Caring Ambassadors Lung Cancer Program
Literature Review, February 2020

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

PTGES/PGE2 signaling links immunosuppression and lung metastasis in Gprc5a-knockout mouse model. Wang T1,2, Jing B1,2, Xu D1,2, et al. Oncogene. 2020 Feb 14. doi: 10.1038/s41388-020-1207-6. [Epub ahead of print]

Chronic inflammation has been linked to promotion of tumorigenesis and metastasis in lung. However, due to lack of a relevant animal model for characterization, the underlying mechanism remains elusive. Lung tumor suppressor gene Gprc5a-knockout (ko) mice are susceptible to lung inflammation, tumorigenesis and metastasis, which resembles the pathological features in human patients. Here, we showed that PTGES/PGE2 signaling was highly associated with lung tumorigenesis and metastasis in Gprc5a-ko mice. Interestingly, Ptges-knockout in mouse lung tumor cells, although reduced their stemness and EMT-like features, still formed tumors and lung metastasis in immune-deficient nude mice, but not in immune-competent mice. This suggests that the major role of PTGES/PGE2 signaling in tumorigenicity and lung metastasis is through immunosuppression. Mechanistically, PTGES/PGE2 signaling intrinsically endows tumor cells resistant to T-cell cytotoxicity, and induces cytokines extrinsically for MDSC recruitment, which is crucial for suppression of T-cell immunity. Importantly, targeting PGE2 signaling in Gprc5a-ko mice by PTGES inhibitor suppressed MDSC recruitment, restored T cells, and significantly repressed lung metastasis. Thus, PTGES/PGE2 signaling links immunosuppression and metastasis in an inflammatory lung microenvironment of Gprc5a-ko mouse model.

Tumor cell-derived angiopoietin-like protein 2 establishes a preference for glycolytic metabolism in lung cancer cells. Osumi H1,2, Horiguchi H1,3, Kadomatsu T1,4, et al. Cancer Sci. 2020 Feb 3. doi: 10.1111/cas.14337. [Epub ahead of print]

We previously revealed that tumor cell-derived angiopoietin-like protein 2 (ANGPTL2) accelerates the metastatic capacity of tumors in an autocrine/paracrine manner by activating tumor cell motility and invasiveness and the epithelial-mesenchymal transition. However, the effects of ANGPTL2 on cancer cell glycolytic metabolism, which is a hallmark of tumor cells, are unknown. Here we report evidence supporting a role for tumor cell-derived ANGPTL2 in establishing a preference for glycolytic metabolism.

We report that a highly metastatic lung cancer cell subline expressing abundant ANGPTL2 showed upregulated expression of the glucose transporter GLUT3 as well as enhanced glycolytic metabolism relative to a less metastatic parental line. Most notably, ANGPTL2 overexpression in the less metastatic line activated glycolytic metabolism by increasing GLUT3 expression. Moreover, ANGPTL2 signaling through integrin α5β1 increased GLUT3 expression by increasing transforming growth factor-β (TGF-β) signaling and expression of the downstream transcription factor zinc finger E-box binding homeobox 1 (ZEB1). Conversely, ANGPTL2 knockdown in the highly metastatic subline decreased TGF-β1, ZEB1, and GLUT3 expression and antagonized glycolytic metabolism. In primary tumor cells from patients with lung cancer, ANGPTL2 expression levels correlated with GLUT3 expression. Overall, this work suggests that tumor cell-derived ANGPTL2 accelerates activities associated with glycolytic metabolism in lung cancer cells by activating TGF-β-ZEB1-GLUT3 signaling.

RALY may cause an aggressive biological behavior and a dismal prognosis in non-small-cell lung cancer. Song G1, Guo G1, Du T1, Li X1, Wang J1, Yan Y2, Zhao Y3. Exp Cell Res. 2020 Feb 1:111884. doi: 10.1016/j.yexcr.2020.111884. [Epub ahead of print]
RALY is a member of the heterogeneous nuclear ribonucleoprotein (hnRNP), an RNA-binding protein that plays a role in mRNA splicing and metabolism, may be involved in tumorigenesis and development. Some studies have shown that RALY plays a role in promoting cancer in a variety of tumors. However, the biological function and molecular mechanism of RALY in non-small cell lung cancer (NSCLC) remain unknown. TCGA databases were used to gather RALY expression data in NSCLC, the results indicate that RALY is highly expressed in cancer tissue of NSCLC patients. Then we demonstrated that RALY gene expression was notably upregulated in NSCLC tissue and cell lines (A549 and SK-MES-1), and was associated with lymph node metastasis (P = 0.007) and poorer overall survival in NSCLC patients. Subsequently, RALY in A549 and SK-MES-1 cells was knocked down by lentivirus to analyze the consequences of RALY on the biological behavior of NSCLC cell lines. Our results indicated that RALY knockdown impaired NSCLC cells proliferation, migration, and invasion, as well as arrested cells in G1 phase, and the reintroduction of RALY recused its biological phenotype. Furthermore, RALY knockdown down-regulated the expression levels of c-Myc, Cyclin D1, CDK4, MMP9, Rho A ,Rho C, N-cadherin and β-catenin, and up-regulated the expression levels of P27, Rho B and E-cadherin. Therefore, targeting RALY could be a promising molecular target for NSCLC treatment

SCREENING, COMPREHENSIVE BIOMARKER TESTING, DIAGNOSIS AND STAGING

Evaluating Knowledge, Attitudes, and Beliefs about Lung Cancer Screening Using Crowdsourcing. Monu J1, Triplette M2, Wood DE1, Wolff EM1, Lavallee DC1, Flum DR1, Farjah F3. Chest. 2020 Feb 6. pii: S0012-3692(20)30251-8. doi: 10.1016/j.chest.2019.12.048. [Epub ahead of print]
BACKGROUND: Lung cancer screening-despite its proven mortality benefit-remains vastly underutilized. Prior studies examined knowledge, attitudes, and beliefs to better understand the reasons underlying low screening rates. These investigations may have limited generalizability because of traditional participant recruitment strategies and examining only subpopulations eligible for screening. We used crowdsourcing to recruit a broader population to assess these factors in a potentially more general population. **METHODS:** We developed a 31-item survey to assess knowledge, attitudes, and beliefs regarding screening among individuals considered high-risk for lung cancer by the United States Preventive Services Task Force (USPSTF). We used Amazon's crowdsourcing platform-Mechanical Turk-to recruit subjects. **RESULTS:** Among 240 respondents that qualified for our study, 106 (44%) reported knowledge of a screening test for lung cancer. However, only 36 of them (35%) correctly identified low-dose computed tomography as the appropriate test. Two hundred twenty-two respondents (93%) reported believing that early-detection of lung cancer has the potential to saves lives and 165 (69%)

were willing to undergo lung cancer screening if it was recommended by their physician. Multivariable regression analysis found that knowledge of lung cancer screening, smoking status, chronic pulmonary disease, and belief in the efficacy of early-detection of lung cancer were associated with willingness to screen. **CONCLUSIONS:** Although a minority of individuals at high-risk for lung cancer are aware of screening, the majority believe early-detection saves lives and would pursue screening if recommended by their primary care physician. Health systems may increase screening rates by improving patient and physician awareness of lung cancer screening.

The OaSiS trial: A hybrid type II, national cluster randomized trial to implement smoking cessation during CT screening for lung cancer. Foley KL1, Miller DP Jr2, et al. Contemp Clin Trials. 2020 Feb 19:105963. doi: 10.1016/j.cct.2020.105963. [Epub ahead of print]
INTRODUCTION: When the Centers for Medicare and Medicaid Services announced coverage for low dose CT lung cancer screening, they also mandated that imaging centers offer smoking cessation services. We designed the Optimizing Lung Screening (OaSiS) trial to evaluate strategies to implement the Public Health Service Guidelines for Treating Tobacco Use and Dependence during CT screening for lung cancer. **METHODS AND DESIGN:** OaSiS was implemented using a pragmatic effectiveness-implementation hybrid design in 26 imaging clinics across the United States affiliated with the National Cancer Institute's National Community Oncology Research Program (NCORP). The 26 sites selected for participation in the OaSiS trial were randomized to receive either a compendium of implementation strategies to add or enhance smoking cessation services during lung screening or to usual care. Usual care sites were given the option to receive the full compendium of implementation strategies at the conclusion of data collection. We have evaluated both the effectiveness of the implementation strategies to improve smoking cessation at six months among patients undergoing LDCT screening as well as the adoption and sustainability of evidence-based tobacco cessation strategies in imaging clinics. **DISCUSSION:** The OaSiS trial was designed to identify opportunities for implementing evidence-based smoking cessation into LDCT lung cancer screening imaging facilities and to establish the effectiveness of these services. We report our study design and evaluation, including strengths of the pragmatic design and the inclusion of a diverse range of screening programs. Establishing these tobacco cessation services will be critical to reducing smoking related morbidity and mortality.

Education Level Predicts Appropriate Follow-Up of Incidental Findings From Lung Cancer Screening. Kapoor S1, Deppen SA2, Paulson AB3, Haddad D4, Cook JP3, Sandler KL3. J Am Coll Radiol. 2020 Jan 10. pii: S1546-1440(19)31477-2. doi: 10.1016/j.jacr.2019.12.014. [Epub ahead of print]
PURPOSE: The aim of this study was to identify predictors of appropriate follow-up for clinically significant incidental findings (IFs) detected with low-dose CT during lung cancer screening.
METHODS: Charts of 1,458 prospectively enrolled lung screening patients from January 1, 2015, to October 31, 2018, were reviewed. IFs, other than coronary artery calcification and emphysema, were identified. ACR practice guidelines defined appropriate patient follow-up. Patient demographic and social characteristics were obtained from the initial shared decision-making visit and the electronic medical record. Factors of interest included age, gender, race, education level, and insurance status. Education level was reported as high school graduate or less or education past high school. A multivariate logistic regression was estimated to assess patient factors associated with appropriate follow-up. **RESULTS:** One hundred thirty-eight participants (9%) with 141 actionable IFs were identified. The overall appropriate follow-up rate was 82%. The most common IFs were renal lesions (16%), dilated thoracic aorta (10%), and pulmonary fibrosis (10%). Univariate analysis of appropriate patient follow-up revealed a significant difference for education level (P = .02). A greater than high school education remained strongly associated with appropriate follow-up after controlling for other demographic factors. **CONCLUSIONS:** Appropriate patient follow-up of clinically significant IFs from lung cancer screening is a well-recognized

avenue to improve population health. Education level is a significant independent predictor of appropriate follow-up of IFs, whether as a surrogate for low socioeconomic status or as an indication of health literacy. To address these realities, lung screening shared decision making should adapt to consider health care access and health literacy.

Evaluating Potential Racial Inequities in Low-dose Computed Tomography Screening for Lung Cancer. Richmond J1, Mbah OM2, Dard SZ3, Jordan LC2, Cools KS4, Samuel CA5, Khan JM6, Manning MA6. J Natl Med Assoc. 2020 Feb 14. pii: S0027-9684(20)30005-5. doi: 10.1016/j.jnma.2019.10.002. [Epub ahead of print]

BACKGROUND: Lung cancer is the leading cause of cancer death in the US, and significant racial disparities exist in lung cancer outcomes. For example, Black men experience higher lung cancer incidence and mortality rates than their White counterparts. New screening recommendations for low-dose computed tomography (LDCT) promote earlier detection of lung cancer in at-risk populations and can potentially help mitigate racial disparities in lung cancer mortality if administered equitably. Yet, little is known about the extent of racial differences in uptake of LDCT. **OBJECTIVE:** To evaluate potential racial disparities in LDCT screening in a large community-based cancer center in central North Carolina. **METHODS:** We conducted a retrospective study of the initial patients undergoing LDCT in a community-based cancer center (n = 262). We used the Pearson chi-squared test to assess potential racial disparities in LDCT screening. **RESULTS:** Study results suggest that Black patients may be less likely than White patients to receive LDCT screening when eligible ($\chi 2 = 51.41$, $p < 0.0001$). **CONCLUSION:** Collaboration among healthcare providers, researchers, and decision makers is needed to promote LDCT equity.

MicroRNA-based biomarkers for diagnosis of non-small cell lung cancer (NSCLC). Liao J1, Shen J1, Leng Q1, Qin M1, Zhan M2, Jiang F1. Thorac Cancer. 2020 Jan 28. doi: 10.1111/1759-7714.13337. [Epub ahead of print]

BACKGROUND: The development of biomarkers for the early detection of non-small cell lung cancer (NSCLC) is clinically important. We have developed miRNA biomarkers in sputum and plasma, respectively, for NSCLC. Herein, we evaluate whether integrated analysis of the miRNAs across the different types of specimens could improve the early detection of NSCLC. **METHODS:** Using reverse transcription PCR, we determined expressions of two miRNAs (miRs-31-5p and 210-3p) in sputum and three miRNAs (miRs-21-5p, 210-3p, and 486-5p) in plasma of a training cohort of 76 NSCLC patients and 72 cancer-free smokers. The results were validated in a testing cohort of 56 NSCLC patients and 55 cancer-free smokers. **RESULTS:** The panels of two sputum miRNAs and three plasma miRNAs had 65.8-75.0% sensitivities and 83.3-87.5% specificities for diagnosis of NSCLC in the training cohort. The individual sputum or plasma miRNA panel had a higher sensitivity for squamous cell carcinoma or adenocarcinoma of the lung, respectively. From the miRNAs, we optimized an integrated panel of biomarkers consisting of two sputum miRNAs (miRs-31-5p and 210-3p) and one plasma miRNA (miR-21-5p) that had higher sensitivity (85.5%) and specificity (91.7%) for diagnosis of NSCLC compared with the individual panels alone. Furthermore, the performance of the integrated panel of biomarkers was independent of histology and stage of NSCLC, and patients' age, sex, and ethnicity. The performance of the integrated panel of biomarkers was confirmed in the testing cohort. **CONCLUSIONS:** Integrating biomarkers across different body fluids would synergistically improve the early detection of NSCLC. **KEY POINTS:** Lung cancer is a heterogeneous disease and develops from complex aberrations. Integrating sputum and plasma miRNAs has higher accuracy than when they are used alone.

Unique molecular features and clinical outcomes in young patients with non-small cell lung cancer harboring ALK fusion genes. Tian P1,2, Liu Y1, Zeng H1, Tang Y3, Lizaso A4, Ye J4, Shao L4, Li Y5. J Cancer Res Clin Oncol. 2020 Jan 1. doi: 10.1007/s00432-019-03116-6. [Epub ahead of print]
PURPOSE: This study aimed to determine the molecular features and clinical outcomes of young patients with non-small cell lung cancer (NSCLC) harboring ALK fusion genes. **METHODS:** We interrogated the genomic profile of 1652 patients with lung cancer who underwent targeted next-generation sequencing to screen for candidate oncogenic drivers using histological specimens acquired from January 2016 to December 2018. **RESULTS:** ALK fusions were identified in 101 NSCLC patients, and 52 of them were diagnosed before the age of 50 years (52/367, 14.2%). Of the 52 patients with early-onset disease, 22 (42.3%) were male and 43 (82.7%) never smoked; the median patient age was 44 years (range 28-50 years). The most frequently occurring ALK fusion partner was EML4, which was identified in 80.8% (42/52) of young patients. Compared to the older patients, patients with early-onset disease were more likely to harbor EML4-ALK variant 1 (38.5% vs. 14.3%; P = 0.007). We also identified rare ALK fusions, including CHRNA7-ALK, TACR1-ALK, HIP1-ALK, DYSF-ALK and ITGAV-ALK, in patients with early-onset disease, and patients with these fusions responded well to crizotinib treatment. A statistically significant difference was observed in progression-free survival (PFS) between the young patients and older patients who received crizotinib as the first-line therapy (17.5 months vs 9.0 months, P = 0.048). However, the median PFS of young patients harboring concurrent TP53 mutations was only 6.2 months. **CONCLUSION:** Unique genetic characteristics were found in ALK-rearranged NSCLC patients with early disease onset, and these patients responded better to crizotinib and had longer PFS compared to patients with later disease onset. However, patients with concomitant TP53 mutations may not have a significant response to treatment.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

The association of robotic lobectomy volume and nodal upstaging in non-small cell lung cancer. Okusanya OT1, Lutfi W2, Baker N2, et al. J Robot Surg. 2020 Jan 16. doi: 10.1007/s11701-020-01044-z. [Epub ahead of print]
Robotic lung resection for lung cancer has gained popularity over the last 10 years. As with many surgical techniques, there are improvements in outcomes associated with increased operative volume. We sought to investigate lymph-node harvest and upstaging rates for robotic lobectomies performed at hospitals with varying robotic experience. The National Cancer Data Base was queried for patients with early stage non-small cell lung cancer who received lobectomy between 2010 and 2015. Hospitals were stratified into volume categories based on the number of robotic resections performed, as a proxy for robotic experience: low at ≤ 12, low-middle 13-26, middle-high 27-52, and high volume at greater than or equal to 53. Lymph-node counts and nodal upstaging were compared among these volume categories. 8360 robotic lobectomies were performed. Mean lymph-node counts were for low, low-middle, middle-high, and high-volume robotic lobectomies were 9.8, 11.4, 12.9, and 12.6, respectively (P < 0.001), while nodal-upstaging rates were 10.3%, 10.2%, 12.8%, and 13.4%, respectively (P < 0.001). Compared to low-volume hospitals, on multivariable analysis, high-volume robotic centers had increased nodal harvest (P < 0.001) and nodal-upstaging rates (P < 0.001). Robotic lobectomies performed at high-volume hospitals have greater lymph-node harvest and upstaging than low-volume hospitals.

Electromagnetic navigational bronchoscopy-directed dye marking for locating pulmonary nodules. Wang LL1, He BF2, Cui JH2, Gao XL2, Chen PP2, Zhong WZ3, Liao RQ3, Li J4, Sun JY5. Postgrad Med J. 2020 Feb 10. pii: postgradmedj-2019-137083. doi: 10.1136/postgradmedj-2019-137083. [Epub ahead of print]

BACKGROUND: Small peripheral pulmonary nodules, which are usually deep-seated with no visual markers on the pleural surface, are often difficult to locate during surgery. At present, CT-guided percutaneous techniques are used to locate pulmonary nodules, but this method has many limitations. Thus, we aimed to evaluate the accuracy and feasibility of electromagnetic navigational bronchoscopy (ENB) with pleural dye to locate small peripheral pulmonary nodules before video-associated thoracic surgery (VATS). **METHODS:** The ENB localisation procedure was performed under general anaesthesia in an operating room. Once the locatable guide wire, covered with a sheath, reached the ideal location, it was withdrawn and 0.2-1.0 mL of methylene blue/indocyanine green was injected through the guide sheath. Thereafter, 20-60 mL of air was instilled to disperse the dye to the pleura near the nodules. VATS was then performed immediately. **RESULTS:** Study subjects included 25 patients with 28 nodules. The mean largest diameter of the pulmonary nodules was 11.8 mm (range, 6.0-24.0 mm), and the mean distance from the nearest pleural surface was 13.4 mm (range, 2.5-34.9 mm). After the ENB-guided localisation procedure was completed, the dye was visualised in 23 nodules (82.1%) using VATS. The average duration of the ENB-guided pleural dye marking procedure was 12.6 min (range, 4-30 min). The resection margins were negative in all malignant nodules. Complications unrelated to the ENB-guided localisation procedure occurred in two patients, including one case of haemorrhage and one case of slow intraoperative heart rate. **CONCLUSION:** ENB can be used to safely and accurately locate small peripheral pulmonary nodules and guide surgical resection.

The Impact of Anlotinib on Brain Metastases of Non-Small Cell Lung Cancer: Post Hoc Analysis of a Phase III Randomized Control Trial (ALTER0303). Jiang S1,2, Liang H1, Liu Z1,3, Zhao S4, Liu J1, Xie Z1, Wang W1, Zhang Y1, Han B5, He J1, Liang W1. Oncologist. 2020 Feb 20. doi: 10.1634/theoncologist.2019-0838. [Epub ahead of print]

BACKGROUND: Anlotinib has been shown to prolong progression-free survival (PFS) and overall survival (OS) for non-small cell lung cancer (NSCLC). Herein we sought to analyze the effect of anlotinib in managing brain metastases (BM) and its brain-associated toxicities.**METHODS:** The PFS and OS of anlotinib versus placebo in those with and without BM recorded at baseline were calculated and compared respectively. Time to brain progression (TTBP), a direct indicator of intracranial control, was also compared between anlotinib and placebo. All calculations were adjusted for confounding factors, including stage, histology, driver mutation type, and therapy history. **RESULTS:** A total of 437 patients were included; 97 cases were recorded with BM at baseline. For patients with BM at baseline, anlotinib was associated with longer PFS (hazard ratio [HR], 0.29; 95% confidence interval [CI], 0.15-0.56) and OS (HR, 0.72; 95% CI, 0.42-1.12), presenting similar extent of improvement in those without BM (PFS: HR, 0.33; 95% CI, 0.24-0.45; OS: HR, 0.67; 95% CI, 0.50-0.91). Specifically, the intracranial objective response rate was 14.3% and the disease control rate was 85.7% in patients with BM who were treated with anlotinib. Anlotinib was associated with longer TTBP (HR, 0.11; 95% CI, 0.03-0.41; p = .001) despite all confounders. Additionally, anlotinib was associated with more neural toxicities (18.4% vs. 8.4%) and psychological symptoms (49.3% vs. 35.7%) but not with infarction or cerebral hemorrhage. **CONCLUSION:** Anlotinib can benefit patients with advanced NSCLC with BM and is highly potent in the management of intracranial lesions. Its special effect on BM and cerebral tissue merits further investigation. (ClinicalTrials.gov ID: NCT02388919).

Impact of pulmonary function on pulmonary complications after robotic-assisted thoracoscopic lobectomy. Cao C1,2, Louie BE3, Melfi F4, Veronesi G5, Razzak R3, Romano G4, Novellis P5,

Ranganath NK6, Park BJ1. Eur J Cardiothorac Surg. 2020 Feb 1;57(2):338-342. doi: 10.1093/ejcts/ezz205.
OBJECTIVES: Percentage-predicted forced expiratory volume in 1 s (FEV1) and diffusing capacity for carbon monoxide (DLCO), and their predicted postoperative (ppo) values are established prognostic factors for postoperative pulmonary complications after thoracotomy. However, their predictive value for minimally invasive pulmonary resections remains controversial. This study assessed the incidence of pulmonary complications after robotic lobectomy for primary lung cancer and analysed the predictive significance of FEV1 and DLCO. **METHODS:** This was a retrospective analysis of patients who underwent robotic lobectomy from 4 institutions. Descriptive and comparative analyses were performed for patients who experienced pulmonary complications versus patients who did not, in relation to FEV1 and DLCO values. To identify thresholds for increased complications, patients were categorized into groups of 10% incremental increases in FEV1 and DLCO, and their ppo values. **RESULTS:** From November 2002 to April 2018, 1088 patients underwent robotic lobectomy. Overall, 169 postoperative pulmonary complications occurred in 141 patients. Male gender and Eastern Cooperative Oncology Group grade ≥1 were associated with increased pulmonary complications on univariable analysis. Patients who experienced pulmonary complications had increased mortality (2.1% vs 0.2%, P = 0.017) and longer hospitalizations (9 vs 4 days, P < 0.001). Pulmonary complications were associated when FEV1 ≤60% and DLCO ≤50%, and when ppo FEV1 or DLCO was ≤50%; ppo FEV1 ≤50% (P < 0.001) and ppo DLCO ≤50% (P = 0.031) remained statistically significant on multivariable analysis. **CONCLUSIONS:** Both FEV1 and DLCO were shown to be significant predictors of pulmonary complications. Furthermore, thresholds of percentage-predicted and ppo FEV1 and DLCO values were identified, below which pulmonary complications occurred significantly more frequently, suggesting their predictive values are particularly useful in patients with poorer pulmonary function.

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

Nab-paclitaxel in older patients with non-small cell lung cancer who have developed disease progression after platinum-based doublet chemotherapy. Weiss JM1, Pennell N2, Deal AM1, et al. Cancer. 2020 Jan 14. doi: 10.1002/cncr.32573. [Epub ahead of print]
BACKGROUND: The selection of later-line treatment for older patients with AJCC (version 7) stage IV non-small cell lung cancer (NSCLC) remains controversial. Nanoparticle albumin-bound (nab)-paclitaxel is approved with carboplatin for the first-line treatment of patients with NSCLC and subgroup analysis of phase 3 data has suggested superior survival in older patients. **METHODS:** The authors conducted a phase 2 study of nab-paclitaxel in 42 patients aged ≥70 years who had been treated previously with a platinum doublet regimen; patients also could have received a PD-1 inhibitor. The primary endpoint of the current study was grade 3 to 5 toxicity (according to the National Cancer Institute Common Terminology Criteria for Adverse Events [version 4.0]). In addition to response rate, progression-free survival (PFS), and overall survival (OS), geriatric assessments also were performed before and during treatment, associations between baseline sarcopenia and outcomes were explored, and changes in T lymphocyte p16 before and during treatment were measured. The authors also performed a retrospective subgroup analysis of 19 older patients who were treated with nab-paclitaxel as part of a larger, randomized, phase 2 study; data were not combined. **RESULTS:** The rate of grade 3 to 5 toxicities was 33.7%. The most common grade 3 to 5 toxicities were decreased white blood cell count (11.9%), neutropenia (9.5%), and fatigue (11.9%). The response rate was 34.2% (2.6% complete response rate and 31.6% partial response rate). The median PFS was 5.2 months and the median OS was 9.3 months. Adverse prognostic factors were common: 42% of patients were frail and 39% of patients were prefrail, whereas 21% had an Eastern Cooperative Oncology Group performance status of 2 and 27% were sarcopenic. Only frailty was found to be predictive of inferior survival. A subgroup analysis of 19 older patients treated with nab-paclitaxel

alone in a prior trial demonstrated a response rate of 15.8%, a PFS of 4.2 months, and an OS of 13.6 months. **CONCLUSIONS:** Fit and prefrail older patients with stage IV NSCLC should be considered for treatment with nab-paclitaxel after disease progression with doublet chemotherapy.

Early Detection of Hyperprogressive Disease in Non-Small Cell Lung Cancer by Monitoring of Systemic T Cell Dynamics. Arasanz H1,2, Zuazo M1, Bocanegra A1, et al. Cancers (Basel). 2020 Feb 4;12(2). pii: E344. doi: 10.3390/cancers12020344.
Hyperprogressive disease (HPD) is an adverse outcome of immunotherapy consisting of an acceleration of tumor growth associated with prompt clinical deterioration. The definitions based on radiological evaluation present important technical limitations. No biomarkers have been identified yet. In this study, 70 metastatic NSCLC patients treated with anti-PD-1/PD-L1 immunotherapy after progression to platinum-based therapy were prospectively studied. Samples from peripheral blood were obtained before the first (baseline) and second cycles of treatment. Peripheral blood mononuclear cells (PBMCs) were isolated and differentiation stages of CD4 lymphocytes quantified by flow cytometry and correlated with HPD as identified with radiological criteria. A strong expansion of highly differentiated CD28- CD4 T lymphocytes (CD4 THD) between the first and second cycle of therapy was observed in HPD patients. After normalizing, the proportion of posttreatment/pretreatment CD4 THD was significantly higher in HPD when compared with the rest of patients (median 1.525 vs. 0.990; p = 0.0007), and also when stratifying by HPD, non-HPD progressors, and responders (1.525, 1.000 and 0.9700 respectively; p = 0.0025). A cut-off value of 1.3 identified HPD with 82% specificity and 70% sensitivity. An increase of CD28- CD4 T lymphocytes ≥ 1.3 (CD4 THD burst) was significantly associated with HPD (p = 0.008). The tumor growth ratio (TGR) was significantly higher in patients with expansion of CD4 THD burst compared to the rest of patients (median 2.67 vs. 0.86, p = 0.0049), and also when considering only progressors (median 2.67 vs. 1.03, p = 0.0126). A strong expansion of CD28- CD4 lymphocytes in peripheral blood within the first cycle of therapy is an early differential feature of HPD in NSCLC treated with immune-checkpoint inhibitors. The monitoring of T cell dynamics allows the early detection of this adverse outcome in clinical practice and complements radiological evaluation.

Immune checkpoint inhibitor-associated interstitial lung diseases correlate with better prognosis in patients with advanced non-small-cell lung cancer. Sugano T1, Seike M1, Saito Y1, Thorac Cancer. 2020 Feb 25. doi: 10.1111/1759-7714.13364. [Epub ahead of print]
BACKGROUND: Interstitial lung disease (ILD) induced by immune checkpoint inhibitors (ICIs) is a potentially life-threatening adverse event. The purpose of this study was to evaluate whether the development of immune-related adverse events (irAEs), especially ILD, was associated with treatment efficacy and to research the features and risk factors of ILD in advanced non-small cell lung cancer (NSCLC). **METHODS:** Between December 2015 and November 2018, 130 advanced NSCLC patients were treated with nivolumab, pembrolizumab or atezolizumab. The patients were categorized into two groups (irAEs group or non-irAEs group). Subsequently, we divided the irAEs group into two groups based on the incidence of ILD (ILD group and irAEs-non-ILD group). Treatment efficacy and the characteristics of ILD were evaluated. **RESULTS:** A total of 39 (30%) patients developed irAEs. ILD was observed in 16 (12%) patients. Patients with ILD had a higher objective response rate (ORR) compared with irAEs-non-ILD patients and non-irAEs patients (63%, 43% and 22%, respectively). Median progression-free survival (mPFS) was 15.9 months in ILD patients, 5.4 months in irAEs-non-ILD patients and 3.3 months in non-irAEs patients (log-rank test, P = 0.033). Pre-existing interstitial pneumonia (IP) was an independent risk factor for ILD-induced ICIs (odds ratio [OR] 14.7; 95% confidence interval [CI]: 2.16-99.6, P = 0.006). **CONCLUSIONS:** ORR and PFS were significantly better in ILD patients than in irAEs-non-ILD and non-irAEs patients. Pre-existing history of IP was an independent risk factor for ILD-induced ICIs.

Brain Metastases in Lung Cancers with Emerging Targetable Fusion Drivers. Tan AC1, Itchins M2,3, Khasraw M4. Int J Mol Sci. 2020 Feb 19;21(4). pii: E1416. doi: 10.3390/ijms21041416.
The management of non-small cell lung cancer (NSCLC) has transformed with the discovery of therapeutically tractable oncogenic drivers. In addition to activating driver mutations, gene fusions or rearrangements form a unique sub-class, with anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) targeted agents approved as the standard of care in the first-line setting for advanced disease. There are a number of emerging fusion drivers, however, including neurotrophin kinase (NTRK), rearrangement during transfection (RET), and neuregulin 1 (NRG1) for which there are evolving high-impact systemic treatment options. Brain metastases are highly prevalent in NSCLC patients, with molecularly selected populations such as epidermal growth factor receptor (EGFR) mutant and ALK-rearranged tumors particularly brain tropic. Accordingly, there exists a substantial body of research pertaining to the understanding of brain metastases in such populations. Little is known, however, on the molecular mechanisms of brain metastases in those with other targetable fusion drivers in NSCLC. This review encompasses key areas including the biological underpinnings of brain metastases in fusion-driven lung cancers, the intracranial efficacy of novel systemic therapies, and future directions required to optimize the control and prevention of brain metastases.

Toxicity management with combination chemotherapy and programmed death 1/programmed death ligand 1 inhibitor therapy in advanced lung cancer. Hoffner B1, Leighl NB2, Davies M3. Cancer Treat Rev. 2020 Feb 4;85:101979. doi: 10.1016/j.ctrv.2020.101979. [Epub ahead of print]
PURPOSE: The combination of an anti-programmed death 1 (PD-1) or anti-programmed death ligand 1 (PD-L1) monoclonal antibody with platinum-based chemotherapy can improve outcomes for patients with advanced non-small-cell lung cancer (NSCLC) or small-cell lung cancer (SCLC) compared with chemotherapy alone. For patients receiving these new treatment regimens, it is important that toxicities be managed effectively. A particular challenge can be determining the etiology of an event, especially when there are overlapping symptoms that can be attributed to either immunotherapy or to platinum-based chemotherapy. Here, we evaluate adverse events (AEs) reported in clinical trials of combination therapy with an anti-PD-1 or anti-PD-L1 (anti-PD-[L]1) immunotherapy and chemotherapy to provide information on toxicity management. **METHODS:** We performed a systematic review of the literature focused on randomized controlled trials of anti-PD-(L)1 therapy combined with platinum-based chemotherapy for advanced/metastatic NSCLC and SCLC. **RESULTS:** Eleven reports from 9 randomized studies evaluating pembrolizumab, nivolumab, and atezolizumab combined with platinum-based chemotherapy in patients with advanced lung cancer were identified. Immune-mediated AEs and infusion reactions occurred more commonly in patients who received anti-PD-(L)1 immunotherapy with platinum-based chemotherapy compared with chemotherapy alone; however, there was no evidence of unexpected or unanticipated toxicity with these combinations. **CONCLUSION:** Combinations of anti-PD-(L)1 immunotherapy with platinum-based chemotherapy regimens improve outcomes for patients with NSCLC and SCLC, and toxicity is generally manageable. Strategies for appropriate workup of AEs to allow clinicians to make informed decisions regarding causality and treatment modifications when appropriate are an important element of management of patients receiving an anti-PD-(L)1 agent combined with platinum-based chemotherapy.

CheckMate 171: A phase 2 trial of nivolumab in patients with previously treated advanced squamous non-small cell lung cancer, including ECOG PS 2 and elderly populations. Felip E1, Ardizzoni A2, Ciuleanu T3, et al. Eur J Cancer. 2020 Mar;127:160-172. doi: 10.1016/j.ejca.2019.11.019. Epub 2020 Feb 3.

BACKGROUND: CheckMate 171 (NCT02409368) is an open-label, multicentre, phase 2 trial of nivolumab in previously treated advanced squamous non-small cell lung cancer (NSCLC), conducted as part of a post-approval commitment to the European Medicines Agency (EMA). We report outcomes from this trial. **METHODS:** Patients with Eastern Cooperative Oncology Group performance status (ECOG PS) 0-2 and disease progression during/after ≥1 systemic treatment (≥1 being platinum-based chemotherapy) for advanced or metastatic disease were treated with nivolumab 3 mg/kg every 2 weeks until progression or unacceptable toxicity. The primary end-point was incidence of grade 3-4 treatment-related select adverse events (AEs). Other end-points included overall survival (OS) and safety. **RESULTS:** Of 811 patients treated, 103 had ECOG PS 2; 278 were aged ≥70 years and 125 were ≥75 years of age. Minimum follow-up was ~18 months. Safety was similar across populations; the most frequent grade 3-4 treatment-related select AEs in all treated patients were diarrhoea (1%), increased alanine aminotransferase (ALT, 1%), pneumonitis (0.7%), colitis (0.6%) and increased aspartate aminotransferase (AST, 0.5%). Median OS was similar in all treated patients and those aged ≥70 and ≥75: 10.0 months, 10.0 months and 11.2 months, respectively. Median OS was 5.2 months in patients with ECOG PS 2. **CONCLUSION:** These results suggest that nivolumab is well tolerated and active in patients with advanced, relapsed squamous NSCLC, including the elderly, with OS outcomes consistent with phase 3 data. In patients with ECOG PS 2, nivolumab had similar tolerability, but outcomes were worse, as expected in this difficult-to-treat, poor prognosis population.

Skeletal muscle mass predicts the outcome of nivolumab treatment for non-small cell lung cancer. Tsukagoshi M1,2, Yokobori T1, Yajima T1,3, et al. Medicine (Baltimore). 2020 Feb;99(7):e19059. doi: 10.1097/MD.0000000000019059.

Nivolumab, a monoclonal antibody targeting programmed cell death-1, significantly prolongs survival for patients with advanced non-small-cell lung cancer (NSCLC). However, little is known about the value of predictive biomarkers. Hence, we investigated the impact of skeletal muscle (SM) mass loss on clinical outcomes in NSCLC patients undergoing nivolumab treatment. Thirty patients with histologically confirmed NSCLC treated with nivolumab were included in this study. Computed tomography was used to determine SM loss based on the SM index (SMI). The SMI is the cross-sectional area of the bilateral psoas muscles at the third lumbar vertebra, divided by height squared. The cut-off values were defined as 6.36 cm/m for men and 3.92 cm/m for women. Among the 30 patients, 13 (43%) had SM loss. There was no significant association between SM loss and immune-related adverse events. The SM loss group had undergone significantly more prior chemotherapy cycles (P = .04). SM loss was significantly associated with fewer nivolumab cycles (P = .01). No patients in the SM loss group achieved a partial response. Patients with SM loss had a significantly shorter progression-free survival period (P = .008) and median overall survival than those with normal SM mass (10 vs 25 months, respectively, P = .03). SM loss was an independent prognostic factor of poor survival. In conclusion, SM loss may be a predictive factor of poor outcomes in NSCLS patients undergoing nivolumab therapy.

The value of immunotherapy for survivors of stage IV non-small cell lung cancer: patient perspectives on quality of life. Park R1, Shaw JW2, Korn A3, McAuliffe J3. J Cancer Surviv. 2020 Jan 16. doi: 10.1007/s11764-020-00853-3. [Epub ahead of print]

PURPOSE: The aim of this study was to examine what personally mattered to 24 patients who received immuno-oncology (IO) therapy for stage IV non-small cell lung cancer (NSCLC), as well as their families and friends, to understand how they evaluated their cancer treatments and the determinants of the quality of life (QoL) of long-term survivors. **METHODS:** Ethnographic research was conducted with 24 patients who had responded to IO (pembrolizumab, nivolumab, atezolizumab, or durvalumab) for stage IV NSCLC, and their families and friends, evenly split among field sites in Denmark, the USA, and the UK. Data were collected using in-depth qualitative interviews, written exercises, and participant observation.

Data analysis methods included interpretative phenomenological analysis, coding, and the development of grounded theory. Researchers spent 2 days with participants in their homes and accompanied them on health-related outings. **RESULTS:** Our findings reveal that long-term survivors on IO experienced their journey in two phases: one in which their cancer had taken over their lives mentally, physically, and spiritually, and another in which their cancer consumed only a part of their everyday lives. Patients who survived longer than their initial prognosis existed in a limbo state in which they were able to achieve some semblance of normalcy in spite of being identified as having a terminal condition. This limbo state impacted their life priorities, decision-making, experience of patient support, and health information-seeking behaviors, all of which shaped their definitions and experience of QoL. **CONCLUSIONS:** The results of this study, which identify the specific challenges of living in limbo, where patients are able to reclaim a portion of their pre-cancer lives while continuing to wrestle with a terminal prognosis, may inform how cancer research can more effectively define and measure the QoL impacts of IO treatments. Also, they may identify approaches that the cancer community can use to support the needs of patients living in a limbo state. These experiences may not be adequately understood by the cancer community or captured by existing QoL measures, which were designed prior to the emergence of IO and without sufficient incorporation of contextual, patient-driven experience. **IMPLICATIONS FOR CANCER SURVIVORS:** Increased awareness of the specific experiences that come with long-term survival on IO may direct how resources should be spent for cancer support for patients and their families. Expanding how QoL is evaluated based on patients' lived experiences of IO can reflect a more accurate depiction of the treatment's benefits and harms.

Patterns of care for older patients with stage IV non-small cell lung cancer in the immunotherapy era. Kehl KL1, Hassett MJ1, Schrag D1. Cancer Med. 2020 Jan 27. doi: 10.1002/cam4.2854. [Epub ahead of print]

BACKGROUND: Historically, older patients with advanced lung cancer have often received no systemic treatment. Immunotherapy has improved outcomes in clinical trials, but its dissemination and implementation at the population level is not well-understood. **METHODS:** A retrospective cohort study of patients with stage IV non-small cell lung cancer (NSCLC) diagnosed age 66 or older from 2012 to 2015 was conducted using SEER-Medicare. Treatment patterns within one year of diagnosis were ascertained. Outcomes included delivery of (a) any systemic therapy; (b) any second-line infusional therapy, following first-line infusional therapy; and (c) any second-line immunotherapy, following first-line infusional therapy. Trends in care patterns associated with second-line immunotherapy approvals in 2015 were assessed using generalized additive models. Sociodemographic and clinical predictors of treatment were explored using logistic regression. **RESULTS:** Among 10 303 patients, 5173 (50.2%) received first-line systemic therapy, with little change between the years 2012 (47.5%) and 2015 (50.3%). Among 3943 patients completing first-line infusional therapy, the proportion starting second-line infusional treatment remained stable from 2012 (30.5%) through 2014 (32.9%), before increasing in 2015 (42.4%) concurrent with second-line immunotherapy approvals. Factors associated with decreased utilization of any therapy included age, black race, Medicaid eligibility, residence in a high-poverty area, nonadenocarcinoma histology, and comorbidity; factors associated with increased utilization of any therapy included Asian race and Hispanic ethnicity. Among patients who received first-line infusional therapy, factors associated with decreased utilization of second-line infusional therapy included age, Medicaid eligibility, nonadenocarcinoma histology, and comorbidity; Asian race was associated with increased utilization of second-line infusional therapy. **CONCLUSION:** United States Food and Drug Administration (FDA) approvals of immunotherapy for the second-line treatment of advanced NSCLC in 2015 were associated with increased rates of any second-line treatment, but disparities based on social determinants of health persisted.

Overcoming acquired resistance of epidermal growth factor receptor-mutant non-small-cell lung cancer cells to osimertinib by combining osimertinib with the histone deacetylase inhibitor panobinostat (LBH589). Zhang H1,2, Qian G2, Zong D2, Fan S1, Owonikoko TK2, Ramalingam SS2, Sun SY2. Cancer. 2020 Jan 30. doi: 10.1002/cncr.32744. [Epub ahead of print]

BACKGROUND: The major clinical obstacle that limits the long-term benefits of treatment with osimertinib (AZD9291) in patients with epidermal growth factor receptor-mutant non-small-cell lung cancer is the development of acquired resistance. Therefore, effective strategies that can overcome acquired resistance to osimertinib are urgently needed. The authors' current efforts in this direction have identified LBH589 (panobinostat), a clinically used histone deacetylase inhibitor, as a potential agent in overcoming osimertinib resistance. **METHODS:** Cell growth and apoptosis in vitro were evaluated by measuring cell numbers and colony formation and by detecting annexin V-positive cells and protein cleavage, respectively. Drug effects on tumor growth in vivo were assessed with xenografts in nude mice. Alterations of tested proteins in cells were monitored with Western blot analysis. Gene knockout was achieved using the CRISPR/Cas9 technique. **RESULTS:** The combination of LBH589 and osimertinib synergistically decreased the survival of different osimertinib-resistant cell lines, including those harboring C797S mutations, with greater inhibition of cell colony formation and growth. The combination enhanced the induction of apoptosis in osimertinib-resistant cells. Importantly, the combination effectively inhibited the growth of osimertinib-resistant xenograft tumors in nude mice. Mechanistically, the combination of LBH589 and osimertinib enhanced the elevation of Bim in osimertinib-resistant cells. Knockout of Bim in osimertinib-resistant cells substantially attenuated or abolished apoptosis enhanced by the LBH589 and osimertinib combination. These results collectively support a critical role of Bim elevation in the induction of apoptosis of osimertinib-resistant cells for this combination.
CONCLUSIONS: The current findings provide strong preclinical evidence in support of the potential for LBH589 to overcome osimertinib resistance in the clinic.

Impact of EGFR mutation and ALK rearrangement on the outcomes of non-small cell lung cancer patients with brain metastasis. Balasubramanian SK1, Sharma M1, Venur VA2, et al. Neuro Oncol. 2020 Feb 20;22(2):267-277. doi: 10.1093/neuonc/noz155.

BACKGROUND: The impact of activating alterations in non-small cell lung cancer (NSCLC) (epidermal growth factor receptor [EGFR] mutation/anaplastic lymphoma kinase [ALK] translocation) in prognosticating patients with brain metastasis (BM) is not well defined. This study was sought to identify this impact in NSCLC patients with BM accounting for the known validated variables. **METHODS:** Among 1078 NSCLC-BM patients diagnosed/treated between January 1, 2000 and December 31, 2015, three hundred and forty-eight with known EGFR/ALK status were analyzed. Overall survival (OS) and intracranial progression-free survival (PFS) were measured from the time of BM. **RESULTS:** Ninety-one patients had either ALK (n = 23) alterations or EGFR (n = 68) mutation and 257 were wild type (WT; negative actionable mutations/alterations). Median age of EGFR/ALK+ NSCLC BM patients was 60 years (range 29.8-82.6 y) and ~50% (n = 44) had Karnofsky performance status (KPS) score >80. Median number of BM was 2 (1 to ≥99). The median OS for the ALK/EGFR+ NSCLC BM was 19.9 versus 10.1 months for the WT (P = 0.028). The number of BM in the EGFR/ALK+ group did not impact OS (BM = 1 with 21.1 months vs 2-3 with 19.1 months and >3 with 23.7 months, P = 0.74), whereas fewer BM in the WT cohort had significantly better OS (BM = 1 with 13.8 mo, 2-3 with 11.0 mo and >3 with 8.1 mo; P = 0.006) with the adjustment of age, KPS, symptoms from BM and synchronicity.
CONCLUSIONS: Number of BM does not impact outcomes in the EGFR/ALK+ NSCLC patients, implying that targeted therapy along with surgery and/or radiation may improve OS irrespective of the number of BM. Number of BM, extracranial metastasis (ECM), and KPS independently affected OS/PFS in WT NSCLC BM, which was consistent with the known literature.

A phase I/II study of weekly nab-paclitaxel plus cisplatin in chemotherapy-naïve patients with advanced non-small-cell lung cancer. Hattori Y1, Kono Y1, Itoh S1, et al. BMC Cancer. 2020 Feb 11;20(1):115. doi: 10.1186/s12885-020-6588-y.
BACKGROUND: The aim of this study was to evaluate the efficacy and safety of nab-paclitaxel plus cisplatin in chemotherapy-naïve patients with advanced non-small-cell lung cancer (NSCLC).
METHODS: Chemotherapy-naïve patients with advanced NSCLC were eligible. In the phase I dose-escalation cohort (3 + 3 design), patients received nab-paclitaxel (80 or 100 mg/m2 given intravenously on days 1, 8 and 15) plus cisplatin (60 or 75 mg/m2 given intravenously on day 1) every 4 weeks. The maximum tolerated dose was not reached. Nab-paclitaxel (100 mg/m2 given intravenously on days 1, 8 and 15) plus cisplatin (75 mg/m2 given intravenously on day 1) every 4 weeks was selected for the phase II cohort. The primary endpoint was the objective response rate (ORR). **RESULTS:** Twenty-three patients (phase I, n = 6; phase II, n = 17) were enrolled, and 22 patients were eligible. The median age was 67.5 years (range 37-75), 90.9% were males, 45.5% had adenocarcinoma and 81.8% had stage IV disease. The ORR was 59.1% (90% confidence interval (CI); 41.8-74.4), and the disease control rate was 86.4% (95% CI; 66.7-95.3). The median progression-free survival was 5.1 months (95% CI; 4.0-6.7), and the median overall survival was 24.2 months (95% CI; 8.4 months to not estimable). The common grade ≥ 3 adverse events were neutropenia (31.8%), leukopenia (27.3%), lung infection (18.2%) and hyponatremia (18.2%). There was one instance of grade 2 interstitial pneumonia and no treatment-related death.
CONCLUSIONS: Nab-paclitaxel plus cisplatin was well tolerated and associated with encouraging response outcomes in chemotherapy-naïve patients with advanced NSCLC. Further investigation is warranted. **TRIAL REGISTRATION:** UMIN Clinical Trials Registry: UMIN000011776; Date of registration: 17 September 2013; Date of enrolment of the first participant to the trial: 23 January 2014.

State-of-the-Art Strategies for Targeting RET-Dependent Cancers. Subbiah V1,2,3, Yang D4, Velcheti V5, Drilon A6,7, Meric-Bernstam F1,4. J Clin Oncol. 2020 Feb 21:JCO1902551. doi: 10.1200/JCO.19.02551. [Epub ahead of print]
Activating receptor tyrosine kinase RET (rarranged during transfection) gene alterations have been identified as oncogenic in multiple malignancies. RET gene rearrangements retaining the kinase domain are oncogenic drivers in papillary thyroid cancer, non-small-cell lung cancer, and multiple other cancers. Activating RET mutations are associated with different phenotypes of multiple endocrine neoplasia type 2 as well as sporadic medullary thyroid cancer. RET is thus an attractive therapeutic target in patients with oncogenic RET alterations. Multikinase inhibitors with RET inhibitor activity, such as cabozantinib and vandetanib, have been explored in the clinic for tumors with activating RET gene alterations with modest clinical efficacy. As a result of the nonselective nature of these multikinase inhibitors, patients had off-target adverse effects, such as hypertension, rash, and diarrhea. This resulted in a narrow therapeutic index of these drugs, limiting ability to dose for clinically effective RET inhibition. In contrast, the recent discovery and clinical validation of highly potent selective RET inhibitors (pralsetinib, selpercatinib) demonstrating improved efficacy and a more favorable toxicity profile are poised to alter the landscape of RET-dependent cancers. These drugs appear to have broad activity across tumors with activating RET alterations. The mechanisms of resistance to these next-generation highly selective RET inhibitors is an area of active research. This review summarizes the current understanding of RET alterations and the state-of-the-art treatment strategies in RET-dependent cancers.

Phase Ib Study of Crizotinib Plus Pembrolizumab in Patients with Previously Untreated Advanced Non-Small Cell Lung Cancer with ALK Translocation. Patel SP1, Pakkala S2, Pennell NA3, et al. Oncologist. 2020 Feb 12. doi: 10.1634/theoncologist.2020-0034. [Epub ahead of print]
LESSONS LEARNED: This study evaluating first-line crizotinib plus pembrolizumab in patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) was

terminated early because increased availability of second-generation ALK inhibitors resulted in difficulty identifying and accruing eligible patients. In the small number of patients enrolled, elevated transaminases were the most common treatment-related toxicity. No other relevant toxicities were observed. Although no definitive conclusions could be drawn because of the small number of patients studied, the higher frequency of severe transaminase increases noted in this sample should be of concern if ALK inhibitor and PD-L1/PD-1 inhibitor combinations are tested in future studies. **BACKGROUND:** Previous research suggests single-agent crizotinib is efficacious for the treatment of anaplastic lymphoma kinase (ALK)-rearranged advanced non-small cell lung cancer (NSCLC). **METHODS:** This study evaluated the safety and preliminary antitumor activity of crizotinib plus pembrolizumab as first-line therapy in patients with ALK-rearranged NSCLC. Patients were initially treated at dose level 0 (DL0) with crizotinib 250 mg twice daily and pembrolizumab 200 mg every 3 weeks (cycle duration was 3 weeks). If a dose-limiting toxicity occurred, subsequent patients were enrolled at a lower dose level (dose level -1 [DL-1]: 3 weeks of crizotinib monotherapy 250 mg twice daily, followed by crizotinib 250 mg twice daily with the addition of pembrolizumab 200 mg every 3 weeks). The primary endpoint was dose-limiting toxicity. Antitumor activity was assessed. **RESULTS:** Nine patients were enrolled: two at DL0, then seven at DL-1. Dose-limiting toxicities occurred in four patients (grade 3 increases in alanine aminotransferase [ALT] and aspartate aminotransferase [AST] and grade 3 fatigue at DL0; grade 3 increase in ALT and grade 3 increases in both ALT and AST at DL-1). **CONCLUSION:** The maximum tolerated dose was not determined because slow accrual resulted in early study termination.

Differential significance of molecular subtypes which were classified into EGFR exon 19 deletion on the first line afatinib monotherapy.
Tokudome N1, Koh Y2, Akamatsu H1, et al. BMC Cancer. 2020 Feb 6;20(1):103. doi: 10.1186/s12885-020-6593-1.
BACKGROUND: Epidermal growth factor receptor (EGFR)-sensitizing mutation, exon 19 deletion consists of several molecular variants. Influences of these variants on clinical response to EGFR tyrosine kinase inhibitors remain elusive. **METHODS:** West Japan Oncology Group 8114LTR is a prospective, multi-institutional biomarker study. Treatment naïve, advanced non-small-cell lung cancer patients with EGFR-sensitizing mutation received afatinib monotherapy. We conducted a preplanned subset analysis of patients harboring exon 19 deletion. Tumor tissue exon 19 deletion molecular variants were identified by blocking-oligo-dependent polymerase chain reaction (PCR) and by Luminex Technology. Plasma cfDNA was also obtained before and after the treatment and EGFR mutations were detected with multiplexed, pico-droplet digital PCR assay. **RESULTS:** Among 57 registered patients, twenty-nine patients were exon 19 deletion. Tissue DNA and cfDNA were available in 26 patients. Among the detected seven molecular variants, the most frequent was p.E746_A750delELREA (65.4%). According to the various classifications of molecular variants, twenty one (80.8%) were classified into 15-nucleotide deletion, one (3.8%) into 18-nucleotide deletion, and four patients (15.4%) into other insertion/substitution variant subgroups. The patient subgroup with 15-nucleotide deletion showed significantly longer progression-free survival than patients in other mixed insertion/substitution variant subgroup ($p = 0.0244$).
CONCLUSIONS: The clinical significance of molecular variants of exon 19 deletion on the first line afatinib monotherapy is reported here for the first time. Further investigation is needed for development of better therapeutic strategies.

NSCLC - RADIOTHERAPY

Confirmatory Analysis of QUARTZ Study Results: Survival Prolongation After Whole-brain Radiotherapy. Nieder C1,2, Dalhaug A3, Pawinski A3. Anticancer Res. 2020 Feb;40(2):977-981. doi: 10.21873/anticanres.14031.

BACKGROUND/AIM: The aim of this study was to analyze the survival of patients with brain metastases treated with best supportive care or additional whole-brain radiotherapy (WBRT), in order to confirm results from the prospective randomized QUARTZ study, which suggested prolonged survival after WBRT (5 fractions of 4 Gy) if favorable prognostic factors were present (age younger than 60 years, graded prognostic assessment score 2.5-3 points). **PATIENTS AND METHODS:** We performed a retrospective single institution analysis of 76 patients with favorable prognosis. In contrast to the QUARTZ trial, inclusion was not limited to patients with non-small cell lung cancer (NSCLC). Furthermore, a cohort treated with higher total doses of WBRT was included (10 fractions of 3 Gy). **RESULTS:** All patients were younger than 60 years or had a graded prognostic assessment score of 2.5-3. The median survival was significantly shorter after best supportive care (1.2 months; 3.2 months after WBRT with 5 fractions of 4 Gy and 3.9 months after 10 fractions of 3 Gy). Also, in multivariate analyses, survival was significantly better after WBRT. Further favorable prognostic factors included better performance status, no or limited extracranial metastases and primary tumor other than gastrointestinal. **CONCLUSION:** In line with the QUARTZ trial results, WBRT prolonged survival in patients with favorable prognostic features.

Stereotactic body radiotherapy (SBRT) for adrenal metastases of oligometastatic or oligoprogressive tumor patients. König L1,2,3, Häfner MF4,5,6, Katayama S4,5,6, et al. Radiat Oncol. 2020 Feb 4;15(1):30. doi: 10.1186/s13014-020-1480-0.
INTRODUCTION: Local ablative treatment strategies are frequently offered to patients diagnosed with oligometastatic disease. Stereotactic body radiotherapy (SBRT), as ablative treatment option, is well established for lung and liver metastases, whereas for isolated adrenal gland metastases the level of evidence is scarce. **MATERIAL AND METHODS:** This single-institution analysis of oligometastatic or oligoprogressive disease was limited to patients who received SBRT to adrenal metastasis between 2012 and 2019. Patient, tumor, treatment characteristics, and dosimetric parameters were analyzed for evaluation of their effect on survival outcomes. **RESULTS:** During the period of review 28 patients received ablative SBRT to their adrenal gland metastases. Most common primary tumors were non-small cell lung cancers (46%) with most patients diagnosed with a single adrenal gland metastasis (61%), which occurred after a median time of 14 months. SBRT was delivered to a median biological effective dose at α/β of 10 (BED10) of 75 Gy (range: 58-151 Gy). Median gross tumor volume (GTV) and median planning target volume (PTV) were 42 and 111 mL, respectively. The homogeneity and conformity indices were 1.17 (range: 1.04-1.64) and 0.5 (range: 0.4.0.99), respectively, with the conformity index being affected by dose restrictions to organs at risk (OARs) in 50% of the patients. Overall response rate based on RECIST criteria was 86% (CR = 29%, PR = 57%) with 2-year local control (LC) of 84.8%, 2-year progression-free survival (PFS) of 26.3%, and 1-and 2-year overall survival (OS) of 46.6 and 32.0%, respectively. During follow up, only two local recurrences occurred. A trend for superior LC was seen if BED10 was $\geq$75Gy ($p = 0.101$) or if the PTV was < 100 ml ($p = 0.072$). SBRT was tolerated well with only mild toxicity. **CONCLUSION:** SBRT for adrenal metastases resulted in promising LC with low toxicity. Treatment response appeared to be superior, if SBRT was applied with higher BED. As the close proximity of OARs often limits the application of sufficiently high doses, further dose escalations strategies and techniques should be investigated in future.

Stereotactic ablative radiation therapy for pulmonary metastases: Improving overall survival and identifying subgroups at high risk of local failure. Pasalic D1, Lu Y2, Betancourt-Cuellar SL3, et al. Radiother Oncol. 2020 Feb 7;145:178-185. doi: 10.1016/j.radonc.2020.01.010. [Epub ahead of print]
BACKGROUND & PURPOSE: Stereotactic ablative radiation therapy (SABR) is an emerging treatment option for patients with pulmonary metastases; identifying patients who would benefit from SABR can improve outcomes. **MATERIALS & METHODS:** We retrospectively analyzed local failure

(LF), distant failure (DF), overall survival (OS), and toxicity in 317 patients with 406 pulmonary metastases treated with SABR in January 2006-September 2017 at a tertiary cancer center. **RESULTS:** Median follow-up time was 23 months. Primary adrenal, colorectal, sarcoma, or pancreatic ("less responsive") tumors led to high rates of LF. LF rates for patients with less responsive vs. responsive tumors were 4.6% vs. 1.6% at 12 months and 12.8% vs. 3.9% at 24 months (hazard ratio [HR] 0.29, 95% confidence interval [CI] 0.11-0.73; Log-Rank P = 0.0087). A nomogram for 24-month local control was created using Cox multivariate factors (surgical history, planning target volume, primary disease site, lung lobe location). Treating patients with ≤3 pulmonary metastases vs. >3 pulmonary metastases was associated with improved 24-month (74.2% vs. 59.3%) and 48-month (47.7% vs. 35.1%) OS (HR 0.66, 95% CI 0.47-0.95; Log-Rank P = 0.043), and reduced 12-month (22.5% vs. 50.8%) and 24-month (31.8% vs. 61.4%) intrathoracic DF (HR 0.53, 95% CI 0.38-0.74; Log-Rank P < 0.0001). The most common toxicity was asymptomatic pneumonitis (14.8%). Six patients had grade 3 events (5 pneumonitis, 1 brachial plexus). **CONCLUSIONS:** SABR for pulmonary metastases was effective and well tolerated. Irradiating limited intrathoracic sites of disease led to improved OS and intrathoracic DM. Higher SABR doses or surgery could be considered for less radio-responsive primary tumors.

SMALL CELL LUNG CANCER - SCLC

The impact of quantitative CT-based tumor volumetric features on the outcomes of patients with limited stage small cell lung cancer. Kamran SC1,2, Coroller T3,4, Milani N4, et al. Radiat Oncol. 2020 Jan 14;15(1):14. doi: 10.1186/s13014-020-1460-4.
INTRODUCTION: Limited stage small cell lung cancer (LS-SCLC) has a poor prognosis. Additional prognostic markers are needed for risk-stratification and treatment intensification. This study compares quantitative CT-based volumetric tumor measurements versus International Association for the Study of Lung Cancer (IASLC) TNM staging to predict outcomes. **MATERIALS & METHODS:** A cohort of 105 patients diagnosed with LS-SCLC and treated with chemoradiation (CRT) from 2000 to 2013 were analyzed retrospectively. Patients were staged by the Union for International Cancer Control (UICC) TNM Classification, 8th edition. Tumor volumes and diameters were extracted from radiation planning CT imaging. Univariable and multivariable models were used to analyze relationships between CT features and overall survival (OS), locoregional recurrence (LRR), in-field LRR, any progression, and distant metastasis (DM). **RESULTS:** Median follow-up was 21.3 months. Two-year outcomes were as follows: 38% LRR, 31% in-field LRR, 52% DM, 62% any progression, and 47% OS (median survival 16.5 months). On univariable analysis, UICC T-stage and N-stage were not associated with any clinical outcome. UICC overall stage was only statistically associated with in-field LRR. One imaging feature (3D maximum tumor diameter) was found to be significantly associated with LRR (HR 1.10, p = 0.003), in-field LRR (HR 1.10, p = 0.007), DM (HR 1.10, p = 0.02), any progression (HR 1.10, p = 0.008), and OS (HR 1.10, p = 0.03). On multivariable analysis, this feature remained significantly associated with all outcomes. **CONCLUSION:** For LS-SCLC, quantitative CT-based volumetric tumor measurements were significantly associated with outcomes after CRT and may be better predictors of outcome than TNM stage.

High Systemic Immune-Inflammation Index (SII) Represents an Unfavorable Prognostic Factor for Small Cell Lung Cancer Treated with Etoposide and Platinum-Based Chemotherapy. Wang C1, Jin S2, Xu S3, Cao S4. Lung. 2020 Feb 3. doi: 10.1007/s00408-020-00333-6. [Epub ahead of print]
PURPOSE: Systemic immune-inflammation index (SII) has been demonstrated to be closely associated with prognosis of a series of solid tumors. However, its role in small cell lung cancer (SCLC) remains poorly understood. The present study aims to evaluate the prognostic significance of pretreatment SII in SCLC treated with etoposide and platinum-based chemotherapy. **METHODS:** Sixty hundred and fifty-

three newly diagnosed SCLC patients were enrolled. The optimal cut-off values for SII and LDH (lactate dehydrogenase) were obtained by a receiver operating characteristic (ROC) curve analysis. Overall survival (OS) was assessed by univariate and multivariate analyses. **RESULTS:** The optimal cut-off values of pretreatment SII and LDH were 748.51 × 109/L and 188.5 U/L, respectively. High pretreatment SII was significantly associated with advanced tumor stage (limited disease, LD vs. extensive disease, ED; 26.3% vs 46.5%; $p < 0.001$). On univariate analysis, age < 65 years, female, non-smoker, limited disease, SII < 748.51 × 109/L, LDH < 188.5 U/L, distant metastasis numbers < 2, chemotherapy + radiotherapy, and chemotherapy + surgery were closely correlated with a prolonged OS ($p < 0.05$). The median OS for patients in high SII group was 12.0 months, compared with that of 17.0 months for patients in low SII group. Multivariate analysis showed smoking history ($p = 0.014$), tumor stage ($p < 0.001$), pretreatment SII ($p < 0.001$), LDH ($p = 0.002$), distant metastasis numbers ($p = 0.006$), and chemotherapy + radiotherapy ($p < 0.001$) were independent prognostic factors of OS. Furthermore, SII remained prognostic significance for SCLC stratified by variable subgroups analysis. **CONCLUSION:** Pretreatment SII represents a powerful prognostic biomarker for SCLC patients treated with etoposide and platinum-based chemotherapy. It is significant for treatment strategy making in clinics.

Immunotherapeutic approaches for small-cell lung cancer. Iams WT1, Porter J2, Horn L3. Nat Rev Clin Oncol. 2020 Feb 13. doi: 10.1038/s41571-019-0316-z. [Epub ahead of print]
Immune-checkpoint inhibitors (ICIs) are approved in the first-line and third-line settings for patients with extensive-stage or relapsed small-cell lung cancer (SCLC), respectively. In the first-line setting, the addition of the anti-programmed cell death 1 ligand 1 (PD-L1) antibody atezolizumab to chemotherapy improves overall survival (OS). In patients with relapsed disease, data from nonrandomized trials have revealed promising responses, although a significant improvement in OS over that obtained with conventional chemotherapy was not achieved in a randomized trial in this setting. Substantial research interest exists in identifying predictive biomarkers that could guide the use of ICIs in patients with SCLC. PD-L1 expression is typically low or absent in SCLC, which has precluded its use as a predictive biomarker. Tumour mutational burden might have some predictive value, although blood-based measures of tumour mutational burden did not have predictive value in patients receiving atezolizumab plus chemotherapy in the first-line setting. After three decades, ICIs have finally enabled an improvement in OS for patients with SCLC; however, a substantial amount of research remains to be done, including identifying the optimal therapeutic strategy and predictive biomarkers. In this Review, we describe the available data on clinical efficacy, the emerging evidence regarding biomarkers and ongoing clinical trials using ICIs and other immunotherapies in patients with SCLC.

Anlotinib in treatment of an elderly patient with recurrent advanced SCLC. Zhang Y1, Jia B1, Li J1, Xu X2. Tumori. 2020 Feb 7:300891619900673. doi: 10.1177/0300891619900673. [Epub ahead of print]
INTRODUCTION: An elderly patient with advanced small cell lung cancer who had a history of smoking and who had previously had tuberculosis and chronic kidney disease relapsed after classical treatment with etoposide combined with carboplatin. **METHODS:** The patient was given chemotherapy again, with albumin-bound paclitaxel, etoposide capsules, apatinib, and other treatment. The last medication was apatinib. **RESULTS:** After treatment with anlotinib, the patient has survived for 15 months with good quality of life. **CONCLUSION:** This is the first report on the precise efficacy of anlotinib in the treatment of advanced small cell lung cancer. Anlotinib is an important option for patients with small cell lung cancer.

New approaches to small cell lung cancer therapy : from the laboratory to the clinic. Poirier JT1, George J2, Owonikoko TK3, et al. J Thorac Oncol. 2020 Feb 1. pii: S1556-0864(20)30056-3. doi: 10.1016/j.jtho.2020.01.016. [Epub ahead of print]
Small cell lung cancer patient outcomes have not yet been significantly impacted by the revolution in precision oncology, primarily due to a paucity of genetic alterations in actionable driver oncogenes. Nevertheless, systemic therapies that include immunotherapy are beginning to show promise in the clinic. While these results are encouraging, many patients do not respond to or rapidly recur after current regimens, necessitating alternative or complementary therapeutic strategies. In this review, we discuss ongoing investigations into the pathobiology of this recalcitrant cancer and the therapeutic vulnerabilities that are exposed by the disease state. Included within this discussion is a snapshot of the current biomarker and clinical trial landscapes for small cell lung cancer. Finally, we identify key knowledge gaps that should be addressed in order to advance the field in pursuit of reduced small cell lung cancer mortality. This review largely summarizes work presented at the Third Biennial IASLC Small Cell Lung Cancer Meeting.

PALLIATIVE AND SUPPORTIVE CARE

Aprepitant for Cough Suppression in Advanced Lung Cancer: A Randomized Trial. Noronha V1, Bhattacharjee A2, Patil VM1, et al. Chest. 2020 Jan 17. pii: S0012-3692(20)30032-5. doi: 10.1016/j.chest.2019.11.048. [Epub ahead of print]
BACKGROUND: Although cough is a common and distressing symptom in lung cancer patients, there is almost no evidence to guide management. Aprepitant, a centrally acting neurokinin-1 inhibitor, significantly decreased cough frequency in a pilot study. **METHODS:** Patients with advanced lung cancer and cough lasting over two weeks despite a cough suppressant, were randomized 1:1 to aprepitant 125 mg orally on day one then 80 mg orally on days two to seven with physician's choice of antitussive; or to physician's choice of antitussive alone. Evaluation was at baseline and on days three, seven, nine and twelve. Primary endpoint was subjective cough improvement on day nine, measured by the Visual Analog Scale (VAS) and Manchester Cough in Lung Cancer Scale (MCLCS). Secondary endpoints included quality of life (QoL) as measured by the EORTC QLQ-C30 and QLQ-LC13 and toxicity. **RESULTS:** Between 2017 and 2018, 128 patients were randomized. Median baseline cough duration was 90 days. Mean VAS scores (in mm) at baseline and day nine were 68 and 39 in the aprepitant arm and 62 and 49 in the control arm respectively, P<0.001; Mean MCLCS scores at baseline and day nine were 33 and 23 in aprepitant arm and 30 and 25 in control arm, P<0.001. Overall QoL was not significantly different between the two arms, however aprepitant led to a significant improvement in the cough-specific QoL domain, P=0.017. Aprepitant did not increase severe adverse events. **CONCLUSIONS:** Aprepitant led to a significant improvement in cough in advanced lung cancer, without increasing severe side-effects.

The association of physical function and quality of life on physical activity for non-small cell lung cancer survivors. Yoo JS1,2, Yang HC3, Lee JM3, Kim MS3, Park EC4, Chung SH5. Support Care Cancer. 2020 Jan 25. doi: 10.1007/s00520-020-05302-6. [Epub ahead of print]
PURPOSE: Our study aimed to assess the association between physical function and quality of life (QOL) with physical activity among non-small cell lung cancer (NSCLC) survivors. **METHODS:** Participants were 92 NSCLC survivors. Physical activity was assessed by a self-report with physiatrist's interview and the Korean version of the short form of the International Physical Activity Questionnaire (IPAQ-SF). All participants were required to perform three standardized fitness tests. The Korean version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) was used to assess QOL. Factors associated with physical functioning and QOL were determined using multiple linear regression. **RESULTS:** A significant correlation between

metabolic equivalent task minutes per week (MET-min/wk) and aerobic fitness was found ($r = 0.277$, $p = 0.008$). Factors associated with aerobic fitness include gender, age, and MET-min/wk. The meeting physical activity guideline group was also a factor associated with aerobic fitness. In the QOL aspect, a significant correlation between MET-min/wk and some QOL score was found. The meeting physical activity guideline group was a factor associated with QOL (global health status, physical function, and role function), not total MET-min/wk. **CONCLUSIONS:** Increased physical activity was associated with higher aerobic fitness and QOL. Engagement in physical activity that met physical activity guidelines was a factor related to aerobic fitness and better QOL in some domains. To improve aspects of aerobic fitness and QOL, we may consider the pattern of physical activity, including regular participation and intensity, rather than total physical activity including basal activity.

COMPLEMENTARY & ALTERNATIVE THERAPY

Efficacy and safety of Jianpishengsui for chemotherapy-related fatigue in patients with non-small cell lung cancer: study protocol for a randomized placebo-controlled clinical trial. Xiao Z1, Hu L2, Lin J1, Lu L3, Huang X1, Zhu X4, Teo C5, Lin L6. Trials. 2020 Jan 16;21(1):94. doi: 10.1186/s13063-019-3982-3.

BACKGROUND: Chemotherapy-related fatigue (CRF) is a common symptom in non-small cell lung cancer (NSCLC) patients. A Chinese herbal formula cream for oral application, called Jianpishengsui (JPSS), is extensively used in the First Affiliated Hospital of Guangzhou University of Chinese Medicine as an internal preparation for CRF and is associated with a promising response. Due to the lack of high-quality clinical evidence, a randomized placebo-controlled trial is required to assess the efficacy and safety of JPSS. **METHODS/DESIGN:** The efficacy and safety of JPSS herbal formula cream will be evaluated through a prospective, randomized, placebo-controlled trial conducted in the First Affiliated Hospital of Guangzhou University of Chinese Medicine. NSCLC patients with CRF will be randomized into two groups at a ratio of 1:1. Each group will receive either 15 g of the oral JPSS herbal formula cream or placebo twice a day from day 6 to day 20 during two courses of paclitaxel + platinum/docetaxel + platinum/pemetrexed + platinum (TP/DP/AP) chemotherapy. The primary endpoint is the difference in the degree of fatigue between baseline (the day before the start of the intervention) and day 42, which will be assessed by the Revised Piper Fatigue Scale score. The secondary endpoints are quality of life (measured by the 43-item European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer C43), Eastern Cooperative Oncology Group Performance Status, and Traditional Chinese Medicine syndrome score. The toxicity of the treatments will also be evaluated at the same time. All outcomes will be measured at baseline, day 6, day 21, and day 42 of the treatment. **DISCUSSION:** This randomized trial will investigate the efficacy and safety of JPSS applied for CRF in patients with NSCLC. **TRIAL REGISTRATION:** Chinese Clinical Trial Registry, ChiCTR1900023451. Registered on 28 May 2019.

MISCELLANEOUS WORKS

Precision medicine and actionable alterations in lung cancer: A single institution experience. Mambetsariev I1, Wang Y2, Chen C2, et al. PLoS One. 2020 Feb 11;15(2):e0228188. doi: 10.1371/journal.pone.0228188. eCollection 2020.

OBJECTIVES: Oncology has become more reliant on new testing methods and a greater use of electronic medical records, which provide a plethora of information available to physicians and researchers. However, to take advantage of vital clinical and research data for precision medicine, we must initially make an effort to create an infrastructure for the collection, storage, and utilization of this information with uniquely designed disease-specific registries that could support the collection of a large

number of patients. **MATERIALS AND METHODS:** In this study, we perform an in-depth analysis of a series of lung adenocarcinoma patients (n = 415) with genomic and clinical data in a recently created thoracic patient registry. **RESULTS:** Of the 415 patients with lung adenocarcinoma, 59% (n = 245) were female; the median age was 64 (range, 22-92) years with a median OS of 33.29 months (95% CI, 29.77-39.48). The most common actionable alterations were identified in EGFR (n = 177/415 [42.7%]), ALK (n = 28/377 [7.4%]), and BRAF V600E (n = 7/288 [2.4%]). There was also a discernible difference in survival for 222 patients, who had an actionable alteration, with a median OS of 39.8 months as compared to 193 wild-type patients with a median OS of 26.0 months (P<0.001). We identified an unprecedented number of actionable alterations [53.5% (222/415)], including distinct individual alteration rates, as compared with 15.0% and 22.3% in TCGA and GENIE respectively. **CONCLUSION:** The use of patient registries, focused genomic panels and the appropriate use of clinical guidelines in community and academic settings may influence cohort selection for clinical trials and improve survival outcomes.

Clinical Characteristics of Patients with Cancer Presenting to the Emergency Department and their Use of Emergency Medical Service Transport. Chen B1,2, Kanaan C1, Jaiyesimi I3, Ezekwudo D3, Swor R4. Prehosp Emerg Care. 2020 Jan 21:1-16. doi: 10.1080/10903127.2020.1718258. [Epub ahead of print]

OBJECTIVES: Although life-threatening emergencies for cancer patients are relatively rare, cancer patients often seek care in the emergency department. The use of emergency medical service (EMS) by these patients is not well studied. The aim of this study was to investigate the characteristics of cancer patients who present to the emergency department (ED) for care, and; compare characteristics of patients transported by EMS versus those transported by private vehicle. **METHODS:** Our retrospective cohort study was conducted in an EMS system with 21,070 annual transports and an academic ED with 129,263 annual visits. Our study consisted of patients with a new diagnosis of cancer between January 1 and July 1, 2015 who subsequently presented to the ED between January 1, 2015 and July 1, 2017. Study variables included patient demographics, mode of ED arrival, cancer type and treatment, patient clinical characteristics and disposition. To describe differences in patient characteristics of EMS vs. private vehicle transport, we report variable frequencies and stratified them by mode of transport. **RESULTS:** Of the 2,727 patients with a new diagnosis of cancer, 1,303 (47.8%) presented to the ED with a total of 3,590 visits in 30 months. EMS transported 22% of cancer patients to the ED versus 78% transported by private vehicle. Thus, cancer patients would make up approximately 1.5% (781/52,675) of all EMS transports during the study period. For those transported by EMS, the most common chief complaints were respiratory distress (16.0%), pain (15.4%), and neurological symptoms (12.6%). Patients with cancer of the lung/respiratory tract (21.5%), upper GI (12.4%), and CNS (11.0%) were most frequently transported by EMS. Older age, presence of CNS cancer, presentation with neurological or cardiovascular complaints, and higher acuity were significantly associated with EMS transport to ED, while gender and pain severity were not. Patients transported by EMS were more likely to be hospitalized and for greater than 2 days ($p < 0.0001$). **CONCLUSIONS:** Cancer patients frequently seek emergency care after initial diagnosis, most commonly present for symptom relief, and are often admitted. Patients transported by EMS are more likely to be admitted and for longer periods of time.

Sex-Based Disparities Among Cancer Clinical Trial Participants. Ludmir EB1, Fuller CD1, Moningi S1, et al. J Natl Cancer Inst. 2020 Feb 1;112(2):211-213. doi: 10.1093/jnci/djz154.

Landmark investigation two decades ago demonstrated sex-based disparities among participants in cancer cooperative group trials. Although federal efforts have aimed to improve representation of female patients in government-sponsored research, less is known about sex disparities in the broader landscape of modern oncologic randomized controlled trials. Using ClinicalTrials.gov, we identified randomized controlled trials related to colorectal or lung cancer (the two most common non-sex-specific disease sites). Among

the 147 included trials, the proportion of female patients enrolled on trial was on average 6.8% (95% confidence interval = -8.8% to -4.9%) less than the proportion of female patients in the population by disease site (P < .001). Whereas no statistically significant underrepresentation of women was noted within the 26 cooperative group trials, sex disparities were markedly heightened for the 121 noncooperative-group-sponsored trials. Furthermore, underrepresentation of women did not improve with time. Future efforts should therefore focus on addressing these pervasive sex-based enrollment disparities beyond cooperative group trials alone.

Social media and mobile health technology for cancer screening: a systematic review and meta-analysis protocol. Ruco A1,2, Dossa F3, Tinmouth J2,4,5, Llovet D2,5, Kishibe T6, Baxter NN MD PhD7,8. BMJ Open. 2020 Feb 5;10(2):e035411. doi: 10.1136/bmjopen-2019-035411.
INTRODUCTION: Cancer is one of the leading causes of death globally and many jurisdictions have developed population-based cancer screening programmes to reduce the public health burden of disease. However, screening participation remains suboptimal. Social media and other mobile health (mHealth) technologies are increasingly being used for health promotion and behaviour change. This paper reports on the protocol for a systematic review exploring the effect of social media and other mHealth interventions on cancer screening participation and intention. **METHODS AND ANALYSIS:** This protocol is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist. We will include any randomised controlled trials or quasi-experimental studies with a pre/post design conducted in adults ≥18 years of age that report on the effectiveness of a social media or mHealth intervention on screening participation or intention (inclusive of breast, cervical, colorectal, prostate and lung cancer). Interventions will be inclusive of those delivered online or through a computer using an established social media platform or a new purpose-built platform, or those delivered through cellphones or other wireless technologies. Any comparator will be acceptable (control group, alternate intervention or pre/post design). We will search Medline, EMBASE, PsycINFO, Scopus, CINAHL, the Cochrane Central Register of Controlled Trials, and Communication and Mass Media Complete from 1 January 2000 to 31 May 2019. Two independent reviewers will screen titles, abstracts and full-text articles with conflicts resolved through discussion or by a third reviewer, as needed. The two reviewers will also independently complete risk of bias assessments for each included study. We will report on the characteristics of the studies, participants and interventions in descriptive narrative form and report the absolute and relative differences in screening and intention attributable to social media and mobile technology interventions. **ETHICS AND DISSEMINATION:** As this is a systematic review, ethical approval for conduct of this study is not required. We will pursue publication of study results in a relevant peer-reviewed journal and report our findings according to the PRISMA checklist.