Caring Ambassadors Lung Cancer Program
Literature Review, June 2022

SCREENING, COMPREHENSIVE BIOMARKER TESTING, DIAGNOSIS AND STAGING

Quantifying Benefits and Harms of Lung Cancer Screening in an Underserved Population: Results From a Prospective Study Semin Thorac Cardiovasc Surg. Summer 2022;34(2):691-700. doi: 10.1053/j.semtcvs.2021.04.055. Epub 2021 Jun 6.Cherie P Erkmen 1 , Simran Randhawa 2 , Freda Patterson 3 , Rachel Kim 4 , Mark Weir 5 , Grace X Ma 6

Lung cancer screening with annual low-dose computed tomography reduces lung cancer death by 20-26%. However, potential harms of screening include false-positive results, procedures from false positives, procedural complications and failure to adhere to follow-up recommendations. In diverse, underserved populations, it is unknown if benefits of early lung cancer detection outweigh harms. We conducted a prospective observational study of lung cancer screening participants in an urban, safety-net institution from September 2014 to June 2020. We measured benefits of screening in terms of cancer diagnosis, stage, and treatment. We measured harms of screening by calculating false-positive rate, procedures as a result of false positive screens, procedural complications, and failure to follow-up with recommended care. Of patients with 3-year follow up, we measured these same outcomes in addition to compliance with annual screening. Of 1509 participants, 55.6% were African American, 35.2% White, 8.1% Hispanic, and 0.5% Asian. Screening resulted in cancer detection and treatment in 2.8%. False positive and procedure as a result of a false positive occurred in 9.2% and 0.8% of participants, respectively with no major complications from diagnostic procedures or treatment. Adherence to annual screening was low, 18.7%, 3.7%, and 0.4% at 1, 2, and 3 years after baseline screening respectively. Multidisciplinary lung cancer screening in a safety-net institution can successfully detect and treat lung cancer with few harms of false-positive screens, procedure after false-positive screens and major complications. However, adherence to annual screening is poor.

Comparative proteomic analysis of exhaled breath condensate between lung adenocarcinoma and CT-detected benign pulmonary nodule patients Cancer Biomark. 2022;34(2):163-174. doi: 10.3233/CBM-203269. Lin Ma 1 2 , Guanghong Xiu 3 , Joshua Muscat 2 , Raghu Sinha 4 , Dongxiao Sun 5 , Guangli Xiu 1

BACKGROUND: Lung cancer is the leading cause of cancer mortality worldwide. The collection of exhaled breath condensate (EBC) is a non-invasive method that may have enormous potential as a biomarker for the early detection of lung cancer. Objective: To investigate the proteomic differences of EBC between lung cancer and CT-detected benign nodule patients, and determine whether these proteins could be potential biomarkers. **METHODS:** Proteomic analysis was performed on individual samples from 10 lung cancer patients and 10 CT-detected benign nodule patients using data-independent acquisition (DIA) mass spectrometry. **RESULTS:** A total of 1,254 proteins were identified, and 21 proteins were differentially expressed in the lung adenocarcinoma group compared to the benign nodule group ($p < 0.05$). The GO analysis showed that most of these proteins were involved in neutrophil-related biological processes, and the KEGG analysis showed these proteins were mostly annotated to pyruvate and propanoate metabolism. Through protein-protein interactions (PPIs) analysis, ME1 and LDHB contributed most to the interaction-network of these proteins. **CONCLUSION:** Significantly differentially expressed proteins were detected between lung cancer and the CT-detected benign nodule group from EBC samples, and these proteins might serve as potential novel biomarkers of EBC for early lung cancer detection.

[Role of Peripheral Blood Markers for Detecting Response and Predicting Prognosis in Patients with Non-small-cell Lung Cancer Undergoing Neoadjuvant Therapy and Surgery](#) Lung. 2022 Jun;200(3):393-400. doi: 10.1007/s00408-022-00541-2. Epub 2022 Jun 2. Filippo Lococo # 1   2 , Marco Chiappetta # 3   4 , Jessica Evangelista # 2 ,et al.

INTRODUCTION: To date, no validated predictors of response before neoadjuvant therapy (NAD) are currently available in locally advanced non-small-cell lung cancer (NSCLC). In this study, different peripheral blood markers were investigated before NAD (pre-NAD) and after NAD/before surgery (post-NAD) to evaluate their influence on the treatment outcomes. **METHODS:** Patients affected by locally advanced NSCLC (cT1-T4/N0-2/M0) who underwent NAD followed by surgery from January 1996 to December 2019 were considered for this retrospective analysis. The impact of peripheral blood markers on downstaging post-NAD and on overall survival (OS) was evaluated using multivariate logistic and Cox regression models. Time to event analysis was performed by means of Kaplan-Meier survival curves and Log Rank tests at 5 years from surgery. **RESULTS:** Two hundred and seventy-two consecutive patients were included. Most of the patients had Stage III NSCLC (83.5%). N2 disease was reported in 188 (69.1%) patients. Surgical resection was performed in patients with stable disease or downstaging post-NAD. Nodal downstaging was observed in 80% of clinical N2 (cN2) patients. The median follow-up of the total series was 74 months (range 6-302). Five-year OS in the overall population and in N2 population was 74.6% and 73.5%, respectively. The pre-surgery platelets level (PLT) ($p = 0.019$) and the variation (pre-NAD/post-NAD) of the neutrophil/lymphocyte ratio ($p = 0.024$) were identified as independent prognostic factors of OS. The preoperative PLT value (p value = 0.031) was confirmed as the only predictor of NAD response. **CONCLUSIONS:** The clinical role of peripheral blood markers in locally advanced NSCLC needs to be further investigated. Based on these preliminary results, these factors may be used as auxiliary markers for the prediction of response to neoadjuvant treatment and as prognostic factors for stratification in multimodal approaches.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

[Pulmonary Parenchymal Changes in COVID-19 Survivors](#) Ann Thorac Surg. 2022 Jul;114(1):301-310. doi: 10.1016/j.athoracsur.2021.06.076. Epub 2021 Jul 31. Ashley Diaz 1 , Daniel Bujnowski 2 , Phillip McMullen 3 , et al.

BACKGROUND: As the COVID-19 pandemic moves into the survivorship phase, questions regarding long-term lung damage remain unanswered. Previous histopathologic studies are limited to autopsy reports. We studied lung specimens from COVID-19 survivors who underwent elective lung resections to determine whether postacute histopathologic changes are present. **METHODS:** This multicenter observational study included 11 adult COVID-19 survivors who had recovered but subsequently underwent unrelated elective lung resection for indeterminate lung nodules or lung cancer. We compared these against an age- and procedure-matched control group who never contracted COVID-19 (n = 5) and an end-stage COVID-19 group (n = 3). A blinded pulmonary pathologist examined the lung parenchyma focusing on 4 compartments: airways, alveoli, interstitium, and vasculature. **RESULTS:** Elective lung resection was performed in 11 COVID-19 survivors with asymptomatic (n = 4), moderate (n = 4), and severe (n = 3) COVID-19 infections at a median 68.5 days (range 24-142 days) after the COVID-19 diagnosis. The most common operation was lobectomy (75%). Histopathologic examination identified no differences between the lung parenchyma of COVID-19 survivors and controls across all compartments examined. Conversely, patients in the end-stage COVID-19 group showed fibrotic diffuse alveolar damage with intra-alveolar macrophages, organizing pneumonia, and focal interstitial emphysema. **CONCLUSIONS:** In this study to examine the lung parenchyma of COVID-19 survivors, we did not find distinct postacute histopathologic changes to suggest permanent pulmonary damage. These results are reassuring for COVID-19 survivors who recover and become asymptomatic.

[Midterm survival of imaging-assisted robotic lung segmentectomy for non-small-cell lung cancer](#)

Zied Chaari 1   2 , François Montagne 2 , Matthieu Sarsam 2 , Benjamin Bottet 2 , Philippe Rinieri 2 , Andre Gillibert 3 , Jean Marc Baste 2   4

OBJECTIVES: Our goal was to report our midterm results using imaging-assisted modalities with robotic segmentectomies for non-small-cell lung cancer (NSCLC). **METHODS:** This was a retrospective study of all robotic segmentectomies, with confirmed NSCLC, performed at our general and thoracic surgery unit in the Rouen University Hospital (France), from January 2012 through December 2019. Benign and metastatic lesions were excluded. Data were extracted from the EPITHOR French nationwide database. **RESULTS:** A total of 121 robotic segmentectomies were performed for 118 patients with a median age of 65 (interquartile range: 60, 69) years. The majority had clinical stage T1aN0M0 (71.9%) or T1bN0M0 (13.2%). The mean (standard deviation) number of resected segments was 1.93 (1.09) with 80.2% imaging-assisted segmentectomies. Oriented (according to tumour location) or systematic lymphadenectomy or sampling was performed for 72.7%, 23.1% and 4.1% of patients. The postoperative course was uneventful for 94 patients (77.7%), whereas 34 complications occurred for 27 patients (22.3%), including 2 patients (1.7%) with Clavien-Dindo ≥III complications. The mean thoracic drainage duration was 4.12 days, and the median hospital stay was 4 days (interquartile range: 3, 5) after the operation. The 2-year survival rate was 93.9% (95% confidence interval: 86.4-97.8%). Excluding stage IV (n = 3) and stage 0 tumours (n = 6), the 2-year survival rate was 95.7% (95% confidence interval: 88.4-98.8%) compared to an expected survival rate of 94.0% according to stage-specific survival rates found in a large external reference cohort. **CONCLUSIONS:** Imaging-guided robotic-assisted thoracic surgery segmentectomy seems to be useful and oncological with good midterm results, especially for patients with early-stage NSCLC.

[Survival and Recurrence Following Wedge Resection Versus Lobectomy for Early-Stage Non-Small Cell Lung Cancer](#)

 Daniel Dolan 1 , Scott J Swanson 1 , Ritu Gill 2 , et al.

To determine if wedge resection is equivalent to lobectomy for Stage I Non-Small Cell Lung Cancer (NSCLC) and to evaluate the impact of radiologic and pathologic variables not available in large national databases. Records were reviewed from 2010-2016 for patients with pathologic Stage I NSCLC who underwent wedge resection or lobectomy. Propensity score matching was performed on pre-operative variables and patients with ≥1 lymph node removed. Clinical variables were compared. Kaplan-Meier curves and multivariable Cox proportional hazard models for 5-year overall survival (OS), disease-free (DFS), and locoregional-recurrence-free survival (LRFS) were created. A total of 1086 patients met inclusion criteria; 391 lobectomies and 695 wedge resections. Propensity score matching yielded 167 pairs of lobectomy and wedge resection patients. Complications were fewer for wedge resections than lobectomies, 19.2% for wedge resection patients vs 34.1% for lobectomy patients, p < 0.01. OS was equivalent between groups, 86.2% for lobectomy patients vs 83.4% for wedge resection patients p = 0.47. DFS was similar, 79.0% for lobectomy patients vs 72.5% for wedge resection patients p = 0.10. Overall LRFS was worse in wedge resection patients vs lobectomy patients, 82.0% vs 93.4% p < 0.01. However, in the matched wedge resection patients with a margin >10 mm the LRFS was equal to that of lobectomy patients, 86.4% for wedge resection patients vs 91.8% for lobectomy patients p = 0.140. Patients with Stage I NSCLC can experience similar OS, DFS, and LRFS with wedge resection as compared to lobectomy, when wedge resection margins are >10 mm and appropriate lymph node dissection is performed.

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

Sachie Koike 1, Takashi Eguchi 1 , Shunichiro Matsuoka 1 , Tetsu Takeda 1 , Kentaro Miura 1 , Kimihiro Shimizu 1, Kazutoshi Hamanaka 1

OBJECTIVES: Following right upper lobectomy, the right middle lobe may shift towards the apex and rotate in a counterclockwise direction with respect to the hilum. This study aimed to investigate the incidence and clinical impact of middle lobe rotation in patients undergoing right upper lobectomy. **METHODS:** From January 2014 to November 2018, 82 patients underwent right upper lobectomy at our institution for lung cancer using a surgical stapler to divide the minor fissure. Postoperative computed tomography scans evaluated the counterclockwise rotation of the middle lobe, in which the staple lines placed on the minor fissure were in contact with the major fissure of the right lower lobe (120° counterclockwise rotation). Clinicoradiological factors were evaluated and compared between patients with and without middle lobe rotation. We also reviewed surgical videos in patients with middle lobe rotation to evaluate the position of the middle lobe at the end of surgery. **RESULTS:** Nine patients had a middle lobe rotation (11%), where 1 patient required surgical derotation. Patients with middle lobe rotation were significantly associated with more frequent right middle lobe atelectasis and severe postoperative complications compared with those without rotation. A surgical video review detected potential middle lobe rotation at the end of the surgery. **CONCLUSIONS:** Middle lobe rotation without torsion following right upper lobectomy is not rare, and it is associated with adverse postoperative courses. Careful positioning of the right middle lobe at the end of surgery is warranted to improve postoperative outcomes.

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

[Phase I Study of Taminadenant (PBF509/NIR178), an Adenosine 2A Receptor Antagonist, with or without Spartalizumab (PDR001), in Patients with Advanced Non-Small Cell Lung Cancer](#)

Alberto A Chiappori 1 , Ben Creelan 1 , Tawee Tanvetyanon 1 , et al.

PURPOSE: The adenosine 2A receptor (A2AR) mediates the immunosuppressive effects of adenosine in the tumor microenvironment and is highly expressed in non-small cell lung cancer (NSCLC). Taminadenant (PBF509/NIR178) is an A2AR antagonist able to reactivate the antitumor immune response. Patients and **METHODS:** In this phase I/Ib, dose-escalation/expansion study, patients with advanced/metastatic NSCLC and ≥1 prior therapy received taminadenant (80-640 mg, orally, twice a day) with or without spartalizumab (anti-programmed cell death-1, 400 mg, i.v., every 4 weeks). Primary endpoints were safety, tolerability, and feasibility of the combination. **RESULTS:** During dose escalation, 25 patients each received taminadenant alone or with spartalizumab; 19 (76.0%) and 9 (36.0%) had received prior immunotherapy, respectively. Dose-limiting toxicities (all Grade 3) with taminadenant alone were alanine/aspartate aminotransferase increase and nausea [n = 1 (4.0%) each; 640 mg], and in the combination group were pneumonitis [n = 2 (8.0%); 160 and 240 mg] and fatigue and alanine/aspartate aminotransferase increase [n = 1 (4.0%) each; 320 mg]; pneumonitis cases responded to steroids rapidly and successfully. Complete and partial responses were observed in one patient each in the single-agent and combination groups; both were immunotherapy naïve. In the single-agent and combination groups, 7 and 14 patients experienced stable disease; 7 and 6 patients were immunotherapy pretreated, respectively. **CONCLUSIONS:** Taminadenant, with and without spartalizumab, was well tolerated in patients with advanced NSCLC. The maximum tolerated dose of taminadenant alone was 480 mg twice a day, and 240 mg twice a day plus spartalizumab. Efficacy was neither a primary or secondary endpoint; however, some clinical benefit was noted regardless of prior immunotherapy or programmed cell death ligand-1 status.

[**Health-Related Quality of Life Outcomes in Patients with Resected Epidermal Growth Factor Receptor-Mutated Non-Small Cell Lung Cancer Who Received Adjuvant Osimertinib in the Phase III ADAURA Trial**](#) Clin Cancer Res. 2022 Jun 1;28(11):2286-2296. doi: 10.1158/1078-0432.CCR-21-3530. Margarita Majem 1 , Jonathan W Goldman 2 , Thomas John 3 , et al.
PURPOSE: In the phase III ADAURA trial, adjuvant treatment with osimertinib versus placebo, with/without prior adjuvant chemotherapy, resulted in a statistically significant and clinically meaningful disease-free survival benefit in completely resected stage IB-IIIA EGFR-mutated (EGFRm) non-small cell lung cancer (NSCLC). We report health-related quality of life (HRQoL) outcomes from ADAURA. Patients and **METHODS:** Patients randomized 1:1 received oral osimertinib 80 mg or placebo for 3 years or until recurrence/discontinuation. HRQoL (secondary endpoint) was measured using the Short Form-36 (SF-36) health survey at baseline, 12, and 24 weeks, then every 24 weeks until recurrence or treatment completion/discontinuation. Exploratory analyses of SF-36 score changes from baseline until week 96 and time to deterioration (TTD) were performed in the overall population (stage IB-IIIA; N = 682). Clinically meaningful changes were defined using the SF-36 manual. **RESULTS:** Baseline physical/mental component summary (PCS/MCS) scores were comparable between osimertinib and placebo (range, 46-47) and maintained to Week 96, with no clinically meaningful differences between arms; difference in adjusted least squares (LS) mean [95% confidence intervals (CI), -1.18 (-2.02 to -0.34) and -1.34 (-2.40 to -0.28), for PCS and MCS, respectively. There were no differences between arms for TTD of PCS and MCS; HR, 1.17 (95% CI, 0.82-1.67) and HR, 0.98 (95% CI, 0.70-1.39), respectively. **CONCLUSIONS:** HRQoL was maintained with adjuvant osimertinib in patients with stage IB-IIIA EGFRm NSCLC, who were disease-free after complete resection, with no clinically meaningful differences versus placebo, further supporting adjuvant osimertinib as a new treatment in this setting. See related commentary by Patil and Bunn, p. 2204.

[**Cost-effectiveness analysis of nivolumab plus ipilimumab versus platinum-doublet chemotherapy for first-line treatment of stage IV or recurrent non-small cell lung cancer in the United States**](#) J Med Econ. Jan-Dec 2022;25(1):703-711. doi: 10.1080/13696998.2022.2077549. Malin Berling 1 ,

Mohammad A Chaudhary 2 , Yong Yuan 2 , Nebibe Varol 3 , Peter Dale 4 , Eleonora Testa 1 , Johan Klint 1 , Adam Lee 3 , Solomon J Lubinga 2 , John R Penrod 2

AIM: We evaluated the cost-effectiveness of nivolumab in combination with ipilimumab (NIVO + IPI) versus platinum-doublet chemotherapy (PDC) for the first-line treatment of stage IV or recurrent non-small cell lung cancer (NSCLC) from a third-party payer perspective in the United States (US).
METHODS: A partitioned survival model was developed using efficacy, safety, and utility inputs derived from Part 1 of the phase 3 CheckMate 227 trial (NCT02477826) with 37.7-month minimum follow-up for overall survival (OS). OS and progression-free (PF) survival were extrapolated over a 20-year time-horizon using parametric spline-based models selected based on goodness of fit and validated with data from external sources. Duration of treatment Kaplan-Meier curves were used for treatment cost calculations. US-specific costs (2021 dollars) for drug acquisition, administration, and monitoring; disease management (PF and progressed disease health states); end-of-life care; adverse events; and subsequent treatments were derived from publicly available sources. Time-to-death utilities were applied in the base case, whereas treatment-specific progression-based utilities were tested in a scenario analysis. Main outcomes included incremental cost per life-year gained (LYG) and quality-adjusted life-year (QALY). Model uncertainty was assessed through deterministic and probabilistic sensitivity analyses.
RESULTS: NIVO + IPI resulted in 1.53 additional life-years, 1.33 additional QALYs, and $142 088 in additional costs compared with PDC. The incremental cost per LYG was $92 651, whereas incremental cost per QALY gained was $106 553. The application of treatment-specific progression-based utilities yielded an incremental cost per QALY gained of $117 076. Probabilistic sensitivity analysis revealed a 98% probability that NIVO + IPI was cost-effective versus PDC at a willingness-to-pay threshold of $150 000 per QALY. **CONCLUSIONS:** NIVO + IPI was estimated to be cost-effective as a first-line treatment for stage IV or recurrent NSCLC in the US, with increased survival and higher cost compared with PDC.

[Continuation of Pembrolizumab with Additional Chemotherapy after Progression with PD-1/PD-L1 Inhibitor Monotherapy in Patients with Advanced NSCLC: A Randomized, Placebo-Controlled Phase II Study](#) Clin Cancer Res. 2022 Jun 1;28(11):2321-2328. doi: 10.1158/1078-0432.CCR-21-3646.
Hyun Ae Jung 1 , Sehhoon Park 1 , Yoon-La Choi 2 , Se-Hoon Lee 1 , Jin Seok Ahn 1 , Myung-Ju Ahn 1 , Jong-Mu Sun 1

PURPOSE: Although programmed cell death 1 (PD-1) or programmed cell death ligand 1 (PD-L1) inhibitors have shown survival benefits in patients with non-small cell lung cancer (NSCLC), most patients progress. This study evaluated whether continuing pembrolizumab with additional chemotherapy after failure of prior PD-1/PD-L1 inhibitor extends survival. Patients and **METHODS:** This placebo-controlled, double-blind, randomized phase II study enrolled patients with NSCLC who received one or two cytotoxic chemotherapy, including at least one platinum-doublet regimen, and progressed on second- or third-line PD-1/PD-L1 inhibitor monotherapy as the last systemic therapy. Patients were randomized (1:1) to pembrolizumab or placebo plus chemotherapy, stratified by histology and clinical outcomes to prior PD-1/PD-L1 inhibitor. The primary endpoint was progression-free survival (PFS). **RESULTS:** A total of 98 patients were randomized to the pembrolizumab-chemotherapy (N = 47) and placebo-chemotherapy arm (N = 51). At the median follow-up duration of 10.5 months, there was no statistical difference in PFS [median 4.1 months vs. 5.9 months; HR = 1.06; 95% confidence interval (CI), 0.69-1.62; P = 0.78) and overall survival (median 11.5 months vs. 12.0 months; HR = 1.09; 95% CI, 0.66-1.83; P = 0.73) between the pembrolizumab-chemotherapy and placebo-chemotherapy arms. In a subgroup with PD-L1 expression in ≥50% of tumor cells and favorable clinical outcomes to prior PD-1/PD-L1 inhibitor (partial response or 6 months or longer of stable disease), the pembrolizumab-chemotherapy arm showed a higher 24-month survival rate than the placebo-chemotherapy arm (74% vs. 38%; HR = 0.52; 95% CI, 0.13-2.1; P = 0.34). **CONCLUSIONS:** This study did not show a survival benefit with the continuation

of pembrolizumab with chemotherapy in patients whose NSCLC progressed on second- or third-line PD-1/PD-L1 inhibitors. See related commentary by Tseng and Gainor, p. 2206.

[FDA Approval Summary: Pembrolizumab, Atezolizumab, and Cemiplimab-rwlc as Single Agents for First-Line Treatment of Advanced/Metastatic PD-L1-High NSCLC](#) Clin Cancer Res. 2022 Jun 1;28(11):2221-2228. doi: 10.1158/1078-0432.CCR-21-3844. Oladimeji Akinboro 1 , Erin Larkins 1 , Lee H Pai-Scherf 1 , et al.

FDA's approval of cemiplimab-rwlc on February 22, 2021, follows prior approvals of pembrolizumab and atezolizumab for similar indications as first-line treatment for patients with programmed death ligand-1 (PD-L1)-high advanced non-small cell lung cancer (NSCLC). Approvals of these anti-PD-L1 agents were supported by statistically significant and clinically meaningful improvements in overall survival (OS) in international, multicenter, active-controlled randomized trials. In KEYNOTE-024, the OS HR was 0.60 [95% confidence interval (CI), 0.41-0.89; P = 0.005] favoring pembrolizumab over platinum-doublet chemotherapy. In IMpower110, the OS HR was 0.59 (95% CI, 0.40-0.89; P = 0.0106) favoring atezolizumab over platinum-doublet chemotherapy. In Study 1624, the OS HR was 0.68 (95% CI, 0.53-0.87; P = 0.0022) favoring cemiplimab-rwlc over platinum-doublet chemotherapy. The progression-free survival (PFS) effect sizes for these anti-PD-L1 antibodies were also comparable across their respective registrational trials, and their safety profiles were consistent with the anti-PD-L1 class adverse event profile. The consistent survival benefits and manageable toxicity profiles of these single-agent anti-PD-L1 antibodies have established them as important treatment options in the PD-L1-high NSCLC treatment landscape. FDA approvals of these anti-PD-L1 antibodies, based on their favorable benefit-risk profiles, present effective chemotherapy-free therapeutic options for patients with advanced PD-L1-high NSCLC in the United States.

[Multicenter Real-World Study on Effectiveness and Early Discontinuation Predictors in Patients With Non-small Cell Lung Cancer Receiving Nivolumab](#) Oncologist. 2022 Jun 8;27(6):e484-e493. doi: 10.1093/oncolo/oyac051. Giulia Pasello 1   2 , Martina Lorenzi 1 , Lorenzo Calvetti 3 , et al.
BACKGROUND: Real-world (RW) evidence on nivolumab in pretreated patients with non-small cell lung cancer (NSCLC) by matching data from administrative health flows (AHFs) and clinical records (CRs) may close the gap between pivotal trials and clinical practice. **METHODS:** This multicenter RW study aims at investigating median time to treatment discontinuation (mTTD), overall survival (mOS) of nivolumab in pretreated patients with NSCLC both from AHF and CR; clinical-pathological features predictive of early treatment discontinuation (etd), budget impact (BI), and cost-effectiveness analysis were investigated; mOS in patients receiving nivolumab and docetaxel was assessed. **RESULTS:** Overall, 237 patients with NSCLC treated with nivolumab were identified from AHFs; mTTD and mOS were 4.2 and 9.8 months, respectively; 141 (59%) received at least 6 treatment cycles, 96 (41%) received < 6 (etd). Median overall survival in patients with and without etd were 3.3 and 19.6 months, respectively (P < .0001). Higher number, longer duration, and higher cost of hospitalizations were observed in etd cases. Clinical records were available for 162 patients treated with nivolumab (cohort 1) and 83 with docetaxel (cohort 2). Median time to treatment discontinuation was 4.8 and 2.6 months, respectively (P < .0001); risk of death was significantly higher in cohort 2 or cohort 1 with etd compared with cohort 1 without etd (P < .0001). Predictors of etd were body mass index <25, Eastern Cooperative Oncology Group performance status >1, neutrophile-to-lymphocyte ratio >2.91, and concomitant treatment with antibiotics and glucocorticoids. The incremental cost-effectiveness ratio of nivolumab was 3323.64 euros ($3757.37) in all patients and 2805.75 euros ($3171.47) for patients without etd. Finally, the BI gap (real-theoretical) was 857 188 euros ($969 050.18). **CONCLUSION:** We defined predictors and prognostic-economic impact of nivolumab in etd patients.

[Essential role for STAT3/FOXM1/ATG7 signaling-dependent autophagy in resistance to Icotinib](#) J Exp Clin Cancer Res. 2022 Jun 11;41(1):200. doi: 10.1186/s13046-022-02390-6. Xin Lyu 1 , Lizhong Zeng 1 , Jie Shi 1 , et al.
BACKGROUND: The contribution of autophagy to cancer therapy resistance remains complex, mainly owing to the discrepancy of autophagy mechanisms in different therapy. However, the potential mechanisms of autophagy-mediated resistance to icotinib have yet to be elucidated. **METHODS:** The effect of autophagy in icotinib resistance was examined using a series of in vitro and in vivo assays. The results above were further verified in biopsy specimens of lung cancer patients before and after icotinib or gefitinib treatment. **RESULTS:** Icotinib increased ATG3, ATG5, and ATG7 expression, but without affecting Beclin-1, VPS34 and ATBG14 levels in icotinib-resistant lung cancer cells. Autophagy blockade by 3-MA or silencing Beclin-1 had no effects on resistance to icotinib. CQ effectively restored lung cancer cell sensitivity to icotinib in vitro and in vivo. Notably, aberrantly activated STAT3 and highly expressed FOXM1 were required for autophagy induced by icotinib, without the involvement of AMPK/mTOR pathway in this process. Alterations of STAT3 activity using genetic and/or pharmacological methods effectively affected FOXM1 and ATG7 levels increased by icotinib, with altering autophagy and icotinib-mediated apoptosis in resistant cells. Furthermore, silencing FOXM1 impaired up-regulated ATG7 induced by STAT3-CA and icotinib. STAT3/FOXM1 signalling blockade also reversed resistance to icotinib in vivo. Finally, we found a negative correlation between STAT3/FOXM1/ATG7 signalling activity and epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) treatment efficacy in patients undergoing EGFR-TKIs treatment. **CONCLUSIONS:** Our findings support that STAT3/FOXM1/ATG7 signalling-induced autophagy is a novel mechanism of resistance to icotinib, and provide insights into potential clinical values of ATG7-dependent autophagy in icotinib treatment.

[Bone Metastasis and Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer (NSCLC): Microenvironment and Possible Clinical Implications](#) Int J Mol Sci. 2022 Jun 20;23(12):6832. doi: 10.3390/ijms23126832. Alessandro Del Conte 1 , Elisa De Carlo 1 , Elisa Bertoli 1 2 , Brigida Stanzione 1 , Alberto Revelant 3 , Manuela Bertola 1 , Michele Spina 1 , Alessandra Bearz 1
Patients with non-small cell lung cancer (NSCLC) develop bone metastasis (BoM) in more than 50% of cases during the course of the disease. This metastatic site can lead to the development of skeletal related events (SREs), such as severe pain, pathological fractures, spinal compression, and hypercalcemia, which reduce the patient's quality of life. Recently, the treatment of advanced NSCLC has radically changed due to the advent of immunotherapy. Immune checkpoint inhibitors (ICI) alone or in combination with chemotherapy have become the main therapeutic strategy for advanced or metastatic NSCLC without driver gene mutations. Since survival has increased, it has become even more important to treat bone metastasis to prevent SRE. We know that the presence of bone metastasis is a negative prognostic factor. The lower efficacy of immunotherapy treatments in BoM+ patients could be induced by the presence of a particular immunosuppressive tumor and bone microenvironment. This article reviews the most important pre-clinical and clinical scientific evidence on the reasons for this lower sensitivity to immunotherapy and the need to combine bone target therapies (BTT) with immunotherapy to improve patient outcome.

[Neoadjuvant Immunotherapy: Leveraging the Immune System to Treat Early-Stage Disease](#) Am Soc Clin Oncol Educ Book. 2022 Apr;42:1-15. doi: 10.1200/EDBK_349411. Elizabeth A Mittendorf 1 2 , Femke Burgers 3 , John Haanen 3 , Tina Cascone 4
Given the success of immunotherapy in treating patients with metastatic disease in a variety of tumor types, there is tremendous enthusiasm for expanding the use of immunotherapy to those with early-stage cancer. Administering immunotherapy in the neoadjuvant, preoperative setting is a biologically sound

approach because preclinical studies have shown that stronger and broader immune responses can be generated if immunotherapy is administered while the tumor and/or draining lymph nodes are intact. It is therefore likely that administering immunotherapy preoperatively will generate optimal immune responses, leading to high rates of pathologic response as well as improved long-term survival. Although neoadjuvant immunotherapy is currently only approved for use in combination with chemotherapy in triple-negative breast cancer and non-small cell lung cancer, it is anticipated that ongoing and future clinical trials will further define the role of neoadjuvant immunotherapy in many cancer types. These trials should be designed with appropriate survival endpoints and rigorous correlative studies to include imaging and biospecimen-based analyses to address currently unanswered questions that must be resolved to optimize the use of immunotherapy in early-stage disease.

[Characteristics and immune checkpoint inhibitor effects on non-smoking non-small cell lung cancer with KRAS mutation: A single center cohort (STROBE-compliant)](#) Medicine (Baltimore). 2022 Jun 17;101(24):e29381. doi: 10.1097/MD.0000000000029381.Jia-Jun Wu 1 2 3 4 5 , Po-Hsin Lee 1 6 7 8 , Zhe-Rong Zheng 1 3 4 , Yen-Hsiang Huang 1 9 10 , Jeng-Sen Tseng 1 6 9 11 , Kuo-Hsuan Hsu 12 , Tsung-Ying Yang 1 13 , Sung-Liang Yu 14 , Kun-Chieh Chen 1 3 4 15 , Gee-Chen Chang 1 3 4 5

Kirsten rat sarcoma (KRAS) mutation (KRASm) is associated with poor prognosis in non-small cell lung cancer (NSCLC) patients. We have aimed to survey NSCLC patients harboring KRASm in Taiwan, where never-smoking lung adenocarcinoma predominates, and analyze the immune checkpoint inhibitor effect on NSCLC harboring KRASm.NSCLC patients with KRASm were enrolled and tested on programmed death-ligand 1 (PD-L1) expression using available tissue. We analyzed their clinical features, PD-L1 status, responses to ICIs, and overall survival (OS).We studied 93 patients with a median age 66.0 years, 23.7% of whom were women, and 22.6% were never-smokers. The results showed that G12C (36.6%) was the most common KRASm. In 47 patients with available tissue for PD-L1 testing, PD-L1 expression was positive in 66.0% of patients, while PD-L1 ≥50% was higher in ever-smokers (P = .038). Among 23 patients receiving ICI treatment, those with PD-L1 ≥50% experience a 45.5% response rate to ICI. There were benefits from ICI treatment on OS compared with no ICI treatment (median OS 35.6 vs 9.8 months, P = .002) for all of our patients, and for patients with PD-L1 ≥50% (median OS not-reached vs 8.4 months, P = .008). There were no differences in survival across different KRAS subtypes (P = .666). Never-smokers composed more than one-fifth of KRASm in NSCLC in Taiwan. A high PD-L1 expression was related to smoking history and responded well to ICI. ICI treatment improved the OS in NSCLC patients with KRASm, particularly those with PD-L1 ≥50%.

[First-Line Osimertinib in Patients with EGFR-Mutant Advanced Non-Small Cell Lung Cancer: Outcome and Safety in the Real World: FLOWER Study](#) Oncologist. 2022 Mar 4;27(2):87-e115. doi: 10.1002/onco.13951. Martina Lorenzi 1 2 , Alessandra Ferro 1 2 , Fabiana Cecere 3 , et al.
BACKGROUND: Osimertinib became the standard treatment for patients with untreated EGFR-mutant advanced non-small cell lung cancer (aNSCLC) following results reported in the phase III randomized FLAURA trial. Because of strict exclusion criteria, patient populations included in pivotal trials are only partially representative of real-world patients. **METHODS:** We designed an observational, prospective, multicenter study enrolling patients with EGFR-mutant aNSCLC receiving first-line osimertinib to evaluate effectiveness, safety, and progression patterns in the real-world. **RESULTS:** At data cutoff, 126 White patients from nine oncology centers were included. At diagnosis, 16 patients (12.7%) had a performance status (PS) ≥2 and 38 (30.2%) had brain metastases. Overall response rate (ORR) was 73%, disease control rate (DCR) 96.0%. After a median follow-up of 12.3 months, median time to treatment discontinuation (mTTD) was 25.3 months, median progression-free-survival (mPFS) was 18.9 months and median overall survival (mOS) was not reached (NR). One hundred and ten patients (87%)

experienced adverse events (AEs), 42 (33%) of grade 3-4, with venous thromboembolism (VTE) as the most common (n = 10, 7.9%). No difference in rates of VTE was reported according to age, PS, comorbidity, and tumor load. We observed longer mTTD in patients without symptoms (NR vs. 18.8 months) and with fewer than three metastatic sites at diagnosis (NR vs. 21.4 months). Patients without brain metastases experienced longer mPFS (NR vs. 13.3 months). No difference in survival outcome was observed according to age, comorbidity, and type of EGFR mutation. Isolated progression and progression in fewer than three sites were associated with longer time to treatment discontinuation (TTD). **CONCLUSION:** Osimertinib confirmed effectiveness and safety in the real world, although thromboembolism was more frequent than previously reported.

[**Effectiveness and safety of camrelizumab combined with chemotherapy in nonsquamous nonsmall cell lung cancer as the second-line therapy: A retrospective analysis**](#) J Cancer Res Ther. 2022 Apr;18(2):576-580. doi: 10.4103/jcrt.jcrt_855_21. Wei Huang 1 , Qinyuan Zhang 1 , Liangshan Da 1 , Yuanyuan Shen 1 , Fuxing Xiong 1 , Congjun Zhang 1
BACKGROUND: The role of camrelizumab combined with chemotherapy as the second-line therapy in nonsquamous nonsmall cell lung cancer (NSCLC) remains unverified. The retrospective study investigated efficacy and safety of camrelizumab combined with chemotherapy in the treatment of nonsquamous NSCLC as the second-line therapy. Subjects and **METHODS:** Patients of nonsquamous NSCLC who were already discharged or died of the First Affiliated Hospital of Anhui Medical University between August 2019 and September 2020. According to the treatment method, the patients who received chemotherapy were denoted as the C group and those who received camrelizumab plus chemotherapy were denoted as the C&C group. Statistical analysis used: Patients responses were statistically analyzed. The Cox proportional hazards regression model was used in the assessment of the prognostic value of factors. Furthermore, adverse event evaluation was estimated. **RESULTS:** Of the 60 patients with nonsquamous NSCLC included in the research, 29 patients received chemotherapy, and 31 patients received camrelizumab plus chemotherapy. The objective response rate was 13.79% and 32.26% for chemotherapy and camrelizumab plus chemotherapy groups, and the disease control rate was 72.41% and 80.65%. The median progression-free survival (mPFS) in camrelizumab plus chemotherapy group was obviously higher than that in the chemotherapy group (9.67 vs. 6.87 months, P = 0.01). The median overall survival of the camrelizumab plus chemotherapy was longer than the chemotherapy (10.89 vs. 7.95 months, P < 0.01). In the current treatment, radiotherapy and smoking were independent risk factors for the mPFS of patients with nonsquamous NSCLC. The occurrence of adverse events was similar between chemotherapy and camrelizumab plus chemotherapy groups. **CONCLUSIONS:** Camrelizumab combined with chemotherapy was an effective regimen with manageable toxicity in treating nonsquamous NSCLC as the second-line therapy.

[**Bone Metastasis and Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer (NSCLC): Microenvironment and Possible Clinical Implications**](#) Int J Mol Sci. 2022 Jun 20;23(12):6832. doi: 10.3390/ijms23126832. Alessandro Del Conte 1 , Elisa De Carlo 1 , Elisa Bertoli 1 2 , Brigida Stanzione 1 , Alberto Revelant 3 , Manuela Bertola 1 , Michele Spina 1 , Alessandra Bearz 1
Patients with non-small cell lung cancer (NSCLC) develop bone metastasis (BoM) in more than 50% of cases during the course of the disease. This metastatic site can lead to the development of skeletal related events (SREs), such as severe pain, pathological fractures, spinal compression, and hypercalcemia, which reduce the patient's quality of life. Recently, the treatment of advanced NSCLC has radically changed due to the advent of immunotherapy. Immune checkpoint inhibitors (ICI) alone or in combination with chemotherapy have become the main therapeutic strategy for advanced or metastatic NSCLC without driver gene mutations. Since survival has increased, it has become even more important to treat bone metastasis to prevent SRE. We know that the presence of bone metastasis is a negative prognostic factor.

The lower efficacy of immunotherapy treatments in BoM+ patients could be induced by the presence of a particular immunosuppressive tumor and bone microenvironment. This article reviews the most important pre-clinical and clinical scientific evidence on the reasons for this lower sensitivity to immunotherapy and the need to combine bone target therapies (BTT) with immunotherapy to improve patient outcome.

[Neoadjuvant Immunotherapy: Leveraging the Immune System to Treat Early-Stage Disease](#) Am Soc Clin Oncol Educ Book. 2022 Apr;42:1-15. doi: 10.1200/EDBK_349411. Elizabeth A Mittendorf 1 2 , Femke Burgers 3 , John Haanen 3 , Tina Cascone 4

Given the success of immunotherapy in treating patients with metastatic disease in a variety of tumor types, there is tremendous enthusiasm for expanding the use of immunotherapy to those with early-stage cancer. Administering immunotherapy in the neoadjuvant, preoperative setting is a biologically sound approach because preclinical studies have shown that stronger and broader immune responses can be generated if immunotherapy is administered while the tumor and/or draining lymph nodes are intact. It is therefore likely that administering immunotherapy preoperatively will generate optimal immune responses, leading to high rates of pathologic response as well as improved long-term survival. Although neoadjuvant immunotherapy is currently only approved for use in combination with chemotherapy in triple-negative breast cancer and non-small cell lung cancer, it is anticipated that ongoing and future clinical trials will further define the role of neoadjuvant immunotherapy in many cancer types. These trials should be designed with appropriate survival endpoints and rigorous correlative studies to include imaging and biospecimen-based analyses to address currently unanswered questions that must be resolved to optimize the use of immunotherapy in early-stage disease.

NSCLC - RADIOTHERAPY

[Predictive value of quantitative metabolic tumor volume and metabolic index analysis in lung cancer stereotactic radiotherapy with F-18 FDG PET/CT](#) Eur Rev Med Pharmacol Sci. 2022 May;26(10):3534-3543. doi: 10.26355/eurrev_202205_28848. F Aras 1 , A Olmezoglu

OBJECTIVE: The objective of this study was to investigate predictive value of quantitative metabolic tumor volume and metabolic index analysis in lung cancer stereotactic radiotherapy with F-18 FDG PET/CT. **PATIENTS AND METHODS:** Overall, 94 early-stage non-small cell lung cancer (NSCLC) patients who were administered stereotactic radiotherapy were included in the study. **RESULTS:** Most of the study patients were male (91.5%). Mean age of the patients was 68.5 ± 9.0 years. The primary lung tumor was located centrally and peripherally in 25 (26.6%) and 69 (73.4%) of the patients, respectively. The median gross tumor volume (GTV) was 16.2 cc [interquartile range (IQR): 7.1-32.9]. Whereas all patients who had peripheral tumors survived, 17 patients with central tumors (70.8%) died during the study period (p = 0.001). Biologically effective dose (BED10) values were significantly higher in patients who had peripheral tumors compared with patients with central tumors (p = 0.001). Significantly more patients died in patients who had BED values below 100 Gy compared to patients who had BED values over 100 Gy (p = 0.001). The survival distributions for the two groups were significantly different (p < 0.001). Only GTV and Pretreatment SUVmean appeared as significant predictors of mortality. BED10 values showed a significant and strong positive correlation with total radiation dose, whereas it showed a significant strong negative correlation with number of fractions. **CONCLUSIONS:** The use of repeated 18F-FDG PET to assess survival early during stereotactic radiotherapy is possible in patients with early-stage non-small cell lung cancer. A decrease in GTV and pretreatment SUVmean according to F-18 FDG PET/CT uptake by the primary tumor correlates with survival.

[Lack of an association between marital status and survival in patients receiving stereotactic bodyradiotherapy for early-stage non-small-cell lung cancer](#) PLoS One. 2022 Jun 3;17(6):e0269463.

Noriko Kishi 1 , Yukinori Matsuo 1 , Hideki Hanazawa 1 , Yusuke Iizuka 1 , Takashi Mizowaki 11 Department of Radiation Oncology and Image-Applied Therapy, Graduate School of Medicine, Kyoto University, Kyoto, Japan.

Marital status has been proposed as a promising prognostic factor in many malignancies, including non-small-cell lung cancer (NSCLC). However, its prognostic value is still unclear for individual non-surgical treatments for stage I NSCLC. This study investigated the prognostic value of marital status in patients with early-stage NSCLC treated with stereotactic body radiotherapy (SBRT). Patients with early-stage NSCLC treated with SBRT between January 2003 and March 2014 at our institute were enrolled, and marital status at the time of SBRT was investigated. Propensity score matching (PSM) was applied to reduce potential selection bias between the married and unmarried groups. Two hundred and forty patients (median age 77 years; 152 married, 87 unmarried) were analyzed. The unmarried included higher proportions of the elderly, women, never smokers, and those with decreased pulmonary function compared to the married. PSM identified 53 matched pairs of married and unmarried patients, with no significant difference in patient background parameters. The 5-year overall survival (OS) was 52.8% and 46.9% in the married and unmarried groups, respectively (P = 0.26). There was no significant difference in NSCLC death or non-NSCLC death between the two groups (P = 0.88 and 0.30, respectively). There was no significant difference in OS between married and unmarried male patients (n = 85, 5-year OS, 52.6% vs. 46.0%; P = 0.42) and between married and unmarried female patients (n = 21, 54.5% vs. 50.0%; P = 0.44). In conclusion, marital status was not associated with OS in patients receiving SBRT for early-stage NSCLC.

[Stereotactic Body Radiotherapy for Stage I Lung Cancer With a New Real-time Tumor Tracking System](#)
 Yuichi Hiroshima 1 2 3 , Yoshio Tamaki 4 5 , Takuya Sawada 4 2 , Toshiki Ishida 4 , Kenji Yasue 4 6 , Kazuya Shinoda 4 , Takashi Saito 2 , Takayuki Kaburagi 7 , Moriyuki Kiyoshima 8 , Toshiyuki Okumura 2 , Hideyuki Sakurai 2

BACKGROUND/AIM: Suppression of respiratory movement is crucial for safe and effective stereotactic body radiotherapy (SBRT). SyncTraX FX4 is a novel device for synchronous respiratory irradiation. The purpose of this study was to evaluate the efficacy and toxicity of SBRT using SyncTraX FX4 for patients with lung cancer. Patients and **METHODS:** Patients treated with SBRT using SyncTraX FX4 between November 2017 and August 2020 were included. In all cases, fiducial markers were inserted into the lung, and the total dose administered was 55 or 60 Gy, depending on the distance from the central region of the lung. Acute and late toxicities were reported, and local control, progression-free survival, cancer-specific survival, and overall survival were analyzed. **RESULTS:** We evaluated 16 patients and 17 sites. The median follow-up period was 14.4 months. In both the acute and late phases, one patient experienced grade 3 radiation pneumonitis; however, grade 4 or higher toxicities were not observed. There was no local recurrence during the observation period, and the overall survival, cancer-specific survival, and progression-free survival at 2 years were 54.6%, 85.1%, and 33.7%, respectively. **CONCLUSION:** SBRT with SyncTraX FX4 can provide safe and effective treatment for lung cancer patients in poor condition.

[Toward Improved Outcomes for Patients With Lung Cancer Globally: The Essential Role of Radiology and Nuclear Medicine](#)
 Miriam N Mikhail Lette 1 , Diana Paez 1 , Lawrence N Shulman 2 , et al.

PURPOSE: Key to achieving better population-based outcomes for patients with lung cancer is the improvement of medical imaging and nuclear medicine infrastructure globally. This paper aims to outline why and spark relevant health systems strengthening. **METHODS:** The paper synthesizes the global lung cancer landscape, imaging referral guidelines (including resource-stratified ones), the reliance of TNM

staging upon imaging, relevant multinational health technology assessments, and precisely how treatment selection and in turn patient outcomes hinge upon imaging findings. The final discussion presents data on current global gaps in both diagnostics (including imaging) and therapies and how, informed by such data, improved population-based outcomes are tangible through strategic planning. **RESULTS:** Imaging findings are central to appropriate lung cancer patient management and can variably lead to life-prolonging interventions and/or to life-enhancing palliative measures. Early-stage lung cancer can be treated with curative intent but, unfortunately, most patients with lung cancer still present at advanced stages and many patients lack access to both diagnostics and therapies. Furthermore, half of lung cancer cases occur in low- and middle-income countries. The role of medical imaging and nuclear medicine in lung cancer management, as outlined herein, may help inform strategic planning. **CONCLUSION:** Lung cancer is the number one cancer killer worldwide. The essential role that medical imaging and nuclear medicine play in early diagnosis and disease staging cannot be overstated, pivotal in selecting the many patients for whom measurably improved outcomes are attainable. Prevention synergized with patient-centered, compassionate, high-quality lung cancer management provision mandate that strategic population-based planning, including universal health coverage strategies, should extend well beyond the scope of disease prevention to include both curative and noncurative treatment options for the millions afflicted with lung cancer.

SMALL CELL LUNG CANCER - SCLC

[Signal pathways and precision therapy of small-cell lung cancer](#) Signal Transduct Target Ther. 2022 Jun 15;7(1):187. doi: 10.1038/s41392-022-01013-y. Min Yuan # 1 , Yu Zhao # 1 , Hendrik-Tobias Arkenau 2 , Tongnei Lao 3 , Li Chu 4 5 , Qing Xu 6
Small-cell lung cancer (SCLC) encounters up 15% of all lung cancers, and is characterized by a high rate of proliferation, a tendency for early metastasis and generally poor prognosis. Most of the patients present with distant metastatic disease at the time of clinical diagnosis, and only one-third are eligible for potentially curative treatment. Recently, investigations into the genomic make-up of SCLC show extensive chromosomal rearrangements, high mutational burden and loss-of-function mutations of several tumor suppressor genes. Although the clinical development of new treatments for SCLC has been limited in recent years, a better understanding of oncogenic driver alterations has found potential novel targets that might be suitable for therapeutic approaches. Currently, there are six types of potential treatable signaling pathways in SCLC, including signaling pathways targeting the cell cycle and DNA repair, tumor development, cell metabolism, epigenetic regulation, tumor immunity and angiogenesis. At this point, however, there is still a lack of understanding of their role in SCLC tumor biology and the promotion of cancer growth. Importantly optimizing drug targets, improving drug pharmacology, and identifying potential biomarkers are the main focus and further efforts are required to recognize patients who benefit most from novel therapies in development. **This review will focus on** the current learning on the signaling pathways, the status of immunotherapy, and targeted therapy in SCLC.

[A study of microwave ablation for small cell lung cancer](#) J Cancer Res Ther. 2022 Apr;18(2):399-404. doi: 10.4103/jcrt.jcrt_1965_21. Jiao Wang 1 , Likuan Hu 2 , Xia Yang 3 , Xin Ye 4 , Yang Ni 5 , Min Meng 3 , Guanghui Huang 3 , Tiehong Zhang 3 , Wenhong Li 3 , Xiaoying Han 3 , Zhigang Wei 4 , Jianjian Dai 3 , Zhigeng Zou 3
PURPOSE: To reveal the survival and safety of percutaneous microwave ablation (MWA) combined with chemoradiotherapy (CRT) in treating small cell lung cancer (SCLC). Materials and **METHODS:** Clinical data of 48 SCLC patients who underwent MWA were retrospectively collected; survival and incidence of major complications were analyzed. **RESULTS:** Totally, 48 SCLC patients underwent 51 MWA procedures. The median overall survival (OS) for all SCLC was 27.0 months (95% confidence

interval 22.4-31.6 months). The OS of limited-stage (LS-SCLC) was longer than the extensive-stage (ES-SCLC) (median 48.0 months vs. 25.0 months, P = 0.022). The OS of SCLC with tumor diameter ≤3.0 cm was longer than that of tumor diameter >3.0 cm (median 48.0 months vs. 27.0 months, P = 0.041). For LS-SCLC, the 1-, 2-, 3-, and 5-year survival rate was 91.67%, 72.22%, 66.67%, and 61.11%, respectively. For ES-SCLC, the 1-, 2-, and 3-year survival rates were 83.33%, 50.0%, and 8.33%. Major complications included pneumothorax needing tube placement (29.4%), rarely arrhythmia (2.0%), empyema (2.0%), pulmonary fungal infection (2.0%), and shingles (2.0%). **CONCLUSION:** For SCLC patients, who received MWA combined with CRT, OS of LS-SCLC and tumor diameter ≤3.0 cm was better than that of the ES-SCLC and tumor diameter >3.0 cm. For inoperable SCLC, MWA was safe.

[**THSD7B Mutation Induces Platinum Resistance in Small Cell Lung Cancer Patients**](#) Drug Des Devel Ther. 2022 Jun 3;16:1679-1695. doi: 10.2147/DDDT.S363665. eCollection 2022. Zifu Yao # 1 2 , Anqi Lin # 1 , Yonglin Yi # 1 , Weitao Shen 1 , Jian Zhang 1 , Peng Luo 1
AIM: Several cases of small cell lung cancer (SCLC) patients demonstrate resistance to the treatment initiatives such as cisplatin after platinum chemotherapy. It is crucial to the improvement of the overall survival (OS) of SCLC patients to discover the gene mutation inducing platinum resistance within this cohort. Patients and **METHODS:** We analyzed the gene mutations significantly associated with the OS from 2 cohorts of SCLC platinum-treated patients. And then we screened out THSD7B mutation. In order to understand the mechanism between THSD7B mutation and platinum resistance, we designed gene mutation co-occurrence and mutual exclusivity analysis, gene set enrichment analysis (GSEA) and gene set variation analysis (GSVA) analysis, and Connectivity Map (CMap) analysis. **RESULTS:** The poor prognosis of THSD7B mutant patients may be related to the inhibition of cell death-related pathways, the up-regulation of cell invasion and metastasis pathways, and the down-regulation of immune response pathways. Lovastatin and cyclooxygenase inhibitors could be used as potential target compounds in THSD7B mutant patients, which provides reference for future research on platinum resistance. **CONCLUSION:** THSD7B can be considered a reliable biomarker that effectively facilitates the prediction of poor survival in SCLC platinum-treated patients.

PALLIATIVE AND SUPPORTIVE CARE

[**Correlation between depression and intimacy in lung cancer patients and their family caregivers**](#)
BMC Palliat Care. 2022 Jun 3;21(1):99. doi: 10.1186/s12904-022-00992-7. Chuanzhen Li # 1 , Juan Yuan # 1 , Xiaoxiao Huang # 1 , Siwen Zhang 1 , Yutong Hong 2 , Jiudi Zhong 3
BACKGROUND: Cancer impacts both patients and their family caregivers. This study aimed to explore the interdependence between depression and intimacy in lung cancer patients and their family caregivers, providing the basis for developing a patient-caregiver centered dyadic intervention. **METHODS:** This cross-sectional study recruited 182 dyads of lung cancer patients and their family caregivers using a convenient sampling. The depression subscale of the Hospital Anxiety and Depression Scale (HADS) and the Mutuality Scale (MS) were used to measure participants' depression and intimacy respectively; and the correlation between depression and intimacy in patients and caregivers was analyzed by establishing the actor-partner interdependence model. **RESULTS:** Thirty four percent of the patients and 19.2% of the caregivers were at risk of depression, with an intimacy score of 2.67 ± 0.74 points and 2.6 ± 0.86 points, respectively; Pearson correlation analysis showed that there was a positive correlation between the depression score (r = 0.226, P < 0.01) and intimacy score (r = 0.344, P < 0.01) in patients and caregivers; and the results of actor-partner interdependence model showed that caregivers' depression had an actor effect on their own intimacy (b = -0.054, P = 0.004) as well as a partner effect on patients' intimacy (b = -0.041, P = 0.011). However, patients' depression has no influence on the intimacy of patients or caregivers. **CONCLUSIONS:** There is an interdependent relationship between depression and intimacy

in lung cancer patients and family caregivers. Therefore, dyadic interventions can help them to cope with cancer together.

[**Patient navigation to address sociolegal barriers for patients with cancer: A comparative-effectiveness study**](#) Cancer. 2022 Jul 1;128 Suppl 13:2623-2635. doi: 10.1002/cncr.33965. Tracy A Battaglia 1 , Christine M Gunn 1   2 , Sharon M Bak 1 , JoHanna Flacks 3 , Kerrie P Nelson 4 , Na Wang 5 , Naomi Y Ko 6 , Samantha J Morton 3

BACKGROUND: Sociolegal barriers to cancer care are defined as health-related social needs like affordable healthy housing, stable utility service, and food security that may be remedied by public policy, law, regulation, or programming. Legal support has not been studied in cancer care. **METHODS:** The authors conducted a randomized controlled trial of patients who had newly diagnosed cancer at a safety-net medical center in Boston from 2014 through 2017, comparing standard patient navigation versus enhanced navigation partnered with legal advocates to identify and address sociolegal barriers. English-speaking, Spanish-speaking, or Haitian Creole-speaking patients with breast and lung cancer were eligible within 30 days of diagnosis. The primary outcome was timely treatment within 90 days of diagnosis. Secondary outcomes included patient-reported outcomes (distress, cancer-related needs, and satisfaction with navigation) at baseline and at 6 months. **RESULTS:** In total, 201 patients with breast cancer and 19 with lung cancer enrolled (response rate, 78%). The mean patient age was 55 years, 51% of patients were Black and 22% were Hispanic, 20% spoke Spanish and 8% spoke Haitian Creole, 73% had public health insurance, 77% reported 1 or more perceived sociolegal barrier, and the most common were barriers to housing and employment. Ninety-six percent of participants with breast cancer and 73% of those with lung cancer initiated treatment within 90 days. No significant effect of enhanced navigation was observed on the receipt of timely treatment among participants with breast cancer (odds ratio, 0.88; 95% CI, 0.17-4.52) or among those with lung cancer (odds ratio, 4.00; 95% CI, 0.35-45.4). No differences in patient-reported outcomes were observed between treatment groups. **CONCLUSIONS:** Navigation enhanced by access to legal consultation and support had no impact on timely treatment, patient distress, or patient needs. Although most patients reported sociolegal barriers, few required intensive legal services that could not be addressed by navigators. **LAY SUMMARY:** In patients with cancer, the experience of sociolegal barriers to care, such as unstable housing, utility services, or food insecurity, is discussed. Addressing these barriers through legal information and assistance may improve care. This study compares standard patient navigation versus enhanced navigation partnered with legal advocates for patients with breast and lung cancers. Almost all patients in both navigation groups received timely care and also reported the same levels of distress, needs, and satisfaction with navigation. Although 75% of patients in the study had at least 1 sociolegal barrier identified, few required legal advocacy beyond what a navigator who received legal information and coaching could provide.

COMPLEMENTARY & ALTERNATIVE THERAPY

[**Apoptotic and Antiproliferative Potential of GAPDH from Mallotus philippensis Seed on Human Lung Carcinoma: In Vitro and In Vivo Approach**](#) Protein Pept Lett. 2022;29(4):340-349. doi: 10.2174/0929866529666220302104935. Periasamy Sakthidhasan 1 , Perumal Sathish Kumar 2 , Madepalli Byrappa Gowdu Viswanathan 1

AIMS: The anticancer potential of a purified seed protein from Mallotus philippensis is scientifically evaluated and reported here. **BACKGROUND:** Seeds of Mallotus philippensis are used to treat various diseases in the indigenous systems of medicine in India. **OBJECTIVES:** The present study deals with the isolation, purification, identification, and screening of protein of interest that exhibit maximum activity against lung cancer cells from the seed crude protein of Mallotus philippensis. **METHODS:** Size-exclusion with HPLC was used to purify crude protein (15 mg) from M. philippensis seeds. Protein of

interest was identified using the LC-MS/MS method and analyzed by in vitro (A549 cell lines) in vivo (B16-F10 cells from melanoma cancer-induced Wistar rats) to estimate anticancer activity. **RESULTS:** SDS-PAGE was applied to isolate and purify elution III (480 μg/ml). Elution III LCMS/ MS data were used to search the UniProt database and were eventually matched with glyceraldehyde 3-phosphate dehydrogenase (GAPDH). MTT assay of GAPDH-treated A549 cells exhibited an IC50 of 3.03 ± 0.39 μg (24 h) and 1.93 ± 0.19 μg (48 h). AO/EtBr staining showed early and late apoptotic characteristics such as cell membrane blebbing, chromatin condensation, and the formation of apoptotic bodies. Hoechst staining confirmed the death of cells by exhibiting bright blue fluorescent, condensed, and fragmented nuclei. GAPDH-treated rats by 10 and 20 mg/kg bw significantly increased body weight by 29.50 ± 3.06 and 31.33 ± 2.69, respectively, and decreased melanoma metastasis in the lungs by 66.79% and 86.57%, respectively. Further, GAPDH treatment significantly increased the levels of SOD, CAT, and GPx and reduced GST and GSH. Histopathological analysis confirmed nuclear alteration in the lung tissue of the treated groups only. **CONCLUSION:** Apoptotic potential of GAPDH against lung carcinoma has been confirmed in the present investigation.

MISCELLANEOUS WORKS

Charting a Path Towards Asian American Cancer Health Equity: A Way Forward J Natl Cancer Inst. 2022 Jun 13;114(6):792-799. doi: 10.1093/jnci/djac055. Moon S Chen 1 , Richard J Lee 2 , Ravi A Madan 3 , Van Ta Park 4 , Susan M Shinagawa 5 , Tracy Sun 6 , Scarlett L Gomez 7
On July 29, 2021, the US Food and Drug Administration's Oncology Center of Excellence convened Conversations on Cancer. This Conversation, the first ever by the US Food and Drug Administration, focused on Asian Americans and served as the platform for this Commentary. Panelists elaborated on topics ranging from heterogeneity in Asian American demographics to racism through a path to health equity and supplemented this Commentary with literature citations. Asian Americans are the fastest-growing US race group, yet data aggregation obscures distinctions and cancer disparities within the more than 24 million Asians living in the United States with harmful impacts on communities and patients, as illustrated by breast cancer survivor Susan Shinagawa's patient-to-advocate journey. Bigotry against Asian Americans has been pervasive since the 19th century, but especially during the COVID-19 pandemic. Asian Americans are unique as the first US population to experience cancer as the leading cause of death. Asian Americans are disproportionately affected by cancers because of infectious origins and have the highest rates of lung cancer among never-smoking women. The infinitesimal proportion of the National Institutes of Health's budget compared with experiencing the highest percentage increases of any US racial population more than 3 decades highlights the dearth of focused research among Asian Americans. Recognizing the heterogeneity of Asian Americans and that disaggregated data are critical for accurately characterizing distinct ethnic groups, focusing on the impact of racism and COVID-19 on cancer disparities, and focusing and prioritizing funding resources are necessary steps forward for achieving health equity for Asian Americans.

Results of the George Washington University cancer center's comprehensive cancer control cancer communication mentorship program and implications for future practice Cancer Causes Control. 2022 Jul;33(7):995-1003. doi: 10.1007/s10552-022-01586-7. Epub 2022 May 17. Dao Duong 1 , Danielle Agraviador 2 , Charlene Cariou 3 , et al.
PURPOSE: The Comprehensive Cancer Control Cancer Communication Mentorship Program ("Mentorship Program") was created by the George Washington University Cancer Center (GWCC) to provide technical assistance (TA) in implementing evidence-based cancer screening communication interventions and support networking for comprehensive cancer control (CCC) professionals. The Mentorship Program matched entry-to mid-level CCC professionals with health communication and/or

CCC experts and offered monthly web-based discussions with academic researchers and practitioners who shared their knowledge and provided applied learning opportunities throughout mentees' project planning, implementation and evaluation. The program objective was for mentees to improve health communication skills and apply evidence-based knowledge to reduce the burden of cancer. **METHODS:** A mixed methods evaluation was conducted, including a qualitative description of each project and its outcomes as well as quantitative measures of satisfaction with the program and self-rated changes in competence. **RESULTS:** Mentees represented the following locations: New Jersey, Arkansas, Michigan, West Virginia, and Republic of Palau. Project topics ranged from increasing Human papillomavirus (HPV) vaccinations to increasing screening uptake for colorectal cancer, lung cancer, cervical cancer, and breast cancer. Evaluation results from pre- and post-program communication competency self-assessments and mid- and post-program surveys revealed that the Mentorship Program advanced personal and professional goals and improved public health communication skills. **CONCLUSION:** The Mentorship Program achieved its objectives for peer networking and offering expert TA in cancer prevention and control communication, offering a promising model for others involved in supporting implementation of evidence in practice.

[Lung Cancer in Young Adults: A Single-Center Experience](#) South Med J. 2022 Jun;115(6):366-370. doi: 10.14423/SMJ.0000000000001404. Stuart Jones 1 , Timothy Mullett 1 , Daniel Davenport 1 , Sibu Saha 1

OBJECTIVE: This single-center retrospective review examines the unique characteristics of young patients (ages 18 to 40 years) who were diagnosed as having non-small-cell lung cancer (NSCLC) at Markey Cancer Center, the only National Cancer Institute-designated cancer center in the state of Kentucky. **METHODS:** This retrospective study examines adult patients with NSCLC who were between ages 18 and 40 at diagnosis. Patients diagnosed between 2012 and 2018 were included. The final cohort consisted of 35 patients. The data collected included patient demographic information, tumor topography, clinical stage, cell type, treatment information/dates, metastasis, and survival data. **RESULTS:** In total, 36 of 3246 total NSCLC cases treated at Markey Cancer Center from 2012 to 2018 were diagnosed in adults aged 18 to 40 (1.11%); 35 of these 36 patients were included in our cohort. The majority (22; 62.86%) presented at an advanced stage of disease (stage III or IV). Furthermore, our cohort consisted of a strong majority of female patients (24; 68.57%). The most common histological type was adenocarcinoma (14; 40.00%). The 5-year survival rate was 47% (standard error 9%). **CONCLUSIONS:** Lung cancer is rare in young patients; when present, often it presents at the advanced stage. Despite many diagnostic tools and treatment modalities available, long-term survival remains poor. Our experience showed a small proportion of patients with NSCLC aged 18 to 40 at diagnosis; among this unique patient population, there is a predominance of smokers, women, adenocarcinoma, and advanced disease.