Caring Ambassadors Lung Cancer Program
Literature Review, January 2017

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

miR-3941: a novel microRNA that controls IGBP1 expression and is associated with malignant progression of lung adenocarcinoma. Sato T1, Shiba-Ishii A2, Kim Y1, et al. Cancer Sci. 2016 Dec 23. doi: 10.1111/cas.13148. [Epub ahead of print]
Immunoglobulin (CD79a) binding protein 1 (IGBP1) is universally overexpressed in lung adenocarcinoma and exerts an anti-apoptotic effect by binding to PP2Ac. However, the molecular mechanism of IGBP1 overexpression is still unclear. In the present study, we used a microRNA (miRNA) array and TargetScan Human software to detect IGBP1-related miRNAs that regulate IGBP1 expression. The miRNA array analysis revealed more than 100 miRNAs that are dysregulated in early invasive adenocarcinoma. On the other hand, in silico analysis using TargetScan Human revealed 79 miRNAs that are associated with IGBP1 protein expression. Among the miRNAs selected by miRNA array analysis, six (miR-34b, miR-138, miR-374a, miR-374b, miR-1909, miR-3941) were also included among those selected by TargetScan analysis. Real-time reverse transcription PCR (real-time RT-PCR) showed that the six microRNAs were down-regulated in invasive adenocarcinoma (IGBP1+) relative to adjacent normal lung tissue (IGBP1-). Among these microRNAs, only miR-34b and miR-3941 depressed luciferase activity by targeting 3'UTR-IGBP1 in the luciferase vector. We transfected miR-34b and miR-3941 into lung adenocarcinoma cell lines (A549, PC-9), and both of them suppressed IGBP1 expression and cell proliferation. Moreover, the transfected miR-34b and miR-3941 induced apoptosis of a lung adenocarcinoma cell line, similarly to the effect of siIGBP1 RNA. As well as miR-34b, we found that miR-3941 targeted IGBP1 specifically and was able to exclusively down-regulate IGBP1 expression. These findings indicate that suppression of miR-3941 has an important role in the progression of lung adenocarcinoma at an early stage. This article is protected by copyright. All rights reserved.

The Notch ligand delta-like 3 promotes tumor growth and inhibits Notch signaling in lung cancer cells in mice. Deng SM1, Yan XC2, Liang L2, Wang L2, Liu Y2, Duan JL3, Yang ZY2, Chang TF4, Ruan B3, Zheng QJ5, Han H6. Biochem Biophys Res Commun. 2016 Dec 19. pii: S0006-291X(16)32177-5. doi: 10.1016/j.bbrc.2016.12.117. [Epub ahead of print]

Although it has been suggested that Dll3, one of the Notch ligands, promotes the proliferation and inhibits the apoptosis of cancer cells, the role of Dll3 in cancers remains unclear. In this study, we found that in the murine Lewis lung carcinoma (LLC) cells, the level of Dll3 mRNA changed upon tumor microenvironment (TME) stimulation, namely, decreased under hypoxia or stimulated with tumor necrosis factor (TNF)-α. Dll3 was also expressed at higher level in human lung carcinoma tissues than in the para-carcinoma tissues. Overexpression of Dll3 in LLC cells promoted cell proliferation and reduced apoptosis in vitro, and enhanced tumor growth when inoculated in vivo in mice. The Dll3-mediated proliferation could be due to increased Akt phosphorylation in LLC cells, because an Akt inhibitor counteracted Dll3-induced proliferation. Moreover, Dll3 overexpression promoted PI3K/Akt signaling through inhibiting Notch signaling.

Longitudinal Assessment of Lung Cancer Progression in Mice Using the Sodium Iodide Symporter Reporter Gene and SPECT/CT Imaging. Price DN1, McBride AA1,2, Anton M3, Kusewitt DF4, Norenberg JP5,6, MacKenzie DA1, Thompson TA1,6, Muttil P1,6. PLoS One. 2016 Dec 30;11(12):e0169107. doi: 10.1371/journal.pone.0169107. eCollection 2016.
Lung cancer has the highest mortality rate of any tissue-specific cancer in both men and women. Research continues to investigate novel drugs and therapies to mitigate poor treatment efficacy, but the lack of a good descriptive lung cancer animal model for preclinical drug evaluation remains an obstacle. Here we describe the development of an orthotopic lung cancer animal model which utilizes the human sodium iodide symporter gene (hNIS; SLC5A5) as an imaging reporter gene for the purpose of non-invasive, longitudinal tumor quantification. hNIS is a glycoprotein that naturally transports iodide (I-) into thyroid cells and has the ability to symport the radiotracer 99mTc-pertechnetate (99mTcO4-). A549 lung adenocarcinoma cells were genetically modified with plasmid or lentiviral vectors to express hNIS. Modified cells were implanted into athymic nude mice to develop two tumor models: a subcutaneous and an orthotopic xenograft tumor model. Tumor progression was longitudinally imaged using SPECT/CT and quantified by SPECT voxel analysis. hNIS expression in lung tumors was analyzed by quantitative real-time PCR. Additionally, hematoxylin and eosin staining and visual inspection of pulmonary tumors was performed. We observed that lentiviral transduction provided enhanced and stable hNIS expression in A549 cells. Furthermore, 99mTcO4- uptake and accumulation was observed within lung tumors allowing for imaging and quantification of tumor mass at two-time points. This study illustrates the development of an orthotopic lung cancer model that can be longitudinally imaged throughout the experimental timeline thus avoiding inter-animal variability and leading to a reduction in total animal numbers. Furthermore, our orthotopic lung cancer animal model is clinically relevant and the genetic modification of cells for SPECT/CT imaging can be translated to other tissue-specific tumor animal models.

SCREENING, DIAGNOSIS AND STAGING

Epidermal Growth Factor Receptor Mutational Testing and Erlotinib Treatment Among Veterans Diagnosed With Lung Cancer in the United States Department of Veterans Affairs.
Lynch JA1, Berse B2, Chun D3, Rivera D4, Filipski KK4, Kulich S5, Viernes B3, DuVall SL3, Kelley MJ6. Clin Lung Cancer. 2016 Dec 7. pii: S1525-7304(16)30372-2. doi: 10.1016/j.cllc.2016.11.018. [Epub ahead of print]
INTRODUCTION: We examined mutational testing of the epidermal growth factor gene (EGFR) and erlotinib treatment among veterans diagnosed with non-small-cell lung cancer in the United States Department of Veterans Affairs (VA). Our objectives were to identify the prevalence of clinically actionable EGFR mutations, to determine whether testing and treatment were guideline concordant, to evaluate the impact of testing and treatment on survival, and to estimate the rate of testing. **PATIENTS AND METHODS:** Test results were linked to electronic health records from VA Corporate Data

Warehouse and the VA Central Cancer Registry. We analyzed patient demographic and clinical characteristics, prevalence of EGFR mutations, and timing of EGFR mutational testing and erlotinib treatment based on pharmacy records. Overall survival was assessed by Kaplan-Meier analysis. **RESULTS:** Among 973 patients tested at 70 VA medical centers between 2011 and 2013, 64 (7%) had sensitizing EGFR mutations, 694 (71%) were EGFR wild type, and 168 (17%) had clinically insignificant polymorphisms or variants of unknown significance. Results were not documented in 47 tests (5%). Erlotinib administration was in agreement with test results in 843 cases (87%). **CONCLUSION:** Veterans have a much lower rate of sensitizing EGFR mutations than the reported average of 10% to 15%, which correlates with a high rate of smoking among veterans. This may partially explain clinicians' reluctance to prescribe EGFR testing, which results in underutilization. Although test results appear to have influenced erlotinib treatment decisions, we documented a substantial number of cases where treatment was not applied in accordance with clinical guidelines, potentially resulting in worse outcomes and unnecessary cost.

Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration in the Nodal Staging of Stereotactic Ablative Body Radiotherapy Patients. Vial MR1, Khan KA2, O'Connell O3, et al. Ann Thorac Surg. 2016 Dec 24. pii: S0003-4975(16)31375-3. doi: 10.1016/j.athoracsur.2016.09.106. [Epub ahead of print]

BACKGROUND: Patients with non-small cell lung cancer (NSCLC) being evaluated for stereotactic ablative body radiotherapy (SABR) are typically staged noninvasively with positron emission tomography/computed tomography (PET/CT). Incorporating endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) into the staging workup of these patients has not been evaluated. Our primary objective was to compare the performance of PET/CT with EBUS-TBNA for intrathoracic nodal assessment among SABR-eligible patients. **METHODS:** This was a retrospective study consisting of two parts. First, we assessed the concordance for nodal metastasis of PET/CT and EBUS-TBNA. Second, we evaluated clinical outcomes among patients who underwent SABR with and without a prior EBUS-TBNA. **RESULTS:** We identified 246 eligible patients. Compared with PET/CT, EBUS-TBNA led to a stage shift in 48 of 246 patients (19%). Of 174 N0 patients by PET/CT, 6 (3.4%) had nodal metastasis on EBUS-TBNA. Among 72 clinical N1 patients, 36 (50%) were downstaged to N0 after EBUS-TBNA, therefore becoming eligible for SABR. Concordance between PET/CT and EBUS-TBNA for nodal metastasis was 83% ($\kappa = 0.53$). Clinical outcomes of patients who underwent SABR with or without a prior EBUS-TBNA did not differ significantly. **CONCLUSIONS:** Concordance of PET/CT and EBUS-TBNA for nodal disease was only moderate. Incorporating EBUS-TBNA into the staging workup was beneficial in identifying occult nodal metastasis that would otherwise be left untreated with SABR and in expanding the pool of potentially SABR-eligible patients.

The Effect of False-Positive Results on Subsequent Participation in Chest X-ray Screening for Lung Cancer. Sato A1, Hamada S, Urashima Y, Tanaka S, Okamoto H, Kawakami K. J Epidemiol. 2016 Dec 5;26(12):646-653. Epub 2016 Jul 2.

BACKGROUND: High attendance rates and regular participation in disease screening programs are important contributors to program effectiveness. The objective of this study was to examine the effects of an initial false-positive result in chest X-ray screening for lung cancer on subsequent screening participation. **METHODS:** This historical cohort study analyzed individuals who first participated in a lung cancer screening program conducted by Yokohama City between April 2007 and March 2011, and these participants were retrospectively tracked until March 2013. Subsequent screening participation was compared between participants with false-positive results and those with negative results in evaluation periods between 365 (for the primary outcome) and 730 days. The association of screening results with subsequent participation was evaluated using a generalized linear regression model, with adjustment for

characteristics of patients and screening. **RESULTS:** The proportions of subsequent screening participation within 365 days were 12.9% in 3132 participants with false-positive results and 6.7% in 15 737 participants with negative results. Although the differences in attendance rates were reduced with longer cutoffs, participants with false-positive results were consistently more likely to attend subsequent screening than patients with negative results ($P < 0.01$). The predictors of subsequent screening participation were false-positive results (risk ratio [RR] 1.72; 95% confidence interval [CI], 1.54-1.92), older age (RR 1.17; 95% CI, 1.11-1.23), male sex (RR 1.46; 95% CI, 1.29-1.64), being a current smoker (RR 0.80; 95% CI, 0.69-0.93), current employment (RR 0.79; 95% CI, 0.70-0.90), and being screened at a hospital cancer center (vs public health centers; RR 1.36; 95% CI, 1.15-1.60). **CONCLUSIONS:** Our findings indicated that subsequent participation in lung cancer screening was more likely among participants with false-positive results in an initial screening than patients with negative results.

Responsiveness of a Brief Measure of Lung Cancer Screening Knowledge. Housten AJ1, Lowenstein LM1, Leal VB1, Volk RJ2. J Cancer Educ. 2016 Dec 14. [Epub ahead of print]
Our aim was to examine the responsiveness of a lung cancer screening brief knowledge measure (LCS-12). Eligible participants were aged 55-80 years, current smokers or had quit within 15 years, and English speaking. They completed a baseline pretest survey, viewed a lung cancer screening video-based patient decision aid, and then filled out a follow-up posttest survey. We performed a paired samples t-test, calculated effect size, and calculated absolute and relative percent improvement for each item. Participants (n = 30) were primarily White (63%) with less than a college degree (63%), and half were female (50%). Mean age was 61.5 years (standard deviation [SD] = 4.67) and average smoking history was 30.4 pack-years (range = 4.6-90.0). Mean score on the 12-item measure increased from 47.3% correct on the pretest to 80.3% correct on the posttest (mean pretest score = 5.67 vs. mean posttest score = 9.63; mean score difference = 3.97, SD = 2.87, 95% CI = 2.90, 5.04). Total knowledge scores improved significantly and were responsive to the decision aid intervention (paired samples t-test = 7.57, $p < .001$; Cohen's effect size = 1.59; standard response mean [SRM] = 1.38). All individual items were responsive, yet two items had lower absolute responsiveness than the others (item 8: "Without screening, is lung cancer often found at a later stage when cure is less likely?" pretest correct = 83.3% vs. posttest = 96.7%, responsiveness = 13.4%; and item 10: "Can a CT scan find lung disease that is not cancer?" pretest correct = 80.0% vs. posttest = 93.3%, responsiveness = 13.3%). The LCS-12 knowledge measure may be a useful outcome measure of shared decision making for lung cancer screening.

Ultrasound-Guided Needle Biopsy of Neck Lymph Nodes in Patients With Suspected Lung Cancer: Are the Specimens Sufficient for Complete Pathologic Evaluation to Guide Patient Management?
Duguay S1, Wagner JM, Zheng W, Ling J, Zhao LC, Allen KS, North JC, Deb SJ. Ultrasound Q. 2016 Dec 14. [Epub ahead of print]
BACKGROUND: The purpose of this study is to determine the ability of ultrasound guided needle biopsy of a neck lymph node to provide adequate tissue for complete pathologic evaluation of suspected metastatic lung cancer, including molecular testing for epidermal growth factor receptor gene mutations by pyrosequencing and anaplastic lymphoma kinase gene rearrangement by fluorescence in situ hybridization. **METHODS:** Institutional review board approval was obtained and the requirement for informed consent was waived. All ultrasound guided neck biopsies performed July 1, 2011, to June 30, 2015, were retrospectively reviewed, and all biopsies performed for suspected lung cancer metastatic to supraclavicular and cervical lymph nodes were included. **RESULTS:** Forty patients with suspected lung cancer underwent ultrasound-guided needle biopsy of an abnormal appearing neck lymph node identified on preprocedure computed tomography or positron emission tomography/computed tomography. Thirty-seven patients were subsequently diagnosed with lung cancer and 3 were diagnosed with lymphoma. A definitive pathologic diagnosis was rendered in 95% of neck node biopsies (38/40; 95% confidence

interval, 84%-99%). Of the 36 specimens diagnostic for lung cancer, 16 were considered for further molecular testing and the specimen was adequate for molecular testing in 15 (94%; 73%-100%) cases. Therefore, the neck node biopsy specimens were adequate for complete pathologic workup in 93% (37/40; 81%-98%). No complications related to the biopsies were observed. **CONCLUSIONS:** In patients presenting with suspected lung cancer and suspicious neck lymph nodes, ultrasound-guided needle biopsy frequently provides adequate tissue for complete pathologic evaluation and eliminates the need for more invasive procedures.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

Establishing a Dedicated General Thoracic Surgery Subspecialty Program Improves Lung Cancer Outcomes. Magee MJ1, Herbert MA2, Tumey L3, Prince SL3. Ann Thorac Surg. 2016 Dec 8. pii: S0003-4975(16)31284-X. doi: 10.1016/j.athoracsur.2016.09.033. [Epub ahead of print]
BACKGROUND: Various factors may influence outcomes after lobectomy for lung cancer. Postgraduate subspecialty training in general thoracic surgery with a focus on minimally invasive surgery (MIS) and thoracic oncology was completed by an established cardiothoracic surgeon on the hospital staff in July 2007, and principles emphasized in that training were incorporated into practice through formation of a subspecialty program. We hypothesized that establishing a dedicated general thoracic surgeon-lead subspecialty program, with focus on MIS and thoracic oncology, would improve short-term and long-term outcomes. **METHODS:** Patients entered into the hospital cancer registry have survival status updated annually through correspondence with patients, physicians, and searches of the Social Security Death Index and obituaries. The registry was queried for all patients undergoing lobectomy for lung cancer, 2002 to 2013, and divided into two groups for comparison, before and after, based on operation date relative to January 2008. Patients (n = 279) who had lobectomy for lung cancer were identified in the registry. Data included surgical approach (percent of video-assisted thoracoscopy [VATS]), pathologic stage, number of lymph nodes and stations sampled, hospital length of stay (LOS), and survival. $\chi 2$ statistics were used for proportions, t tests for continuous variables, and a nonparametric test for LOS. A Cox proportional hazard model was created, and survival curves were constructed using time between operation and death or last follow-up. **RESULTS:** Patients having lobectomy in the after group had substantially more VATS procedures (53.9% versus 9.5%), decreased LOS (median 3.5 versus 7.0 days), greater mean total lymph nodes (9.0 versus 6.3), and nodal stations (4.2 versus 2.8) sampled per patient. Thirty-day, 90-day, and 1-year survival were similar in both groups. Overall survival was better in the after group (hazard ratio [HR] 0.41, 95% confidence interval: 0.25 to 0.68), and this survival benefit remained statistically significant when comparing groups stratified by lung cancer stage (stage I: HR 0.46, stage II: HR 0.32, combined stage III to IV: HR 0.19). **CONCLUSIONS:** Establishing a dedicated general thoracic surgeon-lead subspecialty program, with focus on MIS and thoracic oncology, can substantially improve short-term outcomes with increased VATS utilization, decreased LOS, and increased lymph node sampling. Long-term survival was also significantly improved.

Lung resection is safe and feasible among stage IV cancer patients: An American College of Surgeons National Surgical Quality Improvement Program analysis. Bateni SB1, David EA2, Bold RJ1, Cooke DT2, Meyers FJ3, Canter RJ4. Surgery. 2016 Dec 20. pii: S0039-6060(16)30738-3. doi: 10.1016/j.surg.2016.11.002. [Epub ahead of print]
BACKGROUND: Operative resection can be associated with improved survival for selected patients with stage IV malignancies but may also be associated with prohibitive acute morbidity and mortality. We sought to evaluate rates of acute morbidity and mortality after lung resection in patients with disseminated

malignancy with primary lung cancer and non-lung cancer pulmonary metastatic disease. **METHODS:** For 2011-2012, 6,360 patients were identified from the American College of Surgeons National Surgical Quality Improvement Program undergoing lung resections, including 603 patients with disseminated malignancy. Logistic regression analyses were used to compare outcomes between patients with and without disseminated malignancy. **RESULTS:** After controlling for preoperative and intraoperative differences, we observed no statistically significant differences in rates of 30-day overall and serious morbidity or mortality between disseminated malignancy and non-disseminated malignancy patients ($P > .05$). Disseminated malignancy patients were less likely to have a prolonged duration of stay and be discharged to a facility compared to non-disseminated malignancy patients ($P < .05$). Subgroup analyses by procedure type and diagnosis showed similar results. **CONCLUSION:** Disseminated malignancy patients undergoing lung resections experienced low rates of overall morbidity, serious morbidity, and mortality comparable to non-disseminated malignancy patients. These data suggest that lung resections may be performed safely on carefully selected, disseminated malignancy patients with both primary lung cancer and pulmonary metastatic disease, with important implications for multimodality care.

Video-Assisted Thoracoscopic Lobectomy Is the Preferred Approach Following Induction Chemotherapy. Kamel MK1, Nasar A1, Stiles BM1, Altorki NK1, Port JL1. J Laparoendosc Adv Surg Tech A. 2016 Dec 20. [Epub ahead of print]

OBJECTIVE: A video-assisted thoracoscopic surgical (VATS) resection, after induction chemotherapy, has long been considered a relative contraindication. We report our experience with VATS lobectomy after induction chemotherapy for patients with nonsmall cell lung cancer (NSCLC), with propensity-matched group of patients, who underwent an open approach, to determine safety and oncological outcome. **METHODS:** A retrospective review of a prospective database (2002-2014) was performed to identify patients undergoing potentially curative lobectomy for NSCLC after induction therapy. Propensity score matching (age, gender, and clinical stage) was performed (1:2) to obtain a balanced cohort of patients undergoing VATS resection and thoracotomy. **RESULTS:** A total of 285 patients underwent lobectomy after induction therapy, 114 were propensity matched (VATS, $n = 40$, thoracotomy, $n = 74$). There were no differences in the clinicopathological factors or type of induction therapy (conventional versus targeted) between VATS and thoracotomy groups. Similarly, no differences were found in the number of lymph nodes resected (12 versus 15, $P = .94$), the number of stations sampled (4 for each, $P = .68$), or in the rate of R0 resection (95% versus 96%, $P = .81$) between VATS and thoracotomy groups. Five VATS cases were converted to an open approach because of adhesions. VATS resection was associated with less estimated blood loss (EBL), shorter length of stay (LOS), and a trend toward fewer postoperative complications. There was no difference in 5 years disease-free survival (DFS) between VATS and thoracotomy groups (73% versus 48%, $P = .09$). Similarly, for patients who presented with cN2, there were no differences between thoracotomy and VATS groups in DFS ($P = .37$). On multi-variable analysis (MVA), only the clinical N1/2 status [Hazard ratio (HR): 4.86, $P < .001$] independently predicted poor DFS. **CONCLUSIONS:** A VATS lobectomy is a feasible, safe, and oncologically sound approach after induction therapy for NSCLC. When compared with thoracotomy, VATS lobectomy is associated with lower EBL, shorter LOS, and a trend toward fewer postoperative complications.

The importance of lymph node dissection accompanying wedge resection for clinical stage IA lung cancer†. Stiles BM1, Kamel MK2, Nasar A2, Harrison S2, Nguyen AB2, Lee P2, Port JL2, Altorki NK2. Eur J Cardiothorac Surg. 2016 Dec 22. pii: ezw343. doi: 10.1093/ejcts/ezw343. [Epub ahead of print]

OBJECTIVES: For patients undergoing lobectomy for non-small cell lung cancer (NSCLC), a survival benefit exists with increased number of lymph nodes (LNs) resected. We sought to evaluate the associations of LN removal with outcomes in clinical stage I lung cancer patients undergoing wedge resection. **METHODS:** We evaluated all patients undergoing wedge resection for peripheral, clinical

stage IA NSCLC and grouped patients into those with and without LN assessment. Data were compared and survival analysed using Kaplan-Meier, with differences compared using log-rank. Propensity score matching controlling for age, gender, Charlson comorbidity index, patient tolerability of lobectomy, surgery year, tumour size and surgical approach was done (51 patients in each group, caliper 0.2) RESULTS: We identified196 patients undergoing wedge resection, of whom 138 patients (70%) had LNs resected (median = 4 nodes), while the remaining 58 patients (30%) had none. There were no significant differences in the clinical or pathologic characteristics between the two groups. There was no difference in terms of OR time, estimated blood loss, chest tube duration or length of stay. Median pT size was 1.5 cm in each group (P = 0.73). Among patients with LNs removed, 6 (4.3%) had positive nodes Patients in the LN assessed group had higher probability of freedom from loco-regional recurrence compared to the no lymph node (NLN) group (5-year: 92 vs 74%, P = 0.025).In propensity matched groups, patients who underwent LN dissection also had higher probability of freedom from local recurrence (P = 0.024). **CONCLUSIONS:** Accompanying wedge resection for lung cancer, LN sampling adds no morbidity and does not increase length of stay. Positive nodes are identified in 4.3% of patients thought eligible for wedge resection. LN removal appears to decrease locoregional recurrence and may be associated with a survival benefit.

Socioeconomic factors related to surgical treatment for localized, non-small cell lung cancer.
Jiang X1, Lin G2, Islam KM3. Soc Sci Med. 2016 Dec 29;175:52-57. doi: 10.1016/j.socscimed.2016.12.042. [Epub ahead of print]
Various socioeconomic factors were reported to be associated with receiving surgical treatment in localized, non-small cell lung cancer (NSCLC) patients in previous studies. We wanted to assess the impact of residential poverty on receiving surgical treatment in a state-wide population of localized NSCLC, adjusting for demographic, clinical, residence and tumor factors. Data on 970 patients with primary localized NSCLC were collected from the Nebraska Cancer Registry (NCR), and linked with the Nebraska Hospital Discharge Data (NHDD) between 2005 and 2009, as well as the 2010 Census data. Characteristics of patients with and without surgery were compared using Chi-square tests. Unadjusted and adjusted odds ratios (ORs) of receiving surgery for low versus high poverty were generated based on the series of logistic regression models controlling for demographics, comorbidity, residence and tumor histology. Patients who were 65 year old or younger, without comorbidities, single or married, and with adenocarcinoma histologic type were more likely to receive surgery. Without adjustment, poverty was negatively associated with receiving surgery. Patients who resided in low poverty neighborhoods (less than 5% of the households under poverty line) were twice more likely to receive surgery than those who lived in high poverty neighborhoods (more than 15% of the households under poverty line) (OR 2.13, 95% CI 1.33-3.40). After adjustment, poverty was independently and negatively associated with receiving surgery treatment. Residents in low poverty neighborhoods were still about twice more likely to receive surgery than those in high poverty neighborhoods when the other demographic, urban/rural residency and clinical factors were adjusted (ORs 2.01-2.18, all $p < 0.05$). The mechanism of how living in poverty interacts with other factors and its impact on patient's choice and their chance of getting surgical treatment invites future studies.

Preoperative pulmonary rehabilitation for marginal-function lung cancer patients. Hashmi A1, Baciewicz FA Jr2, Soubani AO3, Gadgeel SM4. Asian Cardiovasc Thorac Ann. 2016 Dec 2. pii: 0218492316683757. [Epub ahead of print]
BACKGROUND: This study aimed to evaluate the impact of preoperative pulmonary rehabilitation in lung cancer patients undergoing pulmonary resection surgery with marginal lung function. **METHODS:** Short-term outcomes of 42 patients with forced expiratory volume in 1 s < 1.6 L who underwent lung resection between 01/2006 and 12/2010 were reviewed retrospectively. They were divided into group A

(no preoperative pulmonary rehabilitation) and group B (receiving pulmonary rehabilitation). In group B, a second set of pulmonary function tests was obtained. **RESULTS:** There were no significant differences in terms of sex, age, race, pathologic stage, operative procedure, or smoking years. Mean forced expiratory volume in 1 s and diffusing capacity for carbon monoxide in group A was 1.40 ± 0.22 L and 10.28 ± 2.64 g·dL-1 vs. 1.39 ± 0.13 L and 10.75 ± 2.08 g·dL-1 in group B. Group B showed significant improvement in forced expiratory volume in 1 s from 1.39 ± 0.13 to 1.55 ± 0.06 L (p = 0.02). Mean intensive care unit stay was 6 ± 5 days in group A vs. 9 ± 9 days in group B (p = 0.22). Mean hospital stay was 10 ± 4 days in group A vs. 14 ± 9 days in group B (p = 0.31). There was no significant difference in morbidity or mortality between groups. **CONCLUSION:** Preoperative pulmonary rehabilitation can significantly improve forced expiratory volume in 1 s in some marginal patients undergoing lung cancer resection. However, it does not improve length of stay, morbidity, or mortality.

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

Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. Mok TS1, Wu YL1, Ahn MJ1, et al. N Engl J Med. 2016 Dec 6. [Epub ahead of print]
BACKGROUND: Osimertinib is an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) that is selective for both EGFR-TKI sensitizing and T790M resistance mutations in patients with non-small-cell lung cancer. The efficacy of osimertinib as compared with platinum-based therapy plus pemetrexed in such patients is unknown. **METHODS:** In this randomized, international, open-label, phase 3 trial, we assigned 419 patients with T790M-positive advanced non-small-cell lung cancer, who had disease progression after first-line EGFR-TKI therapy, in a 2:1 ratio to receive either oral osimertinib (at a dose of 80 mg once daily) or intravenous pemetrexed (500 mg per square meter of body-surface area) plus either carboplatin (target area under the curve, 5 [AUC5]) or cisplatin (75 mg per square meter) every 3 weeks for up to six cycles; maintenance pemetrexed was allowed. In all the patients, disease had progressed during receipt of first-line EGFR-TKI therapy. The primary end point was investigator-assessed progression-free survival. **RESULTS:** The median duration of progression-free survival was significantly longer with osimertinib than with platinum therapy plus pemetrexed (10.1 months vs. 4.4 months; hazard ratio; 0.30; 95% confidence interval [CI], 0.23 to 0.41; P<0.001). The objective response rate was significantly better with osimertinib (71%; 95% CI, 65 to 76) than with platinum therapy plus pemetrexed (31%; 95% CI, 24 to 40) (odds ratio for objective response, 5.39; 95% CI, 3.47 to 8.48; P<0.001). Among 144 patients with metastases to the central nervous system (CNS), the median duration of progression-free survival was longer among patients receiving osimertinib than among those receiving platinum therapy plus pemetrexed (8.5 months vs. 4.2 months; hazard ratio, 0.32; 95% CI, 0.21 to 0.49). The proportion of patients with adverse events of grade 3 or higher was lower with osimertinib (23%) than with platinum therapy plus pemetrexed (47%). **CONCLUSIONS**: Osimertinib had significantly greater efficacy than platinum therapy plus pemetrexed in patients with T790M-positive advanced non-small-cell lung cancer (including those with CNS metastases) in whom disease had progressed during first-line EGFR-TKI therapy. (Funded by AstraZeneca; AURA3 ClinicalTrials.gov number, NCT02151981.).

Differential protein stability and clinical responses of EML4-ALKfusion variants to various ALK inhibitors in advanced ALK-rearranged non-small cell lung cancer. Woo CG1, Seo S2, Kim SW2, Jang SJ3, Park KS4, Song JY5, Lee B6, Richards MW7, Bayliss R7, Lee DH2, Choi J8. Ann Oncol. 2016 Dec 29. pii: mdw693. doi: 10.1093/annonc/mdw693. [Epub ahead of print]
BACKGROUND: Anaplastic lymphoma kinase (ALK) inhibition using crizotinib has become the standard of care in advanced ALK-rearranged non-small cell lung cancer (NSCLC), but the treatment outcomes and duration of response vary widely. Echinoderm microtubule-associated protein-like 4

(EML4)-ALK is the most common translocation, and the fusion variants show different sensitivity to crizotinib in vitro. However, there are only limited data on the specific EML4-ALK variants and clinical responses of patients to various ALK inhibitors. **PATIENTS AND METHODS:** By multiplex reverse-transcriptase PCR, which detects 12 variants of known EML4-ALK rearrangements, we retrospectively determined ALK fusion variants in 54 advanced ALK rearrangement-positive NSCLCs. We subdivided the patients into two groups (variants 1/2/others and variants 3a/b) by protein stability and evaluated correlations of the variant status with clinical responses to crizotinib, alectinib, or ceritinib. Moreover, we established the EML4-ALK variant-expressing system and analyzed patterns of sensitivity of the variants to ALK inhibitors. **RESULTS:** Of the 54 tumors analyzed, EML4-ALK variants 3a/b (44.4%) was the most common type, followed by variants 1 (33.3%) and 2 (11.1%). The 2-year progression-free survival (PFS) rate was 76.0% (95% confidence interval [CI] 56.8-100) in group EML4-ALK variants 1/2/others versus 26.4% (95% CI 10.5-66.6) in group variants 3a/b (P = 0.034) among crizotinib-treated patients. Meanwhile, the 2-year PFS rate was 69.0% (95% CI 49.9-95.4) in group variants 1/2/others versus 32.7% (95% CI 15.6-68.4) in group variants 3a/b (P = 0.108) among all crizotinib-, alectinib-, and ceritinib-treated patients. Variant 3a- or 5a-harboring cells were resistant to ALK inhibitors with >10-fold higher half maximal inhibitory concentration in vitro. **CONCLUSION:** Our findings show that group EML4-ALK variants 3a/b may be a major source of ALK inhibitor resistance in the clinic. The variant-specific genotype of the EML4-ALK fusion allows for more precise stratification of patients with advanced NSCLC.

Potential Predictive Value of TP53 and KRAS Mutation Status for Response to PD-1 Blockade Immunotherapy in Lung Adenocarcinoma. Dong ZY1, Zhong W2, Zhang XC3, et al. Clin Cancer Res. 2016 Dec 30. pii: clincanres.2554.2016. doi: 10.1158/1078-0432.CCR-16-2554. [Epub ahead of print]
PURPOSE: Although clinical studies have shown promise for targeting programmed cell death protein-1 (PD-1) and ligand (PD-L1) signaling in non-small cell lung cancer (NSCLC), the factors that predict which subtype patients will be responsive to checkpoint blockade are not fully understood. **EXPERIMENTAL DESIGN:** We performed an integrated analysis on the multiple-dimensional data types including genomic, transcriptomic, proteomic and clinical data from cohorts of lung adenocarcinoma public (Discovery Set) and internal (Validation Set) database and immunotherapeutic patients. Gene Set Enrichment Analysis (GSEA) was used to determine potentially relevant gene expression signatures between specific subgroups. **RESULTS:** We observed TP53 mutation significantly increased expression of immune checkpoints and activated T-effector and interferon-γ signature. More importantly, TP53/KRAS co-mutated subgroup manifested exclusive increased expression of PD-L1 and a highest proportion of PD-L1+/CD8A+. Meanwhile, TP53 or KRAS mutated tumors showed prominently increased mutation burden and specifically enriched in the transversion-high (TH) cohort. Further analysis focused on the potential molecular mechanism revealed that TP53 or KRAS mutation altered a group of genes involved in cell cycle regulating, DNA replication and damage repair. Finally, immunotherapeutic analysis from public clinical trial and prospective observation in our center were further confirmed that TP53 or KRAS mutation patients, especially those with co-occurring TP53/KRAS mutations, showed remarkable clinical benefit to PD-1 inhibitors. **CONCLUSIONS:** This work provides evidence that TP53 and KRAS mutation in lung adenocarcinoma may be served as a pair of potential predictive factors in guiding anti PD-1/PD-L1 immunotherapy.

Results From the Phase III Randomized Trial of Onartuzumab Plus Erlotinib Versus Erlotinib in Previously Treated Stage IIIB or IV Non-Small-Cell Lung Cancer: METLung.
Spigel DR1, Edelman MJ1, O'Byrne K1, Paz-Ares L1, Mocci S1, Phan S1, Shames DS1, Smith D1, Yu W1, Paton VE1, Mok T1. J Clin Oncol. 2016 Dec 12:JCO2016692160. [Epub ahead of print]

PURPOSE: The phase III OAM4971g study (METLung) examined the efficacy and safety of onartuzumab plus erlotinib in patients with locally advanced or metastatic non-small-cell lung cancer selected by MET immunohistochemistry whose disease had progressed after treatment with a platinum-based chemotherapy regimen. **PATIENTS AND METHODS**: Patients were randomly assigned at a one-to-one ratio to receive onartuzumab (15 mg/kg intravenously on day 1 of each 21-day cycle) plus daily oral erlotinib 150 mg or intravenous placebo plus daily oral erlotinib 150 mg. The primary end point was overall survival (OS) in the intent-to-treat population. Secondary end points included median progression-free survival, overall response rate, biomarker analysis, and safety. **RESULTS:** A total of 499 patients were enrolled (onartuzumab, n = 250; placebo, n = 249). Median OS was 6.8 versus 9.1 months for onartuzumab versus placebo (stratified hazard ratio [HR], 1.27; 95% CI, 0.98 to 1.65; P = .067), with a greater number of deaths in the onartuzumab arm (130 [52%] v 114 [46%]). Median progression-free survival was 2.7 versus 2.6 months (stratified HR, 0.99; 95% CI, 0.81 to 1.20; P = .92), and overall response rate was 8.4% and 9.6% for onartuzumab versus placebo, respectively. Exploratory analyses using MET fluorescence in situ hybridization status and gene expression showed no benefit for onartuzumab; patients with EGFR mutations showed a trend toward shorter OS with onartuzumab treatment (HR, 4.68; 95% CI, 0.97 to 22.63). Grade 3 to 5 adverse events were reported by 56.0% and 51.2% of patients, with serious AEs in 33.9% and 30.7%, for experimental versus control arms, respectively. **CONCLUSION:** Onartuzumab plus erlotinib did not improve clinical outcomes, with shorter OS in the onartuzumab arm, compared with erlotinib in patients with MET-positive non-small-cell lung cancer.

Immune-related response assessment during PD-1 inhibitor therapy in advanced non-small-cell lung cancer patients. Nishino M1, Ramaiya NH1, Chambers ES2, Adeni AE2, Hatabu H1, Jänne PA2, Hodi FS2, Awad MM2. J Immunother Cancer. 2016 Dec 20;4:84. doi: 10.1186/s40425-016-0193-2. eCollection 2016.
BACKGROUND: Tumor response characteristics using immune-related RECIST1.1 (irRECIST1.1) in advanced non-small-cell lung cancer (NSCLC) patients treated with nivolumab monotherapy in the clinical setting have not been previously described with a direct comparison with the assessments according to the conventional RECIST1.1. **METHODS:** Fifty-six advanced NSCLC patients treated with nivolumab monotherapy after its Food and Drug Administration (FDA) approval were retrospectively studied. Tumor burden was quantified on serial CT scans during therapy using irRECIST1.1, which uses unidimensional measurements and includes new lesion measurements in total tumor burden. Response assessments by irRECIST1.1 were compared with assessments by RECIST1.1. Responses of individual lesions in different organs were also compared. **RESULTS:** Tumor burden change at best overall response ranged from -66.8 to +278.1% (median: +3.9%). Response rate was 14% (8/56; 8 partial responses, 0 complete responses) by irRECIST1.1 and by RECIST1.1. Time-to-progression (TTP) by irRECIST1.1 was longer than TTP by RECIST1.1 (median TTP: not reached vs. 1.9 months, respectively). No patients experienced pseudoprogression during the study. Among 128 target lesions, the lesion-based size change at best response differed significantly across different organs, with adrenal lesions and lymph nodes having greater size decrease, followed by lung, while liver and other miscellaneous lesions had lesser degree of size decrease ($p = 0.002$). **CONCLUSIONS:** Immune-related response evaluations using irRECIST1.1 in advanced NSCLC patients treated with nivolumab resulted in the identical response rate and longer TTP compared to RECIST1.1. No pseudoprogression cases were observed during the study. Adrenal lesions and lymph nodes were more responsive and liver lesions were less responsive to nivolumab

Characteristics and Prognostic Impact of Pneumonitis during Systemic Anti-Cancer Therapy in Patients with Advanced Non-Small-Cell Lung Cancer. Fujimoto D1, Kato R1, Morimoto T2,3, et al. PLoS One. 2016 Dec 22;11(12):e0168465. doi: 10.1371/journal.pone.0168465. eCollection 2016.
BACKGROUND: Data on characteristics, outcomes, and prognosis of advanced non-small-cell lung cancer (NSCLC) patients who develop pneumonitis during systemic anti-cancer therapy (pneumonitis) are currently lacking. **METHODS:** We conducted a retrospective cohort study of 910 consecutive patients diagnosed with advanced NSCLC between January 2004 and January 2014. Of these, 140 patients were excluded because they did not receive systemic anti-cancer therapy at this hospital. **RESULTS:** A total of 770 patients were included in the study, of whom 44 (6%) were diagnosed with pneumonitis. The mortality rate of pneumonitis was 36%. The incidence of pneumonitis was independently associated with pre-existing ILD (adjusted odds ratio, 2.99, P = 0.008), and survivors were significantly associated with younger age (P = 0.003) and radiographic non-acute interstitial pneumonia pattern (P = 0.004). In all patients, pneumonitis was identified as an independent predictor of overall survival (OS) (adjusted hazard ratio 1.53, 95% CI, 1.09-2.09, P = 0.015). Performance status was poor in 82% of survivors of pneumonitis; in 62% of survivors, the PS worsened after the pneumonitis improved. Additionally, 54% of survivors received no further systemic anti-cancer therapy after pneumonitis. The median survival time of survivors after pneumonitis was 3.5 months (95% CI, 2.3-7.2 months). **CONCLUSIONS:** Our study indicated that 6% of patients with advanced NSCLC developed pneumonitis during systemic anti-cancer therapy. The early mortality rate of pneumonitis is high, and the survival and PS after pneumonitis is extremely poor. Additionally, pneumonitis has an adverse impact on the survival of patients with advanced NSCLC. These data should be considered for the management of pneumonitis, and we recommend that future work focuses on pneumonitis particularly to improve the survival of patients with advanced NSCLC.

Phase II Study of Dasatinib in Previously Treated Patients with Advanced Non-Small Cell Lung Cancer.
Kelley MJ1,2,3, Jha G4, Shoemaker D2, Herndon JE 2nd2, Gu L2, Barry WT2,5, Crawford J1,2, Ready N1,2. Cancer Invest. 2016 Dec 2:1-4. [Epub ahead of print]
The Src pathway in activated in about one-third of non-small cell lung cancer (NSCLC) tumors. Dasatinib has Src-inhibitor activity. We examined the activity of dasatinib in 37 patients with advanced, previously treated NSCLC. Among the 29 patients who underwent pre-treatment biopsy for RNA biomarker analysis, 25 were treated with dasatinib 70 mg twice daily. There were no responses. Five patients discontinued treatment due to toxicity. Three patients had minor biopsy-related pneumothoraces. Given the lack of responses, no biomarkers were analyzed. Dasatinib 70 mg twice daily does not have activity nor is it well tolerated in unselected patients with advanced stage, previously treated NSCLC.

A prospective, multicenter phase II trial of low-dose erlotinib as maintenance treatment after platinum doublet chemotherapy for advanced non-small cell lung cancer harboring EGFR mutation. Hirano S1, Naka G2, Takeda Y2, et al. Chin Clin Oncol. 2016 Dec;5(6):77. doi: 10.21037/cco.2016.11.02.
BACKGROUND: Maintenance therapy with full-dose erlotinib for patients with advanced non-small cell lung cancer (NSCLC) has demonstrated a significant overall survival (OS) benefit. However, 150 mg/day of erlotinib seems too toxic as maintenance therapy. This study aimed to evaluate the efficacy and safety of low-dose erlotinib (25 mg/day) as maintenance treatment after platinum doublet chemotherapy in NSCLC harboring epidermal growth factor receptor (EGFR) mutation. **METHODS:** Activated EGFR-mutation-positive NSCLC patients who did not progress after first-line platinum-doublet chemotherapy, ≥20 and ≤85 years old, with performance status (PS) 0-3 were included in this study. Low-dose erlotinib (25 mg/day) was administered until disease progression. The primary endpoint was overall response rate

(ORR). Secondary endpoints included progression-free survival (PFS), OS, and safety. The required sample size was 40 patients. **RESULTS:** The study was stopped early, after achieving only 28% of planned enrollment, due to poor accrual. Between April 2011 and May 2014, 11 patients (male/female, 5/6; median age, 72 years; PS 0/1, 8/3; stage IV/relapse after surgery, 9/2; exon 19 deletions/L858R, 7/4) were enrolled and accessible in this study. Partial response (PR) was observed in 6 patients (56%). Median PFS was 14.9 months [95% confidence interval (CI), 2.7-27.1 months] and median OS was not calculable. Toxicities were generally mild. Only one patient developed grade 3 aspartate aminotransferase (AST)/alanine aminotransferase (ALT) elevation. Eight patients developed grade 1 skin rash. No treatment-related deaths were observed. Eight patients progressed, and recurrences included brain metastases (n=3), local recurrence (n=2), local recurrence plus brain metastasis (n=1), bone metastasis (n=1), and pulmonary metastasis (n=1). **CONCLUSIONS:** The study was stopped early due to poor accrual. However, our study suggests that maintenance therapy with low-dose erlotinib might be useful and tolerable in selected NSCLC patients harboring EGFR mutation.

Treatment patterns and survival in patients with ALK-positive non-small-cell lung cancer: a Canadian retrospective study. Kayaniyil S1, Hurry M2, Wilson J1, Wheatley-Price P3, Melosky B4, Rothenstein J5, Cohen V6, Koch C2, Zhang J7, Osenenko K1, Liu G8. Curr Oncol. 2016 Dec;23(6):e589-e597. doi: 10.3747/co.23.3273. Epub 2016 Dec 21.

BACKGROUND: Crizotinib was the first agent approved for the treatment of anaplastic lymphoma kinase (ALK)-positive (+) non-small-cell lung cancer (nsclc), followed by ceritinib. However, patients eventually progress or develop resistance to crizotinib. With limited real-world data available, the objective of the present work was to evaluate treatment patterns and survival after crizotinib in patients with locally advanced or metastatic ALK+ nsclc in Canada. **METHODS:** In this retrospective study at 6 oncology centres across Canada, medical records of patients with locally advanced or metastatic ALK+ nsclc were reviewed. Demographic and clinical characteristics, treatments, and outcomes data were abstracted. Analyses focused on patients who discontinued crizotinib treatment. **RESULTS:** Of the 97 patients included, 9 were crizotinib-naïve, and 39 were still receiving crizotinib at study end. The 49 patients who discontinued crizotinib treatment were included in the analysis. Of those 49 patients, 43% received ceritinib at any time, 20% subsequently received systemic chemotherapy only (but never ceritinib), and 37% received no further treatment or died before receiving additional treatment. Median overall survival from crizotinib discontinuation was shorter in patients who did not receive ceritinib than in those who received ceritinib (1.7 months vs. 20.4 months, $p < 0.001$). In a multivariable analysis, factors associated with poorer survival included lack of additional therapies (particularly ceritinib), male sex, and younger age, but not smoking status; patients of Asian ethnicity showed a nonsignificant trend toward improved survival. **CONCLUSIONS:** A substantial proportion of patients with ALK+ nsclc received no further treatment or died before receiving additional treatment after crizotinib. Treatment with systemic agents was associated with improved survival, with ceritinib use being associated with the longest survival.

Chemotherapy in recurrent advanced non-small-cell lung cancer after adjuvant chemotherapy. Valdes M1, Nicholas G1, Goss GD1, Wheatley-Price P1. Curr Oncol. 2016 Dec;23(6):386-390. doi: 10.3747/co.23.3191. Epub 2016 Dec 21.

INTRODUCTION: Despite adjuvant systemic therapy in patients with completely resected non-small-cell lung cancer (nsclc), many will subsequently relapse. We investigated treatment choices at relapse and assessed the effect of palliative platinum doublet systemic therapy in this population. **METHODS:** With research ethics board approval, we performed a retrospective chart review of all patients with resected nsclc who received adjuvant systemic therapy from January 2002 until December 2008 at our institution. The primary outcome was the response rate to first-line palliative systemic therapy among patients who

relapsed. **RESULTS:** We identified 176 patients who received adjuvant platinum doublet systemic therapy (82% received cisplatin-vinorelbine). In the 85 patients who relapsed (48%), median time to relapse was 18.5 months (95% confidence interval: 15 months to 21.3 months). Palliative systemic therapy was given in 43 patients. Of those 43 patients, 25 (58%) were re-challenged with platinum doublet systemic therapy, with a response rate of 29% compared with 18% in 18 patients who received other systemic therapy ($p = 0.48$). We observed a trend toward an increased clinical benefit rate (complete response + partial response + stable disease) in patients who were treated with a platinum doublet (67% vs. 41%, $p = 0.12$). Median overall survival (os) from relapse was 15.3 months in patients receiving palliative systemic therapy and 7.8 months in those receiving best supportive care alone. Compared with patients treated with non-platinum regimens, the platinum-treated group experienced longer survival after relapse (18.4 months vs. 9.7 months, $p = 0.041$). **CONCLUSIONS:** In patients previously treated with adjuvant systemic therapy, re-treatment with platinum doublet chemotherapy upon relapse is feasible. Moreover, compared with patients receiving other first-line systemic therapy, patients receiving platinum doublets experienced higher response rates and significantly longer survival.

Phase II Trial of Dose-dense Pemetrexed, Gemcitabine, and Bevacizumab in Patients With Advanced, Non-Small-cell Lung Cancer. Schneider BJ1, Kalemkerian GP2, Gadgeel SM3, et al. Clin Lung Cancer. 2016 Dec 2. pii: S1525-7304(16)30373-4. doi: 10.1016/j.cllc.2016.11.019. [Epub ahead of print]

INTRODUCTION: Platinum-based chemotherapy is standard for untreated, advanced non-small-cell lung cancer (NSCLC). We investigated the activity and tolerability of the novel combination of dose-dense pemetrexed, gemcitabine, and bevacizumab in patients with advanced NSCLC. **METHODS:** This multicenter phase II trial evaluated the safety and efficacy of the combination of pemetrexed (400 mg/m2), gemcitabine (1200 mg/m2), and bevacizumab (10 mg/kg), given every 14 days in patients with untreated, advanced NSCLC. The primary endpoint was progression-free survival with secondary endpoints of response rate and overall survival. **RESULTS:** Thirty-nine patients were enrolled. Treatment was well tolerated; the most common grade 3-4 toxicities were neutropenia and fatigue. Of the 38 patients evaluable for tumor response, 1 (3%) had complete response, 15 (39%) had partial response, 12 (31%) had stable disease, and 10 (26%) had progressive disease. Median progression-free survival was 6.1 months (95% confidence interval [CI], 4.2-7.9) and median overall survival was 18.4 months (95% CI, 13.1-29.5). The 1-year overall survival rate was 64% (95% CI, 51%-81%) and the 2-year overall survival rate was 41% (95% CI, 28%-60%). **CONCLUSIONS:** Treatment with dose-dense pemetrexed, gemcitabine, and bevacizumab met the primary endpoint with promising efficacy and a manageable safety profile in patients with untreated advanced NSCLC. This regimen represents a reasonable therapeutic option.

The association between clinical prognostic factors and epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) efficacy in advanced non-small-cell lung cancer patients: a retrospective assessment of 94 cases with EGFR mutations. Lin JH1,2, Lin D1,2, Xu L1,2, Wang Q1,2, Hu HH1,2, Xu HP1,2, He ZY1,2. Oncotarget. 2016 Dec 3. doi: 10.18632/oncotarget.13787. [Epub ahead of print]

OBJECTIVE: This study aimed to examine the association of clinical prognostic factors with epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) efficacy in advanced non-small-cell lung cancer (NSCLC) patients. **METHODS:** The demographic and clinical characteristics of 94 patients with stage IV NSCLC were retrospectively reviewed, and the association between clinical factors and EGFR-TKIs efficacy was evaluated. **RESULTS:** Of the 94 stage IV NSCLC patients enrolled in this study, a 74.5% objective response rate (ORR) and 97.9% disease control rate (DCR) were observed for EGFR-TKIs treatment, and a higher ORR was seen in patients with 0 and 1 ECOG scores than those with 2 or

greater scores (P = 0.049). The subjects had a median PFS of 11 months and a median OS of 31 months after EGFR-TKIs treatment. ECOG score and timing of targeted therapy were factors affecting PFS, and ECOG score, smoking status and brain metastasis were factors affecting OS. In addition, ECOG score was an independent prognostic factor for PFS in stage IV NSCLC patients, and the patients with EGFR 19del mutation had a longer PFS than those with exon 21 L855R mutation (P = 0.003), while ECOG score and brain metastasis were independent prognostic factors for OS. **CONCLUSIONS:** The results of this study demonstrate that EGFR-TKI therapy results in survival benefits for EGFR-mutant advanced NSCLC patients, regardless of gender, smoking history, pathologic type, type of EGFR mutations, brain metastasis and timing of targeted therapy. ECOG score is an independent prognostic factor for PFS, and ECOG score and brain metastasis are independent prognostic factors for OS in advanced NSCLC patients.

Feasibility of adjuvant chemotherapy with S-1 plus carboplatin followed by single-agent maintenance therapy with S-1 for completely resected non-small-cell lung cancer: results of the Setouchi Lung Cancer Group Study 1001. Okumura N1, Sonobe M2, Okabe K3, et al. Int J Clin Oncol. 2016 Dec 5. [Epub ahead of print]

BACKGROUND: This multicenter study evaluated the feasibility of novel adjuvant chemotherapy with S-1 plus carboplatin followed by single-agent, long-term maintenance with S-1 in patients with completely resected stage II-IIIA non-small-cell lung cancer (NSCLC). **METHODS:** Patients received four cycles of S-1 (80 mg/m2/day for 2 weeks, followed by 2 weeks rest) plus carboplatin (area under the curve 5, day 1) followed by S-1 (80 mg/m2/day for 2 weeks, followed by a 1-week rest). Patients unable to continue S-1 plus carboplatin because of severe toxicity converted to single-agent S-1 maintenance. The duration of adjuvant chemotherapy was 10 months in both situations. The primary endpoint was feasibility, defined as the proportion of patients who completed four cycles of S-1 plus carboplatin and single-agent S-1 maintenance for 10 months. The treatment completion rate was determined; treatment was considered feasible if the lower 90% confidence interval (CI) was ≥50%. **RESULTS:** Eighty-nine patients were enrolled, of whom 87 were eligible and assessable. Seventy-eight patients (89.7%) completed four cycles of S-1 plus carboplatin and 55 (63.2%) completed the following S-1 maintenance therapy for a total of 10 months. The treatment completion rate was 63.2% (90% CI, 54.4-71.2%), indicating feasibility. There were no treatment-related deaths. Grade 3/4 toxicities included neutropenia (13.8%), thrombocytopenia (11.5%), and anorexia (4.6%). The 2-year relapse-free survival rate was 59.8%. **CONCLUSIONS:** We concluded that adjuvant chemotherapy with S-1 plus carboplatin followed by single-agent maintenance therapy with S-1 is feasible and tolerable in patients with completely resected NSCLC.

Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. Hellmann MD1, Rizvi NA2, Goldman JW3, et al. Lancet Oncol. 2017 Jan;18(1):31-41. doi: 10.1016/S1470-2045(16)30624-6. Epub 2016 Dec 5.

BACKGROUND: Nivolumab has shown improved survival in the treatment of advanced non-small-cell lung cancer (NSCLC) previously treated with chemotherapy. We assessed the safety and activity of combination nivolumab plus ipilimumab as first-line therapy for NSCLC. **METHODS:** The open-label, phase 1, multicohort study (CheckMate 012) cohorts reported here were enrolled at eight US academic centres. Eligible patients were aged 18 years or older with histologically or cytologically confirmed recurrent stage IIIb or stage IV, chemotherapy-naive NSCLC. Patients were randomly assigned (1:1:1) by an interactive voice response system to receive nivolumab 1 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks, nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 12 weeks, or nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks until disease progression, unacceptable toxicities, or withdrawal of consent. Data from the latter two cohorts, which were

considered potentially suitable for further clinical development, are presented in this report; data from the other cohort (as well as several earlier cohorts) are described in the appendix. The primary outcome was safety and tolerability, assessed in all treated patients. This ongoing study is registered with ClinicalTrials.gov, number NCT01454102. **FINDINGS:** Between May 15, 2014, and March 25, 2015, 78 patients were randomly assigned to receive nivolumab every 2 weeks plus ipilimumab every 12 weeks (n=38) or nivolumab every 2 weeks plus ipilimumab every 6 weeks (n=40). One patient in the ipilimumab every-6-weeks cohort was excluded before treatment; therefore 77 patients actually received treatment (38 in the ipilimumab every-12-weeks cohort; 39 in the ipilimumab every-6-weeks cohort). At data cut-off on Jan 7, 2016, 29 (76%) patients in the ipilimumab every-12-weeks cohort and 32 (82%) in the ipilimumab every-6-weeks cohort had discontinued treatment. Grade 3-4 treatment-related adverse events occurred in 14 (37%) patients in the ipilimumab every-12-weeks cohort and 13 (33%) patients in the every-6-weeks cohort; the most commonly reported grade 3 or 4 treatment-related adverse events were increased lipase (three [8%] and no patients), pneumonitis (two [5%] and one [3%] patients), adrenal insufficiency (one [3%] and two [5%] patients), and colitis (one [3%] and two [5%] patients). Treatment-related serious adverse events were reported in 12 (32%) patients in the ipilimumab every-12-weeks cohort and 11 (28%) patients in the every-6-weeks cohort. Treatment-related adverse events (any grade) prompted treatment discontinuation in four (11%) patients in the every-12-weeks cohort and five (13%) patients in the every-6-weeks cohort. No treatment-related deaths occurred. Confirmed objective responses were achieved in 18 (47% [95% CI 31-64]) patients in the ipilimumab every-12-weeks cohort and 15 (38% [95% CI 23-55]) patients in the ipilimumab every-6-weeks cohort; median duration of response was not reached in either cohort, with median follow-up times of 12·8 months (IQR 9·3-15·5) in the ipilimumab every-12-weeks cohort and 11·8 months (6·7-15·9) in the ipilimumab every-6-weeks cohort. In patients with PD-L1 of 1% or greater, confirmed objective responses were achieved in 12 (57%) of 21 patients in the ipilimumab every-12-weeks cohort and 13 (57%) of 23 patients in the ipilimumab every-6-weeks cohort. **INTERPRETATION:** In NSCLC, first-line nivolumab plus ipilimumab had a tolerable safety profile and showed encouraging clinical activity characterised by a high response rate and durable response. To our knowledge, the results of this study are the first suggestion of improved benefit compared with anti-PD-1 monotherapy in patients with NSCLC, supporting further assessment of this combination in a phase 3 study. **FUNDING:** Bristol-Myers Squibb.

NSCLC - RADIOTHERAPY

Stereotactic radiotherapy following surgery for brain metastasis: Predictive factors for local control and radionecrosis. Doré M1, Martin S2, Delpon G3, Clément K4, Campion L5, Thillays F4. Cancer Radiother. 2016 Dec 7. pii: S1278-3218(16)30477-2. doi: 10.1016/j.canrad.2016.06.010. [Epub ahead of print]

PURPOSE: To evaluate local control and adverse effects after postoperative hypofractionated stereotactic radiosurgery in patients with brain metastasis. **METHODS:** We reviewed patients who had hypofractionated stereotactic radiosurgery (7.7Gy×3 prescribed to the 70% isodose line, with 2mm planning target volume margin) following resection from March 2008 to January 2014. The primary endpoint was local failure defined as recurrence within the surgical cavity. Secondary endpoints were distant failure rates and the occurrence of radionecrosis. **RESULTS:** Out of 95 patients, 39.2% had metastatic lesions from a non-small cell lung cancer primary tumour. The median Graded Prognostic Assessment score was 3 (48% of patients). One-year local control rates were 84%. Factors associated with improved local control were no cavity enhancement on pre-radiation MRI (P<0.00001), planning target volume less than 12cm3 (P=0.005), Graded Prognostic Assessment score 2 or above (P=0.009). One-year distant cerebral control rates were 56%. Thirty-three percent of patients received whole brain radiation therapy. Histologically proven radionecrosis of brain tissue occurred in 7.2% of cases. The size of the

preoperative lesion and the volume of healthy brain tissue receiving 21Gy (V21) were both predictive of the incidence of radionecrosis (P=0.010 and 0.036, respectively). **CONCLUSION:** Adjuvant hypofractionated stereotactic radiosurgery to the postoperative cavity in patients with brain metastases results in excellent local control in selected patients, helps delay the use of whole brain radiation, and is associated with a relatively low risk of radionecrosis.

Stereotactic Body Radiotherapy for Large (> 5 cm) Non-Small-Cell Lung Cancer. Peterson J1, Niles C1, Patel A2, Boujaoude Z3, Abouzgheib W3, Goldsmith B2, Asbell S2, Xu Q2, Khrizman P4, Kubicek GJ5. Clin Lung Cancer. 2016 Dec 8. pii: S1525-7304(16)30374-6. doi: 10.1016/j.cllc.2016.11.020. [Epub ahead of print]
BACKGROUND: Stereotactic body radiotherapy (SBRT) is a well-established treatment option for early stage non-small-cell lung cancer (NSCLC) tumors < 5 cm. There is limited information on tumors > 5 cm. **PATIENTS AND METHODS:** We performed retrospective data collection of patients enrolled onto a prospective SBRT registry study. Eligible patients for this study had node-negative NSCLC measuring > 5 cm in any dimension. Data from 41 patients were analyzed. Median patient age was 75 years, and median tumor size was 5.6 cm (range, 5.0-12.2 cm). Sixteen patients had squamous disease, 20 patients adenocarcinoma, and 1 mixed tumor; 4 patients had no biopsy. Median radiation dose per fraction was 50 Gy in 5 fractions. Radiation was prescribed to isodose line, median 66% (range, 50%-84%). **RESULTS:** Before SBRT, 6 patients had previous chemotherapy and 7 patients had previous radiation. Median follow-up for all patients was 15.2 months (range, 0.56-48.1 months). At last follow-up, 16 patients were still alive, with a median follow-up of 16.1 months for surviving patients. The median survival was 17.5 months with 1- and 2-year survivals of 65% and 34%. Two patients (4.8%) had local failure, and 13 patients (31%) had distant failure. Four patients (9.8%) had acute toxicity, and 7 patients (17.1%) had late toxicity, including 2 (4.8%) grade 3 late toxicities. **CONCLUSION:** SBRT for tumors > 5 cm is effective, with good local control rates and acceptable toxicity. The main pattern of failure is distant, suggesting a possible role for systemic chemotherapy in these patients.

SMALL CELL LUNG CANCER - SCLC

Clinical Features of Brain Metastases in Small Cell Lung Cancer: an Implication for Hippocampal Sparing Whole Brain Radiation Therapy. Guo WL1, He ZY2, Chen Y3, Zhou D1, Tang K1, Wang P1, Zhan SQ4, Wu SG5. Transl Oncol. 2016 Dec 7;10(1):54-58. doi: 10.1016/j.tranon.2016.11.002. [Epub ahead of print]
PURPOSE: To assess the clinical features and distribution of brain metastases (BMs) of small cell lung cancer (SCLC) in the hippocampal and perihippocampal region, with the purpose of exploring the viability of hippocampal-sparing whole-brain radiation therapy (HS-WBRT) on reducing neurocognitive deficits. **METHODS:** This was a retrospective analysis of the clinical characteristics and patterns of BMs in patients with SCLC. Associations between the clinical characteristics and hippocampal metastases (HMs)/perihippocampal metastases (PHMs) were evaluated in univariate and multivariate regression analyses. **RESULTS:** A total of 1594 brain metastatic lesions were identified in 180 patients. Thirty-two (17.8%) patients were diagnosed with BMs at the time of primary SCLC diagnosis. The median interval between diagnosis of primary SCLC and BMs was 9.3 months. There were 9 (5.0%) and 22 (12.2%) patients with HMs and PHMs (patients with BMs located in or within 5 mm around the hippocampus), respectively. In the univariate and multivariate analysis, the number of BMs was the risk factor for HMs and PHMs. Patients with BMs≥5 had significantly higher risk of HMs (odds ratio [OR] 7.892, 95% confidence interval [CI] 1.469-42.404, P=.016), and patients with BMs≥7 had significantly higher risk of PHMs (OR 5.162, 95% CI 2.017-13.213, P=.001). Patients with extracranial metastases are also associated with HMs. **CONCLUSIONS:** Our results indicate that patients with nonoligometastatic

disease are significantly associated with HMs and PHMs. The incidence of PHMs may be acceptably low enough to perform HS-WBRT for SCLC. Our findings provide valuable clinical data to assess the benefit of HS-WBRT in SCLC patients with BMs.

Nine-year Experience: Prophylactic Cranial Irradiation in Extensive Disease Small-cell Lung Cancer. Bernhardt D1, Adeberg S2, Bozorgmehr F3, et al. Clin Lung Cancer. 2016 Dec 2. pii: S1525-7304(16)30366-7. doi: 10.1016/j.cllc.2016.11.012. [Epub ahead of print]

BACKGROUND: In 2007, the European Organization for Research and Treatment of Cancer (EORTC) study (ClinicalTrials.gov identifier, NCT00016211) demonstrated a beneficial effect on overall survival (OS) with the use of prophylactic cranial irradiation (PCI) for extensive disease (ED) small-cell lung cancer (SCLC). Nevertheless, debate is ongoing regarding the role of PCI, because the patients in that trial did not undergo magnetic resonance imaging (MRI) of the brain before treatment. Also, a recent Japanese randomized trial showed a detrimental effect of PCI on OS in patients with negative pretreatment brain MRI findings. **MATERIALS AND METHODS:** We examined the medical records of 136 patients with ED SCLC who had initially responded to chemotherapy and undergone PCI from 2007 to 2015. The outcomes, radiation toxicity, neurologic progression-free survival, and OS after PCI were analyzed. Survival and correlations were calculated using log-rank and univariate Cox proportional hazard ratio analyses. **RESULTS:** The median OS and the median neurologic progression-free survival after PCI was 12 and 19 months, respectively. No significant survival difference was seen for patients who had undergone MRI before PCI compared with patients who had undergone contrast-enhanced computed tomography (P = .20). Univariate analysis for OS did not show a statistically significant effect for known cofactors. **CONCLUSION:** In the present cohort, PCI was associated with improved survival compared with the PCI arm of the EORTC trial, with a nearly doubled median OS period. Also, the median OS was prolonged by 2 months compared with the irradiation arm of the Japanese trial.

Selected patients can benefit more from the management of etoposide and platinum-based chemotherapy and thoracic irradiation-a retrospective analysis of 707 small cell lung cancer patients. Cao S1, Jin S1, Shen J1, et al. Oncotarget. 2016 Dec 31. doi: 10.18632/oncotarget.14395. [Epub ahead of print]

The management of small cell lung cancer (SCLC) has reached a plateau. Etoposide and platinum-based chemotherapy plus thoracic irradiation remain the standard treatment strategy for SCLC. Our study aims to assess the potential prognostic factors of patients treated with etoposide and platinum-based chemotherapy and explore which group of patients can benefit more from standard treatment strategies. On univariate analysis, age>65 years, male patients, KPS (Karnofsky Performance Status)≤80 points, positive smoking history, anemia, lymphocyte counts≤1.65×109/L, neutrophil to lymphocyte ratio (NLR)>3.18, lymphocyte to monocyte ratio (LMR)≤2.615, lactate dehydrogenase (LDH)>216.5 U/L, alkaline phosphatase (ALP)>119.5 U/L, absence of surgery, absence of thoracic irradiation, chemotherapy cycles<4, metastatic sites≥2 and extensive disease were correlated with a poor prognosis. Gender, KPS, chemotherapy cycles, thoracic irradiation, metastatic sites, LDH and tumor stage held statistical significance on multivariate analysis ($p<0.05$). High LDH was closely correlated with extensive disease, metastatic sites≥2, anemia, low LMR, high NLR and ALP levels. Subgroup analysis showed patients with male gender, KPS≤80 points, LDH≤216.5U/L, extensive disease and metastatic sites<2 could benefit more from ≥4 chemotherapy cycles. Patients with male gender, KPS>80 points, LDH≤216.5U/L, limited disease and metastatic sites<2 could benefit more from thoracic irradiation ($p<0.05$ on uni- and multivariate analysis). In conclusion, female patients, KPS>80 points, chemotherapy cycles≥4, thoracic irradiation, metastatic sites<2, LDH≤216.5U/L and limited disease were independent positive prognostic factors for SCLC patients treated with etoposide and platinum-based chemotherapy. Selected patients can benefit more from the management of ≥4 cycles of chemotherapy and thoracic irradiation.

Lidocaine 5% medicated plaster for localized neuropathic pain in thoracic surgical patients. Freo U1, Ori C1, Ambrosio F1. Curr Med Res Opin. 2016 Dec 8:1-5. [Epub ahead of print]
Neuropathic pain is a common and distressing symptom in thoracic surgical patients. When it consistently presents with measurable sensory changes in a circumscribed area, neuropathic pain can be diagnosed as localized neuropathic pain (LNP).
OBJECTIVE: The purpose of this study was to report the efficacy of lidocaine 5% medicated plaster (Lido5%P) in the treatment of LNP in thoracic surgical patients. **METHODS:** We retrospectively reviewed the records of sixteen cancer and noncancer thoracic patients treated with Lido5%P for LNP. Patients had been assessed before and during treatment with standardized forms and questionnaires for pain intensity, sleep quality, drug dosages and adverse events. **RESULTS:** Treatment with Lido5%P yielded a significant and lasting improvement in pain symptomatology. In oncological patients as an add-on therapy, Lido5%P improved pain intensity and sleep quality, and delayed opioid dose escalation. In non-oncological patients as monotherapy or in association with antineuropathic drugs, Lido5%P attenuated LNP. No local or systemic adverse events were recorded. **CONCLUSIONS:** Lido5%P was effective in relieving thoracic LNP, and was well tolerated.

Family Perspectives on Hospice Care Experiences of Patients with Cancer. Kumar P1, Wright AA1, Hatfield LA1, Temel JS1, Keating NL1. J Clin Oncol. 2016 Dec 19:JCO2016689257. [Epub ahead of print]
PURPOSE: To determine whether hospice use by patients with cancer is associated with their families' perceptions of patients' symptoms, goal attainment, and quality of end-of-life (EOL) care. **METHODS:** We interviewed 2,307 families of deceased patients with advanced lung or colorectal cancer who were enrolled in the Cancer Care Outcomes Research and Surveillance study (a multiregional, prospective, observational study) and died by 2011. We used propensity-score matching to compare family-reported outcomes for patients who did and did not receive hospice care, including the presence and relief of common symptoms (ie, pain, dyspnea), concordance with patients' wishes for EOL care and place of death, and quality of EOL care. We also examined associations between hospice length of stay and these outcomes among hospice enrollees. **RESULTS:** In a propensity-score-matched sample of 1,970 individuals, families of patients enrolled in hospice reported more pain in their patient compared with those not enrolled in hospice. However, families of patients enrolled in hospice more often reported that patients received "just the right amount" of pain medicine (80% v 73%; adjusted difference, 7 percentage points; 95% confidence interval [CI], 1 to 12 percentage points) and help with dyspnea (78% v 70%; adjusted difference, 8 percentage points; 95% CI, 2 to 13 percentage points). Families of patients enrolled in hospice also more often reported that patients' EOL wishes were followed (80% v 74%; adjusted difference, 6 percentage points; 95% CI, 2 to 11 percentage points) and "excellent" quality EOL care (57% v 42%; adjusted difference, 15 percentage points; 95% CI, 11 to 20). Families of patients who received > 30 days of hospice care reported the highest quality EOL outcomes. **CONCLUSION:** Hospice care is associated with better symptom relief, patient-goal attainment, and quality of EOL care. Encouraging earlier and increased hospice enrollment may improve EOL experiences for patients with cancer and their families.

Efficacy of triple antiemetic therapy (palonosetron, dexamethasone, aprepitant) for chemotherapy-induced nausea and vomiting in patients receiving carboplatin-based, moderately emetogenic chemotherapy. Miya T1, Kobayashi K2, Hino M3, et al. Springerplus. 2016 Dec 7;5(1):2080. doi: 10.1186/s40064-016-3769-x. eCollection 2016.

BACKGROUND: Chemotherapy-induced nausea and vomiting (CINV) is a major adverse toxicity of cancer chemotherapy. Recommended treatments for prevention of CINV vary among published guidelines, and optimal care for CINV caused by moderately emetogenic chemotherapy has not been established. This study assessed the efficacy and safety of triple antiemetic therapy comprising palonosetron, dexamethasone and aprepitant for carboplatin-based chemotherapy. Chemotherapy-naïve patients with lung cancer scheduled for a first course of a carboplatin-containing regimen formed the study cohort. Patients were pretreated with antiemetic therapy comprising palonosetron (0.75 mg, i.v.) and dexamethasone (9.9 mg, i.v.) on day 1, and aprepitant (125 mg, p.o.) on day 1 followed by 80 mg on days 2 and 3. Primary endpoint was the proportion of patients who did not experience vomiting and did not require rescue medication [complete response (CR)] in the acute phase (0-24 h), late phase (24-168 h) and overall. Secondary endpoint was the proportion of patients who experienced no vomiting episodes and no more than mild nausea without the need for rescue medication [complete control (CC)]. **RESULTS:** Prevalence of a CR during the acute phase, delayed phase, and overall was 100, 91.9 and 91.9%, whereas that of CC was 100, 84.4 and 84.4%, respectively. The most common adverse event was mild constipation; severe adverse events related to antiemetic treatment were not observed. **CONCLUSION:** Triple antiemetic therapy comprising palonosetron, dexamethasone and aprepitant shows excellent effects in the prevention of CINV in patients receiving a carboplatin-containing regimen.

Does physical exercise improve quality of life of advanced cancer patients? Navigante A1, Morgado PC. Curr Opin Support Palliat Care. 2016 Dec;10(4):306-309.
PURPOSE OF REVIEW: We discuss the principal issues about physical activity in advanced cancer patients through the analyses of the last articles and our experience in this field. **RECENT FINDINGS:** The efficacy of exercise training intervention could improve quality of life (QOL), fatigue and well being in advanced cancer patients. Several published studies have included, nevertheless, patients with early stage of disease and more recently, populations of patients with local advanced tumors of the breast, rectum and lung, who are undergoing neoadjuvant therapy. Despite the insufficient sample of patients in these studies, physical exercise is considered to improve both cardiopulmonary function and physical muscle fitness. Cancer-related fatigue is a devastating symptom in advanced cancer patients that implies loss of mobility and independence. **SUMMARY:** Physical exercise could be a treatment to increase skeletal muscle endurance and improve well-being. In palliative medicine, physical activity could be applied to medical assistance or to design prospective and controlled trials so as to evaluate possible usefulness.

Practical multimodal care for cancer cachexia. Maddocks M1, Hopkinson J, Conibear J, Reeves A, Shaw C, Fearon KC. Curr Opin Support Palliat Care. 2016 Dec;10(4):298-305.
PURPOSE OF REVIEW: Cancer cachexia is common and reduces function, treatment tolerability and quality of life. Given its multifaceted pathophysiology a multimodal approach to cachexia management is advocated for, but can be difficult to realise in practice. We use a case-based approach to highlight practical approaches to the multimodal management of cachexia for patients across the cancer trajectory. **RECENT FINDINGS:** Four cases with lung cancer spanning surgical resection, radical chemoradiotherapy, palliative chemotherapy and no anticancer treatment are presented. We propose multimodal care approaches that incorporate nutritional support, exercise, and anti-inflammatory agents, on a background of personalized oncology care and family-centred education. Collectively, the cases reveal that multimodal care is part of everyone's remit, often focuses on supported self-management, and demands buy-in from the patient and their family. Once operationalized, multimodal care approaches can be tested pragmatically, including alongside emerging pharmacological cachexia treatments. **SUMMARY:** We demonstrate that multimodal care for cancer cachexia can be achieved using simple treatments and without a dedicated team of specialists. The sharing of advice between health professionals

can help build collective confidence and expertise, moving towards a position in which every team member feels they can contribute towards multimodal care.

Structural distress screening and supportive care for patients with lung cancer on systemic therapy: A randomised controlled trial.

Geerse OP1, Hoekstra-Weebers JE2, Stokroos MH3, Burgerhof JG4, Groen HJ3, Kerstjens HA3, Hiltermann TJ3. Eur J Cancer. 2016 Dec 23;72:37-45. doi: 10.1016/j.ejca.2016.11.006. [Epub ahead of print]

INTRODUCTION: Gaining regular insight into the nature and severity of distress by a psychosocial nurse coupled with referral to psychosocial and/or paramedical healthcare provider(s) is an experimental supportive care approach. We sought to examine the effects of this approach on quality of life (QoL), patient's mood and satisfaction, end-of-life care and survival in patients with lung cancer.
METHODS: Patients with newly diagnosed or recurrent lung cancer starting systemic therapy were randomly assigned to receive usual care or the experimental approach. Patients were followed up at 1, 7, 13 and 25 weeks after randomisation with the EORTC-QLQ-C30, the European Quality of Life-5D, the Hospital Anxiety and Depression Scale and the Patient Satisfaction Questionnaire-III. Primary outcome was the mean change in the EORTC-QLQ-C30 global QoL-score between 1 and 25 weeks. **RESULTS:** A total of 223 patients were randomised of whom 111 (50%) completed all four assessments (44% in the usual care group versus 55% in the experimental group). No significant difference was found in the mean change global QoL-score (-2.4, 95% CI: 12.1-7.2; P = 0.61), nor in the other patient-reported outcomes. Fewer patients in the experimental group received chemotherapy shortly before the end-of-life, and median survival was comparable (10.3 versus 10.1 months, P = 0.62). Of the 112 dropouts, 33 died and 79 discontinued participation for other reasons. **CONCLUSIONS:** This supportive care approach neither improved QoL nor other patient-reported outcomes in patients with lung cancer. However, it reduced the use of chemotherapy shortly before the end of life. Possibly, (late) side effects of systemic therapy may have obscured effects of our intervention on QoL.

Defining the role of dietary intake in determining weight change in patients with cancer cachexia.

Nasrah R1, Kanbalian M2, Van Der Borch C2, Swinton N3, Wing S2, Jagoe RT4. Clin Nutr. 2016 Dec 21. pii: S0261-5614(16)31353-X. doi: 10.1016/j.clnu.2016.12.012. [Epub ahead of print]

BACKGROUND & AIMS: Weight loss is a cardinal feature of cachexia and is frequently associated with reduced food intake and anorexia. It is still unclear how much reduced food intake contributes to cancer-related weight loss and how effective increasing dietary energy and protein is in combating this weight loss. The relationship between weight change and both diet and change in dietary intake, was examined in patients with advanced stage cancer referred to a multidisciplinary clinic for management of cancer cachexia. **METHODS:** A retrospective study of data for each of the first three clinic visits for patients seen between 2009 and 2015. Data on weight change, dietary intake and change in dietary intake were compared. Regression analysis was used to determine independent explanatory factors for weight change, including the impact of appetite level and a marker of systemic inflammation. **RESULTS:** Of 405 eligible patients, 320 had data on dietary intake available. Dietary intake varied widely at baseline: 26.9% reported very poor diet and only 17% were consuming recommended levels of energy and protein. A highly significant positive correlation was found between dietary energy or protein intake and weight change, both before and after being seen in the clinic. Anorexia was also significantly correlated with weight loss at each clinic visit. However, there was no similar overall correlation between change in dietary intake and change in weight. **CONCLUSIONS:** Many patients with advanced cancer and weight loss are consuming diets that would likely be insufficient to maintain weight even in healthy individuals. Higher consumption of protein and energy correlates with greater weight gain, but it is impossible to predict the response to increased nutritional intake when patients are first assessed. There is a pressing

need to improve understanding of factors that modulate metabolic responses to dietary intake in patients with cancer cachexia.

The Intensive Palliative Care Unit: Changing Outcomes for Hospitalized Cancer Patients in an Academic Medical Center.
Zhang H1, Barysauskas C2, Rickerson E1, Catalano P2, Jacobson J3, Dalby C4, Lindvall C1, Selvaggi K5. J Palliat Med. 2016 Dec 21. doi: 10.1089/jpm.2016.0225. [Epub ahead of print]
BACKGROUND: Patients with advanced cancer often require complex symptom management. At Dana-Farber/Brigham and Women's Cancer Center, the intensive palliative care unit (IPCU) admits symptomatic oncology patients with uncontrolled symptoms throughout the trajectory of illness. Patients are uniquely managed by an interdisciplinary team of clinicians who focus on symptom management and advance care planning. **OBJECTIVE:** The purpose of our analysis was to investigate goals-of-care outcomes and healthcare utilization after admission to the IPCU. **DESIGN:** We retrospectively reviewed 74 oncology patients admitted to the IPCU in August and September, 2013. **RESULTS:** A total of 67 IPCU patients who were admitted received palliative intent treatment, whereas 7 patients received curative intent care. All patients were engaged in a goals-of-care discussion during admission. Of the palliative intent patients, 58% were transferred to the IPCU from medical oncology and 42% were directly admitted. Forty-eight percent of the patients were diagnosed with metastatic lung, genitourinary, or gastrointestinal cancer. Eighty-seven percent of patients reported pain as the chief complaint at admission. Twenty-five patients experienced a change in code status from Full Code to do-not-resuscitate/do-not-incubate. A total of eight patients died in the IPCU, and 50% experienced a code status change. Eighty-eight percent of patients were discharged alive. Of those, 49% were discharged to home hospice, general inpatient hospice, or an inpatient hospice facility. The risk of 30-day readmission was 4%.
CONCLUSIONS: Among advanced cancer patients, our findings suggest that an inpatient palliative care unit helps clarify goals of care, aids in appropriate hospice referrals, and decreases hospital readmissions.

COMPLEMENTARY & ALTERNATIVE THERAPY

Traditional Chinese medicine Jianpi Bushen therapy suppresses the onset of pre-metastatic niche in a murine model of spontaneous lung metastasis. Zhu X1, Zhou Y2, Xu Q3, Wu J4. Biomed Pharmacother. 2016 Dec 21;86:434-440. doi: 10.1016/j.biopha.2016.12.013. [Epub ahead of print]
BACKGROUND & AIM: Distinct metastasis accounts for the leading cause of mortality among patients with gastric cancer. The formation of pre-metastatic niche in the target organs provides permissive environments for the adhesion and subsequent growth of metastasized cancer cells. Targeting the pre-metastatic niche is a potential approach to prevent metastasis. Traditional Chinese medicine regimen called Jianpi Bushen therapy (JPBS) has been widely used in clinics to strengthen patients' abilities to fight cancer. The present work is aimed to study the modulating effect of JPBS on the lungs expressions of Rac1, Cdc42, SDF-1, and FN in a murine gastric cancer model showing spontaneous lung metastasis.
METHODS: Mice of strain 615 were inoculated with tumor cells derived from mouse forestomach carcinoma (MFC) to induce spontaneous lung metastasis, and were then treated with JPBS, JPBS combined with fluorouracil (5-FU), or 5-FU. Gene and protein expressions of Rac1, Cdc42, SDF-1, and FN in lungs were determined using real-time PCR and immunohistochemistry, respectively. Serum levels of SDF-1 and FN were also measured using ELISA. **RESULTS:** Gene and protein expressions of Rac1, Cdc42, SDF-1, and FN were significantly elevated in the lungs of model mice comparing to the counterpart mice received no tumor cell inoculation. JPBS treatment reduced protein expressions of Rac1, Cdc42, SDF-1 and FN in the lungs of model mice. The treatment could also suppress SDF-1 and FN in blood. For serum SDF-1 the level was further lower in model mice treated with combination therapy of JPBS and 5-FU. **CONCLUSION:** The present work identified the potential roles of Rac1, Cdc42, SDF-1

and FN in the early onset of pre-metastatic niche of gastric cancer, and provided insights into the molecular mechanism by which Jianpi Bushen therapy prevent and suppress cancer metastasis.

Recent highlights of Chinese medicine for advanced lung cancer. He XR1, Han SY1, Li PP2. Chin J Integr Med. 2016 Dec 27. doi: 10.1007/s11655-016-2736-2. [Epub ahead of print]
Owing to its unique superiority in improving quality of life and prolonging survival time among advanced lung cancer patients, Chinese medicine (CM) has, in recent years, received increased attentions worldwide. We utilized a bibliometric statistical method based on MEDLINE/GoPubMed to conduct a comprehensive analysis of the current application status of CM in lung cancer, by including annual and accumulated publications, origin distribution of countries and journals, and keywords with a higher frequency score. Then the relevant clinical trials and mechanistic studies were systematically summarized within the field according to research types. We have raised potential problems and provided potentially useful reference information that could guide similar studies in the future. The basic experimental results are highly consistent with clinical trials, leading us to conclude that CM can offer better overall therapeutic benefits when used in combination with routine Western medicine for patients with advanced lung cancer.

Therapeutic effects of gold nanoparticles synthesized using Musa paradisiaca peel extract against multiple antibiotic resistant Enterococcus faecalis biofilms and human lung cancer cells (A549). Vijayakumar S1, Vaseeharan B2, Malaikozhundan B1, et al. Microb Pathog. 2017 Jan;102:173-183. doi: 10.1016/j.micpath.2016.11.029. Epub 2016 Dec 1.
Botanical-mediated synthesis of nanomaterials is currently emerging as a cheap and eco-friendly nanotechnology, since it does not involve the use of toxic chemicals. In the present study, we focused on the synthesis of gold nanoparticles using the aqueous peel extract of Musa paradisiaca (MPPE-AuNPs) following a facile and cheap fabrication process. The green synthesized MPPE-AuNPs were bio-physically characterized by UV-Vis spectroscopy, FTIR, XRD, TEM, Zeta potential analysis and EDX. MPPE-AuNPs were crystalline in nature, spherical to triangular in shape, with particle size ranging within 50 nm. The biofilm inhibition activity of MPPE-AuNPs was higher against multiple antibiotic resistant (MARS) Gram-positive Enterococcus faecalis. Light and confocal laser scanning microscopic observations evidenced that the MPPE-AuNPs effectively inhibited the biofilm of E. faecalis when tested at 100 μg mL-1. Cytotoxicity studies demonstrated that MPPE-AuNPs were effective in inhibiting the viability of human A549 lung cancer cells at higher concentrations of 100 μg mL-1. The morphological changes in the MPPE-AuNPs treated A549 lung cancer cells were visualized under phase-contrast microscopy. Furthermore, the ecotoxicity of MPPE-AuNPs on the freshwater micro crustacean Ceriodaphnia cornuta were evaluated. Notably, no mortality was recorded in MPPE-AuNPs treated C. cornuta at 250 μg mL-1. This study concludes that MPPE-AuNPs are non-toxic, eco-friendly and act as a multipurpose potential biomaterial for biomedical applications.

MISCELLANEOUS WORKS

Patient Preferences in Treatment Choices for Early-Stage Lung Cancer. Tong BC1, Wallace S2, Hartwig MG3, D'Amico TA3, Huber JC2. Ann Thorac Surg. 2016 Dec;102(6):1837-1844. doi: 10.1016/j.athoracsur.2016.06.031. Epub 2016 Sep 9.
BACKGROUND: Decision-making for lung cancer treatment can be complex because it involves both provider recommendations based on the patient's clinical condition and patient preferences. This study describes the relative importance of several considerations in lung cancer treatment from the patient's perspective. **METHODS:** A conjoint preference experiment began by asking respondents to imagine that they had just been diagnosed with lung cancer. Respondents then chose among procedures that differed

regarding treatment modalities, the potential for treatment-related complications, the likelihood of recurrence, provider case volume, and distance needed to travel for treatment. Conjoint analysis derived relative weights for these attributes. **RESULTS:** A total of 225 responses were analyzed. Respondents were most willing to accept minimally invasive operations for treatment of their hypothetical lung cancer, followed by stereotactic body radiation therapy (SBRT); they were least willing to accept thoracotomy. Treatment type and risk of recurrence were the most important attributes from the conjoint experiment (each with a relative weight of 0.23), followed by provider volume (relative weight of 0.21), risk of major complications (relative weight of 0.18), and distance needed to travel for treatment (relative weight of 0.15). Procedural and treatment preferences did not vary with demographics, self-reported health status, or familiarity with the procedures. **CONCLUSIONS:** Survey respondents preferred minimally invasive operations over SBRT or thoracotomy for treatment of early-stage non-small cell lung cancer. Treatment modality and risk of cancer recurrence were the most important factors associated with treatment preferences. Provider experience outweighed the potential need to travel for lung cancer treatment.

Dumping the information bucket: A qualitative study of clinicians caring for patients with early stage non-small cell lung cancer.

Golden SE1, Thomas CR Jr2, Moghanaki D3, Slatore CG4; Early Stage Lung Cancer Comparative Effectiveness Research Consortium. Patient Educ Couns. 2016 Dec 21. pii: S0738-3991(16)30576-6. doi: 10.1016/j.pec.2016.12.023. [Epub ahead of print]

OBJECTIVE: To evaluate the quality of patient-clinician communication and shared decision making (SDM) when two disparate treatments for early stage non-small cell lung cancer (NSCLC) are discussed. **METHODS:** We conducted a qualitative study to evaluate the experiences of 20 clinicians caring for patients with clinical Stage I NSCLC prior to treatment, focusing on communication practices. We used directed content analysis and a patient-centered communication theoretical model to guide understanding of communication strategies. **RESULTS:** All clinicians expressed the importance of providing information, especially for mitigating patient worry, despite recognition that patients recall only a small amount of the information given. When patients expressed distress, clinicians exhibited empathy but preferred to provide more information in order to address patient concerns. Most clinicians reported practicing SDM, however, they also reported not clearly eliciting patient preferences and values, a key part of SDM. **CONCLUSION:** Communication with patients about treatment options for early stage NSCLC primary includes information giving. We found that only a few communication domains associated with SDM occurred regularly, and SDM may not be necessary in this clinical context. **PRACTICE IMPLICATIONS:** Clinicians may need to incorporate nurse navigators or more written materials for effectively discussing potentially equivalent treatment options with their patients.

Treatment Burden of Medicare Beneficiaries With Stage I Non-Small-Cell Lung Cancer.

Presley CJ1, Soulos PR1, Tinetti M1, Montori VM1, Yu JB1, Gross CP1. J Oncol Pract. 2016 Dec 20:JOP2016014100. [Epub ahead of print]

PURPOSE: To quantify the burden and complexity associated with treatment of Medicare beneficiaries with stage I non-small-cell lung cancer (NSCLC). **METHODS:** Using the SEER-Medicare database, we conducted a retrospective cohort study of Medicare beneficiaries who were diagnosed with stage I NSCLC from 2007 to 2011 and who were treated with surgery, stereotactic body radiation therapy, or external beam radiation therapy. Main outcome measures were the number of days a patient was in contact with the health care system (encounter days), the number of physicians involved in a patient's care, and the number of medications prescribed. Logistic regression modeled the association between patient characteristics, treatment type, and high treatment burden (defined as ≥ 66 encounter days). **RESULTS:** On average, 7,955 patients spent 1 in 3 days interacting with the health care system during the initial 60 days of treatment. Patients experienced a median of 44 encounter days with high variability

(interquartile range [IQR], 29 to 66) in the 12 months after treatment initiation. The median number of physicians involved was 20 (IQR, 14 to 28), and the median number of medications prescribed was 12 (IQR, 8 to 17). Patients who were treated with surgery had high treatment burden (predicted probability, 21.6%; 95% CI, 20.2 to 23.1) compared with patients who were treated with stereotactic body radiation therapy (predicted probability, 16.1%; 95% CI, 12.9 to 19.3), whereas patients who were treated with external beam radiation therapy had the highest burden (predicted probability, 46.8%; 95% CI, 43.3 to 50.2). **CONCLUSION:** The treatment burden imposed on patients with early-stage NSCLC was substantial in terms of the number of encounters, physicians involved, and medications prescribed. Because treatment burden varied markedly across patients and treatment types, future work should identify opportunities to understand and ameliorate this burden.