



Caring Ambassadors Lung Cancer Program

Literature Review, August 2020

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BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

[Detection of miR-155-5p and imaging lung cancer for early diagnosis: in vitro and in vivo study](#)

J Cancer Res Clin Oncol. 2020 Aug;146(8):1941-1951. doi: 10.1007/s00432-020-03246-2. Epub 2020 May 23. Hai-Zhen Zhu 1, Chun-Ju Fang 1, Yi Guo 2, Qi Zhang 1, Li-Min Huang 1, Dong Qiu 1, Guang-Peng Chen 3, Xiu-Feng Pang 4, Jian-Jun Hu 5, Jian-Guo Sun 6, Zheng-Tang Chen 7

PURPOSE: Currently, the routine screening program has insufficient capacity for the early diagnosis of lung cancer. Therefore, a type of chitosan-molecular beacon (CS-MB) probe was developed to recognize the miR-155-5p and image the lung cancer cells for the early diagnosis. **METHODS:** Based on the molecular beacon (MB) technology and nanotechnology, the CS-MB probe was synthesized self-assembly. There are four types of cells-three kinds of animal models and one type of histopathological sections of human lung cancer were utilized as models, including A549, SPC-A1, H446 lung cancer cells, tumor-initiating cells (TICs), subcutaneous and lung xenografts mice, and lox-stop-lox(LSL) K-ras G12D transgenic mice. The transgenic mice dynamically displayed the process from normal lung tissues to atypical hyperplasia, adenoma, carcinoma in situ, and adenocarcinoma. The different miR-155-5p expression levels in these cells and models were measured by quantitative real-time polymerase chain reaction (qRT-PCR). The CS-MB probe was used to recognize the miR-155-5p and image the lung cancer cells by confocal microscopy in vitro and by living imaging system in vivo. **RESULTS:** The CS-MB probe could be used to recognize the miR-155-5p and image the lung cancer cells significantly in these cells and models. The fluorescence intensity trends detected by the CS-MB probe were similar to the expression levels trends of miR-155 tested by qRT-PCR. Moreover, the fluorescence intensity showed an increasing trend with the tumor progression in the transgenic mice model, and the occurrence and development of lung cancer were dynamically monitored by the different fluorescence intensity. In addition, the miR-155-5p in human lung cancer tissues could be detected by the miR-155-5p MB. **CONCLUSION:** Both in vivo and in vitro experiments demonstrated that the CS-MB probe could be utilized to recognize the miR-155-5p and image the lung cancer cells. It provided a novel experimental and theoretical basis for the early diagnosis of the disease. Also, the histopathological sections of human lung cancer research laid the foundation for subsequent preclinical studies. In addition, different MBs could be designed to detect other miRNAs for the early diagnosis of other tumors.

[The oncogenic potential of a mutant TP53 gene explored in two spontaneous lung cancer mice models](#) BMC Cancer. 2020 Aug 8;20(1):738. doi: 10.1186/s12885-020-07212-6. Julian Ramelow 1 2

3 , Christopher D Brooks 4 , Li Gao 1 , Abeer A Almiman 1 , Terence M Williams 4 , Miguel A Villalona-Calero 5 , Wenrui Duan 6 7 8

BACKGROUND: Lung cancer is the number one cancer killer worldwide. A major drawback in the lung cancer treatment field is the lack of realistic mouse models that replicate the complexity of human malignancy and immune contexture within the tumor microenvironment. Such models are urgently needed. Mutations of the tumor protein p53 are among the most common alterations in human lung cancers. **METHODS:** Previously, we developed a line of lung cancer mouse model where mutant human TP53-273H is expressed in a lung specific manner in FVB/N background. To investigate whether the human TP53 mutant has a similar oncogenic potential when it is expressed in another strain of mouse, we crossed the FVB/N-SPC-TP53-273H mice to A/J strain and created A/J-SPC-TP53-273H transgenic mice. We then compared lung tumor formation between A/J-SPC-TP53-273H and FVB/N-SPC-TP53-273H. **RESULTS:** We found the TP53-273H mutant gene has a similar oncogenic potential in lung tumor formation in both mice strains, although A/J strain mice have been found to be a highly susceptible strain in terms of carcinogen-induced lung cancer. Both transgenic lines survived more than 18 months and developed age related lung adenocarcinomas. With micro CT imaging, we found the FVB-SPC-TP53-273H mice survived more than 8 weeks after initial detection of lung cancer, providing a sufficient window for evaluating new anti-cancer agents. **CONCLUSIONS:** Oncogenic potential of the most common genetic mutation, TP53-273H, in human lung cancer is unique when it is expressed in different strains of mice. Our mouse models are useful tools for testing novel immune checkpoint inhibitors or other therapeutic strategies in the treatment of lung cancer.

[Cells of origin of lung cancers: lessons from mouse studies](#) Genes Dev. 2020 Aug 1;34(15-16):1017-1032. doi: 10.1101/gad.338228.120. Giustina Ferone 1 , Myung Chang Lee 2 3 , Julien Sage 2 3 , Anton Berns 1

As one of the most common forms of cancer, lung cancers present as a collection of different histological subtypes. These subtypes are characterized by distinct sets of driver mutations and phenotypic appearance, and they often show varying degrees of heterogeneity, aggressiveness, and response/resistance to therapy. Intriguingly, lung cancers are also capable of showing features of multiple subtypes or converting from one subtype to another. The intertumoral and intratumoral heterogeneity of lung cancers as well as incidences of subtype transdifferentiation raise the question of to what extent the tumor characteristics are dictated by the cell of origin rather than the acquired driver lesions. We provide here an overview of the studies in experimental mouse models that try to address this question. These studies convincingly show that both the cell of origin and the genetic driver lesions play a critical role in shaping the phenotypes of lung tumors. However, they also illustrate that there is far from a direct one-to-one relationship between the cell of origin and the cancer subtype, as most epithelial cells can be reprogrammed toward diverse lung cancer fates when exposed to the appropriate set of driver mutations.

[The association between gut butyrate-producing bacteria and non-small-cell lung cancer](#) J Clin Lab Anal. 2020 Aug;34(8):e23318. doi: 10.1002/jcla.23318. Epub 2020 Mar 29.

Qifeng Gui 1 , Hanyu Li 1 , Ange Wang 1 , Xinxiu Zhao 1 , Zhongju Tan 1 , Lufang Chen 1 , Keying Xu 1 , Chi Xiao 2

BACKGROUND: Recently, it has been found that the gut microbiota may affect the development of lung cancer through the "gut-lung axis." To investigate this relationship, we performed this study to determine whether the gut microbiota in non-small-cell lung cancer (NSCLC) patients is different from that in healthy adults. **METHODS:** Quantitative PCR (qPCR) was used to detect the expression levels of eight gut butyrate-producing bacteria in healthy adults and NSCLC patients. We enrolled 30 patients with

NSCLC and 30 subjects from 100 healthy adults after matching for age and sex. **RESULTS:** Compared to healthy adults, most of the gut butyrate-producing bacteria in NSCLC patients were significantly decreased; these included *Faecalibacterium prausnitzii*, *Clostridium leptum*, Clostridial cluster I, *Ruminococcus* spp., Clostridial Cluster XIVa, and *Roseburia* spp. Among the gut butyrate-producing bacteria, we analyzed Clostridial cluster IV and *Eubacterium rectale* were not decreased in NSCLC patients. **CONCLUSIONS:** We conclude that NSCLC patients had gut butyrate-producing bacteria dysbiosis. Further studies should be performed to investigate the underlying mechanisms of how these specific bacteria affect lung cancer progression and prognosis.

[Florescence Imaging Lung Cancer with a Small Molecule MHI-148](#) J Fluoresc. 2020 Aug 11. doi: 10.1007/s10895-020-02605-z. Online ahead of print. Xiaotian Xia 1 2 , Yongkang Gai 1 2 , Hongyan Feng 1 2 , Chunxia Qin 1 2 , Dongfeng Pan 3 , Yiling Song 1 2 , Yongxue Zhang 1 2 , Xiaoli Lan 4 5 MHI-148 is a type of heptamethine cyanine dye that can cross the cytoplasmic membrane of lung cancer cells. Here we tested the cytotoxic, in vivo imaging of MHI-148 in lung-cancer nude mice model. Ex vivo imaging was also been measured by testing the major tissue fluorescence intensity. And, the small molecular compound MHI-148 had low cytotoxicity which could be visualized at 1 h post-injection in tumor. From ex vivo fluorescence imaging, the tumor showed the highest uptake of MHI-148 among all the selected organs expect for the time point of 2 h. MHI-148 could be used for effective imaging in lung cancer tissue with good stability and specificity, which suggested that MHI-148 could be an effective tumor clinical imaging agent.

SCREENING, COMPREHENSIVE BIOMARKER TESTING, DIAGNOSIS AND STAGING

[Occurrence of Discussion about Lung Cancer Screening Between Patients and Healthcare Providers in the USA, 2017](#) J Cancer Educ. 2020 Aug;35(4):678-681. doi: 10.1007/s13187-019-01510-9. Samir Soneji 1 , JaeWon Yang 2 , Nichole T Tanner 3 4 , Gerard A Silvestri 3 Computed tomography lung cancer screening reduces lung cancer mortality. However, screening is underutilized. This study assesses the extent to which providers discuss lung cancer screening with their patients, as a lack of discussion and counseling may serve as a potential cause of low utilization rates. Data from 1667 adults aged 55-80 years sampled in the 2017 Health Information National Trends Survey was utilized. A weighted multivariable logistic regression model was fit with past-year discussion about lung cancer screening with a provider as the outcome. The adjusted odds of discussion were higher for current cigarette smokers compared to non-cigarette smokers (adjusted odds ratio = 3.91; 95% confidence interval [CI], 1.75 to 8.74). Despite higher odds, the absolute prevalence was low with only 18% (95% CI, 11.8 to 24.2%) of current adult smokers reporting a past-year discussion. Knowledge of screening from trusted sources of medical information, such as doctors, can increase screening rates and may ultimately reduce lung cancer mortality.

[Telephone-Based Shared Decision-making for Lung Cancer Screening in Primary Care](#) J Cancer Educ. 2020 Aug;35(4):766-773. doi: 10.1007/s13187-019-01528-z. Heather Bittner Fagan 1 , Nicole A Fournakis 2 3 , Claudine Jurkovitz 4 , Anett M Petrich 5 , Zugui Zhang 4 , Nora Katurakes 6 , Ronald E Myers 5

The national rate of lung cancer screening, approximately 3-5%, is too low and strategies which include shared decision-making and increase screening are needed. A feasibility study in one large primary care practice of telephone-based delivery of decision support via an online tool, the Decision Counseling Program© (DCP) was administered to patients eligible for lung cancer screening according to USPSTF screening guidelines. We collected data on demographics, decisional conflict, and conducted chart audits to ascertain screening. From electronic medical record data, we identified 829 age-eligible current or

former smokers. Of the 297 individuals reached, 54 were eligible and 28 were recruited to the study and 20 underwent the DCP© intervention. Participants in the intervention were more likely to complete low-dose CT scans at 90 days. Current smokers were less likely to complete the DCP. Women were less likely to complete LDCT. This non-persuasive, high-quality shared decision-making intervention significantly increased lung cancer screening and was feasible in real-world clinical care. This intervention offers a promising model whereby patients can be supported in a decision, based on their values and beliefs while also supporting gains in lung cancer screening.

[Risk Prediction Model versus United States Preventive Services Task Force Lung Cancer Screening Eligibility Criteria - Reducing Race Disparities](#) J Thorac Oncol. 2020 Aug 17;S1556-0864(20)30638-9. doi: 10.1016/j.jtho.2020.08.006. Online ahead of print.

Mary M Pasquinelli ¹, Martin C Tammemägi ², Kevin L Kovitz ³, et al.

INTRODUCTION: Disparities exist in lung cancer outcomes between African American and White people. The current United States Preventive Services Task Force (USPSTF) lung cancer screening eligibility criteria which is based solely on age and smoking history may exacerbate racial disparities. We evaluate whether the PLCOm2012 risk prediction model more effectively selects African American ever-smokers for screening. **METHODS:** Lung cancer cases diagnosed between 2010-2019 at an urban medical center serving a racially and ethnically diverse population were retrospectively reviewed for lung cancer screening eligibility based on the USPSTF criteria versus the PLCOm2012 model. **RESULTS:** This cohort of 883 ever-smokers was comprised of the following racial/ethnic makeup: 258 (29.2%) White, 497 (56.3%) African American, 69 (7.8%) Hispanic, 24 (2.7%) Asian, and 35 (4.0%) other. Compared to the USPSTF criteria the PLCOm2012 model increased the sensitivity for the African American cohort at lung cancer risk thresholds of 1.51%, 1.70%, and 2.00% per 6-years ($p < 0.0001$). For example, at the 1.70% risk threshold the PLCOm2012 model identified 71.3% African American cases whereas the USPSTF criteria only identified 50.3% ($p < 0.0001$). In contrast, in White cases there was no difference [66.0% vs 62.4%, respectively ($p = 0.203$)]. Of African American ever-smokers who were PLCO1.7%+/USPSTF-, the criteria missed from the USPSTF were pack-years < 30 (67.7%), quit-time > 15 years (22.5%), and age < 55 years (13.0%). **CONCLUSIONS:** The PLCOm2012 model was found to be preferable over the USPSTF criteria at identifying African American ever-smokers for lung cancer screening. Broader use of this model in racially diverse populations may help overcome disparities in lung cancer screening and outcomes.

[Low-Dose Computed Tomography: Effects of Oncology Nurse Navigation on Lung Cancer Screening](#) Clin J Oncol Nurs. 2020 Aug 1;24(4):421-429. doi: 10.1188/20.CJON.421-429. Joni Watson ¹, Marion E Broome ², Susan M Schneider ²

BACKGROUND: Low-dose computed tomography (LDCT) lung cancer screening is an evidence-based and reimbursable strategy to decrease lung cancer and all-cause mortality in qualifying patients, but there remains low use and variation in providers' LDCT screening, ordering, and referring knowledge.

OBJECTIVES: The purpose of this quality improvement project was to examine the effects of oncology nurse navigation on assisting patients and ensuring optimal LDCT lung cancer screening. **METHODS:** Oncology nurse navigators conducted LDCT provider education and navigated 133 eligible patients to LDCT during a five-month intervention time period. **FINDINGS:** Provider education resulted in improved documented tobacco cessation discussions and increased LDCT screening ordering fidelity. Mean days from LDCT to provider notification and mean days from LDCT to patient notification improved significantly.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

[**Airway inflammation and lung function recovery after lobectomy in patients with primary lung cancer**](#) Gen Thorac Cardiovasc Surg. 2020 Aug 28. doi: 10.1007/s11748-020-01464-6. Online ahead of print. Keigo Okamoto 1 , Kazuki Hayashi 2 , Ryosuke Kaku 2 , Yo Kawaguchi 2 , Yasuhiko Oshio 2 , Jun Hanaoka 2

OBJECTIVE: Fractional exhaled nitric oxide (FeNO), which represents airway inflammation, is an indicator of postoperative complication after lung surgery. However, its effects in the late postoperative period are unknown. The aim of this prospective study was to clarify the impact of FeNO on postoperative lung function in patients with lung cancer. **METHODS:** We measured preoperative FeNO using NIOX VERO® in patients with primary lung cancer. Patients were divided into two groups according to their potential airway inflammatory status: preoperative FeNO levels below 25 ppb (N group) and above 25 ppb (H group). They were evaluated by spirometry at 3 and 6 months after surgery during follow-up. The relationship between postoperative lung function and preoperative FeNO was evaluated. **RESULTS:** Between September 2017 and March 2019, 61 participants were enrolled. All of them underwent lobectomy as a curative surgery. There were no significant background variables between the two groups. Postoperative vital capacity (VC) and forced expiratory volume in 1 s (FEV1) in the H group achieved less predictive values than those in the N group, which were not significant. The postoperative VC and FEV1 from 3 to 6 months in the H group were significantly increased as compared to those in the N group ($p < 0.001$). **CONCLUSIONS:** Preoperative FeNO is a predictor of delayed lung function recovery 3 months after lobectomy in lung cancer patients. The impact had extended to VC and FEV1. Although this impact is temporary, early postoperative intervention is expected to reduce the adverse effect.

[**Analyzing the Time From Discovery to Definitive Surgical Therapy for Lung Cancer Based on Referral Patterns**](#) Am J Clin Oncol. 2020 Aug;43(8):582-585. doi: 10.1097/COC.0000000000000710. Michael A Napolitano 1 , Matthew D Skancke, Keith D Mortman

OBJECTIVE: Surgery for early stage non-small cell lung cancer can be curative. A delay from diagnosis to surgery can lead to increased mortality. Our objective was to determine if referring patients to specialists before a thoracic surgeon caused a delay in definitive treatment. **MATERIALS AND METHODS:** A retrospective review was conducted of patients who had surgery for non-small cell lung cancer by a single surgeon at our institution from 2013 to 2016. Patients were divided into 2 groups: those who saw a specialist before a thoracic surgeon and patients who were referred directly to a surgeon once the pulmonary nodule was identified on computed tomography (CT). The time from initial CT to resection was compared. Secondary analysis compared private insurance versus Medicare/Medicaid. Percentage of patients upstaged was compared. **RESULTS:** There was no significant difference between groups when comparing time from CT to surgery (79.88 vs. 79.90 d; $P=0.58$). There was a significant decrease in time from CT to surgery for patients with private insurance compared with Medicare/Medicaid patients (66.05 vs. 86.99 d; $P=0.03$) and fewer private insurance patients were upstaged (22.9% vs. 31.8%; $P=0.32$). More patients who saw a different specialist first were upstaged compared with patients sent directly to thoracic surgery (32.6% vs. 22.2%; $P=0.22$). **CONCLUSIONS:** When comparing time from CT detection of a lung nodule to surgery, no significant difference was found between patients sent to nonthoracic specialists first and those referred directly to a thoracic surgeon. There was a significant decrease in time from CT to surgery for patients with private insurance compared with Medicare/Medicaid.

[Minimizing the Risk of Aerosol Contamination During Elective Lung Resection Surgery](#) Ann Surg. 2020 Aug;272(2):e125-e128. doi: 10.1097/SLA.0000000000004087. George Rakovich 1 , Robert Urbanowicz 2 , Rami Issa 2 , Han Ting Wang 3

BACKGROUND: In the setting of the COVID-19 pandemic, the conduct of elective cancer surgery has become an issue because of the need to balance the requirement to treat patients with the possibility of transmission of the virus by asymptomatic carriers. A particular concern is the potential for viral transmission by way of aerosol which may be generated during perioperative care. There are currently no guidelines for the conduct of elective lung resection surgery in this context. **METHODS:** A working group composed of 1 thoracic surgeon, 2 anesthesiologists and 1 critical care specialist assessed the risk for aerosol during lung resection surgery and proposed steps for mitigation. After external review, a final draft was approved by the Committee for the Governance of Perioperative and Surgical Activities of the Hôpital Maisonneuve-Rosemont, in Montreal, Canada. **RESULTS:** The working group divided the risk for aerosol into 6 time-points: (1) intubation and extubation; (2) Lung isolation and patient positioning; (3) access to the chest; (4) conduct of the surgical procedure; (5) procedure termination and lung re-expansion; (6) chest drainage. Mitigating strategies were proposed for each time-point.

CONCLUSIONS: The situation with COVID-19 is an opportunity to re-evaluate operating room protocols both for the purposes of this pandemic and similar situations in the future. In the context of lung resection surgery, specific time points during the procedure seem to pose specific risks for the genesis of aerosol and thus should be the focus of attention.

[Clinical course of coronavirus disease 2019 in 11 patients after thoracic surgery and challenges in diagnosis](#) J Thorac Cardiovasc Surg. 2020 Aug;160(2):585-592.e2. doi: 10.1016/j.jtcvs.2020.04.005.

Epub 2020 Apr 10. Shu Peng 1 , Liu Huang 2 , Bo Zhao 1 , Shuchang Zhou 3 , Irene Braithwaite 4 , Ni Zhang 1 , Xiangning Fu 5

OBJECTIVES: To illustrate the clinical course and difficulties in early diagnosis of coronavirus disease 2019 (COVID-19) in patients after thoracic surgery. **METHODS:** We retrospectively analyzed the clinical course of the first 11 patients diagnosed with COVID-19 after thoracic surgery in early January 2020. Postoperative clinical, laboratory, and radiologic records and the timeline of clinical course were summarized. Potential prognostic factors were evaluated. **RESULTS:** In the 11 confirmed cases (3 female, 8 male), median days from symptom onset to case detection was 8. Insidious symptom onset and misinterpreted postoperative changes on chest computed tomography (CT) resulted in delay in diagnosis. There were 3 fatalities due to respiratory failure, whereas 4 severe and 4 mild cases recovered and were discharged. All patients had once experienced leukocytosis and eosinopenia. Remittent fever and resected lung segments ≥ 5 were associated with fatality. **CONCLUSIONS:** The case fatality rate of postsurgical patients subsequently diagnosed with COVID-19 was 27.3%. Insidious symptom onset, postoperative leukocytosis with lymphopenia, and postsurgical CT changes overshadowed the early signs of viral pneumonia. Dynamic symptom monitoring, serial chest CTs, and tests for viral RNA and serum antibody improve the chance for prompt detection of COVID-19. Consideration should be given to preadmission and preoperative screening and strict contact isolation during the postoperative period.

[Clinical Outcomes of Surgical Resection for Brain Metastases from Non-small Cell Lung Cancer](#)

Anticancer Res. 2020 Aug;40(8):4801-4804. doi: 10.21873/anticancer.14483. Takayuki Nakao 1 , Takeshi Okuda 2 , Hiromasa Yoshioka 1 , Mitsugu Fujita 1 3

BACKGROUND/AIM: Recent advances in systemic chemotherapy, including molecularly targeted therapy, have dramatically improved survival for patients with advanced non-small cell lung cancer. We retrospectively analyzed the clinical outcomes of surgical resection for brain metastases of non-small cell lung cancer cases performed at the Department of Neurosurgery of Kindai University Hospital, Osaka, Japan. **PATIENTS AND METHODS:** Craniotomy and tumor resection were performed for 56 patients

with brain metastases of non-small cell lung cancer. Adenocarcinoma was the most common histological type, appearing in 40 cases, of which 18 were positive for driver gene mutations. **RESULTS:** Median survival for all 56 patients was 14.5 months, and single brain metastasis and adenocarcinoma were identified as favorable prognostic factors. Analysis limited to the 40 cases of adenocarcinoma identified single brain metastasis as a favorable prognostic factor. Although no significant difference was found for systemic chemotherapy, patients who received molecularly targeted therapy showed a better prognosis than those who received cytotoxic chemotherapy. Analyses of both the entire group and of adenocarcinoma patients alone found that whole-brain radiotherapy showed no significant association with survival. **CONCLUSION:** Single brain metastasis and adenocarcinoma were identified as favorable prognostic factors, but did not confirm any benefit from whole-brain radiotherapy. These results suggest that multimodal treatment strategies utilizing various methods of treatment, including systemic chemotherapy, may help prolong patient survival in the future.

Outcomes of Anatomic Lung Resection for Cancer are Better When Performed by Cardiothoracic Surgeons Ann Thorac Surg. 2020 Aug 12;S0003-4975(20)31311-4. doi:

10.1016/j.athoracsur.2020.06.022. Online ahead of print. John D Vossler 1 , Ayman Abdul-Ghani 1 , Peter I Tsai 1 , Paul T Morris 2

BACKGROUND: Anatomic lung resection (ALR) outcomes are superior for cardiothoracic surgeons (CTS) by analysis of Medicare, National Inpatient Sample, South Carolina Office of Research and Statistics, and Surveillance, Epidemiology, and End Results databases. Similar findings have been reported for all non-cardiac thoracic procedures using the ACS-NSQIP database. Our aim was to further delineate outcome differences between CTS and general surgeons (GS) specifically for ALR.

METHODS: A retrospective analysis of 15,574 non-emergent, non-pediatric, ALR for lung cancer was conducted using the ACS-NSQIP 2013-2017 database. Included procedures were all ALR for lung cancer. Surgeons were classified as CTS or GS. Other specialties were excluded. Pre-operative characteristics and 30-day outcomes were compared by bivariate (χ^2) and multivariate analysis. Multivariate analysis was conducted by multiple logistic regression. **RESULTS:** CTS performed 14,172 (91.0%) of included procedures, and GS performed 1,402 (9.0%). Thoracoscopic approach was utilized at a similar rate (49.08% CTS vs. 49.71% GS, $p=0.7474$). The extent of resection differed in a statistically, but not clinically, significant fashion. CTS patients had a higher rate of pre-operative dyspnea (22.66% CTS vs. 17.62% GS, $p=0.0001$). Procedures performed by CTS had a lower risk-adjusted odd ratio of overall morbidity, pulmonary morbidity, sepsis/septic shock, bleeding requiring transfusion, and length of stay (LOS) >median (5 days). **CONCLUSIONS:** ALR outcomes are superior for CTS when compared to GS. This is consistent with prior studies looking at this specific subset of patients and studies looking at a different subset of patients using the ACS-NSQIP database.

Striving toward Improved Outcomes for Surgically Resectable Non-Small Cell Lung Cancer: the Promise and Challenges of Neoadjuvant Immunotherapy Curr Oncol Rep. 2020 Aug 15;22(11):109. doi: 10.1007/s11912-020-00969-w. Ryan D Gentzler 1 , David O Riley 2 , Linda W Martin 3

doi: 10.1007/s11912-020-00969-w. Ryan D Gentzler 1 , David O Riley 2 , Linda W Martin 3

PURPOSE OF REVIEW: Immunotherapy has revolutionized the treatment of non-surgical stage III and stage IV non-small cell lung cancer (NSCLC). Here, we review emerging data on the safety, feasibility, and efficacy of neoadjuvant immunotherapy in the setting of earlier stage surgically resectable lung cancer. **RECENT FINDINGS:** Several small studies support the safety and feasibility of neoadjuvant immunotherapy, noting similar perioperative rates of morbidity and mortality compared with historical controls. Data from several phase II trials have shown high rates of major pathologic response (MPR), though it is unclear if this will correlate with a survival benefit. Phase III trials of neoadjuvant immunotherapy alone or in combination with chemotherapy are ongoing. Neoadjuvant immunotherapy

offers a promising treatment modality in earlier stage NSCLC patients. Results of ongoing phase II and phase III trials will be essential in determining how to best integrate this treatment modality in the future.

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

[Impact of PD-1 Blockade on Severity of COVID-19 in Patients with Lung Cancers](#) Cancer Discov. 2020 Aug;10(8):1121-1128. doi: 10.1158/2159-8290.CD-20-0596. Epub 2020 May 12. Jia Luo ¹, Hira Rizvi ¹, Jacklynn V Egger ¹, Isabel R Preeshagul ¹, Jedd D Wolchok ^{2 3 4}, Matthew D Hellmann ^{5 2 4}

The coronavirus disease 2019 (COVID-19) pandemic has led to dramatic changes in oncology practice. It is currently unknown whether programmed death 1 (PD-1) blockade therapy affects severity of illness from COVID-19 in patients with cancer. To address this uncertainty, we examined consecutive patients with lung cancers who were diagnosed with COVID-19 and examined severity on the basis of no or prior receipt of PD-1 blockade. Overall, the severity of COVID-19 in patients with lung cancer was high, including need for hospitalization in more than half of patients and death in nearly a quarter. Prior PD-1 blockade was, as expected, associated with smoking status. After adjustment for smoking status, PD-1 blockade exposure was not associated with increased risk of severity of COVID-19. PD-1 blockade does not appear to affect the severity of COVID-19 in patients with lung cancers. **SIGNIFICANCE:** A key question in oncology practice amidst the COVID-19 pandemic is whether PD-1 blockade therapy affects COVID-19 severity. Our analysis of patients with lung cancers supports the safety of PD-1 blockade treatment to achieve optimal cancer outcomes.

[A Multivariable Regression Model-based Nomogram for Estimating the Overall Survival of Patients Previously Treated With Nivolumab for Advanced Non-small-cell Lung Cancer](#)

Anticancer Res. 2020 Aug;40(8):4229-4236. doi: 10.21873/anticancerres.14424. Akihiro Tamiya ¹, Motohiro Tamiya ², Hirofumi Go ³, et al.

AIM: Although nivolumab improves progression-free (PFS) and overall (OS) survival of patients previously treated for metastatic non-small-cell lung cancer (NSCLC), approximately 50% of treated patients experience disease progression within 3 months. As predictive biomarkers of response are not yet established, development of biomarkers to predict longer PFS and OS of patients treated with nivolumab is crucial. Therefore, we analyzed the impact of predictive markers of response to nivolumab and quantified the impact of each factor using nomograms. **PATIENTS AND METHODS:** Clinical data at nivolumab commencement were retrospectively collected from 201 patients treated with nivolumab between December 2015 and July 2016. Immunohistochemistry for programmed cell death ligand 1 (PD-L1) was performed using two assay systems (22C3 and 28-8). OS was calculated from nivolumab treatment initiation. Multivariate Cox regression analysis was conducted to identify independent predictors of OS. A nomogram was constructed to estimate OS. **RESULTS:** The median patient age was 68 years (135 males). Thirty-nine patients had driver mutations (epidermal growth factor receptor mutations and anaplastic lymphoma kinase rearrangement). In 22C3 and 28-8 immunostaining assays, 36.3% and 36.8% patients had PD-L1-negative cells, 17.4% and 14.4% had 1-49% PD-L1-positive cells, 11.9% and 14.9% had $\geq 50\%$ PD-L1-positive cells, and 34.3% and 33.8% had unknown PD-L1 status, respectively. Kendall's rank correlation coefficient between the staining assays was 0.8414. The median OS of the whole patient cohort was 12.27 months [95% confidence interval (CI)=10.87-15.6]. Performance status ≥ 2 [hazard ratio (HR)=2.15, 95% CI=1.35-3.42, p=0.001] and high baseline lactate dehydrogenase (HR=1.15, 95% CI=1.05-1.26, p=0.004) were independent predictors of shorter OS. There was no significant correlation between PD-L1 status and OS. We constructed a nomogram to estimate the OS of patients previously treated with nivolumab. **CONCLUSION:** The multivariate analysis-based

nomogram might be useful to estimate the OS of patients previously treated with nivolumab for advanced NSCLC.

Outcomes to first-line pembrolizumab in patients with PD-L1-high ($\geq 50\%$) non-small cell lung cancer and a poor performance status J Immunother Cancer. 2020 Aug;8(2):e001007. doi:

10.1136/jitc-2020-001007. Joao V Alessi 1 , Biagio Ricciuti 1 , Elizabeth Jiménez-Aguilar 2 , et al.

BACKGROUND: Patients with non-small cell lung cancer (NSCLC) and a poor Eastern Cooperative Oncology Group Performance Status (ECOG PS) have been excluded from phase III immunotherapy clinical trials. We sought to evaluate clinical outcomes to first-line pembrolizumab in patients with advanced NSCLC, a PD-L1 Tumor Proportion Score (TPS) of $\geq 50\%$, and an ECOG PS of 2.

METHODS: We performed a multicenter retrospective analysis of patients with metastatic NSCLC and a PD-L1 TPS of $\geq 50\%$ (negative for genomic alterations in EGFR and ALK) who received treatment with first-line pembrolizumab. Clinical outcomes were compared in patients based on ECOG PS.

RESULTS: Among the 234 patients, 83.3% (n=195) had an ECOG PS of 0 or 1, and 16.7% (n=39) had an ECOG PS of 2. The baseline clinicopathological characteristics were balanced between the ECOG PS 0-1 vs 2 groups in terms of age, sex, tobacco use, histology, KRAS mutation status, presence of other potentially targetable driver mutations (BRAF, MET, HER2, RET), presence of brain metastases, and PD-L1 TPS distribution. Compared with patients with an ECOG PS of 0 or 1, patients with an ECOG PS of 2 had a significantly lower objective response rate (43.1% vs 25.6%; p=0.04), a numerically shorter median progression-free survival (6.6 months vs 4.0 months; HR 0.70 (95% CI 0.47 to 1.06); p=0.09), and a significantly shorter median overall survival (20.3 months vs 7.4 months; HR 0.42 (95% CI 0.26 to 0.68); p<0.001). On disease progression, patients with an ECOG PS of 2 were significantly less likely to receive second-line systemic therapy compared with patients with an ECOG PS of 0-1 (65% vs 22.2%, p=0.001).

CONCLUSIONS: A subset of patients with NSCLC and an ECOG PS of 2 can respond to first-line pembrolizumab. However, clinical outcomes in this population are often poor and use of second-line systemic therapy is infrequent.

Ipilimumab plus nivolumab and chemoradiotherapy followed by surgery in patients with resectable and borderline resectable T3-4N0-1 non-small cell lung cancer: the INCREASE trial BMC Cancer.

2020 Aug 14;20(1):764. doi: 10.1186/s12885-020-07263-9. Chris Dickhoff 1 , Suresh Senan 2 , Famke L Schneiders 2 , et al.

BACKGROUND: The likelihood of a tumor recurrence in patients with T3-4N0-1 non-small cell lung cancer following multimodality treatment remains substantial, mainly due distant metastases. As pathological complete responses (pCR) in resected specimens are seen in only a minority (28-38%) of patients following chemoradiotherapy, we designed the INCREASE trial (EudraCT-Number: 2019-003454-83; Netherlands Trial Register number: NL8435) to assess if pCR rates could be further improved by adding short course immunotherapy to induction chemoradiotherapy. Translational studies will correlate changes in loco-regional and systemic immune status with patterns of recurrence.

METHODS/DESIGN: This single-arm, prospective phase II trial will enroll 29 patients with either resectable, or borderline resectable, T3-4N0-1 NSCLC. The protocol was approved by the institutional ethics committee. Study enrollment commenced in February 2020. On day 1 of guideline-recommended concurrent chemoradiotherapy (CRT), ipilimumab (IPI, 1 mg/kg IV) and nivolumab (NIVO, 360 mg flat dose IV) will be administered, followed by nivolumab (360 mg flat dose IV) after 3 weeks. Radiotherapy consists of once-daily doses of 2 Gy to a total of 50 Gy, and chemotherapy will consist of a platinum-doublet. An anatomical pulmonary resection is planned 6 weeks after the last day of radiotherapy. The primary study objective is to establish the safety of adding IPI/NIVO to pre-operative CRT, and its impact on pathological tumor response. Secondary objectives are to assess the impact of adding IPI/NIVO to CRT on disease free and overall survival. Exploratory objectives are to characterize tumor inflammation

and the immune contexture in the tumor and tumor-draining lymph nodes (TDLN), and to explore the effects of IPI/NIVO and CRT and surgery on distribution and phenotype of peripheral blood immune subsets. **DISCUSSION:** The INCREASE trial will evaluate the safety and local efficacy of a combination of 4 modalities in patients with resectable, T3-4N0-1 NSCLC. Translational research will investigate the mechanisms of action and drug related adverse events.

[Chemotherapy and COVID-19 Outcomes in Patients With Cancer](#) J Clin Oncol. 2020 Aug 14;JCO2001307. doi: 10.1200/JCO.20.01307. Online ahead of print. Justin Jee¹, Michael B Foote¹, Melissa Lumish¹, et al.

PURPOSE: Coronavirus-2019 (COVID-19) mortality is higher in patients with cancer than in the general population, yet the cancer-associated risk factors for COVID-19 adverse outcomes are not fully characterized. **PATIENTS AND METHODS:** We reviewed clinical characteristics and outcomes from patients with cancer and concurrent COVID-19 at Memorial Sloan Kettering Cancer Center until March 31, 2020 (n = 309), and observed clinical end points until April 13, 2020. We hypothesized that cytotoxic chemotherapy administered within 35 days of a COVID-19 diagnosis is associated with an increased hazard ratio (HR) of severe or critical COVID-19. In secondary analyses, we estimated associations between specific clinical and laboratory variables and the incidence of a severe or critical COVID-19 event. **RESULTS:** Cytotoxic chemotherapy administration was not significantly associated with a severe or critical COVID-19 event (HR, 1.10; 95% CI, 0.73 to 1.60). Hematologic malignancy was associated with increased COVID-19 severity (HR, 1.90; 95% CI, 1.30 to 2.80). Patients with lung cancer also demonstrated higher rates of severe or critical COVID-19 events (HR, 2.0; 95% CI, 1.20 to 3.30). Lymphopenia at COVID-19 diagnosis was associated with higher rates of severe or critical illness (HR, 2.10; 95% CI, 1.50 to 3.10). Patients with baseline neutropenia 14-90 days before COVID-19 diagnosis had worse outcomes (HR, 4.20; 95% CI, 1.70 to 11.00). Findings from these analyses remained consistent in a multivariable model and in multiple sensitivity analyses. The rate of adverse events was lower in a time-matched population of patients with cancer without COVID-19. **CONCLUSION:** Recent cytotoxic chemotherapy treatment was not associated with adverse COVID-19 outcomes. Patients with active hematologic or lung malignancies, peri-COVID-19 lymphopenia, or baseline neutropenia had worse COVID-19 outcomes. Interactions among antineoplastic therapy, cancer type, and COVID-19 are complex and warrant further investigation.

[Targeting PD-L1 in non-small cell lung cancer using CAR T cells](#) Oncogenesis. 2020 Aug 13;9(8):72. doi: 10.1038/s41389-020-00257-z. Ming Liu¹, Xu Wang², Wei Li², Xinfang Yu², et al.

Antibodies against programmed cell death protein 1 (PD-1) and its ligand (PD-L1) have dramatically changed the landscape of therapies for non-small cell lung carcinoma (NSCLC); however, the majority of patients do not respond to these agents. In addition, hyperprogressive disease (HPD) develops in a larger portion of NSCLC patients treated with PD-1/PD-L1 inhibitors than in patients treated with standard chemotherapy. The use of chimeric antigen receptor (CAR) T cells has been successful to treat blood cancers but not for solid tumors like NSCLC. In this work, we constructed CAR T cells that target PD-L1 and evaluated their efficacy in NSCLC with either high or low PD-L1 expression. PD-L1-CAR T cells exhibited antigen-specific activation, cytokine production, and cytotoxic activity against PD-L1^{high} NSCLC cells and xenograft tumors. Furthermore, the addition of a subtherapeutic dose of local radiotherapy improved the efficacy of PD-L1-CAR T cells against PD-L1^{low} NSCLC cells and tumors. Our findings indicate that PD-L1-CAR T cells represent a novel therapeutic strategy for patients with PD-L1-positive NSCLC, particularly for those who are susceptible to HPD.

Comparing incidences of infusion site reactions between brand-name and generic vinorelbine in patients with non-small cell lung cancer Br J Clin Pharmacol. 2020 Aug 13. doi: 10.1111/bcp.14516.

Online ahead of print. Naoya Ozawa 1 , Tetsunari Hase 1 , Takahiro Hatta 1 , et al.

AIM: This study aimed to compare the incidence of infusion site reactions (ISRs) induced by intravenous administration of brand-name and generic vinorelbine (VNR) for treating non-small cell lung cancer.

METHOD: This single-centre retrospective cohort study was conducted by medical chart review of VNR infusions. ISRs were defined as symptoms around the infusion site, including pain, redness, and swelling. ISRs requiring treatment were defined as ISRs requiring treatments including steroid ointments, vein re-puncture, and local steroid injections. **RESULTS:** In all, 1973 VNR infusions were administered to 340 patients (brand-name, 141 patients; generic, 199 patients). ISRs and ISRs requiring treatment were observed in 161 and 100 patients, respectively. The ISR incidence per patient and per injection were significantly higher in generic VNR-treated patients than in brand-name VNR-treated patients (53.3% vs. 39.0%, $P = 0.0112$, and 15.0% vs. 9.9%, $P = 0.0008$, respectively). The frequency of ISRs requiring treatment was also significantly higher in the generic group (per patient: 36.7% vs. 19.2%, $P = 0.0005$; per injection: 11.3% vs. 5.5%, $P < 0.0001$). Multivariate analysis revealed that generic VNR was significantly associated with an increased risk of ISRs (per patient: adjusted odds ratio [AOR] 1.775, $P = 0.0155$; per injection: AOR 1.672, $P = 0.004$) and ISRs requiring treatment (per patient: AOR 2.422, $P = 0.0012$; per injection: AOR 2.286, $P = 0.001$). **CONCLUSION:** Intravenous infusion of generic VNR was associated with an increased risk of ISRs. Further research is needed to elucidate the mechanism underlying the increased incidence of ISRs with generic VNR.

Efficacy and Safety of Sintilimab Plus Pemetrexed and Platinum as First-Line Treatment for Locally Advanced or Metastatic Nonsquamous NSCLC: a Randomized, Double-Blind, Phase 3 Study (Oncology pROgram by InnovENT anti-PD-1-11) J Thorac Oncol. 2020 Aug 8;S1556-0864(20)30595-5. doi: 10.1016/j.jtho.2020.07.014. Online ahead of print.

Yunpeng Yang 1 , Zhehai Wang 2 , Jian Fang 3 , et al.

INTRODUCTION: Sintilimab, an anti-programmed death 1 antibody, plus pemetrexed and platinum had revealed promising efficacy for nonsquamous NSCLC in a phase 1b study. We conducted a randomized, double-blind, phase 3 study to compare the efficacy and safety of sintilimab with placebo, both in combination with such chemotherapy (ClinicalTrials.gov: NCT03607539). **METHODS:** A total of 397 patients with previously untreated, locally advanced or metastatic nonsquamous NSCLC without sensitizing EGFR or anaplastic lymphoma kinase genomic aberration were randomized (2:1 ratio) to receive either sintilimab 200 mg or placebo plus pemetrexed and platinum once every 3 weeks for four cycles, followed by sintilimab or placebo plus pemetrexed therapy. Crossover or treatment beyond disease progression was allowed. The primary end point was progression-free survival (PFS) as judged by an independent radiographic review committee. **RESULTS:** As of November 15, 2019, the median follow-up was 8.9 months. The median PFS was significantly longer in the sintilimab-combination group than that in the placebo-combination group (8.9 versus 5.0 mo; hazard ratio, 0.482, 95% confidence interval [CI]: 0.362-0.643; $p < 0.00001$). The confirmed objective response rate was 51.9% (95% CI: 45.7%-58.0%) in the sintilimab-combination group and 29.8% (95% CI: 22.1%-38.4%) in placebo-combination group. The incidence of grade 3 or higher adverse events was 61.7% in sintilimab-combination group and 58.8% in placebo-combination group. **CONCLUSIONS:** In Chinese patients with previously untreated, locally advanced or metastatic nonsquamous NSCLC, the addition of sintilimab to chemotherapy with pemetrexed and platinum resulted in considerably longer PFS than with chemotherapy alone with manageable safety profiles.

[Brigatinib Versus Crizotinib in Advanced ALK Inhibitor-Naive ALK-Positive Non-Small Cell Lung Cancer: Second Interim Analysis of the Phase III ALTA-1L Trial](#) J Clin Oncol. 2020 Aug 11;JCO2000505. doi: 10.1200/JCO.20.00505. Online ahead of print. D Ross Camidge 1, Hye Ryun Kim 2, Myung-Ju Ahn 3, et al.

PURPOSE: Brigatinib, a next-generation anaplastic lymphoma kinase (ALK) inhibitor, demonstrated superior progression-free survival (PFS) and improved health-related quality of life (QoL) versus crizotinib in advanced ALK inhibitor-naive ALK-positive non-small cell lung cancer (NSCLC) at first interim analysis (99 events; median brigatinib follow-up, 11.0 months) in the open-label, phase III ALTA-1L trial (ClinicalTrials.gov identifier: NCT02737501). We report results of the second prespecified interim analysis (150 events). **METHODS:** Patients with ALK inhibitor-naive advanced ALK-positive NSCLC were randomly assigned 1:1 to brigatinib 180 mg once daily (7-day lead-in at 90 mg once daily) or crizotinib 250 mg twice daily. The primary end point was PFS as assessed by blinded independent review committee (BIRC). Investigator-assessed efficacy, blood samples for pharmacokinetic assessments, and patient-reported outcomes were also collected. **RESULTS:** Two hundred seventy-five patients were randomly assigned (brigatinib, n = 137; crizotinib, n = 138). With median follow-up of 24.9 months for brigatinib (150 PFS events), brigatinib showed consistent superiority in BIRC-assessed PFS versus crizotinib (hazard ratio [HR], 0.49 [95% CI, 0.35 to 0.68]; log-rank P < .0001; median, 24.0 v 11.0 months). Investigator-assessed PFS HR was 0.43 (95% CI, 0.31 to 0.61; median, 29.4 v 9.2 months). No new safety concerns emerged. Brigatinib delayed median time to worsening of global health status/QoL scores compared with crizotinib (HR, 0.70 [95% CI, 0.49 to 1.00]; log-rank P = .049). Brigatinib daily area under the plasma concentration-time curve was not a predictor of PFS (HR, 1.005 [95% CI, 0.98 to 1.031]; P = .69). **CONCLUSION:** Brigatinib represents a once-daily ALK inhibitor with superior efficacy, tolerability, and QoL over crizotinib, making it a promising first-line treatment of ALK-positive NSCLC.

[Patient-reported outcomes in RELAY, a phase 3 trial of ramucirumab plus erlotinib versus placebo plus erlotinib in untreated EGFR-mutated metastatic non-small-cell lung cancer](#) Curr Med Res Opin. 2020 Aug 28;1-9. doi: 10.1080/03007995.2020.1808781. Online ahead of print.

Kiyotaka Yoh 1, Shinji Atagi 2, Martin Reck 3, et al.

OBJECTIVE: In the phase 3 RELAY trial, ramucirumab/erlotinib demonstrated superior progression-free survival (PFS) over placebo/erlotinib in patients with EGFR-mutated metastatic NSCLC (median PFS 19.4 versus 12.4 months; HR = 0.59, 95% CI = 0.46-0.76; p < .0001). Safety was consistent with established profiles for ramucirumab and erlotinib in NSCLC. Here, we present patient-reported outcomes. **METHODS:** Patients received oral erlotinib (150 mg daily) plus intravenous ramucirumab (10 mg/kg) or placebo Q2W until progressive disease or unacceptable toxicity. Patients completed the Lung Cancer Symptom Scale (LCSS) and EQ-5D questionnaires at baseline and every other cycle. Analyses included time to deterioration (TtD) for LCSS via Kaplan-Meier method and Cox models and changes from baseline using mixed-model repeated-measures regression analysis. **RESULTS:** Overall patient compliance for LCSS and EQ-5D was >95%. TtD did not differ between treatment arms for LCSS Total Score (HR = 0.962, 95% CI = 0.690-1.343) and Average Symptom Burden Index (HR = 1.012, 95% CI = 0.732-1.400). TtD of individual LCSS items (appetite loss, fatigue, cough, shortness of breath, pain, symptom distress, difficulties with daily activities, quality of life) indicated no difference between arms; however, patient-reported blood in sputum was worse for ramucirumab/erlotinib (HR = 1.987, 95% CI = 1.206-3.275). Results of LCSS mean changes from baseline were consistent with TtD, indicating no significant differences between treatment arms except for blood in sputum. Mean changes from baseline in EQ-5D index score (p = .94) and visual analogue scale (p = .95) revealed no overall differences in health status between treatment arms. **CONCLUSIONS:** Patients' overall quality of life and symptom

burden did not differ with the addition of ramucirumab to erlotinib compared to placebo/erlotinib. These data support the clinical benefit of ramucirumab/erlotinib in untreated EGFR-mutated metastatic NSCLC.

Dabrafenib and Trametinib in Patients With Tumors With BRAF V600E Mutations: Results of the NCI-MATCH Trial Subprotocol H J Clin Oncol. 2020 Aug 6;JCO2000762. doi:

10.1200/JCO.20.00762. Online ahead of print. April K S Salama¹, Shuli Li², Erin R Macrae³, et al. **PURPOSE:** BRAFV600 mutations are commonly found in melanoma and thyroid cancers and to a lesser degree in other tumor types. Subprotocol H (EAY131-H) of the NCI-MATCH platform trial sought to investigate the selective BRAF inhibitor dabrafenib and the MEK1/2 inhibitor trametinib in patients with solid tumors, lymphomas, or multiple myeloma whose tumors harbored a BRAFV600 mutation. **PATIENTS AND METHODS:** EAY131-H is an open-label, single-arm study. Patients with melanoma, thyroid, or colorectal cancer were excluded; patients with non-small-cell lung cancer were later excluded in an amendment. Patients received dabrafenib 150 mg twice per day and trametinib 2 mg per day continuously until disease progression or intolerable toxicity. The primary end point was centrally assessed objective response rate (ORR); secondary end points included progression-free survival (PFS), 6-month PFS, and overall survival. **RESULTS:** Thirty-five patients were enrolled, and 29 were included in the primary efficacy analysis as prespecified in the protocol. Median age was 59 years, and 45% of the patients had received ≥ 3 lines of therapy. The confirmed ORR was 38% (90% CI, 22.9% to 54.9%) with $P < .0001$ against a null rate of 5%, and PFS was 11.4 months (90% CI, 8.4 to 16.3 months); responses were seen in 7 distinct tumor types. Seven patients had a duration of response of > 12 months, including 4 patients with a duration of response of > 24 months. An additional 8 patients had a PFS > 6 months. The median overall survival was 28.6 months. Reported adverse events were comparable to those noted in previously reported profiles of dabrafenib and trametinib. **CONCLUSION:** This study met its primary end point, with an ORR of 38% ($P < .0001$) in this mixed histology, pretreated cohort. This promising activity warrants additional investigations in BRAFV600-mutated tumors outside of currently approved indications.

Outcomes to first-line pembrolizumab in patients with PD-L1-high ($\geq 50\%$) non-small cell lung cancer and a poor performance status J Immunother Cancer. 2020 Aug;8(2):e001007. doi:

10.1136/jitc-2020-001007. Joao V Alessi¹, Biagio Ricciuti¹, Elizabeth Jiménez-Aguilar², et al. **BACKGROUND:** Patients with non-small cell lung cancer (NSCLC) and a poor Eastern Cooperative Oncology Group Performance Status (ECOG PS) have been excluded from phase III immunotherapy clinical trials. We sought to evaluate clinical outcomes to first-line pembrolizumab in patients with advanced NSCLC, a PD-L1 Tumor Proportion Score (TPS) of $\geq 50\%$, and an ECOG PS of 2. **METHODS:** We performed a multicenter retrospective analysis of patients with metastatic NSCLC and a PD-L1 TPS of $\geq 50\%$ (negative for genomic alterations in EGFR and ALK) who received treatment with first-line pembrolizumab. Clinical outcomes were compared in patients based on ECOG PS. **RESULTS:** Among the 234 patients, 83.3% (n=195) had an ECOG PS of 0 or 1, and 16.7% (n=39) had an ECOG PS of 2. The baseline clinicopathological characteristics were balanced between the ECOG PS 0-1 vs 2 groups in terms of age, sex, tobacco use, histology, KRAS mutation status, presence of other potentially targetable driver mutations (BRAF, MET, HER2, RET), presence of brain metastases, and PD-L1 TPS distribution. Compared with patients with an ECOG PS of 0 or 1, patients with an ECOG PS of 2 had a significantly lower objective response rate (43.1% vs 25.6%; $p=0.04$), a numerically shorter median progression-free survival (6.6 months vs 4.0 months; HR 0.70 (95% CI 0.47 to 1.06); $p=0.09$), and a significantly shorter median overall survival (20.3 months vs 7.4 months; HR 0.42 (95% CI 0.26 to 0.68); $p<0.001$). On disease progression, patients with an ECOG PS of 2 were significantly less likely to receive second-line systemic therapy compared with patients with an ECOG PS of 0-1 (65% vs 22.2%, $p=0.001$).

CONCLUSIONS: A subset of patients with NSCLC and an ECOG PS of 2 can respond to first-line pembrolizumab. However, clinical outcomes in this population are often poor and use of second-line systemic therapy is infrequent.

Comparative effectiveness of pembrolizumab vs. nivolumab in patients with recurrent or advanced NSCLC Sci Rep. 2020 Aug 4;10(1):13160. doi: 10.1038/s41598-020-70207-7. Pengfei Cui ^{1 2}, Ruixin

Li ², Ziwei Huang ^{2 3}, Zhaozhen Wu ^{2 3}, Haitao Tao ², Sujie Zhang ², Yi Hu ^{4 5 6}
The efficacies of pembrolizumab and nivolumab have never been directly compared in a real-world study. Therefore, we sought to retrospectively evaluate the objective response rate (ORR) and the progression-free survival (PFS) of patients with recurrent or advanced non-small cell lung cancer (NSCLC) in a real-world setting. This study included patients with recurrent or advanced NSCLC diagnosed between September 1, 2015 and August 31, 2019, who were treated with programmed cell death 1 (PD-1) inhibitors at the Cancer Center of the Chinese People's Liberation Army. PFS was estimated for each treatment group using Kaplan-Meier curves and log-rank tests. The multivariate analysis of PFS was performed with Cox proportional hazards regression models. A total of 255 patients with advanced or recurrent NSCLC treated with PD-1 inhibitors were identified. The ORR was significantly higher in the pembrolizumab group than in the nivolumab group, while PFS was not significantly different between the two groups. Subgroup analysis showed that the ORR was significantly higher for pembrolizumab than for nivolumab in patients in the first-line therapy subgroup and in those in the combination therapy as first-line therapy subgroup. Survival analysis of patients receiving combination therapy as second- or further-line therapy showed that nivolumab had better efficacy than pembrolizumab. However, the multivariate analysis revealed no significant difference in PFS between patients treated with pembrolizumab and those treated with nivolumab regardless of the subgroup. In our study, no significant difference in PFS was noted between patients treated with pembrolizumab and those treated with nivolumab in various clinical settings. This supports the current practice of choosing either pembrolizumab or nivolumab based on patient preferences.

ROS1-dependent cancers - biology, diagnostics and therapeutics Nat Rev Clin Oncol. 2020 Aug 5. doi: 10.1038/s41571-020-0408-9. Online ahead of print. Alexander Drilon ^{1 2}, Chelsea Jenkins ³, Sudarshan Iyer ³, Adam Schoenfeld ^{4 5}, Clare Keddy ³, Monika A Davare ⁶

The proto-oncogene ROS1 encodes a receptor tyrosine kinase with an unknown physiological role in humans. Somatic chromosomal fusions involving ROS1 produce chimeric oncoproteins that drive a diverse range of cancers in adult and paediatric patients. ROS1-directed tyrosine kinase inhibitors (TKIs) are therapeutically active against these cancers, although only early-generation multikinase inhibitors have been granted regulatory approval, specifically for the treatment of ROS1 fusion-positive non-small-cell lung cancers; histology-agnostic approvals have yet to be granted. Intrinsic or extrinsic mechanisms of resistance to ROS1 TKIs can emerge in patients. Potential factors that influence resistance acquisition include the subcellular localization of the particular ROS1 oncoprotein and the TKI properties such as the preferential kinase conformation engaged and the spectrum of targets beyond ROS1. Importantly, the polyclonal nature of resistance remains underexplored. Higher-affinity next-generation ROS1 TKIs developed to have improved intracranial activity and to mitigate ROS1-intrinsic resistance mechanisms have demonstrated clinical efficacy in these regards, thus highlighting the utility of sequential ROS1 TKI therapy. Selective ROS1 inhibitors have yet to be developed, and thus the specific adverse effects of ROS1 inhibition cannot be deconvoluted from the toxicity profiles of the available multikinase inhibitors. Herein, we discuss the non-malignant and malignant biology of ROS1, the diagnostic challenges that ROS1 fusions present and the strategies to target ROS1 fusion proteins in both treatment-naive and acquired-resistance settings.

[Brain metastases of lung cancer: comparison of survival outcomes among whole brain radiotherapy, whole brain radiotherapy with consecutive boost, and simultaneous integrated boost](#)

J Cancer Res Clin Oncol. 2020 Aug 26. doi: 10.1007/s00432-020-03359-8. Online ahead of print.

Tian-Qi Du 1 , Xiang Li 1 , Wei-Si Zhong 1 , Jian-Dong Tian 1 , Yu-Xia Zhao 2 , Dan Liu 3

PURPOSE: Radiotherapy is the mainstay for treating brain metastasis (BM). The objective of this study is to evaluate the overall survival (OS) of patients with BM of lung cancer treated with different radiotherapy modalities. **METHODS:** Patients with BM of lung cancer who underwent radiotherapy between July 2007 and November 2017 were collected, and their baseline demographics, clinicopathological characteristics and treatments were recorded. Survival was estimated by the Kaplan-Meier method and compared by using the log-rank test. Univariate and multivariate analysis of the prognostic factors were performed using the Cox proportional hazard regression model. **RESULTS:** A total of 144 patients were enrolled, of whom 77 underwent whole-brain radiotherapy (WBRT), 39 underwent whole brain radiotherapy with consecutive boost (WBRT + boost), and 28 underwent integrated simultaneous integrated boost intensity-modulated radiotherapy (SIB-IMRT). The OS in SIB-IMRT group was significantly longer than that in WBRT group (median OS 14 (95% confidence interval [CI] 8.8-19.1) vs.7 (95% CI 5.5-8.5) months, log-rank $p < 0.001$) and WBRT + boost group (median OS: 14 (95% CI 8.8-19.1) vs.11 (95% CI 8.3-13.7) months, log-rank $p = 0.037$). Multivariable analysis showed that mortality risk of patients treated with SIB-IMRT decrease by 56, 59, 64 and 64% in unadjusted model (hazard ratio [HR] = 0.44; 95% CI 0.28-0.70, $p < 0.001$), model 1 (HR = 0.41; 95% CI 0.26-0.65, $p < 0.001$), model 2 (HR = 0.36; 95% CI 0.21-0.61, $p < 0.001$), and model 3 (HR = 0.36; 95% CI 0.21-0.61, $p < 0.001$). **CONCLUSIONS:** For patients with BM of lung cancer, SIB-IMRT seems to be associated with a more favorable prognosis.

[Functionally weighted airway sparing \(FWAS\): a functional avoidance method for preserving post-treatment ventilation in lung radiotherapy](#)

Phys Med Biol. 2020 Aug 19;65(16):165010. doi:

10.1088/1361-6560/ab9f5d. E Vicente 1 , A Modiri, J Kipritidis, A Hagan, K Yu, H Wibowo, Y Yan, D R Owen, M M Matuszak, P Mohindra, R Timmerman, A Sawant

Recent changes to the guidelines for screening and early diagnosis of lung cancer have increased the interest in preserving post-radiotherapy lung function. Current investigational approaches are based on spatially mapping functional regions and generating regional avoidance plans that preferentially spare highly ventilated/perfused lung. A potentially critical, yet overlooked, aspect of functional avoidance is radiation injury to peripheral airways, which serve as gas conduits to and from functional lung regions. Dose redistribution based solely on regional function may cause irreparable damage to the 'supply chain'. To address this deficiency, we propose the functionally weighted airway sparing (FWAS) method. FWAS (i) maps the bronchial pathways to each functional sub-lobar lung volume; (ii) assigns a weighting factor to each airway based on the relative contribution of the sub-volume to overall lung function; and (iii) creates a treatment plan that aims to preserve these functional pathways. To evaluate it, we used four cases from a retrospective cohort of SAbR patients treated for lung cancer. Each patient's airways were auto-segmented from a diagnostic-quality breath-hold CT using a research virtual bronchoscopy software. A ventilation map was generated from the planning 4DCT to map regional lung function. For each terminal airway, as resolved by the segmentation software, the total ventilation within the sub-lobar volume supported by that airway was estimated and used as a function-based weighting factor. Upstream airways were weighted based on the cumulative volumetric ventilation supported by corresponding downstream airways. Using a previously developed model for airway radiosensitivity, dose constraints were determined for each airway corresponding to a <5% probability of airway collapse. Airway dose constraints, ventilation scores, and clinical dose constraints were input to a swarm optimization-based

inverse planning engine to create a 3D conformal SAbR plan (CRT). The FWAS plans were compared to the patients' prescribed CRT clinical plans and the inverse-optimized clinical plans. Depending on the size and location of the tumour, the FWAS plan showed superior preservation of ventilation due to airflow preservation through open pathways (i.e. cumulative ventilation score from the sub-lobar volumes of open pathways). Improvements ranged between 3% and 23%, when comparing to the prescribed clinical plans, and between 3% and 35%, when comparing to the inverse-optimized clinical plans. The three plans satisfied clinical requirements for PTV coverage and OAR dose constraints. These initial results suggest that by sparing pathways to high-functioning lung subregions it is possible to reduce post-SAbR loss of respiratory function.

Potentiating anti-tumor efficacy through radiation and sustained intratumoral delivery of anti-CD40 and anti-PDL1 Int J Radiat Oncol Biol Phys. 2020 Aug 5;S0360-3016(20)33745-7. doi:

10.1016/j.ijrobp.2020.07.2326. Online ahead of print. Hsuan-Chen Liu 1, Dixita I Viswanath 2, et al.

PURPOSE: Mounting evidence demonstrates that combining radiotherapy (RT) with immunotherapy can reduce tumor burden in a subset of patients. However, conventional systemic delivery of immunotherapeutics is often associated with significant adverse effects, which force treatment cessation.

The aim of this study is to investigate a minimally invasive therapeutics delivery approach to improve clinical response while attenuating toxicity. **METHODS:** We utilized a nanofluidic drug-eluting seed (NDES) for the sustained intratumoral delivery of combinational antibodies, CD40 and PDL1. To enhance immune and tumor response, we combined the NDES intratumoral platform with RT to treat the 4T1 murine model of advanced triple negative breast cancer (TNBC). We compared the efficacy of NDES against intraperitoneal (IP) administration, which mimics conventional systemic treatment. Tumor growth was recorded, and local and systemic immune responses were assessed via imaging mass cytometry and flow cytometry. Livers and lungs were histologically analyzed for evaluation of toxicity and metastasis, respectively. **RESULTS:** The combination of RT and sustained intratumoral immunotherapy delivery of CD40 and PDL1 via the NDES (NDES CD40/PDL1) showed an increase in both local and systemic immune response. In combination with RT, NDES CD40/PDL1 achieved significant tumor burden reduction and liver inflammation mitigation when compared to systemic treatment. Importantly, our treatment strategy boosted the abscopal effect towards attenuating lung metastatic burden.

CONCLUSIONS: Overall, our study demonstrated superior efficacy of combination treatment with RT and sustained intratumoral immunotherapy via the NDES, offering promise for improving therapeutic index and clinical response.

Two months of radiation oncology in the heart of Italian "red zone" during COVID-19 pandemic: paving a safe path over thin ice Radiat Oncol. 2020 Aug 10;15(1):191. doi: 10.1186/s13014-020-01631-2.

Michela Buglione 1, Luigi Spiazzi 2, Andrea Emanuele Guerini 1, et al.

BACKGROUND: Coronavirus Disease 2019 (COVID-19) pandemic had an overwhelming impact on healthcare worldwide. Outstandingly, the aftermath on neoplastic patients is still largely unknown, and only isolated cases of COVID-19 during radiotherapy have been published. We will report the two-months experience of our Department, set in Lombardy "red-zone". **METHODS:** Data of 402 cancer patients undergoing active treatment from February 24 to April 24, 2020 were retrospectively reviewed; several indicators of the Department functioning were also analyzed. **RESULTS:** Dedicated measures allowed an overall limited reduction of the workload. Decrease of radiotherapy treatment number reached 17%, while the number of administration of systemic treatment and follow up evaluations kept constant. Conversely, new treatment planning faced substantial decline. Considering the patients, infection rate was 3.23% (13/402) and mortality 1.24% (5/402). Median age of COVID-19 patients was 69.7 years, the large majority were male and smokers (84.6%); lung cancer was the most common tumor type (61.5%), 84.6% of subjects were stage III-IV and 92.3% had comorbidities. Remarkably, 92.3% of the cases were detected

before March 24. Globally, only 2.5% of ongoing treatments were suspended due to suspect or confirmed COVID-19 and 46.2% of positive patients carried on radiotherapy without interruption. Considering only the last month, infection rate among patients undergoing treatment precipitated to 0.43% (1/232) and no new contagions were reported within our staff. **CONCLUSIONS:** Although mortality rate in COVID-19 cancer patients is elevated, our results support the feasibility and safety of continuing anticancer treatment during SARS-Cov-2 pandemic by endorsing consistent preventive measures.

SMALL CELL LUNG CANCER - SCLC

[Atezolizumab plus carboplatin and etoposide in small cell lung cancer patients previously treated with platinum-based chemotherapy](#) Invest New Drugs. 2020 Aug 11. doi: 10.1007/s10637-020-00983-6. Online ahead of print. Hidenobu Ishii 1 , Koichi Azuma 2 , Akihiko Kawahara 3 , Norikazu Matsuo 2 , Takaaki Tokito 2 , Tomoaki Hoshino 2

Although immune checkpoint inhibitors have improved the survival of small cell lung cancer (SCLC) patients, their efficacy in SCLC patients who relapsed after systemic chemotherapy is unclear. This retrospective study aimed to investigate the utility of treatment with atezolizumab plus carboplatin and etoposide in SCLC patients previously treated with platinum-based chemotherapy. We retrospectively screened consecutive eight SCLC patients who received atezolizumab plus carboplatin and etoposide after platinum-based chemotherapy. We evaluated the efficacy of this treatment and its association with programmed cell death-ligand 1 (PD-L1) expression. Three and five patients had sensitive relapse and refractory relapse for first-line platinum-based chemotherapy, respectively. The overall response rate and disease control rate was 37.5% and 75.0%, respectively. Median progression-free survival was 4.0 months. Out of three patients who achieved clinical response, two patients had refractory relapse for first-line platinum-based chemotherapy. No patient exhibited PD-L1 expression. Atezolizumab plus carboplatin and etoposide therapy was effective in SCLC patients with sensitive and refractory relapse and might be a second-line treatment option for SCLC patients previously treated with platinum-based chemotherapy.

[Prolonging Survival: The Role of Immune Checkpoint Inhibitors in the Treatment of Extensive-Stage Small Cell Lung Cancer](#) Oncologist. 2020 Aug 29. doi: 10.1634/theoncologist.2020-0193. Online ahead of print. Barbara Melosky 1 , Parneet K Cheema 2 , Anthony Brade 3 , Deanna McLeod 4 , Geoffrey Liu 5 , Paul Wheatley Price 6 , Kevin Jao 7 , Devin D Schellenberg 8 , Rosalyn Juergens 9 , Natasha Leighl 5, Quincy Chu 10

BACKGROUND: Small cell lung cancer (SCLC) represents approximately 15% of lung cancers, and approximately 70% are diagnosed as extensive-stage SCLC (ES-SCLC). Although ES-SCLC is highly responsive to chemotherapy, patients typically progress rapidly, and there is an urgent need for new therapies. Immune checkpoint inhibitors (ICIs) have recently been investigated in SCLC, and this review provides guidance on the use of these agents in ES-SCLC based on phase III evidence. **METHODS:** Published and presented literature on phase III data addressing use of ICIs in ES-SCLC was identified using the key search terms "small cell lung cancer" AND "checkpoint inhibitors" (OR respective aliases). Directed searches of eligible studies were periodically performed to ensure capture of the most recent data. **RESULTS:** Six phase III trials were identified, with four assessing the benefits of ICIs plus chemotherapy first-line, one evaluating ICIs as first-line therapy maintenance, and one assessing ICI monotherapy after progression on platinum-based chemotherapy. The addition of ipilimumab or tremelimumab to first-line treatment or as first-line maintenance did not improve survival. Two out of three studies combining PD-1/PD-L1 inhibitors with first-line platinum-based chemotherapy demonstrated significant long-lasting survival benefits and improved quality of life with no unexpected safety concerns. PD-1/PD-L1 inhibitors as first-line maintenance or in later lines of therapy did not

improve survival. Biomarker research is ongoing as well as research into the role of ICIs in combination with radiation therapy in limited-stage SCLC. **CONCLUSION:** The addition of atezolizumab or durvalumab to first-line platinum-based chemotherapy for ES-SCLC prolongs survival and improves quality of life. **IMPLICATIONS FOR PRACTICE:** Platinum-based chemotherapy has been standard of care for extensive-stage small cell lung cancer (ES-SCLC) for more than a decade. Six recent phase III trials investigating immune checkpoint inhibitors (ICIs) have clarified the role of these agents in this setting. Although ICIs were assessed first-line, as first-line maintenance, and in later lines of therapy, the additions of atezolizumab or durvalumab to first-line platinum-based chemotherapy were the only interventions that significantly improved overall survival and increased quality of life. These combinations should therefore be considered standard therapy for first-line ES-SCLC. Biomarker research and investigations into the role of ICIs for limited-stage disease are ongoing.

[Choice of second-line systemic therapy in stage IV small cell lung cancer \(SCLC\) - A decision-making analysis amongst European lung cancer experts](#) Lung Cancer. 2020 Aug;146:6-11. doi: 10.1016/j.lungcan.2020.03.024. Epub 2020 Mar 30. M Früh 1 , C M Panje 2 , M Reck 3 , et al.

OBJECTIVES: Stage IV small cell lung cancer (SCLC) is associated with short survival and progression after first-line systemic therapy frequently occurs within months. Although topotecan is approved for second-line treatment, its efficacy is limited, and treatment heterogeneity exists. **MATERIAL AND METHODS:** The decision-making patterns for second line treatment of 13 European medical oncologists with expertise in SCLC were analyzed. **RESULTS:** The two criteria most relevant to decision-making were the performance status and the interval of recurrence since first-line treatment. With an interval of less than 3 months since the end of first-line chemotherapy, 62 % of the experts recommended cyclophosphamide, doxorubicin and vincristine (CAV) for fit patients and 54 % recommended topotecan for unfit patients. For an interval of more than 6 months, a clear consensus for a re-challenge with a platinum doublet was achieved (92 %). However, there was no consensus on the second-line therapy with an interval of 3-6 months since the end of first-line therapy. **CONCLUSION:** Real world practice may differ from recommendations in general guidelines and cannot always be directly derived from trial results as other factor such as habits, patient's preference, convenience or costs have to be factored in.

[The impact of symptoms and comorbidity on health utility scores and health-related quality of life in small cell lung cancer using real world data](#) Qual Life Res. 2020 Aug 26. doi: 10.1007/s11136-020-02615-1. Online ahead of print. Ali Vedadi 1 , Sharara Shakik 1 2 , M Catherine Brown 1 , et al.

PURPOSE: Small cell lung cancer (SCLC) is a highly fatal disease associated with significant morbidity, with a need for real-world symptom and health utility score (HUS) data. HUS can be measured using an EQ-5D-5L questionnaire, however most captured data is available in non-SCLC (NSCLC) only. As new treatment regimens become available in SCLC it becomes important to understand factors which influence health-related quality of life and health utility. **METHODS:** A prospective observational cohort study (2012-2017) of ambulatory histologically confirmed SCLC evaluated patient-reported EQ-5D-5L-derived HUS, toxicity and symptoms. A set of NSCLC patients was used to compare differential factors affecting HUS. Clinical and demographic factors were evaluated for differential interactions between lung cancer types. Comorbidity scores were documented for each patient. **RESULTS:** In 75 SCLC and 150 NSCLC patients, those with SCLC had lower mean HUS ((SCLC vs NSCLC: mean 0.69 vs 0.79); ($p < 0.001$)) when clinically stable and with progressive disease: ((SCLC mean HUS = 0.60 vs NSCLC mean HUS = 0.77), ($p = 0.04$)). SCLC patients also had higher comorbidity scores ((1.11 vs 0.73); ($p < 0.015$)). In multivariable analyses, increased symptom severity and comorbidity scores decreased HUS in both SCLC and NSCLC ($p < 0.001$); however, only comorbidity scores differentially affected HUS ($p < 0.0001$), with a greater reduction of HUS adjusted per unit of comorbidity in SCLC. **CONCLUSION:** Patients with advanced SCLC had significantly lower HUS than NSCLC. Both patient cohorts are

impacted by symptoms and comorbidity, however, comorbidity had a greater negative effect in SCLC patients.

PALLIATIVE AND SUPPORTIVE CARE

[Prognosis in metastatic lung cancer: vitamin D deficiency and depression-a cross-sectional analysis](#)

BMJ Support Palliat Care. 2020 Aug 27;bmjspcare-2020-002457. doi: 10.1136/bmjspcare-2020-002457. Online ahead of print. Daniel C McFarland 1 , Madalyn Fernbach 2 , William S Breitbart 2 , Christian Nelson 2

BACKGROUND: Depression and vitamin D deficiency are common in patients with lung cancer and have prognostic implications in cancer settings. However, their relationship and concomitant survival implications have not been evaluated in patients with metastatic lung cancer specifically. We hypothesised that vitamin D deficiency would be associated with depression and inferior cancer-related survival in patients receiving therapies for stage IV lung cancer. **METHODS:** This was a cross-sectional analysis of vitamin D, depression and lung cancer characteristics. Vitamin D levels were stratified by level (no deficiency ≥ 30 units, mild deficiency 20 to 29 units and moderate-to-severe < 20 units). Depression was measured by the Hospital Anxiety and Depression Scale-Depression (HADS-D). Survival estimations were made using Cox proportional hazard model and Kaplan-Meier analyses. **RESULTS:** Vitamin D deficiency was evident in almost half of the sample ($n=98$) and was associated with significant depression (HADS-D ≥ 8) ($\chi^2=4.35$, $p<0.001$) even when controlling for age, sex and inflammation ($\beta=-0.21$, $p=0.03$). Vitamin D deficiency and depression were associated with worse survival and showed evidence of an interaction effect (HR 1.5, $p=0.04$). **CONCLUSION:** Vitamin D deficiency is associated with depression in patients with metastatic lung cancer. Depression modulates the survival implications of vitamin D deficiency in this population. The role of vitamin D deficiency in cancer-related depression warrants further investigation since both are amenable to treatment. Psychological and nutritional prognostic considerations may help inform treatment paradigms that enhance quality of life and survival.

[Early childhood adversity in adult patients with metastatic lung cancer: Cross-sectional analysis of symptom burden and inflammation](#)

Brain Behav Immun. 2020 Aug 11;S0889-1591(20)31361-1. doi: 10.1016/j.bbi.2020.08.006. Online ahead of print. Daniel C McFarland 1 , Christian Nelson 2 , Andrew H Miller 3

OBJECTIVE: Psychological and physical symptoms commonly occur in patients with metastatic lung cancer and are associated with reduced quality of life and decreased survival. Previous work has associated these symptoms with inflammation. The experience of Early Childhood Adversity (ECA) is linked to chronic inflammation and may identify adult cancer patients who are at-risk for psychological and physical symptoms. We thus hypothesized that ECA in lung cancer patients would be associated with increased psychological symptoms (distress, anxiety, and depression) and physical symptoms and that this relationship would be explained by inflammation. **METHODS:** Patients with metastatic lung cancer ($n = 92$) were evaluated for ECA using the Risky Families Questionnaire. Concomitant assessments were made of distress (Distress Thermometer and Problem List [DT&PL]), anxiety (Generalized Anxiety Disorder-7), depression (Patient Hospital Questionnaire-9), physical symptoms (DT&PL), and inflammation (C-reactive protein [CRP]). Multivariate models were created to explain associations of ECA with depression, anxiety, distress, number of physical problems, and inflammation. **RESULTS:** ECA was associated with distress ($r = 0.24$, $p = .03$), anxiety ($r = 0.30$, $p = .004$), depression ($r = 0.35$, $p = .001$), greater physical problems ($r = 0.25$, $p = .03$), younger age ($r = -0.29$, $p = .006$), and elevated CRP ($r = 0.22$, $p = .04$). Multivariate analyses of outcomes found that depression severity was independently explained by both ECA and inflammation ($\beta = 0.37$, $p = .001$) but not distress or anxiety, while

controlling for age and sex. Number of physical problems were also associated with ECA ($\beta = 0.35$, $p = .004$) but not inflammation. The association between ECA and physical problems was not significant after controlling for depression. **CONCLUSION:** ECA is associated with increased depression and physical symptoms independent of inflammation. Moreover, depression appears to mediate the impact of ECA on physical symptoms. ECA may identify patients at risk for psychological and physical symptoms.

[Interstitial pneumonitis in the COVID-19 era: a difficult differential diagnosis in patients with lung cancer](#)

Tumori. 2020 Aug 26;300891620951863. doi: 10.1177/0300891620951863. Online ahead of print. Chiara Catania 1 , Valeria Stati 1 , Gianluca Spitaleri 1

In this coronavirus 2019 (COVID-19) era, when pneumonitis occurs in patients with lung cancer receiving immune checkpoint inhibitors (ICIs), a major challenge is to make a rapid and correct differential diagnosis among drug-induced pulmonary toxicity, tumour progression, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced pneumonitis. While waiting for polymerase chain reaction (PCR) testing results, an accurate evaluation of the symptoms and serologic features can help us make a first diagnostic hypothesis and quickly start correct treatment. Physicians need a collaborative effort to develop and share a common database reporting clinical (anosmia, dysgeusia), serologic, and radiologic data in ICI-treated patients with lung cancer developing interstitial disease to create an evidence-based clinical diagnostic algorithm. This tool will continue to be helpful when we emerge from the pandemic crisis into a world in which COVID-19 may not have been eradicated to better select the target population requiring the most resource-consuming PCR tests.

[Mechanisms of Fritillariae Thunbergii Flos in Lung Cancer Treatment from a Systems Pharmacology Perspective](#)

J Ethnopharmacol. 2020 Aug 14;113245. doi: 10.1016/j.jep.2020.113245. Online ahead of print. Mingchao Cui 1 , Shaojun Chen 2 , Hanhua Wang 2 , Ping Pan 2 , Yiyuan Luo 2 , Xiuxiu Sha 2

ETHNOPHARMACOLOGICAL RELEVANCE: Fritillariae Thunbergii Flos (FTF) included in the Chinese Pharmacopoeia (1977 Edition) is a Chinese medicinal herb traditionally used to treat bronchitis. In recent years, it has been applied in the treatment of lung cancer. However, the molecular mechanism remains largely unknown. **METHODS:** The screening of bioactive compounds, acquisition of drug targets, network construction, and experimental validation in vivo were combined to explore the mechanism of FTF in the treatment of lung carcinoma with regards to systems pharmacology.

RESULTS: The network Lung Cancer Pathway consisted of 114 nodes (44 compounds and 70 potential targets) and 361 edges, as well as modules that included inflammatory response, angiogenesis, negative regulation of the apoptotic process, and positive regulation of cell proliferation and migration. It was examined by conducting experiments that involved the administration of ethanol-based extracts of FTF in Lewis lung carcinoma mice. The extracts exerted excellent anti-lung cancer effects in vivo by significantly inhibiting tumor proliferation, thereby extending the survival period of tumor-bearing mice. Moreover, FTF induced the downregulation of PIK3CG, Bcl-2, eNOS, VEGF, p-STAT3, and STAT3 genes in tumor-bearing mice. **CONCLUSIONS:** The findings of the present study verify the therapeutic effects and mechanism of FTF on lung cancer and provide a theoretical basis to support the comprehensive utilization of FTF resources.

[Evaluating relationships between lung cancer stigma, anxiety, and depressive symptoms and the absence of empathic opportunities presented during routine clinical consultations](#)

Patient Educ Couns. 2020 Aug 11;S0738-3991(20)30406-7. doi: 10.1016/j.pec.2020.08.005. Online ahead of print. Timothy J Williamson 1 , Jamie S Ostroff 2 , Chloé M Martin 2 , Smita C Banerjee 2 , Carma L Bylund 3 , Heidi A Hamann 4 , Megan Johnson Shen 5

OBJECTIVE: Empathic communication in clinical consultations is mutually constructed, with patients first presenting empathic opportunities (statements communicating emotions, challenges, or progress) to which clinicians can respond. We hypothesized that lung cancer patients who did not present empathic opportunities during routine consultations would report higher stigma, anxiety, and depressive symptoms than patients who presented at least one. **METHODS:** Audio-recorded consultations between lung cancer patients (N = 56) and clinicians were analyzed to identify empathic opportunities. Participants completed questionnaires measuring sociodemographic and psychosocial characteristics. **RESULTS:** Twenty-one consultations (38 %) did not contain empathic opportunities. Unexpectedly, there was a significant interaction between presenting empathic opportunities and patients' race on disclosure-related stigma (i.e., discomfort discussing one's cancer; $F = 4.49$, $p = .041$) and anxiety ($F = 8.03$, $p = .007$). Among racial minority patients (self-identifying as Black/African-American, Asian/Pacific Islander, or other race), those who did not present empathic opportunities reported higher stigma than those who presented at least one ($t = -5.47$, $p = .038$), but this difference was not observed among white patients ($t = 0.38$, $p = .789$). Additional statistically significant findings emerged for anxiety. **CONCLUSION:** Disclosure-related stigma and anxiety may explain why some patients present empathic opportunities whereas others do not. **PRACTICE IMPLICATIONS:** Clinicians should intentionally elicit empathic opportunities and encourage open communication with patients (particularly from diverse racial backgrounds).

[Changes in chronic medication adherence, costs, and health care use after a cancer diagnosis among low-income patients and the role of patient-centered medical homes](#) Cancer. 2020 Aug 11.

doi: 10.1002/cncr.33147. Online ahead of print. Lisa P Spees^{1, 2}, Stephanie B Wheeler^{1, 2}, Xi Zhou², et al.

BACKGROUND: Approximately 40% of patients with cancer also have another chronic medical condition. Patient-centered medical homes (PCMHs) have improved outcomes among patients with multiple chronic comorbidities. The authors first evaluated the impact of a cancer diagnosis on chronic medication adherence among patients with Medicaid coverage and, second, whether PCMHs influenced outcomes among patients with cancer. **METHODS:** Using linked 2004 to 2010 North Carolina cancer registry and claims data, the authors included Medicaid enrollees who were diagnosed with breast, colorectal, or lung cancer who had hyperlipidemia, hypertension, and/or diabetes mellitus. Using difference-in-difference methods, the authors examined adherence to chronic disease medications as measured by the change in the percentage of days covered over time among patients with and without cancer. The authors then further evaluated whether PCMH enrollment modified the observed differences between those patients with and without cancer using a differences-in-differences-in-differences approach. The authors examined changes in health care expenditures and use as secondary outcomes. **RESULTS:** Patients newly diagnosed with cancer who had hyperlipidemia experienced a 7-percentage point to 11-percentage point decrease in the percentage of days covered compared with patients without cancer. Patients with cancer also experienced significant increases in medical expenditures and hospitalizations compared with noncancer controls. Changes in medication adherence over time between patients with and without cancer were not determined to be statistically significantly different by PCMH status. Some PCMH patients with cancer experienced smaller increases in expenditures (diabetes) and emergency department use (hyperlipidemia) but larger increases in their inpatient hospitalization rates (hypertension) compared with non-PCMH patients with cancer relative to patients without cancer. **CONCLUSIONS:** PCMHs were not found to be associated with improvements in chronic disease medication adherence, but were associated with lower costs and emergency department visits among some low-income patients with cancer.

COMPLEMENTARY & ALTERNATIVE THERAPY

[Combination of traditional Chinese medicine and epidermal growth factor receptor tyrosine kinase inhibitors in the treatment of non-small cell lung cancer: A systematic review and meta-analysis](#)

Medicine (Baltimore). 2020 Aug 7;99(32):e20683. doi: 10.1097/MD.00000000000020683.

Xinbing Sui 1 2 , Mingming Zhang 1 2 , Xueming Han 1 2 , Ruonan Zhang 1 2 , Liuxi Chen 1 , Ying Liu 3 , Yu Xiang 1 2 , Tian Xie 1 2

BACKGROUND: In China, traditional Chinese medicine (TCM) is an increasingly important part of the treatment of non-small cell lung cancer (NSCLC), which usually includes a combination of prescription and syndrome differentiation. Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have been proven to be the first-line drugs for the treatment of advanced EGFR mutation-positive NSCLC. In China, EGFR-TKIs are used in combination with traditional Chinese medicines to reduce side effects and/or enhance effectiveness. Nevertheless, the relationship between TCMs and EGFR-TKIs remain unclear. This meta-review aimed to explore the clinical evidence of TCMs combined with EGFR-TKIs in the treatment of NSCLC. **METHODS:** Related studies were found by searching the databases of EMBASE, PubMed, Web of Science, MEDLINE, Cochrane library database, China Academic Journals (CNKI), Wanfang and Weipu. This study included 57 randomized controlled trials, all of these were processed by Stata software (version 12.0). In the study, all the materials are published articles, patient anonymity and informed consent and ethics Approval/Institutional review board are not necessary.

RESULTS: This study demonstrated that the objective response rate was higher in the group of TCMs plus EGFR-TKIs than in the group of EGFR-TKIs alone (risk ratios 1.39, 95% confidence intervals [1.29, 1.50]). Further research of specific herbal medicines showed that Huangqi, Baishu, Fuling, Gancao, Maidong, Baihuashicao, Shashen, Dangshen and Renshen, had significant higher contributions to results.

CONCLUSION: TCMs may improve the efficacy of EGFR-TKIs in the treatment of NSCLC.

[Efficacy and safety of TCM combined with chemotherapy for SCLC: a systematic review and meta-analysis](#)

J Cancer Res Clin Oncol. 2020 Aug 14. doi: 10.1007/s00432-020-03353-0. Online ahead of print. Shuntai Chen 1 2 , Yanju Bao 3 , Jing Xu 4 , et al.

Abstract

BACKGROUND: Chemotherapy is the standard treatment for small cell lung cancer (SCLC), but chemotherapy resistance and adverse reactions remain major problems. Although Traditional Chinese Medicine (TCM) is widely applied for patients with SCLC in China, the evidence of TCM in the treatment for SCLC is limited. **PURPOSE:** To evaluate the efficacy and safety of TCM combined with chemotherapy for patients with SCLC. **Method:** We conducted a systematic search of PubMed, EMBASE, the Chinese National Knowledge Infrastructure, the VIP Information Database, and the Wanfang Database for randomized-controlled trials (RCTs) that are relevant. The included studies were reviewed by two investigators, with relevant data extracted independently. The effect estimate of interest was the relative risk (RR) or mean difference with 95% confidence intervals (95% CIs). **RESULTS:** 22 RCTs involving 1887 patients were included in this study. Compared with patients treated with chemotherapy alone, those with Chinese herbal medicine and chemotherapy (TCM-C) had better therapeutic effects (RR = 1.295, 95% CI 1.205-1.391, P < 0.001), KPS scores (RR = 1.310, 95% CI 1.210-1.418, P < 0.001), 1-year survival rate (RR = 1.282, 95% CI 1.129-1.456, P < 0.001), 3-year survival rate (RR = 2.109, 95% CI 1.514-2.939, P < 0.001), and 5-year survival rate (RR = 2.373, 95% CI 1.227-4.587, P = 0.01). The incidence of gastrointestinal reaction (RR of = 0.786, 95% CI 0.709-0.870, P < 0.000) and bone marrow depression (RR = 0.837, 95% CI 0.726-0.965, P = 0.014) in TCM-C group were lower than that in the C group. **CONCLUSION:** The systematic review indicated that TCM combined with chemotherapy may improve therapeutic effect, quality of life, and prolong survival time. More large-scale and higher quality RCTs are warranted to support our findings.

[Elephantopus mollis Kunth extracts induce antiproliferation and apoptosis in human lung cancer and myeloid leukemia cells](#) J Ethnopharmacol. 2020 Aug 5;263:113222. doi: 10.1016/j.jep.2020.113222. Online ahead of print. Truong Thi Bich Ngoc 1 , Nguyen Thi Hoai Nga 2 , Nguyen Thi My Trinh 3 , Tran Linh Thuoc 1 , Dang Thi Phuong Thao 4

ETHNOPHARMACOLOGICAL RELEVANCE: *Elephantopus mollis* Kunth (EM), which belongs to Asteraceae family, has been used as a folk medicine with diverse therapeutic properties. Previous studies reported that crude extracts of this plant could inhibit several cancer cell lines, including breast carcinoma MCF-7, liver carcinoma HepG2, colorectal carcinoma DLD-1, lung carcinoma NCI-H23, etc. AIM: In this study, the anticancer activity and associated molecular mechanism of EM which is distributed in Vietnam were investigated. **MATERIALS AND METHODS:** The cytotoxicity of various EM extracts was evaluated on different cell lines by MTT assay. In addition, the effects of EM extracts on cell growth, cell morphology, nuclear morphology, caspase-3 activation, and mRNA expression levels of apoptosis-related genes were also examined. **RESULTS:** Our results demonstrated that ethyl acetate extract (EM-EA) caused proliferative inhibition and apoptotic induction towards A549 lung cancer cells (IC₅₀ = 18.66 µg/ml, SI = 5.8) and HL60 leukemia cells (IC₅₀ = 7.45 µg/ml, SI = 14.5) while petroleum ether extract (EM-PE) showed high toxicity to HL60 cell line (IC₅₀ = 11.14 µg/ml, SI = 6.7). Notably, Raji lymphoma cells were also affected by these extracts (IC₅₀ < 20 µg/ml, SI > 4), which has not been reported yet. Furthermore, mechanisms of EM extracts were elucidated. The significant downregulation of PCNA mRNA level induced by EM-EA/PE extracts contributed to the cell-growth restraint. EM-EA extract might activate apoptosis in A549 cells through both extrinsic and intrinsic signaling pathways by causing a 1.55-fold increase in BID, 3.65-fold increase in BAK and 3.11-fold decrease in BCL-2 expression level. Meanwhile, with EM-EA-extract treatment, HL60 cells might encounter P53-dependent apoptotic deaths. **CONCLUSIONS:** The combination of antiproliferation and apoptosis activation contributed to the high efficacy of EM extracts. These findings not only proved the anticancer potential of EM but also provided further insights into the mechanisms of EM extracts.

MISCELLANEOUS WORKS

[Rurality, Stage-Stratified Use of Treatment Modalities, and Survival of Non-small Cell Lung Cancer](#) Chest. 2020 Aug;158(2):787-796. doi: 10.1016/j.chest.2020.04.042. Epub 2020 May 6. Meredith A Ray 1 , Nicholas R Faris 2 , Anna Derrick 3 , Matthew P Smeltzer 1 , Raymond U Osarogiagbon 4 **BACKGROUND:** To eliminate them, non-small cell lung cancer (NSCLC) care and outcome disparities need to be better understood. **RESEARCH QUESTION:** How does rurality interact with NSCLC care and outcome disparities? Study **DESIGN AND METHODS:** We examined guideline-concordant use of active treatment for NSCLC across five institutions in one community-based health care system spanning 44% of the Delta Regional Authority catchment area from 2011 to 2017. **INSTITUTION- AND PATIENT-LEVEL RURALITY WERE BASED ON RURAL-URBAN COMMUTING AREA CODES.** Chi-squared, F-tests, and logistic regressions were used to analyze differences across institutions and rurality; survival was examined using log-rank tests and Cox regression. **RESULTS:** Of 6,259 patients, 47% resided in rural areas; two of five institutions were rurally located and provided care for 20% of patients. Compared with rural residents at rural institutions, urban and rural residents attending urban institutions were more likely to receive stage-preferred treatment: OR 1.68 (95% CI, 1.44-1.96), and 1.33 (1.11-1.61), respectively, after adjusting for insurance, age, and clinical stage. Urban and rural residents attending urban institutions had a lower hazard of death compared with rural residents attending rural institutions: hazard ratio (HR) 0.69 (0.64-0.75) and 0.61 (0.55-0.67), respectively. Among recipients of stage-preferred treatment, care at urban institutions remained less hazardous: HR 0.7 (0.63-0.79). When further stratified by stage, care for late-stage patients at urban institutions remained less hazardous: HR 0.8 (0.71-0.91). **INTERPRE-TATION:** Rurality-associated treatment and survival disparities were

present at the patient and institution levels, but the institution-level disparity was greater. Rural residents receiving care at urban institutions had similar outcomes to urban residents receiving care at urban hospitals. To overcome rurality-associated NSCLC survival disparity, interventions should preferentially target the institution level, including expanding access to higher-quality guideline-concordant care.

[Analyzing the Time From Discovery to Definitive Surgical Therapy for Lung Cancer Based on Referral Patterns](#) Am J Clin Oncol. 2020 Aug;43(8):582-585. doi: 10.1097/COC.0000000000000710.

Michael A Napolitano¹, Matthew D Skancke, Keith D Mortman

OBJECTIVE: Surgery for early stage non-small cell lung cancer can be curative. A delay from diagnosis to surgery can lead to increased mortality. Our objective was to determine if referring patients to specialists before a thoracic surgeon caused a delay in definitive treatment. **MATERIALS AND METHODS:** A retrospective review was conducted of patients who had surgery for non-small cell lung cancer by a single surgeon at our institution from 2013 to 2016. Patients were divided into 2 groups: those who saw a specialist before a thoracic surgeon and patients who were referred directly to a surgeon once the pulmonary nodule was identified on computed tomography (CT). The time from initial CT to resection was compared. Secondary analysis compared private insurance versus Medicare/Medicaid. Percentage of patients upstaged was compared. **RESULTS:** There was no significant difference between groups when comparing time from CT to surgery (79.88 vs. 79.90 d; P=0.58). There was a significant decrease in time from CT to surgery for patients with private insurance compared with Medicare/Medicaid patients (66.05 vs. 86.99 d; P=0.03) and fewer private insurance patients were upstaged (22.9% vs. 31.8%; P=0.32). More patients who saw a different specialist first were upstaged compared with patients sent directly to thoracic surgery (32.6% vs. 22.2%; P=0.22). **CONCLUSIONS:** When comparing time from CT detection of a lung nodule to surgery, no significant difference was found between patients sent to nonthoracic specialists first and those referred directly to a thoracic surgeon. There was a significant decrease in time from CT to surgery for patients with private insurance compared with Medicare/Medicaid.

[Artificial intelligence for the detection of COVID-19 pneumonia on chest CT using multinational datasets](#) Nat Commun. 2020 Aug 14;11(1):4080. doi: 10.1038/s41467-020-17971-2.

Stephanie A Harmon^{1,2}, Thomas H Sanford³, Sheng Xu⁴, et al.

Chest CT is emerging as a valuable diagnostic tool for clinical management of COVID-19 associated lung disease. Artificial intelligence (AI) has the potential to aid in rapid evaluation of CT scans for differentiation of COVID-19 findings from other clinical entities. Here we show that a series of deep learning algorithms, trained in a diverse multinational cohort of 1280 patients to localize parietal pleura/lung parenchyma followed by classification of COVID-19 pneumonia, can achieve up to 90.8% accuracy, with 84% sensitivity and 93% specificity, as evaluated in an independent test set (not included in training and validation) of 1337 patients. Normal controls included chest CTs from oncology, emergency, and pneumonia-related indications. The false positive rate in 140 patients with laboratory confirmed other (non COVID-19) pneumonias was 10%. AI-based algorithms can readily identify CT scans with COVID-19 associated pneumonia, as well as distinguish non-COVID related pneumonias with high specificity in diverse patient populations.

[Medical management of brain metastases](#) Neurooncol Adv. 2020 Aug 9;2(1):vdaa015. doi:

10.1093/noajnl/vdaa015. eCollection Jan-Dec 2020. Adam Lauko¹, Yasmeen Rauf¹, Manmeet S Ahluwalia¹

The development of brain metastases occurs in 10-20% of all patients with cancer. Brain metastases portend poor survival and contribute to increased cancer mortality and morbidity. Despite multimodal treatment options, which include surgery, radiotherapy, and chemotherapy, 5-year survival remains low.

Besides, our current treatment modalities can have significant neurological comorbidities, which result in neurocognitive decline and a decrease in a patient's quality of life. However, innovations in technology, improved understanding of tumor biology, and new therapeutic options have led to improved patient care. Novel approaches in radiotherapy are minimizing the neurocognitive decline while providing the same therapeutic benefit. In addition, advances in targeted therapies and immune checkpoint inhibitors are redefining the management of lung and melanoma brain metastases. Similar approaches to brain metastases from other primary tumors promise to lead to new and effective therapies. We are beginning to understand the appropriate combination of these novel approaches with our traditional treatment options. As advances in basic and translational science and innovative technologies enter clinical practice, the prognosis of patients with brain metastases will continue to improve.

[Face masks: benefits and risks during the COVID-19 crisis](#) Eur J Med Res. 2020 Aug 12;25(1):32. doi: 10.1186/s40001-020-00430-5. Christiane Matuschek 1 , Friedrich Moll 2 , Heiner Fangerau 2 , et al.

BACKGROUND: The German government has made it mandatory to wear respiratory masks covering mouth and nose (MNC) as an effective strategy to fight SARS-CoV-2 infections. In many countries, this directive has been extended on shopping malls or public transportation. The aim of this paper is to critically analyze the statutory regulation to wear protective masks during the COVID-19 crisis from a medical standpoint. **METHODS:** We performed an extensive query of the most recent publications addressing the prevention of viral infections including the use of face masks in the community as a method to prevent the spread of the infection. We addressed the issues of practicability, professional use, and acceptability based on the community and the environment where the user resided. **RESULTS:** Upon our critical review of the available literature, we found only weak evidence for wearing a face mask as an efficient hygienic tool to prevent the spread of a viral infection. However, the use of MNC seems to be linked to relevant protection during close contact scenarios by limiting pathogen-containing aerosol and liquid droplet dissemination. Importantly, we found evidence for significant respiratory compromise in patients with severe obstructive pulmonary disease, secondary to the development of hypercapnia. This could also happen in patients with lung infections, with or without SARS-CoV-2. **CONCLUSION:** Epidemiologists currently emphasize that wearing MNC will effectively interrupt airborne infections in the community. The government and the politicians have followed these recommendations and used them to both advise and, in some cases, mandate the general population to wear MNC in public locations. Overall, the results seem to suggest that there are some clinically relevant scenarios where the use of MNC necessitates more defined recommendations. Our critical evaluation of the literature both highlights the protective effects of certain types of face masks in defined risk groups, and emphasizes their potential risks.

[The Effect of Advances in Lung-Cancer Treatment on Population Mortality](#) N Engl J Med. 2020 Aug 13;383(7):640-649. doi: 10.1056/NEJMoa1916623. Nadia Howlader 1 , Gonçalo Forjaz 1 , Meghan J Mooradian 1 , Rafael Meza 1 , Chung Yin Kong 1 , Kathleen A Cronin 1 , Angela B Mariotto 1 , Douglas R Lowy 1 , Eric J Feuer 1

BACKGROUND: Lung cancer is made up of distinct subtypes, including non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). Although overall mortality from lung cancer has been declining in the United States, little is known about mortality trends according to cancer subtype at the population level because death certificates do not record subtype information. **METHODS:** Using data from Surveillance, Epidemiology, and End Results (SEER) areas, we assessed lung-cancer mortality and linked deaths from lung cancer to incident cases in SEER cancer registries. This allowed us to evaluate population-level mortality trends attributed to specific subtypes (incidence-based mortality). We also

evaluated lung-cancer incidence and survival according to cancer subtype, sex, and calendar year.

Joinpoint software was used to assess changes in incidence and trends in incidence-based mortality.

RESULTS: Mortality from NSCLC decreased even faster than the incidence of this subtype, and this decrease was associated with a substantial improvement in survival over time that corresponded to the timing of approval of targeted therapy. Among men, incidence-based mortality from NSCLC decreased 6.3% annually from 2013 through 2016, whereas the incidence decreased 3.1% annually from 2008 through 2016. Corresponding lung cancer-specific survival improved from 26% among men with NSCLC that was diagnosed in 2001 to 35% among those in whom it was diagnosed in 2014. This improvement in survival was found across all races and ethnic groups. Similar patterns were found among women with NSCLC. In contrast, mortality from SCLC declined almost entirely as a result of declining incidence, with no improvement in survival. This result correlates with limited treatment advances for SCLC in the time frame we examined. **CONCLUSIONS:** Population-level mortality from NSCLC in the United States fell sharply from 2013 to 2016, and survival after diagnosis improved substantially. Our analysis suggests that a reduction in incidence along with treatment advances - particularly approvals for and use of targeted therapies - is likely to explain the reduction in mortality observed during this period.

Vascular inflammation and endothelial injury in SARS-CoV-2 infection: The overlooked regulatory cascades implicated by the ACE2 gene cluster

QJM. 2020 Aug 10;hcaa241. doi: 10.1093/qjmed/hcaa241. Online ahead of print. Claire L Shovlin^{1 2}, Marcela P Vizcaychipi³ COVID-19 has presented physicians with an unprecedented number of challenges and mortality. The basic question is why, in contrast to other "respiratory" viruses, SARS-CoV-2 infection can result in such multi-systemic, life-threatening complications and a severe pulmonary vasculopathy. It is widely known that SARS-CoV-2 uses membrane-bound angiotensin-converting enzyme 2 (ACE2) as a receptor, resulting in internalisation of the complex by the host cell. We discuss the evidence that failure to suppress coronaviral replication within 5 days results in sustained downregulation of ACE2 protein expression, and that ACE2 is under negative-feedback regulation. We then expose openly-available experimental repository data that demonstrate the gene for ACE2 lies in a novel cluster of interregulated genes on the X chromosome including PIR encoding pirin (quercetin 2,3-dioxygenase), and VEGFD encoding the predominantly lung-expressed vascular endothelial growth factor D. The five double-elite enhancer/promoters that are known to be operational, and shared read-through lncRNA transcripts, imply that ongoing SARS-CoV-2 infection will reduce host defences to reactive oxygen species, directly generate superoxide O₂⁻ and H₂O₂ (a "ROS storm"), and impair pulmonary endothelial homeostasis. Published cellular responses to oxidative stress complete the loop to pathophysiology observed in severe COVID-19. Thus for patients who fail to rapidly suppress viral replication, the newly-appreciated ACE2 co-regulated cluster predicts delayed responses that would account for catastrophic deteriorations. We conclude that ACE2 homeostatic drives provide a unified understanding which should help optimise therapeutic approaches during the wait until safe, effective vaccines and antiviral therapies for SARS-CoV-2 are delivered.

SARS-CoV-2 Infection and Lung Cancer: Potential Therapeutic Modalities

Cancers (Basel). 2020 Aug 5;12(8):E2186. doi: 10.3390/cancers12082186. Ishita Gupta^{1 2}, Balsam Rizeq^{1 2}, Eyad Elkord^{3 4}, Semir Vranic¹, Ala-Eddin Al Moustafa^{1 2} Human coronaviruses, especially SARS-CoV-2, are emerging pandemic infectious diseases with high morbidity and mortality in certain group of patients. In general, SARS-CoV-2 causes symptoms ranging from the common cold to severe conditions accompanied by lung injury, acute respiratory distress syndrome in addition to other organs' destruction. The main impact upon SARS-CoV-2 infection is damage to alveolar and acute respiratory failure. Thus, lung cancer patients are identified as a particularly high-risk group for SARS-CoV-2 infection and its complications. On the other hand, it has been reported

that SARS-CoV-2 spike (S) protein binds to angiotensin-converting enzyme 2 (ACE-2), that promotes cellular entry of this virus in concert with host proteases, principally transmembrane serine protease 2 (TMPRSS2). Today, there are no vaccines and/or effective drugs against the SARS-CoV-2 coronavirus. Thus, manipulation of key entry genes of this virus especially in lung cancer patients could be one of the best approaches to manage SARS-CoV-2 infection in this group of patients. We herein provide a comprehensive and up-to-date overview of the role of ACE-2 and TMPRSS2 genes, as key entry elements as well as therapeutic targets for SARS-CoV-2 infection, which can help to better understand the applications and capacities of various remedial approaches for infected individuals, especially those with lung cancer.

Immune complement and coagulation dysfunction in adverse outcomes of SARS-CoV-2 infection

Nat Med. 2020 Aug 3. doi: 10.1038/s41591-020-1021-2. Online ahead of print. Vijendra Ramlall ^{1 2}, Phyllis M Thangaraj ^{1 3}, Cem Meydan ^{4 5}, et al.

Understanding the pathophysiology of SARS-CoV-2 infection is critical for therapeutic and public health strategies. Viral-host interactions can guide discovery of disease regulators, and protein structure function analysis points to several immune pathways, including complement and coagulation, as targets of coronaviruses. To determine whether conditions associated with dysregulated complement or coagulation systems impact disease, we performed a retrospective observational study and found that history of macular degeneration (a proxy for complement-activation disorders) and history of coagulation disorders (thrombocytopenia, thrombosis and hemorrhage) are risk factors for SARS-CoV-2-associated morbidity and mortality-effects that are independent of age, sex or history of smoking. Transcriptional profiling of nasopharyngeal swabs demonstrated that in addition to type-I interferon and interleukin-6-dependent inflammatory responses, infection results in robust engagement of the complement and coagulation pathways. Finally, in a candidate-driven genetic association study of severe SARS-CoV-2 disease, we identified putative complement and coagulation-associated loci including missense, eQTL and sQTL variants of critical complement and coagulation regulators. In addition to providing evidence that complement function modulates SARS-CoV-2 infection outcome, the data point to putative transcriptional genetic markers of susceptibility. The results highlight the value of using a multimodal analytical approach to reveal determinants and predictors of immunity, susceptibility and clinical outcome associated with infection.