants randomized to the intervention group (a patient decision aid) were included in this analysis. A logistic regression was performed to identify determinants of obtaining LCS 6 months after the intervention. **RESULTS:** There were 204 participants included in this study. Regarding individual attitudes, high and moderate levels of concern about overdiagnosis were associated with a decreased likelihood of obtaining LCS compared with lower levels of concern (high levels of concern, odds ratio [OR] 0.17, 95% confidence interval [CI] 0.04-0.65; moderate levels of concern, OR 0.15, 95% CI 0.05-0.53). In contrast, higher levels of anticipated regret about not obtaining LCS and later being diagnosed with lung cancer were associated with an increased likelihood of being screened compared with lower levels of anticipated regret (OR 5.59, 95% CI 1.72-18.10). Other potential harms related to LCS were not significant. **Limitations.** Follow-up may not have been long enough for all individuals who wished to be screened to complete the scan. Additionally, participants may have been more health motivated due to recruitment via tobacco quitlines. **CONCLUSIONS:** Anticipated regret about not obtaining screening is associated with screening behavior, whereas concern about overdiagnosis is associated with decreased likelihood of LCS. **Implications.** Decision support research may benefit from further examining anticipated regret in screening decisions. Additional training and information may be helpful to address concerns regarding overdiagnosis.

[**NAVIGATE 24-Month RESULTS: Electromagnetic Navigation Bronchoscopy for Pulmonary Lesions at 37 Centers in Europe and the United States**](#) J Thorac Oncol. 2021 Dec 29;S1556-0864(21)03414-6. doi: 10.1016/j.jtho.2021.12.008. Online ahead of print. Erik E Folch¹, Mark R Bowling², Michael A Pritchett³, et al.

INTRODUCTION: Electromagnetic navigation bronchoscopy (ENB) is a minimally invasive, image-guided approach to access lung lesions for biopsy or localization for treatment. However, no studies have reported prospective 24-month follow-up from a large, multinational, generalizable cohort. This study evaluated ENB safety, diagnostic yield, and usage patterns in an unrestricted, real-world observational design. **METHODS:** The NAVIGATE single-arm, pragmatic cohort study (NCT02410837) enrolled subjects at 37 academic and community sites in seven countries with prospective 24-month follow-up. Subjects underwent ENB using the superDimension navigation system versions 6.3 to 7.1. The prespecified primary end point was procedure-related pneumothorax requiring intervention or hospitalization. **RESULTS:** A total of 1388 subjects were enrolled for lung lesion biopsy (1329; 95.7%), fiducial marker placement (272; 19.6%), dye marking (23; 1.7%), or lymph node biopsy (36; 2.6%). Concurrent endobronchial ultrasound-guided staging occurred in 456 subjects. General anesthesia (78.2% overall, 56.6% Europe, 81.4% United States), radial endobronchial ultrasound (50.6%, 4.0%, 57.4%), fluoroscopy (85.0%, 41.7%, 91.0%), and rapid on-site evaluation use (61.7%, 17.3%, 68.5%) differed between regions. Pneumothorax and bronchopulmonary hemorrhage occurred in 4.7% and 2.7% of subjects, respectively (3.2% [primary end point] and 1.7% requiring intervention or hospitalization). Respiratory failure occurred in 0.6%. The diagnostic yield was 67.8% (range: 61.9%-70.7%; 55.2% Europe, 69.8% United States). Sensitivity for malignancy was 62.6%. Lung cancer clinical stage was I to II in 64.7% (55.3% Europe, 65.8% United States). **CONCLUSIONS:** Despite a heterogeneous cohort and regional differences in procedural techniques, ENB demonstrates low complications and a 67.8% diagnostic yield while allowing biopsy, staging, fiducial placement, and dye marking in a single procedure.

[Cost-effectiveness Evaluation of the 2021 US Preventive Services Task Force Recommendation for Lung Cancer Screening](#)

Iakovos Toumazis 1, Koen de Nijs 2, Pianpian Cao 3, Mehrad Bastani 4, Vidit Munshi 5, Kevin Ten Haaf 2, Jihyoun Jeon 3, G Scott Gazelle 5, Eric J Feuer 6, Harry J de Koning 2, Rafael Meza 3, Chung Yin Kong 7, Summer S Han 8, Sylvia K Plevritis 9

IMPORTANCE: The US Preventive Services Task Force (USPSTF) issued its 2021 recommendation on lung cancer screening, which lowered the starting age for screening from 55 to 50 years and the minimum cumulative smoking exposure from 30 to 20 pack-years relative to its 2013 recommendation. Although costs are expected to increase because of the expanded screening eligibility criteria, it is unknown whether the new guidelines for lung cancer screening are cost-effective. **OBJECTIVE:** To evaluate the cost-effectiveness of the 2021 USPSTF recommendation for lung cancer screening compared with the 2013 recommendation and to explore the cost-effectiveness of 6 alternative screening strategies that maintained a minimum cumulative smoking exposure of 20 pack-years and an ending age for screening of 80 years but varied the starting ages for screening (50 or 55 years) and the number of years since smoking cessation (≤ 15 , ≤ 20 , or ≤ 25). **DESIGN, SETTING, AND PARTICIPANTS:** A comparative cost-effectiveness analysis using 4 independently developed microsimulation models that shared common inputs to assess the population-level health benefits and costs of the 2021 recommended screening strategy and 6 alternative screening strategies compared with the 2013 recommended screening strategy. The models simulated a 1960 US birth cohort. Simulated individuals entered the study at age 45 years and were followed up until death or age 90 years, corresponding to a study period from January 1, 2005, to December 31, 2050. Exposures: Low-dose computed tomography in lung cancer screening programs with a minimum cumulative smoking exposure of 20 pack-years. **MAIN OUTCOMES AND MEASURES:** Incremental cost-effectiveness ratio (ICER) per quality-adjusted life-year (QALY) of the 2021 vs 2013 USPSTF lung cancer screening recommendations as well as 6 alternative screening strategies vs the 2013 USPSTF screening strategy. Strategies with a mean ICER lower than \$100 000 per QALY were deemed cost-effective. **RESULTS:** The 2021 USPSTF recommendation was estimated to be cost-effective compared with the 2013 recommendation, with a mean ICER of \$72 564 (range across 4 models, \$59 493-\$85 837) per QALY gained. The 2021 recommendation was not cost-effective compared with 6 alternative strategies that used the 20 pack-year criterion. Strategies associated with the most cost-effectiveness included those that expanded screening eligibility to include a greater number of former smokers who had not smoked for a longer duration (ie, ≤ 20 years and ≤ 25 years since smoking cessation vs ≤ 15 years since smoking cessation). In particular, the strategy that screened former smokers who quit within the past 25 years and began screening at age 55 years was associated with screening coverage closest to that of the 2021 USPSTF recommendation yet yielded greater cost-effectiveness, with a mean ICER of \$66 533 (range across 4 models, \$55 693-\$80 539). **CONCLUSIONS AND RELEVANCE:** This economic evaluation found that the 2021 USPSTF recommendation for lung cancer screening was cost-effective; however, alternative screening strategies that maintained a minimum cumulative smoking exposure of 20 pack-years but included individuals who quit smoking within the past 25 years may be more cost-effective and warrant further evaluation.

[Engaging veteran stakeholders to identify patient-centred research priorities for optimizing implementation of lung cancer screening](#)

Health Expect. 2021 Dec 10. doi: 10.1111/hex.13401. Online ahead of print. Alice Yan 1, Katinka Hooyer 2, Onur Asan 3, Mark Flower 4, Jeff Whittle 5

BACKGROUND: Patient engagement in research agenda setting is increasingly being seen as a strategy to improve the responsiveness of healthcare to patient priorities. Implementation of low-dose computed tomography (LDCT) screening for lung cancer is suboptimal, suggesting that research is needed.

Objectives: This study aimed to describe an approach by which a Veteran patient group worked with other stakeholders to develop a research agenda for LDCT screening and to describe the research questions that

they prioritized. **METHODS:** We worked with Veterans organizations to identify 12 Veterans or family members at risk for or having experience with lung cancer to form a Patient Advisory Council (PAC). The PAC met repeatedly from June 2018 to December 2020, both independently and jointly, with stakeholders representing clinicians, health administrators and researchers to identify relevant research topics. The PAC prioritized these topics and then identified questions within these areas where research was needed using an iterative process. Finally, they ranked the importance of obtaining answers to these questions. **RESULTS:** PAC members valued the co-learning generated by interactions with stakeholders, but emphasized the importance of facilitation to avoid stakeholders dominating the discussion. The PAC prioritized three broad research areas-(1) the impact of insurance on uptake of LDCT; (2) how best to inform Veterans about LDCT; and (3) follow-up and impact of screening results. Using these areas as guides, PAC members identified 20 specific questions, ranking as most important (1) innovative outreach methods, (2) the impact of screening on psychological health, and (3) the impact of outsourcing scans from VA to non-VA providers on completion of recommended follow-up of screening results. The latter two were not identified as high priority by the stakeholder group. **CONCLUSIONS:** We present an approach that facilitates co-learning between Veteran patients and providers, researchers and health system administrators to increase patient confidence in their ability to contribute important information to a research agenda. The research questions prioritized by the Veterans who participated in this project illustrate that for this new screening technology, patients are concerned about the practical details of implementation (e.g., follow-up) and the technology's impact on quality of life. **PATIENT OR PUBLIC CONTRIBUTION:** Veterans and Veteran advocates contributed to our research team throughout the entire research process, including conceiving and co-authoring this manuscript.

[Trends in Use of Next-Generation Sequencing in Patients With Solid Tumors by Race and Ethnicity After Implementation of the Medicare National Coverage Determination](#) JAMA Netw Open. 2021 Dec 1;4(12):e2138219. doi: 10.1001/jamanetworkopen.2021.38219. Daniel M Sheinson 1 , William B Wong 1 , Craig S Meyer 1 , Stella Stergiopoulos 2 , Katherine T Lofgren 2 , Carlos Flores 3 , Devon V Adams 4 , Mark E Fleury 4

IMPORTANCE: In March 2018, Medicare issued a national coverage determination (NCD) for next-generation sequencing (NGS) to facilitate access to NGS testing among Medicare beneficiaries. It is unknown whether the NCD affected health equity issues for Medicare beneficiaries and the overall population. **OBJECTIVE:** To examine the association between the Medicare NCD and NGS use by insurance types and race and ethnicity. Design, setting, and participants: A retrospective cohort analysis was conducted using electronic health record data derived from a real-world database. Data originated from approximately 280 cancer clinics (approximately 800 sites of care) in the US. Patients with advanced non-small cell lung cancer (aNSCLC), metastatic colorectal cancer (mCRC), metastatic breast cancer (mBC), or advanced melanoma diagnosed from January 1, 2011, through March 31, 2020, were included. Exposure: Pre- vs post-NCD period. **MAIN OUTCOMES AND MEASURES:** Patients were classified by insurance type and race and ethnicity to examine patterns in NGS testing less than or equal to 60 days after diagnosis. Difference-in-differences models examined changes in average NGS testing in the pre- and post-NCD periods by race and ethnicity, and interrupted time-series analysis examined whether trends over time varied by insurance type and race and ethnicity. **RESULTS:** Among 92 687 patients with aNSCLC, mCRC, mBC, or advanced melanoma, mean (SD) age was 66.6 (11.2) years, 51 582 (55.7%) were women, and 63 864 (68.9%) were Medicare beneficiaries. The largest racial and ethnic categories according to the database used and further classification were Black or African American (8605 [9.3%]) and non-Hispanic White (59 806 [64.5%]). Compared with Medicare beneficiaries, changes in pre- to post-NCD NGS testing trends were similar in commercially insured patients (odds ratio [OR], 1.03; 95% CI, 0.98-1.08; P = .25). Pre- to post-NCD NGS testing trends increased at a slower rate among patients in assistance programs (OR, 0.93; 95% CI, 0.87-0.99; P = .03) compared with Medicare

beneficiaries. The rate of increase for patients receiving Medicaid was not statistically significantly different compared with those receiving Medicare (OR, 0.92; 95% CI, 0.84-1.01; P = .07). The NCD was not associated with statistically significant changes in NGS use trends by racial and ethnic groups within Medicare beneficiaries alone or across all insurance types. Compared with non-Hispanic White individuals, increases in average NGS use from the pre-NCD to post-NCD period were 14% lower (OR, 0.86; 95% CI, 0.74-0.99; P = .04) among African American and 23% lower (OR, 0.77; 95% CI, 0.62-0.96; P = .02) among Hispanic/Latino individuals; increases among Asian individuals and those with other races and ethnicities were similar. **CONCLUSIONS AND RELEVANCE:** The findings of this study suggest that expansion of Medicare-covered benefits may not occur equally across insurance types, thereby further widening or maintaining disparities in NGS testing. Additional efforts beyond coverage policies are needed to ensure equitable access to the benefits of precision medicine.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

[Single Chest Drain Practice Reduces Discharge Opioid Prescriptions in Thoracic Surgery](#)

Thorac Cardiovasc Surg. 2021 Dec 11. doi: 10.1055/s-0041-1740322. Online ahead of print.

Andres Zorrilla-Vaca 1 , Hope Feldman 2 , Maria Antonoff 2 , Boris Sepesi 2 , Wayne Hofstetter 2 , Ravi Rajaram 2 , Stephen Swisher 2 , Gabriel Mena 3 , Ara Vaporciya 2 , Reza Mehran 2 , David Rice 2

INTRODUCTION: Chest drains are placed following pulmonary resection to promote lung re-expansion. The superiority of two chest drains at preventing postoperative complications has not been established, and practice remains largely dictated by surgeon preference. We sought to compare patient outcomes based on number of chest drains used. **METHODS:** This is a retrospective analysis including patients undergoing lobectomies and segmentectomies between March 2016 and April 2020. Patients were categorized based on number of chest drains placed and were matched 1:1 using the nearest neighbor (greedy) technique. Our primary outcome was opioid prescriptions at discharge (in morphine equivalent daily dose [MEDD]). Associations were tested using multilevel mixed-effects regression to account for variability between surgeons. **RESULTS:** A total of 1,094 patients met inclusion criteria. Single chest drain was used in 922 patients, whereas 172 had two chest tubes. After matching, there were 111 patients in each group. In multilevel mixed-effects logistic regression, patients treated with a single chest drain received fewer opioid prescriptions (β : -194 MEDD, 95% confidence interval [CI]: -302 to -86 MEDD, $p < 0.01$), were more likely to be opioid-free at hospital discharge (odds ratio [OR] = 2.11, 95% CI: 1.08-4.12, $p = 0.03$), and had lower readmission rates within 30 days (OR = 0.33, 95% CI: 0.13-0.84, $p = 0.02$). Single chest drain practice did not affect the risk of pulmonary complications and there was no statistically significant difference in length of hospital stay (3 days [interquartile range: 2-5] vs. 4 days [3-6], $p = 0.08$). **CONCLUSION:** Single chest drain practice in lobectomies and segmentectomies was associated with less opioid prescription requirement without any increase in complications.

[Impact of Chest Wall Resection on Mortality Following Lung Resection for Non-Small Cell Lung Cancer](#)

Ann Thorac Surg. 2021 Dec 10;S0003-4975(21)02041-5. doi: 10.1016/j.athoracsur.2021.10.060.

Online ahead of print. Christopher W Towe 1 , Elliot L Servais 2 , Maria Grau-Sepulveda 3 , et al.

BACKGROUND: Lung cancer invading the chest wall is treated with concomitant en bloc lung and chest wall resection (CWR). It is unclear how CWR affects postoperative outcomes of lung resection. We hypothesized that CWR would be associated with increased risk of adverse outcomes after lung cancer resection. **METHODS:** We performed a retrospective analysis of The Society of Thoracic Surgeons General Thoracic Surgery Database from 2016-2019. Patients with superior sulcus tumors were excluded. Patient demographic and operative outcomes were compared between those with and without CWR.

Chest wall resection was added to existing STS lung risk models to determine the association with a composite adverse outcome, which included major morbidity and death. **RESULTS:** Among 41,310 lung resections, 306 (0.74%) occurred with concomitant CWR. Differences between those with and without CWR included demographic and comorbidities. Patients undergoing CWR were more likely to have the composite adverse outcome (64/306 (20.9%) vs 3128/41004 (7.6%) for non-CWR resections, $p<0.001$). Mortality was also increased among the CWR cohort (2.9% vs 1.1%, $p=0.003$). CWR was associated with an increased risk of adverse composite outcome amongst all lung resection patients in a multivariable model (OR 1.74, $p=0.0003$) and the lobectomy subgroup (OR 2.35, $p<0.0001$). Among institutions with ≥ 10 lung resections, 49.1% performed lung resections with CWR. **CONCLUSIONS:** Concomitant CWR adds risk of adverse outcomes after lung cancer resection. As a subset of institutions perform CWR, quality assessments should control for CWR. This variable will be incorporated into the STS lung cancer and lobectomy quality composite measures.

[The impact of persistent smoking after surgery on long-term outcomes following stage I non-small cell lung cancer resection](#) Chest. 2021 Dec 14;S0012-3692(21)05082-0. doi:

10.1016/j.chest.2021.12.634. Online ahead of print. Brendan T Heiden 1 , Daniel B Eaton Jr 2 , Su-Hsin Chang 3 , et al.

BACKGROUND: Smoking at the time of surgical treatment for lung cancer increases the risk for peri-operative morbidity and mortality. The prevalence of persistent smoking in the post-operative period and its association with long-term oncologic outcomes are poorly described. **RESEARCH QUESTION:** What is the relationship between persistent smoking and long-term outcomes in early-stage lung cancer following surgical treatment? **STUDY DESIGN AND METHODS:** We performed a retrospective cohort study using a uniquely compiled Veterans Health Administration (VHA) dataset of patients with clinical stage I non-small cell lung cancer (NSCLC) undergoing surgical treatment between 2006 and 2016. We defined persistent smoking as individuals who continued smoking 1 year after surgery and characterized the relationship between persistent smoking and disease-free survival and overall survival. **RESULTS:** This study included 7489 patients undergoing surgical treatment for clinical stage I NSCLC. Of 4562 (60.9%) patients who were smoking at the time of surgery, 2648 (58.0%) continued to smoke at 1 year after surgery. Among 2927 (39.1%) patients who were not smoking at the time of surgical treatment, 573 (19.6%) relapsed and were smoking at 1 year after surgery. Persistent smoking at 1 year after surgery was associated with significantly shorter overall survival (adjusted hazard ratio [aHR], 1.291; 95% CI, 1.197-1.392; $p<0.001$). However, persistent smoking was not associated with inferior disease-free survival (aHR, 0.989; 95% CI, 0.884-1.106; $P=0.84$). **INTERPRETATION:** Persistent smoking following surgery for stage I NSCLC is common and is associated with inferior overall survival. Providers should continue to assess smoking habits in the post-operative period given its disproportionate impact on long-term outcomes after potentially curative treatment for early-stage lung cancer.

[Barriers to surveillance imaging adherence in early-staged lung cancer J Thorac Dis. 2021](#)

Dec;13(12):6848-6854. doi: 10.21037/jtd-21-1254. Ian C Bostock 1 , Wayne Hofstetter 1 , Reza Mehran 1 , Ravi Rajaram 1 , David Rice 1 , Boris Sepesi 1 , Stephen Swisher 1 , Ara Vaporciyan 1 , Garrett Walsh 1 , Mara B Antonoff 1

BACKGROUND: Frequency of post-treatment surveillance is highly variable following curative resection of non-small cell lung cancer (NSCLC). We sought to characterize surveillance practices after lobectomy for early-stage NSCLC and to identify the impact of various demographic factors on patterns of surveillance. **METHODS:** We included patients who underwent anatomic lobectomy for pathologic stage I NSCLC from 2007-2017. Demographic characteristics, post-operative imaging studies (internal and external), and travel distance were recorded. We defined the minimal standard of surveillance imaging studies (MSSIS) as ≥ 7 studies in the first 5 years (computed tomography/positron emission

tomography). Patient sex, ethnicity, marital status, and distance traveled were evaluated as predictors of imaging receipt. Standard descriptive statistics, univariate, and multivariate analysis (MVR) were performed. **RESULTS:** A total of 1,288 patients were included. The mean age was 65.5±10.1 years, 589 (45.7%) were male, 1,081 (83.9%) were Caucasian, and 924 (71.7%) were married. Only 464 (36%) achieved MSSIS; being married [75.6% (351/464) vs. 68.8% (567/824), P=0.01] and having larger tumor size (2.63±0.04 vs. 2.49±0.05 cm, P=0.03) were both associated with MSSIS. Patients residing <100 miles from the hospital were more likely to have MSSIS, and more imaging at 24 months (4.1±2.2 vs. 3.7±2.0; P=0.006), 60 months (8.0±5.1 vs. 6.6±4.2, P=0.001) and overall (10±7.3 vs. 8.2±6.3; P=0.001). On MVR, tumor size and marital status were associated with MSSIS. **CONCLUSIONS:** Two-thirds of patients at our institution did not undergo recommended surveillance imaging. Tumor size, being married, and living <100 miles from the medical center were associated with an increased number of imaging studies and greater adherence to guidelines.

[Neurosurgical resection for locally recurrent brain metastasis](#) Neuro Oncol. 2021 Dec 1;23(12):2085-2094. doi: 10.1093/neuonc/noab173. Alexander F C Hulsbergen 1 2 , Abdullah M Abunimer 1 , Fidelia Ida 1 3 , et al.

BACKGROUND: In patients with locally recurrent brain metastases (LRBMs), the role of (repeat) craniotomy is controversial. This study aimed to analyze long-term oncological outcomes in this heterogeneous population. **METHODS:** Craniotomies for LRBMs were identified from a tertiary neuro-oncological institution. First, we assessed overall survival (OS) and intracranial control (ICC) stratified by molecular profile, prognostic indices, and multimodality treatment. Second, we compared LRBMs to propensity score-matched patients who underwent craniotomy for newly diagnosed brain metastases (NDBM). **RESULTS:** Across 180 patients, median survival after LRBMs resection was 13.8 months and varied by molecular profile, with >24 months survival in ALK/EGFR+ lung adenocarcinoma and HER2+ breast cancer. Furthermore, 102 patients (56.7%) experienced intracranial recurrence; median time to recurrence was 5.6 months. Compared to NDBMs (n = 898), LRBMs patients were younger, more likely to harbor a targetable mutation and less likely to receive adjuvant radiation (P < 0.05). After 1:3 propensity matching stratified by molecular profile, LRBMs patients generally experienced shorter OS (hazard ratio 1.67 and 1.36 for patients with or without a mutation, P < 0.05) but similar ICC (hazard ratio 1.11 in both groups, P > 0.20) compared to NDBM patients with similar baseline. Results across specific molecular subgroups suggested comparable effect directions of varying sizes. **CONCLUSIONS:** In our data, patients with LRBMs undergoing craniotomy comprised a subgroup of brain metastasis patients with relatively favorable clinical characteristics and good survival outcomes. Recurrent status predicted shorter OS but did not impact ICC. Craniotomy could be considered in selected, prognostically favorable patients.

[Impact of counterclockwise rotation of the right middle lobe following right upper lobectomy](#)

Interact Cardiovasc Thorac Surg. 2021 Dec 18;ivab356. doi: 10.1093/icvts/ivab356. Online ahead of print. Sachie Koike 1 , Takashi Eguchi 1 , Shunichiro Matsuoka 1 , Tetsu Takeda 1 , Kentaro Miura 1 , Kimihiro Shimizu 1 , Kazutoshi Hamanaka 1

OBJECTIVES: Following right upper lobectomy, the right middle lobe may shift towards the apex and rotate in a counterclockwise direction with respect to the hilum. This study aimed to investigate the incidence and clinical impact of middle lobe rotation in patients undergoing right upper lobectomy. **METHODS:** From January 2014 to November 2018, 82 patients underwent right upper lobectomy at our institution for lung cancer using a surgical stapler to divide the minor fissure. Postoperative computed tomography scans evaluated the counterclockwise rotation of the middle lobe, in which the staple lines placed on the minor fissure were in contact with the major fissure of the right lower lobe (120° counterclockwise rotation). Clinicoradiological factors were evaluated and compared between patients

with and without middle lobe rotation. We also reviewed surgical videos in patients with middle lobe rotation to evaluate the position of the middle lobe at the end of surgery. **RESULTS:** Nine patients had a middle lobe rotation (11%), where 1 patient required surgical derotation. Patients with middle lobe rotation were significantly associated with more frequent right middle lobe atelectasis and severe postoperative complications compared with those without rotation. A surgical video review detected potential middle lobe rotation at the end of the surgery. **CONCLUSIONS:** Middle lobe rotation without torsion following right upper lobectomy is not rare, and it is associated with adverse postoperative courses. Careful positioning of the right middle lobe at the end of surgery is warranted to improve postoperative outcomes.

Thoracoscopic anatomical individual basilar segmentectomy Eur J Cardiothorac Surg. 2021 Dec 29;ezab509. doi: 10.1093/ejcts/ezab509. Online ahead of print. Satoshi Takamori 1 , Hiroyuki Oizumi 1 , Jun Suzuki 1 , Hikaru Watanabe 1 , Kaito Sato 1 , Shoko Saito 1 , Takanobu Kabasawa 2

OBJECTIVES: Thoracoscopic anatomical single or combined anatomical individual basilar segmentectomy, including subsegmentectomy, is technically challenging due to variations and the deep location of vessels and bronchi in the parenchyma. However, the long-term perioperative outcomes of various anatomical subsegmentectomy approaches have not been reported. Thus, we investigated the effectiveness of thoracoscopic basilar segmentectomy. **METHODS:** We evaluated the records of 119 patients who underwent thoracoscopic single or complex basilar segmentectomy between January 2005 and December 2020 and compared the fissure and non-fissure approach for S9 and/or S10. **RESULTS:** A total of 29 patients underwent single segmentectomy, and 90 patients underwent various combined anatomical segmentectomies via video-assisted thoracoscopic surgery and planning using three-dimensional simulation. There were 39 cases of S9 and/or S10 segmentectomy. The median chest tube indwell duration and postoperative hospital stay were 1 and 4 days, respectively. The postoperative morbidity (Clavien-Dindo grade II/IIIa) rate was 5.9% without perioperative mortality. Pathological examination revealed 83 cases of lung cancer, 21 cases of metastasis and 15 cases of benign lesions. The postoperative hospitalization duration showed significant differences in the perioperative outcomes between the fissure and non-fissure approaches for S9 and/or S10. **CONCLUSIONS:** Thoracoscopic anatomical basilar individual segmentectomy has emerged as a safe and feasible procedure. The non-fissure approach enabled anatomic resection of a single segment or combined basal segments, helped avoid dissection of an incomplete fissure and facilitated surgical outcomes similar to the fissure approach.

Conversion to Thoracotomy During Thoracoscopic versus Robotic Lobectomy: Predictors and Outcomes Ann Thorac Surg. 2021 Dec 15;S0003-4975(21)02094-4. doi: 10.1016/j.athoracsur.2021.10.067. Online ahead of print. Elliot L Servais 1 , Daniel L Miller 2 , Dylan P Thibault 3 , et al.

BACKGROUND: Conversion to thoracotomy during minimally invasive lobectomy for lung cancer is occasionally necessary. Differences between video-assisted thoracoscopic (VATS) and robotic-assisted (RATS) lobectomy conversion have not been described. **METHODS:** We queried The Society of Thoracic Surgeons (STS) General Thoracic Surgery Database (GTSD) from January 1, 2015 to December 31, 2018. Patients with prior thoracic operations and metastatic disease were excluded. Univariable comparisons with Chi-squared and Kruskal-Wallis tests and multivariable logistic regression modeling were performed. **RESULTS:** There were 27,695 minimally invasive lobectomies from 269 centers. Conversion to thoracotomy occurred in 11.0% of VATS and 6.0% of RATS ($p<0.001$). Conversion was associated with increased mortality ($p<0.001$), major complications ($p<0.001$), and intra- ($p<0.001$) and post-operative ($p<0.001$) blood transfusions. Conversion from RATS occurred emergently ($p<0.001$) and for vascular injury ($p<0.001$) more frequently than from VATS, but there was no difference in overall major complications or mortality. Mortality following conversion was 3.1% for RATS and 2.2% for

VATS (p=0.24). Clinical cancer stage II or III (p<0.001), preoperative chemotherapy (p=0.003), FEV1 (p=0.006), BMI (p<0.001), and left-sided resection (p=0.0002) independently predicted VATS conversion. For RATS, clinical stage III (p=0.037), left-sided resection (0.041), and FEV1 (p=0.002) predicted conversion. Lower volume centers had increased rates of conversion (p<0.001) in both groups. **CONCLUSIONS:** Conversion from minimally invasive to open lobectomy is associated with increased morbidity and mortality. Conversion occurs more frequently during VATS compared to RATS, although less often emergently, and with similar rates of overall mortality and major complication. Predictors, urgency, and reasons for conversion differ between RATS and VATS lobectomy and may assist in patient selection.

[Complex segmentectomy is not a complex procedure relative to simple segmentectomy](#) Eur J Cardiothorac Surg. 2021 Dec 27;61(1):100-107. doi: 10.1093/ejcts/ezab367. Yu Okubo 1 2 , Yukihiro Yoshida 1 , Masaya Yotsukura 1 , Kazuo Nakagawa 1 , Shun-Ichi Watanabe 1

OBJECTIVES: Segmentectomies can be classified as simple or complex and are increasingly performed for early-stage lung cancer. Complex segmentectomy requires the creation of multiple intersegmental planes and is considered a more arduous procedure with higher risks of postoperative complications, relative to simple segmentectomy. **METHODS:** This retrospective study evaluated patients who underwent simple or complex segmentectomy for primary lung cancer during 2012-2018. Perioperative factors were compared according to the procedure type. **RESULTS:** The 538 eligible segmentectomies included 251 complex segmentectomies and 287 simple segmentectomies. There were no significant differences in terms of age, sex, smoking history or comorbidities. The most common procedure in the complex segmentectomy group was upper-lobe segmentectomy (e.g. S1, S2, S3 and S1 + 2; n = 170), which was followed by S8 segmentectomy (n = 39) and two-segment segmentectomies (e.g. S7 + 8, S8 + 9 and S9 + 10; n = 24). Simple segmentectomies involved left upper division (n = 117), the lingular segment (n = 30) and the S6 segment (n = 140). Comparing complex and simple segmentectomies revealed equivalent median operative times (113 vs 113 min) and blood loss (20 vs 20 ml). Complex segmentectomy had fewer postoperative complications (2.0% vs 7.0%, P = 0.006), including prolonged air leak (0.8% vs 3.5%, P = 0.035) and shorter median postoperative stays (3 vs 4 days, P < 0.001). However, median surgical margins were closer for complex segmentectomy (22 vs 25 mm, P = 0.005). **CONCLUSIONS:** The perioperative outcomes of complex segmentectomy were satisfactory and comparable to those of simple segmentectomy. Surgeons should pay careful attention to the surgical margins during complex segmentectomy.

[Gender Bias in Judging Frailty and Fitness for Lung Surgery](#) Ann Thorac Surg. 2021 Dec 10;S0003-4975(21)02038-5. doi: 10.1016/j.athoracsur.2021.11.013. Online ahead of print. Andy Chao Hsuan Lee , Maria Lucia L Madariaga 1 , Chuanhong Liao 2 , Mark K Ferguson 3

BACKGROUND: Disparities in surgical care for lung cancer have been well documented, and unconscious bias may be a source of inequity. We assessed whether gender biases exist when nonclinical decision makers render decisions about major lung surgery. **METHODS:** Amazon Mechanical Turk workers, remotely located "crowdworkers" readily available for hire to perform discrete on-demand tasks on the Amazon Mechanical Turk platform, were each shown 4 videos of different standardized patients (SPs) in a clinic setting, 1 video in each energy level (vigorous or frail) and race category (White or Black), randomized to male or female. Workers scored video characteristics and whether they would support the SP's decision to undergo a major lung operation. **RESULTS:** A total of 855 workers were recruited. The frail White male SP was more likely to have support to undergo lung surgery than the frail White female SP, while the frail Black male SP was much less likely to have support to undergo lung surgery than the frail Black female SP. There were no significant differences in support for surgery between the vigorous male and female SPs and ratings by male and female workers in their

recommendations. **CONCLUSIONS:** Biases related to patient gender exist in the general population and affect views on surgery, particularly in the setting of frailty. Understanding such differences may aid in educational efforts directed at reducing gender-based biases in treatment recommendations.

[Can Acute Postoperative Pain Management After Tumour Resection Surgery Modulate Risk of Later Recurrence or Metastasis?](#) Front Oncol. 2021 Dec 16;11:802592. doi:

10.3389/fonc.2021.802592. eCollection 2021. Aneurin Moorthy 1 , Aisling Ní Eochagáin 2 , Donal J Buggy 3 4

BACKGROUND: Cancer is a leading cause of mortality worldwide, but death is rarely from the primary tumour: Rather it is multi-organ dysfunction from metastatic disease that is responsible for up to 90% of cancer-related deaths. Surgical resection of the primary tumour is indicated in 70% of cases. The perioperative stress response, tissue hypoxia at the site of surgery, and acute pain contribute to immunosuppression and neo-angiogenesis, potentially promoting tumour survival, proliferation, and metastasis. Poorly controlled acute postoperative pain decreases Natural Killer (NK) immune cell activity, which could potentially facilitate circulating tumour cells from evading immune detection. This consequently promotes tumour growth and distal metastasis. **METHODS:** We conducted a comprehensive literature search for links between acute pain and cancer outcomes using multiple online databases. Relevant articles from January 1st, 2010 to September 1st, 2021 were analysed and appraised on whether postoperative pain control can modulate the risk of recurrence, metastasis, and overall cancer survival. **RESULTS:** Although experimental and retrospective clinical data suggest a plausible role for regional anaesthesia in cancer outcome modulation, this has not been supported by the single, largest prospective trial to date concerning breast cancer. While there are mixed results on anaesthesiology drug-related interventions, the most plausible data relates to total intravenous anaesthesia with propofol, and to systemic administration of lidocaine. **CONCLUSION:** The hypothesis that anaesthetic and analgesic technique during cancer surgery could influence risk of subsequent recurrence or metastasis has been prevalent for >15 years. The first, large-scale definitive trial among women with breast cancer found robust equivalent findings between volatile anaesthesia with opioid analgesia and regional anaesthesia. Therefore, while regional anaesthesia during tumour resection does not seem to have any effect on cancer outcomes, it remains plausible that other anaesthetic techniques (e.g. total intravenous anaesthesia and systemic lidocaine infusion) might influence oncologic outcome in other major tumour resection surgery (e.g. colorectal and lung). Therefore, another large trial is needed to definitively answer these specific research questions. Until such evidence is available, perioperative analgesia for cancer surgery of curative intent should be based on patient co-morbidity and non-cancer endpoints, such as optimising analgesia and minimising postoperative complications.

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

[A Randomized Phase II Study Comparing Nivolumab with Carboplatin-Pemetrexed for EGFR-Mutated NSCLC with Resistance to EGFR Tyrosine Kinase Inhibitors \(WJOG8515L\)](#)

Clin Cancer Res. 2021 Dec 17. doi: 10.1158/1078-0432.CCR-21-3194. Online ahead of print.

Hidetoshi Hayashi 1 , Shunichi Sugawara 2 , Yasushi Fukuda 3 , et al.

PURPOSE: Although the efficacy of programmed cell death-1 (PD-1) blockade is generally poor for non-small cell lung cancer (NSCLC) with activating mutations of the epidermal growth factor receptor (EGFR) gene, EGFR tyrosine kinase inhibitors (TKIs) may improve the tumor immune microenvironment. We performed a randomized study to assess whether nivolumab improves outcome compared with chemotherapy in such patients previously treated with EGFR-TKIs. Patients and

METHODS: Patients with EGFR-mutated NSCLC who acquired EGFR-TKI resistance not due to a secondary T790M mutation of EGFR were randomized 1:1 to nivolumab (n = 52) or carboplatin-

pemetrexed (n = 50). The primary endpoint was progression-free survival (PFS). **RESULTS:** Median PFS and 1-year PFS probability were 1.7 months and 9.6% for nivolumab versus 5.6 months and 14.0% for carboplatin-pemetrexed [log-rank P < 001; hazard ratio (HR) of 1.92, with a 60% confidence interval (CI) of 1.61-2.29]. Overall survival was 20.7 and 19.9 months [HR, 0.88 (95% CI, 0.53-1.47)], and response rate was 9.6% and 36.0% for nivolumab and carboplatin-pemetrexed, respectively. No subgroup including patients with a high tumor mutation burden showed a substantially longer PFS with nivolumab than with carboplatin-pemetrexed. The T-cell-inflamed gene expression profile score (0.11 vs. -0.17, P = 0.036) and expression of genes related to cytotoxic T lymphocytes or their recruitment were higher in tumors that showed a benefit from nivolumab. **CONCLUSIONS:** Nivolumab did not confer a longer PFS compared with carboplatin-pemetrexed in the study patients. Gene expression profiling identified some cases with a favorable tumor immune microenvironment that was associated with nivolumab efficacy.

[INSIGHT 2: a Phase II study of tepotinib plus osimertinib in MET-amplified NSCLC and first-line osimertinib resistance](#) Future Oncol. 2021 Dec 17. doi: 10.2217/fon-2021-1406. Online ahead of print. Egbert F Smit ¹, Christophe Dooms ², Jo Raskin ³, et al.

MET amplification (METamp), a mechanism of acquired resistance to EGFR tyrosine kinase inhibitors, occurs in up to 30% of patients with non-small-cell lung cancer (NSCLC) progressing on first-line osimertinib. Combining osimertinib with a MET inhibitor, such as tepotinib, an oral, highly selective, potent MET tyrosine kinase inhibitor, may overcome METamp-driven resistance. **INSIGHT 2** (NCT03940703), an international, open-label, multicenter Phase II trial, assesses tepotinib plus osimertinib in patients with advanced/metastatic EGFR-mutant NSCLC and acquired resistance to first-line osimertinib and METamp, determined centrally by fluorescence in situ hybridization (gene copy number ≥ 5 and/or MET/CEP7 ≥ 2) at time of progression. Patients will receive tepotinib 500 mg (450 mg active moiety) plus osimertinib 80 mg once-a-day. The primary end point is objective response, and secondary end points include duration of response, progression-free survival, overall survival and safety. Trial registration number: NCT03940703 (clinicaltrials.gov). **PLAIN LANGUAGE SUMMARY:** Lay abstract Osimertinib is used to treat a type of lung cancer that has specific changes (mutations) in a gene called EGFR. Although tumors will usually shrink (respond) during treatment with osimertinib, they can stop responding, or become resistant, to osimertinib. A common cause of resistance is 'MET amplification,' which describes when extra copies of a gene called MET are present. Lung cancer that is resistant to osimertinib due to MET amplification could be treated by combining osimertinib with a treatment that blocks MET, such as tepotinib. **INSIGHT 2** is an ongoing study that is designed to learn about the effects and safety of tepotinib combined with osimertinib, in patients with lung cancer that has stopped responding to osimertinib because of MET amplification. A plain language version of this article is available and is published alongside the paper online: www.futuremedicine.com/doi/suppl/10.2217/fon-2021-1406.

[Alectinib Together with Intracranial Therapies Improved Survival Outcomes in Untreated ALK-Positive Patients with Non-Small-Cell Lung Cancer and Symptomatic and Synchronic Brain Metastases: A Retrospective Study](#) Onco Targets Ther. 2021 Dec 30;14:5533-5542. doi: 10.2147/OTT.S345439. eCollection 2021. Qiang Yin ¹, Peng Li ¹, Peng Wang ¹, Zhen Zhang ¹, Qun Liu ¹, Zengfeng Sun ¹, Wenliang Li ¹, Li Ma ¹, Xiaoguang Wang ¹

PURPOSE: The performance of alectinib and crizotinib in untreated anaplastic lymphoma kinase (ALK)-positive patients with non-small-cell lung cancer (NSCLC) and symptomatic and synchronic brain metastases is largely unknown. This retrospective study assessed the effectiveness of alectinib and crizotinib, together with intracranial therapies in a cohort of these patients. Patients and **METHODS:** This study included 34 previously untreated ALK-positive NSCLC patients with three or fewer intracranial metastases. Of these patients, 13 received oral alectinib 600 mg twice daily, and 21 received

oral crizotinib 250 mg twice daily, until progressive disease, unacceptable toxicity, or death. All intracranial metastases were treated with craniotomy, CyberKnife, or both. **RESULTS:** Median overall progression-free survival (PFS) was 32.8 months (95% CI 24.4-41.2 months) in patients treated with alectinib and 8.0 months (95% CI 7.3-8.7 months) in patients treated with crizotinib. Median PFS of brain lesions was not yet reached with alectinib (95% CI 30.1 months-not estimated) and was 8.5 months (95% CI 7.2-12.3 months) with crizotinib. Median PFS of lung lesions was 38.5 months (95% CI 27.5-49.5 months) with alectinib and 9.2 months (95% CI 7.4-11.0 months) with crizotinib. Median overall survival was not yet reached with alectinib (95% CI 31.0 months-not estimated) and 30.3 months (95% CI 27.3-37.1 months) with crizotinib. **CONCLUSION:** Compared with crizotinib, alectinib showed superior efficacy and lower toxicity in the treatment of ALK-positive patients with NSCLC and symptomatic and synchronic brain metastases. The inclusion of intracranial therapies such as craniotomy or CyberKnife further improved the brain PFS and overall survival of these patients.

[The incidence and predictors of new brain metastases in patients with non-small cell lung cancer following discontinuation of systemic therapy](#) J Neurosurg. 2021 Dec 10;1-11. doi:

10.3171/2021.9.JNS212150. Online ahead of print. Dennis London 1, Dev N Patel 1, Bernadine Donahue 2 3, et al.

OBJECTIVE: Patients with non-small cell lung cancer (NSCLC) metastatic to the brain are living longer. The risk of new brain metastases when these patients stop systemic therapy is unknown. The authors hypothesized that the risk of new brain metastases remains constant for as long as patients are off systemic therapy. **METHODS:** A prospectively collected registry of patients undergoing radiosurgery for brain metastases was analyzed. Of 606 patients with NSCLC, 63 met the inclusion criteria of discontinuing systemic therapy for at least 90 days and undergoing active surveillance. The risk factors for the development of new tumors were determined using Cox proportional hazards and recurrent events models. **RESULTS:** The median duration to new brain metastases off systemic therapy was 16.0 months. The probability of developing an additional new tumor at 6, 12, and 18 months was 26%, 40%, and 53%, respectively. There were no additional new tumors 22 months after stopping therapy. Patients who discontinued therapy due to intolerance or progression of the disease and those with mutations in RAS or receptor tyrosine kinase (RTK) pathways (e.g., KRAS, EGFR) were more likely to develop new tumors (hazard ratio [HR] 2.25, 95% confidence interval [CI] 1.33-3.81, $p = 2.5 \times 10^{-3}$; HR 2.51, 95% CI 1.45-4.34, $p = 9.8 \times 10^{-4}$, respectively). **CONCLUSIONS:** The rate of new brain metastases from NSCLC in patients off systemic therapy decreases over time and is uncommon 2 years after cessation of cancer therapy. Patients who stop therapy due to toxicity or who have RAS or RTK pathway mutations have a higher rate of new metastases and should be followed more closely.

[Effectiveness and safety of pembrolizumab monotherapy in patients with locally advanced or metastatic non-small-cell lung cancer](#) J Oncol Pharm Pract. 2021 Dec 21;10781552211061117. doi:

10.1177/10781552211061117. Online ahead of print. Rocio Tamayo-Bermejo 1 2, Juan Carlos Del Rio-Valencia 3, Beatriz Mora-Rodriguez 3, Isabel Muñoz-Castillo 3

INTRODUCTION: Immunotherapy has become a standard treatment for lung cancer; the objective of this study was to evaluate the effectiveness, safety of pembrolizumab monotherapy in patients with advanced or metastatic non-small-cell lung cancer used in real-world clinical practice. **METHODS:** Retrospective observational study of every patient treated with pembrolizumab in our centre from January 2017 to June 2019. Outcomes collected: sex, age, Eastern Cooperative Oncology Group, programmed death receptor 1 level, previous metastatic line therapies, adverse events and smoking status. **RESULTS:** A total of 62 patients were reviewed. The median age was 62.34 ± 10.62 years, 48 (77.41%) were men and 91.93% of patients had Eastern Cooperative Oncology Group 0. The median dose administered was 170.5 mg (108 - 240 mg) and the median follow-up was 3 months (range: 1 - 38). A

median of four cycles of pembrolizumab (range: 1 - 56) were administered as monotherapy. The reason for treatment discontinuation was mainly due to disease progression in 38.70% of patients or death in 30.64%. As first-line pembrolizumab monotherapy, median progression-free survival was 7.7 months (95% CI: 3.66 - 11.73) (N = 33). With respect to patients who were treated in second-third-line treatment, median progression-free survival was 3.5 months (95% CI: 2.40 - 4.59) (N=29). As to overall survival, pembrolizumab-treated patients as first-line treatment reached 19 months median OS (95% CI: 13.36 - 24.63) (N = 33) and those treated in second-third-line treatment got 11 months (95% CI: 3.4 - 18.5). A total of 64.51% of patients presented some adverse events to pembrolizumab however, only, 9.38% of them were grade 3. **CONCLUSION:** Pembrolizumab represents an effective and feasible alternative in terms of progression-free survival. It is a well-tolerated treatment option.

Safety and Efficacy of Extended Interval Dosing for Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer During the COVID-19 Pandemic Clin Lung Cancer. 2021 Dec 24;S1525-7304(21)00305-3. doi: 10.1016/j.clcc.2021.12.005. Online ahead of print. L B M Hijmering-Kappelle 1 , T J N Hiltermann 2 , F Bensch 2

INTRODUCTION: Extended interval (EI) dosing for immune checkpoint inhibitor (ICI) mono- or consolidation therapy initiated due to the COVID-19 pandemic led to a significant reduction in ICI-related site visits for patients with stage III and IV non-small cell lung cancer. Here we report the safety and efficacy compared to standard dose (SD) schedules. Method: In this retrospective analysis, patients who received ICI mono- or consolidation therapy, or adjuvant ICI therapy were assessed. Safety and efficacy of EI dosing with data of SD schedules were compared. **RESULTS:** One hundred seventeen patients received EI dosing for ICI and 88 patients SD. Patient characteristics were comparable. We observed 237 adverse events in the EI dosing cohort versus 118 in the SD group (P= .02). Overall, there was no difference in the occurrence of grade ≥ 3 adverse events (EI dosing: 21/237 [8.9%]; SD group: 20/118 [17.0%], P = .42), except for the pembrolizumab EI dosing cohort. Of all patients who received an EI dosing schedule, however, only 8 (6.8%) were reduced to SD because of toxicity. In 5 (4.3%) patients ICI was permanently stopped because of severe toxicity compared to 11 (12.5%) discontinuations in the SD group. Short-term treatment interruption occurred with similar frequencies in both groups. Progression-free survival and overall survival were comparable in patients receiving pembrolizumab and in those receiving adjuvant durvalumab. Progression-free survival and OS were better in the EI dosing cohort of nivolumab. **CONCLUSION:** EI dosing for ICI did not lead to an increase of clinically relevant toxicities resulting in dose reduction and/or treatment discontinuation. Efficacy of EI dosing of pembrolizumab and durvalumab were comparable to SD. Based on our safety and efficacy data EI dosing for ICI seems a safe and effective strategy.

Real-World Outcomes Among Crizotinib-Treated Patients with ROS1-Positive Advanced Non-Small-Cell Lung Cancer: A Community Oncology-Based Observational Study Target Oncol. 2022 Jan;17(1):25-33. doi: 10.1007/s11523-021-00860-z. Epub 2021 Dec 29. David Waterhouse 1 2 , Laura Iadeluca 3 , Sneha Sura 4 , Keith Wilner 3 , Birol Emir 3 , Stan Krulewicz 5 , Janet Espirito 4 , Lauren Bartolome 6

BACKGROUND: Crizotinib was the first oral targeted therapy approved by the US Food and Drug Administration (FDA), on 11 March 2016, for c-ros oncogene 1 (ROS1)-positive advanced non-small-cell lung cancer (NSCLC). Data to support long-term clinical benefit in a real-world setting are limited. Objective: This study aimed to assess real-world clinical outcomes among patients with ROS1-positive advanced NSCLC treated with crizotinib in the US community oncology setting. Patients and **METHODS:** We conducted a retrospective cohort study using iKnowMed electronic health record data to identify adult patients with ROS1-positive advanced NSCLC who initiated crizotinib between 17 January 2013 (time of the addition of crizotinib for ROS1-positive NSCLC to National Comprehensive

Cancer Network (NCCN) treatment guidelines) and 1 June 2019 with a potential follow-up period through 1 December 2019. Patient characteristics were assessed descriptively. Kaplan-Meier analyses were used to evaluate time to treatment discontinuation (TTD), time to next treatment (TTNT), and overall survival (OS). A Cox proportional hazards model was conducted to determine factors associated with OS. **RESULTS:** The study cohort included 38 ROS1-positive patients treated with crizotinib. The median age was 68 years (interquartile range 60.0-73.0) and 65.8% were female. Over 50% were current/former smokers, and 18.4% had an Eastern Cooperative Oncology Group (ECOG) performance status of 2. Overall, 21 (55.3%) patients remained on crizotinib, 10 (26.3%) had evidence of subsequent treatment, and 16 (42.1%) died. The median TTD, TTNT, and OS were 25.2 months [95% confidence interval (CI): 5.2-not reached (NR)], 25.0 months (95% CI 5.2-61.0), and 36.2 months (95% CI 15.9-NR), respectively. In a multivariate Cox regression model, ECOG performance status of 2 was associated with a 4.9-fold higher risk of death (hazard ratio = 4.9; 95% CI 1.1-21.4) compared to ECOG performance status of 0 or 1. **CONCLUSIONS:** This ROS1-positive NSCLC real-world population was older and had a higher proportion of smokers and of patients with poorer ECOG performance status than those investigated in clinical trials. Nevertheless, our findings support the clinical benefit of crizotinib in this patient population with ROS1-positive advanced NSCLC.

[RELAY, Ramucirumab Plus Erlotinib Versus Placebo Plus Erlotinib in Patients with Untreated, Epidermal Growth Factor Receptor Mutation-Positive, Metastatic Non-Small-Cell Lung Cancer: Safety Profile and Manageability](#) Drug Saf. 2022 Jan;45(1):45-64. doi: 10.1007/s40264-021-01127-2. Epub 2021 Dec 20. Ernest Nadal ¹, Hidehito Horinouchi ², Jin-Yuan Shih ³, et al.

INTRODUCTION: RELAY was a global, double-blind, placebo-controlled phase III study that demonstrated superior progression-free survival (PFS) for ramucirumab plus erlotinib (RAM + ERL) versus placebo plus erlotinib (PBO + ERL) in the first-line treatment of patients with epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 (L858R) mutation-positive, metastatic non-small-cell lung cancer (NSCLC). Objective: This article provides an in-depth analysis of the safety profile of RAM + ERL versus PBO + ERL observed in RELAY. **METHODS:** Eligible patients met these criteria: stage IV NSCLC; EGFR exon 19 deletion or exon 21 substitution (L858R) mutation; Eastern Cooperative Oncology Group performance status 0 or 1; and no central nervous system metastases. Patients were randomized (1:1) to receive erlotinib 150 mg/day orally plus either ramucirumab 10 mg/kg intravenously or matching placebo once every 2 weeks, until disease progression or unacceptable toxicity. The primary endpoint was PFS. Safety was evaluated based on reported treatment-emergent adverse events (AEs) and clinical laboratory assessments. **RESULTS:** The safety population comprised 446 patients (221 in RAM+ERL arm; 225 in PBO + ERL arm) who received at least one dose of study drug between January 2016 and February 2018. The overall incidence of grade ≥ 3 AEs was higher with RAM + ERL than with PBO + ERL, primarily driven by grade 3 hypertension. Grade ≥ 3 dermatitis acneiform and diarrhea were also reported more frequently in the RAM + ERL arm. The increased incidence of AEs with RAM + ERL was easily detected through routine monitoring and managed through dose adjustments and appropriate supportive care. **CONCLUSION:** This in-depth safety analysis from RELAY supports that RAM + ERL, irrespective of the increased incidence of AEs, does not affect a patient's ability to benefit from treatment.

[Prospective, Noninterventional Study of Nivolumab in Real-world Patients With Locally Advanced or Metastatic Non-small Cell Lung Cancer After Prior Chemotherapy \(ENLARGE-Lung\)](#) J Immunother. 2021 Dec 15. doi: 10.1097/CJI.0000000000000397. Online ahead of print. Martin Sebastian ¹, Andreas Gröschel, Sylvia Gütz, Holger Schulz, et al.

Nivolumab was the first immune checkpoint inhibitor approved for use in advanced non-small cell lung cancer (NSCLC). This noninterventional, prospective cohort study investigates real-world effectiveness of nivolumab in pretreated NSCLC patients in Germany (Enlarge-Lung/CA209-580). Patients with

squamous (SQ) or nonsquamous (NSQ) NSCLC previously treated for locally advanced or metastatic (stage IIIB/IV) disease received nivolumab according to the current Summary of Product Characteristics. Overall survival (OS) was the primary endpoint. Of 907 patients enrolled, 660 patients who were followed for at least 12 months across 79 study centers in Germany, were analyzed. Median OS was 11.2 months [95% confidence interval (CI), 9.1-12.9]; outcomes for the 418 patients with NSQ histology [13.1 mo (95% CI, 10.6-15.6)] were more favorable than outcomes for the 242 patients with SQ histology [8.9 mo (95% CI, 6.4-11.3)]. Patients' age, presence of distant or brain metastases, or line of therapy did not affect outcomes; however, patients with poor performance status (ECOG-PS ≥ 2 , n=80) had shorter median OS [4.7 mo (95% CI, 3.1-5.4)]. **This study represents one** of the largest real-world cohorts providing outcomes of nivolumab in pretreated NSCLC. The results match well with the published evidence from pivotal clinical trials and demonstrate clinical effectiveness of nivolumab in advanced NSCLC.

[Application of Evidence-Based Nursing Intervention in the Treatment of Advanced Squamous Cell Carcinoma of the Lung by Erlotinib Combined with Tegafur, Gimeracil, and Oteracil Potassium and Its Influence on Quality of Life](#) J Healthc Eng. 2021 Dec 13;2021:6801779. doi:

10.1155/2021/6801779. eCollection 2021. Shan Liu 1 , Xiaocheng Huang 1 , Jin Wen 2 , Fangfang Fu 2 , Huifen Wang 1

OBJECTIVE: To explore the application of evidence-based nursing intervention in the treatment of advanced squamous cell carcinoma of the lung by erlotinib combined with tegafur, gimeracil, and oteracil potassium (TS-1) and its influence on quality of life (QOL). **METHODS:** Clinical data of 92 patients with advanced squamous cell carcinoma of the lung treated with erlotinib and TS-1 in our hospital (January 2017-January 2021) were retrospectively analyzed. Forty-six patients receiving conventional nursing were set as the control group (CG), and other 46 patients receiving evidence-based nursing intervention additionally were set as the study group (SG). The clinical observation indexes of the two groups were compared and analyzed. **RESULTS:** No obvious difference in general data between both groups ($P > 0.05$). According to EORTC QLQ-C30, compared with the CG, the scores of role function, physical function, social function, cognitive function, and emotional function in the SG were remarkably higher ($P < 0.05$). After intervention, scores of VAS of patients were obviously lower than those before intervention ($P < 0.05$), and scores of VAS in the SG after intervention were obviously lower than those in the CG ($P < 0.05$). After intervention, scores of SAS and SDS were lower than those before intervention, and those of the SG were obviously lower than those of the CG ($P < 0.05$). Compared with the CG, incidences of adverse reactions such as diarrhoea, nausea and vomiting, erythra, pressure sores, and leukopenia in the SG were obviously lower ($P < 0.05$). Compared with the CG, "very satisfied" and total satisfaction in the SG were obviously higher ($P < 0.05$). **CONCLUSION:** Application of evidence-based nursing intervention in the treatment of advanced squamous cell carcinoma of the lung by erlotinib combined with TS-1 can help patients to relieve pain, improve their psychological state, reduce the incidence of adverse reactions, significantly improve the QOL, and also enhance the satisfaction of clinical nursing.

[Treatment Outcomes and Safety of Mobocertinib in Platinum-Pretreated Patients With EGFR Exon 20 Insertion-Positive Metastatic Non-Small Cell Lung Cancer: A Phase 1/2 Open-label Nonrandomized Clinical Trial](#) JAMA Oncol. 2021 Dec 1;7(12):e214761. doi:

10.1001/jamaoncol.2021.4761. Epub 2021 Dec 16. Caicun Zhou 1, Suresh S Ramalingam 2 , Tae Min Kim 3 , et al.

IMPORTANCE: Metastatic non-small cell lung cancer (mNSCLC) with EGFR exon 20 insertion (EGFR_{ex20ins}) mutations is associated with a poor prognosis. Mobocertinib is an oral tyrosine kinase inhibitor designed to selectively target EGFR_{ex20ins} mutations. **OBJECTIVE:** To evaluate treatment

outcomes and safety of mobocertinib in patients with previously treated EGFRex20ins-positive mNSCLC. Design, setting, and participants: This 3-part, open-label, phase 1/2 nonrandomized clinical trial with dose-escalation/dose-expansion cohorts (28 sites in the US) and a single-arm extension cohort (EXCLAIM; 40 sites in Asia, Europe, and North America) was conducted between June 2016 and November 2020 (data cutoff date). The primary analysis populations were the platinum-pretreated patients (PPP) cohort and the EXCLAIM cohort. The PPP cohort included 114 patients with platinum-pretreated EGFRex20ins-positive mNSCLC who received mobocertinib 160 mg once daily from the dose-escalation (n = 6), dose-expansion (n = 22), and EXCLAIM (n = 86) cohorts. The EXCLAIM cohort included 96 patients with previously treated EGFRex20ins-positive mNSCLC (10 were not platinum pretreated and thus were excluded from the PPP cohort). Interventions: Mobocertinib 160 mg once daily. **MAIN OUTCOMES AND MEASURES:** The primary end point of the PPP and EXCLAIM cohorts was confirmed objective response rate (ORR) assessed by independent review committee (IRC). Secondary end points included confirmed ORR by investigator, duration of response, progression-free survival, overall survival, and safety. **RESULTS:** Among the PPP (n = 114) and EXCLAIM (n = 96) cohorts, the median (range) age was 60 (27-84) and 59 (27-80) years, respectively; most patients were women (75 [66%] and 62 [65%], respectively) and of Asian race (68 [60%] and 66 [69%], respectively). At data cutoff, median follow-up was 14.2 months in the PPP cohort (median 2 prior anticancer regimens; 40 [35%] had baseline brain metastases), with confirmed ORR of 28% (95% CI, 20%-37%) by IRC assessment and 35% (95% CI, 26%-45%) by investigator assessment; median duration of response by IRC assessment was 17.5 months (95% CI, 7.4-20.3). Median progression-free survival by IRC assessment was 7.3 months (95% CI, 5.5-9.2). Median overall survival was 24.0 months (95% CI, 14.6-28.8). In the EXCLAIM cohort, median follow-up was 13.0 months, with confirmed ORR by IRC assessment of 25% (95% CI, 17%-35%) and by investigator assessment of 32% (95% CI, 23%-43%). The most common treatment-related adverse events were diarrhea and rash. **CONCLUSIONS AND RELEVANCE:** In this open-label, phase 1/2 nonrandomized clinical trial, mobocertinib was associated with clinically meaningful benefit in patients with previously treated EGFRex20ins-positive mNSCLC, with a manageable safety profile.

[Immunotherapy plus chemotherapy showed superior clinical benefit to chemotherapy alone in advanced NSCLC patients after progression on osimertinib](#) Thorac Cancer. 2021 Dec 27. doi:

10.1111/1759-7714.14271. Online ahead of print.

BACKGROUND: Osimertinib is the standard first-line treatment for non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) mutation. Resistance to osimertinib remains a clinical challenge. However, the optimal therapy for these patients is still controversial. In this study, we aimed to assess the efficacy and safety of immunotherapy plus chemotherapy (IO+C) compared with chemotherapy (C) in NSCLC patients after progression on osimertinib. **METHODS:** Advanced NSCLC patients after progression on osimertinib were retrospectively reviewed. Progression-free survival (PFS), overall survival (OS), objective response rate (ORR), disease control rate (DCR), and safety were evaluated between the patients treated with IO+C and C. **RESULTS:** A total of 40 patients were included in the study. There were 20 patients each in the IO+C group or C group. The ORR was significantly higher in patients in the IO+C group (45% vs. 25%, $p < 0.01$). The median PFS was 6.4 months for patients in the IO+C group compared to 2.8 months for patients in C group (HR: 0.41, 95% confidence interval [CI]: 0.20-0.82, $p < 0.01$). The median OS was significantly longer in the IO+C group than the C group (OS: 12.8 vs. 10.5 months, HR: 0.39, 95% CI: 0.19-0.80, $p < 0.01$). In subgroup analysis, patients of both sexes, age ≤ 65 , bone or adrenal metastasis, exon19 del mutation, and third-line treatment obtained more OS benefits from immunotherapy. The safety profile of both groups was comparable. **CONCLUSIONS:** Our study provides the clinical evidence of favoring immunotherapy plus chemotherapy in NSCLC patients after progression on osimertinib.

[**Pralsetinib \(Gavreto\): Treatment of metastatic non-small-cell lung cancer in patients positive for RET fusions**](#) Am J Health Syst Pharm. 2021 Dec 5;zxab462. doi: 10.1093/ajhp/zxab462. Online ahead of print. Ly Nguyen 1 , Shanada Monestime 2

DISCLAIMER: In an effort to expedite the publication of articles, AJHP is posting manuscripts online as soon as possible after acceptance. Accepted manuscripts have been peer-reviewed and copyedited, but are posted online before technical formatting and author proofing. These manuscripts are not the final version of record and will be replaced with the final article (formatted per AJHP style and proofed by the authors) at a later time. **PURPOSE:** To review the pharmacology, efficacy, safety, dosing and administration, and place in therapy of pralsetinib, a tyrosine kinase inhibitor, for the treatment of non-small-cell lung cancer (NSCLC) in patients with RET fusions. **SUMMARY:** RET fusion-positive NSCLC is a rare cancer caused by chromosomal rearrangements that lead to fusions of the RET gene with other genes, such as KIF5B and CCDC6. Until recently, patients were treated with platinum-based chemotherapy or multitargeted tyrosine kinase inhibitors. However, because of their nonspecific mechanism of action, these drugs did not have high response rates. In September 2020, the Food and Drug Administration approved pralsetinib (Gavreto), the first once-daily oral tyrosine kinase inhibitor, for patients with metastatic RET fusion-positive NSCLC. Pralsetinib has been demonstrated to have response rates of 57% and 70% in patients who were previously treated with platinum chemotherapy and patients who were treatment naive, respectively. Clinicians using pralsetinib should monitor for liver-related adverse events, hypertension, myelosuppression, pyrexia, sepsis, gastrointestinal symptoms, dyspnea, pneumonitis, and pneumonia, as these may require treatment interruption, dose reduction, or treatment discontinuation. **CONCLUSION:** Pralsetinib is a unique targeted tyrosine kinase inhibitor approved for the treatment of patients with RET fusion-positive NSCLC who may desire a once-daily regimen. The recent approval of pralsetinib represents an important addition for the treatment of patients with RET fusion-positive NSCLC.

[**Safety and activity of alectinib plus bevacizumab in patients with advanced ALK-rearranged non-small-cell lung cancer: a phase I/II study**](#) ESMO Open. 2021 Dec 9;7(1):100342. doi: 10.1016/j.esmoop.2021.100342. Online ahead of print. J J Lin 1 , A Muzikansky 1 , E Kennedy 1 , H Kuberski 1 , L L Stober 1 , A C Wanat 1 , C G Azzoli 1 , I Lennes 1 , L V Sequist 1 , I Dago-Jack 1 , A T Shaw 2 , J F Gainor 3

BACKGROUND: Alectinib, a second-generation anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI), is highly effective in advanced ALK-rearranged non-small-cell lung cancer and represents a standard first-line therapy. New strategies are needed, however, to delay resistance. We conducted a phase I/II study to assess the safety and efficacy of combining alectinib with bevacizumab, a monoclonal antibody against vascular endothelial growth factor. Patients and **METHODS:** Patients with advanced ALK-rearranged non-squamous non-small-cell lung cancer were enrolled. The phase I portion employed a dose de-escalation strategy with alectinib and bevacizumab starting at the individual standard doses. The primary objective was to determine the recommended phase II dose (RP2D). In phase II, the primary objective was to evaluate the safety of the combination at the RP2D; the secondary objective was to determine extracranial and intracranial efficacy. **RESULTS:** Eleven patients were enrolled between September 2015 and February 2020. Most patients (82%) had baseline brain metastases. Six patients (55%) were treatment-naive; five (46%) had received prior ALK TKIs (crizotinib, n = 3; ceritinib, n = 1; crizotinib then brigatinib, n = 1). No dose-limiting toxicities occurred. RP2D was determined as alectinib 600 mg orally twice daily plus bevacizumab 15 mg/kg intravenously every 3 weeks. Three patients experienced grade 3 treatment-related adverse events: pneumonitis related to alectinib, proteinuria related to bevacizumab, and hypertension related to bevacizumab. Treatment-related intracranial hemorrhage was not observed. Six (100%) of six treatment-naive patients and three (60%) of five ALK TKI-pretreated

patients had objective responses; median progression-free survival was not reached (95% confidence interval, 9.0 months-not reached) and 9.5 months (95% confidence interval, 4.3 months-not reached), respectively. Intracranial responses occurred in four (100%) of four treatment-naive and three (60%) of five TKI-pretreated patients with baseline brain metastases. The study was stopped prematurely because of slow accrual. **CONCLUSIONS:** Alectinib plus bevacizumab was well tolerated without unanticipated toxicities or dose-limiting toxicities.

NSCLC - RADIOTHERAPY

[PD-1 Blockade With Concurrent Radiotherapy for Locally Advanced Inoperable Cutaneous Squamous Cell Carcinoma](#)

J Cutan Med Surg. 2021 Dec 4;12034754211064273. doi: 10.1177/12034754211064273. Online ahead of print. Kurian Joseph 1 , John Walker 2 , Hamid Raziee 3 , Salman Faruqi 4 , Michael Smylie 2

INTRODUCTION: For patients with locally advanced cutaneous squamous cell carcinoma (LA-cSCC), radiotherapy alone (RT) is often the only treatment option with modest tumor response. We report the outcomes of using combination of programmed cell death protein-1 (PD-1) inhibitor and RT in the treatment of inoperable LA-cSCC. The study presents the efficacy and safety data for the patients with LA-cSCC treated with this combination. **METHODS:** During the period 2018-2020, a total of 7 patients with biopsy proven inoperable LA-cSCC were treated with combination of PD-1 inhibitor cemiplimab and concurrent RT (Cem-RT). The patients were followed up for safety and efficacy of the Cem-RT regimen and the primary endpoints were objective tumor response and toxicity. **RESULTS:** The median age of patients was 68 years (range, 64-94). All patients had ECOG performance score 0-1. Six patients initially received cemiplimab and concurrent RT was added to PD-1 inhibitor when there was an inadequate therapeutic response. One patient received concurrent Cem-RT. RT with PD-1 antibody was well tolerated. Six patients developed grade ≤ 2 dermatitis and 1 patient (patient no. 3) developed acute grade 3 skin reaction. During the post-RT follow up, 3 patients discontinued cemiplimab due to significant toxicities. At the time of reporting , 5 patients remain in complete remission. One patient developed lung metastasis and is currently receiving best supportive care. **CONCLUSIONS:** The Cem-RT combination was safe and well tolerated with significant tumor response suggesting Cem-RT may be a viable therapeutic option for LA-cSCC. Our hypothesis generating data support the rationale for future prospective studies.

[Outcomes of Gamma Knife Radiosurgery for Brain Metastases From Anaplastic Lymphoma Kinase Rearrangement-Positive and EGFR Mutation-Positive Non-Small Cell Lung Cancer](#)

Cureus. 2021 Dec 13;13(12):e20398. doi: 10.7759/cureus.20398. eCollection 2021 Dec. Shigeo Matsunaga 1 , Takashi Shuto 1

INTRODUCTION: The outcomes after gamma knife radiosurgery (GKRS) were retrospectively analysed in patients with brain metastases from anaplastic lymphoma kinase (ALK) rearrangement-positive and epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC) to evaluate the efficacy, safety and difference for overall survival and local tumor control. **METHODS:** The medical records were retrospectively reviewed of 607 patients (25 ALK-positive, 171 EGFR-positive, and 411 wild type) with 2959 tumors who had undergone GKRS. **RESULTS:** The median overall survival time after initial GKRS was 14 months. Driver gene mutation-positive patients had significantly longer overall survival than wild type patients ($p < 0.0001$), and ALK-positive patients survived significantly longer than EGFR-positive patients ($p = 0.04$). Multivariate analysis showed the unfavorable factors significantly affecting overall survival outcomes were older age, lower Karnofsky Performance Status score, multiple intracranial metastases, uncontrolled primary cancer, uncontrolled extracranial metastases, no administration of immune checkpoint inhibitors, and driver gene mutation-

negative cases. Seventy-three patients died of uncontrolled brain metastases at a median of 12 months. Driver gene mutations had no influence ($p = 0.33$), and ALK-positive and EGFR-positive patients showed no significant difference in neurological survival ($p = 0.83$). A total of 174 patients demonstrated distant brain control failure at a median of 15 months. ALK-positive type was significant compared with EGFR-positive type ($p = 0.047$), but driver gene mutation-positive and -negative types showed no significant difference in the development of new brain metastases ($p = 0.2$). The median tumor volume was 1.06 cm³ in the driver gene mutation-positive type and 1.85 cm³ in wild type. The median marginal dose was 20 Gy in both types. The 6-, 12-, and 24-month local tumor control rates were 97.3%, 96.1%, and 95.9%, respectively. Driver gene mutations had a significantly positive impact on local tumor control ($p = 0.001$), and ALK-positive and EGFR-positive types showed no significant difference ($p = 0.95$). A total of 193 tumors had radiation injury at a median of 12 months after GKRS. The 6-, 12-, and 24-month GKRS-related complication rates were 3.3%, 8.1%, and 8.7%, respectively. Driver gene mutations significantly induced radiation damage ($p = 0.021$), and the ALK-positive type was affected more than the EGFR-positive type ($p = 0.02$). **CONCLUSIONS:** ALK rearrangement-positive NSCLC patients tended to have significantly longer survival, but had higher incidence of new intracranial metastases due to long-term survival after GKRS, compared with EGFR mutation-negative and driver gene mutation-negative NSCLC patients. GKRS induced significantly satisfactory local tumor control in driver gene mutation-positive tumors but GKRS-related complication frequency was higher, especially in ALK-positive NSCLC patients. Therefore, more careful imaging follow-up is necessary after GKRS for patients with driver gene mutation-positive NSCLC.

Efficacy and safety of WBRT+EGFR-TKI versus WBRT only in the treatment of NSCLC patients with brain metastasis: An updated meta-analysis

Thorac Cancer. 2021 Dec 30. doi: 10.1111/1759-7714.14299. Online ahead of print. Kai Zhou ¹, Xiaoping Cai ², Xiaoqiu Wang ³, Xiang Lan ⁴, Xuexia Zhang ⁵

BACKGROUND: To investigate the efficacy and safety of whole brain radiotherapy (WBRT) combined with epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) versus WBRT only in the treatment of brain metastasis in non-small cell lung cancer (NSCLC) patients by pooling open published data. **METHODS:** Prospective clinical studies relevant to WBRT+EGFR-TKI versus WBRT only in the treatment of NSCLC brain metastasis were electronically searched in the Pubmed, Embase, Cochrane, Wangfang, CNKI and Google scholar databases. The treatment response, 1-year survival and treatment-associated toxicity were pooled and expressed by odds ratio (OR) under a fixed or random effect model. The publication bias was evaluated by Begg's funnel plot and Egger's line regression test. **RESULTS:** Eighteen prospective clinical studies were included in the study. The combined results indicated that the objective response rate (ORR) in the WBRT+TKI group was superior to WBRT only with a statistical difference (OR = 2.67, 95% CI: 2.10-3.38, $p < 0.05$) under a fixed effect model. Ten studies reported the 1-year survival rate between the WBRT+TKI and WBRT only groups. The combined results showed that 1-year survival rate in the WBRT+TKI group was higher than that of the WBRT only group with a statistical difference (OR = 2.70, 95% CI: 1.95-3.74, $p < 0.05$). For treatment-associated toxicity, the combined data indicated that the treatment-related rash in the WBRT+TKI group was significantly higher than that of the WBRT only group with a statistical difference (OR = 2.72, 95% CI: 1.53-4.84, $p < 0.05$). However, the incidence of nausea/vomiting (OR = 0.84, 95% CI: 0.60-1.17, $p > 0.05$), diarrhea (OR = 1.31, 95% CI: 0.83-2.07, $p > 0.05$), fatigue (OR = 1.40, 95% CI: 0.70-2.81, $p > 0.05$) and myelosuppression (OR = 0.86, 95% CI: 0.56-1.32, $p > 0.05$) were not statistically different between the two groups. **CONCLUSIONS:** Based on the current publications, WBRT+EGFR-TKI can improve the treatment response and 1-year survival rate but not increase the toxicity except for rash compared to WBRT alone in the treatment of brain metastasis in NSCLC patients.

[The markerless lung target tracking AAPM Grand Challenge \(MATCH\) results](#) Med Phys. 2021 Dec 16. doi: 10.1002/mp.15418. Online ahead of print. Marco Mueller 1 , Per Poulsen 2 , Rune Hansen 3 , Wilko Verbakel 4 , Ross Berbeco 5 , Dianne Ferguson 5 , Shinichiro Mori 6 , Lei Ren 7 , John C Roeske 8 , Lei Wang 9 , Pengpeng Zhang 10 , Paul Keall 1

PURPOSE: Lung stereotactic ablative body radiotherapy (SABR) is a radiation therapy success story with level 1 evidence demonstrating its efficacy. To provide real-time respiratory motion management for lung SABR, several commercial and preclinical markerless lung target tracking (MLTT) approaches have been developed. However, these approaches have yet to be benchmarked using a common measurement methodology. This knowledge gap motivated the MArkerless lung target Tracking CHallenge (MATCH). The aim was to localize lung targets accurately and precisely in a retrospective in silico study and a prospective experimental study. **METHODS:** MATCH was an American Association of Physicists in Medicine sponsored Grand Challenge. Common materials for the in silico and experimental studies were the experiment setup including an anthropomorphic thorax phantom with two targets within the lungs, and a lung SABR planning protocol. The phantom was moved rigidly with patient-measured lung target motion traces, which also acted as ground truth motion. In the retrospective in silico study a volumetric modulated arc therapy treatment was simulated and a dataset consisting of treatment planning data and intra-treatment kilovoltage (kV) and megavoltage (MV) images for four blinded lung motion traces was provided to the participants. The participants used their MLTT approach to localize the moving target based on the dataset. In the experimental study, the participants received the phantom experiment setup and five patient-measured lung motion traces. The participants used their MLTT approach to localize the moving target during an experimental SABR phantom treatment. The challenge was open to any participant, and participants could complete either one or both parts of the challenge. For both the in silico and experimental studies the MLTT results were analyzed and ranked using the prospectively defined metric of the percentage of the tracked target position being within 2 mm of the ground truth. **RESULTS:** A total of 30 institutions registered and 15 result submissions were received, four for the in silico study and 11 for the experimental study. The participating MLTT approaches were: Accuray CyberKnife (2), Accuray Radixact (2), BrainLab Vero, C-RAD, and preclinical MLTT (5) on a conventional linear accelerator (Varian TrueBeam). For the in silico study the percentage of the 3D tracking error within 2 mm ranged from 50% to 92%. For the experimental study, the percentage of the 3D tracking error within 2 mm ranged from 39% to 96%. **CONCLUSIONS:** A common methodology for measuring the accuracy of MLTT approaches has been developed and used to benchmark preclinical and commercial approaches retrospectively and prospectively. Several MLTT approaches were able to track the target with sub-millimeter accuracy and precision. The study outcome paves the way for broader clinical implementation of MLTT. MATCH is live, with datasets and analysis software being available online at <https://www.aapm.org/GrandChallenge/MATCH/> to support future research.

SMALL CELL LUNG CANCER - SCLC

[Small Cell Lung Cancer Staging: Prospective Comparison of Conventional Staging Tests, FDG PET/CT, Whole-Body MRI, and Coregistered FDG PET/MRI](#) AJR Am J Roentgenol. 2021 Dec 8. doi: 10.2214/AJR.21.26868. Online ahead of print. Yoshiharu Ohno 1 2 3 , Takeshi Yoshikawa 3 4 , Daisuke Takenaka 4 5 , et al. .

BACKGROUND: Whole-body MRI and FDG PET/MRI have shown encouraging results for staging of thoracic malignancy, but are poorly studied for staging of small cell lung cancer (SCLC). Objective: To compare the performance of conventional staging tests, FDG PET/CT, whole-body MRI, and FDG PET/MRI for staging of SCLC. **METHODS:** This prospective study included 98 patients (64 men, 34 women; median age, 74 years) with SCLC who underwent conventional staging tests (brain MRI; neck,

chest, and abdominopelvic CT; bone scintigraphy), FDG PET/CT, and FDG PET/MRI, within 2 weeks before treatment; coregistered FDG PET/MRI was generated. Two nuclear medicine physicians independently reviewed conventional tests and FDG PET/CT examinations in separate sessions; two chest radiologists independently reviewed whole-body MRI and FDG PET/MRI examinations in separate sessions. Readers assessed T, N, and M categories; TNM stage; and Veterans Administration Lung Cancer Study Group (VALSG) stage. Reader pairs subsequently reached consensus. Stages determined clinically during tumor board sessions served as reference. **RESULTS:** Accuracy for T category was higher ($p < .05$) for whole-body MRI (94.9%) and FDG PET/MRI (94.9%) than for FDG PET/CT (85.7%). Accuracy for N category was higher ($p < .05$) for whole-body MRI (84.7%), FDG PET/MRI (83.7%), and FDG PET/CT (81.6%) than for conventional staging tests (75.5%). Accuracy for M category was higher ($p < .05$) for whole-body MRI (94.9%), FDG PET/MRI (94.9%), and FDG PET/CT (94.9%) than for conventional staging tests (84.7%). Accuracy for TNM stage was higher ($p < .05$) for whole-body MRI (88.8%) and FDG PET/MRI (86.7%) than for FDG PET/CT (77.6%) and conventional staging tests (72.4%). Accuracy for VALSG stage was higher ($p < .05$) for whole-body MRI (95.9%), FDG PET/MRI (95.9%), and FDG PET/CT (98.0%) than for conventional staging tests (82.7%). Interobserver agreement, expressed as kappa, ranged from 0.81 to 0.94 across imaging tests and staging endpoints. **CONCLUSION:** FDG PET/CT, whole-body MRI, and coregistered FDG PET/MRI outperformed conventional tests for various staging endpoints in patients with SCLC. Whole-body MRI and FDG PET/MRI outperformed FDG PET/CT for T category and thus TNM stage, indicating utility of MRI for assessing extent of local invasion in SCLC. Clinical Impact: Incorporation of either MRI approach may improve initial staging evaluation in SCLC.

[Patterns of relapse following hippocampal avoidance prophylactic cranial irradiation for small cell lung carcinoma](#) Rep Pract Oncol Radiother. 2021 Dec 30;26(6):968-975. doi:

10.5603/RPOR.a2021.0119. eCollection 2021. Theresa A Cook 1, Matthew R Hoffmann 2, Amie J Ross 1, Kirsty J Turnbull 1, Justin Westhuyzen 1, Noel J Aherne 1 3 4

BACKGROUND: Hippocampal avoidance techniques are an evolving standard of care for patients undergoing cranial irradiation. Our aim was to assess the oncological outcomes and patterns of failure following hippocampal avoidance prophylactic cranial irradiation (HA-PCI) as a standard of care in unselected patients with both limited and extensive stage small cell lung carcinoma. **MATERIALS AND METHODS:** Consecutive patients with small cell lung carcinoma with a complete (limited stage) or good partial (extensive stage) response following chemotherapy were eligible to receive HA-PCI, with a total dose of 25 Gray in 10 fractions. All patients had a negative baseline MRI brain scan with gadolinium prior to HA-PCI. Patients had baseline and follow up Common Toxicity Criteria Adverse Event assessments. Following completion of HA-PCI, all patients had three-monthly MRI brain scans with gadolinium until confirmation of intracranial relapse, as well as three-monthly CT of the chest, abdomen and pelvis. Overall and progression-free survival were calculated using the Kaplan-Meier method. **RESULTS:** A total of 17 consecutive patients, 9 men and 8 women, with a mean age of 70 years received HA-PCI between May 2016 and June 2020 after completion of their initial chemotherapy. There were no Grade 4 or greater adverse events. No patient had an isolated hippocampal avoidance zone relapse alone; three of 17 patients had multifocal relapses that included the hippocampal avoidance zone. **CONCLUSION:** In our series, there were no hippocampal only relapses and we conclude that HA-PCI is a safe alternative to standard PCI in the setting of small cell lung cancer.

[Clinical Activity and Safety of Anlotinib Combined with PD-1 Blockades for Patients with Previously Treated Small Cell Lung Cancer](#) Int J Gen Med. 2021 Dec 30;14:10483-10493. doi:

10.2147/IJGM.S337316. eCollection 2021. Yan-Yan Hao # 1 2, Yi-Peng Qiao # 3, Jian-De Cheng 1 2

OBJECTIVE: Anlotinib was the standard monotherapy for patients with previously treated small cell lung cancer (SCLC) in recent years. Programmed cell death protein 1 (PD-1) blockade combined with antiangiogenic targeted drugs have proved to play a synergistic action for cancer treatment clinically. Consequently, the present study was to investigate the efficacy and safety of anlotinib combined with PD-1 blockades for patients with previously treated SCLC. **METHODS:** A total of 36 patients with SCLC who were treated with at least one previous systemic chemotherapy regimen participated in this study retrospectively. All the patients were administered with anlotinib plus PD-1 blockades therapy. Clinical activity was assessed according to the change of target lesion by imaging evidence and all the subjects were followed up regularly. Safety profiles were collected and documented during the treatment. Univariate analysis was carried out using Log rank test and multivariate analysis was adjusted by Cox regression analysis. **RESULTS:** All the 36 patients with previously treated SCLC were able to have their efficacy and safety profile evaluated. The best overall response of the combination regimen showed that complete response was observed in one patient, partial response was noted in 9 patients, stable disease was reported in 19 patients, progressive disease was seen in 7 patients. Therefore, the objective response rate (ORR) of the 36 patients was 27.8% (95% CI: 14.2-45.2%), disease control rate (DCR) was 80.6% (95% CI: 64.0-91.8%). Regarding the prognostic data, the median PFS and OS of the 36 patients was 4.6 months (95% CI: 3.13-6.07) and 9.3 months (95% CI: 3.30-15.30), respectively. The most common treatment-related adverse reactions were hypertension (52.8%), fatigue (47.2%), diarrhea (38.9%), hand and foot reaction (38.9%) and dermal toxicity (33.3%). Furthermore, multivariate Cox regression analysis for PFS indicated that ECOG performance status was an independent factor to predict PFS. **CONCLUSION:** Anlotinib combined with PD-1 blockades regimen preliminarily demonstrated encouraging efficacy and tolerable safety for patients with previously treated SCLC. The conclusion should be validated in prospective clinical trials subsequently.

[Survival of Black and White Patients With Stage IV Small Cell Lung Cancer](#) Front Oncol. 2021 Dec 10;11:773958. doi: 10.3389/fonc.2021.773958. eCollection 2021. Huashan Shi 1 , Kexun Zhou 1 , Jordan Cochuyt 2 , David Hodge 2 , Hong Qin 3 , Rami Manochakian 3 , Yujie Zhao 3 , Sikander Ailawadhi 3 , Alex A Adjei 4 , Yanyan Lou 3

BACKGROUND: Small cell lung cancer (SCLC) is associated with aggressive biology and limited treatment options, making this disease a historical challenge. The influence of race and socioeconomic status on the survival of stage IV SCLC remains mostly unknown. Our study is designed to investigate the clinical survival outcomes in Black and White patients with stage IV SCLC and study the demographic, socioeconomic, clinical features, and treatment patterns of the disease and their impact on survival in Blacks and Whites. **METHODS AND RESULTS:** Stage IV SCLC cases from the National Cancer Database (NCDB) diagnosed between 2004 and 2014 were obtained. The follow-up endpoint is defined as death or the date of the last contact. Patients were divided into two groups by white and black. Features including demographic, socioeconomic, clinical, treatments and survival outcomes in Blacks and Whites were collected. Mortality hazard ratios of Blacks and Whites stage IV SCLC patients were analyzed. Survival of stage IV SCLC Black and White patients was also analyzed. Adjusted hazard ratios were analyzed by Cox proportional hazards regression models. Patients' median follow-up time was 8.18 (2.37-15.84) months. Overall survival at 6, 12, 18 and 24 months were 52.4%, 25.7%, 13.2% and 7.9% in Blacks in compared to 51.0%, 23.6%, 11.5% and 6.9% in Whites. White patients had significantly higher socioeconomic status than Black patients. By contrast, Blacks were found associated with younger age at diagnosis, a significantly higher chance of receiving radiation therapy and treatments at an academic/research program. Compared to Whites, Blacks had a 9% decreased risk of death. **CONCLUSION:** Our study demonstrated that Blacks have significant socioeconomic disadvantages compared to Whites. However, despite these unfavorable factors, survival for Blacks was significantly improved compared to Whites after covariable adjustment. This may be due to Blacks with Stage IV SCLC having a higher

chance of receiving radiation therapy and treatments at an academic/research program. Identifying and removing the barriers to obtaining treatments at academic/research programs or improving the management in non-academic centers could improve the overall survival of stage IV SCLC.

[Impact of Chronic Obstructive Pulmonary Disease on the Mortality of Patients with Small Cell Lung Cancer](#) Int J Chron Obstruct Pulmon Dis. 2021 Dec 1;16:3255-3262. doi:

10.2147/COPD.S328938. eCollection 2021. Kuang-Ming Liao 1, Chao-Ming Hung 2, Chin-Chung Shu 3 4, Ho-Sheng Lee 5, Yu-Feng Wei 6 7

BACKGROUND: Limited studies have focused on the impact of the coexistence of small cell lung cancer (SCLC) and chronic obstructive pulmonary disease (COPD). The study was to examine the impact of COPD on mortality in SCLC patients. **METHODS:** We analyzed SCLC patients from the Taiwan Cancer Registry Database between January 1, 1997, and December 31, 2015. The COPD population was composed of patients with a COPD diagnosis before the diagnosis of SCLC. The control group was composed of randomly selected SCLC patients without COPD who were propensity score matched with those with concomitant COPD according to age, sex, index date, cancer staging and comorbidities at a 1:1 ratio. **RESULTS:** Among 9425 SCLC patients in the database, eligible subjects were divided into the COPD group (n = 4235) and the non-COPD group (n = 2334). Compared to patients in the non-COPD group, the patients in the COPD group were older (71.4 versus 65.7 years, $p < 0.0001$), had a lower percentage of stage IV disease (60.1% versus 68.3%, $p < 0.0001$) and had more comorbidities. After matching, there were 1457 patients in each group. Older age, lower body mass index (BMI), and some comorbidities were associated with higher mortality, and comorbid COPD was associated with lower 1-year mortality in SCLC patients. Multivariate analysis identified older age, lower BMI, and concomitant congestive heart failure or diabetes as risk factors for OS. **CONCLUSION:** A diagnosis of COPD was associated with reduced 1-year mortality in SCLC patients, but no significant difference after 1-year in this population.

[First-line pembrolizumab plus chemotherapy for extensive-stage small-cell lung cancer: a United States-based cost-effectiveness analysis](#) Cost Eff Resour Alloc. 2021 Dec 4;19(1):77. doi:

10.1186/s12962-021-00329-w. Youwen Zhu 1, Huabin Hu 2 3, Dong Ding 1, Shuoshu Li 1, Mengting Liao 4, Yin Shi 5, Jin Huang 6 7

BACKGROUND: The clinical trial of Keynote-604 showed that pembrolizumab plus chemotherapy could generate clinical benefits for extensive-stage small-cell lung cancer (ES-SCLC). We aim to assess the efficacy and cost of pembrolizumab combined with chemotherapy in the first-line treatment setting of ES-SCLC from the United States (US) payers' perspective. **METHODS:** A synthetic Markov model was used to evaluate cost and effectiveness of pembrolizumab plus platinum-etoposide (EP) versus EP in first-line therapy for ES-SCLC from the data of Keynote-604. Lifetime costs, life-years (LYs), quality adjusted LYs (QALYs) and incremental cost-effectiveness ratios (ICERs) were estimated. One-way and probabilistic sensitivity analyses were performed. Furthermore, we performed subgroup analysis. **RESULTS:** Pembrolizumab plus EP resulted in additional 0.18 QALYs (0.32 LYs) and corresponding incremental costs \$113,625, resulting an ICER of \$647,509 per QALY versus EP. The price of pembrolizumab had a significant impact on ICER. Probabilistic sensitivity analysis indicated that pembrolizumab combined chemotherapy may become a cost-effective option with a probability of 0%. Besides, subgroup analysis suggested that all subgroups were not cost-effective. **CONCLUSION:** From the perspective of the US payer, pembrolizumab plus EP is not a cost-effective option for first-line treatment patients with ES-SCLC at a WTP threshold of \$150,000 per QALY.

[Role of Prophylactic Cranial Irradiation in Extensive-Stage Small Cell Lung Cancer](#) J Natl Compr Canc Netw. 2021 Dec;19(12):1465-1469. doi: 10.6004/jnccn.2021.7105. Nathan Y Yu 1 , Terence T Sio 1 , Vinicius Ernani 2 , Panayiotis Savvides 2 , Steven E Schild 1

Patients with small cell lung cancer (SCLC) are at significant risk of developing brain metastases during their disease course. Prophylactic cranial irradiation (PCI) has been incorporated into SCLC treatment guidelines to diminish the risk of developing brain metastases. In 2007, a randomized trial suggested that PCI decreases the incidence of brain metastases and prolongs overall survival (OS) in patients with extensive-stage SCLC (ES-SCLC) who have responded to initial therapy. However, this study did not include modern central nervous system imaging with CT or MRI prior to randomization. A more recent Japanese trial with MRI staging and surveillance demonstrated that PCI diminished the incidence of brain metastases but did not improve survival. **This review examines** the largest clinical studies, controversies, and future directions of PCI in patients with ES-SCLC.

[Prognostic Value of Clinical Staging According to TNM in Patients With SCLC: A Real-World Surveillance Epidemiology and End-Results Database Analysis](#) TO Clin Res Rep. 2021 Dec 10;3(1):100266. doi: 10.1016/j.jto.2021.100266. eCollection 2022 Jan. Edurne Arriola 1 , José Manuel Trigo 2 , Amparo Sánchez-Gastaldo 3 , Alejandro Navarro 4 , Coral Perez 5 , Leonardo Crama 5 , Santiago Ponce-Aix 6

INTRODUCTION: SCLC is one of the most lethal malignancies. Classically, staging has been performed using a dual classification distinguishing limited from the extensive stage. This study aimed to evaluate the prognostic value of TNM staging in a real-world population of patients with SCLC.

METHODS: Patients were selected from the Surveillance Epidemiology and End Results database. Chi-square bivariate analysis was used for the association of binary qualitative variables. A multivariate Cox regression analysis was performed to determine the impact of these prognostic factors on median overall survival (mOS) and long-term survival. **RESULTS:** A total of 26,221 patients were included (50.7% men, 55.7% ≥ 65 y, 82% White). At diagnosis, 18,574 (70.83%) presented metastases, which were more frequent in the liver (n = 11,896, 64%). In the overall population, mOS was 8 (7.86-8.14) months, which decreased according to each increasing category of TNM staging (p < 0.0001). The worse mOS was found among patients with stage IV SCLC (6 mo, 95% confidence interval: 5.83-6.17). Long-term survival decreased according to TNM staging, with patients having stage IV SCLC exhibiting the lowest survival rates at all follow-up time points. Within stage IV, the lowest mOS values were found in patients greater than or equal to 65 years and in those with liver metastases. Among the TNM stages corresponding to the limited stage, stage IB revealed the lowest hazard ratios value for risk of death compared with stage IA (hazard ratio = 1.161, 95% confidence interval: 0.97-1.40, p = 0.114), which increased gradually within the limited-stage SCLC. In the multivariate analysis, TNM staging, male sex, and older age resulted in poor prognostic factors for survival. **CONCLUSIONS:** TNM staging seems to define prognosis in patients with SCLC in the real-world setting, particularly for those patients with earlier disease.

PALLIATIVE AND SUPPORTIVE CARE

[Association Between Household Income and Self-Perceived Health Status and Poor Mental and Physical Health Among Cancer Survivors](#) Front Public Health. 2021 Dec 7;9:752868. doi: 10.3389/fpubh.2021.752868. eCollection 2021. L Joseph Su 1, Sarah N O'Connor 1, Tung-Chin Chiang 2

BACKGROUND: Health-related quality of life (HRQoL) is multidimensional and is composed of, at a minimum, self-perceived health status, physical functioning, and psychological well-being. HRQoL measures reflect the extent of disability and dysfunction associated with a chronic disease such as cancer. The objective of this study is to examine factors associated with HRQoL among cancer survivors.

METHODS: Data from the 2009 Behavioral Risk Factor Surveillance System survey was used to examine factors associated with HRQoL among participants who reported having ever been diagnosed with cancer. Four questions associated with HRQoL included self-perceived health status, number of bad physical health days, and number of bad mental health days per month. Least square regression and logistic regression models, adjusted for confounding variables, were used for an ordinal and dichotomous [5 (bad) vs. 1-4 (excellent, very good, good, fair)] scale of HRQoL, respectively. **RESULTS:** Fifty nine thousand one hundred seventy three participants reported having ever been diagnosed with cancer. Adjusted mean self-perceived health status (5-point scale) among survivors of thyroid, colon, lung, cervical, breast, prostate, and ovarian cancer was 3.83 (0.05), 4.02 (0.04), 4.36 (0.06), 3.77 (0.03), 3.88 (0.03), 3.78 (0.04), and 3.96 (0.05), respectively. After adjusting for confounders, a positive dose-response effect was observed between income range and all three HRQoL measures across all seven cancer sites. Income was consistently and inversely associated with a higher chance for reporting poorer HRQoL [OR: 0.64, 95% CI: 0.57-0.71], [OR: 0.63, 95% CI: 0.48-0.82], [OR: 0.67, 95% CI: 0.56-0.80], [OR: 0.69, 95% CI: 0.56-0.86], [OR: 0.55, 95% CI: 0.49-0.62], [OR: 0.55, 95% CI: 0.44-0.69], [OR: 0.75, 95% CI: 0.62-0.91] among those with thyroid, colon, lung, cervical, breast, prostate, and ovarian cancer, respectively. **DISCUSSION:** This study found that income range was associated with HRQoL among cancer survivors. It is plausible that financial resources may lessen the overall burden of cancer survivors, which could improve health-related quality of life among cancer survivors.

Spiritual Needs of Lung Cancer Patients and Their Relation to Psychological Distress and Quality of Life Cureus. 2021 Dec 7;13(12):e20225. doi: 10.7759/cureus.20225. eCollection 2021 Dec. Evangelos C Fradelos 1 , Eleni Albani 2 , Ioanna V Papathanasiou 3 , Paraskevi-Maria Prapa 4 , Effrosyni Tsomaka 5 , Vissarion Bakalis 1 , Sofia Artemi 6 , Maria Lavdaniti 7

BACKGROUND: This study aimed to investigate the spiritual needs of patients suffering from lung cancer in relation to their mental health and quality of life. **METHODOLOGY:** A cross-sectional quantitative study design was employed to investigate 110 lung cancer patients receiving chemotherapy. A four-part self-assessment instrument was used to gather the data comprising a sheet containing demographic and clinical information, Spiritual Needs Questionnaire, The Depression, Anxiety, and Stress Scale-21 Items, and the 12-item Health Survey. Descriptive inferential statistics were applied. **RESULTS:** Of the 110 patients, 71.8% were men, the mean age was 64.25 (± 9.3) years, and 71.8% were married. In total, 40.9% of the patients were retired, and 92.7% had a public insurance company. Regarding education, 30% were primary school graduates and 31.8% were high school graduates. Regarding the clinical features of the sample, 23.6% of the patients had small-cell carcinoma, 71.9% had non-small-cell carcinoma, and 4.5% had large-cell carcinoma. Spiritual needs have a negative effect on the mental health component of quality of life ($p < 0.001$) and can increase psychological distress in lung cancer patients. **CONCLUSIONS:** In contrast to the findings of other international studies, spiritual needs appeared to be lower; however, similar to other studies, spiritual needs increased in those suffering from depression and anxiety. Moreover, the subtype of lung cancer also appeared to play a role.

Clinical Decision Support for Symptom Management in Lung Cancer Patients: A Group RCT

J Pain Symptom Manage. 2021 Dec 16;S0885-3924(21)00665-5. doi: 10.1016/j.jpainsymman.2021.12.006. Online ahead of print. Mary E Cooley 1 , Emanuele Mazzola 2 , Niya Xiong 2 , Fangxin Hong 2 , David F Lobach 3 , Ilana M Braun 4 , Barbara Halpenny 5 , Michael S Rabin 6 , Ellis Johns 7 , Kathleen Finn 8 , Donna Berry 9 , Ruth McCorkle 10 , Janet L Abraham 4 **CONTEXT:** Clinical guidelines are available to enhance symptom management during cancer treatment but often are not used in the practice setting. Clinical decision support can facilitate the implementation and adherence to clinical guidelines. and improve the quality of cancer care. **OBJECTIVES:** Clinical decision support offers an innovative approach to integrate guideline-based symptom management into

oncology care. This study evaluated the effect of clinical decision support-based recommendations on clinical management of symptoms and health-related quality of life (HR-QOL) among outpatients with lung cancer. **METHODS:** Twenty providers and 179 patients were allotted in group randomization to attention control (AC) or Symptom Assessment and Management Intervention (SAMI) arms. SAMI entailed patient-report of symptoms and delivery of recommendations to manage pain, fatigue, dyspnea, depression, and anxiety; AC entailed symptom reporting prior to the visit. Outcomes were collected at baseline, two, four and six-months. Adherence to recommendations was assessed through masked chart review. HR-QOL was measured by the Functional Assessment of Cancer Therapy-Lung questionnaire. Descriptive statistics with linear and logistic regression accounting for the clustering structure of the design and a modified chi-square test were used for analyses. **RESULTS:** Median age of patients was 63 years, 58% female, 88% white, and 32% ≤high school education. Significant differences in clinical management were evident in SAMI vs. AC for all target symptoms that passed threshold. Patients in SAMI were more likely to receive sustained-release opioids for constant pain, adjuvant medications for neuropathic pain, opioids for dyspnea, stimulants for fatigue and mental health referrals for anxiety. However, there were no statistically significant differences in HR-QOL at any time point. **CONCLUSION:** SAMI improved clinical management for all target symptoms but did not improve patient outcomes. A larger study is warranted to evaluate effectiveness.

[Survival impact of treatment for chronic obstructive pulmonary disease in patients with advanced non-small-cell lung cancer](#) Sci Rep. 2021 Dec 8;11(1):23677. doi: 10.1038/s41598-021-03139-5. Hitomi Ajimizu 1 , Hiroaki Ozasa 1 , Susumu Sato 2 , et al.

Chronic obstructive pulmonary disease (COPD) may coexist with lung cancer, but the impact on prognosis is uncertain. Moreover, it is unclear whether pharmacological treatment for COPD improves the patient's prognosis. We retrospectively investigated patients with advanced non-small-cell lung cancer (NSCLC) who had received chemotherapy at Kyoto University Hospital. Coexisting COPD was diagnosed by spirometry, and the association between pharmacological treatment for COPD and overall survival (OS) was assessed. Of the 550 patients who underwent chemotherapy for advanced NSCLC between 2007 and 2014, 347 patients who underwent spirometry were analyzed. Coexisting COPD was revealed in 103 patients (COPD group). The median OS was shorter in the COPD group than the non-COPD group (10.6 vs. 16.8 months). Thirty-seven patients had received COPD treatment, and they had a significantly longer median OS than those without treatment (16.7 vs. 8.2 months). Multivariate Cox regression analysis confirmed the positive prognostic impact of COPD treatment. Additional validation analysis revealed similar results in patients treated with immune checkpoint inhibitors (ICIs). Coexisting COPD had a significant association with poor prognosis in advanced NSCLC patients if they did not have pharmacological treatment for COPD. Treatment for coexisting COPD has the potential to salvage the prognosis.

[Matched Pairs Comparison of an Enhanced Recovery Pathway Versus Conventional Management on Opioid Exposure and Pain Control in Patients Undergoing Lung Surgery](#) Ann Surg. 2021 Dec 1;274(6):1099-1106. doi: 10.1097/SLA.0000000000003587. David Rice 1 , Andrea Rodriguez-Restrepo 2 , Gabriel Mena 2 , Juan Cata 2 , et al.

OBJECTIVE: The aim of this study was to assess the effect of an enhanced recovery after surgery (ERAS) pathway on pain and opioid use following lung resection. **SUMMARY BACKGROUND DATA:** A major component ERAS pathways is opioid-sparing analgesia; however, the effect on postoperative pain and opioid use in patients undergoing lung resection is unknown. **METHODS:** Following implementation of an ERAS pathway for lung resection, 123 consecutive patients were identified. Patients were propensity-matched 1:1 with a group of consecutive patients (n = 907) undergoing lung resection before ERAS. Differences regarding in-hospital opioid consumption, discharge

prescribing of opioids, and postoperative pain scores were examined. Morphine milligram equivalents were separately calculated including and excluding tramadol as an opioid medication. **RESULTS:** There were no significant differences between matched patients regarding age, sex, performance status, receipt of preoperative treatment, extent of lung resection, or operative approach. Epidural analgesia was used in 66% of controls and in none of the ERAS group ($P < 0.001$). The number of adjunct analgesics used postoperatively was greater in the ERAS group (median 3 vs 2, $P < 0.001$). There was a major reduction in morphine milligram equivalents in the ERAS group whether tramadol was included (median 14.2 vs 57.8, $P < 0.001$) or excluded (median 2.7 vs 57.8, $P < 0.001$) and regardless of surgical approach. Average daily pain scores were lower in the ERAS group (median 1.3 vs 1.8, $P = 0.004$); however, this difference was present only among patients undergoing thoracotomy. The proportion of patients who were prescribed discharge opioids varied whether tramadol was included (96% each group, $P = 1.00$) or excluded (39% vs 80%, $P < 0.001$) in the analysis. **CONCLUSIONS:** Implementation of an ERAS pathway was associated with effective post-operative analgesia, major reductions in in-hospital consumption of opioids, and reduced pain, compared to conventional management.

COMPLEMENTARY & ALTERNATIVE THERAPY

[Effects of Complementary and Alternative Medicine on Chemotherapy Delivery in Thai Patients](#)

Asian Pac J Cancer Prev. 2021 Dec 1;22(12):3977-3983. doi: 10.31557/APJCP.2021.22.12.3977.

Chawanya Rabilossaporn^{1 2}, Ploytuangporn Wongchanapai², Nattaya Poovoravan², Piyada Sitthideatphaiboon², Virote Sriuranpong^{1 2}, Suebpong Tanasanvimon¹

BACKGROUND: Complementary and Alternative Medicine (CAM) is widely used among cancer patients worldwide. This prospective observational study aimed to show the effect of CAM use on chemotherapy delivery in Thai patients. **METHODS:** During March 2014 to February 2015, the patients with breast, lung or colorectal cancer receiving first cycle chemotherapy at King Chulalongkorn Memorial Hospital were enrolled. The correlation between CAM using and chemotherapy schedule delay and dose reduction, dose intensity, quality of life and adverse event rates were analyzed. **RESULTS:** There were 80 (44.20%) patients using CAM among 181 enrolled patients. Seventy six CAM users and 97 non-CAM users receiving 2nd cycle of chemotherapy were included for primary analysis. The chemotherapy schedules were delayed and/or reduced in 40 (52.6%) and 48 (49.5%) in CAM users and non-CAM users, respectively, $p = 0.681$. The mean relative dose intensity (RDI) were 92.4% and 94.1% in CAM and non-CAM users, respectively, $p = 0.244$. However, there were significantly more CAM users receiving chemotherapy less than 90% RDI (34.8% vs 19.8%, $p = 0.033$). As compared to first cycle, at third cycle, the mean QOL score changes were -4.63 (95% CI -2.49-9.27) and -8.02 (-2.36- 9.142) in CAM user and non-CAM user, respectively ($p = 0.255$). There were significantly higher rates of grade 3 or 4 anemia (5.1% vs 0%, $p = 0.024$), and grade 2 malaise (19.0% vs 5.1%, $p = 0.004$) in CAM users. **CONCLUSIONS:** There were similar overall rates of chemotherapy schedule delay and dose reduction between CAM- and non-CAM users. However, there were less CAM-users achieving 90% chemotherapy RDI.

[Anticancer Action of Xiaoxianxiong Tang in Non-Small Cell Lung Cancer by Pharmacological Analysis and Experimental Validation](#)

Evid Based Complement Alternat Med. 2021 Dec

13;2021:9930082. doi: 10.1155/2021/9930082. eCollection 2021. Rongzhen Ding¹, Lijing Jiao^{1 2}, Shuliu Sang¹, Yinan Yin¹, Yichao Wang¹, Yabin Gong¹, Ling Xu¹, Ling Bi¹

Xiaoxianxiong Tang (XXXT) is a well-known traditional Chinese medicine formula. Evidence is emerging supporting the benefits of XXXT in ameliorating therapy for non-small cell lung cancer (NSCLC). The purpose of this study aimed to explore the effects and mechanisms of XXXT through network pharmacological analysis and biological validation. TCMSP database was used to identify potentially active compounds in XXXT with absorption, distribution, metabolism, excretion screening,

and their potential targets. The disease targets related to NSCLC were predicted by searching for Therapeutic Target database, GeneCards database, DrugBank database, and DisGeNET database. Of the 4385 NSCLC-related targets, 156 targets were also the targets of compounds present in XXXT. Subsequently, GO function and KEGG pathway enrichment and PPI network analyses revealed that, of the 95 targets and 20 pathways influenced by 20 ingredients in XXXT, 20 targets were associated with patient survival, and XXXT could exert an inhibitory action on the PI3K-AKT signaling pathway. Moreover, XXXT restrained the proliferation of A549 and H460 cells in a concentration-dependent manner and suppressed the mRNA and protein levels of key targets CCNA2, FOSL2, and BIRC5 closely linked to the PI3K-AKT pathway. Hence, XXXT has the potential to improve therapy for NSCLC by targeting the PI3K-AKT signaling pathway.

Evaluation of Antimicrobial and Anticancer Activities of Selected Medicinal Plants of Himalayas,

Pakistan Plants (Basel). 2021 Dec 24;11(1):48. doi: 10.3390/plants11010048. Farzana Kausar ¹, Kyung-Hwan Kim ², Hafiz Muhammad Umer Farooqi ^{2 3}, et al.

Medicinal plants are known for their diverse use in the traditional medicine of the Himalayan region of Pakistan. The present study is designed to investigate the anticancer and antimicrobial activities of *Prunus cornuta* and *Quercus semicarpifolia*. The anticancer activity was performed using cancerous human cell lines (HepG2, Caco-2, A549, MDA-MB-231, and NCI-H1437 carcinoma cells), while the antimicrobial activity was conducted with the agar-well diffusion method. Furthermore, toxicity studies were performed on alveolar and renal primary epithelial cells. Initially, different extracts were prepared by maceration techniques using n-hexane, chloroform, ethyl acetate, butanol, and methanol. The preliminary phytochemical screening showed the presence of secondary metabolites such as alkaloids, tannins, saponins, flavonoids, glycosides, and quinones. The chloroform extract of *P. cornuta* (PCC) exhibited significant inhibitory activity against *Acinetobacter baumannii* (16 mm) and *Salmonella enterica* (14.5 mm). The *A. baumannii* and *S. enterica* strains appeared highly susceptible to n-hexane extract of *P. cornuta* (PCN) with an antibacterial effect of 15 mm and 15.5 mm, respectively. The results also showed that the methanolic extracts of *Quercus semicarpifolia* (QSM) exhibited considerable antibacterial inhibitory activity in *A. baumannii* (18 mm), *Escherichia coli* (15 mm). The QSN and QSE extracts also showed good inhibition in *A. baumannii* with a 16 mm zone of inhibition. The *Rhizopus oryzae* strain has shown remarkable mycelial inhibition by PCM and QSN with 16 mm and 21 mm inhibition, respectively. Furthermore, the extracts of *P. cornuta* and *Q. semicarpifolia* exhibited prominent growth inhibition of breast (MDA-MB-231) and lung (A549) carcinoma cells with 19-30% and 22-39% cell viabilities, respectively. The gut cell line survival was also significantly inhibited by *Q. semicarpifolia* (24-34%). **The findings of this study** provide valuable information for the future development of new antibacterial and anticancer medicinal agents from *P. cornuta* and *Q. semicarpifolia* extracts.

MISCELLANEOUS WORKS

Immunotherapy, the promise for present and future of malignant pleural mesothelioma (MPM) treatment

Ther Adv Med Oncol. 2021 Dec 10;13:17588359211061956. doi: 10.1177/17588359211061956. eCollection 2021. Valérie Gounant ¹, Solenn Brosseau ¹, Gérard Zalcman ²

Due to occupational asbestosis exposure, the incidence of malignant pleural mesothelioma (MPM) has continuously increased over the last 30 years, with a plateau anticipated around the year 2030 in Western countries. Molecular MPM carcinogenesis involves alterations of NF2, RASSF1, LATS2WT1, p16, as well as BAP-1 tumor-suppressor genes, which usually regulate apoptosis, cell invasion, motility, cell division, chromatin remodeling, as well as control of DNA repair. In few selected patients, debulking

surgery consisting of pleurectomy-decortication is carried out, resulting in unsatisfactory long-term results. For about 15 years, first-line chemotherapy has been primarily based on a doublet of pemetrexed and cisplatin. Adding the monoclonal antibody bevacizumab (Avastin®), which targets vascular endothelial growth factor (VEGF), has been shown to improve overall survival (OS) by nearly 19 months. The emergence of immune check-point inhibitors (ICIs) in MPM treatment has recently been associated with substantial survival improvements in both second- and first-line settings. Similarly to non-small-cell lung cancer (NSCLC) patients, on-going trials are presently exploring the chemotherapy-ICI combination in MPM management, and depending on their results, this combination could represent a further major advance in this previously orphan disease. The current article reviews recent clinical trial results, as well as future clinical trials results, as well as future clinical developments in this moving field.

[Update of Incidence, Prevalence, Survival, and Initial Treatment in Patients With Non-Small Cell Lung Cancer in the US](#) JAMA Oncol. 2021 Dec 1;7(12):1824-1832. doi: 10.1001/jamaoncol.2021.4932.

Apar Kishor Ganti 1 2 , Alyssa B Klein 3 , Ion Cotarla 3 , Brian Seal 3 , Engels Chou 3

IMPORTANCE: Updated estimates of non-small cell lung cancer (NSCLC) in the US are needed.

OBJECTIVE: To calculate the most recent epidemiologic estimates of NSCLC in the US. Design,

SETTING, AND PARTICIPANTS: This cross-sectional epidemiological analysis used the most recently released data from US cancer registries. The population-based US Cancer Statistics (USCS) database (2010-2017), comprised of the Surveillance, Epidemiology, and End Results (SEER) program and the National Program of Cancer Registries (NPCR) (collectively, SEER-NPCR) provided the NSCLC incidence estimate. The SEER-18 database provided data for incidence, prevalence, survival, and initial treatment by NSCLC stage. Adults aged 18 years or older diagnosed with NSCLC identified by International Classification of Diseases for Oncology, Third Edition, morphology codes were included.

Main outcomes and measures: Annual age-adjusted NSCLC incidence per 100 000 persons; annual prevalence per 100 000 persons; survival rate; initial treatment. Due to database release delays, incidence data were available through 2017, and other parameters through 2016. The analysis was conducted from June 2020 to July 2020. **RESULTS:** There were 1.28 million new NSCLC cases recorded during 2010 to 2017 in the US (SEER-NPCR: 53% male; 67% ≥ 65 years). From 2010 to 2017, NSCLC incidence per 100 000 decreased from 46.4 to 40.9 overall (age <65 years: 15.5 to 13.5; age ≥65 years: 259.9 to 230.0); the incidence of stage II, IIIA, and IIIB NSCLC was stable, and stage IV decreased slightly from 21.7 to 19.6, whereas stage I incidence increased from 10.8 to 13.2. From 2010 to 2016, NSCLC prevalence per 100 000 increased from 175.3 to 198.3 (nationwide projection of SEER-18); prevalence increased among younger patients (77.5 to 87.9) but decreased among older patients (825.1 to 812.4). Period survival analysis found that 26.4% of patients survived 5 years, which is higher than previously reported. The proportion of stage I NSCLC treated with radiation as single initial treatment rose markedly from 14.7% in 2010 to 25.7% in 2016. Patients with stage IV NSCLC aged 65 years or older were most likely to be untreated (38.3%). **CONCLUSIONS AND RELEVANCE:** The findings of this cross-sectional epidemiological analysis suggest that the increased incidence of stage I NSCLC at diagnosis likely reflected improved evaluation of incidental nodules. A smaller proportion of patients aged 65 years or older with stage IV NSCLC were treated. Earlier detection and availability of effective treatments may underlie increased overall NSCLC prevalence, and higher than previously reported survival.

[Online public interest in common malignancies and cancer screening during the COVID-19 pandemic in the United States](#) J Clin Transl Res. 2021 Nov 6;7(6):723-732. eCollection 2021 Dec 28.

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BACKGROUND AND AIM: The COVID-19 pandemic was declared a national emergency in the United States in March 2020. The Centers for Medicare and Medicaid Services subsequently released recommendations that health-care facilities temporarily delay elective surgeries and non-essential medical

procedures. Disruptions to medical care significantly impacted cancer patients, with cancer screenings halted and nonurgent cancer surgeries postponed as health-care facilities shifted resources toward the COVID-19 pandemic. Although it has been reported that cancer screening rates decreased dramatically in the United States in 2020, it is unclear whether this trend was driven by factors related to public interest in cancer and/or cancer screening as opposed to other factors such as clinical backlogs, pandemic-related policies, and/or resource limitations. The purpose of this study was to use the Google Trends tool to evaluate public interest in six common malignancies and four common cancer screening methods during the COVID-19 pandemic. **METHODS:** We used the Google Trends tool to quantify public interest in six different malignancies (Breast Cancer, Colon Cancer, Lung Cancer, Prostate Cancer, Thyroid Cancer, and Cervical Cancer) and four cancer screening methods (Pap Smear, Lung Cancer Screening, Mammogram, and Colonoscopy) in the United States during the COVID-19 pandemic. Welch's t-tests were used to compare monthly search volumes during the COVID-19 pandemic (2020) to the 4 years before the pandemic (2016 - 2019) for all ten search terms included in our study. We used Benjamini-Hochberg to adjust raw p values to account for multiple statistical comparisons. The level of statistical significance was defined by choosing a false discovery rate of 0.05. **RESULTS:** Our results indicate significantly reduced interest in all malignancies studied at the beginning of the COVID-19 pandemic. Public interest in ['Breast Cancer'], ['Colon Cancer'], ['Lung Cancer'], ['Thyroid Cancer'], and ['Cervical Cancer'] significantly decreased in the months of March, April, May, and June 2020 when compared with public interest in 2016-2019. Public interest in cancer screening methods such as ['Pap Smear'], ['Lung Cancer Screening'], ['Mammogram'], and ['Colonoscopy'] significantly decreased in the months of April and May compared to 2016 - 2019 values. However, decreased public interest in cancer screening methods was temporary, with Google search volumes returning to pre-pandemic levels in June 2020 - December 2020. **CONCLUSION:** There was significantly reduced public interest in both common malignancies and cancer screening methods at the beginning of the COVID-19 pandemic in the United States. However, after an initial decline, public interest as indicated by Google search volumes quickly returned to pre-pandemic levels in the second half of the calendar year 2020. In addition, trends in public interest in cancer screening as indicated by Google search volumes aligned with cancer screening uptake rates in the United States during the study period. This finding suggests that Google Trends may serve as an effective tool in gauging the public's interest in cancer and/or cancer screenings in the United States, which makes it a valuable resource that can be used to inform decisions aimed at improving cancer screening rates in the future. **RELEVANCE FOR PATIENTS:** The Google Trends tool can be used to measure public interest in various malignancies and their associated screening methods. Google Trends data may be used to inform measures aimed at improving cancer screening uptake.

[The Survival Impact of Second Primary Lung Cancer in Patients with Lung Cancer](#) J Natl Cancer Inst. 2021 Dec 10;djab224. doi: 10.1093/jnci/djab224. Online ahead of print. Eunji Choi 1 , Sophia J Luo 1 , Jacqueline V Aredo 2 , et al.

BACKGROUND: Lung cancer survivors have a high risk of developing second primary lung cancer (SPLC), but little is known about the survival impact of SPLC diagnosis. **METHODS:** We analyzed data from 138,969 patients in the Surveillance, Epidemiology, and End Results (SEER), who were surgically treated for initial primary lung cancer (IPLC) in 1988-2013. Each patient was followed from the date of IPLC diagnosis to SPLC diagnosis (for those with SPLC) and last vital status through 2016. We performed multivariable Cox regression to evaluate the association between overall survival and SPLC diagnosis as a time-varying predictor. To investigate potential effect modification, we tested interaction between SPLC and IPLC stage. Using data from the Multiethnic Cohort Study (MEC) (N = 1,540 IPLC patients with surgery), we evaluated the survival impact of SPLC by smoking status. All statistical tests were 2-sided. **RESULTS:** A total of 12,115 (8.7%) patients developed SPLC in SEER over 700,421 person-years of follow up. Compared to patients with single primary lung cancer, those with SPLC had

statistically significantly reduced overall survival (hazard ratio [HR]=2.12, 95% confidence interval [CI] = 2.06-2.17; $P < .001$). The effect of SPLC on reduced survival was more pronounced among patients with early-stage IPLC vs. advanced-stage IPLC (HR = 2.14 [95% CI = 2.08-2.20] vs. 1.43 [95% CI = 1.21-1.70], respectively; $P_{\text{interaction}} < 0.001$). Analysis using MEC data showed that the effect of SPLC on reduced survival was statistically significantly larger among persons who actively smoked at initial diagnosis vs. those who formerly or never smoked (HR = 2.31 [95% CI = 1.48-3.61] vs. 1.41 [95% CI = 0.98-2.03], respectively; $P_{\text{interaction}} = 0.04$). **CONCLUSIONS:** SPLC diagnosis is statistically significantly associated with decreased survival in SEER and MEC. Intensive surveillance targeting patients with early-stage IPLC and active smoking at IPLC diagnosis may lead to a larger survival benefit.