



Caring Ambassadors Lung Cancer Program Literature Review, August 2017

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES	1-2
SCREENING, DIAGNOSIS AND STAGING	2-8
CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES	
NSCLC SURGERY	8-10
NSCLC CHEMOTHERAPY	10-15
NSCLC RADIOTHERAPY	15-18
SMALL CELL LUNG CANCER (SCLC)	18-21
PALLIATIVE AND SUPPORTIVE CARE	21-24
COMPLEMENTARY AND ALTERNATIVE THERAPY	24-25
MISCELLANEOUS WORKS	26

BASIC AND APPLIED SCIENCE, PRE-CLINICAL STUDIES

[Glucose metabolism-targeted therapy and withaferin A are effective for epidermal growth factor receptor tyrosine kinase inhibitor-induced drug-tolerant persisters.](#) Kunimasa K1, Nagano T1, Shimono Y2, et al. *Cancer Sci.* 2017 Jul;108(7):1368-1377. doi: 10.1111/cas.13266. Epub 2017 Jun 19. In pathway-targeted cancer drug therapies, the relatively rapid emergence of drug-tolerant persisters (DTPs) substantially limits the overall therapeutic benefit. However, little is known about the roles of DTPs in drug resistance. In this study, we investigated the features of epidermal growth factor receptor-tyrosine kinase inhibitor-induced DTPs and explored a new treatment strategy to overcome the emergence of these DTPs. We used two EGFR-mutated lung adenocarcinoma cell lines, PC9 and H1975. They were treated with 2 μ M gefitinib for 6, 12, or 24 days or 6 months. We analyzed the mRNA expression of the stem cell-related markers by quantitative RT-PCR and the expression of the cellular senescence-associated proteins. Then we sorted DTPs according to the expression pattern of CD133 and analyzed the features of sorted cells. Finally, we tried to ablate DTPs by glucose metabolism targeting therapies and a stem-like cell targeting drug, withaferin A. Drug-tolerant persisters were composed of at least two types of cells, one with the properties of cancer stem-like cells (CSCs) and the other with the properties of therapy-induced senescent (TIS) cells. The CD133^{high} cell population had CSC properties and the CD133^{low} cell population had TIS properties. The CD133^{low} cell population containing TIS cells showed a senescence-associated secretory phenotype that supported the emergence of the CD133^{high} cell population containing CSCs. Glucose metabolism inhibitors effectively eliminated the CD133^{low} cell population. Withaferin A effectively eliminated the CD133^{high} cell population. The combination of phloretin and withaferin A effectively suppressed gefitinib-resistant tumor growth.

[Spatial distribution of EGFR and KRAS mutation frequencies correlates with histological growth patterns of lung adenocarcinomas.](#) Dietz S1,2,3, Harms A2,4, Endris V4, et al. *Int J Cancer.* 2017 Jul 12. doi: 10.1002/ijc.30881. [Epub ahead of print]

Multiregional analysis provided first indications for morphological and molecular heterogeneity in lung adenocarcinomas (ADCs), but comprehensive morpho-molecular comparisons are still lacking. The purpose of our study was to investigate the spatial distribution of EGFR and KRAS alterations systematically throughout whole tumor cross-sections in correlation with the tumor cell content and the histopathological patterns. Central sections of 19 ADCs were subdivided into 467 segments of 5 mm × 5 mm. We determined the predominant histological growth pattern and the allele frequencies of driver gene mutations by digital PCR in every segment. We further quantified the absolute cell counts and proportions of tumor and non-neoplastic cells in all segments to normalize the mutant allele frequencies. Driver gene mutations could be detected in >99% of the tumor containing segments, with high levels of inter- and intratumor heterogeneity regarding the mutant allele frequency (range: 0.04-19.36). Different patterns for the distribution of the variant allele frequency within a tumor were recognizable. While some cases showed ubiquitously low or high levels, others revealed regions with focally elevated frequencies. Differences between KRAS and EGFR alterations were not significant. The great majority of the analyzed tumor sections (16/19) exhibited two or more morphological growth patterns. Mutant allele frequencies were significantly higher in segments with a predominant solid pattern compared to all other histologies (p < 0.01). Our data indicate that driver gene mutations are present with high levels of inter- and intratumor heterogeneity throughout the whole tumor, with a correlation between the allele frequencies and histological growth patterns.

[Dihydroartemisinin and gefitinib synergistically inhibit NSCLC cell growth and promote apoptosis via the Akt/mTOR/STAT3 pathway.](#)

Jin H1, Jiang AY2, Wang H3, Cao Y4, Wu Y5, Jiang XF1.

Non small cell lung cancer (NSCLC) is among the leading causes of cancer associated mortality worldwide. In clinical practice, therapeutic strategies based on drug combinations are often used for the treatment of various types of cancer. The present study aimed to investigate the effects of the combination of dihydroartemisinin (DHA) and gefitinib on NSCLC. Cell Counting kit 8 assay was used to evaluate cell viability. Transwell assays were performed to investigate cellular migration and invasion, and cellular apoptosis was evaluated using the terminal deoxynucleotidyl transferase dUTP nick end labeling assay. Flow cytometry was used to investigate cell cycle distribution and the expression levels of target proteins were determined using western blot analysis. The results of the present study demonstrated that DHA (5, 10, 20, 50 and 100 µM) reduced cancer cell viability in a dose dependent manner in the NCI H1975 human NSCLC cell line and significantly enhanced gefitinib induced apoptosis. Furthermore, DHA and gefitinib co administration induced cell cycle arrest in G2/M phase, which was associated with a marked decline in the protein expression levels of G2/M regulatory proteins, including cyclin B1 and cyclin dependent kinase 1. The addition of DHA appeared to potentiate the inhibitory actions of gefitinib on the migratory and invasive capabilities of NCI H1975 cells. DHA and gefitinib co administration also downregulated the expression levels of phosphorylated (p) Akt, p mechanistic target of rapamycin, p signal transducer and activator of transcription 3 and B cell lymphoma 2 (Bcl 2), and upregulated the expression of Bcl 2 associated X protein. In conclusion, the present results suggested that the combination of DHA and gefitinib may have potential as a novel and more effective therapeutic strategy for the treatment of patients with NSCLC.

SCREENING, DIAGNOSIS AND STAGING

[Impact of EBUS-TBNA on PET-CT Imaging of Mediastinal Nodes.](#) Sivapalan P1, Naur TMH, Colella S, Richter Larsen K, Konge L, Frost Clementsen P. J Bronchology Interv Pulmonol. 2017 Jul;24(3):188-192. doi: 10.1097/LBR.0000000000000373.

BACKGROUND: Positron emission tomography-computed tomography (PET-CT) with fluorine-18-fluorodeoxyglucose has a high sensitivity in detecting malignancy in patients suspected of lung cancer but a low specificity as inflammatory reactions can also result in metabolic activity. Furthermore, it is assumed that invasive pulmonary procedures with biopsies from benign lesions can induce metabolic activity resulting in false-positive results. However, this hypothesis lacks solid evidence. We aimed to evaluate how often endobronchial ultrasound (EBUS) with biopsies from benign lesions are followed by false-positive results. **METHODS:** Patients with suspected or proven lung cancer admitted for invasive pulmonary procedures in a 6-year period were retrospectively reviewed. Patients who had at least 1 nonmalignant mediastinal lymph node (MLN) biopsied 1 to 13 days before PET-CT were included. The number of false-positive and true-negative results shortly after EBUS biopsy of nonmalignant MLN was reviewed. **RESULTS:** Of 1025 patients, 216 patients were referred for PET-CT 1 to 13 days after biopsy. Of these, 107 patients had at least 1 MLN biopsied. From a total of 198 biopsied MLNs, we found 62% without metabolic activity (benign) and 38% with metabolic activity. In 5% the metabolic activity could be explained by an infection or inflammatory disorder, in 15% no cytologic follow-up was available, in 1% malignancy was confirmed at follow-up, and in 3% the patients were not possible to follow-up. In the remaining 14%, no other reasonable explanation for the metabolic activity was found other than the biopsy. **CONCLUSIONS:** EBUS with biopsy do not necessarily result in PET activity. Therefore, PET-positive results should always be taken seriously, even when PET is performed shortly after biopsies.

[Conventional real-time PCR-based detection of T790M using tumor tissue or blood in patients with EGFR TKI-resistant NSCLC.](#) Wu YL1,2, Tong RZ1, Zhang Y1, et al. *Onco Targets Ther.* 2017 Jul 5;10:3307-3312. doi: 10.2147/OTT.S136823. eCollection 2017.

Blood biopsy has many advantages over tissue biopsy for diagnosing acquired T790M mutation in patients with non-small-cell lung cancer, such as being less risky and painful. New techniques with high sensitivity (eg, droplet digital PCR) show promising results during blood biopsy, but the positive rates of identification are still quite unclear. Whether there are other factors, except technology, affecting the results of blood biopsy is unclear. In this study, we used conventional amplification refractory mutation system to detect tumor tissue or blood for T790M mutation in patients clinically resistant to tyrosine kinase inhibitors. A total of 45 patients treated at West China Hospital between 2014 and 2016 were analyzed. The positive rate of T790M mutation was 70.8% based on tissue biopsy and 37.5% based on blood biopsy. Of the 24 patients whose epidermal growth factor receptor gene was genotyped through tissue and blood biopsy, 10 (41.7%) were concordant for T790M mutation status ($\kappa=0.006$). Of the 17 patients positive for T790M by tissue biopsy, 7 (41.2%) were positive for T790M by blood biopsy, and 3 of these 7 were only weakly positive. Of the 7 patients negative for T790M by tissue biopsy, 2 (28.6%) were positive by blood biopsy. Our T790M detection rate is higher than that reported by other studies using digital droplet PCR. These results suggest that other factors (eg, clinical features), intrinsically connected with circulating tumor DNA level, also affect the results of blood biopsy, and thus cannot be controlled through technological optimization.

[The role of endobronchial ultrasound elastography in the diagnosis of mediastinal and hilar lymph nodes.](#) Gu Y1, Shi H2, Su C3, et al. *Oncotarget.* 2017 Jul 6. doi: 10.18632/oncotarget.19031. [Epub ahead of print]

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has been widely used for diagnosis and mediastinal lymph nodes staging in patients with suspicious lung cancer. Ultrasound elastography is a novel sonographical technique that can evaluate tissue compressibility. The aim of the present study was to investigate the diagnostic yield of elastography for differentiating malignant and benign mediastinal lymph nodes. Conventional EBUS B-mode features, including size, shape, border distinction, echogenicity, central hilar structure with central blood vessel and coagulation necrosis were

also evaluated. The ultrasonic features were compared with the pathological results from EBUS-TBNA. 133 lymph nodes in 60 patients were assessed. Elastography displayed the highest area under the curve (AUC) (type 3 versus type 1: AUC, 0.825; 95% confidence interval [CI], 0.707-0.910) with an impressive sensitivity (100%) and an acceptable specificity (65%). The combined model covering the four positive criteria (elastography, heterogeneity, size, and shape) showed that the odds ratio for malignance is 9.44 with a 95% CI of 3.99 to 22.32 ($p < 0.0001$). The combined model was superior to elastography alone (AUC, 0.851; sensitivity, 89.89%; specificity, 72.73%; $p < 0.0001$). **This prospective study showed** that elastography is a feasible technique for classifying mediastinal lymph nodes, especially in combination with conventional EBUS imaging.

[Influence of the Learning Effect on the Diagnostic Yield of Endobronchial Ultrasound-guided Transbronchial Needle Aspiration of Mediastinal and Hilar Lymph Nodes.](#)

Fuso L1, Varone F, Magnini D, Pecoriello A, Montemurro G, Angeletti G, Valente S. J Bronchology Interv Pulmonol. 2017 Jul;24(3):193-199. doi: 10.1097/LBR.0000000000000372.

BACKGROUND: The diagnostic yield of conventional transbronchial needle aspiration (TBNA) is characterized by a learning effect. The aim of this retrospective study was to verify whether a learning curve similarly affected the yield of endobronchial ultrasound-guided (EBUS)-TBNA. To this end, we evaluated the sensitivity and diagnostic accuracy of EBUS-TBNA during the first 3 years of activity. **METHODS:** EBUS-TBNA was performed by 2 operators with no previous experience in this technique. Cytologic samples were obtained from mediastinal and hilar lymph nodes enlarged at a chest computed tomography scan and/or with increased fluorodeoxyglucose uptake at computed tomography/positron emission tomography scan in patients with suspected lung cancer. The cytologic diagnosis of EBUS-TBNA samples has been compared with the final diagnosis obtained from further diagnostic procedures, surgery, or clinical-radiologic follow-up. **RESULTS:** From October 2012 to October 2015, we collected 408 EBUS-TBNA cytologic samples from 313 patients: 223 samples were positive for metastatic involvement and 185 were nonmetastatic. The latter included 137 true-negative and 48 false-negative results. The final diagnosis comprised 271 metastatic and 137 nonmetastatic lymph nodes. The overall sensitivity for cancer was 82% and diagnostic accuracy was 88%. Sensitivity and accuracy per year were as follows: first year, 78% and 82% in 90 nodal samples; second year, 83% and 89% in 144 nodal samples; third year, 85% and 91% in 174 nodal samples. **CONCLUSIONS:** EBUS-TBNA can be considered as a reliable tool even if performed by operators without previous experience in this procedure, and the diagnostic yield continues to increase progressively over a long time.

[Comparison of Bayesian penalized likelihood reconstruction versus OS-EM for characterization of small pulmonary nodules in oncologic PET/CT.](#)

Howard BA1, Morgan R2,3, Thorpe MP2, Turkington TG2, Oldan J4, James OG2, Borges-Neto S2. Ann Nucl Med. 2017 Jul 8. doi: 10.1007/s12149-017-1192-1. [Epub ahead of print]

OBJECTIVE: To determine whether the recently introduced Bayesian penalized likelihood PET reconstruction (Q.Clear) increases the visual conspicuity and SUVmax of small pulmonary nodules near the PET resolution limit, relative to ordered subset expectation maximization (OS-EM). **METHODS:** In this institutional review board-approved and HIPAA-compliant study, 29 FDG PET/CT scans performed on a five-ring GE Discovery IQ were retrospectively selected for pulmonary nodules described in the radiologist's report as "too small to characterize", or small lung nodules in patients at high risk for lung cancer. Thirty-two pulmonary nodules were assessed, with mean CT diameter of 8 mm (range 2-18). PET images were reconstructed with OS-EM and Q.Clear with noise penalty strength β values of 150, 250, and 350. Lesion visual conspicuity was scored by three readers on a 3-point scale, and lesion SUVmax and background liver and blood pool SUVmean and SUVstdev were recorded. Comparison was made by linear mixed model with modified Bonferroni post hoc testing; significance cutoff was $p < 0.05$.

RESULTS: Q.Clear improved lesion visual conspicuity compared to OS-EM at $\beta = 150$ ($p < 0.01$), but not 250 or 350. Lesion SUVmax was increased compared to OS-EM at $\beta = 150$ and 250 ($p < 0.01$), but not 350. **CONCLUSION:** In a cohort of small pulmonary nodules with size near an 8 mm PET full-width half maximum, Q.Clear significantly increased lesion visual conspicuity and SUVmax compared to our standard non-time-of-flight OS-EM reconstruction, but only with low noise penalization. Q.Clear with $\beta = 150$ may be advantageous when evaluation of small pulmonary nodules is of primary concern.

[Validation of the Disease-Specific GPA for Patients With 1 to 3 Synchronous Brain Metastases in Newly Diagnosed NSCLC.](#) Woody NM1, Greer MD2, Reddy CA3, et al. Clin Lung Cancer. 2017 Jul 6. pii: S1525-7304(17)30198-5. doi: 10.1016/j.clcc.2017.06.011. [Epub ahead of print]

BACKGROUND: The disease-specific graded prognostic assessment (DS-GPA) for brain metastases is a powerful prognostic tool but has not been validated for patients with synchronous brain metastases (SBM) in newly diagnosed non-small-cell lung cancer (NSCLC). **PATIENTS AND METHODS:** We identified patients with newly diagnosed NSCLC with 1 to 3 SBM treated with stereotactic radiosurgery (SRS) between 1997 and 2012. We included patients whose brain metastases were treated with SRS alone or combined SRS and whole-brain radiotherapy (WBRT). Patients were stratified according to NSCLC DS-GPA to evaluate the accuracy of survival estimates. **RESULTS:** One hundred sixty-four patients were treated with either SRS alone ($n = 85$; 52%) or SRS and WBRT ($n = 79$; 48%). Median overall survival (OS) stratified according to DS-GPA of 0 to 1, 1.5 to 2, 2.5 to 3, and 3.5 to 4 were 2.8, 6.7, 9.8, and 13.2 months, respectively, consistent with OS reported for brain metastases in NSCLC DS-GPA (3.0, 6.5, 11.3, and 14.8 months, respectively). No difference in median progression-free survival or OS was noted with combined use of SRS and WBRT: 6.0 versus 6.1 months ($P = .81$) and 8.5 versus 9.1 months ($P = .093$), respectively. In multivariable analysis, Karnofsky performance status (hazard ratio [HR], 0.98; $P = .008$), extracranial metastases (HR, 0.498; $P = .0003$), squamous histology (HR, 1.81; $P = .02$), and number of brain metastases (2 vs. 1; HR, 1.504; $P = .04$, and 3 vs. 1; HR, 1.66; $P = .05$) were significant predictors of OS. **CONCLUSION:** The DS-GPA accurately estimates the prognosis of patients with SBM in newly diagnosed NSCLC. Patients with synchronous brain metastasis in newly diagnosed NSCLC should be carefully stratified for consideration of aggressive therapy. Copyright © 2017 Elsevier Inc. All rights reserved.

[Evaluation of Appropriate Mediastinal Staging among Endobronchial Ultrasound Bronchoscopists.](#) Miller RJ1, Mudambi L1, Vial MR1, Hernandez M2, Eapen GA1. Ann Am Thorac Soc. 2017 Jul;14(7):1162-1168. doi: 10.1513/AnnalsATS.201606-487OC.

RATIONALE: Endobronchial ultrasound (EBUS) has transformed mediastinal staging in lung cancer. A systematic approach, beginning with lymph nodes contralateral to the primary tumor (N3), is considered superior to selective sampling of radiographically abnormal nodes. However, the extent to which this recommendation is followed in practice remains unknown. **OBJECTIVES:** To assess the frequency with which pulmonologists, pulmonary fellows, and interventional pulmonologists endoscopically stage lung cancer appropriately. **METHODS:** Bronchoscopists currently performing EBUS were surveyed about their practice patterns, procedural volume, and self-confidence in EBUS skills; they then performed a proctored simulated staging EBUS. The primary outcome was the proportion of participants who appropriately initiated ultrasonographic evaluation with the N3 nodal stations in a simulated patient undergoing EBUS for mediastinal staging. **RESULTS:** Sixty physicians (22 interventional pulmonologists, 18 general pulmonologists, and 20 pulmonary fellows) participated in the study. The rates of appropriate staging by study group were 95.5% (21 of 22) for interventional pulmonologists, 44.4% (8 of 18) for general pulmonologists, and 30.0% (6 of 20) for pulmonary fellows ($P < 0.001$). Increased procedural volume correlated with appropriate staging practices ($P < 0.001$). Within each group, we assessed the concordance between self-confidence in EBUS and simulation performance. Among

interventional pulmonologists, the concordance was 95.4%, followed by 61.1% for general pulmonologists and 40.0% for pulmonary fellows. **CONCLUSIONS:** General pulmonologists and pulmonary fellows were less likely than interventional pulmonologists to perform appropriate EBUS staging. In addition, the lack of concordance between self-confidence and appropriate staging performance among noninterventionists signals a need for improved dissemination of guidelines for EBUS-guided mediastinal staging.

[A novel molecular diagnostics platform for somatic and germline precision oncology.](#)

Cabanillas R1, Diñeiro M1, Castillo D2, et al. Mol Genet Genomic Med. 2017 Apr 23;5(4):336-359. doi: 10.1002/mgg3.291. eCollection 2017 Jul.

BACKGROUND: Next-generation sequencing (NGS) opens new options in clinical oncology, from therapy selection to genetic counseling. However, realization of this potential not only requires succeeding in the bioinformatics and interpretation of the results, but also in their integration into the clinical practice. We have developed a novel NGS diagnostic platform aimed at detecting (1) somatic genomic alterations associated with the response to approved targeted cancer therapies and (2) germline mutations predisposing to hereditary malignancies. **METHODS:** Next-generation sequencing libraries enriched in the exons of 215 cancer genes (97 for therapy selection and 148 for predisposition, with 30 informative for both applications), as well as selected introns from 17 genes involved in drug-related rearrangements, were prepared from 39 tumors (paraffin-embedded tissues/cytologies), 36 germline samples (blood) and 10 cell lines using hybrid capture. Analysis of NGS results was performed with specifically developed bioinformatics pipelines. **RESULTS:** The platform detects single-nucleotide variants (SNVs) and insertions/deletions (indels) with sensitivity and specificity >99.5% (allelic frequency ≥ 0.1), as well as copy-number variants (CNVs) and rearrangements. Somatic testing identified tailored approved targeted drugs in 35/39 tumors (89.74%), showing a diagnostic yield comparable to that of leading commercial platforms. A somatic EGFR p.E746_S752delinsA mutation in a mediastinal metastasis from a breast cancer prompted its anatomopathologic reassessment, its definite reclassification as a lung cancer and its treatment with gefitinib (partial response sustained for 15 months). Testing of 36 germline samples identified two pathogenic mutations (in CDKN2A and BRCA2). We propose a strategy for interpretation and reporting of results adaptable to the aim of the request, the availability of tumor and/or normal samples and the scope of the informed consent. **CONCLUSION:** With an adequate methodology, it is possible to translate to the clinical practice the latest advances in precision oncology, integrating under the same platform the identification of somatic and germline genomic alterations.

[Lung cancer screening with low-dose spiral computed tomography: evidence from a pooled analysis of two Italian randomized trials.](#)

Infante M1, Sestini S, Galeone C, et al. Eur J Cancer Prev. 2017 Jul;26(4):324-329. doi: 10.1097/CEJ.0000000000000264.

The benefits and harms of lung cancer (LC) screening with low-dose computed tomography (LDCT) are debatable. Positive results from the US National Lung Screening Trial were not evident in the European trials, possibly due to their smaller sample sizes. To address this issue, we conducted a patient-level pooled analysis of two Italian randomized controlled trials. Data from DANTE and MILD trials were combined for a total of 3640 individuals in the LDCT arm and 2909 in the control arm. LC and overall mortality were analyzed using multivariate hazard ratios (HRs) and log-rank tests stratified by study. The median follow-up was 8.2 years, with a total of 30 480 person-years in the LDCT arm and 22 157 in the control arm. A total of 192 patients developed LC in the LDCT arm and 105 in the control arm. Half of the LC cases in the LDCT arm had stage IA or IB cancer, as compared with 21% in the control arm. Overall mortality rates/100 000 person-years were 925 in the LDCT arm and 1074 in the control arm, and LC mortality rates were 299 and 357, respectively. The multivariate pooled overall mortality HR was 0.89 (95% confidence interval: 0.74-1.06) and the LC mortality HR was 0.83 (95% confidence interval: 0.61-

1.12) for the LDCT arm as compared with the control arm. The present pooled analysis shows a nonsignificant 11% reduction in overall mortality in individuals undergoing LDCT screening as compared with the control arm. A pooled analysis of all European trials would be a useful contribution to assess the real benefit of LDCT screening.

[Presence of Even a Small Ground-Glass Component in Lung Adenocarcinoma Predicts Better](#)

[Survival](#). Berry MF1, Gao R2, Kunder CA3, Backhus L2, Khuong A2, Kadoch M4, Leung A4, Shrager J2. Clin Lung Cancer. 2017 Jul 8. pii: S1525-7304(17)30207-3. doi: 10.1016/j.clcc.2017.06.020. [Epub ahead of print]

BACKGROUND: While lepidic-predominant lung adenocarcinomas are known to have better outcomes than similarly sized solid tumors, the impact of smaller noninvasive foci within predominantly solid tumors is less clearly characterized. We tested the hypothesis that lung adenocarcinomas with even a small ground-glass opacity (GGO) component have a better prognosis than otherwise similar pure solid (PS) adenocarcinomas. **PATIENTS AND METHODS:** The maximum total and solid-component diameters were determined by preoperative computed tomography in patients who underwent lobar or sublobar resection of clinical N0 adenocarcinomas without induction therapy between May 2003 and August 2013. Survival between patients with PS tumors (0% GGO) or tumors with a minor ground-glass (MGG) component (1%-25% GGO) was compared by Kaplan-Meier and Cox analyses. **RESULTS:** A total of 123 patients met the inclusion criteria, comprising 54 PS (44%) and 69 MGG (56%) whose mean ground-glass component was $18 \pm 7\%$. The solid component tumor diameter was not significantly different between the groups (2.3 ± 1.2 cm vs. 2.5 ± 1.3 cm, $P = .2$). Upstaging to pN1-2 was more common for the PS group (13% [7/54] vs. 3% [2/69], $P = .04$), but the distribution of pathologic stage was not significantly different between the groups (PS 76% stage I [41/54] vs. MGG 80% stage I [55/69], $P = .1$). Having a MGG component was associated with markedly better survival in both univariate analysis (MGG 5-year overall survival 86.7% vs. PS 64.5%, $P = .001$) and multivariable survival analysis (hazard ratio, 0.30, $P = .01$). **CONCLUSION:** Patients with resected cN0 lung adenocarcinoma who have even a small GGO component have markedly better survival than patients with PS tumors, which may have implications for both treatment and surveillance strategies.

[Molecular Profiling of Malignant Pleural Effusion in Metastatic Non-Small-Cell Lung Carcinoma.](#)

[The Effect of Preanalytical Factors](#). Carter J1, Miller JA1, Feller-Kopman D2, Ettinger D3, Sidransky D3, Maleki Z1. Ann Am Thorac Soc. 2017 Jul;14(7):1169-1176. doi: 10.1513/AnnalsATS.201609-709OC.

RATIONALE: Non-small-cell lung cancer (NSCLC)-associated malignant pleural effusions (MPEs) are sometimes the only available specimens for molecular analysis. **OBJECTIVES:** This study evaluates diagnostic yield of NSCLC-associated MPE, its adequacy for molecular profiling and the potential influence of MPE volume/cellularity on the analytic sensitivity of our assays. **METHODS:** Molecular results of 50 NSCLC-associated MPE cases during a 5-year period were evaluated. Molecular profiling was performed on cell blocks and consisted of fluorescent in situ hybridization (FISH) for ALK gene rearrangements and the following sequencing platforms: Sanger sequencing (for EGFR) and high-throughput pyrosequencing (for KRAS and BRAF) during the first 4 years of the study period, and targeted next-generation sequencing performed thereafter. **RESULTS:** A total of 50 NSCLC-associated MPE cases were identified where molecular testing was requested. Of these, 17 cases were excluded: 14 cases (28%) due to inadequate tumor cellularity and 3 cases due to unavailability of the slides to review. A total of 27 out of 50 MPE cases (54%) underwent at least EGFR and KRAS sequencing and FISH for ALK rearrangement. Of the 27 cases with molecular testing results available, a genetic abnormality was detected in 16 cases (59%). The most common genetic aberrations identified involved EGFR (9) and KRAS (7). Six cases had ALK FISH only, of which one showed rearrangement. MPE volume was not

associated with overall cellularity or tumor cellularity ($P = 0.360$). **CONCLUSIONS:** Molecular profiling of MPE is a viable alternative to testing solid tissue in NSCLC. This study shows successful detection of genetic aberrations in 59% of samples with minimal risk of false negative.

Shared Gene Expression Alterations in Nasal and Bronchial Epithelium for Lung Cancer Detection. AEGIS Study Team.

Collaborators: (14) Perez-Rogers JF^{1,2}, Gerrein J^{1,2}, Anderlind C², Liu G², Zhang S², Alekseyev Y³, Smith KP⁴, Whitney D^{2,4}, Evan Johnson W², Elashoff DA⁵, Dubinett SM⁶, Brody J², Spira A², Lenburg ME². *J Natl Cancer Inst.* 2017 Jul 1;109(7). doi: 10.1093/jnci/djw327.

BACKGROUND: We previously derived and validated a bronchial epithelial gene expression biomarker to detect lung cancer in current and former smokers. Given that bronchial and nasal epithelial gene expression are similarly altered by cigarette smoke exposure, we sought to determine if cancer-associated gene expression might also be detectable in the more readily accessible nasal epithelium. **METHODS:** Nasal epithelial brushings were prospectively collected from current and former smokers undergoing diagnostic evaluation for pulmonary lesions suspicious for lung cancer in the AEGIS-1 ($n = 375$) and AEGIS-2 ($n = 130$) clinical trials and gene expression profiled using microarrays. All statistical tests were two-sided. **RESULTS:** We identified 535 genes that were differentially expressed in the nasal epithelium of AEGIS-1 patients diagnosed with lung cancer vs those with benign disease after one year of follow-up ($P < .001$). Using bronchial gene expression data from the AEGIS-1 patients, we found statistically significant concordant cancer-associated gene expression alterations between the two airway sites ($P < .001$). Differentially expressed genes in the nose were enriched for genes associated with the regulation of apoptosis and immune system signaling. A nasal lung cancer classifier derived in the AEGIS-1 cohort that combined clinical factors (age, smoking status, time since quit, mass size) and nasal gene expression (30 genes) had statistically significantly higher area under the curve (0.81; 95% confidence interval [CI] = 0.74 to 0.89, $P = .01$) and sensitivity (0.91; 95% CI = 0.81 to 0.97, $P = .03$) than a clinical-factor only model in independent samples from the AEGIS-2 cohort. **CONCLUSIONS:** These results support that the airway epithelial field of lung cancer-associated injury in ever smokers extends to the nose and demonstrates the potential of using nasal gene expression as a noninvasive biomarker for lung cancer detection.

CLINICAL TRIALS, COHORT STUDIES, PILOT STUDIES

NSCLC - SURGERY

Novel Techniques and Approaches to Minimally Invasive Thoracic Surgery. Onugha O¹, Ivey R², McKenna R¹. *Surg Technol Int.* 2017 Jul 25;30:231-235.

Approximately two decades ago, thoracic surgery witnessed the leap from thoracotomy to the first video-assisted thoracic surgery (VATS) lobectomy. Minimally invasive lobectomy and hilar lymphadenectomy is now widely established as a safe and oncological sound technique that is the standard of care for early-stage lung cancer. The move toward less invasive surgery has no doubt driven the innovation of sophisticated instruments and technology to cope with the demanding need of working through a restricted incision. We will discuss the use of minimally invasive thoracic surgery techniques for sympathectomy, cardiac arrhythmia, and first rib resection, as well as traditional lung resections (e.g., pneumonectomy, lobectomy, and segmentectomy). We will also discuss thoracic incisions and approaches using VATS, single port VATS, and robot-assisted thoracic surgery.

[Intraoperative Molecular Imaging Combined With Positron Emission Tomography Improves Surgical Management of Peripheral Malignant Pulmonary Nodules.](#)

Predina JD1, Newton AD, Keating J, et al. *Ann Surg*. 2017 Jul 25. doi: 10.1097/SLA.0000000000002382. [Epub ahead of print]

OBJECTIVE: To determine if intraoperative molecular imaging (IMI) can improve detection of malignant pulmonary nodules. **BACKGROUND:** 18-Fluorodeoxyglucose positron emission tomography (PET) is commonly utilized in preoperative assessment of patients with solid malignancies; however, false negatives and false positives remain major limitations. Using patients with pulmonary nodules as a study model, we hypothesized that IMI with a folate receptor targeted near-infrared contrast agent (OTL38) can improve malignant pulmonary nodule identification when combined with PET. **METHODS:** Fifty patients with pulmonary nodules with imaging features suspicious for malignancy underwent preoperative PET. Patients then received OTL38 before pulmonary resection. During resection, IMI was utilized to evaluate known pulmonary nodules and identify synchronous lesions. Tumor size, PET standardized uptake value, and IMI tumor-to-background ratios were compared for known and synchronous nodules via paired and unpaired t tests, when appropriate. Test characteristics of PET and IMI with OTL38 were compared. **RESULTS:** IMI identified 56 of 59 (94.9%) malignant pulmonary nodules identified by preoperative imaging. IMI located an additional 9 malignant lesions not identified preoperatively. Nodules only detected by IMI were smaller than nodules detected preoperatively (0.5 vs 2.4 cm; $P < 0.01$), but displayed similar fluorescence (tumor-to-background ratio 3.3 and 3.1; $P = 0.50$). Sensitivity of IMI and PET were 95.6% and 73.5% ($P = 0.001$), respectively; and positive predictive values were 94.2% and 89.3%, respectively ($P > 0.05$). Additionally, utilization of IMI clinically upstaged 6 (12%) subjects and improved management of 15 (30%) subjects. **CONCLUSIONS:** These data suggest that combining IMI with PET may provide superior oncologic outcomes for patients with resectable lung cancer.

[Outcomes of Curative-Intent Surgery and Adjuvant Treatment for Pulmonary Large Cell](#)

[Neuroendocrine Carcinoma.](#) Kim KW1, Kim HK2, Kim J3, Shim YM3, Ahn MJ4, Choi YL5. *World J Surg*. 2017 Jul;41(7):1820-1827. doi: 10.1007/s00268-017-3908-8.

BACKGROUND: Pulmonary large cell neuroendocrine carcinoma (LCNEC) is pathologically classified as non-small-cell lung cancer (NSCLC), but its clinical behavior is more aggressive than other types of NSCLC. Accordingly, the optimal treatment strategy for LCNEC, including the indication of adjuvant treatment, remains controversial. **METHODS:** A retrospective review of 139 patients who underwent curative-intent surgery for LCNEC was performed to investigate clinicopathologic features and survival outcomes and to evaluate whether adjuvant treatment affected survival outcomes. **RESULTS:** The mean patient age was 64 years (126 men, 90.6%). Operative procedures included 111 lobectomies (79.8%), 12 pneumonectomies (8.6%), and 2 sublobar resections. Pathologic stage was IA in 31 (22%), IB in 36 (26%), IIA in 34 (24%), IIB in 9 (6%), IIIA in 19 (14%), IIIB in 2 (1.4%), and IV in 4 patients (2.9%). Postoperatively, 50 patients (36%) received adjuvant treatment. The median follow-up duration was 33 months. The 5-year overall survival (OS) rate was 53%, and 5-year disease-free survival (DFS) rate was 39%. In patients with pathologic stage I, there was no significant difference in either OS or DFS according to the addition of adjuvant treatment. However, in patients with pathologic stage II or higher, patients who underwent adjuvant treatment showed significantly better OS ($p = 0.023$) and DFS ($p = 0.038$). **CONCLUSIONS:** Our findings showed that patients who underwent curative-intent surgery for LCNEC benefitted from the use of adjuvant treatment especially in pathologic stage II or higher.

[Pulmonary Resection for Second Lung Cancer After Pneumonectomy: A Population-Based Study.](#)

Ayub A1, Rehmani SS1, Al-Ayoubi AM1, Raad W1, Flores RM1, Bhora FY2.

Ann Thorac Surg. 2017 Jul 11. pii: S0003-4975(17)30606-9. doi: 10.1016/j.athoracsur.2017.04.043.

[Epub ahead of print]

BACKGROUND: Pulmonary resection for a second lung cancer after pneumonectomy is generally considered to be at prohibitive risk. Using a population-based database, we examined treatment patterns and survival in patients who underwent pulmonary resection after pneumonectomy for lung cancer.

METHODS: We queried the Surveillance, Epidemiology, and End Results (SEER) database (1988-2012) to identify patients who underwent pneumonectomy and subsequently experienced contralateral non-small cell lung cancer (NSCLC). Multivariate logistic regression was performed to identify the factors associated with the receipt of surgical resection. Survival was estimated with the Kaplan-Meier method.

RESULTS: Of 13,370 patients who underwent pneumonectomy, 402 (3.0%) experienced subsequent contralateral NSCLC, and 170 (42%) met the selection criteria. Surgical resection was performed in 63 (37.1%) cases (sublobar n = 56, lobectomy, n = 7). Patients with stage I/II disease and tumor size 2 cm or smaller were more likely to undergo surgical procedures. The 1-month and 3-month mortality after resection was 11.1% (sublobar resection 10.7%, lobectomy 14.3%) and 12.7% (sublobar 12.5%, lobectomy 14.3%), respectively. The overall 1-year and 3-year survival after surgical resection was 79% and 54%, respectively. The patients who underwent sublobar resection had higher median overall survival than did those who underwent lobectomy (42 vs 18 months). Similarly, median survival after resection for metachronous tumors was higher than after resection for metastatic cancers (40 vs 28 months).

CONCLUSIONS: On the basis of our analysis of the SEER database, sublobar resection can be performed in selected patients with small tumors (≤ 2 cm) and early-stage disease (stage I/II). Although perioperative mortality is significant, the favorable 1-year and 3-year survival may justify the role of an additional procedure on the single lung.

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

[Pneumotoxicity associated with immune checkpoint inhibitor therapies.](#) Shannon VR1. *Curr Opin Pulm Med.* 2017 Jul;23(4):305-316. doi: 10.1097/MCP.0000000000000382.

PURPOSE OF REVIEW: Immune checkpoint inhibitor therapies represent a new paradigm in cancer therapeutics, in which the targets are not the cancer cells, but the body's own immune system. Harnessing the immune system to better fight cancer has generated a unique spectrum of immune-related adverse events (IrAEs) that affect virtually every major organ system. Although lung involvement is less common than other forms of IrAEs, its consequences are potentially lethal. This review focuses on the evolving spectrum of lung toxicities associated with the two major classes of immune checkpoint inhibitor therapies, cytotoxic T-cell ligand-4, and programmed cell death-1 (PDL-1). **RECENT FINDINGS:** Lung injury was not reported in the earliest clinical trials of immune checkpoint inhibitors. More recent studies, however, have described unique radiographic and clinical toxicity profiles that differ significantly from lung injury patterns associated with conventional cytotoxic therapies. The pathophysiologic mechanisms of immune-related lung injury, its radiographic and clinical disease spectrum, associated risk factors, and optimal treatment strategies remain poorly understood. **SUMMARY:** Adverse immune-mediated lung events are increasingly recognized as unique and potentially life-threatening sequelae of checkpoint inhibitor therapies. Early recognition of symptoms and radiographic abnormalities is essential to proper management and successful outcome.

[Development and Validation of an Individualized Immune Prognostic Signature in Early-Stage Nonsquamous Non-Small Cell Lung Cancer.](#) Li B1, Cui Y2, Diehn M3, Li R4. *JAMA Oncol.* 2017 Jul 6. doi: 10.1001/jamaoncol.2017.1609. [Epub ahead of print]

IMPORTANCE:

The prevalence of early-stage non-small cell lung cancer (NSCLC) is expected to increase with recent implementation of annual screening programs. Reliable prognostic biomarkers are needed to identify patients at a high risk for recurrence to guide adjuvant therapy.

OBJECTIVE: To develop a robust, individualized immune signature that can estimate prognosis in patients with early-stage nonsquamous NSCLC. **DESIGN, SETTING, AND PARTICIPANTS:** This retrospective study analyzed the gene expression profiles of frozen tumor tissue samples from 19 public NSCLC cohorts, including 18 microarray data sets and 1 RNA-Seq data set for The Cancer Genome Atlas (TCGA) lung adenocarcinoma cohort. Only patients with nonsquamous NSCLC with clinical annotation were included. Samples were from 2414 patients with nonsquamous NSCLC, divided into a meta-training cohort (729 patients), meta-testing cohort (716 patients), and 3 independent validation cohorts (439, 323, and 207 patients). All patients underwent surgery with a negative surgical margin, received no adjuvant or neoadjuvant therapy, and had publicly available gene expression data and survival information. Data were collected from July 22 through September 8, 2016. **MAIN OUTCOMES AND MEASURES:** Overall survival. **RESULTS:** Of 2414 patients (1205 men [50%], 1111 women [46%], and 98 of unknown sex [4%]; median age [range], 64 [15-90] years), a prognostic immune signature of 25 gene pairs consisting of 40 unique genes was constructed using the meta-training data set. In the meta-testing and validation cohorts, the immune signature significantly stratified patients into high- vs low-risk groups in terms of overall survival across and within subpopulations with stage I, IA, IB, or II disease and remained as an independent prognostic factor in multivariate analyses (hazard ratio range, 1.72 [95% CI, 1.26-2.33; $P < .001$] to 2.36 [95% CI, 1.47-3.79; $P < .001$]) after adjusting for clinical and pathologic factors. Several biological processes, including chemotaxis, were enriched among genes in the immune signature. The percentage of neutrophil infiltration (5.6% vs 1.8%) and necrosis (4.6% vs 1.5%) was significantly higher in the high-risk immune group compared with the low-risk groups in TCGA data set ($P < .003$). The immune signature achieved a higher accuracy (mean concordance index [C-index], 0.64) than 2 commercialized multigene signatures (mean C-index, 0.53 and 0.61) for estimation of survival in comparable validation cohorts. When integrated with clinical characteristics such as age and stage, the composite clinical and immune signature showed improved prognostic accuracy in all validation data sets relative to molecular signatures alone (mean C-index, 0.70 vs 0.63) and another commercialized clinical-molecular signature (mean C-index, 0.68 vs 0.65). **CONCLUSIONS AND RELEVANCE:** The proposed clinical-immune signature is a promising biomarker for estimating overall survival in nonsquamous NSCLC, including early-stage disease. Prospective studies are needed to test the clinical utility of the biomarker in individualized management of nonsquamous NSCLC.

[Crizotinib Versus Chemotherapy in Asian Patients with Advanced ALK-positive Non-small Cell Lung Cancer.](#) Nishio M1, Kim DW2, Wu YL3, et al. *Cancer Res Treat.* 2017 Jul 6. doi: 10.4143/crt.2017.280. [Epub ahead of print]

PURPOSE: Crizotinib has demonstrated superior progression-free survival (PFS) and objective response rates (ORRs) versus chemotherapy in previously treated and untreated patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). We report the safety and efficacy of crizotinib in Asian subpopulations of two global phase III trials. **MATERIALS AND METHODS:** This analysis evaluated previously treated and untreated patients in two randomized, open-label phase III trials of crizotinib versus chemotherapy in ALK-positive advanced NSCLC in second-line (PROFILE 1007) and first-line settings (PROFILE 1014). Efficacy and safety were analyzed by race in the intention-to-treat and "as-treated" populations for efficacy and safety endpoints, respectively. **RESULTS:** In previously treated (n=157) and untreated (n=157) Asian patients, PFS was statistically significantly longer with crizotinib versus chemotherapy (hazard ratio for PFS, 0.526; 95% confidence interval, 0.363-0.762 [$p < 0.001$] and 0.442; 95% confidence interval, 0.302-0.648 [$p < 0.001$], respectively). Similar antitumor activity was seen in the non-Asian and overall populations. ORRs were statistically significantly higher with crizotinib versus chemotherapy in both Asian and non-Asian previously treated and untreated patients ($p < 0.05$). The most common treatment-emergent adverse events (any grade) with crizotinib were vision disorder, diarrhea, and nausea, which were observed at a comparable incidence across Asian and

non-Asian populations, irrespective of previous treatment status. Most adverse events were mild to moderate in severity. **CONCLUSION:** These data, currently the only analysis showing Asian and non-Asian populations in the same study, support the efficacy and safety of crizotinib in Asian patients with previously treated or untreated ALK-positive advanced NSCLC.

[Hair Repigmentation During Immunotherapy Treatment With an Anti-Programmed Cell Death 1 and Anti-Programmed Cell Death Ligand 1 Agent for Lung Cancer.](#) Rivera N1, Boada A1, Bielsa M1, Fernández-Figueras MT2, Carcereny E3, Moran MT3, Ferrándiz C1. JAMA Dermatol. 2017 Jul 12. doi: 10.1001/jamadermatol.2017.2106. [Epub ahead of print]

IMPORTANCE: New targeted therapies for cancer have been released in recent years, opening new horizons in the treatment of patients with cancer. However, their related adverse events (AE) are not fully characterized. Hair repigmentation (HR) is a nondescribed effect secondary to anti-programmed cell death 1 (anti-PD-1) and anti-programmed cell death ligand 1 (anti-PD-L1) therapy for treatment of lung cancer (LC), in opposition to the vitiligo reactions that develop during melanoma treatment. **OBJECTIVE:** To describe a new adverse event occurring during anti-PD-1/anti-PD-L1 therapy for LC. **DESIGN, SETTING, AND PARTICIPANTS:** A case series from a descriptive observation of 14 patients with HR after anti-PD-1/anti-PD-L1 treatment, recruited between September and December, 2016, who were followed up to detect whether they developed cutaneous AE at the time HR was detected. The patients had all been treated in the dermatology department at Hospital Universitari Germans Trias i Pujol, Badalona, Spain. **MAIN OUTCOMES AND MEASURES:** Clinical observation of HR during anti-PD-1/anti-PD-L1 therapy for LC, proved by comparing old pictures provided by the patients and recent pictures taken during the follow-up. **RESULTS:** Fourteen patients (13 men and 1 woman; mean age, 64.9 years) receiving anti-PD-1 or anti-PD-L1 therapy for non-small-cell lung cancer (NSCLC) presented hair repigmentation during follow-up. This hair repigmentation consisted in a diffuse darkening of the hair in 13 of 14 patients, or in black patches between white hairs in 1. Thirteen of 14 patients presented a good clinical response to the treatment, with at least stable disease, and only 1 had to stop the therapy after only 4 cycles of treatment owing to a life-threatening progression of the disease. **CONCLUSIONS AND RELEVANCE:** We present to our knowledge the first report of hair repigmentation owing to anti-PD-1/anti-PD-L1 therapy for lung cancer in a series of 14 patients. Hair repigmentation may be a good response marker in patients receiving anti-PD1/anti-PD-L1 therapy for LC.

[Tumor response dynamics of advanced non-small-cell lung cancer patients treated with PD-1 inhibitors: Imaging markers for treatment outcome.](#) Nishino M1, Dahlberg SE2, Adeni AE3, Lydon C4, Hatabu H5, Janne PA3, Hodi FS3, Awad MM6. Clin Cancer Res. 2017 Jul 5. pii: clincanres.1434.2017. doi: 10.1158/1078-0432.CCR-17-1434. [Epub ahead of print]

PURPOSE: We evaluated tumor burden dynamics in advanced non-small-cell lung cancer (NSCLC) patients treated with commercial PD-1 inhibitors to identify imaging markers associated with improved overall survival (OS). **Experimental Design:** The study included 160 advanced NSCLC patients treated with commercial nivolumab or pembrolizumab monotherapy as a part of clinical care. Tumor burden dynamics were studied for the association with OS. **Results:** Tumor burden change at best overall response (BOR) ranged from -100% to +278% (median: +3.5%). Response rate (RR) was 18% (29/160). Current and former smokers had a higher RR than never smokers (p=0.04). Durable disease control for at least 6 months was noted in 26 patients (16%), which included 10 patients with stable disease as BOR. Using a landmark analysis, patients with <20% tumor burden increase from baseline within 8 weeks of therapy had longer OS than patients with ≥20% increase (median OS:12.4 vs. 4.6 months, p<0.001). Patients with <20% tumor burden increase throughout therapy had significantly reduced hazards of death (HR=0.24, Cox p<0.0001) after adjusting for smoking (HR=0.86, p=0.61) and baseline tumor burden (HR=1.55, p=0.062), even though some patients met criteria for RECIST

progression while on therapy. One patient (0.6%) had atypical response pattern consistent with pseudoprogression.

Conclusions: Objective response or durable disease control was noted in 24% of advanced NSCLC patients treated with commercial PD-1 inhibitors. A tumor burden increase of <20% from baseline during therapy was associated with longer OS, proposing a practical marker of treatment benefit. Pseudoprogression is rare in NSCLCs treated with PD-1 inhibitors.

[Mild pulmonary emphysema a risk factor for interstitial lung disease when using cetuximab for squamous cell carcinoma of the head and neck.](#) Okamoto I1, Tsukahara K1, Sato H1, Motohashi R1, Yunaiyama D2, Shimizu A1. Acta Otolaryngol. 2017 Jul 25:1-4. doi: 10.1080/00016489.2017.1355566. [Epub ahead of print]

BACKGROUND: Interstitial lung disease (ILD) is an occasionally fatal adverse event associated with cetuximab (Cmab) therapy. Our objective was to clarify to what degree pulmonary emphysema is a risk factor in the treatment of head and neck cancer with Cmab through a retrospective analysis. **METHODS:** Subjects were 116 patients who were administered Cmab for head and neck squamous cell carcinoma. The degree of pulmonary emphysema before initiating treatment with Cmab was visually assessed retrospectively, with scoring according to the Goddard classification used in Japanese chronic obstructive pulmonary disease (COPD) guidelines for chest computed tomography (CT). Scoring was conducted by two diagnostic radiologists and mean scores were used. Cutoffs for the development and nondevelopment of ILD were examined by receiver operating characteristic (ROC) analysis and Fisher's exact test. Values of $p < .05$ were considered to indicate a significant difference. **RESULTS:** Among the 116 patients, 11 (9.5%) developed ILD, and 105 (90.5%) did not. In ROC analysis, the optimal Goddard score cut-off of <3.0 offered 55% sensitivity and 81% specificity ($p = .015$). With a cutoff of <3.0, even very mild pulmonary emphysema would represent a risk factor for ILD when using Cmab.

Yang JC1, Ou SI2, De Petris L3, Gadgeel S4, Gandhi L5, Kim DW6, Barlesi F7, Govindan R8, Dingemans AC9, Crino L10, Lena H11, et al. J Thorac Oncol. 2017 Jul 5. pii: S1556-0864(17)30570-1. doi: 10.1016/j.jtho.2017.06.070. [Epub ahead of print]

[Pooled Systemic Efficacy and Safety Data from the Pivotal Phase II Studies \(NP28673 and NP28761\) of Alectinib in ALK-positive Non-Small-Cell Lung Cancer.](#)

INTRODUCTION: Alectinib demonstrated clinical efficacy and an acceptable safety profile in two phase II studies (NP28761 and NP28673). Here we report pooled efficacy and safety data after 15 and 18 months' longer follow-up than the respective primary analyses. **MATERIALS AND METHODS:** Enrolled patients had ALK-positive NSCLC and had progressed on, or were intolerant to, crizotinib. Patients received oral alectinib 600 mg twice daily. The primary endpoint in both studies was objective response rate (ORR) assessed by an independent review committee (IRC) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Secondary endpoints included disease control rate (DCR); duration of response (DOR); progression-free survival (PFS); overall survival (OS); and safety. **RESULTS:** The pooled dataset included 225 patients (n=138 NP28673; n=87 NP28761). The response-evaluable (RE) population included 189 patients (84%; n=122 NP28673; n=67 NP28761). In the RE population, ORR by IRC was 51.3% (95% confidence interval [CI], 44.0-58.6; all partial responses), DCR was 78.8% (95% CI, 72.3-84.4), and median DOR was 14.9 months (95% CI, 11.1-20.4) after 58% of events. Median PFS by IRC was 8.3 months (95% CI, 7.0-11.3) and median OS was 26.0 months (95% CI, 21.4-not estimable). Grade ≥ 3 adverse events (AEs) occurred in 40% of patients, 6% withdrew treatment due to AEs and 33% had AEs leading to dose interruptions/modification. **CONCLUSION:** This pooled data analysis confirmed the robust systemic efficacy of alectinib in ALK-positive NSCLC with a durable response rate. Alectinib also had an acceptable safety profile with a longer duration of follow-up.

[Spotlight on ceritinib in the treatment of ALK+ NSCLC: design, development and place in therapy.](#)

Santarpia M1, Daffinà MG1, D'Aveni A1, et al. *Drug Des Devel Ther.* 2017 Jul 5;11:2047-2063. doi: 10.2147/DDDT.S113500. eCollection 2017.

The identification of echinoderm microtubule-associated protein-like 4 (EML4) and anaplastic lymphoma kinase (ALK) fusion gene in non-small cell lung cancer (NSCLC) has radically changed the treatment of a subset of patients harboring this oncogenic driver. Crizotinib was the first ALK tyrosine kinase inhibitor to receive fast approval and is currently indicated as the first-line therapy for advanced, ALK-positive NSCLC patients. However, despite crizotinib's efficacy, patients almost invariably progress, with the central nervous system being one of the most common sites of relapse. Different mechanisms of acquired resistance have been identified, including secondary ALK mutations, ALK copy number alterations and activation of bypass tracks. Different highly potent and brain-penetrant next-generation ALK inhibitors have been developed and tested in NSCLC patients with ALK rearrangements. Ceritinib, a structurally distinct and selective ALK inhibitor, showed 20 times higher potency than crizotinib in inhibiting ALK and had activity against the most common crizotinib-resistant mutations, including L1196M and G1269A, in preclinical models. In Phase I and II studies, ceritinib demonstrated pronounced activity in both crizotinib-naïve and crizotinib-refractory patients, with responses observed regardless of the presence of ALK resistance mutations. Ceritinib was the first ALK inhibitor to be approved for the treatment of crizotinib-refractory, ALK-rearranged NSCLC, and recent results from a Phase III study have demonstrated superior efficacy compared to standard chemotherapy in the first- and second-line setting. We provide an extensive overview of ceritinib from the design of the compound through preclinical data until efficacy and toxicity results from Phase I-III clinical studies. We review the molecular alterations associated with resistance to ceritinib and highlight the importance of obtaining tumor biopsy at progression to tailor therapy based upon the underlying resistance mechanism. We finally provide an outlook on novel rational therapeutic combinations.

[Efficacy of alectinib in central nervous system metastases in crizotinib-resistant ALK-positive non-small-cell lung cancer: Comparison of RECIST 1.1 and RANO-HGG criteria.](#)

Gandhi L1, Ou SI2, Shaw AT3, et al. *Eur J Cancer.* 2017 Jul 10;82:27-33. doi: 10.1016/j.ejca.2017.05.019. [Epub ahead of print]

BACKGROUND: Central nervous system (CNS) progression is common in patients with anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer (NSCLC) receiving crizotinib. Next-generation ALK inhibitors have shown activity against CNS metastases, but accurate assessment of response and progression is vital. Data from two phase II studies in crizotinib-refractory ALK+ NSCLC were pooled to examine the CNS efficacy of alectinib, a CNS-active ALK inhibitor, using Response Evaluation Criteria in Solid Tumours (RECIST version 1.1) and Response Assessment in Neuro-Oncology high-grade glioma (RANO-HGG) criteria. **METHODS:** Both studies enrolled patients aged ≥ 18 years who had previously received crizotinib. NP28761 was conducted in North America and NP28673 was a global study. All patients received 600 mg oral alectinib twice daily and had baseline CNS imaging. CNS response for those with baseline CNS metastases was determined by an independent review committee. **RESULTS:** Baseline measurable CNS disease was identified in 50 patients by RECIST and 43 by RANO-HGG. CNS objective response rate was 64.0% by RECIST (95% confidence interval [CI]: 49.2-77.1; 11 CNS complete responses [CCRs]) and 53.5% by RANO-HGG (95% CI: 37.7-68.8; eight CCRs). CNS responses were durable, with consistent estimates of median duration of 10.8 months with RECIST and 11.1 months with RANO-HGG. Of the 39 patients with measurable CNS disease by both RECIST and RANO-HGG, only three (8%) had CNS progression according to one criteria but not the other (92% concordance rate). **CONCLUSION:** Alectinib demonstrated promising efficacy in the CNS for ALK+ NSCLC patients pretreated with crizotinib, regardless of the assessment criteria used.

[Neoadjuvant chemotherapy by bronchial arterial infusion in patients with unresectable stage III squamous cell lung cancer.](#) Zhu J1, Zhang HP1, Jiang S2, Ni J1. Ther Adv Respir Dis. 2017

Aug;11(8):301-309. doi: 10.1177/1753465817717169. Epub 2017 Jul 4.

BACKGROUND: We investigated the effects of neoadjuvant chemotherapy administered via bronchial arterial infusion (BAI) on unresectable stage III lung squamous cell carcinoma (SCC). **METHODS:** This was a single-arm retrospective study of chemotherapy with gemcitabine plus cisplatin (GP) administered via BAI to patients with unresectable lung SCC. Data regarding the post-treatment response rate, downstage rate, and surgery rate, as well as progression-free survival (PFS), overall survival (OS), quality of life, and post-BAI side effects were collected. **RESULTS:** A total of 36 patients were enrolled in this study between August 2010 and May 2014. The response rate was 72.2%, and the downstage rate was 22.2%. Among the patients who were downstaged, 16 (44.4%) patients were because of their T stage, and 5 (13.9%) patients were downstaged due to their N stage. The surgery rate was 52.8%, the 1-year survival rate was 75.4%, and the 2-year survival rate was 52.1%. The median PFS was 14.0 months [95% confidence interval (CI): 8.6-19.4], and the median OS was 25.0 months (95% CI: 19.1-30.9). The quality of life was significantly improved, and the chemotherapy was well tolerated. **CONCLUSIONS:** Compared with intravenous neoadjuvant chemotherapy, BAI chemotherapy significantly improved the surgery rate, prolonged PFS and OS, and improved the quality of life in patients with unresectable stage III lung SCC.

NSCLC - RADIOTHERAPY

[Sequential tracking of PD-L1 expression and RAD50 induction in circulating tumor and stromal cells of lung cancer patients undergoing radiotherapy.](#) Adams DL1, Adams DK2, He J3, et al. Clin

Cancer Res. 2017 Jul 5. pii: clincanres.0802.2017. doi: 10.1158/1078-0432.CCR-17-0802. [Epub ahead of print]

Evidence suggests that PD-L1 can be induced with radiotherapy and may be an immune escape mechanism in cancer. Monitoring this response is limited as repetitive biopsies during therapy is impractical, dangerous and misses tumor stromal cells. Monitoring PD-L1 expression in both circulating tumor cells (CTCs) and circulating stromal cells (CStCs) in blood based biopsies might be a practical alternative for sequential, non-invasive assessment of changes in tumor and stromal cells. Peripheral blood was collected before and after radiotherapy from 41 lung cancer patients, as was primary biopsies. We evaluated the expression of PD-L1 and formation of RAD50 foci in CTCs and a CStC subtype, cancer associated macrophage-like cells (CAMLs), in response to DNA damage caused by radiotherapy at the tumor site. Only 24% of primary biopsies had sufficient tissue for PD-L1 testing, tested with IHC clones 22c3 and 28-8. A CTC or CAML was detectable in 93% and 100% of samples, prior to and after radiotherapy, respectively. RAD50 foci significantly increased in CTCs (>7X, p<0.001) and CAMLs (>10X, p=0.001) after radiotherapy confirming their origin from the radiated site. PD-L1 expression increased overall, 1.6X in CTCs (p=0.021) and 1.8X in CAMLs (p=0.004): however, individual patient PD-L1 expression varied, consistently low/negative (51%), consistently high (17%) or induced (31%). These data suggest that RAD50 foci formation in CTCs and CAMLs may be used to track cells subjected to radiation occurring at primary tumors, and following PD-L1 expression in circulating cells may be used as a surrogate for tracking adaptive changes in immunotherapeutic targets.

[Proton Beam Radiotherapy and Concurrent Chemotherapy for Unresectable Stage III Non-Small-Cell Lung Cancer: Final Results of a Phase 2 Study.](#) Chang JY1, Verma V2, Li M1, et al. JAMA

Oncol. 2017 Jul 20:e172032. doi: 10.1001/jamaoncol.2017.2032. [Epub ahead of print]

IMPORTANCE: Proton beam radiotherapy (PBT) has the potential to reduce toxic effects in the definitive management of locally advanced non-small-cell lung cancer (NSCLC), but long-term prospective data are lacking. **OBJECTIVE:** To report the final (5-year) results of a prospective study evaluating concurrent chemotherapy and high-dose PBT to treat unresectable stage III NSCLC. **DESIGN, SETTING, AND PARTICIPANTS:**

In this open-label, single-group assignment study, with median follow-up of 27.3 months for all patients and 79.6 months for survivors, 64 patients were enrolled and analyzed; inclusion criteria were unresectable IIIA/IIIB histologically confirmed NSCLC, Karnofsky performance status 70 to 100, and 6-month prediagnosis weight loss of no more than 10%. Staging used positron emission tomography and/or computed tomography. Induction chemotherapy was allowed. **INTERVENTIONS:** Concurrent chemotherapy (carboplatin-paclitaxel) and passively scattered PBT (74-Gy relative biological effectiveness) in all patients. **MAIN OUTCOMES AND MEASURES:** Kaplan-Meier analysis of overall survival (OS), progression-free survival (PFS), actuarial distant metastasis, and locoregional recurrence. Patterns of treatment failure were categorized as local/regional or distant. Acute and late toxic effects were prospectively assigned using Common Terminology Criteria for Adverse Events, v3.0. **RESULTS:** Of 64 patients (22 [34%] female; median [range] age, 70 [37-78] years; stage IIIA, 30 [47%]; IIIB, 34 [53%]), 17 (27%) were alive at last follow-up. Median OS was 26.5 months (5-year OS, 29%; 95% CI, 18%-41%). Five-year PFS was 22% (95% CI, 12%-32%); 5-year actuarial distant metastasis and locoregional recurrence were 54% (n = 36) and 28% (n = 22), respectively. Treatment failures were largely (31 [48%] patients) distant, with low rates of crude local (10 [16%]) and regional (9 [14%]) recurrences. Rates of grade 2 and 3 acute esophagitis were 18 (28%) and 5 (8%), respectively. Acute grade 2 pneumonitis occurred in 1 (2%) patient. Late toxic effects were uncommon: 1 (2%) patient developed an esophageal stricture (grade 2) and 1 (2%) grade 4 esophagitis. Late grades 2 and 3 pneumonitis occurred in 10 (16%) and 8 (12%), respectively. Two (3%) patients developed a bronchial stricture (grade 2), and 1 (2%) a grade 4 bronchial fistula. There were no acute or late grade 5 toxic effects. **CONCLUSIONS AND RELEVANCE:** Concurrent chemotherapy and PBT to treat unresectable NSCLC afford promising clinical outcomes and rates of toxic effects compared with historical photon therapy data. Further optimization of proton therapy, particularly intensity-modulated proton therapy, is still needed.

[An individualized radiation dose escalation trial in non-small cell lung cancer based on FDG-PET imaging.](#) Wanet M1, Delor A2, Hanin FX3, et al. *Strahlenther Onkol.* 2017 Jul 21. doi: 10.1007/s00066-017-1168-z. [Epub ahead of print]

AIM: The aim of the study was to assess the feasibility of an individualized 18F fluorodeoxyglucose positron emission tomography (FDG-PET)-guided dose escalation boost in non-small cell lung cancer (NSCLC) patients and to assess its impact on local tumor control and toxicity. **PATIENTS AND METHODS:** A total of 13 patients with stage II-III NSCLC were enrolled to receive a dose of 62.5 Gy in 25 fractions to the CT-based planning target volume (PTV; primary tumor and affected lymph nodes). The fraction dose was increased within the individual PET-based PTV (PTVPET) using intensity modulated radiotherapy (IMRT) with a simultaneous integrated boost (SIB) until the predefined organ-at-risk (OAR) threshold was reached. Tumor response was assessed during follow-up by means of repeat FDG-PET/computed tomography. Acute and late toxicity were recorded and classified according to the CTCAE criteria (Version 4.0). Local progression-free survival was determined using the Kaplan-Meier method. **RESULTS:** The average dose to PTVPET reached 89.17 Gy for peripheral and 75 Gy for central tumors. After a median follow-up period of 29 months, seven patients were still alive, while six had died (four due to distant progression, two due to grade 5 toxicity). Local progression was seen in two patients in association with further recurrences. One and 2-year local progression free survival rates were 76.9% and 52.8%, respectively. Three cases of acute grade 3 esophagitis were seen. Two patients with central

tumors developed late toxicity and died due to severe hemoptysis. **CONCLUSION:** These results suggest that a non-uniform and individualized dose escalation based on FDG-PET in IMRT delivery is feasible. The doses reached were higher in patients with peripheral compared to central tumors. This strategy enables good local control to be achieved at acceptable toxicity rates. However, dose escalation in centrally located tumors with direct invasion of mediastinal organs must be performed with great caution in order to avoid severe late toxicity.

[Hypofractionated stereotactic radiation therapy activates the peripheral immune response in operable stage I non-small-cell lung cancer.](#) Zhang T1,2, Yu H3, Ni C4, et al. Sci Rep. 2017 Jul 7;7(1):4866. doi: 10.1038/s41598-017-04978-x.

It has been reported that in patients with operable stage I non-small cell lung cancer (NSCLC), overall survival (OS) is better in those who undergo hypofractionated stereotactic radiation therapy (HSRT) than in those who undergo surgery. However, the reason that HSRT has a better OS has not been fully explored. Here, we analyzed reconstitution kinetics in immune cells in the peripheral blood of NSCLC patients after HSRT. We found that HSRT increased the frequency of total T cells, especially the proportion of CD8+ T cells, but decreased the frequency of inhibitory Tregs. Intracellular staining showed that after HSRT, peripheral CD8+ T cells were transformed into activated T cells, which express high levels of TNF- α , IFN- γ , granzyme B and IL-2. HSRT also increased the production of IL-2, TNF- α , and IFN- γ but down-regulated the production of TGF- β in CD4+ T cells. The frequencies of naïve B cells and double-negative B cells were lower, while the proportions of MZ-like B cells, transitional B cells and plasmablast cells were higher after HSRT. Collectively, our results demonstrate that HSRT activates the peripheral immune response and indicate the dynamic variation in peripheral lymphocytes after HSRT, which is very important for optimizing combination treatments in clinical practice.

[Lung stereotactic body radiation therapy \(SBRT\) for early-stage non-small cell lung cancer in the very elderly \(>80years old\): Extremely safe and effective.](#) Kreinbrink P1, Blumenfeld P1, Tolekidis G1, Sen N1, Sher D2, Marwaha G3. J Geriatr Oncol. 2017 Jul 21. pii: S1879-4068(17)30129-7. doi: 10.1016/j.jgo.2017.07.002. [Epub ahead of print]

OBJECTIVE: Stereotactic body radiotherapy (SBRT) for early-stage non-small-cell lung cancer (NSCLC) is the standard of care in medically inoperable patients. In very elderly patients, previous studies have shown SBRT to offer excellent local control, though with higher toxicities than in younger populations. We report our institutional experience using SBRT in the definitive management of NSCLC in patients ≥ 80 years old. **MATERIALS AND METHODS:** Using an IRB-approved registry of 158 patients treated with definitive-intent lung SBRT for early-stage NSCLC at our institution between 2010 and 2016, 31 consecutively treated patients ≥ 80 years of age were identified. CTCAEv4 scales were prospectively recorded during follow-ups and utilized for toxicity assessments. Kaplan-Meier estimates were utilized for survival analyses. **RESULTS:** For the 31 patients (with 34 lesions) included, median age was 83 (R: 80-93), median ECOG performance status was 2 (R: 0-3), and median follow-up was 15.8 months (R: 3.1-48.3). Median PTV size was 24.0 cm³ (R: 5.83-62.1 cm³). Median prescription dose was 54 Gy in 3 fractions (R: 50-60 Gy in 3-8 fractions). Local control was 100% at 1 year and 92.3% at 2 years. Median survival was 29.1 months. There were no grade 2-5 toxicities. Grade 1 toxicities included: fatigue in 5 patients (16.1%), asymptomatic (radiographic) pneumonitis in 12 (38.7%), and dyspnea in 2 (6.5%). **CONCLUSIONS:** Lung SBRT with a BED of ≥ 100 Gy₁₀ for very elderly patients with NSCLC is extremely safe and effective, with inordinately low toxicity rates (zero grade 2-5 toxicities). With stringent dosimetric parameters and planning guidelines, patients ≥ 80 years remain excellent candidates for full-dose SBRT. **SUMMARY:** SBRT for early-stage NSCLC is the accepted standard of care in medically inoperable patients, though in many very elderly patients, dose is either de-intensified or withheld for concern of toxicity in the setting of advanced age and competing risks. In this study of our

very elderly (≥ 80 years old) early-stage NSCLC patients, we highlight both the extremely high efficacy and tolerability (zero grade 2 or above toxicities) associated with definitive intent SBRT.

SMALL CELL LUNG CANCER - SCLC

[Comparison of irinotecan/platinum versus etoposide/platinum chemotherapy for extensive-stage small cell lung cancer: A meta-analysis.](#) Han D1, Wang G1, Sun L1, Ren X1, Shang W1, Xu L1, Li S2. *Eur J Cancer Care (Engl)*. 2017 Jul 13. doi: 10.1111/ecc.12723. [Epub ahead of print]

This meta-analysis was performed to compare the effects and toxicities between irinotecan/platinum (IP) and etoposide/platinum (EP) regimens as the first-line treatment of patients with extensive-stage small cell lung cancer (E-SCLC). A systematic search was made of MEDLINE, Cochrane, ISI Web of Science and SCOPUS databases. Randomised clinical trials on treatment of E-SCLC with the IP regimens, compared with EP regimens, were reviewed. Studies were pooled to hazard ratio (HR), relative risk (RR) and odds ratio (OR), with 95% confidence interval (CI). Eight trials (enrolling 2089 participants) met the inclusion criteria. Overall survival (OS) and 1-year survival rate were superior in the IP group (HR 0.83; 95% CI 0.75 to 0.91 and RR 1.19; 95% CI 1.06 to 1.34). Grades 3 and 4 anaemia, leukopenia, neutropenia, thrombocytopenia and febrile neutropenia were less frequent in the IP regimens than that in the EP regimens. And grades 3 and 4 nausea/vomiting, diarrheal, anorexia and fatigue were less frequent in the EP regimens. IP combination chemotherapy achieved a superior OS and 1-year survival rate, compared with EP doublets, in patients with E-SCLC.

[Evaluation of short-term and long-term efficacy of surgical and non-surgical treatment in patients with early-stage small cell lung cancer: A comparative study.](#) Hou SZ, Cheng ZM, Wu YB, Sun Y, Liu B, Yuan MX, Wang XD. *Cancer Biomark*. 2017 Jul 4;19(3):249-256. doi: 10.3233/CBM-160332.

OBJECTIVE: The aim of this study is to compare surgery with adjuvant chemoradiotherapy versus non-surgical treatments for patients with early-stage small cell lung cancer (SCLC) based on the short-term and long-term efficacy. **METHODS:** SCLC patients who underwent a pulmonary lobectomy with post-surgical radiotherapy or chemotherapy were assigned to the surgical group. SCLC patients who received radiotherapy or chemotherapy alone were classified into the non-surgical group. The clinical efficacy was evaluated as complete remission (CR), partial remission (PR), stable disease (SD), or progressive disease (PD). The total effectiveness rate was calculated as CR + PR. The 1-, 3-, and 5-year survival rates of the two groups were compared. **RESULTS:** Compared with the non-surgical group, the CR rate and the total effectiveness rate were higher in the surgical group, and the total effectiveness rate for male patients and patients without a smoking history were also higher in the surgical group. Distant metastasis and local recurrence concurrent with distant metastasis in the surgical group were both lower in the surgical group than in the non-surgical group. Compared with the non-surgical group, the local recurrence in male patients was lower in the surgical group, and patients in the surgical group had lower distant metastasis at TNM stage IIb. The 1-, 3-, and 5-year survival rates were higher in the surgical group than in the non-surgical group. **CONCLUSIONS:** These findings indicate that for patients with early-stage SCLC, better scores in effectiveness rate, disease progression, and 1-, 3-, and 5-year survival rates were observed in patients who underwent surgery followed by adjuvant chemoradiotherapy when compared with patients without surgical treatment.

[Prospective study of proton-beam radiation therapy for limited-stage small cell lung cancer.](#)

Rwigema JM1,2, Verma V3, Lin L1, Berman AT1, Levin WP1, Evans TL4, Aggarwal C4, Rengan R5, Langer C4, Cohen RB4, Simone CB 2nd6. *Cancer*. 2017 Jul 5. doi: 10.1002/cncr.30870. [Epub ahead of print]

BACKGROUND: Existing data supporting the use of proton-beam therapy (PBT) for limited-stage small cell lung cancer (LS-SCLC) are limited to a single 6-patient case series. This is the first prospective study to evaluate clinical outcomes and toxicities of PBT for LS-SCLC. **METHODS:** This study prospectively analyzed patients with primary, nonrecurrent LS-SCLC definitively treated with PBT and concurrent chemotherapy from 2011 to 2016. Clinical backup intensity-modulated radiotherapy (IMRT) plans were generated for each patient and were compared with PBT plans. Outcome measures included local control (LC), recurrence-free survival (RFS), and overall survival (OS) rates and toxicities. **RESULTS:** Thirty consecutive patients were enrolled and evaluated. The median dose was 63.9 cobalt gray equivalents (range, 45-66.6 cobalt gray equivalents) in 33 to 37 fractions delivered daily (n = 18 [60.0%]) or twice daily (n = 12 [40.0%]). The concurrent chemotherapy was cisplatin/etoposide (n = 21 [70.0%]) or carboplatin/etoposide (n = 9 [30.0%]). In comparison with the backup IMRT plans, PBT allowed statistically significant reductions in the cord, heart, and lung mean doses and the volume receiving at least 5 Gy but not in the esophagus mean dose or the lung volume receiving at least 20 Gy. At a median follow-up of 14 months, the 1-/2-year LC and RFS rates were 85%/69% and 63%/42%, respectively. The median OS was 28.2 months, and the 1-/2-year OS rates were 72%/58%. There was 1 case each (3.3%) of grade 3 or higher esophagitis, pneumonitis, anorexia, and pericardial effusion. Grade 2 pneumonitis and esophagitis were seen in 10.0% and 43.3% of patients, respectively. **CONCLUSIONS:** In the first prospective registry study and largest analysis to date of PBT for LS-SCLC, PBT was found to be safe with a limited incidence of high-grade toxicities. Cancer 2017. © 2017 American Cancer Society.

Small cell lung cancer: model of circulating tumor cell tumorspheres in chemoresistance. Klameth L1, Rath B2, Hochmaier M3, et al. Sci Rep. 2017 Jul 13;7(1):5337. doi: 10.1038/s41598-017-05562-z. Small cell lung cancer (SCLC) represents 15% of lung cancers and is characterized by early dissemination, development of chemoresistance and a poor prognosis. A host of diverse drugs failed invariably and its mechanisms of global chemoresistance have not been characterized so far. SCLC represents the prototype of an aggressive and highly metastatic tumor which is ultimately refractory to any treatment. High numbers of circulating tumor cells (CTCs) allowed us to establish 5 CTC cell lines (BHGc7, 10, 16, 26 and UHGc5) from patients with recurrent SCLC. These cell lines exhibit the typical SCLC markers and CTCs of all patients developed spontaneously large multicellular aggregates, termed tumorspheres. Ki67 and carbonic anhydrase 9 (CAIX) staining of tumorsphere sections revealed quiescent and hypoxic cells, respectively. Accordingly, comparison of the chemosensitivity of CTC single cell suspensions with tumorspheres demonstrated increased resistance of the clusters against chemotherapeutics commonly used for treatment of SCLC. Therefore, global chemoresistance of relapsing SCLC seems to rely on formation of large tumorspheres which reveal limited accessibility, lower growth fraction and hypoxic conditions. Since similar tumor spheroids were found in other tumor types, SCLC seems to represent a unique tumor model to study the association of CTCs, metastasis and drug resistance.

Targeting AXL and mTOR pathway overcomes primary and acquired resistance to WEE1 inhibition in small cell lung cancer. Sen T1, Tong P2, Diao L2, Li L3, Fan Y4, Hoff J4, Heymach J5, Wang J6, Byers LA7. Clin Cancer Res. 2017 Jul 11. pii: clincanres.1284.2017. doi: 10.1158/1078-0432.CCR-17-1284. [Epub ahead of print]

Purpose: Drugs targeting DNA repair and cell cycle checkpoints have emerged as promising therapies for small cell lung cancer (SCLC). Among these, the WEE1 inhibitor AZD1775 has shown clinical activity in a subset of SCLC patients, but resistance is common. Understanding primary and acquired resistance mechanisms will be critical for developing effective WEE1 inhibitor combinations. <p>Experimental Design: AZD1775 sensitivity in SCLC cell lines was correlated with baseline expression level of 200 total or phosphorylated proteins measured by reverse phase protein array (RPPA) to identify predictive

markers of primary resistance. We further established AZD1775 acquired-resistant models to identify mechanism of acquired resistance. Combination regimens were tested to overcome primary and acquired resistance to AZD1775 in in vitro and in vivo SCLC models.

Results: High-throughput proteomic profiling demonstrate that SCLC models with primary resistance to AZD1775 express high levels of AXL and phosphorylated S6 and that WEE1/AXL or WEE1/mTOR inhibitor combinations overcome resistance in vitro and in vivo. Furthermore, AXL, independently and via mTOR, activates the ERK pathway, leading to recruitment and activation of another G2-checkpoint protein, CHK1. AZD1775 acquired-resistant models demonstrated upregulation of AXL, pS6, and MET, and resistance was overcome with the addition of AXL (TP0903), dual-AXL/MET (cabozantinib), or mTOR (RAD001) inhibitors.

Conclusions: AXL promotes resistance to WEE1 inhibition via downstream mTOR signaling and resulting activation of a parallel DNA damage repair pathway, CHK1. These findings suggest rational combinations to enhance the clinical efficacy of AZD1775, which is currently in clinical trials for SCLC and other malignancies.

[Therapy of Small-cell Lung Cancer \(SCLC\) With a Topoisomerase-I-inhibiting Antibody-Drug Conjugate \(ADC\) Targeting Trop-2, Sacituzumab Govitecan.](#) Gray JE1, Heist RS2, Starodub AN3, et al. Clin Cancer Res. 2017 Jul 5. pii: clincanres.0933.2017. doi: 10.1158/1078-0432.CCR-17-0933. [Epub ahead of print]

PURPOSE: We evaluated a Trop-2-targeting antibody conjugated with SN-38 in metastatic small-cell lung cancer (mSCLC) patients.

Experimental Design: Sacituzumab govitecan was studied in patients with pretreated (median, 2; range, 1-7) mSCLC who received either 8 or 10 mg/kg i.v. on days 1 and 8 of 21-day cycles. The primary endpoints were safety and objective response rate (ORR); duration of response, progression-free survival (PFS), and overall survival (OS) were secondary endpoints.

Results: Sixty percent of patients showed tumor shrinkage from baseline CTs. On an intention-to-treat basis (N= 50), the ORR was 14% (17% for 10 mg/kg group); the median response duration, 5.7 months; the clinical benefit rate (CBR>4 months), 34%; median PFS, 3.7 months; median OS, 7.5 months. There was a suggested improvement in PR, CBR, and PFS with sacituzumab govitecan in second-line patients who were sensitive to frontline therapy, but no difference between frontline chemosensitive vs chemoresistant patients in the overall population. There was a statistically significant higher OS in those patients who received prior topotecan vs no topotecan therapy in a small subgroup. Grade >3 adverse events included neutropenia (34%), fatigue (13%), diarrhea (9%), and anemia (6%). Trop-2 tumor staining was not required for patient selection. No antibodies to the drug conjugate or its components were detected on serial blood collections.

Conclusions: Sacituzumab govitecan appears to have a safe and effective therapeutic profile in heavily-pretreated, mSCLC patients, including those who are chemosensitive or chemoresistant to frontline chemotherapy. Additional studies as a monotherapy or combination therapy are warranted.

[What's new in small cell lung cancer - extensive disease? An overview on advances of systemic treatment in 2016.](#) Seeber A1, Leitner C1, Philipp-Abbrederis K1, Spizzo G1, Kocher F1. Future Oncol. 2017 Jul 7. doi: 10.2217/fon-2017-0046. [Epub ahead of print]

Systemic therapy options for small cell lung cancer patients with extensive disease remain poor. After an initial response on first-line therapy, virtually all patients develop disease progression. For those who showed an initial response only few therapy options with low response rates are currently available. Until now, many experimental and targeted agents have failed to yield convincing clinical benefits, and new therapy options are clearly warranted for these patients. In this year's oncological congresses, several new therapy strategies, including checkpoint inhibition, showed promising results in ongoing trials. Furthermore, a potential benefit of new agents targeting DLL3, Aurora A kinase and PARP-inhibitor was

reported. In this review we summarize new developments and critically highlight the most important and promising data in the relapsed small cell lung cancer disease.

[State-of-the-art considerations in small cell lung cancer brain metastases.](#) Lukas RV1, Gondi V2, Kamson DO3, Kumthekar P1, Salgia R4. *Oncotarget*. 2017 Jul 18. doi: 10.18632/oncotarget.19333. [Epub ahead of print]

BACKGROUND: Small cell lung cancer (SCLC) frequently leads to development of brain metastases. These unfortunately continue to be associated with short survival. Substantial advances have been made in our understanding of the underlying biology of disease. This understanding on the background of previously evaluated and currently utilized therapeutic treatments can help guide the next steps in investigations into this disease with the potential to influence future treatments. **DESIGN:** A comprehensive review of the literature covering epidemiology, pathophysiology, imaging characteristics, prognosis, and therapeutic management of SCLC brain metastases was performed. **RESULTS:** SCLC brain metastases continue to have a poor prognosis. Both unique aspects of SCLC brain metastases as well as features seen more universally across other solid tumor brain metastases are discussed. Systemic therapeutic studies and radiotherapeutic approaches are reviewed. **CONCLUSIONS:** A clearer understanding of SCLC brain metastases will help lay the framework for studies which will hopefully translate into meaningful therapeutic options for these patients.

[Evaluation of factors associated with platinum-sensitivity status and survival in limited-stage small cell lung cancer patients treated with chemoradiotherapy.](#) Wen Q1,2, Meng X1,2, Xie P1,2, Wang S1,2, Sun X1,2, Yu J1,2. *Oncotarget*. 2017 Jul 7. doi: 10.18632/oncotarget.19073. [Epub ahead of print] In this retrospective study, we analyzed the association of clinicopathological factors and therapeutic plans with platinum-sensitivity status and survival of limited-stage small cell lung cancer (LS-SCLC) patients. We enrolled 452 LS-SCLC patients with 279 platinum sensitive and 173 platinum refractory patients. The low serum neuro-specific enolase levels (NSE; $p = 0.011$), neutrophil-to-lymphocyte ratios (NLR; $p = 0.013$) and higher objective response rates ($p = 0.003$) were associated with sensitive group but not the refractory group. Multivariate analysis showed that treatment modality (HR = 0.267, $p < 0.001$), serum lactate dehydrogenase (LDH; HR = 1.894, $p = 0.016$), NLR (HR = 2.043, $p = 0.043$) and platinum-sensitivity status (HR = 0.561, $p = 0.036$) were independent prognostic factors for survival. We further showed that the numbers of chemotherapy cycles and response to first-line therapy were independent prognostic factors for refractory patients only. Our study demonstrates that platinum-sensitivity status is of prognostic importance, as it is strongly associated with survival in LS-SCLC patients.

PALLIATIVE AND SUPPORTIVE CARE

[Supportive care for patients undergoing immunotherapy.](#) Rapoport BL1,2, van Eeden R3, Sibaud V4,5, Epstein JB6, Klastersky J7, Aapro M8, Moodley D9. *Support Care Cancer*. 2017 Jul 13. doi: 10.1007/s00520-017-3802-9. [Epub ahead of print]

Immune checkpoint inhibitors, a new class of cancer therapeutic agents, play an important role in the management of melanoma, NSCLC, and other malignancies. A workshop organized by three MASCC Study Groups: Oral Care, Skin Toxicities, and Neutropenia, Infection, and Myelosuppression during the MASCC Annual Meeting held in Adelaide, Australia on 23-25 June, 2016 focused on the new class of anti-cancer therapeutic agents. Topics in the workshop included the mechanism of action and clinical uses of immune anti-CTLA4 and anti-PD1 antibodies, checkpoint inhibitor toxicities, including skin adverse events, gastrointestinal toxicities, oral complications, pulmonary toxicities, and endocrinological and immune-related infections. Checkpoint inhibitors have been approved for use in different malignancies including metastatic melanoma, advanced non-small cell lung cancer, metastatic renal cell carcinoma,

refractory Hodgkin's lymphoma, metastatic bladder cancer, and advanced head and neck cancer, and the list continues to grow. In general, these agents seem to be better tolerated in most patients and less toxic compared to conventional chemotherapy. However, the toxicities here, termed immune-related adverse events (irAEs), are unique and different from what we have seen in the past. There is no prospective data on these toxicities, and guidelines or recommendations are currently based on symptomatic management from the ongoing clinical trials. Treating oncologists need to be aware and alert themselves to the subtleties in presentation and the big difference in the way we manage the irAEs. Although most irAEs are low-grade and manageable, they have the potential to be life-threatening and extremely severe if not promptly treated. Additionally, irAEs could even lead to death, if managed incorrectly. The MASCC workshop addressed the various irAEs, per organ system, clinical presentation, management recommendations, and individual toxicities.

[Perspectives of newly diagnosed advanced cancer patients receiving dignity therapy during cancer treatment.](#) Dose AM1, Rhudy LM2. Support Care Cancer. 2017 Jul 21. doi: 10.1007/s00520-017-3833-2. [Epub ahead of print]

PURPOSE: Dignity therapy is a psychosocial intervention that has been used primarily at the end of life to improve quality of life and other patient outcomes, but many individuals are unable to complete it due to health decline and death. The purpose of this study was to identify what individuals with advanced pancreatic or lung cancer with limited life expectancy, undergoing active cancer treatment describe during the dignity therapy intervention as important to them when not immediately facing end of life.

METHODS: Twenty patients undergoing chemotherapy for advanced cancer participated in a dignity therapy intervention study. Initial interviews were analyzed using descriptive content analysis.

RESULTS: Family provided the overall context and background for emerging themes of defining events, accomplishments, and God's plan, which led to lessons learned, and resulted in messages of hope. Interviews were often autobiographical in nature and contained much reminiscence, consistent with dignity therapy's intent. Few participants spoke about their cancer diagnoses during the interview.

CONCLUSIONS: This study adds unique insight into the use of dignity therapy for those still receiving active cancer treatment, different from work by others in which it was offered only at end of life. As part of supportive care, clinicians need to validate the importance of family to those with advanced cancer and to provide opportunities for patients to share what they have learned throughout life and to impart messages of hope to those closest to them.

[The role of medical/nursing skills training in caregiver confidence and burden: A CanCORS study.](#) Mollica MA1, Litzelman K2, Rowland JH3, Kent EE1. Cancer. 2017 Jul 20. doi: 10.1002/cncr.30875. [Epub ahead of print]

BACKGROUND: Informal cancer caregivers provide essential support to cancer patients, including performing direct medical/nursing tasks, assisting with activities of daily living, and offering social support. This study examined associations between the receipt of medical/nursing skills training and the caregiver burden as well as the mediation of caregiving confidence on this relationship in a sample of caregivers of lung and colorectal cancer patients. **METHODS:** Caregivers who had been identified by cancer patients in the Cancer Care Outcomes Research and Surveillance consortium completed a questionnaire assessing the care provided, the type of medical/nursing skills training received, the burden (measured with the modified short-form Zarit Burden Interview), and the confidence in caring for their patient's physical needs. Regression models that had been adjusted for sociodemographic, caregiver, and care recipient characteristics assessed the relationship between training received and burden, and a mediation analysis assessed the role of confidence in this relationship. **RESULTS:** Six hundred forty-one caregivers performed some type of medical/nursing task, with 59% (n = 377) reporting that they did not receive training for all the care provided. Caregivers reported moderate levels of burden (mean summary

score, 32.07; standard deviation, 12.66; possible range, 14-70), and a lack of receipt of training was associated with greater levels of burden ($b = 2.60$; standard error, 0.98; $P = .01$). Confidence partially mediated the relation between training and burden (Sobel's $t = 1.90$; $P = 0.03$). **CONCLUSIONS:** As the number of cancer patients and caregivers increases, understanding how best to reduce the caregiver burden is necessary. Skills training is a potential area for interventions, but research on how best to provide training for caregivers (ie, the content, mode of delivery, and timing) is needed. Cancer 2017. © 2017 American Cancer Society.

Comparison of Fatigue, Depression, and Anxiety as Factors Affecting Posttreatment Health-Related Quality of Life in Lung Cancer Survivors. Jung JY1, Lee JM2, Kim MS2, Shim YM3, Zo JI3, Yun YH1,4. *Psychooncology*. 2017 Jul 29. doi: 10.1002/pon.4513. [Epub ahead of print]

OBJECTIVE: To compare the effects of fatigue, anxiety, and depression on health-related quality of life (HRQoL) in survivors of surgically resectable lung cancer **METHODS:** In total, 830 lung cancer survivors participated in the study. They completed a questionnaire consisting of items pertaining to sociodemographic characteristics, clinical variables, and HRQoL. We calculated prevalence rates for fatigue, anxiety, and depression and performed multiple logistic regression and general linear modeling to determine the main factors affecting HRQoL. **RESULTS:** The prevalence rates for moderate fatigue (Brief Fatigue Inventory mean score: ≥ 4), borderline depression (Hospital Anxiety and Depression Scale-Depression score: ≥ 8), and borderline anxiety (Hospital Anxiety and Depression Scale-Anxiety score: ≥ 8) were 42.2%, 38.9%, and 20.9%, respectively. The main factor was fatigue, which demonstrated the strongest explanatory power for HRQoL including all five functional HRQoL components (i.e., physical, role, emotional, cognitive, and social functioning) and global health status (partial R^2 range: .13 to .19). However, anxiety (partial $R^2 = .21$) and fatigue (partial $R^2 = .19$) both demonstrated strong explanatory power for emotional HRQoL. In addition, depression demonstrated weak explanatory power for HRQoL including emotional HRQoL. **CONCLUSIONS:** Relative to depression and anxiety, fatigue exerted a stronger effect on lung cancer survivors' HRQoL. Health professionals should consider the reduction of fatigue a priority in improving cancer patients' HRQoL following the completion of cancer treatment. This article is protected by copyright. All rights reserved.

Impact of pulmonary rehabilitation on postoperative complications in patients with lung cancer and chronic obstructive pulmonary disease. Saito H1, Hatakeyama K2, Konno H1, Matsunaga T2, Shimada Y3, Minamiya Y1. *Thorac Cancer*. 2017 Jul 11. doi: 10.1111/1759-7714.12466. [Epub ahead of print]

BACKGROUND: Given the extent of the surgical indications for pulmonary lobectomy in breathless patients, preoperative care and evaluation of pulmonary function are increasingly necessary. The aim of this study was to assess the contribution of preoperative pulmonary rehabilitation (PR) for reducing the incidence of postoperative pulmonary complications in non-small cell lung cancer (NSCLC) patients with chronic obstructive pulmonary disease (COPD). **METHODS:** The records of 116 patients with COPD, including 51 patients who received PR, were retrospectively analyzed. Pulmonary function testing, including slow vital capacity (VC) and forced expiratory volume in one second (FEV1), was obtained preoperatively, after PR, and at one and six months postoperatively. The recovery rate of postoperative pulmonary function was standardized for functional loss associated with the different resected lung volumes. Propensity score analysis generated matched pairs of 31 patients divided into PR and non-PR groups. **RESULTS:** The PR period was 18.7 ± 12.7 days in COPD patients. Preoperative pulmonary function was significantly improved after PR (VC 5.3%, FEV1 5.5%; $P < 0.05$). The FEV1 recovery rate one month after surgery was significantly better in the PR (101.6%; $P < 0.001$) than in the non-PR group (93.9%). In logistic regression analysis, predicted postoperative FEV1, predicted postoperative %FEV1, and PR were independent factors related to postoperative pulmonary complications after pulmonary

lobectomy (odds ratio 18.9, 16.1, and 13.9, respectively; $P < 0.05$). **CONCLUSIONS:** PR improved the recovery rate of pulmonary function after lobectomy in the early period, and may decrease postoperative pulmonary complications.

[The pervasive nature of uncertainty-a qualitative study of patients with advanced cancer and their informal caregivers.](#) Shilling V1, Starkings R2, Jenkins V2, Fallowfield L2. *J Cancer Surviv.* 2017 Jul 18. doi: 10.1007/s11764-017-0628-x. [Epub ahead of print]

PURPOSE: The aim of this study was to explore the impact of extended cancer survival on broader aspects of life and wellbeing such as occupational, financial and family life for patients with advanced cancer and their nominated informal caregivers. **METHODS:** In-depth qualitative interviews were transcribed verbatim. A thematic framework was developed from an initial process of open coding and tested iteratively as new data were collected. **RESULTS:** Twenty-four patient-caregiver dyads with advanced ovarian (9), melanoma (9) or lung cancer (6). Patients were aged 39-84 (median 62 years) and caregivers 19-85 (median 54 years). Caregivers were the partners/spouses (15), children (5), siblings (2) and friends (2) of patients. One particular theme, 'uncertainty', encompassed many issues such as planning for the future, providing for one's family, employment and finances. Uncertainties were related to the timescale and trajectory of the disease and lack of control or ability to make plans. There were marked age effects. Accounts from within the same dyad often differed and patients and caregivers rarely discussed concerns with each other. **CONCLUSIONS:** Both patients and their informal caregivers were challenged by the uncertainties around living with advanced cancer and the lack of a defined trajectory. This impacted many diverse areas of life. Although distressing, dyads seldom discussed these concerns with each other. **IMPLICATIONS FOR CANCER SURVIVORS:** Uncertainty is a recurrent issue for cancer survivors and their families impacting broad aspects of their lives and their ability to move forward; however, patients and caregivers in this study rarely discussed these concerns together. Uncertainty should be discussed periodically, together, and healthcare professionals could facilitate these discussions. The use of one or more 'trigger questions' in clinic appointments may provide an opportunity to start these dialogues.

COMPLEMENTARY & ALTERNATIVE THERAPY

[Liposomal honokiol induced lysosomal degradation of Hsp90 client proteins and protective autophagy in both gefitinib-sensitive and gefitinib-resistant NSCLC cells.](#) Yang J1, Wu W2, Wen J1, et al. *Biomaterials.* 2017 Oct;141:188-198. doi: 10.1016/j.biomaterials.2017.07.002. Epub 2017 Jul 4. Honokiol (HK), a natural chemical isolated from *Magnolia officinalis*, has shown antitumorigenic activities when used to treat a variety of tumor cell lines. The mechanism of honokiol activity when used to treat gefitinib-sensitive and gefitinib-resistant non-small cell lung cancer (NSCLC) requires elucidation. Here, the presence of liposomal honokiol (LHK) induced apoptotic and antitumor activities in four xenograft models generated using NSCLC cell lines such as HCC827 (gefitinib-sensitive) and H1975 (gefitinib-resistant). Mechanistic studies revealed that LHK inhibited the Akt and Erk1/2, both EGFR signaling cascade effectors, by promoting degradation of HSP90 client proteins (HCP), including wild-type or mutant EGFR, Akt and C-Raf. Molecular biology assays showed that LHK induced HCP degradation through a lysosomal pathway, rather than the canonical proteasome protein degradation pathway. As a result of misfolded protein accumulation, LHK induced endoplasmic reticulum (ER) stress and autophagy. Inhibition of ER stress (with 4-phenylbutyrate) or autophagy (with small interfering RNA) reduced LHK-induced HCP degradations. Additionally, LHK induced autophagy showed a protective role for cancer cell as inhibition of autophagy in vitro and in vivo by autophagosome degradation inhibitors could promote the anticancer activity of LHK. LHK has been approved by the

China Food and Drug Administration for first-in-human clinical trials in NSCLC. The current study will guide the design of future LHK clinical trials.

[Acupuncture for cancer-related fatigue in lung cancer patients: a randomized, double blind, placebo-controlled pilot trial.](#) Cheng CS^{1,2}, Chen LY^{1,2}, Ning ZY^{1,2}, Zhang CY^{1,2}, Chen H^{1,2}, Chen Z^{1,2}, Zhu XY^{3,4}, Xie J^{5,6}. Support Care Cancer. 2017 Jul 13. doi: 10.1007/s00520-017-3812-7. [Epub ahead of print]

BACKGROUND: Cancer-related fatigue (CRF) is a distressing symptom that is the most common unpleasant side effect experienced by lung cancer patients and is challenging for clinical care workers to manage. **METHODS:** We performed a randomized, double-blind, placebo-controlled pilot trial to evaluate the clinical effect of acupuncture on CRF in lung cancer patients. Twenty-eight patients presenting with CRF were randomly assigned to active acupuncture or placebo acupuncture groups to receive acupoint stimulation (LI-4, Ren-6, St-36, KI-3, and Sp-6) twice per week for 4 weeks, followed by 2 weeks of follow-up. The primary outcome was the change in intensity of CFR based on the Chinese version of the Brief Fatigue Inventory (BFI-C). As the secondary endpoint, the Functional Assessment of Cancer Therapy-Lung Cancer Subscale (FACT-LCS) was adopted to assess the influence of acupuncture on patients' quality of life (QOL). Adverse events and safety of treatments were monitored throughout the trial. **RESULTS:** Our pilot study demonstrated feasibility among patients with appropriate inclusion criteria and good compliance with acupuncture treatment. A significant reduction in the BFI-C score was observed at 2 weeks in the 14 participants who received active acupuncture compared with those receiving the placebo ($P < 0.01$). At week 6, symptoms further improved according to the BFI-C ($P < 0.001$) and the FACT-LCS ($P = 0.002$). There were no significant differences in the incidence of adverse events in either group ($P > 0.05$). **CONCLUSION:** Fatigue is a common symptom experienced by lung cancer patients. Acupuncture may be a safe and feasible optional method for adjunctive treatment in cancer palliative care, and appropriately powered trials are warranted to evaluate the effects of acupuncture.

[Brucea javanica oil emulsion alleviates cachexia induced by Lewis lung cancer cells in mice.](#) Chen C¹, Wang B². J Drug Target. 2017 Jul 18:1-9. doi: 10.1080/1061186X.2017.1354003. [Epub ahead of print]

This study was conducted to evaluate the efficacy and possible mechanism of Brucea javanica oil emulsion (BJOE) on cachexia, by observing changes in related indexes in mice with cachexia and identifying the genes responsible based on gene chip analysis. In the BJOE treatment group, body weight loss, tumour growth and metastasis were found obviously inhibited, food and water intake had markedly increased, and survival time was significantly prolonged, as compared to the control group. Moreover, the BJOE witnessed improvement in body weight, prevention of tumour metastasis and overall increase in survival time, as compared to Indometacin (IND, the positive control medicine). It was also found that TNF- α and IL-6 in serum were significantly lower in both groups of BJOE and IND, than in the control group ($p < .01$). Based on the gene expression data, seven and six hub genes of BJOE and IND groups were found in the potential prognostic impacts networks, and three common genes comprising of Nmd3, Bcl2 and Nhp211 were screened. Thus, BJOE could reduce tumour growth and effectively alleviate cancer cachexia, due to inhibition of pro-inflammatory cytokines. Nmd3, Bcl2, Nhp211 may be important drug targets, establishing the role of BJOE in the treatment of lung cancer induced cachexia.

MISCELLANEOUS WORKS

[Rural-Urban Differences in Cancer Incidence and Trends in the United States.](#) Zahnd WE¹, James AS², Jenkins WD³, Izadi SR², Fogleman AJ³, Steward DE⁴, Colditz GA², Brard L⁵. Cancer Epidemiol

Biomarkers Prev. 2017 Jul 27. pii: cebp.0430.2017. doi: 10.1158/1055-9965.EPI-17-0430. [Epub ahead of print]

BACKGROUND: Cancer incidence and mortality rates in the US are declining, but this decrease may not be observed in rural areas where residents are more likely to live in poverty, smoke, and forego cancer screening. However, there is limited research exploring national rural-urban differences in cancer incidence and trends. **METHODS:** We analyzed data from the North American Association of Central Cancer Registries' public use dataset, which includes population-based cancer incidence data from 46 states. We calculated age-adjusted incidence rates, rate ratios, and annual percentage change (APC) for: all cancers combined; selected individual cancers; and cancers associated with tobacco use and human papillomavirus (HPV). Rural-urban comparisons were made by demographic, geographic, and socioeconomic characteristics for 2009 to 2013. Trends were analyzed for 1995 to 2013. **RESULTS:** Combined cancers incidence rates were generally higher in urban populations, except for the South, though the urban decline in incidence rate was greater than in rural populations (10.2% vs. 4.8%, respectively). Rural cancer disparities included higher rates of tobacco associated, HPV associated, lung and bronchus, cervical, and colorectal cancers across most population groups. Further, HPV-associated cancer incidence rates increased in rural areas (APC=0.724, p<0.05) while temporal trends remained stable in urban areas. **CONCLUSIONS:** Cancer rates associated with modifiable risks - tobacco, HPV, and some preventive screening modalities (e.g. colorectal and cervical cancers) - were higher in rural compared to urban populations. **IMPACT:** Population-based, clinical, and/or policy strategies and interventions that address these modifiable risk factors could help reduce cancer disparities experienced in rural populations.

Medicare Beneficiaries With Advanced Lung Cancer Experience Diverse Patterns Of Care From Diagnosis To Death. Schuler MS1, Joyce NR2, Huskamp HA3, Lamont EB4, Hatfield LA5. Health Aff (Millwood). 2017 Jul 1;36(7):1193-1200. doi: 10.1377/hlthaff.2017.0448.

Characterizations of average end-of-life care for people with cancer can obscure important differences in patients' experiences. Using Medicare claims data for 14,257 patients diagnosed with extensive-stage small-cell lung cancer in the period 1995-2009, we used latent class analysis to identify classes of people with different care patterns. We characterized care trajectories from diagnosis to death using time spent in five care settings-home, hospital inpatient unit (acute), hospital intensive care unit (ICU), postacute skilled nursing facility, and hospice-and transitions across these settings. We identified four classes of patients: 66 percent spent the time primarily at home, 11 percent were primarily in hospice, 17 percent were largely in an acute setting, and 6 percent were largely in an ICU. Patients in these classes differed significantly in terms of baseline clinical characteristics, survival length, time spent in hospice, site of death, and spending. The findings show substantial heterogeneity in patterns of care for patients with advanced cancer, which should be accounted for in efforts to improve end-of-life care.