Caring Ambassadors Lung Cancer Program
Literature Review, July 2022

SCREENING, COMPREHENSIVE BIOMARKER TESTING, DIAGNOSIS AND STAGING

Expert opinion on NSCLC small specimen biomarker testing - Part 1: Tissue collection and management Virchows Arch. 2022 Jul 20. doi: 10.1007/s00428-022-03343-2. Online ahead of print.
Frédérique Penault-Llorca 1 , Keith M Kerr 2 , Pilar Garrido 3 , et al.
DOI: 10.1007/s00428-022-03343-2
Biomarker testing is crucial for treatment selection in advanced non-small cell lung cancer (NSCLC). However, the quantity of available tissue often presents a key constraint for patients with advanced disease, where minimally invasive tissue biopsy typically returns small samples. In Part 1 of this two-part series, we summarise evidence-based recommendations relating to small sample processing for patients with NSCLC. Generally, tissue biopsy techniques that deliver the greatest quantity and quality of tissue with the least risk to the patient should be selected. Rapid on-site evaluation can help to ensure sufficient sample quality and quantity. Sample processing should be managed according to biomarker testing requirements, because tissue fixation methodology influences downstream nucleic acid, protein and morphological analyses. Accordingly, 10% neutral buffered formalin is recommended as an appropriate fixative, and the duration of fixation is recommended not to exceed 24-48 h. Tissue sparing techniques, including the 'one biopsy per block' approach and small sample cutting protocols, can help preserve tissue. Cytological material (formalin-fixed paraffin-embedded [FFPE] cytology blocks and non-FFPE samples such as smears and touch preparations) can be an excellent source of nucleic acid, providing either primary or supplementary patient material to complete morphological and molecular diagnoses. Considerations on biomarker testing, reporting and quality assessment are discussed in Part 2.

A Randomized Trial of Telephone-Based Smoking Cessation Treatment in the Lung Cancer Screening Setting J Natl Cancer Inst. 2022 Jul 12;djac127. doi: 10.1093/jnci/djac127. Online ahead of print. Kathryn L Taylor 1 , Randi M Williams 1 , Tengfei Li 2 , George Luta 2 , Laney Smith 1 , Kimberly M Davis 1 , Cassandra Stanton 3 , Raymond Niaura 4 , David Abrams 4 , Tania Lobo 1 , Jeanne Mandelblatt 1 , Jinani Jayasekera 1 , Rafael Meza 5 , Jihyoun Jeon 5 , Pianpian Cao 5 , Eric D Anderson 6 , Georgetown Lung Screening, Tobacco, and Health Trial

BACKGROUND: Lung cancer mortality is reduced via low-dose CT screening and treatment of early-stage disease. Evidence-based smoking cessation treatment in the lung screening setting can further reduce mortality. We report the results of a cessation trial from the NCI's SCALE collaboration. **METHODS:** Eligible patients (N = 818) aged 50-80 were randomized (May 2017-January 2021) to the Intensive vs. Minimal arms (8 vs. 3 phone sessions plus 8 vs. 2 weeks of nicotine patches, respectively). Bio-verified (primary) and self-reported 7-day abstinence rates were assessed 3-, 6-, and 12-months post-randomization. Logistic regression analyses evaluated the effects of study arm. All statistical tests were two-sided. **RESULTS:** Participants reported 48.0 (SD = 17.2) pack-years and 51.6% were not ready to quit in < 30 days. Self-reported 3-month quit rates were significantly higher in the Intensive vs. Minimal arm (14.3% vs. 7.9%; OR = 2.00, 95% confidence interval [CI] = 1.26,3.18). Bio-verified abstinence was lower but with similar relative differences between arms (9.1% vs. 3.9%; OR = 2.70, 95% CI = 1.44, 5.08). Compared to the Minimal arm, the Intensive arm was more effective among those with greater nicotine dependence (OR = 3.47, 95% CI = 1.55, 7.76), normal screening results (OR = 2.58, 95% CI = 1.32, 5.03), high engagement in counseling (OR = 3.03, 95% CI = 1.50, 6.14) and patch use (OR = 2.81, 95% CI = 1.39, 5.68). Abstinence rates did not differ significantly between arms at 6-months (OR = 1.2, 95% CI = 0.68, 2.11) or 12-months (OR = 1.4, 95% CI = 0.82, 2.42). **CONCLUSIONS:** Delivering intensive telephone counseling and nicotine replacement with lung screening is an effective strategy to increase short-term smoking cessation. Methods to maintain short-term effects are needed. Even with modest quit rates, integrating cessation treatment into lung screening programs may have a large impact on tobacco-related mortality.

[Molecular biomarkers and liquid biopsies in lung cancer](#) Semin Oncol. 2022 Jul 3;S0093-7754(22)00047-1. doi: 10.1053/j.seminoncol.2022.06.007. Online ahead of print. Kamya Sankar 1 , Mina Zeinali 2 , Sunitha Nagrath 2 , Nithya Ramnath 3
Liquid biopsy refers to the identification of tumor-derived materials in body fluids including in blood circulation. In the age of immunotherapy and targeted therapies used for the treatment of advanced malignancies, molecular analysis of the tumor is considered a crucial step to guide management. In lung cancer, the concept of liquid biopsies is particularly relevant given the invasiveness of tumor biopsies in certain locations, and the potential risks of biopsy in a patient population with significant co-morbidities. Liquid biopsies have many advantages including non-invasiveness, lower cost, potential for genomic testing, ability to monitor tumor evolution through treatment, and the ability to overcome spatial and temporal intertumoral heterogeneity. The potential clinical applications of liquid biopsy are vast and include screening, detection of minimal residual disease and/or early relapse after curative intent treatment, monitoring response to immunotherapy, and identifying mutations that might be targetable or can confer resistance. Herein, we review the potential role of circulating tumor DNA and circulating tumor cells as forms of liquid biopsies and blood biomarkers in non-small cell lung cancer. We discuss the methodologies/platforms available for each, clinical applications, and limitations/challenges in incorporation into clinical practice. We additionally review emerging forms of liquid biopsies including tumor educated platelets, circular RNA, and exosomes.

[Impact of U.S. Preventive Services Task Force lung cancer screening update on drivers of disparities in screening eligibility](#) Cancer Med. 2022 Jul 24. doi: 10.1002/cam4.5066. Online ahead of print. Kristin G Maki 1 , Rajesh Talluri 2 , Iakovos Toumazis 1 , Sanjay Shete 3 4 5 , Robert J Volk 1
BACKGROUND: In 2021, the U.S. Preventive Services Task Force (USPSTF) updated its recommendation to expand lung cancer screening (LCS) eligibility and mitigate disparities. Although this increased the number of non-White individuals who are eligible for LCS, the update's impact on drivers of disparities is less clear. This analysis focuses on racial disparities among Black individuals because members of this group disproportionately share late-stage lung cancer diagnoses, despite typically having

a lower intensity smoking history compared to non-Hispanic White individuals. **METHODS:** We used data from the National Health Interview Survey to examine the impact of the 2021 eligibility criteria on racial disparities by factors such as education, poverty, employment history, and insurance status. We also examined preventive care use and reasons for delaying medical care. **RESULTS:** When comparing Black individuals and non-Hispanic White individuals, our analyses show significant differences in who would be eligible for LCS: Those who do not have a high school diploma (28.7% vs. 17.0%, p = 0.002), are in poverty (26.2% vs. 14.9%, p < 0.001), and have not worked in the past 12 months (66.5% vs. 53.9%, p = 0.009). Further, our analyses also show that more Black individuals delayed medical care due to not having transportation (11.1% vs. 3.6%, p < 0.001) compared to non-Hispanic White individuals. **CONCLUSIONS:** Our results suggest that despite increasing the number of Black individuals who are eligible for LCS, the 2021 USPSTF recommendation highlights ongoing socioeconomic disparities that need to be addressed to ensure equitable access.

Challenges in initiating a lung cancer screening program: Experiences from two VA medical centers Semin Oncol. 2022 Jul 3;S0093-7754(22)00046-X. doi: 10.1053/j.seminoncol.2022.06.006. Online ahead of print. Stephen Bujarski 1 , Robert Flowers 2 , Mansour Alkhunaizi 3 , Dave Cuvi 4 , Sneha Sathya 5 , Jennifer Melcher 6 , Farrah Kheradmand 7 , Gregory Holt 8
Establishing a lung cancer screening (LCS) program is an important endeavor that delivers life-saving healthcare to an at-risk population. However, developing a comprehensive LCS program requires critical elements including obtaining institutional level buy-in, hiring necessary personnel, developing appropriate infrastructure and actively engaging primary care providers, subspecialty services, and radiology. The process required to connect such services to deliver an organized LCS program that reaches all eligible candidates must be individualized to each institution's needs and infrastructure. Here we provide detailed experiences from two successful LCS programs, one using a primary care provider-based service and the other using a consult-based service. In each case, we provide the pros and cons of each system. We propose that the decision to setup an ideal LCS program could include a hybrid design that combines aspects of each system.

Expert opinion on NSCLC small specimen biomarker testing - Part 2: Analysis, reporting, and quality assessment Virchows Arch. 2022 Jul 20;1-16. doi: 10.1007/s00428-022-03344-1. Online ahead of print. Frédérique Penault-Llorca 1 , Keith M Kerr 2 , Pilar Garrido 3 , Erik Thunnissen 4 , Elisabeth Dequeker 5 , Nicola Normanno 6 , Simon J Patton 7 , Jenni Fairley 8 , Joshua Kapp 9 , Daniëlle de Ridder 10 , Aleš Ryška 11 , Holger Moch 12
The diagnostic work-up for non-small cell lung cancer (NSCLC) requires biomarker testing to guide therapy choices. This article is the second of a two-part series. In Part 1, we summarised evidence-based recommendations for obtaining and processing small specimen samples (i.e. pre-analytical steps) from patients with advanced NSCLC. Here, in Part 2, we summarise evidence-based recommendations relating to analytical steps of biomarker testing (and associated reporting and quality assessment) of small specimen samples in NSCLC. As the number of biomarkers for actionable (genetic) targets and approved targeted therapies continues to increase, simultaneous testing of multiple actionable oncogenic drivers using next-generation sequencing (NGS) becomes imperative, as set forth in European Society for Medical Oncology guidelines. This is particularly relevant in advanced NSCLC, where tissue specimens are typically limited and NGS may help avoid tissue exhaustion compared with sequential biomarker testing. Despite guideline recommendations, significant discrepancies in access to NGS persist across Europe, primarily due to reimbursement constraints. The use of increasingly complex testing methods also has implications for the reporting of results. Molecular testing reports should include clinical interpretation with additional commentary on sample adequacy as appropriate. Molecular tumour boards are recommended to facilitate the interpretation of complex genetic information arising from NGS, and to

collaboratively determine the optimal treatment for patients with NSCLC. Finally, whichever testing modality is employed, it is essential that adequate internal and external validation and quality control measures are implemented.

[National Cancer Institute Smoking Cessation at Lung Examination Trials Brief Report: Baseline Characteristics and Comparison With the U.S. General Population of Lung Cancer Screening-Eligible Patients](#) JTO Clin Res Rep. 2022 Jun 3;3(7):100352. doi: 10.1016/j.jtocrr.2022.100352. eCollection 2022 Jul. Rafael Meza 1 , Jihyoun Jeon 1 , Evelyn Jimenez-Mendoza 1 , et al.

INTRODUCTION: The National Cancer Institute Smoking Cessation at Lung Examination (SCALE) Collaboration includes eight clinical trials testing smoking cessation interventions delivered with lung cancer screening (LCS). This investigation compared pooled participant baseline demographic and smoking characteristics of seven SCALE trials to LCS-eligible smokers in three U.S. nationally representative surveys. **METHODS:** Baseline variables (age, sex, race, ethnicity, education, income, cigarettes per day, and time to the first cigarette) from 3614 smokers enrolled in SCALE trials as of September 2020 were compared with pooled data from the Tobacco Use Supplement-Current Population Survey (2018-2019), National Health Interview Survey (2017-2018), and Population Assessment of Tobacco and Health (wave 4, 2016-2017) using the U.S. Preventive Services Task Force 2013 (N = 4803) and 2021 (N = 8604) LCS eligibility criteria. **RESULTS:** SCALE participants have similar average age as the U.S. LCS-eligible smokers using the 2013 criteria but are 2.8 years older using the 2021 criteria (p < 0.001). SCALE has a lower proportion of men, a higher proportion of Blacks, and slightly higher education and income levels than national surveys (p < 0.001). SCALE participants smoke an average of 17.9 cigarettes per day (SD 9.2) compared with 22.4 (SD 9.3) using the 2013 criteria and 19.6 (SD 9.7) using the 2021 criteria (p < 0.001). The distribution of time to the first cigarette differs between SCALE and the national surveys (p < 0.001), but both indicate high levels of nicotine dependence. **CONCLUSIONS:** SCALE participants smoke slightly less than the LCS-eligible smokers in the general population, perhaps related to socioeconomic status or race. Other demographic variables reveal small but statistically significant differences, likely of limited clinical relevance with respect to tobacco treatment outcomes. SCALE trial results should be applicable to LCS-eligible smokers from the U.S. population.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

[Optimal Chest Drainage Method After Anatomical Lung Resection: A Prospective Observational Study](#) Ann Thorac Surg. 2022 Jul 19;S0003-4975(22)00971-7. doi: 10.1016/j.athoracsur.2022.06.042. Online ahead of print. Hiroyuki Adachi 1 , Shin Wakimoto 2 , Kohei Ando 3 , Taketsugu Yamamoto 4 , Yuichi Saito 5 , Satoshi Shiono 6 , Tekkan Woo 7 , Hiroyuki Ito 8 , Yukinori Sakao 5 , Noriyoshi Sawabata 9

BACKGROUND: Several methods for chest drainage following pulmonary resection of malignant lung tumors exist, but consensus on the ideal method has not been reached. **METHODS:** We conducted a multicenter prospective observational study. We enrolled 2,200 patients who underwent lung resection for lung tumors. Among the 1,470 patients who underwent anatomical resection, 347 showed air leak on the morning of postoperative day 1. They were classified into three groups according to their chest drainage methods on postoperative day 1. **RESULTS:** Of 347 patients with postoperative air leaks, 107 (30.8%), 179 (51.6%), and 61 (17.6%) were assigned water-seal, continuous suction, and digital drainage, respectively. The median postoperative air leak duration with digital drainage (4.0 days) was significantly longer than that with either water-seal (2.5 days) or continuous suction (3.0 days) (p=0.009). Chest tubes were required for significantly more days on average with digital drainage (6.0 days) than with water-seal

(4.0 days) or continuous suction (4.0 days) (p=0.003). Prolongation of air leak duration was significantly more likely to occur in patients with a body mass index < 18.5 kg/m2 (HR 1.6, 95% CI 1.1-2.3), a moderate or severe air leak on postoperative day 1 (HR 2.0, 95% CI 1.5-2.6), or digital drainage (HR 1.4, 95% CI 1.01-1.9). **CONCLUSIONS:** Water-seal was associated with significantly shorter duration of postoperative air leak and chest drainage compared to continuous suction and digital drainage.

A guide for managing patients with stage I NSCLC: deciding between lobectomy, segmentectomy, wedge, SBRT and ablation-part 2: systematic review of evidence regarding resection extent in generally healthy patients J Thorac Dis. 2022 Jun;14(6):2357-2386. doi: 10.21037/jtd-21-1824. Frank C Detterbeck 1 , Vincent J Mase Jr 1 , Andrew X Li 2 , Ulas Kumbasar 3 , Brett C Bade 4 , Henry S Park 5 , Roy H Decker 5, David C Madoff 6 , Gavitt A Woodard 1 Whitney S Brandt 7 , Justin D Blasberg 1
BACKGROUND: Clinical decision-making for patients with stage I lung cancer is complex. It involves multiple options (lobectomy, segmentectomy, wedge, stereotactic body radiotherapy, thermal ablation), weighing multiple outcomes (e.g., short-, intermediate-, long-term) and multiple aspects of each (e.g., magnitude of a difference, the degree of confidence in the evidence, and the applicability to the patient and setting at hand). A structure is needed to summarize the relevant evidence for an individual patient and to identify which outcomes have the greatest impact on the decision-making. **METHODS:** A PubMed systematic review from 2000-2021 of outcomes after lobectomy, segmentectomy and wedge resection in generally healthy patients is the focus of this paper. Evidence was abstracted from randomized trials and non-randomized comparisons with at least some adjustment for confounders. The analysis involved careful assessment, including characteristics of patients, settings, residual confounding etc. to expose degrees of uncertainty and applicability to individual patients. Evidence is summarized that provides an at-a-glance overall impression as well as the ability to delve into layers of details of the patients, settings and treatments involved. **RESULTS:** In healthy patients there is no short-term benefit to sublobar resection vs. lobectomy in randomized and non-randomized comparisons. A detriment in long-term outcomes is demonstrated by adjusted non-randomized comparisons, more marked for wedge than segmentectomy. Quality-of-life data is confounded by the use of video-assisted approaches; evidence suggests the approach has more impact than the resection extent. Differences in pulmonary function tests by resection extent are not clinically meaningful in healthy patients, especially for multi-segmentectomy vs. lobectomy. The margin distance is associated with the risk of recurrence. **CONCLUSIONS:** A systematic, comprehensive summary of evidence regarding resection extent in healthy patients with attention to aspects of applicability, uncertainty and effect modifiers provides a foundation on which to build a framework for individualized clinical decision-making.

Pulmonary completion lobectomy after segmentectomy: An integrated analysis of perioperative outcomes Thorac Cancer. 2022 Jul 5. doi: 10.1111/1759-7714.14565. Online ahead of print. Yu-Wei Liu 1 2 3 , Chieh-Ni Kao 1 , Hung-Hsing Chiang 1 3 , Jui-Ying Lee 1 , Hsien-Pin Li 1 , Po-Chih Chang 1 2 , Shah-Hwa Chou 1 2
BACKGROUND: Completion lobectomy (CL) after anatomical segmentectomy is technically challenging and rarely performed. Here, we aimed to report perioperative outcomes of a single center real-world CL data. **METHODS:** Seven patients who underwent CL after segmentectomy were retrospectively evaluated between 2015-2021. Additionally, 34 patients were included in the review based on relevant studies in the literature until March 2022. A total of 41 patients were finally analyzed and classified into groups, according to surgical approach (video-assisted thoracic surgery [VATS] and thoracotomy; 12 and 29 patients, respectively) or interval-to-CL following initial segmentectomy (≤8 weeks [short] and >8 weeks [long]; 11 and 30 patients, respectively). **RESULTS:** There were no significant differences in estimated blood loss, postoperative hospital stay, or complications between the predefined groups. However, a longer operative time was observed in the long interval-to-CL group than

in the short interval-to-CL group (267 vs. 226 min, p = 0.02). The rate of severe hilar adhesions was higher in the thoracotomy versus VATS groups (72 vs. 42%, p = 0.06) and in the long versus short interval-to-CL groups (70 vs. 45%, p = 0.15). On multivariable logistic regression analysis of a subgroup (n = 30), completion lobectomy of upper lobes may be associated with severe hilar adhesions (p = 0.02, odds ratio: 13.98; 95% confidence interval [CI]: 1.36-143.71). **CONCLUSION:** Completion lobectomy after segmentectomy can be performed securely by either VATS or thoracotomy. Although the thoracotomy and long interval-to-CL groups retained a greater percentage of severe hilar adhesions, the perioperative outcomes were similar to those of VATS and short interval-to-CL groups, respectively.

[**Adverse Events Following Limited Resection versus Stereotactic Body Radiation Therapy for Early-Stage Lung Cancer**](#) Ann Am Thorac Soc. 2022 Jul 11. doi: 10.1513/AnnalsATS.202203-275OC. Online ahead of print. Qian Wang 1 , Kimberly Stone 2 , Jeffrey A Kern 3 , Christopher G Slatore 4 5 6 , Scott Swanson 7 , William Blackstock Jr 8 , Rabia Saeed Khan 9 , Cardinale B Smith 10 , Rajwanth R Veluswamy 10 , Mark Chidel 11 , Juan P Wisnivesky 12

RATIONALE: Approximately a quarter of early-stage lung cancer patients are not medically fit for lobectomy. Limited resection and stereotactic body radiation therapy (SBRT) have emerged as alternatives for these patients. Given the equipoise on the effectiveness of the two treatments, treatment-related adverse events (AEs) could have a significant impact on patients' decision-making and treatment outcomes. **OBJECTIVES:** To compare the AE profile between SBRT vs. limited resection. **METHODS:** Data were derived from a prospective cohort of stage I-IIA non-small cell lung cancer patients who were deemed as high-risk for lobectomy recruited from 5 centers across the United States. Propensity scores and inverse probability weighting were used to compare the rates of 30- and 90-day AEs among patients treated with limited resection vs. SBRT. **RESULTS:** Overall, 65% of 252 patients underwent SBRT. After adjusting for propensity scores, there was no significant difference in developing at least one AE comparing SBRT to limited resection (odds ratio [OR]: 1.00; 95% confidence interval [CI]: 0.65-1.55 and OR: 1.27; 95% CI: 0.84-1.91 at 30 and 90 days, respectively). SBRT was associated with lower risk of infectious AEs than limited resection at 30 days (OR: 0.05; 95% CI: 0.01-0.39) and 90 days post-treatment (OR: 0.41; 95% CI: 0.17-0.98). Additionally, SBRT was associated with persistently elevated risk of fatigue (OR: 2.47; 95% CI: 1.34-4.54 at 30 days and OR: 2.69; 95% CI: 1.52-4.77 at 90 days, respectively), but significantly lower risks of respiratory AEs (OR: 0.36; 95% CI: 0.20-0.65 and OR: 0.51; 95% CI: 0.31-0.86 at 30 and 90 days, respectively). **CONCLUSIONS:** Though equivalent in developing at least one AE, we found that SBRT is associated with less toxicity than limited resection in terms of infectious and respiratory AEs but higher rates of fatigue that persisted up to 3 months post-treatment. This information, combined with data about oncologic effectiveness, can help patients' decision-making regarding these alternative therapies.

[**Brief Report: Contralateral Lobectomy for Second Primary NSCLC: Perioperative and Long-Term Outcomes**](#) JTO Clin Res Rep. 2022 Jun 18;3(8):100362. doi: 10.1016/j.jtocrr.2022.100362. eCollection 2022 Aug. Jennie K Choe 1 , Amy Zhu 1 , Alexander J Byun 1 , et al.

INTRODUCTION: Anatomical resection-often by lobectomy-is the standard of care for patients with early stage NSCLC. With increased diagnosis, survival, and prevalence of persons with early stage NSCLC, the incidence of second primary NSCLC, and consequently, the need for contralateral lobectomy for a metachronous cancer, is increasing. Perioperative outcomes after contralateral lobectomy are unknown. **METHODS:** Among patients who underwent contralateral lobectomy for second primary NSCLC during 1995 to 2020, we evaluated 90-day mortality and major morbidity (Clavien-Dindo grades 3-5) rates and their association with clinicopathologic variables, including the year of contralateral lobectomy and duration between lobectomies. **RESULTS:** A total of 98 patients underwent contralateral lobectomy for second primary NSCLC; 51 during an early time period (1995-2009) and 47 from a late

time period (2010-2020). There were five mortalities and 23 patients with major morbidities after contralateral lobectomy; both rates decreased in 2010 to 2020 compared with 1995 to 2009 (mortality 10%-0%, major morbidity 35%-11%). Major morbidity was associated with an interval of less than 1 year between lobectomies, a diffusing capacity of the lung for carbon monoxide <80%, and right lower lobe resections. Mortality was associated with squamous cell carcinoma. Patients who underwent contralateral lobectomy for stage I NSCLC had 74% (95% confidence interval: 64%-85%) 3-year overall survival and 15% (95% confidence interval: 6.5%-24%) 3-year lung cancer cumulative incidence of death. **CONCLUSIONS:** Contralateral lobectomy for second primary early stage NSCLC was associated with poor outcomes before 2010. Since 2010, perioperative and long-term outcomes of contralateral lobectomy have been comparable with reported outcomes after unilateral lobectomy.

[A guide for managing patients with stage I NSCLC: deciding between lobectomy, segmentectomy, wedge, SBRT and ablation-part 3: systematic review of evidence regarding surgery in compromised patients or specific tumors](#) J Thorac Dis. 2022 Jun;14(6):2387-2411. doi: 10.21037/jtd-21-1825. Brett C Bade 1 , Justin D Blasberg 2 , Vincent J Mase Jr 2 , Ulas Kumbasar 3 , Andrew X Li 4 , Henry S Park 5 , Roy H Decker 5 , David C Madoff 6 , Whitney S Brandt 7 , Gavitt A Woodard 2 , Frank C Detterbeck 2

BACKGROUND: Clinical decision-making for patients with stage I lung cancer is complex. It involves multiple options [lobectomy, segmentectomy, wedge, stereotactic body radiotherapy (SBRT), thermal ablation], weighing multiple outcomes (e.g., short-, intermediate-, long-term) and multiple aspects of each (e.g., magnitude of a difference, the degree of confidence in the evidence, and the applicability to the patient and setting at hand). A structure is needed to summarize the relevant evidence for an individual patient and to identify which outcomes have the greatest impact on the decision-making. **METHODS:** A PubMed systematic review from 2000-2021 of outcomes after lobectomy, segmentectomy and wedge resection in older patients, patients with limited pulmonary reserve and favorable tumors is the focus of this paper. Evidence was abstracted from randomized trials and non-randomized comparisons (NRCs) with adjustment for confounders. The analysis involved careful assessment, including characteristics of patients, settings, residual confounding etc. to expose degrees of uncertainty and applicability to individual patients. Evidence is summarized that provides an at-a-glance overall impression as well as the ability to delve into layers of details of the patients, settings and treatments involved. **RESULTS:** In older patients, perioperative mortality is minimally altered by resection extent and only slightly affected by increasing age; sublobar resection may slightly decrease morbidity. Long-term outcomes are worse after lesser resection; the difference is slightly attenuated with increasing age. Reported short-term outcomes are quite acceptable in (selected) patients with severely limited pulmonary reserve, not clearly altered by resection extent but substantially improved by a minimally invasive approach. Quality-of-life (QOL) and impact on pulmonary function hasn't been well studied, but there appears to be little difference by resection extent in older or compromised patients. Patient selection is paramount but not well defined. Ground-glass and screen-detected tumors exhibit favorable long-term outcomes regardless of resection extent; however solid tumors <1 cm are not a reliably favorable group. **CONCLUSIONS:** A systematic, comprehensive summary of evidence regarding resection extent in compromised patients and favorable tumors with attention to aspects of applicability, uncertainty and effect modifiers provides a foundation for a framework for individualized decision-making.

NSCLC – Systemic Therapies (Chemotherapy, Targeted Therapy, and Immunotherapy)

[A novel immune checkpoints-based signature to predict prognosis and response to immunotherapy in lung adenocarcinoma](#) J Transl Med. 2022 Jul 25;20(1):332. doi: 10.1186/s12967-022-03520-6. Nan Sun # 1   2 , Yuejun Luo # 1   2 , et al.

BACKGROUND: Except for B7-CD28 family members, more novel immune checkpoints are being discovered. They are closely associated with tumor immune microenvironment and regulate the function of many immune cells. Various cancer therapeutic studies targeting these novel immune checkpoints are currently in full swing. However, studies concerning novel immune checkpoints phenotypes and clinical significance in lung adenocarcinoma (LUAD) are still limited. **METHODS:** We enrolled 1883 LUAD cases from nine different cohorts. The samples from The Cancer Genome Atlas (TCGA) were used as a training set, whereas seven microarray data cohorts and an independent cohort with 102 qPCR data were used for validation. The immune profiles and potential mechanism of the system were also explored. **RESULTS:** After univariate Cox proportional hazards regression and stepwise multivariable Cox analysis, a novel immune checkpoints-based system (LTA, CD160, and CD40LG) were identified from the training set, which significantly stratified patients into high- and low-risk groups with different survivals. Furthermore, this system has been well validated in different clinical subgroups and multiple validation cohorts. It also acted as an independent prognostic factor for patients with LAUD in different cohorts. Further exploration suggested that high-risk patients exhibited distinctive immune cells infiltration and suffered an immunosuppressive state. Additionally, this system is closely linked to various classical immunotherapy biomarkers. **CONCLUSION:** we constructed a novel immune checkpoints-based system for LUAD, which predicts prognosis and immunotherapeutic implications. We believe that these findings will not only aid in clinical management but will also shed some light on screening appropriate patients for immunotherapy.

[Anlotinib as third- or further-line therapy for short-term relapsed small-cell lung cancer: subgroup analysis of a randomized phase 2 study (ALTER1202)](#) Front Med. 2022 Jul 16. doi: 10.1007/s11684-021-0916-8. Online ahead of print. Jianhua Shi 1 , Ying Cheng 2 , Qiming Wang 3 , Kai Li 4 , Lin Wu 5 , Baohui Han 6 , Gongyan Chen 7 , Jianxing He 8 , Jie Wang 9 , Haifeng Qin 10 , Xiaoling Li 11 Patients with small-cell lung cancer (SCLC) relapse within months after completing previous therapies. **This study aimed to** investigate the efficacy and safety of anlotinib as third- or further-line therapy in patients with short-term relapsed SCLC from ALTER1202. Patients with short-term relapsed SCLC (disease progression within 3 months after completing $\geqslant$ two lines of chemotherapy) in the anlotinib (n = 67) and placebo (n = 34) groups were analyzed. The primary endpoint was progression-free survival (PFS). The secondary endpoints included overall survival, objective response rate (ORR), disease control rate, and safety. Anlotinib significantly improved median PFS/OS (4.0 vs. 0.7 months, P < 0.0001)/(7.3 vs. 4.4 months, P = 0.006) compared with placebo. The ORR was 4.5%/2.9% in the anlotinib/placebo group (P = 1.000). The DCR in the anlotinib group was higher than that in the placebo group (73.1% vs. 11.8%, P < 0.001). The most common adverse events (AEs) were hypertension (38.8%), loss of appetite (28.4%), and fatigue (22.4%) in the anlotinib group and gammaglutamyl transpeptidase elevation (20.6%) in the placebo group. No grade 5 AEs occurred. For patients with short-term relapsed SCLC, third- or further-line anlotinib treatment was associated with improved survival benefit. Further studies are warranted in this regard.

[Treatment Considerations for Patients With Advanced Squamous Cell Carcinoma of the Lung](#) Clin Lung Cancer. 2022 Jun 21;S1525-7304(22)00146-2. doi: 10.1016/j.cllc.2022.06.002. Online ahead of print. Edgardo S Santos 1 , Estelamari Rodriguez 2 Squamous cell carcinoma (SCC) of the lung has a markedly different molecular profile to adenocarcinoma of the lung and remains difficult to treat because of the lack of targeted therapies for this type of non-small cell lung cancer (NSCLC). With immune checkpoint inhibitors moving from second-line treatment to first-line in NSCLC, effective second-line options following immunotherapy is an urgent unmet need. Appropriate treatment decisions are currently hindered by a lack of prospective clinical data. However, available real-world data suggest that ramucirumab plus docetaxel warrants prospective

evaluation in this setting. Also, afatinib is approved in the second line in patients with SCC progressing on first-line platinum-based chemotherapy and may also be an option following immunochemotherapy combinations. Afatinib has the advantage of oral administration with a well-defined tolerability profile. Docetaxel, gemcitabine and platinum-based chemotherapy may be options for some patients, but overall, there are very few options for patients requiring second-line treatment after immunotherapy. This lack of options has prompted efforts to further define the molecular profile of lung SCC to match patients with relevant targeted therapies and to elucidate additional genomic targets. In order to ensure patients with SCC of the lung receive optimal treatment, genomic testing is essential to identify those patients who might benefit from existing targeted agents or clinical trials, and further prospective data are urgently required to assess potential second-line regimens following immunotherapy.

[Comparison of efficacy and safety of bevacizumab biosimilar and original bevacizumab in non-squamous non-small cell lung cancer: a systematic review and meta-analysis](#) Transl Cancer Res. 2022 Jun;11(6):1472-1482. doi: 10.21037/tcr-22-71. Xian Xiao # 1 2 3 , Guixing Zhang # 1 2 3 , Binxu Sun 1 2 , Chaoran Wang 1 2 3 , Xiaoqun Wang 1 2 , Fanming Kong 1 2 , Yingjie Jia 1 2
BACKGROUND: Bevacizumab (Avastin®), a monoclonal antibody targeting vascular endothelial growth factor (VEGF)-A, is widely used in treating a variety of malignant tumors. Several biosimilars of bevacizumab have been developed and marketed with the expiration of bevacizumab's patent. The objective of this study was to collate available data from head-to-head randomized controlled trials (RCTs) and evaluate the efficacy and safety of biosimilar bevacizumab compared with the bevacizumab (Avastin®) in patients with non-squamous non-small cell lung cancer (NSCLC). **METHODS:** Literature search of Web of Science, PubMed, Cochrane Library, EMBASE, and ClinicalTrials.gov was performed from inception until October 15, 2021. The efficacy outcome indicators were objective response rate (ORR), progression-free survival (PFS) and overall survival (OS). The occurrence of adverse events (AEs) was evaluated for safety outcome. **RESULTS:** Ten RCTs recruiting 6,416 patients with non-squamous NSCLC were included. All RCTs studies included the biosimilar bevacizumab group as the experimental group and the original bevacizumab group as the control group. The patients in the experimental group and control group received the same dose and duration of chemotherapy combined with carboplatin and paclitaxel. The results of meta-analysis showed that there were no significant differences in ORR [risk ratio (RR): 0.97, 95% confidence interval (95% CI): 0.93-1.02. P=0.841, I2=0], PFS (RR: 1.04, 95% CI: 0.98-1.10, P=0.235, I2=0) and OS (RR: 1.05, 95% CI: 1.00-1.10, P=0.692, I2=0) between the biomarker and original groups. The P values of ORR, PFS and OS were 0.533, 0.970 and 0.916 respectively as shown by Egger's test, suggesting that there was no publication bias. Subgroup analysis showed no significant differences in ORR, PFS, and OS between the Chinese and multicenter trials. The pooled incidence rate of AEs between two groups was similar, and there was also no significant difference between the two groups. **DISCUSSION:** This is the first study to independently report biosimilar bevacizumab in a meta-analysis on NSCLC treatment. The results showed that biosimilar bevacizumab had similar efficacy and safety compared with the original bevacizumab.

[Brief Report: Safety and Antitumor Activity of Alectinib Plus Atezolizumab From a Phase 1b Study in Advanced ALK-Positive NSCLC](#) JTO Clin Res Rep. 2022 Jun 25;3(8):100367. doi: 10.1016/j.jtocrr.2022.100367. eCollection 2022 Aug. Dong-Wan Kim 1 , Shirish Gadgeel 2 , Scott N Gettinger 3 , et al.
INTRODUCTION: Alectinib is a preferred first-line treatment option for advanced ALK-positive NSCLC. Combination regimens of alectinib with immune checkpoint inhibitors are being evaluated for synergistic effects. **METHODS:** Adults with treatment-naive, stage IIIB/IV, or recurrent ALK-positive NSCLC were enrolled into a two-stage phase 1b study. Patients received alectinib 600 mg (twice daily during cycle 1 and throughout each 21-d cycle thereafter) plus atezolizumab 1200 mg (d8 of cycle 1 and

then d1 of each 21-d cycle). Primary objectives were to evaluate safety and tolerability of alectinib plus atezolizumab. Secondary objectives included assessments of antitumor activity. **RESULTS:** In total, 21 patients received more than or equal to 1 dose of alectinib or atezolizumab. As no dose-limiting toxicities were observed in stage 1 (n = 7), the starting dose and schedule were continued into stage 2 (n = 14). Median duration of follow-up was 29 months (range: 1-39). Grade 3 treatment-related adverse events occurred in 57% of the patients, most often rash (19%). No grade 4 or 5 treatment-related adverse events were reported. Confirmed objective response rate was 86% (18 of 21; 95% confidence interval [CI]: 64-97). Median progression-free survival was not estimable (NE) (95% CI: 13 mo-NE), neither was median overall survival (95% CI: 33 mo-NE). **CONCLUSIONS:** The combination of alectinib and atezolizumab is feasible, but increased toxicity was found compared with the individual agents. With small sample sizes and relatively short follow-up, definitive conclusions regarding antitumor activity cannot be made.

[**Does Molecular Profiling of KRAS-Mutant Non-Squamous Non-Small Cell Lung Cancer (NSCLC) Help in Treatment Strategy Planning?**](#) Curr Oncol. 2022 Jul 7;29(7):4779-4790. doi: 10.3390/curroncol29070379. Nagla Abdel Karim 1 , Asad Ullah 2 , Peterson Pathrose 3 , Hassana Fathallah 4 , Ashley Perry 4 , John C Morris 4 , Jiang Wang 5 , Sandra L Starnes 3
BACKGROUND: Several studies suggest that patients with KRAS-mutant NSCLC fail to benefit from standard systemic therapies and do not respond to EGFR inhibitors. Most recently, KRAS 12c data suggest specific treatment for improving ORR and OS. There is a clear need for therapies specifically developed for these patients. Moreover, data that might be suggestive of a response to specific therapies, such as BRCA1, are needed, and two mutations that were studied in other malignancies show more response to PARP inhibitors. Molecular profiling has the potential to identify other potential targets that may provide better treatment and novel targeted therapy for KRAS-mutated NSCLC. **METHODS:** We purified RNA from archived tissues of patients with stage I and II NSCLC with wild-type (wt) and mutant (mt) KRAS tumors; paired normal tissue adjacent to the tumor from 20 and 17 patients, respectively, and assessed, using real-time reverse transcriptase-polymerase chain reaction (RT-PCR), the expression of four genes involved in DNA synthesis and repair, including thymidylate synthase (TS), BRCA1, ECCR1, RAP80, and the proto-oncogene SRC. Additionally, we assessed the expression of PD-L1 in mt&nbsp;KRAS tumors with immunohistochemistry using an antibody against PD-L1. **RESULTS:** Our results show that in mtKRAS tumors, the level of expression of ERCC1, TS, and SRC was significantly increased in comparison to paired normal lung tissue (p ≤ 0.04). The expression of BRCA1 and RAP80 was similar in both mt&nbsp;KRAS tumors and paired normal tissue. Furthermore, the expression of BRCA1, TS, and SRC was significantly increased in wt&nbsp;KRAS tumors relative to their expression in the normal lung tissue (p < 0.044). The expression of ERCC1 and RAP80 was similar in wt&nbsp;KRAS tumors and paired normal tissue. Interestingly, SRC expression in mtKRAS tumors was decreased in comparison to wt&nbsp;KRAS tumors. Notably, there was an expression of PD-L1 in the tumor and stromal cells in a few (5 out of 20) mtKRAS tumors. Our results suggest that a greater ERCC1 expression in mt KRAS tumors might increase platinum resistance in this group of patients, whereas the greater expression of BRCA1 in wt&nbsp;KRAS tumor might be suggestive of the sensitivity of taxanes. Our data also suggest that the combination of an SRC inhibitor with a TS inhibitor, such as pemetrexed, might improve the outcome of patients with NSCLC and in particular, patients with wt&nbsp;KRAS tumors. PD-L1 expression in tumors, and especially stromal cells, suggests a better outcome. **CONCLUSION:** mt&nbsp;KRAS NSCLC patients might benefit from a treatment strategy that targets KRAS in combination with therapeutic agents based on pharmacogenomic markers, such as SRC and BRCA1. mtKRAS tumors are likely to be platinum-, taxane-, and pemetrexed-resistant, as well as having a low level of PD-L1 expression; thus, they are less likely to receive single-agent immunotherapy, such as pembrolizumab, as the first-line therapy. wt&nbsp;KRAS tumors with BRCA1 positivity tend to be sensitive to taxane therapy and,

potentially, platinum. Our results suggest the need to develop targeted therapies for KRAS-mutant NSCLC or combine the targeting of oncogenic KRAS in addition to other therapeutic agents specific to the molecular profile of the tumor.

[Therapy for Stage IV Non-Small-Cell Lung Cancer Without Driver Alterations: ASCO Living Guideline](#) J Clin Oncol. 2022 Jul 11;JCO2200825. doi: 10.1200/JCO.22.00825. Online ahead of print. Navneet Singh 1 , Sarah Temin 2 , Sherman Baker Jr 3 , et al.
PURPOSE: To provide evidence-based recommendations updating the 2020 ASCO and Ontario Health (Cancer Care Ontario) guideline on systemic therapy for patients with stage IV non-small-cell lung cancer without driver alterations. **METHODS:** ASCO updated recommendations on the basis of an ongoing systematic review of randomized clinical trials from 2018 to 2021. **RESULTS:** This guideline update reflects changes in evidence since the previous update. Five randomized clinical trials provide the evidence base. Outcomes of interest include efficacy and safety. **RECOMMENDATIONS:** In addition to 2020 options for patients with high programmed death ligand-1 (PD-L1) expression (tumor proportion score [TPS] ≥ 50%), nonsquamous cell carcinoma (non-SCC), and performance status (PS) 0-1, clinicians may offer single-agent atezolizumab. With high PD-L1 expression (TPS ≥ 50%), non-SCC, and PS 0-1, clinicians may offer nivolumab and ipilumumab alone or nivolumab and ipilimumab plus chemotherapy. With negative (0%) and low positive PD-L1 expression (TPS 1%-49%), non-SCC, and PS 0-1, clinicians may offer nivolumab and ipilimumab alone or nivolumab and ipilimumab plus chemotherapy. With high PD-L1 expression, SCC, and PS 0-1, clinicians may offer single-agent atezolizumab. With high PD-L1 expression, squamous cell carcinoma (SCC), and PS 0-1, clinicians may offer nivolumab and ipilimumab alone or in combination with two cycles of platinum-based chemotherapy. With negative and low positive PD-L1 expression, SCC, and PS 0-1, clinicians may offer nivolumab and ipilimumab alone or in combination with two cycles of platinum-based chemotherapy. With non-SCC who received an immune checkpoint inhibitor and chemotherapy as first-line therapy, clinicians may offer second-line paclitaxel plus bevacizumab. With non-SCC, who received chemotherapy with or without bevacizumab and immune checkpoint inhibitor therapy, clinicians should offer the options of third-line single-agent pemetrexed, docetaxel, or paclitaxel plus bevacizumab. Additional information is available at www.asco.org/thoracic-cancer-guidelines.

[Real-World Efficacy and Tolerability of Brigatinib in Patients with Non-Small Cell Lung Cancer with Prior ALK-TKIs in the United States](#) Oncologist. 2022 Jul 4;oyac116. doi: 10.1093/oncolo/oyac116. Online ahead of print. Mohammad Jahanzeb 1 , Huamao M Lin 2 , Yanyu Wu 2 , Pingkuan Zhang 2 , Magdaliz Gorritz 3 , Catherine B McGuiness 3 , Wei-Ti Huang 3 , Kainan Sun 3 , Chi-Chang Chen 3 , D Ross Camidge 4
BACKGROUND: Real-world evidence for brigatinib, a next-generation anaplastic lymphoma kinase-tyrosine kinase inhibitor (ALK-TKI) used in ALK-rearranged non-small cell lung cancer, is scarce. This retrospective study evaluated real-world brigatinib utilization in the US post other ALK-TKIs. Materials and **METHODS:** Adults with ≥1 brigatinib claim (index date) between 1 April 2017 and 30 September 2020 in the IQVIA longitudinal pharmacy claims database were followed until dose reduction, discontinuation, or end of follow-up. Patients had ≥12 months pre- and ≥1-month post-index observations. **RESULTS:** A total of 413 patients treated with brigatinib were analyzed. Over 80% received ≥1 prior ALK-TKI; alectinib and crizotinib were the most common (58.8% and 51.3% patients, respectively). The median follow-up was 8.4 months. The median time to treatment discontinuation (TTD) for brigatinib was 10.3 months (95% CI, 8.2-15.0), with 45% remaining on therapy at 12 months. The TTD was shortest (~8 months) in patients receiving both crizotinib and alectinib and longest in patients who received alectinib only prior to brigatinib (11.8 months). Adherence was high, with 92.7% of patients having a medication possession ratio of >80%. The mean dose compliance score was 1.0. Most patients reached

the brigatinib dose of 180 mg/day (77%); 13.2% of patients had a dose reduction, with 89.3% and 84.6% continuing 180 mg/day therapy at 3 and 6 months, respectively. **CONCLUSIONS:** Brigatinib appears to be effective and well-tolerated in the real-world ALK+ NSCLC population in the US, showing benefit in patients after a next-generation ALK-TKI. Notably, dose reduction rates appeared markedly less than those seen in trials when most trial-related dose reductions were for asymptomatic laboratory abnormalities.

[Overall survival indirect treatment comparison between brigatinib and alectinib for the treatment of front-line anaplastic lymphoma kinase-positive non-small cell lung cancer using data from ALEX and final results from ALTA-1L](#) Curr Med Res Opin. 2022 Jul 11;1-24. doi: 10.1080/03007995.2022.2100653. Online ahead of print.

Karen L Reckamp 1 , Huamao M Lin 2 , Holly Cranmer 3 , Yanyu Wu 2 , Pingkuan Zhang 2 , Stephen Kay 4 , Laura J Walton 5 , Junwu Shen 2 , Sanjay Popat 6 , D Ross Camidge 7

BACKGROUND: Second-generation anaplastic lymphoma kinase (ALK) gene targeted tyrosine kinase inhibitors (TKIs) alectinib and brigatinib have shown efficacy as front-line treatments for ALK-positive non-small cell lung cancer (NSCLC). No head-to-head data are currently available for brigatinib vs alectinib in the ALK-TKI-naive population. Objective: To estimate the relative overall survival (OS) for brigatinib vs alectinib with indirect treatment comparisons (ITCs) using ALEX and ALTA-1L clinical trial data. **METHODS:** The latest aggregate data from the ALEX trial and final patient-level data from ALTA-1L were used. ITCs were conducted with/without treatment crossover adjustments to estimate relative OS. Bucher methods, anchored matching-adjusted indirect comparisons (MAICs), and unanchored MAICs were employed in ITCs without treatment crossover adjustments. An inverse probability of censoring weight Cox model, a marginal structure model, and rank-preserving structural failure time models (with/without re-censoring) within an anchored MAIC were used in ITCs with treatment crossover adjustments. Hazard ratios (HR) and 95% confidence intervals (CI) were reported. **RESULTS:** HRs for brigatinib vs alectinib for relative OS generated from ITCs without treatment crossover adjustments ranged from 0.90 (95% CI: 0.59-1.38) in the unanchored MAIC to 1.20 (95% CI: 0.69-2.11) using the Bucher method. Methods employing treatment switching adjustments estimated HRs for relative OS ranging from 0.74 (95% CI: 0.38-1.45) to 1.11 (95% CI: 0.63-1.94). Results from all ITCs did not indicate statistically different survival profiles. **CONCLUSION:** Regardless of ITC methodology, OS is comparable for brigatinib vs alectinib in patients with ALK+ NSCLC previously untreated with an ALK inhibitor.

[The rest period between chemotherapy and immunotherapy influences the efficacy of immune checkpoint inhibitors in lung cancer](#) Thorac Cancer. 2022 Jul 11. doi: 10.1111/1759-7714.14568. Online ahead of print. Da Hyun Kang 1 , Seong-Woo Choi 1 , Pureum Sun 2 , Chaeuk Chung 1 , Dongil Park 1 , Song-I Lee 1 , Jeong Suk Koh 1 , Yoonjoo Kim 1 , Jeong Eun Lee 1

BACKGROUND: The use of immune checkpoint inhibitors (ICIs) as first-line treatment rather than as second-line treatment makes a big difference in the drug efficacy and progression-free survival. However, the mechanism for this is still not clear. This study aimed to analyze the effects of the rest period between chemotherapy and immunotherapy on the efficacy of ICIs. **METHODS:** This study included 100 patients with advanced NSCLC treated with PD-1/PD-L1 inhibitors at Chungnam National University Hospital (CNUH) between May 2016 and August 2019. The rest period was defined from the last dose of cytotoxic chemotherapy to the first dose of ICIs. We retrospectively reviewed patients' clinical data and blood test records and analyzed lymphocyte subsets using flow cytometry. **RESULTS:** The median rest period was 64 days. The long rest period group (≥36 days) showed significantly higher clinical benefits than the short rest period group (<36 days) (69.4% vs. 39.5%, p = 0.003). White blood cell (WBC) count, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and neutrophil-lymphocyte ratio (NLR) just

before chemotherapy were not different between the two groups. However, the blood test after chemotherapy immediately before immunotherapy showed significantly higher ANC and NLR in the short rest period group than in the long rest period group. The frequency of the Th1 subset and PD-1 + CD8+ T cells were significantly higher in the long rest period group than in the short rest period group. **CONCLUSION:** Time interval from chemotherapy to immunotherapy may affect immune cell status and efficacy of ICIs.

[Therapy for Stage IV Non-Small-Cell Lung Cancer With Driver Alterations: ASCO Living Guideline](#) J Clin Oncol. 2022 Jul 11;JCO2200824. doi: 10.1200/JCO.22.00824. Online ahead of print. Navneet Singh 1 , Sarah Temin 2 , Sherman Baker Jr 3 , et al.
PURPOSE: To provide evidence-based recommendations updating the 2021 ASCO and Ontario Health (Cancer Care Ontario) guideline on systemic therapy for patients with stage IV non-small-cell lung cancer (NSCLC) with driver alterations. **METHODS:** ASCO updated recommendations on the basis of an ongoing systematic review of randomized control trials from 2020 to 2021. **RESULTS:** This guideline update reflects changes in evidence since the previous update. Two studies provide the evidence base. Outcomes of interest include efficacy and safety. **RECOMMENDATIONS:** For patients with an anaplastic lymphoma kinase rearrangement, a performance status (PS) of 0-2, and previously untreated NSCLC, clinicians should offer alectinib or brigatinib or lorlatinib. For patients with an anaplastic lymphoma kinase rearrangement, a PS of 0-2, and previously untreated NSCLC, if alectinib, brigatinib, or lorlatinib are not available, clinicians should offer ceritinib or crizotinib. For patients with a RET rearrangement, a PS of 0-2, and previously untreated NSCLC, clinicians may offer selpercatinib or pralsetinib. In second line, for patients with a RET rearrangement who have not received RET-targeted therapy, clinicians may offer selpercatinib or pralsetinib.Additional information is available at www.asco.org/thoracic-cancer-guidelines.

[Efficacy and safety of camrelizumab plus apatinib in previously treated patients with advanced non-small cell lung cancer harboring EGFR or ALK genetic aberration](#) Transl Lung Cancer Res. 2022 Jun;11(6):964-974. doi: 10.21037/tlcr-22-22. Guanghui Gao # 1 , Jian Ni # 1 , Yina Wang 2 , et al.
BACKGROUND: Camrelizumab plus apatinib shows encouraging antitumor activity and acceptable toxicity in chemotherapy-pretreated patients with advanced non-small cell lung cancer (NSCLC); however, clinical benefits from this combination regimen in NSCLC patients with EGFR mutations or ALK rearrangements (EGFR+/ALK+) have not been reported. We assessed the efficacy and safety of this combined regimen in pretreated patients with advanced NSCLC and defined EGFR/ALK status (EGFR+/ALK+) in a phase 1b/2 trial. **METHODS:** Previously treated patients with advanced EGFR+/ALK+ NSCLC were enrolled and given camrelizumab 200 mg intravenously every 2 weeks plus apatinib at the recommended dose of 250 mg orally once daily. Patients harboring sensitive EGFR mutations or ALK fusion genes had received at least one EGFR/ALK TKI and a platinum-based chemotherapy regimen before the enrollment. The primary endpoint was objective response rate (ORR). **RESULTS:** All 43 enrolled patients comprised the efficacy and safety analysis population. The confirmed ORR was 18.6% (95% CI: 8.4-33.4%) and the clinical benefit response rate was 27.9% (95% CI: 15.3-43.7%). Median progression-free survival (PFS) was 2.8 months (95% CI: 1.9-5.5 months) and median overall survival was not reached (95% CI: 7.3 months-not reached), with a median follow-up period of 15.7 months (range, 0.5-24.4 months). The most common grade ≥3 treatment-related adverse events (TRAEs) were hypertension (16.3%), proteinuria (11.6%) and palmar-plantar erythrodysaesthesia syndrome (9.3%). No unexpected adverse events were recorded. **CONCLUSIONS:** Camrelizumab plus apatinib showed moderate antitumor activity and acceptable safety profile in previously treated patients with advanced NSCLC and EGFR or ALK genetic aberrations, which warranted further validation.

[**Non-small cell lung cancer in the era of immunotherapy**](#) Semin Oncol. 2022 Jul 8;S0093-7754(22)00049-5. doi: 10.1053/j.seminoncol.2022.06.009. Online ahead of print. Quillan Huang 1 , Jan Kemnade 1 , Loraine Cornwell 2 , Farrah Kheradmand 3 , Anita L Sabichi 4 , Devika Das 5 Immunotherapy for non-small cell lung cancer (NSCLC) has revolutionized treatment for those with advanced disease, and recent data have emerged providing evidence for its benefits in earlier stages of the disease. Several pivotal clinical trials provide compelling data that adaptive immune cells may be highly effective and possibly even curative for NSCLC. Immune checkpoint inhibitors (ICIs) can unleash highly reactive memory immune responses to tumor antigens with durable effects against advanced or recurrent disease. Despite these encouraging results, many critical questions remain in the field including, for example, how to identify the subsets of NSCLC patients who most benefit from ICI treatment, and how ICI efficacy might be enhanced by utilizing combinations or sequencing of agents. A deeper understanding of biological mechanisms involved in lung cancer offers a unique opportunity to further explore the interaction between the adaptive immune landscape and NSCLC. Given the high incidence of lung cancer in Veterans and many Veterans being treated with immunotherapy for this disease, it is timely to have their adequate representation in future clinical trials. New clinical trials focused on Veterans can assist in exploring ways to mitigate resistant mechanisms as well as to investigate predictive and prognostic biomarkers for response to ICIs and other treatments. This paper will review current data and indications for immunotherapy in NSCLC, introduce new areas of research within immunotherapy, and discuss its applicability to the Veteran population.

[**A Phase 2 Study of Lorlatinib in Patients With ROS1-Rearranged Lung Cancer With Brain-Only Progression on Crizotinib**](#) JTO Clin Res Rep. 2022 Jun 8;3(7):100347. doi: 10.1016/j.jtocrr.2022.100347. eCollection 2022 Jul. Jaime L Schneider 1   2 , Alona Muzikansky 1 , Jessica J Lin 1   2 , Elizabeth A Krueger 1 , Inga T Lennes 1   2 , Joseph O Jacobson 3 , Michael Cheng 3 , Rebecca S Heist 1   2 , Zofia Piotrowska 1   2 , Justin F Gainor 1   2 , Alice T Shaw 1   2 , Ibiay Dagogo-Jack 1   2
INTRODUCTION: The central nervous system (CNS) is a common site of progression among patients with ROS1-rearranged lung cancer receiving crizotinib. We conducted a phase 2 study to evaluate the intracranial efficacy of lorlatinib in patients with ROS1-rearranged lung cancer who developed CNS-only progression on crizotinib. **METHODS:** Patients with metastatic ROS1-rearranged lung cancer with CNS-only progression on crizotinib received lorlatinib 100 mg daily. The primary end point was intracranial disease control rate at 12 weeks per modified Response Evaluation Criteria in Solid Tumors version 1.1. Secondary end points included intracranial and extracranial progression-free survival, intracranial objective response rate, and safety/tolerability. **RESULTS:** A total of 16 patients were enrolled between November 2016 and January 2019. Nine patients (56%) had received prior CNS radiation, with a median of 10.9 months between radiation and lorlatinib. At 12 weeks, the intracranial disease control rate was 100% and intracranial objective response rate was 87%. While on study, the complee intracranial response rate was 60%. With median follow-up of 22 months, seven patients experienced disease progression, including five patients with CNS relapse. The median intracranial and extracranial progression-free survivals were 38.8 months (95% confidence interval: 16.9-not reported) and 41.1 months (95% confidence interval: 17.6-not reported), respectively. Molecular analysis of plasma or tissue from patients with extracranial progression on lorlatinib revealed ROS1 G2032R (n = 1), ROS1 L2086F (n = 1), and CCDC6-RET fusion plus ROS1 G2032R (n = 1). The safety profile of lorlatinib was consistent with prior studies. There were 11 patients (69%) who required dose reduction, including one patient who discontinued treatment for grade 3 edema. No grade greater than or equal to 4 adverse events were observed. **CONCLUSIONS:** Lorlatinib induced durable intracranial responses in patients with ROS1-rearranged NSCLC and prior isolated CNS progression on crizotinib.

[Patient and Treatment Factors Associated with Improved Local Control and Survival in Oligometastatic Bone Disease: Results from a Large Single-Institution Experience Using Stereotactic Body Radiation Therapy](#) Int J Radiat Oncol Biol Phys. 2022 Jul 12;S0360-3016(22)00713-1. doi: 10.1016/j.ijrobp.2022.06.096. Online ahead of print. Maria C Thomas 1 , Yu-Hui Chen 2 , Elliot Fite 3 , Andrew Pangilinan 3 , Katerina Bubelo 3 , Alexander Spektor 3 , Tracy A Balboni 3 , Mai Anh Huynh 4

PURPOSE: Limited data exists to guide optimal patient selection and treatment of bone metastases with curative intent despite the increasing application of stereotactic body radiation therapy (SBRT) for oligometastatic (OM) disease control and re-irradiation(ReRT). **METHODS:** Clinical characteristics for 434 patients consecutively treated with bone SBRT at a single institution from 3/2011-6/2020 were analyzed by OM, spine, and non-spine bone using Cox regression to determine association with local control (LC), progression-free survival (PFS), and overall survival (OS), and the Kaplan-Meier method to estimate PFS and OS. **RESULTS:** Most patients had prostate (39%) or breast/lung (21%) cancer and 1-3 lesions (96%), with 651 lesions (spine 63%) treated for ReRT (12%) or OMD (88%), including synchronous (10%), metachronous (28%), repeat (27%), or induced (23%) states as defined by ESTRO/EORTC criteria. Biologically effective dose (BED10) ≥50 (HR 0.68, CI 0.48-0.96, p<0.03) predicted improved LC among OM lesions and planning target volume (PTV)≥150 cc (HR 1.94, CI 1.02 to 3.70, p<0.04) predicted worse LC for non-spine bone. Prostate histology, performance status (PS) 0-1, and MFI ≥2 year predicted improved PFS and OS (p<0.05). Metachronous, synchronous, or repeat OM had higher PFS and OS (p≤0.001) than induced OM. With median follow-up 25.7 months, 1 and 2-year PFS was 63% and 47% for OM and 36% and 25% for ReRT;1 and 2-yr OS was 87% and 73% for OM, 58% and 43% for ReRT. Acute toxicities included grade 1-2 pain flare (9%) and fatigue (14%). Late toxicities included fracture (1%) for OM and myelopathy (2.5%) or nerve pain (1.2%) for ReRT. **CONCLUSIONS:** BED10 ≥ 50 for OM and PTV<150cc for non-spine bone lesions was associated with improved LC. Prostate histology, PS 0-1, MFI≥2 years, and metachronous, synchronous, or repeat presentations per EORTC/ESTRO OM criteria predicted improved PFS and OS among OM patients treated with bone SBRT.

[Real world use of radiation for newly diagnosed brain metastases in ALK-positive lung cancer receiving a first line ALK inhibitor](#) Int J Radiat Oncol Biol Phys. 2022 Jul 20;S0360-3016(22)00730-1. doi: 10.1016/j.ijrobp.2022.07.010. Online ahead of print. Sameera Kumar 1 , Xiaoliang Wang 2 , Harlan Pittell 2 , Gregory S Calip 3 , Stephanie E Weiss 1 , Joshua E Meyer 1 , Trevor J Royce 4

PURPOSE: Management paradigms now allow systemic targeted drugs before central nervous system (CNS)-directed radiotherapy (RT) in selected asymptomatic patients with non-small cell lung cancer (NSCLC) with brain metastases (BM). We aim to quantify how novel targeted agents with improved CNS activity, such as second-generation ALK inhibitors (e.g. alectinib), might impact the role of CNS-directed RT. **METHODS AND MATERIALS:** This retrospective, observational, real world patterns of care study used a nationwide electronic health record-derived de-identified longitudinal database. A random sample of patients with ALK+ advanced NSCLC and BM on first-line ALK-inhibitor monotherapy between January 1, 2014 and August 31, 2019 were included. Using an index date of the first instance of BM, the outcome was brain-directed local treatment within four months. Trends over time were reported and tested using multivariable modified Poisson regression with robust error variance, including an indicator of in or after 2017 (when alectinib was approved). **RESULTS:** Of 352 patients, 146 had BM. 104 received CNS-directed local therapy and 42 did not. The majority (89.4%) were treated with RT alone. Of those receiving RT, stereotactic radiosurgery (SRS) monotherapy was the most common (53%) followed by whole brain radiotherapy (WBRT) alone (39%). On multivariable analysis, those patients

who had their first BM in or after 2017 had a decreased rate of receiving local BM treatment versus those prior to 2017 with an adjusted incidence rate ratio (aIRR) 0.63 (95% confidence interval [CI]: 0.41-0.95; p=0.026). We found no change in the proportion of BM treated with WBRT in or after 2017 vs before (aIRR = 0.70; 95% CI: 0.24-2.06; p = 0.517). **CONCLUSIONS:** We found decreasing use of CNS-directed RT in patients with NSCLC with new BM on first-line ALK inhibitors. Clinical outcomes for these patients require continued investigation as physicians may be increasingly comfortable deferring upfront local therapy for BM in lieu of novel targeted agents with improved CNS activity.

[**Isolated Nodal Recurrence After Definitive Stereotactic Ablative Radiotherapy for Non-Small Cell Lung Cancer**](#) Pract Radiat Oncol. 2022 Jul 17;S1879-8500(22)00208-9. doi: 10.1016/j.prro.2022.06.013. Online ahead of print. Max Devine 1 , David J Merriott 2 , Hyunsoo J No 1 , et al.
PURPOSE/OBJECTIVES: Stereotactic ablative radiotherapy (SABR) results in high rates of primary tumor control for early-stage non-small cell lung cancer (NSCLC). For patients with isolated hilar or mediastinal nodal recurrences (INR) after SABR, the optimal salvage treatment strategy is unclear. The purpose of this study is to determine the rate of INR after SABR for early-stage NSCLC and to describe patterns of care and treatment outcomes after salvage therapy. **METHODS:** This retrospective cohort study included 342 patients with Stage T1-3N0M0 NSCLC treated with definitive SABR from 2003-2018. We evaluated the incidence of INR and baseline factors between patients who did and did not experience INR. Among patients who experienced INR, we described treatment patterns and outcomes including overall (OS) and progression free survival (PFS) from the time of nodal failure using the Kaplan-Meier method. **RESULTS:** With a median follow-up of 3.3 years, the 3-year INR rate was 10.6% (6.6% -13.4%). Among the 34 patients experiencing INR, the 3-year rates of OS and PFS were 39.3% (24.4 - 63.3%) and 26.7% (14.1 - 50.3%), respectively. The 34 patients with INR were treated with RT alone (26.7 %), concurrent chemoradiotherapy (CRT) (43.3 %), chemotherapy alone (13.3%), or observation (16.7%). CRT had the best survival outcomes with a 3-year OS and PFS of 81.5% (61.1 - 100.0%) and 63.9% (40.7 - 100.0%), respectively. Of the patients treated with salvage RT or CRT, 14.3% experienced grade 3 toxicity with no patients having grade 4+ toxicity. **CONCLUSION:** INR occurred in approximately 10% of patients treated with SABR for early-stage NSCLC. The highest rates of OS an PFS among patients with INR were observed in those treated with salvage chemoradiotherapy.

[**Stereotactic Body Radiation Therapy For Metastases In Long Bones**](#) Int J Radiat Oncol Biol Phys. 2022 Jul 15;S0360-3016(22)00723-4. doi: 10.1016/j.ijrobp.2022.07.003. Online ahead of print. Indira Madani 1 , Arjun Sahgal 2 , et al.
OBJECTIVE: To evaluate the cumulative incidence of fracture and local failure and associated risk factors after stereotactic body radiotherapy (SBRT) for long bone metastases. **MATERIAL AND METHODS:** Data from 111 patients with 114 metastases in the femur, humerus and tibia treated with SBRT in 7 international centers between October 2011 and February 2021 were retrospectively reviewed and analyzed using a competing risk regression model. **RESULTS:** The median follow-up was 21 months (range 6-91 months). All but one patient had a Karnofsky performance status ≥70. There were 84 femur (73.7%), 26 humerus (22.8%) and 4 tibia (3.5%) metastases from prostate (45 [39.5%]), breast (22 [19.3%]), lung (15 [13.2%]), kidney (13 [11.4%]) and other (19 [16.6%]) malignancies. Oligometastases accounted for 74.8% of metastases and 28.1% were osteolytic. The most common total doses were 30-50 Gy in 5 daily fractions (50.9%). Eight fractures (5 in the femur, 2 in the tibia and 1 in the humerus) were observed with a median time to fracture of 12 months (range 0.8-33 months). In 6/8 patients, fracture was not associated with local failure. The cumulative incidence of fracture was 3.5%, 6.1% and 9.8% at 1, 2 and 3 years, respectively. The cumulative incidence of local failure (9/110 metastases with imaging follow-up) was 5.7%, 7.2% and 13.5% at 1, 2 and 3 years, respectively. On multivariate analysis, extraosseous disease extension was significantly associated with fracture (P=0.001; subhazard ratio

[SHR] 10.8; 95% CI 2.8-41.9) and local failure (P=0.02; SHR 7.9; 95% CI 1.4-44.7). **CONCLUSION:** SBRT for metastases in long bones achieved high rates of durable local metastasis control without an increased risk of fracture. Similar to spine SBRT, patients with extraosseous disease extension are at higher risk of local failure and fracture.

[Sociodemographic and Clinical Factors Associated with Radiation Treatment Nonadherence and Survival among Rural and Nonrural Cancer Patients](#) Int J Radiat Oncol Biol Phys. 2022 Jun 28;S0360-3016(22)00638-1. doi: 10.1016/j.ijrobp.2022.06.075. Online ahead of print. Bonny B Morris 1 , Ryan Hughes 2 , Emma C Fields 3 , Roy T Sabo 4 , Kathryn E Weaver 5 , Bernard F Fuemmeler 6 **PURPOSE:** Cancer treatment nonadherence is associated with higher rates of cancer recurrence and decreased survival. Rural cancer patients experience a 10% higher mortality rate compared with their nonrural counterparts; geographic differences in nonadherence may contribute to this increased mortality. The goal of this study was to assess for geographic disparities and determine sociodemographic and clinical factors associated with radiation treatment (RT) nonadherence and survival among rural and nonrural cancer patients. **METHODS:** We examined cancer registry, medical records, and billing claims data at a safety net academic medical center. Geographic residence was defined as rural vs nonrural by USDA 2013 Rural-Urban Continuum Codes (RUCC). Other factors assessed were: age, sex, race, marital status, insurance type, employment, area median household income, residential distance to cancer treatment center, clinical stage, cancer type, treatment modality, total radiation dose received, and radiation dose per fraction. We used Cox proportional hazards modeling to examine 7 ways of operationalizing nonadherence and selected the definition that resulted in the best model fit statistics and prediction of mortality. Overall survival rates were estimated with the Kaplan-Meier method. We then examined nonadherence as the main exposure along with additional covariates in LASSO-penalized survival analyses and as the outcome in our multivariable generalized linear regression analyses predicting nonadherence. We considered two-way interaction terms with the main exposure, geographic residence. **RESULTS:** We identified 3077 cancer patients that averaged 62 years old, were 59% female, 34% Black, and 14% rural. 22% of patients missed at least two fractions and missed an average of 10% of their treatment plan. Rural patients experienced a higher mortality rate than nonrural patients (53% vs 42%, p<0.0001). Survival was assessed through December 31, 2021 with a mean follow-up of 4.5 years. Proportion of missed fractions as the indicator of nonadherence provided the best model fit statistics and prediction of survival. Marital status, employment status, TNM stage, cancer type, and age at diagnosis significantly impacted survival, in addition to a treatment delay by geographic residence interaction effect. Specifically, patients residing in rural areas who experienced a treatment delay were more than twice as likely to die as nonrural residents who also experienced a treatment delay, and nearly twice as likely to die as rural residents who did not experience a treatment delay. The two-year survival rate was 76% for nonrural residents who did not experience a treatment delay versus 27% for rural residents who experienced a treatment delay. Patients who were widowed, had Stage 4 cancer, or lung cancer were more likely to be nonadherent. Finally, patients residing in rural areas who experienced a treatment delay were more likely to subsequently be nonadherent. **CONCLUSIONS:** In a geographically and racially diverse population, RT nonadherence is a significant concern that affects survival, yet is a modifiable risk factor. We demonstrated that rural residence was associated with both RT nonadherence and poorer overall survival. Rural patients with a treatment delay had the lowest overall survival, compared to both nonrural survivors and rural survivors without delay. Rural residents who are delayed in starting treatment are at heightened risk for poor outcomes and should receive targeted support to mitigate the observed disparities. Additional patient populations that may benefit from targeted treatment adherence support include widowed patients and those with Stage 4 cancer or lung cancer.

[**Practical considerations of single-fraction stereotactic ablative radiotherapy to the lung**](#) Lung Cancer. 2022 Jun 30;170:185-193. doi: 10.1016/j.lungcan.2022.06.014. Online ahead of print. Therese Mj Kang 1 , Nicholas Hardcastle 2 , Anurag K Singh 3 , et al.

Stereotactic ablative radiotherapy (SABR) is a well-established treatment for patients with medically inoperable early-stage non-small cell lung cancer (NSCLC) and pulmonary oligometastases. The use of single-fraction SABR in this setting is supported by excellent local control and safety profiles which appear equivalent to multi-fraction SABR based on the available data. The resource efficiency and reduction in hospital outpatient visits associated with single-fraction SABR have been particularly advantageous during the COVID-19 pandemic. Despite the increased interest, single-fraction SABR in subgroups of patients remains controversial, including those with centrally located tumours, synchronous targets, proximity to dose-limiting organs at risk, and concomitant severe respiratory illness. This review provides an overview of the published randomised evidence evaluating single-fraction SABR in primary lung cancer and pulmonary oligometastases, the common clinical challenges faced, immunogenic effect of SABR, as well as technical and cost-utility considerations.

[**Rationale for Combing Stereotactic Body Radiation Therapy with Immune Checkpoint Inhibitors in Medically Inoperable Early-Stage Non-Small Cell Lung Cancer**](#) Cancers (Basel). 2022 Jun 27;14(13):3144. doi: 10.3390/cancers14133144. Alexander Chi 1   2 , Nam P Nguyen 3

Stereotactic body radiation therapy (SBRT) has been widely adopted as an alternative to lobar resection in medically inoperable patients with lymph-node negative (N0) early-stage (ES) non-small cell lung cancer (NSCLC). Excellent in-field local control has been consistently achieved with SBRT in ES NSCLC ≤ 3 cm in size. However, the out-of-field control following SBRT remains suboptimal. The rate of recurrence, especially distant recurrence remains high for larger tumors. Additional systemic therapy is warranted in N0 ES NSCLC that is larger in size. Radiation has been shown to have immunomodulatory effects on cancer, which is most prominent with higher fractional doses. Strong synergistic effects are observed when immune checkpoint inhibitors (ICIs) are combined with radiation doses in SBRT's dose range. Unlike chemotherapy, ICIs can potentiate a strong systemic response outside of the irradiated field when combined with SBRT. Together with their less toxic nature, ICIs represent a very suitable class of systemic agents to be combined with SBRT when treating ES NSCLC with high-risk features, such as larger tumor size. In this review, we describe the rationale and emerging evidence, as well as ongoing investigations in this area.

SMALL CELL LUNG CANCER - SCLC

[**Efficacy and Safety of Programmed Death-Ligand 1 Inhibitor Plus Platinum-Etoposide Chemotherapy in Patients With Extensive-Stage SCLC: A Prospective Observational Study**](#) JTO Clin Res Rep. 2022 Jun 8;3(7):100353. doi: 10.1016/j.jtocrr.2022.100353. eCollection 2022 Jul. Kenji Morimoto 1 , Tadaaki Yamada 1 , Takayuki Takeda 2 , et al.

INTRODUCTION: To date, the efficacy and safety of programmed death-ligand 1 (PD-L1) inhibitor plus platinum-etoposide chemotherapy for patients with extensive-stage SCLC (ES-SCLC), with real-world evidence, stratified on the basis of age and performance status (PS), have not been fully investigated. The aim of this study was to evaluate the efficacy and safety of PD-L1 inhibitor plus platinum-etoposide chemotherapy in patients with ES-SCLC. **METHODS:** This multicenter prospective study evaluated patients with ES-SCLC who received PD-L1 inhibitor plus platinum-etoposide chemotherapy between September 2019 and October 2021. **RESULTS:** A total of 45 patients with ES-SCLC received the aforementioned treatment, including 18 elderly (≥75 y old) patients and six patients with a PS of 2. Multivariate analysis indicated that a PS of 2 was a significant independent prognostic factor for progression-free survival and overall survival (p = 0.008 and p = 0.001, respectively). Of

patients with PS of 2 at the initial phase, those that achieved PS improvement during treatment had significantly longer progression-free survival and overall survival than those who did not (p = 0.02 and p = 0.02, respectively). The incidence of adverse events accompanied with treatment discontinuation was significantly higher in the elderly patients than in the non-elderly patients (p = 0.03). **CONCLUSIONS:** This real-world prospective study found that PD-L1 inhibitor plus platinum-etoposide chemotherapy had limited efficacy in patients with ES-SCLC with a PS of 2, except for cases with improvement of PS during treatment. Owing to the emergence of adverse events and treatment discontinuation, this treatment should be administered with caution in elderly patients with ES-SCLC.

[Impact of Socioeconomic Factors on Overall Survival in SCLC](#) TO Clin Res Rep. 2022 Jun 18;3(7):100360. doi: 10.1016/j.jtocrr.2022.100360. eCollection 2022 Jul. Logan Roof 1 , Wei Wei 1 , Katherine Tullio 1 , Nathan A Pennell 1 , James P Stevenson 1

OBJECTIVES: To determine how the incidence and demographics of SCLC have changed over time and to evaluate whether patient demographics, disease presentation, and treatment characteristics affect patient outcomes. **METHODS:** We identified patients with SCLC in the National Cancer Database from 2004 to 2016. Differences in demographics, disease, and treatment characteristics were assessed by year of diagnosis using chi-square test. The effect of age, race, insurance status, income, distance to treatment center, and education level on overall survival (OS) was evaluated by multivariable Cox proportional hazard model. **RESULTS:** Patients diagnosed after 2010 were significantly older, more frequently treated at academic centers, had more comorbidities, had government payer insurance, had more stage IV disease, and lived further from treatment centers. More females, African Americans, patients without high school diplomas, and those from rural areas were diagnosed after 2010. In patients diagnosed between 2004 and 2010, 5-year OS was 6.8% (95% confidence interval: 6.6-6.9), and after 2010, 5-year OS was 8.7% (95% confidence interval: 8.5-8.9), despite an increase in stage IV disease in the latter group. Older patients, males, Caucasians, patients with stage IV disease, those with government primary payer insurance, and those from rural areas had significantly worse OS. Patients without comorbidities and treated at academic centers had significantly better OS. OS significantly increased with community income and education level. **CONCLUSIONS:** Despite improvement in OS, disparities were noted in demographics which may complicate patient and provider access to health care resources, including rural communities, distance to academic centers, income, insurer, and education level. Efforts to affect these variables will improve outcomes for patients with SCLC.

[Lurbinectedin shows clinical activity and immune-modulatory functions in patients with pre-treated small cell lung cancer and malignant pleural mesothelioma](#) Eur J Cancer. 2022 Jul 11;172:357-366. doi: 10.1016/j.ejca.2022.06.020. Online ahead of print. Daphne W Dumoulin 1 , Luca Cantini 2 , Robin Cornelissen 1 , et al.

PURPOSE: Lurbinectedin is a promising new drug being investigated in pre-treated patients with small cell lung cancer (SCLC) or malignant pleural mesothelioma (MPM). Its clinical activity in the real-world setting has not been investigated yet. Patients and **METHODS:** Clinical data of patients with SCLC and MPM who were treated with lurbinectedin were prospectively collected. Comprehensive immune cell profiling by flow cytometry was performed on screening and treating peripheral blood samples. **RESULTS:** A total of 95 patients (43 SCLC and 52 MPM) were treated, mostly as ≥3-line of therapy. In the SCLC cohort, a median progression-free survival (mPFS) was 1.5 months (95% CI: 1.4-3.0), and median overall survival was 7.0 months (95% CI: 4.7-not reached). Objective radiological response and disease control rate after 12 weeks were 16% and 28%, respectively. In the MPM cohort, median progression-free survival was 2.8 months (95% CI: 1.4-4.2), and median overall survival was 7.2 months (95% CI: 5.9-not reached). Disease control rate after 12 weeks was 29%, whereas no partial responses were registered. No new safety signals were observed. Lurbinectedin treatment was significantly

associated with the depletion of circulating classical monocytes, which correlated with a better PFS in patients with SCLC. Lurbinectedin increased the proliferation of CD4+ and CD8+ T cells (SCLC) and natural killer and natural killer T cells (SCLC and MPM) and altered co-stimulatory and co-inhibitory receptor expression on circulating lymphocytes. **CONCLUSION:** Lurbinectedin has a manageable safety profile and shows clinical activity in pre-treated patients with SCLC and MPM. Its immune-modulatory functions make lurbinectedin a potential platform for immunotherapy combinations.

[Improving the efficacy of immunotherapy in small cell lung cancer: Leveraging recent scientific discoveries and tumor-specific antigens](#) Semin Oncol. 2022 Jul 2;S0093-7754(22)00043-4. doi: 10.1053/j.seminoncol.2022.06.003. Online ahead of print. Joseph B Hiatt 1 , Perrin E Romine 2 , Daniel Y Wu 3

Small cell lung cancer (SCLC) is an aggressive neuroendocrine neoplasm with poor survival outcomes and little change to treatment standards over decades. SCLC is associated with heavy tobacco exposure and a high rate of somatic mutations in tumor cells, leading to hope that immune checkpoint inhibitors would dramatically reshape the treatment landscape of SCLC. Instead, immune checkpoint inhibitors have led to real but modest gains in outcomes, with only a small minority of patients deriving more durable benefit. Furthermore, biomarkers of ICI efficacy that have succeeded in other tumor types have not been validated in SCLC. However, recent research advances have suggested that epigenetic heterogeneity and plasticity play especially key roles in SCLC biology. Leveraging this emerging perspective, a new slate of candidate biomarkers of immune checkpoint inhibitor benefit have been described, and the novel treatment strategies combining rational epigenetic perturbation with immune checkpoint inhibitors are being developed. Finally, other immunotherapy strategies targeting SCLC-specific mechanisms are being tested. Together, these developments may lead to a second generation of much more efficacious immunotherapies in SCLC.

[Pharmacokinetic Drug-Drug Interaction Studies Between Trilaciclib and Midazolam, Metformin, Rifampin, Itraconazole, and Topotecan in Healthy Volunteers and Patients with Extensive-Stage Small-Cell Lung Cancer](#) Clin Drug Investig. 2022 Jul 16. doi: 10.1007/s40261-022-01179-x. Online ahead of print. Chao Li 1   2 , Janet K Horton 1 , Mark Sale 3 , Laura Curd 3 , Vineet Goti 3   4 , Wenli Tao 1   5 , Andrew Beelen 6

BACKGROUND AND OBJECTIVE: Trilaciclib is a cyclin-dependent kinase 4/6 inhibitor indicated to decrease the incidence of chemotherapy-induced myelosuppression in patients with extensive-stage small-cell lung cancer. Trilaciclib is a substrate and time-dependent inhibitor of cytochrome P450 3A4 and an inhibitor of multidrug and toxin extrusion 1, multidrug and toxin extrusion 2-K, organic cation transporter 1, and organic cation transporter 2. Here, we investigate the pharmacokinetic drug-drug interaction potential of trilaciclib. **METHODS:** Two phase I studies were conducted as prospective, open-label, fixed-sequence drug-drug interaction studies in healthy subjects (n = 57, n = 20) to investigate potential interactions between intravenously administered trilaciclib (200 or 240 mg/m2) and orally administered midazolam (5 mg), metformin (1000 mg), itraconazole (200 mg), and rifampin (600 mg). A population pharmacokinetic model was fit to phase Ib/IIa data in patients with extensive-stage small-cell lung cancer (n = 114) to assess the impact of trilaciclib dose and exposure (area under the plasma concentration-time curve) on topotecan clearance. **RESULTS:** Coadministration with trilaciclib had minimal effects on the exposure (area under the plasma concentration-time curve from time 0 to infinity) of midazolam (geometric least-square mean ratio [GMR] vs midazolam alone 1.065; 90% confidence interval [CI] 0.984-1.154) but statistically significantly increased plasma exposure (GMR 1.654; 90% CI 1.472-1.858) and decreased renal clearance (GMR 0.633; 90% CI 0.572-0.701) of metformin. Coadministration of trilaciclib with rifampin or itraconazole decreased trilaciclib area under the plasma concentration-time curve from time 0 to infinity by 17.3% (GMR 0.827; 90% CI 0.785-0.871) and 14.0% (GMR 0.860;

0.820-0.902), respectively, vs trilaciclib alone. Population pharmacokinetic modeling showed no significant effect of trilaciclib on topotecan clearance. **CONCLUSIONS:** Overall, the drug-drug interaction and safety profiles of trilaciclib in these studies support its continued use in patients with extensive-stage small-cell lung cancer.

PALLIATIVE AND SUPPORTIVE CARE

"The whole of humanity has lungs, doesn't it? We are not all the same sort of people": patient preferences and choices for an online, self-guided chronic breathlessness supportive intervention: SELF-BREATHE ERJ Open Res. 2022 Jul 11;8(3):00093-2022. doi: 10.1183/23120541.00093-2022. eCollection 2022 Jul. Charles C Reilly 1   2 , Katherine Bristowe 2 , Anna Roach 2 , Trudie Chalder 3 , Matthew Maddocks 2 , Irene J Higginson 2

INTRODUCTION: The burden of chronic breathlessness on individuals, family, society and health systems is significant and set to increase exponentially with an ageing population with complex multimorbidity, yet there is a lack of services. This has been further amplified by the coronavirus disease 2019 pandemic. Online breathlessness interventions have been proposed to fill this gap, but need development and evaluation based on patient preferences and choices. This study aimed to explore the preferences and choices of patients regarding the content of an online self-guided chronic breathlessness supportive intervention (SELF-BREATHE). **METHODS:** Semi-structured telephone interviews were conducted with adults living with advanced malignant and nonmalignant disease and chronic breathlessness (July to November 2020). Interviews were analysed using conventional and summative content analysis. **RESULTS:** 25 patients with advanced disease and chronic breathlessness (COPD n=13, lung cancer n=8, interstitial lung disease n=3, bronchiectasis n=1; 17 male; median (range) age 70 (47-86) years; median (range) Medical Research Council dyspnoea score 3 (2-5)) were interviewed. Individuals highlighted strong preferences for focused education, methods to increase self-motivation and engagement, interventions targeting breathing and physical function, software capability to personalise the content of SELF-BREATHE to make it more meaningful to the user, and aesthetically designed content using various communication methods including written, video and audio content. Furthermore, they identified the need to address motivation as a key potential determinant of the success of SELF-BREATHE. **CONCLUSION:** Our findings provide an essential foundation for future digital intervention development (SELF-BREATHE) and scaled research.

The Impact of Mindfulness-Based Stress Reduction (MBSR) on Psychological Outcomes and Quality of Life in Patients With Lung Cancer: A Meta-Analysis Front Psychol. 2022 Jun 28;13:901247. doi: 10.3389/fpsyg.2022.901247. eCollection 2022. Xu Tian 1 , Li-Juan Yi 2 , Chen-Si-Sheng Liang 3 , Lei Gu 4 , Chang Peng 5 , Gui-Hua Chen 6 , Maria F Jiménez-Herrera 1

OBJECTIVE: The impact of the mindfulness-based stress reduction (MBSR) program on psychological outcomes and quality of life (QoL) in lung cancer patients remains unclear. This meta-analysis aimed to evaluate the effectiveness of the MBSR program on psychological states and QoL in lung cancer patients. **METHODS:** Eligible studies published before November 2021 were systematically searched from PubMed, EMBASE, Cochrane Library, PsycINFO, China National Knowledge Infrastructure (CNKI), and Wanfang databases. The risk of bias in eligible studies was assessed using the Cochrane tool. Psychological variables and QoL were evaluated as outcomes. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to grade the levels of evidence. Statistical analysis was conducted using RevMan 5.4 and STATA 14.0. **RESULTS:** A total of 17 studies involving 1,680 patients were included for meta-analysis eventually. MBSR program significantly relieved cancer-related fatigue (standard mean difference [SMD], -1.26; 95% confidence interval [CI], -1.69 to -0.82; moderate evidence) and negative psychological states (SMD, -1.35; 95% CI, -1.69 to -1.02; low

evidence), enhanced positive psychological states (SMD, 0.91; 95% CI, 0.56-1.27; moderate evidence), and improved quality of sleep (MD, -2.79; 95% CI, -3.03 to -2.56; high evidence). Evidence on MBSR programs' overall treatment effect for QoL revealed a trend toward statistical significance (p = 0.06, low evidence). **CONCLUSION:** Based on our findings, the MBSR program shows positive effects on psychological states in lung cancer patients. This approach should be recommended as a part of the rehabilitation program for lung cancer patients.

[**Immune checkpoint inhibitor-related pneumonitis: Acute lung injury with rapid progression and organizing pneumonia with less severe clinical disease**](#) Histopathology. 2022 Jul 1. doi: 10.1111/his.14704. Online ahead of print. Saira Imran # 1 , Andrew Golden # 2 , Marc Feinstein 1 , Andrew Plodkowski 3 , Francis Bodd 2 , Natasha Rekhtman 2 , William D Travis 2 , Diane E Stover 1 , Jennifer L Sauter 2

AIMS: To improve understanding of the pathology of immune checkpoint inhibitor (ICI)-related pneumonitis, clinical, radiographic and histopathologic features and outcomes were investigated in a cohort of patients treated exclusively with ICI who underwent lung biopsy, and in whom and all other potential causes of lung injury were excluded. **METHODS:** Patients were retrospectively identified via searches of institutional pathology and clinical records. Patients treated with other modalities for cancer and patients with lung infections or other etiologies that could cause pneumonitis were excluded. Clinical records were reviewed by pulmonologists. Imaging studies at presentation and follow up were reviewed by a thoracic radiologist. Pathology was reviewed by thoracic pathologists. **RESULTS:** Six patients with ICI-related pneumonitis were identified. Two patients presented with respiratory failure requiring mechanical ventilation, diffuse ground glass opacities (GGOs) on chest computed tomography (CT) and acute lung injury (ALI) pattern on transbronchial lung biopsies and had fatal outcomes despite treatment. The remaining four patients presented with less severe symptoms, predominantly consolidations and patchy ground glass and part solid opacities on chest CT, organizing pneumonia (OP) and/or cellular interstitial pneumonitis (CIP) histologically, and showed favorable responses to treatment and remission within months. **CONCLUSIONS:** This study highlights two radiologic-pathologic patterns of ICI-related pneumonitis with different behavior: (1) Severe respiratory symptoms and diffuse GGOs on imaging correlating closely with ALI pattern histologically and poor prognosis; (2) and absent/mild respiratory symptoms and consolidations or patchy subsolid opacities on imaging correlating with OP and/or CIP histologically and good outcomes.

[**Clinical and economic value of oral nutrition supplements in patients with cancer: a position paper from the Survivorship Care and Nutritional Support Working Group of Alliance Against Cancer Support Care Cancer. 2022 Jul 6. doi: 10.1007/s00520-022-07269-y. Online ahead of print.**](#) Riccardo Caccialanza 1 , Alessandro Laviano 2 , Cristina Bosetti 3 , Mariateresa Nardi 4 ,Valentina Casalone 5 , Lucilla Titta 6 , Roberto Mele 7 , Giovanni De Pergola 8 , Francesco De Lorenzo 9 , Paolo Pedrazzoli 10 , Alliance Against Cancer (ACC) Survivorship Care, Nutritional Support Working Group Malnutrition is a common clinical and public health problem that can frequently affect patients in hospital and community settings. In particular, cancer-related malnutrition results from a combination of metabolic dysregulation and anorexia, caused both by the tumor itself and by its treatment. Patients with head-neck cancer, or with gastroesophageal, pancreatic, lung, and colorectal cancer, are particularly at risk of developing malnutrition, with a prevalence varying between 30 and 50% depending on tumor location and anti-cancer treatment complications. Prevention and adequate management of malnutrition is now considered an essential key point of therapeutic pathways of patients with cancer, with the aim to enhance their quality of life, reduce complications, and improve clinical outcomes. Oral nutritional supplements (ONS) are part of the nutritional therapy and represent an effective tool to address cancer-related malnutrition, as supported by growing literature data. However, patients' access to ONS - which is

regulated by different national and regional policies in terms of reimbursement - is quite heterogeneous. This narrative review aims to summarize the current knowledge about the role of ONS in terms of cost-effectiveness in the management of actively treated patients with cancer, following surgery and/or radiotherapy/chemotherapy treatment and to present the position on this issue of the Alliance Against Cancer, the Italian National Oncology Network, coming up from a focused virtual roundtable of the Survivorship Care and Nutritional Support Working Group.

COMPLEMENTARY & ALTERNATIVE THERAPY

Clinical efficacy and safety of NSCLC ancillary treatment with compound Kushen injection through immunocompetence regulation: A systematic review and meta-analysis

Phytomedicine. 2022 Jul 6;104:154315. doi: 10.1016/j.phymed.2022.154315. Online ahead of print. Dan Wang 1, Yong Xu 2 , Tongxing Huang 1 , Wenpan Peng 3 , Dongwei Zhu 1 , Xianmei Zhou 4 , Qi Wu 5
BACKGROUND: Compound Kushen injection (CKI) is a Chinese patented medicine that improves the immunity level of cancer patients and inhibits tumor cell proliferation and metastasis. Clinically, CKI is widely used in combination with platinum-based chemotherapy (PBC) for non-small cell lung cancer (NSCLC) treatment. This study attempted to systemically evaluate the efficacy and safety of a combination of CKI and PBC for NSCLC treatment by modulating the immune function. Purpose: To evaluate the clinical efficacy and safety of CKI in combination with PBC for NSCLC. Materials and **METHODS:** English and Chinese databases were retrieved for randomized controlled trials (RCTs) of NSCLC treatment using a combination of CKI and PBC, and the changes of peripheral blood T lymphocytes (such as CD3+ T cells, CD4+ T cells, CD8+ T cells), and CD4+/CD8+ T cell ratio among NSCLC patients were detected before and after treatment using CKI with PBC. The search deadline was set as November 2021. The systemic evaluation was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The methodology and quality of each study included in the systemic evaluation were assessed. Review Manager 5.4, Stata12.0, and trial sequential analysis (TSA) were used for data analysis. The outcome indicators were qualified using GRADEprofiler software. **RESULTS:** A total of 25 RCTs involving 2460 cases of patients were included. The results showed that the combination of CKI with PBC effectively increased the objective response rate (ORR) [relative risk (RR) = 1.31, 95% confidence interval (CI) (1.19, 1.44)] and disease control rate (DCR) [RR = 1.16, 95%CI (1.09,1.23)], regulated the expression of peripheral blood T lymphocytes (such as CD3+T cells, CD4+T cells, CD8+T cells, and CD4+/CD8+T cell ratio), upregulated the level of serum immune-globulins (such as IgA, IgG, and IgM), and reduced the frequency of gastrointestinal reaction, marrow inhibition, hepatorenal toxicity, reduction of white blood cells and blood platelets, baldness, infection, neutrophilic granulocyte counts, diarrhea, or constipation. According to subgroup analysis results, chemotherapy cycles (1-2) had a more significant effect on DCR. A combination of CKI and GP regimens had better effects on improving CD3+T cell levels, and there were no significant changes among other chemotherapies regiments. **CONCLUSION:** A combination of CKI and PBC had a marked effect in improving tumor response, priming immune function, and decreasing the frequency of adverse reactions, which was safe for NSCLC treatment.

Effects and mechanisms of resveratrol for prevention and management of cancers: An updated review

Crit Rev Food Sci Nutr. 2022 Jul 19;1-19. doi: 10.1080/10408398.2022.2101428. Online ahead of print. Si-Xia Wu 1 , Ruo-Gu Xiong 1 , Si-Yu Huang 1 , Dan-Dan Zhou 1 , Adila Saimaiti 1 , Cai-Ning Zhao 2 , Ao Shang 3 , Yun-Jian Zhang 4 , Ren-You Gan 5 , Hua-Bin Li 1
Cancer is a severe public health problem. Resveratrol is a famous natural compound that has various bioactivities, such as antioxidant, anti-inflammatory, antidiabetic and antiaging activities. Especially, resveratrol could prevent and treat various cancers, such as oral, thyroid, breast, lung, liver, pancreatic,

gastric, colorectal, bladder, prostate and ovarian cancers. The underlying mechanisms have been widely studied, such as inhibiting cell proliferation, suppressing metastasis, inducing apoptosis, stimulating autophagy, modulating immune system, attenuating inflammation, regulating gut microbiota and enhancing effects of other anticancer drugs. In this review, we summarize effects and mechanisms of resveratrol on different cancers. This paper is helpful to develop resveratrol, crude extract containing resveratrol, or foods containing resveratrol into functional food, dietary supplements or auxiliary agents for prevention and management of cancers.

MISCELLANEOUS WORKS

[The effect of smoking on survival in lung carcinoma patients with brain metastasis: a systematic review and meta-analysis](#) Neurosurg Rev. 2022 Jul 14. doi: 10.1007/s10143-022-01832-1. Online ahead of print. Shreya Chawla 1   2 , Ishaan A Tewarie 3   4   5 , Qingwei O Zhang 6 , Alexander F C Hulsbergen 2   7   8 , Rania A Mekary 2   9 , Marike L D Broekman 7   8   10

The effects of smoking on survival in BM patients have yet to be reviewed and meta-analysed. However, previous studies have shown that smokers had a greater risk of dying from lung cancer compared to non-smokers. This meta-analysis, therefore, aimed to analyse the effects of cigarette smoking on overall survival (OS) and progression-free survival (PFS) in lung cancer BM patients. PubMed, Embase, Web of Science, Cochrane and Google Scholar were searched for comparative studies regarding the effects of smoking on incidence and survival in brain metastases patients up to December 2020. Three independent reviewers extracted overall survival (OS) and progression-free survival data (PFS). Random-effects models were used to pool multivariate-adjusted hazard ratios (HR). Out of 1890 studies, fifteen studies with a total of 2915 patients met our inclusion criteria. Amongst lung carcinoma BM patients, those who were smokers (ever or yes) had a worse overall survival (HR: 1.34, 95% CI 1.13, 1.60, I2: 72.1%, p-heterogeneity < 0.001) than those who were non-smokers (never or no). A subgroup analysis showed the association to remain significant in the ever/never subgroup (HR: 1.34, 95% CI 1.11, 1.63) but not in the yes/no smoking subgroup (HR: 1.30, 95% CI 0.44, 3.88). This difference between the two subgroups was not statistically significant (p = 0.91). Amongst lung carcinoma BM patients, smoking was associated with a worse OS and PFS. Future studies examining BMs should report survival data stratified by uniform smoking status definitions.

[Consensus Recommendations to Optimize Testing for New Targetable Alterations in Non-Small Cell Lung Cancer](#) Curr Oncol. 2022 Jul 15;29(7):4981-4997. doi: 10.3390/curroncol29070396. Diana N Ionescu 1 , Tracy L Stockley 2   3 , et al.

Non-small cell lung cancer (NSCLC) has historically been associated with a poor prognosis and low 5-year survival, but the use of targeted therapies in NSCLC has improved patient outcomes over the past 10 years. The pace of development of new targeted therapies is accelerating, with the associated need for molecular testing of new targetable alterations. As the complexity of biomarker testing in NSCLC increases, there is a need for guidance on how to manage the fluid standard-of-care in NSCLC, identify pragmatic molecular testing requirements, and optimize result reporting. An expert multidisciplinary working group with representation from medical oncology, pathology, and clinical genetics convened via virtual meetings to create consensus recommendations for testing of new targetable alterations in NSCLC. The importance of accurate and timely testing of all targetable alterations to optimize disease management using targeted therapies was emphasized by the working group. Therefore, the panel of experts recommends that all targetable alterations be tested reflexively at NSCLC diagnosis as part of a comprehensive panel, using methods that can detect all relevant targetable alterations. In addition, comprehensive biomarker testing should be performed at the request of the treating clinician upon development of resistance to targeted therapy. The expert multidisciplinary working group also made

recommendations for reporting to improve clarity and ease of interpretation of results by treating clinicians and to accommodate the rapid evolution in clinical actionability of these alterations. Molecular testing of all targetable alterations in NSCLC is the key for treatment decision-making and access to new therapies. These consensus recommendations are intended as a guide to further optimize molecular testing of new targetable alterations.

[Cost-Effectiveness of 12 First-Line Treatments for Patients With Advanced EGFR Mutated NSCLC in the United Kingdom and China](#)
Front Oncol. 2022 Jun 6;12:819674. doi: 10.3389/fonc.2022.819674. eCollection 2022. Haijing Guan 1 2 , Chunping Wang 3 , Chen Chen 2 4 , Sheng Han 3 , Zhigang Zhao 1

BACKGROUND: Lung cancer is imposing significant pressure on the national health insurance system worldwide, especially under the COVID-19 pandemic. However, the cost-effectiveness of all available first-line treatments for patients with advanced epidermal growth factor receptor (EGFR) mutated non-small cell lung cancer (NSCLC) is still uncertain. The aim of this study was to evaluate the cost-effectiveness of 12 first-line treatments for patients with advanced EGFR mutated NSCLC from the perspective of the United Kingdom (UK) National Health Service and Chinese health care system. **METHODS:** We used a Markov model to estimate the cost-effectiveness of 12 treatments, including 6 EGFR tyrosine kinase inhibitors, 4 combination treatments and 2 chemotherapies. The key clinical efficacy and safety data were from a network meta-analysis. The cost and health preference were mainly collected from the literature. The most cost-effective treatment was inferred through a sequential analysis. Uncertainty was tested with one-way sensitivity analyses, scenario analyses, and probabilistic sensitivity analyses. Quality-adjusted life years (QALYs), direct medical costs, and incremental cost-effectiveness ratio (ICER) were estimated, at willingness-to-pay thresholds of £20000 to £50000 and £8000 to £24000 per QALY in the UK and China respectively. **RESULTS:** For clinical effectiveness, osimertinib and gefitinib plus pemetrexed based chemotherapy (PbCT) yielded the highest QALYs, while two chemotherapy treatments gained the lowest QALYs. For costs, gefitinib treatment was the cheapest option in both countries (£24529 in the UK and £12961 in China). For cost-effectiveness, 4 treatments including gefitinib, gefitinib plus pemetrexed, gefitinib plus PbCT, and osimertinib formed the cost-effectiveness frontier in both countries. Gefitinib alone (70.7% and 80.0% under the threshold of £20000 and £8000 per QALY in the UK and China, respectively) and gefitinib plus PbCT (62.3% and 71.2% under the threshold of £50000 and £24000 per QALY in the UK and China, respectively) were most likely to be cost-effective compared with other first-line treatments. **CONCLUSIONS:** Gefitinib and gefitinib plus PbCT were likely to be cost-effective for patients with advanced EGFR mutated NSCLC in both countries.

[Tribal Tobacco Use Project II: Planning, Implementation, and Dissemination Using Culturally Relevant Data Collection among American Indian Communities](#)
Int J Environ Res Public Health. 2022 Jun 23;19(13):7708. doi: 10.3390/ijerph19137708. Kendra M Roland 1 , Madison D Anderson 1 2 , Dana M Carroll 3 , Anna G Webber 1 , Kristine L Rhodes 4 , John Poupart 5 , Jean L Forster 2 , Melanie Peterson-Hickey 6 , Wyatt J Pickner 1

American Indians have substantially higher commercial tobacco-related cancer rates when compared to the general population. To effectively combat commercial tobacco-related cancer, it is important that tribal nations obtain current and accurate community-specific data on commercial tobacco use and exposure-related attitudes and behaviors. With the goal to collect, synthesize, and disseminate data on tobacco use, including the role traditional tobacco plays among American Indian people, the American Indian Cancer Foundation (AICAF) and various stakeholders developed and implemented the Tribal Tobacco Use Project II (TTUP II) during 2018-2021. Building upon its predecessor, the Tribal Tobacco Use Project I (TTUP I), TTUP II used principles of community-based participatory research and culturally appropriate methods, such as Reality-Based Research, in partnership with tribal nations. We

describe the TTUP II rationale, methods for participant recruitment and data collection, emphasizing the importance of using culturally relevant survey items to disentangle commercial tobacco use from traditional tobacco use. American Indian traditional tobacco is viewed as medicine in these communities with a unique socio-cultural context that must be addressed when engaging in commercial tobacco control efforts in American Indian communities. This approach may be useful to other tribal nations who are interested in conducting culturally relevant tobacco surveillance efforts.

[Impacts of Medicaid Expansion on Stage at Cancer Diagnosis by Patient Insurance Type](#) Am J Prev Med. 2022 Jul 20;S0749-3797(22)00325-7. doi: 10.1016/j.amepre.2022.06.001. Online ahead of print.

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INTRODUCTION: The expansion of Medicaid under the Affordable Care Act increased access to health care for millions of low-income Americans. However, the longer-term impacts of the policy on cancer outcomes remain unknown. This study examined the impact of Medicaid expansion on early- and late-stage diagnosis for 4 common cancers (breast, cervical, colorectal, and lung) using 4 full years of postpolicy data. **METHODS:** Patients aged 40-64 years diagnosed with breast, cervical, colorectal, or lung cancer from 2010 to 2017 were identified using the National Cancer Database. Difference-in-difference analyses compared changes in early-stage and late-stage diagnoses among expansion states with those among nonexpansion states. Subgroup analyses explored potential effect modification by insurance type. Data analysis was performed from June to October 2021. **RESULTS:** The proportion of early stage diagnosis of breast (difference in difference=1.58, 95% CI=0.89, 2.27), cervical (difference in difference=3.20; 95% CI=0.44, 5.95), colorectal (difference in difference=1.98; 95% CI=1.18, 2.78), and lung (difference in difference=1.74; 95% CI=0.98, 2.50) cancers increased more in expansion states than in nonexpansion states, whereas late-stage diagnosis of colorectal (difference in difference= -2.12; 95% CI= -2.98, -1.27) and lung (difference in difference= -1.87; 95% CI= -2.89, -0.84) cancers decreased more in expansion states following implementation of the Affordable Care Act. In subgroup analyses, difference-in-difference estimates for all sites and stages (except late-stage cervical cancer) were significant and larger in magnitude among Medicaid-insured than among privately insured patients. **CONCLUSIONS:** Study results highlight the positive impacts of Medicaid expansion on earlier diagnosis of several cancers for which screening and early detection exist, and subgroup analyses revealed greater positive effects among Medicaid-insured patients most targeted by the policy.