**7500** **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

# START: A phase III study of L-BLP25 cancer immunotherapy for unresectable stage III non-small cell lung cancer.

*Charles Andrew Butts, Mark A. Socinski, Paul Mitchell, Nick Thatcher, Libor Havel, Maciej Jerzy Krzakowski, Sergiusz Nawrocki, Tudor-Eliade Ciuleanu, Lionel Bosquée, Jose Manuel Trigo Perez, Alexander I. Spira, Lise Tremblay, Jan Nyman, Rodryg Ramlau, Christoph Helwig, Martin H. Falk, Frances A. Shepherd; Cross Cancer Institute, Edmonton, AB, Canada; University of Pittsburgh Medical Center, UPMC Cancer Pavilion, Pittsburgh, PA; Joint Austin-Ludwig Oncology Unit, Austin Health, Melbourne, Australia; Christie Hospital NHS Foundation Trust, Manchester, United Kingdom; Klinika pneumologie a hrudní chirurgie 3. LF UK, Praha 8, Czech Republic; The Maria Sklodowska-Curie Institute of Oncology, Warsaw, Poland; Department of Oncology Univeristy of Warmia and Mazury in Olsztyn, Department of Radiation Oncology, ZOZ MSWiA z Warminsko-Mazurskim Centrum Onkologii, Olsztyn, Poland; Ion Chiricuta Cancer Institute, Cluj-Napoca, Romania; Centre Hospitalier du Bois de l'abbaye et de Hesbaye (CHBAH), Seraing, Belgium; Hospital Virgen de la Victoria, Malaga, Spain; Virginia Cancer Specialists, Fairfax, VA; Hôpital Laval, Sainte Foy, QC, Canada; Sahlgrenska University Hospital, Göteborg, Sweden; Poznan University of Medical Sciences, Wielkopolskie Centrum Pulmonologii i Torakochirurgii, Poznan, Poland; Merck KGaA, Darmstadt, Germany; University Health Network-Princess Margaret Hospital, Toronto, ON, Canada*

**Background:** L-BLP25 is a MUC1 antigen specific cancer immunotherapy. We report results from the phase III START study of L-BLP25 in patients (pts) not progressing after primary chemoradiotherapy (CRT) for stage III NSCLC. **Methods:** From Jan 2007 to Nov 2011, 1513 pts with unresectable stage III NSCLC that did not progress after CRT (platinum based chemo and ≥50 Gy) were randomized (2:1; double-blind) to L-BLP25 (806 $\mu$g lipopeptide) or placebo (PBO) SC weekly x 8 then Q6 weeks until disease progression or withdrawal. Cyclophosphamide 300 mg/m$^2$ x 1 or saline was given 3 days prior to first L-BLP25/PBO dose. Primary endpoint was overall survival (OS). **Results:** The primary analysis population (n=1239) was defined prospectively to try to account for a clinical hold by excluding pts randomized 6 months (m) before the hold. Arms were balanced for baseline characteristics. Median age was 61 y; 38.2% had stage IIIA and 61.3% IIIB; 65% had concurrent and 35% sequential CRT. Median OS was 25.6 m with L-BLP25 vs. 22.3 m with PBO (adjusted HR 0.88, 95% CI 0.75-1.03, p=0.123). Secondary endpoints time-to-progression and time-to-symptom-progression support consistency of results: HR 0.87 (95% CI 0.75-1.00, p=0.053) and 0.85 (95% CI 0.73-0.98, p=0.023). In predefined subgroup analyses, pts with concurrent CRT (n=806) had median OS of 30.8 m (L-BLP25) vs. 20.6 m (PBO; HR 0.78, 95% CI 0.64-0.95, p=0.016), while median OS with sequential CRT was 19.4 m (L-BLP25) vs. 24.6 m (PBO; HR 1.12, 95% CI 0.87-1.44, p=0.38; interaction p=0.032, Cox PH model). Sensitivity analyses revealed that there was no OS benefit in pts randomized 6 m before the hold (HR 1.09, CI 0.75-1.56, p=0.663). LEBLP25 was well tolerated with no safety concerns identified and no emergent evidence of immune related adverse events. **Conclusions:** L-BLP25 maintenance therapy in stage III NSCLC was well tolerated, but did not significantly prolong OS. Sensitivity analyses showed a smaller treatment effect due to the clinical hold, suggesting that longer uninterrupted treatment with L-BLP25 is required. Clinically meaningful prolongation of OS was observed in the predefined subgroup of pts with primary concurrent CRT. Clinical trial information: NCT00409188.

**7501** **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

# A randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy with or without cetuximab for stage III non-small cell lung cancer: Results on radiation dose in RTOG 0617.

*Jeffrey D Bradley, Rebecca Paulus, Ritsuko Komaki, Gregory A. Masters, Kenneth Forster, Steven E. Schild, Jeffrey Bogart, Yolanda I. Garces, Samir Narayan, Vivek Kavadi, Lucien Alexander Nedzi, Jeff M. Michalski, Douglas Johnson, Robert Malcolm MacRae, Walter John Curran, Hak Choy, Radiation Therapy Oncology Group; Washington University School of Medicine in St. Louis, St. Louis, MO; Radiation Therapy Oncology Group, Statistical Center, Philadelphia, PA; The University of Texas MD Anderson Cancer Center, Houston, TX; Helen F. Graham Cancer Center, Christiana Care, Newark, DE; Moffitt Cancer Center, Tampa, FL; Mayo Clinic, Scottsdale, AZ; SUNY Upstate Medical University, Syracuse, NY; Mayo Clinic, Rochester, MN; St Joseph Mercy Hosp, Ann Arbor, MI; Texas Oncology, Sugarland, TX; The University of Texas Southwestern Medical Center, Dallas, TX; Florida Radiation Oncology Group, Jacksonville, FL; The Ottawa Hospital, Ottawa, ON, Canada; Emory University, Atlanta, GA*

**Background:** The first objective of RTOG 0617 was to compare the overall survival(OS) of patients(pts) treated with standard-dose(SD)(60Gy) versus high-dose(HD)(74Gy) radiotherapy with concurrent chemotherapy(CT). **Methods:** This Phase III Intergroup trial randomized 464 pts with Stage III NSCLC to the SD(60Gy) vs. HD(74Gy) arms prior to closure of the HD arm. Concurrent CT included weekly paclitaxel(45 mg/m2) and carboplatin(AUC=2). Pts randomized to cetuximab received a 400 mg/m2 loading dose on Day 1 followed by weekly doses of 250 mg/m2. All pts were to receive consolidation CT. We are reporting the final results on radiation dose. **Results:** 464 pts were accrued prior to closure of the HD arm in 6/11, of which 419 were eligible for analysis. Median follow up was 17.2 months. There were 2 and 10 grade 5 treatment-related adverse events(AEs) on the SD and HD arms, respectively. Grade 3+AEs were 74.2% and 78.2% on SD and HD arms, respectively (p=0.34). The median survival times and 18-month OS rates for the SD and HD arms were 28.7 vs 19.5 months, and 66.9% vs 53.9% respectively (p=0.0007). The primary cause of death was lung cancer (72.2% vs 73.5%)(p=0.84). Local failure rates at 18 months were 25.1% vs 34.3% for SD and HD patients, respectively(p=0.03). Local-regional and distant failures at 18 months were 35.3% vs 44%(p=0.04) and 42.4% vs 47.8%(p=0.16) for SD and HD arms, respectively. Factors predictive of less favorable OS on multivariate analysis were higher radiation dose, higher esophagitis/dysphagia grade, greater gross tumor volume, and heart volume >5 Gy. **Conclusions:** In this setting of chemoradiation for locally-advanced Stage III NSCLC, 60 Gy is superior to 74 Gy in terms of OS and local-regional control. The effect of the anti-EGFR antibody (cetuximab) awaits further follow up. This project was supported by RTOG grant U10 CA21661, CCOP grant U10 CA37422, and ATC U24 CA 81647 from the National Cancer Institute (NCI) and Eli Lilly and Company. Clinical trial information: NCT00533949.

# Impact of brachytherapy on local recurrence after sublobar resection: Results from ACOSOG Z4032 (Alliance), a phase III randomized trial for high-risk operable non-small cell lung cancer (NSCLC).

*Hiran Chrishantha Fernando, Rodney Jerome Landreneau, Sumithra J. Mandrekar, Francis C Nichols, Shauna L Hillman, Dwight Earl Heron, Bryan F Meyers, Thomas A. DiPetrillo, David Randolph Jones, Sandra Lynne Starnes, Angelina D. Tan, Benedict Daly, Joe B. Putnam, Alliance for Clinical Trials; Boston Medical Center, Boston University, Boston, MA; University of Pittsburgh Shadyside Medical Center, Pittsburgh, PA; Alliance Statistics and Data Center, Mayo Clinic, Rochester, MN; Mayo Clinic, Rochester, MN; University of Pittsburgh, Pittsburgh, PA; Washington University School of Medicine in St. Louis, St. Louis, MO; Department of Radiation Oncology, Rhode Island Hospital, Providence, RI; University of Virginia, Charlottesville, VA; University of Cincinnati, Cincinnati, OH; Boston University Medical Center, Boston, MA; Vanderbilt University Medical Center, Nashville, TN*

**Background:** Prior studies suggest that adjuvant brachytherapy reduces local recurrence (LR) after sublobar resection (SR) for NSCLC. A multicenter randomized study was undertaken in patients (pts) with stage I NSCLC $\leq$3cm comparing SR to SR with brachytherapy (SRB). **Methods:** High-risk operable patients with NSCLC were randomized to SR or SRB. Brachytherapy involved placement of $I^{125}$ seeds incorporated into Vicryl sutures or into Vicryl mesh placed over the staple line. Wedge or segmental resection was allowed. The primary endpoint was time to local recurrence (LR) defined as recurrence within the primary tumor lobe at the staple line (local progression), away from the staple line or within hilar nodes. The trial was designed to have 90% power to detect a hazard ratio (HR) of 0.315 in favor of the SRB arm using a one-sided $\alpha$ of 0.05 with a sample size of 100 eligible pts per arm. Follow-up CT scans were obtained serially for 36 months. **Results:** 224 pts were randomized; 213 (109 SR,104 SRB) were eligible. Median (range) age was 71 (49-87) yrs; 94 (44%) were male. No differences were found in baseline characteristics. Adverse events, previously reported, were not different between arms. Median (range) follow-up was 4.06 (0.04, 5.0) yrs. There was no difference between arms in time to LR (HR = 0.87; 5% CI: 0.41, 1.86, p=0.72) or to LR or death (LRD) (HR = 0.81, 95% CI: 0.50, 1.32, p=0.40). There was no difference between arms in pattern of LR (table). In subgroups of pts with potentially compromised surgical margin (margin $<$ 1cm; margin:tumor ratio $<$1; positive staple line cytology) SRB did not reduce LR or LRD at 3-yrs. Overall 3-yr survival was similar for SR (71%) and SRB (72%) (p=0.81). **Conclusions:** LR remains a concern after sublobar resection. However, local progression at the staple line was low. This trial demonstrated that adjuvant brachytherapy does not impact oncologic outcomes. Clinical trial information: NCT00107172.

| Arm | Any local recurrence | Local progression at staple line | Lobar recurrence away from staple line | Nodal (N1) recurrence |
|---|---|---|---|---|
| SR* | 14 (12.8%) | 7 (6.4%) | 4 (3.7%) | 2 (1.8%) |
| SRB | 13 (12.5%) | 5 (4.8%) | 4 (3.8%) | 4 (3.8%) |
| Fisher's Exact P value | 0.94 | 0.77 | 1.00 | 0.44 |

*1 missing type of LR.

**7503** **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

# Neoadjuvant chemotherapy with or without preoperative irradiation in stage IIIA/N2 non-small cell lung cancer (NSCLC): A randomized phase III trial by the Swiss Group for Clinical Cancer Research (SAKK trial 16/00).

*Miklos Pless, Roger Stupp, Hans-Beat Ris, Rolf A. Stahel, Walter Weder, Sandra Thierstein, Alexandros Xyrafas, Martin Frueh, Richard Cathomas, Alfred Zippelius, Arnaud Roth, Milorad Bijelovic, Adrian Ochsenbein, Urs R. Meier, Christoph Mamot, Daniel Rauch, Oliver Gautschi, Daniel C. Betticher, Rene-Olivier Mirimanoff, Solange Peters, on behalf of the SAKK Lung Cancer Project Group; Medical Oncology and Tumorcenter Kantonsspital Winterthur, Winterthur, Switzerland; University of Lausanne Hospitals (CHUV), Lausanne, Switzerland; Department of Surgery, Center Hospitalier Universitaire de Vaud, Lausanne, Switzerland; University Hospital Zurich, Zurich, Switzerland; Department of Thoracic Surgery, University Hospital, Zürich, Switzerland; SAKK - Swiss Group for Clinical Cancer Research, Coordinating Center, Berne, Switzerland; Medical Oncology, Kantonsspital St. Gallen, St. Gallen, Switzerland; Department of Medical Oncology, Kantonsspital Graubuenden, Chur, Switzerland; University Hospital Basel, Basel, Switzerland; University Hospital Geneva, Geneva, Switzerland; Department of Thoracic Surgery, Hospital of Pulmonary diseases, NoviSad, Serbia; Department of Medical Oncology, University Hospital, Bern, Switzerland; Department of Radio-Oncology, Kantonsspital, Winterthur, Switzerland; Department of Medical Oncology, Kantonsspital, Aarau, Switzerland; Regionalspital Thun, Thun, Switzerland; Medical Oncology, Kantonsspital Luzern, Lucerne, Switzerland; Hospital of Fribourg, Fribourg, Switzerland; Centre Hospitalier Univ Vaudois, Lausanne, Switzerland; Centre Hospitalier Universitaire de Vaud, Lausanne, Switzerland*

**Background:** For stage III/N2 NSCLC neoadjuvant chemotherapy (NCT) followed by radical surgery is one standard treatment approach. In our previous trial, this strategy led to a median survival of 33 months (Betticher et al. JCO 2003). We now investigated whether the addition of preoperative radiotherapy (RT) would improve outcome. We report the results of a planned interim analysis on data of the first 219 patients (pts). The trial was closed to accrual in December 2012 due to futility after enrollment of 232 of 240 planned pts. **Methods:** Pts with pathologically proven, resectable stage IIIA/N2 NSCLC, performance status 0-1, adequate heart, kidney, liver and bone marrow function were randomized 1:1 to receive 3 cycles of NCT (cisplatin 100 mg/m2 and docetaxel 85 mg/m2 d1, q3weeks) followed by accelerated concomitant boost RT (44 Gy/22 fractions in 3 weeks) or NCT alone, with subsequent surgery for all pts. The primary endpoint was event-free survival (EFS). **Results:** 23 centers included 219 pts. Median age was 60 years. Pts characteristics were well balanced. Toxicity to CT was substantial, but 91% completed 3 cycles of NCT. RT-induced grade 3 esophagitis was seen in 5 pts, grade 3 skin toxicity in 2 pts. One pt in each treatment arm died during NCT, there was one postoperative death (arm NCT alone). The efficacy results are summarized below, all comparisons are statistically non-significant. **Conclusions:** This is the first completed phase III trial to investigate the value of the addition of neoadjuvant radiotherapy to CT and surgery. RT did not improve EFS or survival, nor did it reduce the local failure rate. Nevertheless, the overall survival rates of our neoadjuvant chemotherapy strategy confirm our previous report, and are among the best results reported to date in a multicenter setting. Clinical trial information: NCT00030771.

| | CT - RT - Surgery | CT - Surgery |
|---|---|---|
| **3 cycles of CT given** | 93% (91/98) | 89% (85/96) |
| **RT completed** | 85% (81/95) | Not applicable |
| **Operated** | 82% (80/97) | 81% (76/94) |
| **Complete resection** | 90% (72/80) | 80% (61/76) |
| **Local failure** | 22% (21/97) | 24% (23/94) |
| **EFS, median (95% CI)** | 12.8 mo (8.1 , 22.6) | 11.8 mo (7.1 , 16.1) |
| **Survival, median (95%CI)** | 27.1 mo (18.8 , 42.8) | 26.2 mo (21.0 , 52.1) |

**7504** **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

# Surgery for NSCLC stages T1-3N2M0 having preoperative pathologically verified N2 involvement: A prospective randomized multinational phase III trial by the Nordic Thoracic Oncology Group.

*Jens Benn Sorensen, Jesper Ravn, Han Kristian Pilegaard, Torben Palshof, Stein Sundstrom, Bengt Bergman, Jan Nyrop Jakobsen, Ulf Aasebø, Olfred Hansen, Peter Meldgaard, Bente Thornfeldt Soerensen, Erik Jakobsen, Per Jonsson, Marianne Ryberg, Jarmo Salo, Rune Haverstad, Henrik Riska; Department of Oncology, Finsen Centre, National University Hospital, Copenhagen, Denmark; Department of Thoracic Surgery, National University Hospital, Copenhagen, Denmark; Department of Thoracic Surgery, Skejby Hospital, Aarhus, Denmark; Department of Oncology, Aarhus University Hospital, Aarhus, Denmark; Sct. Olafs Hospital, Trondheim, Norway; Sahlgrenska University Hospital, Göteborg, Sweden; National University Hospital, Copenhagen, Denmark; University of Tromsø, Tromsø, Norway; Department of Oncology, Odense University Hospital, Odense, Denmark; Aarhus University Hospital, Aarhus, Denmark; Vejle Hospital, Vejle, Denmark; Thoracic Surgery, Odense University Hospital, Odense, Denmark; Thoracic Surgery, Lund University Hospital, Lund, Sweden; Herlev University Hospital, Herlev, Denmark; Thoracic Surgery, helsinki University Hospital, Helsinki, Finland; Thoracic Surgery, Haukeland University Hospital, Bergen, Norway; Helsinki University Hospital, Helsinki, Finland*

**Background:** Surgery is not generally considered standard of care in preoperative pathological verified spread to N2 mediastinal lymph nodes in NSCLC. **Methods:** Previously untreated histologically verified NSCLC stages T1-3N2M0 were randomized to reg. A (Paclitaxel 225 mg/m2 + Carboplatin AUC6 day 1 q 3 wks for 3 courses, followed by surgery with ipsilateral mediastinal lymph node sampling followed by radiotherapy 2Gy x 30 fractions, 5F/W) or reg. B: same as A without surgery (sequential chemo-radiotherapy). 406 pts were needed to detect a 10% 5-year survival increase with 80% power and type 1-error of 5%. The study was approved by ethical committees. Pts gave informed consent. **Results:** 170 pts were randomized to A and 171 to B from 1998-2009 when study closed due to concomitant chemo-radiotherapy becoming standard instead of sequential treatment. Median age was 61 years (range 33-76 yrs), 59% were males, 43% had performance status 0. Stages T1N2M0, T2N2M0, and T3N2M0 occurred in 19%, 60%, and 21%, respectively. Adenocarcinoma (ADC) and squamous cell carcinoma occurred in 50% and 29%, respectively. In reg. A, surgery was possible in 132 out of 170 pts (78%), 121 pts (71%) had complete resection while 11 pts (6%) had incomplete resection. Pathological-surgical stage pT0 occurred in 4%. Median progression free survival (PFS), OS and 5-years survival rate were 10 mths, 17 mths, and 20% for A (+ surgery) compared to 8 mths ($p=0.144$), 15 mths ($p=0.172$), and 16% ($p=0.310$) for B, respectively. ADC pts had better OS in A than in B (HR 0.60; $p=0.002$), and 5-year survivals 20% and 7% ($p=0.017$) respectively. Stage T1N2 had better OS in A than in B (HR 0.47; $p=0.010$), 5-year survivals 36% and 17%. **Conclusions:** There were no statistical overall significant advantage for surgery in addition to chemo-radiotherapy (A) compared to chemo-radiotherapy alone (B) but ADC pts and pts with T1N2 had significantly improved OS and 5-year survival rates in the surgery arm. Current standard treatment for T1-3N2M0 NSCLC is concomitant chemo-radiotherapy which was not used in this study, hence conclusions should be further tested with use of such treatment as reference arm.

**7505** **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

# Results of the prospective, randomized, and customized NSCLC adjuvant phase II trial (IFCT-0801, TASTE trial) from the French Collaborative Intergroup.

*Jean-Charles Soria, Fabrice Barlesi, Benjamin Besse, Julien Mazieres, Patrick Merle, Jacques Cadranel, Clarisse Audigier-Valette, Denis Moro-Sibilot, Laure Gautier-Felizot, Francois Goupil, Patrick Renault, Elisabeth A. Quoix, Pierre Jean Souquet, Anne Madroszyk, Romain Corre, David Pérol, Laurence Baudrin, Franck Morin, Gerard Zalcman, Marie Wislez, Intergroupe Francophone de Cancérologie Thoracique (IFCT); Institut Gustave Roussy, INSERM U981, Villejuif, France; Aix Marseille University, Assistance Publique Hôpitaux de Marseille, Marseille, France; Institut Gustave Roussy, Villejuif, France; Hôpital Larrey CHU Toulouse, Toulouse, France; Centre Hospitalier Universitaire Clermont-Ferrand, Clermont-Ferrand, France; Service de Pneumologie and GRC-04 Theranoscan, Pierre et Marie Curie Université, Hôpital Tenon, Paris, France; Service de Pneumologie - CH Toulon, Toulon, France; Thoracic Oncology unit CHU Grenoble, Inserm U823, Grenoble, France; Centre Hospitalier Dax, Dax, France; Centre Hospitalier Le Mans, Le Mans, France; Centre Hospitalier Pau, Pau, France; Hôpitaux Universitaires de Strasbourg, Strasbourg, France; Centre Hospitalier Lyon-Sud, Pierre-Bénite, France; Institut Paoli Calmettes, Marseille, France; Rennes University Hospital, Rennes, France; Centre Léon Bérard, Lyon, France; Intergroupe Francophone de Cancérologie Thoracique, Paris, France; Caen University Hospital, Caen, France; Hôpital Tenon, AP-HP and Faculté de Médecine Pierre et Marie Curie, Université Paris VI, Paris, France*

**Background:** Surgical resection followed by adjuvant platinum-based CT is the standard of care in stages II and III of NSCLC. ERCC1 is considered as a molecular determinant of benefit to platin-based CT and is an independent good prognostic marker in resected NSCLC. EGFR mutations predict for erlotinib efficacy. We included ERCC1 IHC status and EGFR mutational status in a prospective randomized multicentric phase II/III customized adjuvant CT trial. **Methods:** Completely resected patients (pts) with non-squamous tumors, mediastinal lymph node dissection and pathological stage IIA, IIB or IIIA (N2 excluded) ($6^{th}$ TNM edition) were randomized either to a control arm (A) or a customized arm (B). Surgical blocks were centralized for biomarkers analyses. The control arm encompassed 4 cycles of standard dose cisplatin-pemetrexed (CP). In the experimental arm, EGFR mutated pts received erlotinib 150 mg for one year. ERCC1 negative pts received four cycles of CP. ERCC1 positive pts were closely monitored. The Fleming's single stage phase II primary endpoint was feasibility (ie % of patients able to start therapy within 2 months of surgery and for which the biomarker's status was readily available) ($H_0$ 64%, $H_1$80%, $\alpha$ 5% and $\beta$ 95%). **Results:** 150 pts were randomized between May 2009 and July 2012, 74 in arm A and 76 in arm B. Most pts were male (61%), $\leq$ 60 years (51%), and smokers (91%). Pathological stage was IIA in 69 pt, IIB in 48 pt and IIIA in 32 pt. ERCC1 was positive in 38 pts (19 in each arm), EGFR mutation was identified in 10 pts (3 in arm A, 7 in arm B). In arm A, all pts received CP. In arm B, 7 pts received erlotinib, 53 pts received CP and 16 were followed-up. The median exposure time to erlotinib was 276 days (10-365). Out of 127 pts allocated to CP, 82% received the expected 4 cycles with a very good tolerability profile (no febrile neutropenia). The success rate was 80% (120 out of 150 pts). **Conclusions:** This adjuvant trial met its primary end point for its phase II component, demonstrating the feasibility of a national biology-driven trial in the adjuvant setting. Nevertheless the phase III was canceled due to the unexpected unreliability of the ERCC1 IHC read-out. Clinical trial information: NCT00775385.

**7506** **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

# Chemotherapy with or without maintenance sunitinib for untreated extensive-stage small cell lung cancer: A randomized, placebo controlled phase II study CALGB 30504 (ALLIANCE).

*Neal Ready, Herbert Pang, Lin Gu, Gregory Alan Otterson, Sachdev P. Thomas, Antonius Arthur Miller, Maria Quintos Baggstrom, Gregory A. Masters, Stephen L. Graziano, Jeffrey Crawford, Jeffrey Bogart, Everett E. Vokes; Duke University Medical Center, Durham, NC; Duke University, Durham, NC; Cancer and Leukemia Group B Statistical Center, Durham, NC; Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, OH; Illinois Cancer Care, Peoria, IL; Wake Forest University, Winston-Salem, NC; Washington University School of Medicine in St. Louis, St. Louis, MO; Helen F. Graham Cancer Center, Christiana Care, Newark, DE; SUNY Upstate Medical University, Syracuse, NY; The University of Chicago Medicine and Biological Sciences, Chicago, IL*

**Background:** Sunitinib (S) inhibits small cell lung cancer (SCLC) targets VEGFR1-3, PDGFR, and KIT. We tested whether giving S after chemotherapy (C) for extensive stage SCLC improves progression free survival (PFS). **Methods:** CALGB 30504 was a randomized, double-blind, placebo (P) controlled phase II study for untreated SCLC, performance status 0-2, adequate organ function, and no S risk factors: bleeding, hypertension, or brain metastases. Enrollment was prior to C: cisplatin 80 mg/m$^2$ or carboplatin AUC5 day 1 plus etoposide 100 mg/m$^2$days 1-3 every 21 days 4-6 cycles. Patients without progression after C were stratified cisplatin vs carboplatin, and 4-5 vs 6 cycles C, and randomized 1:1 to P or S 37.5 mg daily until progression assessed every 6 weeks. Prophylactic cranial irradiation was offered to responders (CR or PR) to start about 4-6 weeks after C. S was held during radiation. Crossover from P to S was allowed at progression. Primary endpoint was PFS (from time of randomization) for maintenance (M) P vs S using a 1-sided log rank test with a=0.15; 80 randomized and treated patients provide »89% power to detect a hazard ratio (HR) of 1.67. **Results:** Between 5/09 and 12/11, 144 enrolled and 138 received C. Ninety five were randomized to P vs S; 10 did not receive M due to progression, refusal, and AE (5 each arm). Eighty five received M, 41 P and 44 S. Demographics were balanced. M toxicities grade $>$ 3 and incidence $>$ 5% included (%): grade 3 (S: fatigue 19, neutrophils 10, leukocytes 7, platelets 7) (P: fatigue 5); grade 4 (S: 1case GI hemorrhage, 1case lipase) P zero; grade 5 zero both arms. Efficacy (90% CI): PFS on maintenance after C was P 2.3 mo (CI: 1.7-2.6) and S 3.8 mo (2.7-4.4) (HR=1.54, CI 1.03-2.32, p=0.04). Overall survival (OS) was P 6.7 mo (5.5-9.5) and S 8.8 mo (8.0-9.8) (HR=1.10, CI 0.71-1.70, p=0.36). At progression on P, 17 received S and among 14 evaluable 10 (71%) had stable disease receiving 2-9 cycles S. **Conclusions:** The primary objective was met showing improved PFS for maintenance S. There was a non-significant trend toward improved OS despite crossover design. S was well tolerated. Further study of sunitinib after chemotherapy for SCLC is justified. Clinical trial information: NCT00453154.

**7507 Poster Discussion Session (Board #1), Sat, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

# Result of phase III trial of amrubicin/cisplatin versus etoposide/cisplatin as first-line treatment for extensive small cell lung cancer.

*Yan Sun, Ying Cheng, Xuezhi Hao, Jie Wang, Chengping Hu, Baohui Han, Xiaoqing Liu, Li Zhang, Huiping Wan, Zhongjun Xia, Yunpeng Liu, Wei Li, Mei Hou, Helong Zhang, Qingyu Xiu, Yunzhong Zhu, Jifeng Feng, Shukui Qin; Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China; Jilin Provincial Cancer Hospital, Changchun, China; Cancer Hospital of Chinese Academy of Medical Science, Beijing, China; Beijing Cancer Hospital, Beijing, China; Xiangya Hospital Central-South University, Changsha, China; Shandong Provincial Chest Hospital, Shanghai, China; 307 Hospital of the Academy of Military Medical Sciences, Cancer Center, Beijing, China; Perking Union Medical Hospital, Beijing, China; Jiangxi Provincial People's Hospital, Nanchang, China; Sun Yat-sen University Cancer Center, Guangzhou, China; Department of Medical Oncology, the First Hospital of Chinese Medical University, Shenyang, China; Jilin University Affiliated First Hospital, Changchun, China; West China Hospital, Sichuan University, Chengdu, China; Tangdu Hospital, 4th Military Medical University, Xi'an, China; Shanghai Changzheng Hospital, Shanghai, China; Beijing Chest Hospital, Capital Medical Hospital, Beijing, China; Department of Medical Oncology, Nanjing Medical University affiliated Cancer Hospital, Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research, Nanjing, China; PLA Cancer Center of Nanjing Bayi Hospital, Nanjing, China*

**Background:** Etoposide combined with cisplatin (EP) has been the first-line chemotherapy regimen for small cell lung cancer (SCLC) for >20 years; however, a more effective regimen has been recommended by many clinical oncologists. Thus, we here present our preliminary results of a phase III clinical trial of the novel drug amrubicin in combination with cisplatin (AP) in comparison to EP in patients with previously untreated extensive SCLC (ED-SCLC). **Methods:** A total of 299 previously untreated ED-SCLC patients were randomized (ratio, 1:1) into two treatment groups: (1) the AP group (n = 149): 4–6 cycles of amrubicin (40 mg/m$^2$/day on days 1–3) and cisplatin (60 mg/m$^2$/day on day 1) and (2) the EP group (n = 150): 4–6 cycles of etoposide (100 mg/m$^2$/day on days 1–3) and cisplatin (80 mg/m$^2$/day on day 1 every 21 days). Patients were evaluated for therapy response and electrocardiography results every 2 cycles. The primary endpoint was overall survival (OS), and the secondary endpoints were progression-free survival (PFS), overall response rate (ORR), and general safety. **Results:** Baseline characteristics were similar among the two groups. For AP and EP groups, the median OS was 11.79 and 10.28 months, the median PFS was 7.13 and 6.37 months, and ORR was 69.8% and 57.3%, respectively. The most frequent adverse events (≥grade 3) in AP and EP groups were bone marrow failure (23.5% and 21.3%, respectively), neutropenia (54.4% and 44.0%, respectively), and leukopenia (34.9% and 19.3%, respectively). **Conclusions:** Our phase III trial demonstrated that for previously untreated ED-SCLC patients, AP therapy was not inferior to EP therapy in terms of OS and offered predictable and manageable toxicities. Clinical trial information: NCT00660504.

**7508 Poster Discussion Session (Board #2), Sat, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

# Three-arm randomized phase II study of cisplatin and etoposide (CE) versus CE with either vismodegib (V) or cixutumumab (Cx) for patients with extensive stage-small cell lung cancer (ES-SCLC) (ECOG 1508).

*Chandra Prakash Belani, Suzanne Eleanor Dahlberg, Charles M. Rudin, Martin Fleisher, Helen X. Chen, Naoko Takebe, Suresh S Ramalingam, Joan H. Schiller; Penn State Hershey Cancer Institute, Hershey, PA; Dana-Farber Cancer Institute, Boston, MA; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Memorial Sloan-Kettering Cancer Center, New York, NY; CTEP National Cancer Institute, Bethesda, MD; Investigational Drug Branch, Cancer Therapy Evaluation Program, Rockville, MD; The Winship Cancer Institute of Emory University, Atlanta, GA; The University of Texas Southwestern Medical Center, Dallas, TX*

**Background:** Targeted inhibition of the Hedgehog (HH) pathway by V & Insulin-like Growth Factor type-1 Receptor (IGF-1R) by Cx enhances efficacy of chemotherapy, and also demonstrates activity against the tumor cell fraction responsible for disease recurrence in SCLC. **Methods:** Patients (Pts) with newly diagnosed ES-SCLC with measurable disease, ECOG PS 0-1 were randomized to receive (four 21-day cycles) CE alone [(C 75 mg/m$^2$ D1 & E 100 mg/m$^2$ D1-3) Arm A] or in combination with either V [(150 mg/day PO) Arm B] or Cx [(6mg/kg weekly IV) Arm C]. Pts with responsive or stable disease on Arms B & C were continued on V or Cx respectively until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS), stratified on gender. Circulating tumor cells (CTCs) were isolated/enumerated by Veridex Cell Search Platform at baseline, after 1or 2 cycles of chemotherapy, at completion of 4 cycles & 3 months (m). thereafter for correlation with efficacy parameters. The study was designed to detect a PFS HR of 0.58 with 90% power & an overall one-sided type I error rate of 0.10 for each of the comparisons of the V and Cx arms to CE alone. **Results:** 155 eligible pts were treated; 136 have died & 149 have experienced a PFS event. Pt. demographics & disease characteristics are well-balanced between the three arms except higher rate of PS 0 on Arm B ($p=0.03$). The median PFS on Arms A, B & C are 4.7, 4.4 & 4.6 m, the median OS 9.1, 9.8 & 10.1 m, & the RR are 43%, 52% & 49% respectively. None of the comparisons of these outcomes are statistically significant. PFS HR for V+CE *vs.* CE: 1.32, $p=0.21$, and for Cx+CE *vs.* CE: 1.12, $p=0.58$. The median OS among those with low CTC count ($\leq$100 per 7.5ml) at baseline is 10.7 m *vs.* 7.2 m for those with high CTC count [HR1.70, $p=0.01$]. Toxicities in all three arms are as expected with the combination of CE alone. **Conclusions:** There is no significant improvement in PFS or OS with the addition of either V or Cx to CE *vs.*CE alone in pts with ED-SCLC. Low baseline CTC count is associated with improved OS, suggesting its role as a prognostic biomarker in SCLC. Clinical trial information: NCT00887159.

**7509 Poster Discussion Session (Board #3), Sat, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

# A randomized double-blind phase II study of the Seneca Valley virus (NTX-010) versus placebo for patients with extensive stage SCLC (ES-SCLC) who were stable or responding after at least four cycles of platinum-based chemotherapy: Alliance (NCCTG) N0923 study.

*Julian R. Molina, Sumithra J. Mandrekar, Grace K. Dy, Marie-Christine Aubry, Katie L Allen Ziegler, Shaker R. Dakhil, Bradley A. Sachs, Jorge J. Nieva, Steven E. Schild, Kevin Burroughs, Anthony Williams, Charles M. Rudin, Alex A. Adjei; Mayo Clinic, Rochester, MN; Mayo Clinic and NCCTG, Rochester, MN; Roswell Park Cancer Institute, Buffalo, NY; Cancer Center of Kansas, Wichita, KS; Toledo cancer Center, Maumee, OH; Billings Clinic Cancer Center, Billings, MT; Mayo Clinic, Scottsdale, AZ; Neotropix Inc, Chester Springs, PA; Neotropix Inc, Lexington, MA; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

**Background:** NTX-010 is a naturally occurring replication-competent picornavirus with potent and selective tropism for SCLC tumor cells expressing neuroendocrine markers. A phase I study of NTX-010 showed evidence of antitumor activity in patients with SCLC. **Methods:** ES-SCLC patients (pts) with SD, PR or CR after at least 4 cycles of platinum-based chemotherapy were pre-registered to confirm diagnosis of SCLC with $>$ 1 neuroendocrine marker by a central pathology review. Eligible pts were.randomized 1:1 to placebo (B) or NTX-010 (A). NTX-010 or placebo was administered intravenously as a 1-hour infusion in 100 mL normal saline as a single dose of 1 $x10^{11}$vp/kg. Viral studies to determine distribution, clearance of the virus and the presence of neutralizing antibodies were done. The primary goal of this trial was to compare the progression-free survival (PFS) of arm A to B based on a sample size of 45 patients per arm to detect an improvement in median PFS from 3 to 5 months (m). A pre-planned interim futility analysis was done after 40 PFS events, and reported here. **Results:** The trial is permanently closed to accrual. One-hundred and twenty pts were pre-registered, of whom 58 were randomized. Baseline age, gender, ECOG performance status, and histology were balanced between arms. Median age was 63 (range: 44 - 82). 31% of pts had a PS of 0 and 69% of 1. Grade 4 adverse events were seen in 3 (12.5%) patients in arm A and none in arm B. Based on the interim futility analysis, PFS was 1.7 m (95% CI: 1.3-3.1) for arm A and 1.7 m (95% CI: 1.4-4.3) for arm B. Pts with viral RNA at 7 (7 pts) and 14 (6 pts) days had worse PFS compared to those with no detectable levels within arm A (1.0 vs 1.6 m, p=0.02; 0.9 vs. 1.2 m, p=0.06). Median follow-up in pts is 6.1 m. The 3-month OS estimates are 83% (95% CI: 69%-100%) and 85% (70%-100%) for arms A and B respectively. **Conclusions:** This phase II study showed no benefit in PFS for ES-SCLC patients receiving NTX-010. Pts with detectable virus at 7 and 14 days had worse PFS. Clinical trial information: NCT01017601.

**7510 Poster Discussion Session (Board #4), Sat, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

# Multitrial evaluation of progression-free survival (PFS) as a surrogate endpoint for overall survival (OS) in previously untreated extensive-stage small cell lung cancer (ES-SCLC): An Alliance-led analysis.

*Nathan R. Foster, Lindsay A. Renfro, Steven E. Schild, Mary Weber Redman, Xiaofei F. Wang, Suzanne Eleanor Dahlberg, Keyue Ding, Penelope Ann Bradbury, Suresh S. Ramalingam, David R. Gandara, Everett E. Vokes, Alex A. Adjei, Sumithra J. Mandrekar; Alliance Statistics and Data Center, Mayo Clinic, Rochester, MN; Mayo Clinic, Rochester, MN; Mayo Clinic, Scottsdale, AZ; Fred Hutchinson Cancer Research Center, Seattle, WA; Alliance Statistics and Data Center, Duke University, Durham, NC; Dana-Farber Cancer Institute, Boston, MA; NCIC Clinical Trials Group, Queen's University, Kingston, ON, Canada; The Winship Cancer Institute of Emory University, Atlanta, GA; University of California Davis Comprehensive Cancer Center, Sacramento, CA; The University of Chicago Medicine and Biological Sciences, Chicago, IL; Roswell Park Cancer Institute, Buffalo, NY*

**Background:** We previously demonstrated that PFS may be a candidate surrogate endpoint for OS in ES-SCLC using data from 3 randomized trials (Foster, Cancer 2011). Here, we sought to formally assess the patient- and trial-level surrogacy of PFS using data from 9 additional randomized phase II and III trials conducted by the NCI-funded cancer cooperative groups since 1986. **Methods:** Individual patient data from all 12 trials (3178 patients: 9 phase III and 3 phase II) were pooled. OS was the primary endpoint in all phase III trials; 3 phase III and 1 phase II trial were positive per protocol. Patient-level surrogacy (Kendall's tau) was assessed using the Clayton copula bivariate survival model. Trial-level surrogacy was assessed via association of the log hazard ratios on OS and PFS across trials, including: weighted (by trial size) least squares regression of Cox model effects ($R^2$ WLS) and weighted (by trial size) correlation of the copula effects ($R^2$ Copula). One trial had 4 treatment arms thus 14 total two-arm comparisons were made. **Results:** With a median follow-up of 41.8 months in the 106 patients still alive, the median OS and PFS across trials were 9.7 months (95% CI: 9.5, 9.9) and 5.7 months (95% CI: 5.5, 5.8), respectively. There were 3120 PFS events in total (2564 disease progressions and 556 deaths without progression). The median time from progression to death was 4.1 months (95% CI: 3.9, 4.3). PFS showed modest association with OS at the patient-level (tau= 0.56) and at the trial-level ($R^2$ WLS = 0.58; $R^2$ Copula (standard error) = 0.55 (0.29)). The 95% CIs for the predicted HR for OS given observed HR on PFS under a weighted leave-one-out prediction always included the observed HR for OS; however such intervals were wide, suggesting uncertainty on the practical use of PFS as a surrogate for OS in this setting. **Conclusions:** PFS failed to demonstrate surrogacy for OS in ES-SCLC based on this large pooled analysis. Given that the difference in the median PFS and OS is less than 6 months, we recommend using OS as the primary endpoint in phase III trials of previously untreated ES-SCLC.

**7511 Poster Discussion Session (Board #5), Sat, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

# Relevance of platinum (plat) sensitivity status in previously treated extensive-stage small cell lung cancer (ES-SCLC) in the modern era: A patient level analysis of SWOG trials.

*Primo Lara, James Moon, Mary Weber Redman, Karen Kelly, Jeffrey Warren Allen, Barbara Jennifer Gitlitz, Philip C. Mack, David R. Gandara; Division of Hematology and Oncology, UC Davis Comprehensive Cancer Center, Sacramento, CA; Southwest Oncology Group Statistical Center, Seattle, WA; Fred Hutchinson Cancer Research Center, Seattle, WA; Humboldt Medical Specialists, Hematology/Oncology, Eureka, CA; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; University of California Davis Comprehensive Cancer Center, Sacramento, CA; University of California, Davis Comprehensive Cancer Center, Sacramento, CA*

**Background:** ES-SCLC patients (pts) with progressive disease (PD) following plat-based chemo are traditionally categorized as plat-sensitive (PD >/= 90 days from last plat dose) or refractory (PD < 90 days). This practice arose from seminal observations in the early 1980s of worse survival in refractory pts. Subsequent trial designs accounted for plat-sensitivity status, resulting in higher sample sizes and increased resource use. Whether this relationship holds in the modern era is less clear. **Methods:** Updated data from recent SWOG trials in 2nd and/or 3rd line ES-SCLC (S0802: topotecan + aflibercept: S0435: sorafenib; and S0327: PS-341) were pooled. Accrual goals were specified for sensitive and refractory in each trial. Hazard ratios (HRs) for overall (OS) and progression-free survival (PFS) were calculated using Cox Proportional Hazard (PH) models [unadjusted and adjusted]. **Results:** Of 329 pts, 151 were classified as sensitive, 178 refractory; median age = 63 years; males = 52%; PS 1 = 67%; weight loss >5% = 28%; > 2 prior chemo = 16%; and elevated LDH = 43%. HRs from unadjusted Cox models for OS for refractory vs. sensitive were 1.0 (95% CI 0.81-1.25, p=0.98) and 1.24 (95% CI 0.99, 1.57; p=0.06). Cox PH models adjusted for baseline prognostic factors for PFS and OS are shown. **Conclusions:** In this large database analysis, plat-sensitivity status is no longer a significant independent variable for OS or PFS. Baseline PS, sex, LDH, and weight loss remain independent OS variables. These data have critical implications in the design of future trials in ES-SCLC.

| | PFS | | | | OS | | | |
|---|---|---|---|---|---|---|---|---|
| Variable | HR | 95% CI | | P value | HR | 95% CI | | P value |
| Plat-refractory | 1.11 | 0.83 | 1.49 | 0.49 | 1.25 | 0.93 | 1.69 | 0.14 |
| Age ≥ 65 | 1.07 | 0.8 | 1.43 | 0.63 | 1.06 | 0.78 | 1.43 | 0.72 |
| PS 1 | 1.33 | 0.99 | 1.77 | 0.06 | 1.43 | 1.05 | 1.94 | 0.02 |
| Current smoker (vs. former/never) | 0.90 | 0.67 | 1.22 | 0.51 | 1.05 | 0.77 | 1.43 | 0.77 |
| Male sex | 1.14 | 0.87 | 1.51 | 0.35 | 1.36 | 1.01 | 1.83 | 0.04 |
| Elevated LDH | 1.83 | 1.37 | 2.43 | <.0001 | 2.04 | 1.52 | 2.76 | <.0001 |
| >= 2 prior regimens (vs. only 1) | 0.87 | 0.51 | 1.47 | 0.59 | 0.79 | 0.44 | 1.4 | 0.42 |
| Weight loss ≥ 5% | 1.09 | 0.8 | 1.48 | 0.59 | 1.53 | 1.11 | 2.12 | 0.01 |
| Prior radiation | 1.22 | 0.87 | 1.70 | 0.26 | 0.89 | 0.64 | 1.25 | 0.51 |
| S0802 (vs. S0435 or S0327) | 1.82 | 1.29 | 2.55 | 0.001 | 1.28 | 0.90 | 1.81 | 0.17 |

**7512 Poster Discussion Session (Board #6), Sat, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

## Comprehensive genomic analysis of small cell lung cancer in Asian patients.

*Shigeki Umemura, Koichi Goto, Sachiyo Mimaki, Genichiro Ishii, Hironobu Ohmatsu, Seiji Niho, Kiyotaka Yoh, Shingo Matsumoto, Akiko Takahashi, Kanji Nagai, Yuichiro Ohe, Hiroyasu Esumi, Katsuya Tsuchihara; National Cancer Center Hospital East, Kashiwa, Japan; Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan; Division of Translational Research, Research Center for Innovative Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan; Pathology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, Kashiwa, Japan; Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan*

**Background:** Small cell lung cancer (SCLC) is an aggressive disease with poor prognosis. There is an urgent need for detecting well-defined therapeutic targets, however, little is known about the molecular events causing SCLC. This report describes findings from the integrated genomic analyses of 47 human SCLC samples in Asian population. **Methods:** We performed whole exome sequencing and copy number analysis on surgically resected tumor and matched normal samples from previously untreated Japanese patients with SCLC. Frequency of driver gene alterations were compared with previous two reports intended for non-Asian population (Peifer et al. Nature Gen 2012 and Rudin et al. Nature Gen 2012). **Results:** The demographics of 47 patients were as follows: median age 67 years (range: 42-86); female 8 (17%); history of smoking 47 (100%) and pathological stage I/II/III/IV=26/12/8/1. The average of protein-altering mutations was 193 (range: 51-633, standard deviation: 129). Genomic alterations including copy number amplifications and deletions in at least one of three frequently occurred driver genes, TP53, RB1, and MYC family, were detected in 93.6% of tumors. Mutation frequencies were 76.6%, 42.6%, and 12.8% for TP53, RB1, and MYC family respectively, which were equivalent to the previous reports. Recently reported candidate new driver genes were also recurrently confirmed in the present study: PTEN 4.3%, CREBBP 4.3%, EP300 4.3%, SLIT2 4.3%, MLL 4.3%, CCNE1 8.5% and SOX2 2.1%. Many of them were potentially targetable with currently available drugs. **Conclusions:** The genomic landscape of SCLC was not significantly different between Asian and non-Asian population. We perform additional targeted re-sequencing on biopsy samples obtained from metastatic SCLC to further assess the relevance of our results.

**7513 Poster Discussion Session (Board #7), Sat, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

## Custom (Molecular Profiling and Targeted Therapy for Advanced Non-Small Cell Lung Cancer, Small Cell Lung Cancer, and Thymic Malignancies) trial.

*Giuseppe Giaccone, Ariel Lopez-Chavez, Anish Thomas, Arun Rajan, Mark Raffeld, Regan M. Duffy, Betsy Morrow, Yisong Wang, Corey Allan Carter, Udayan Guha, Keith Killian, Christopher Y. Lau, Zied Abdullaev, Liqiang Xi, Svetlana Pack, Paul S. Meltzer, Christopher L. Corless, Carol Beadling, Andrea Warrick, Eva Szabo; National Cancer Institute, Bethesda, MD; Oregon Health & Science University, Portland, OR; Molecular Diagnostics Core Laboratory, CCR, NCI, NIH, Bethesda, MD; Knight Diagnostic Laboratories, Oregon Health & Science University, Portland, OR*

**Background:** CUSTOM is the first completed prospective clinical trial using molecular selection for treatment assignments into multiple targeted therapy arms and in multiple cancer histological subtypes concurrently. **Methods:** All patients with advanced NSCLC, SCLC or TM were eligible to participate in the study. Oncogenic mutations, amplifications or translocations in 12 genes detected in CLIA-certified laboratories were used to assign patients to 1 of 5 biomarker/treatment groups per histological subtype: *EGFR* mutations/erlotinib; *KRAS*, *NRAS*, *HRAS* or *BRAF* mutations/AZD6244; *PIK3CA*, *AKT* or *PTEN* mutations/MK2206; *ERBB2* mutations or amplifications/lapatinib; and *KIT* or *PDGFRA* mutations/sunitinib; or to standard-of-care therapy. For each arm, the study was conducted as an optimal two-stage phase II trial in favor of a response rate of 40% or more. **Results:** 668 patients were enrolled at two academic institutions. The most frequent genetic alterations in NSCLC were *KRAS* and *EGFR* mutations (25.2 and 19.7% respectively), *ALK* rearrangements 7.8%, *HER2* amplifications 2.7% and mutations in *PIK3CA* 2.5%, *BRAF* 1.9%, *HRAS* 1.5%, *ERBB2* 1.7%, *AKT1* 0.4%, and *NRAS* 0.7%. *PTEN* mutation analysis was only feasible in 13 patients with NSCLC of which 3 were positive (23%). The most frequent genetic alterations in SCLC were mutations in *PIK3CA* 6.5%, *ERBB2* amplifications 5.3% and mutations in *HRAS* 3.4%, *AKT1* 2.2%, *BRAF* 2% and *KRAS* 2%. The most frequent genetic alterations in TMs were *HER2* amplifications 7.7% and mutations in *HRAS* 4.7%, *PIK3CA* 1.4% and *EGFR* 1.4%. Only 6.2% (n=42) of patients met criteria for enrollment into the treatment arms of the study. Efficacy analyses including response rates will be presented. **Conclusions:** CUSTOM is the first completed prospective clinical trial demonstrating the feasibility of conducting efficacy analyses of multiple biomarker-matched therapies in multiple cancer histological subtypes concurrently. CUSTOM is also the largest prospective molecular profiling study of patients with SCLC and TMs. Clinical trial information: NCT01306045.

**7514** **Poster Discussion Session (Board #8), Sat, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

# The European Thoracic Oncology Platform Lungscape project: Clinical outcome data as a basis for molecular correlations in resected non-small cell lung cancer.

*Solange Peters, Walter Weder, Peter Meldgaard, Kenneth John O'Byrne, Ania Wrona, Christophe Dooms, Javier Hernandez-Losa, Antonio Marchetti, Marianne Nicolson, Qiang Tan, Egbert F. Smit, Anne-Marie C. Dingemans, Spasenija Savic, Fiona Helen Blackhall, Paul Baas, Eloisa Jantus-Lewintre, Keith M Kerr, Urania Dafni, Rafael Rosell, Rolf A. Stahel, European Thoracic Oncology Platform (ETOP); Centre Hospitalier Universitaire de Vaud, Lausanne, Switzerland; Department of Thoracic Surgery, University Hospital, Zürich, Switzerland; Aarhus University Hospital, Aarhus, Denmark; Department of Medical Oncology, St. James's Hospital, Dublin, Ireland; Medical University of Gdańsk, Gdańsk, Poland; University Hospital Leuven, Leuven, Belgium; Pathology Department, Vall d'Hebron University Hospital, Barcelona, Spain; Center of Predictive Molecular Medicine, SS. Annunziata Hospital, University G. D'Annunzio, Chieti, Italy; Aberdeen Royal Infirmary, Aberdeen, United Kingdom; Shandong Provincial Chest Hospital, Shanghai, China; VU University Medical Center, Amsterdam, Netherlands; University Hospital Maastricht, Maastricht, Netherlands; Institute for Pathology, University Hospital Basel, Basel, Switzerland; The Christie National Health Services Foundation Trust, Manchester, United Kingdom; Netherlands Cancer Institute, Amsterdam, Netherlands; Fundación para la Investigación del Hospital General Universitario de Valencia, Valencia, Spain; Frontier Science Foundation-Hellas & University of Athens, Athens, Greece; Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Pangaea Biotech, Cancer Therapeutics Innovation Group, USP Institut Universitari Dexeus, Barcelona, Spain; University Hospital Zurich, Zurich, Switzerland*

**Background:** Lungscape allowed building the largest virtual biobank of radically resected NSCLC with comprehensive annotated clinical data, with the aims of expediting knowledge on biomarkers and facilitating translation of research to the clinic. **Methods:** 2,403 stage I-III radically resected NSCLC cases from 15 sites with mandatory comprehensive clinical annotations including at least 2 years of follow-up have been collected retrospectively. A systematic data review of every single case was performed. Relapse-free survival (RFS), time to relapse (TTR) and overall survival (OS) have been analyzed overall and by subgroups. **Results:** Median age of the cohort is 66 years, with 35% women, and respectively 14%, 32% and 49% never, current and former smokers. Histological types included 52% adenocarcinoma, 40% squamous cell carcinoma, and 4.5% large cell carcinoma and some rarer/mixed subtypes. As shown in the Table, median RFS, TTR and OS differ significantly by stage ($p<0.001$). Stage remained a significant predictor for outcome in the multivariate Cox models in the presence of other potential prognostic factors. **Conclusions:** This is the first report on the full Lungscape series based on 7th TNM classification on OS, RFS and TTR across clinical and pathological subgroups. This complete clinical dataset, in particular the information on TTR will be invaluable to investigate the impact of molecular characteristics on outcome, allowing refining TNM staging using biomarkers. Ultimately Lungscape will provide a platform for marker-driven trials of novel therapeutics.

| | | | RFS p<0.001 | | TTR p<0.001 | | OS p<0.001 | |
|---|---|---|---|---|---|---|---|---|
| | | N | 5 year (95% CI) | Median > (months) | 5 year | Median | 5 year | Median |
| | | 2403 | 47.3 (45.1, 49.4) | 52.4 | 58.1 (55.9, 60.2) | 108 | 53.1 (51.0, 55.2) | 68.3 |
| Stage | Ia | 549 | 63.0 (58.4, 67.3) | 99.2 | 74.1 (69.6, 78.0) | NR* | 69.5 (65.0, 73.5) | NR* |
| | Ib | 634 | 57.6 (53.4, 61.5) | 84.7 | 69.7 (65.6, 73.4) | NR* | 63.5 (59.4, 67.3) | 128 |
| | IIa | 412 | 47.9 (42.7, 53.0) | 54.2 | 58.2 (52.8, 63.2) | 103 | 51.8 (46.4, 56.9) | 64.1 |
| | IIb | 283 | 43.2 (37.1, 49.1) | 35.9 | 52.8 (46.3, 58.8) | NR* | 47.3 (41.0, 53.2) | 48.7 |
| | IIIa | 487 | 20.5 (16.7, 24.5) | 16.8 | 29.6 (25.1, 34.3) | 19.2 | 28.7 (24.3, 33.1) | 29.0 |
| | IIIb | 38 | 14.7 (5.5, 28.3) | 10.0 | 23.7 (10.9, 39.1) | 11.0 | 10.4 ( 1.1, 31.7) | 18.0 |

**7515 Poster Discussion Session (Board #9), Sat, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

# A DNA-repair prognostic signature for early-stage NSCLC patients, in IFCT-0002 trial of neoadjuvant chemotherapy.

*Gerard Zalcman, Guenaelle Levallet, Pierre Fouret, Martine Antoine, Elisabeth Brambilla, Emmanuel Bergot, Francoise Galateau-Salle, Armelle Lavole, Elisabeth A. Quoix, Didier Debieuvre, Julien Mazieres, Denis Moro-Sibilot, Jean-Louis Pujol, Denis Braun, Michele Beau-Faller, Laurence Baudrin, Franck Morin, Virginie Westeel, Intergroupe Francophone de Cancérologie Thoracique (IFCT); Caen University Hospital, Caen, France; Pathology Department, Caen Universtiy Hospital, Caen, France; Groupe Hospitalier Pitié-Salpêtrière, APHP, Paris, France; Servie d'Anatomie Pathologique, Hopital Tenon, Université Pierre et Marie Curie, Paris, France; Centre Hospitalier Universitaire, Albert Michallon, INSERM U823, Grenoble, France; Thoracic Oncology Department, Caen University Hospital, Caen, France; Hôpital Tenon, AP-HP and Faculté de Médecine Pierre et Marie Curie, Université Paris VI, Paris, France; Hôpitaux Universitaires de Strasbourg, Strasbourg, France; Emile Muller Hospital, Mulhouse, France; Hôpital Larrey CHU Toulouse, Toulouse, France; Thoracic Oncology unit CHU Grenoble, Inserm U823, Grenoble, France; Centre Hospitalier Universitaire, Maladies Respiratoires, Montpellier, France; Clinique Claude Bernard, Metz, France; Centre Hospitalier Universitaire Strasbourg, Strasbourg, France; Intergroupe Francophone de Cancérologie Thoracique, Paris, France; Besançon University Hospital, Besançon, France*

**Background:** IFCT-0002 trial compared two perioperative CT regimens, CDDP-Gemcitabine *vs.*CBDCA-Paclitaxel in 528 stage I-II NSCLC patients. Paraffin-embedded post-chemo specimens were collected in the 490 non-complete responder patients for tissue expression studies of DNA-repair proteins. **Methods:** Surgical specimens were processed for immunohistochemistry as previously published. Variables were studied as continuous variables. Cut-off values were validated by bootstrap. Multivariate backward Cox regressions were used to adjust for patients' characteristics associated with the corresponding outcome at $p<0.20$ in univariate analysis. Discrimination of the proposed Cox models was estimated using the c-indexes corrected for over-optimism by a resampling procedure. Median follow-up was 72.0 months, 95%CI [69.7-73.5]. **Results:** ERCC1, MSH2, XRCC5/Ku80 and BRCA1 immunostainings were available in 413, 356, 396 and 221 specimens. Expressed as a continuous variable, only MSH2 staining score correlated with overall survival. XRCC5 showed no influence on survival. When dichotomised, low BRCA1 (under median value) and ERCC1 (ERCC1=0), while high MSH2 protein expression (over median value), adversely affected overall survival with respective adj. HRs of 1.56, 95%CI [1.05-2.32], p=0.028 ; 1.37 95%CI [1.01-1.86], p=0.042 and 1.53, 95%CI [1.12-2.09], p=0.007. No interaction was found between the attributed treatment and any of the 4 markers. High MSH2 and low ERCC1 variables were tested in 200 bootstrap multivariate Cox models and correlated with OS in respectively 87% and 78.5% (c-index=0.570), whereas stage predicted survival in only 49% of those theoretical samples. A prognostic score led to the definition of three groups of high-, intermediate- and low-risk of death with respective HRs of 2.83, 1.60 and 1. Median OS were respectively 28.3 months, 71.5 and not reached, 5-y survival rates were 34.2%, 54.8% and 66.3% (Log-Rank $p<0.0001$). **Conclusions:** With a 6-year median follow-up, a prognostic score derived from multivariate Cox regression, validated by bootstraping, accurately discriminates a sub-group with high risk of death according to tumor expression of MSH2 and ERCC1.

**7516 Poster Discussion Session (Board #10), Sat, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

## Surgery for early non-small cell lung cancer with preoperative erlotinib (SELECT): A correlative biomarker study.

*Adrian G. Sacher, Humberto Lara-Guerra, Thomas K. Waddell, Lucia Kim, Zhuo Chen, Alexandra Salvarrey, Gail Darling, Kazuhiro Yasufuku, Shaf Keshavjee, Marc de Perrot, Frances A. Shepherd, Geoffrey Liu, Ming Sound Tsao, Natasha B. Leighl; Division of Medical Oncology and Hematology, Princess Margaret Hospital, University of Toronto, Toronto, ON, Canada; Division of Thoracic Surgery, Toronto General Hospital, University of Toronto, Toronto, ON, Canada; University of Toronto, Department of Surgery, Division of Thoracic Surgery, University Health Network, Toronto, ON, Canada; Princess Margaret Hospital, Toronto, ON, Canada; Princess Margaret Hospital, Ontario Cancer Institute, Toronto, ON, Canada; University of Toronto, Department of Surgery, Division of Thoracic Surgery, Toronto General Hospital, University Health Network, Toronto, ON, Canada; Division of Thoracic Surgery, Toronto General Hospital, University Health Network, Toronto, ON, Canada; Department of Thoracic Surgery, Toronto General Hospital, University Health Network, Toronto, ON, Canada; Princess Margaret Hospital, University of Toronto, Toronto, ON, Canada; Princess Margaret Hospital, University Health Network, University of Toronto, Toronto, ON, Canada*

**Background**: Erlotinib has demonstrated major activity in *EGFR* mutation positive NSCLC, but may also benefit those with wild-type tumours. We conducted a single-arm trial of pre-operative erlotinib in early stage NSCLC to assess radiologic and functional response as well as correlation with known and investigational biomarkers. **Methods**: Patients with clinical stage IA-IIB NSCLC received erlotinib 150 mg daily for 4 weeks followed by surgical resection. Tumor response was assessed using pre- and post-treatment CT and PET imaging. Pharmacodynamic changes were assessed through comparison of pre- and post-treatment tumour samples (including Sequenom MassARRAY analysis) and measurement of circulating markers/ligands for *EGFR* activation (TGF-$\alpha$, amphiregulin, epiregulin, *EGFR* SNP, *EGFR* ECD). Secondary endpoints included pathological response, toxicity and progression-free survival. **Results**: Twenty-five patients were enrolled; 22 received erlotinib treatment with a median follow up of 4.4 years (range 2.2 to 6.4 years). Histology was predominantly adenocarcinoma (14) with smaller numbers of squamous carcinoma (7) and large cell carcinoma (1). PET response (25% SUV reduction) was observed in 2 patients (9%), both with confirmed squamous carcinoma histology. All patients met criteria for stable disease by RECIST and several experienced minor radiographic regression with histologic findings of fibrosis/necrosis, including 2 with squamous histology. The presence of an *EGFR* exon 19 deletion was detected in one adenocarcinoma case; the patient experienced a minor radiographic response to treatment. Genotyping, functional protein assays and ligand analysis are ongoing. **Conclusions**: Erlotinib appears to demonstrate some activity in patients with squamous histology. While *EGFR* mutations have been infrequently demonstrated in squamous NSCLC, the potential exists for other biomarkers predictive of benefit. Clinical trial information: NCT00462995.

**7517 Poster Discussion Session (Board #11), Sat, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

## Prognostic and predictive effects of a gene expression signature for NRF2 pathway activation in lung squamous cell carcinoma (SqCC).

*David W. Cescon, Desmond She, ChangQi Zhu, Shingo Sakashita, Melania Pintilie, Frances A. Shepherd, Ming Sound Tsao; Princess Margaret Hospital, University Health Network, University of Toronto, Toronto, ON, Canada; Princess Margaret Hospital, Toronto, ON, Canada*

**Background:** Genomic profiling of SqCC in TCGA identified somatic alterations that activate the NRF2 transcriptional program – a master regulator of the oxidative stress response – in ~35% of tumors (NFE2L2 mutations/amplifications, KEAP1 or CUL3 mutations/deletions). This pathway has been implicated in resistance to chemotherapy. To evaluate the clinical significance of this molecular subset, we developed a gene expression classifier and tested this signature as a predictor of adjuvant chemotherapy benefit with cisplatin/vinorelbine (cis/vin) in a subset of SqCC patients with microarray data from the NCIC JBR.10 Phase III clinical trial. **Methods:** Logistic regression (LR) and SAM analysis were independently applied to 104 TCGA SqCC cases that had both microarray gene expression and mutation data to identify genes associated with NRF2 pathway mutational status. Overlapping genes were used to define the signature, which was then tested in 3 independent SqCC datasets (62 JBR.10; 54 UHN; 129 UM) to evaluate the prognostic and predictive values of putative NRF2 pathway activation. **Results:** 29 genes comprising the signature were identified by overlap between LR (291 genes) and SAM (45 genes). The signature consistently separated SqCC into 2 groups in all datasets, corresponding to putatively activated and wild type (WT) NRF2 pathway tumors. No prognostic effect of the activated signature was observed in independent datasets (UHN HR 0.86, 95%CI 0.28 – 2.67; UM HR 1.43, 95%CI 0.82 – 2.48). Similarly, in JBR10, no prognostic effect was observed in the observation arm (n=24, HR 0.66, 95%CI 0.13 – 3.29). A trend toward improved survival with adjuvant chemotherapy was observed in patients with the WT signature (HR 0.34, 95%CI 0.08 – 1.78, p=0.13), but not in patients with the activated signature (HR 1.16, 95%CI 0.19 – 6.97, p=0.87; interaction p=0.18). **Conclusions:** A gene expression signature based on mutational activation of the NRF2 pathway may be predictive of benefit from adjuvant cis/vin in SqCC. Patients with NRF2 pathway activating somatic alterations may have reduced benefit from this therapy. Validation of this potentially ″actionable″ finding in additional datasets is necessary.

**7518 Poster Discussion Session (Board #12), Sat, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

# Biomarker analysis of WJOG4107, a randomized phase II trial of adjuvant chemotherapy with S-1 versus CDDP+S-1 for resected stage II-IIIA non-small cell lung cancer (NSCLC).

*Tetsuya Mitsudomi, Yasuo Iwamoto, Kazuto Nishio, Takeharu Yamanaka, Hiroshige Yoshioka, Hirohito Tada, Masahiro Yoshimura, Ichiro Yoshino, Isamu Okamoto, Shunichi Sugawara, Shinzoh Kudoh, Nobuyuki Yamamoto, Mitsunori Ohta, Yukito Ichinose, Shinji Atagi, Morihito Okada, Hideo Saka, Nobuyuki Katakami, Kazuhiko Nakagawa, Yoichi Nakanishi, West Japan Oncology Group; Kinki Univerisity Faculty of Medicine, Sayama, Japan; Department of Medical Oncology, Hiroshima City Hospital, Hiroshima, Japan; Kinki University School of Medicine, Osaka, Japan; Research Center for Innovative Oncology, National Cancer Center Hospital East, Chiba, Japan; Department of Respiratory Medicine, Kurashiki Central Hospital, Kurashiki, Japan; Department of General Thoracic Surgery, Osaka City General Hospital, Osaka, Japan; Division of Thoracic Surgery, Hyogo Cancer Center, Akashi, Hyogo, Japan; Department of General Thoracic Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan; Kinki University, Osakasayama, Japan; Sendai Kousei Hospital, Sendai, Japan; Department of Clinical Oncology, Graduate School of Medicine, Osaka City University, Osaka, Japan; Division of Thoracic Oncology, Shizuoka Cancer Center, Nagaizumi-cho, Shizuoka, Japan; Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Habikino, Japan; Clinical Research Institute, National Kyushu Cancer Center, Fukuoka, Japan; National Hospital Organization Kinki-Chuo Chest Medical Center, Osaka, Japan; Department of Surgical Oncology, Hiroshima University, Hiroshima, Japan; Department of Medical Oncology,National Hospital Organization Nagoya Medical Center, Nagoya, Japan; Division of Integrated Oncology, Institute of Biomedical Research and Innovation, Kobe, Japan; Kinki University Faculty of Medicine, Higashi-Osaka City, Japan; Kyushu University Hospital, Fukuoka, Japan*

**Background:** We conducted a randomized phase II trial for patients with resected stage II-IIIA NSCLC comparing postoperative oral S-1 (80 mg/m2/day for consecutive 2 weeks q3w for 1 year) (S) (N=100) or cisplatin (CDDP) (60 mg/m2 day1) plus oral S-1, (80 mg/m2/day for 2 weeks) q3w for 4 cycles (PS)(N=100). We reported that the disease-free survival rate at 2 years (DFS@2) (95% confidence interval: CI), a primary endpoint, was 66 (55-74) % for S and 58 (48-67)% for PS. Here, we report the preliminary results of preplanned biomarker analysis, a co-primary endpoint, to identify molecules whose expression is significantly associated with patient outcome. **Methods:** cDNA extracted from macro-dissected formalin-fixed paraffin-embedded specimens were available for 197/200 patients. Thirty-one genes including those whose expressions have been potentially associated withCDDP (e.g. ERCC1, XRCC1, BRCA1, GSTpi, HMG1, TBP) or fluorouracil (FU) sensitivity (TS, DHFR, DPD, UMPS, UPP1) were measured by QGE analysis (MassArray, Sequenom, CA). Expression of each gene was dichotomized according to its median value of expression. **Results:** The only gene with interaction $P<0.05$ after adjustment with sex, histology, age, stage was UMPS (uridine monophosphate synthase) ($P=0.0348$). UMPS catalyzes the conversion of fluoro UMP from 5FU and thus high UMPS expression is implicated to enhance 5FU effect. DFS@2 % (95% CI) for UMPS high/S, UMPS high/CS, UMPS low/S, UMPS low/CS were 69 (54-80), 53 (37-66), 64 (49-76), 61 (46-73)%, respectively. However, molecules such as ERCC1 and GSTpi whose expression have been previously associated with CDDP sensitivity did not emerge as predictive markers ($P=0.7908$, 0.6406, respectively). **Conclusions:** UMPS expression may define patient subset that would benefit from postoperative S-1 therapy. Clinical trial information: 000001658.

**7519 Poster Discussion Session (Board #13), Sat, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

## Pemetrexed-carboplatin adjuvant chemotherapy with or without gefitinib in resected stage IIIA-N2 non-small cell lung cancer harbouring EGFR mutations: A randomized phase II study.

*Si-Yu Wang, Wei Ou, Ning Li, Haibo Sun, Liang Zhang, Qin Fang; Sun Yat-sen University Cancer Center, Guangzhou, China; Henan Cancer Hospital, Zhengzhou, China*

**Background:** Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) show great efficacy in patients with advanced non-small cell lung cancer (NSCLC) with EGFR mutations. The BR.19 trial exploring the role of adjuvant gefitinib in resected early stage NSCLC (stage IB 49%, II 38%, III 13%) did not show significant progression-free survival (PFS) or overall survival (OS) improvement in all patients. The efficacy of gefitinib following adjuvant chemotherapy in patients with EGFR mutation is unknown. **Methods:** In this open-label, phase II study, patients with resected stage IIIA-N2 NSCLC harbouring EGFR mutations (either the exon 19 deletion or L858R point mutation) were randomly assigned to receive pemetrexed (500mg/m$^2$) and carboplatin (AUC=5), administered every 21 days for 4 cycles, followed with (n=30) or without (n=30) gefitinib (250mg per day) for 6 months. The primary end point was PFS. The second end point was OS. **Results:** From August 2008 toSeptember 2011, 60 patients (35 males and 25 females) were included in our center. Of the 60 patients (56 adenocarcinomas, 2 squamous cell carcinomas, 2 adenosquamous carcinomas), 20 patients (33.3%) had exon 19 deletion mutation, 40 (66.7%) patients had exon 21 L858R point mutation. The most common adverse event was rash (43.3%, 13 of 30) in the pemetrexed and carboplatin (PC)-gefitinib group and the addition of gefitinib to chemotherapy was well tolerated. The PFS was significantly longer among those who received PC-gefitinib than among those who received PC alone (median,39.8 months vs 27.0 months; hazard ratio [HR],0.369; 95% confidence interval [CI], 0.161-0.847; P=0.014). There was no significant difference in OS between the two group(median,41.6 months vs 32.6 months,P=0.066). The rates of 2-year PFS and OS were 78.9% and 92.4% in PC-gefitinib group, and 54.2% and 77.4% in PC alone group, respectively. **Conclusions:** The addition of gefitinib to pemetrexed and carboplatin adjuvant therapy showed significant improvement in PFS for patients with resected stage IIIA-N2 NSCLC harbouring EGFR mutations.

**7520 Poster Discussion Session (Board #14), Sat, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

## Blinded assessment of radiological changes after stereotactic ablative radiotherapy (SABR) for early-stage lung cancer: Local recurrences versus fibrosis.

*Suresh Senan, Kitty Huang, Sashendra Senthi, Femke Spoelstra, Andrew Warner, Ben J. Slotman, David Palma; Department of Radiation Oncology, VU University Medical Center, Amsterdam, Netherlands; Department of Radiation Oncology, London Regional Cancer Program, London, ON, Canada; London Regional Cancer Program, London, ON, Canada*

**Background:** Stereotactic ablative radiotherapy (SABR) is a guideline-recommended treatment for unfit patients with early-stage lung cancer. The 5-year local recurrence rates are approximately 10% but fibrotic changes are common during follow-up, leading to difficulty with timely detection and salvage therapies. Previously reported high-risk features (HRFs) on computed tomography (CT) are 1) enlarging opacity at the primary site; 2) sequential enlarging opacity; 3) enlarging opacity after 12 months; 4) bulging margin; 5) loss of linear margin and 6) loss of air bronchograms. We performed a blinded assessment of CT imaging of patients with and without local recurrences. **Methods:** Patients treated with SABR for early stage lung cancer between 2003 and 2012, who developed pathology-proven local recurrence (n=12), were matched 1:2 to patients without recurrences (n=24), based on baseline factors. The median age at diagnosis was 68 years and median post-SABR imaging follow-up was 24 months (range 6 to 67 months). Patients were well-matched in the recurrence and non-recurrence groups. A total of 153 CT scans were available. Serial CT images were assessed by 3 radiation oncologists blinded to outcomes, viewing anonymized images projected onto a large screen. **Results:** All established HRFs were significantly associated with local recurrence ($p<0.01$), and one additional HRF was identified: cranio-caudal growth ($p<0.001$). The best individual predictor of local recurrence was opacity enlargement after 12 months(100% sensitivity, 83% specificity, $p<0.001$). The odds of recurrence increased 4-fold for each additional HRF detected in an individual patient. The presence of $\geq 3$ HRFs in an individual patient was highly sensitive and specific for recurrence (both $>90\%$). The HRFs enlarging opacity and cranio-caudal growth were each detected $\geq 3$ months prior to the actual diagnosis of local recurrence in 42% of patients. **Conclusions:** Local recurrences following SABR can be accurately predicted by the presence of HRF's on post-treatment CT scans. This approach may reduce unnecessary diagnostic procedures, and ensure earlier use of salvage therapies.

**7521 Poster Discussion Session (Board #15), Sat, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

# Examining the influence of incidentally using ACEI on survival outcomes in stage III non-small cell lung cancer patients treated with definitive radiotherapy.

*Hongmei Wang, Zhongxing X. Liao, Yan Zhuang, Lawrence B. Levy, Ting Xu, Daniel Richard Gomez; Department of Radiation Oncology, Nanfagng Hospital, Southern Medical University, Guangzhou, China; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Radiation Oncology, University of Texas M. D. Anderson Cancer Center, Houston, TX; Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** The influence of angiotensin-converting enzyme inhibitors (ACEIs) on tumor progression is controversial, with some reports showing an antitumor mechanism and others demonstrating an increased risk of progression while on these agents. Our aim was to better elucidate the effect of ACEIs on locally advanced non-small cell lung cancer (NSCLC) outcomes in the setting of conflicting prior results. **Methods:** We retrospectively reviewed 673 patients with stage III NSCLC who received definitive radiotherapy +/- chemotherapy. Cox proportional hazard models were utilized to determine the association between ACEI intake and locoregional progression-free survival (LRPFS), distant metastasis-free survival (DMFS), disease-free survival (DFS), and overall survival (OS). **Results:** Univariate analysis showed an increased hazard of LRP among patients who used ACEI. After adjusting for multiple variables, ACEI use remained significant. No association was found regarding DMFS, DFS, or OS (Table). **Conclusions:** The use of ACEI was associated with an increased risk of locoregional progression in this population of patients. These findings provide implications for continuing this treatment through radiation therapy, if further validated through prospective studies.

**Multivariable Cox proportional hazards model for all patients.**

| | LRPFS | | | DMFS | | | DFS | | | OS | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Variable | HR | 95%CI | P | HR | 95%CI | P | HR | 95%CI | P | HR | 95%CI | P |
| ACEI use, yes vs no | 1.63 | 1.09-2.03 | 0.02 | 0.97 | 0.68-1.40 | 0.88 | 1.22 | 0.89-1.66 | 0.22 | 1.19 | 0.91-1.54 | 0.20 |
| Age, years, ≥65 vs <65 | 0.74 | 0.56-0.99 | 0.04 | / | / | / | 0.75 | 0.61-0.92 | <0.01 | / | / | / |
| KPS, >80 vs ≤80 | / | / | / | 0.77 | 0.60-0.99 | 0.04 | 0.78 | 0.62-0.98 | 0.03 | 0.73 | 0.60-0.89 | <0.01 |
| Tumor histology, nonsquamous cell vs squamous cell | / | / | / | 0.69 | 0.54-0.88 | <0.01 | / | / | / | / | / | / |
| Concurrent chemotherapy, no vs yes | / | / | / | 0.63 | 0.45-0.87 | <0.01 | 0.70 | 0.52-0.94 | 0.02 | 0.54 | 0.43-0.68 | <0.01 |
| Gross tumor volume, ≥121cm$^3$ vs <121cm$^3$ | 1.86 | 1.39-2.48 | <0.01 | 1.43 | 1.14-1.78 | <0.01 | 1.47 | 1.20-1.79 | <0.01 | 2.03 | 1.55-2.67 | <0.01 |
| Radiation dose, Gy 60-63 vs >63 | 1.53 | 1.15-2.05 | <0.01 | / | / | / | / | / | / | / | / | / |
| Beta blocker use, yes vs no | / | / | / | 0.66 | 0.49-0.90 | <0.01 | 0.72 | 0.55-0.94 | 0.01 | 0.78 | 0.63-0.97 | 0.03 |
| Aspirin use, yes vs no | / | / | / | 0.73 | 0.54-0.99 | 0.05 | / | / | / | / | / | / |

**7522 Poster Discussion Session (Board #16), Sat, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

# A phase II trial of mid-treatment FDG-PET adaptive, individualized radiation therapy plus concurrent chemotherapy in patients with non-small cell lung cancer (NSCLC).

*Fengming Kong, Randall K Ten Haken, Matthew J Schipper, James Hayman, Nithya Ramnath, Khaled Aref Hassan, Martha Matuszak, Timothy Ritter, Nan Bi, Weili Wang, Mark Orringer, Kemp Bailey Cease, Theodore Steven Lawrence, Gregory Peter Kalemkerian; Department of Radiation Oncology, University of Michigan, Ann Arbor, MI; Department of Radiation Oncology, University of Michigan 48109, Ann Arbor, MI; University of Michigan, Ann Arbor, MI; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; University of Michigan Medical Center, Ann Arbor, MI; Department of Radiation Oncology, University of Michigan Health System, Ann Arbor, MI*

**Background:** We have found that FDG-PET response during chemoradiation for patients with NSCLC is heterogeneous and predicts outcome. We hypothesized that dose escalated treatment targeted to the FDG-avid tumor would improve local tumor control. **Methods:** This is a phase II trial for patients with locally advanced, inoperable/unresectable NSCLC. Conformal radiotherapy (RT) was given in 30 daily fractions. RT dose was individualized to a fixed risk of lung toxicity and adaptively escalated to the residual tumor on mid-tx FDG-PET up to a total physical dose of 86 Gy. Patients had concurrent weekly followed by consolidation carboplatin/paclitaxel. The primary endpoint was local-regional tumor control (LRTC) at 2 years. Survival was calculated from RT start. Results were compared to stage-matched patients treated during the same time period with standard RT dosing (60-66 Gy). The data are presented as median (95% CI) unless otherwise specified. **Results:** 42 patients were enrolled: median age 63 years (range 45-83); 28 (67%) male; 39 (93%) smokers; 39 (93%) stage III; and 45% squamous cell. The mean gross tumor volume was 154 cc (range 10-617 cc). Median physical dose reached was 84 Gy (range 63-86 Gy), equivalent to 90 Gy in 2 Gy fractions (biological effective dose 108 Gy). 8 patients (19%) had RT-induced lung toxicity and 13 (31%) grade $\geq$2 esophagitis. Minimum and median follow-up were 10 and 25 months, respectively. The 2-year rates of in-field LRTC, overall LRTC, and LR-PFS were 84% (63-94%), 68% (47-82%), and 43% (27-58%), respectively. 14 patients progressed: 7 (50%) first at distant sites; 5 (36%) at nodal regions; 2 (14%) at primary tumor. Median overall survival was 26 months and 2-year overall survival rate was 51% (34-65%). These results compared favorably to stage-matched patients treated with standard-dose RT [2-year overall survival 23% (8-41%)]. **Conclusions:** These results support our hypothesis that adapting RT by escalating dose to the FDG avid region detected mid-tx improves 2-year local-regional tumor control. Adaptive RT may also improve overall survival. RTOG 1106 is currently testing this regimen in a randomized fashion. Clinical trial information: NCT01190527.

**7523 Poster Discussion Session (Board #17), Sat, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

## RTOG 0618: Stereotactic body radiation therapy (SBRT) to treat operable early-stage lung cancer patients.

*Robert D. Timmerman, Rebecca Paulus, Harvey I. Pass, Elizabeth Gore, Martin J. Edelman, James M. Galvin, Hak Choy, William Straube, Lucien Alexander Nedzi, Ronald McGarry, Cliff Grant Robinson, Peter B. Schiff, Jeffrey D. Bradley; The University of Texas Southwestern Medical Center, Dallas, TX; Radiation Therapy Oncology Group, Statistical Center, Philadelphia, PA; New York University School of Medicine, New York, NY; Medical College of Wisconsin, Milwaukee, WI; University of Maryland, Marlene and Stewart Greenebaum Cancer Center, Baltimore, MD; Thomas Jefferson University Hospital, Philadelphia, PA; Washington University in St. Louis, St. Louis, MO; University of Kentucky, Lexington, KY*

**Background:** The Radiation Therapy Oncology Group (RTOG) protocol 0618 was a phase II trial utilizing SBRT to treat early stage non-small cell lung cancer in operable patients (pts). **Methods:** All pts were deemed operable by a thoracic surgeon utilizing specific criteria. Pts with biopsy proven peripheral T1-T3, N0, M0 tumors were eligible. The prescription dose was 18 Gy X 3 fractions delivered in 1½-2 weeks. The primary endpoint was 2-year primary tumor control (PTC, avoidance of in-field (INF) and marginal failure (MF)) with overall and progression free survival (OS, PFS), adverse events (AE), local (LF), regional (RF), and distant failure (DF) as secondary endpoints. Early surgical salvage was directed as part of protocol design in the event of LF after SBRT. **Results:** The study opened December 2007 and closed May 2010 after accruing a total of 33 pts. Of 26 evaluable pts, 23 had T1, and 3 had T2 tumors. Median age was 72 years. Median $FEV_1$, DLCO at enrollment were 72%, 68% predicted, respectively. 4 pts (16%) had SBRT related grade 3 AEs while 0 had grade 4-5 AEs. Median follow-up was 25 months. 2 pts have been scored with INF (11.7 and 12.4 months post SBRT) and 1 with MF (32.5 months post SBRT) giving an estimated 2-year primary tumor failure rate of 7.7% (95% CI: 0.0%, 18.1%). 2-year estimates of LF (primary tumor plus involved lobe failure), RF, and DF are 19.2% (95% CI: 3.7%, 34.7%), 11.7% (95% CI: 0.0%, 24.5%), and 15.4% (95% CI: 1.2%, 29.6%), respectively. Only one patient was eligible for attempted surgical salvage and underwent lobectomy 1.2 years post SBRT complicated by a grade 4 cardiac arrhythmia. 2-year estimates of PFS and OS are 65.4% (95% CI: 44.0%, 80.3%) and 84.4% (95% CI: 63.7%, 93.9%), respectively. **Conclusions:** SBRT given appears to be associated with a high rate of PTC, moderate treatment related morbidity, and infrequent need for surgical salvage in operable early stage lung cancer pts with peripheral lesions. These results support ongoing enrollment into the ACOSOG Z4099-RTOG 1021 trial comparing SBRT to sublobar resection in high risk operable pts. The project was supported by RTOG grant U10 CA21661, CCOP grant U10 CA37422, and ATC U24 CA81647 from the National Cancer Institute. Clinical trial information: NCT00551369.

**7524 Poster Discussion Session (Board #18), Sat, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

# Factors impacting oncologic outcomes after sublobar pulmonary resection: Results from ACOSOG Z4032 (Alliance), a randomized trial for high-risk operable non-small cell lung cancer (NSCLC).

*Michael S Kent, Rodney Jerome Landreneau, Sumithra J. Mandrekar, Francis C Nichols, Thomas A. DiPetrillo, Bryan F Meyers, Dwight Earl Heron, Joe B. Putnam, David R Jones, Sandra Lynne Starnes, Benedict Daly, Angelina D. Tan, Hiran Chrishantha Fernando, Alliance for Clinical Trials; Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA; University of Pittsburgh Shadyside Medical Center, Pittsburgh, PA; Alliance Statistics and Data Center, Mayo Clinic, Rochester, MN; Mayo Clinic, Rochester, MN; Department of Radiation Oncology, Rhode Island Hospital, Providence, RI; Washington University School of Medicine in St. Louis, St. Louis, MO; University of Pittsburgh Cancer Institute, Pittsburgh, PA; Vanderbilt University Medical Center, Nashville, TN; University of Virginia School of Medicine, Charlottesville, VA; University of Cincinnati, Cincinnati, OH; Boston University Medical Center, Boston, MA; Boston Medical Center, Boston University, Boston, MA*

**Background:** A multicenter study (Z4032) compared sublobar resection (SR) to sublobar resection with brachytherapy (SRB) for stage I NSCLC. Local recurrence (LR) and overall survival (OS) rates at 3-years (3-yr) were similar between arms (see abstract 113613). This analysis combines arms, and evaluates the effect of factors previously reported to impact oncological outcomes after SR. **Methods:** 213 patients (pts) were evaluable for analysis. LR was defined as recurrence at the staple line (local progression), same lobe away from the staple line, or within hilar nodes. Factors assessed for impact on 3-yr outcomes were: resection type (wedge/segmentectomy), margin size ($<$1cm /$\geq$1cm), margin:tumor ratio ($<$1/ $\geq$1), tumor size ($\leq$2cm/$>$2cm) and staple line cytology (+/-). **Results:** LR occurred in 27/213 (12.6%) pts and included local progression in 12/213 (5.6%). OS rate at 3-yr was 152/213 (71.4%). Trends favored the use of segmentectomy, margin:tumor ratio$\geq$1, tumor size $\leq$2cm and negative staple line cytology; no factor reached statistical significance at 3-yr. The only factor significantly ($p=0.02$) associated with decreased 3-yr LR was margin size $\geq$1cm (8.3%) compared to margin$<$1cm (19.3%). **Conclusions:** SR is a good option for high-risk pts with NSCLC. The 3-yr OS rate of 71.4% and local progression rate of 5.6% are useful benchmarks to compare to other therapies. A resection margin of at least 1 cm is desirable. Clinical trial information: NCT00107172.

**Univariate logistic model result on factors predicting outcomes.**

| | Local recurrence-free at 3 yrs | | Overall survival at 3 yrs | |
|---|---|---|---|---|
| Factor | Odds ratio (95% CL) | P value | Odds ratio (95% CL) | P value |
| Wedge vs. segmentectomy | 0.43 (0.14, 1.31) | 0.14 | 0.75 (0.37, 1.50) | 0.41 |
| Margin size <1cm vs. ≥1 cm | 0.38 (0.16, 0.89) | 0.02 | 1.00 (0.54, 1.87) | 1.00 |
| Margin:tumor ratio <1 vs. ≥1 | 0.57 (0.20, 1.61) | 0.29 | 0.62 (0.30, 1.29) | 0.20 |
| Tumor size >2cm vs. ≤2cm | 1.07 (0.47, 2.48) | 0.87 | 0.59 (0.32, 1.08) | 0.09 |
| Staple line cytology Positive vs. negative | 0.83 (0.17, 3.96) | 0.82 | 0.71 (0.23, 2.21) | 0.55 |

**7525 Poster Discussion Session (Board #19), Sat, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

## The effects of physician-delivered brief smoking cessation on ACRIN/NLST participants' smoking behaviors.

*Ilana F Gareen, Elyse R. Park, Jeremy Gorelick, Sandra Japuntich, Inga Tolin Lennes, Sarah Baum, JoRean Sicks, Nancy Rigotti; Brown University Center for Statistical Sciences, Providence, RI; Massachusetts General Hospital, Boston, MA; Brown University, Providence, RI; VA Boston Healthcare System, Boston, MA; Massachusetts General Hospital Cancer Center, Boston, MA; Brown Univeristy, Providence, RI*

**Background:** The National Lung Screening Trial (NLST) demonstrated a 20% relative reduction in lung cancer mortality for current and former heavy smokers screened with low-dose CT vs. radiography. The NCCN and ACS recently released lung screening guidelines which promote smoking cessation counseling, but there is no information about the prevalence or effectiveness of brief physician-delivered smoking cessation interventions, such as the 5As (Ask, Advise, Assess, Assist, and Arrange follow-up) among lung screening patients. **Methods:** Among 8,878 NLST participants from 23 ACRIN sites who were smoking at enrollment, we conducted a longitudinal examination of the 1) rates and patterns of each reported 5A receipt and 2) association between each A and quitting. Using a case-control logistic regression, which matched participants according to trial arm; sociodemographic; medical; and smoking characteristics, we compared self-reported point-prevalence abstinence following 5A receipt. **Results:** Participants were 54% male, 90.6% white, and mean age 60.8 years. Receipt of 5As was consistent for the first 3 study years; rates of Ask (75%) and Advise (74%), exceeded rates of Assess (64%), Assist (58%), and Arrange follow-up (13%). Receipt of Ask, Advise, and Assess did not significantly increase the odds of a participant quitting smoking. Assist (cessation counseling, medication) increased the odds of quitting smoking by 22% ($p=0.0002$), and Arrange follow-up increased the odds of quitting by 20% ($p=0.002$). Older age and lower nicotine dependence were significantly associated with quitting, after accounting for the effectiveness of Assist (OR=1.34, CI: 1.16-1.55; OR== 0.95, CI: .93-.97) and Arrange follow-up (OR=1.34, CI: 1.16, 1.54; OR=.95, CI: .93-.97). **Conclusions:** Among high risk patients undergoing lung screening, Advice to quit was not associated with improved odds of smokers' quitting. Assist and Arrange follow-up were associated with improved odds of smokers' quitting, but unfortunately, rates of receipt of these As were low. Physician-delivered smoking cessation assistance and follow-up has the potential to enhance the effectiveness and cost effectiveness of lung screening. Clinical trial information: CDR0000257938.

**7526 Poster Discussion Session (Board #20), Sat, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

## Accelerated hypofractionated hemithoracic intensity modulated radiation therapy (IMRT) followed by extrapleural pneumonectomy (EPP) for malignant pleural mesothelioma (MPM): Results of a phase I/II study.

*Marc de Perrot, Ronald Feld, Natasha B. Leighl, Isabelle Opitz, Masaki Anraku, BC John Cho; Toronto General Hospital, Toronto, ON, Canada; Princess Margaret Cancer Center, Toronto, ON, Canada*

**Background:** We developed a protocol with accelerated hypofractionated hemithoracic IMRT followed by EPP for MPM. Advantages include optimal delivery of radiation to the whole tumor bed in a short period limiting the risk of viable tumor cell spread during surgery. **Methods:** Patients with resectable clinical T1-3N0M0 histology proven MPM were eligible for the study. 25 Gy in 5 daily fractions over 1 week was delivered to the entire ipsilateral hemithorax by IMRT with concomitant boost of 5 Gy to volumes at high risk based on CT and PET scan findings. EPP was performed one week after the end of radiation. Adjuvant chemotherapy was offered to patients with ypN2 on final pathology. The primary end-point was treatment related mortality. Secondary endpoint included overall survival and disease-free survival (DFS). Initial sites of recurrence were also recorded. **Results:** Twenty five patients were accrued between 11/2008 and 10/2012. Patients had a median age of 64 years (range, 45-75), 76% were males, 64% had epithelioid histology. All patients completed IMRT and EPP. IMRT was well tolerated with no grade 3-5 toxicity. EPP was performed $6 \pm 2$ days after completion of IMRT. Surgical complications occurred in 18 patients. One patient died from empyema at 88 days. All but one patient (stage IB) had stage III (n=11) or IV (n=13) disease on final pathology. Five out of 13 patients with ypN2 disease underwent adjuvant chemotherapy. After a median follow-up of 19 months (range, 3-51), the estimated 3-year survival reached 62%. Survival was significantly better in epithelioid compared to biphasic pathologic subtypes (83% survival at 3 years vs 19%, respectively; $p=0.004$). 14 patients remain disease free after a median follow-up of 17 months (range, 3-37). 2-year DFS was 85% in stage III and 37% in stage IV disease (p=0.03). Recurrences occurred in the ipsilateral chest only (n=2), ipsilateral chest and distant sites (n=2), and distant sites only (n=6). **Conclusions:** Accelerated hypofractionated hemithoracic IMRT followed by EPP is feasible. This treatment could improve survival in selected patients with epithelial subtype. Clinical trial information: NCT00797719.

**7527 Poster Discussion Session (Board #21), Sat, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

# A phase I study of cediranib (NSC #732208) in combination with cisplatin and pemetrexed in chemonaive patients with malignant pleural mesothelioma (SWOG S0905).

*Anne S. Tsao, James Moon, Ignacio Ivan Wistuba, Nicholas J. Vogelzang, Gregory Peter Kalemkerian, Mary Weber Redman, David R. Gandara, Southwest Oncology Group; The University of Texas MD Anderson Cancer Center, Houston, TX; Southwest Oncology Group Statistical Center, Seattle, WA; Comprehensive Cancer Centers of Nevada, The US Oncology Network, Las Vegas, NV; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; Fred Hutchinson Cancer Research Center, Seattle, WA; University of California, Davis Comprehensive Cancer Center, Sacramento, CA*

**Background:** The VEGF/VEGFR and PDGF/PDGFR pathways are potential therapeutic targets in mesothelioma. Cediranib, a VEGFR/PDGFR inhibitor, showed anti-tumor activity in a salvage monotherapy study S0509. **Methods:** S0905 combined cediranib (2 dose cohorts 30 mg and 20 mg daily) with cisplatin and pemetrexed for 6 cycles followed by maintenance cediranib in unresectable chemo-naïve MPM patients. **Results:** A total of 20 patients (7 to cohort 1 - 30 mg, 13 to cohort 2 - 20 mg) were enrolled. In first cohort, 2 patients reported grade 3 DLTs of diarrhea and fatigue. Cohort 2 DLTs included 2 patients with grade 3 hyponatremia/dehydration and mucositis. For all cycles, 12 patients reported Grade 3 AEs, the most common being diarrhea (4), dehydration (3), fatigue (3) and neutropenia (3). Two grade 4 thrombocytopenia were reported with 1 treatment-related death (cohort 2) due to pneumonia/sepsis. Based on the toxicity profile, a decision was made to proceed with cediranib 20 mg daily for the remaining phase I/II trial. Two radiographic response measurements were utilized (RECIST 1.1, modified RECIST). 18/20 patients were evaluable for response by RECIST 1.1 (7 - 30 mg cohort, 11 - 20 mg cohort). The RECIST 1.1 RR was 22% (95% CI: 6% - 48%) and median PFS was 14 months (95% CI: 8 – 17). Two patients had inadequate assessments and are classified as non-responders. There were 19 patients measurable by modified RECIST with RR 53% (95% CI: 29%-76%) and median PFS 10 months (7-13). For all patients, the median OS was 16 months (95% CI: 11-19). One patient in the 30 mg cohort remains on trial after 25 cycles of therapy; 2 patients at the 20 mg cohort remain on trial on cycles 19 and 15 of therapy. **Conclusions:** Cisplatin-pemetrexed-cediranib shows significant clinical activity and acceptable toxicity with cediranib 20 mg/day. The randomized phase II portion of the trial is ongoing. Clinical trial information: NCT01064648.

| Cohorts | RECIST 1.1 RR | RECIST 1.1 DCR | RECIST 1.1 Median PFS | Modified RECIST RR | Modified RECIST DCR | Modified RECIST Median PFS | Median OS |
|---|---|---|---|---|---|---|---|
| All patients (n=20) | 22% | 89% | 14 months | 53% | 79% | 10 months | 16 months |
| 30 mg cediranib (n=7) | 29% | 86% | 13 months | 71% | 86% | 10 months | 16 months |
| 20 mg cediranib (n=13) | 18% | 75% | 14 months | 42% | 75% | 13 months | 14 months |

**7528 Poster Discussion Session (Board #22), Sat, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

## A randomized phase II study adding axitinib to pemetrexed-cisplatin in patients with malignant pleural mesothelioma (MPM): Clinical results of a single-center trial.

*Wieneke A. Buikhuisen, Andrew D. Vincent, Marion M. Scharpfenecker, Catharina M. Korse, Arjan W. Griffioen, Renee van Pel, Paul Baas; Department of Thorax Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands; Biometrics Department, The Netherlands Cancer Institute/Antoni van Leeuwenhoek Ziekenhuis, Amsterdam, Netherlands; Netherlands Cancer Institute, Amsterdam, Netherlands; Angiogenesis Laboratory, Free University Amsterdam, Amsterdam, Netherlands; Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands*

**Background:** Since standard chemotherapy treatment does not lead to long-term survival, new treatment approaches are required. MPM is known for a high vessel count and high levels of vascular growth factors. Suppression of the neo-vasculature by adding the oral VEGF-TKI axitinib to standard chemotherapy may lead to improvement. This study had both clinical and translational objectives. We here report the secondary endpoints response, PFS, OS and toxicity. **Methods:** Treatment naïve patients with suspected or proven malignant mesothelioma and medically suitable for limited surgical intervention were eligible after informed consent. Patients were treated with pemetrexed (500mg/$m^2$q3wk) and cisplatin (75mg/$m^2$q3wk) and were randomised to daily axitinib (2x5mg tablets). Before treatment a thoracosopy was performed to confirm the diagnosis. After 3 cycles of chemotherapy a palliative pleurectomy was performed. During both interventions material was obtained for research purposes. Patients could receive an additional 2 cycles of chemotherapy. **Results:** From July 2009 until October 2012, 26 patients were randomised. Six consecutive patients who received chemotherapy plus axitinib to demonstrate the feasibility and safety of the study design, were also included. In total twenty patients received axitinib. There was one protocol violation in the control arm. Median age: 61 yrs (35 yrs – 75 yrs), 84% epithelial type, 94% WHO 0-1 and 6% WHO 2. Median follow up was 18 months. Toxicity: There was more grade 3, 4 toxicity in the axitinib group concerning neutropenia (40% vs. 9%; p=0.11). One patient in the axitinib group developed a CVA, one patient pulmonary emboli. No thromboembolic events occurred in the control arm. Partial response was observed in 35% of patients in the experimental arm vs. 27% in the control group (p=0.99). Median PFS was 8 months in the experimental arm vs. 8.3 months in the control arm. There was also no difference in overall survival 17 vs 18 months, respectively. **Conclusions:** Axitinib was well tolerated in combination with cisplatin and pemetrexed. There was no evidence of benefit in response rate, progression free or overall survival. Clinical trial information: NCT01211275.

**7529 Poster Discussion Session (Board #23), Sat, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

# A multicenter prospective study of carboplatin and paclitaxel for advanced thymic carcinoma: West Japan Oncology Group 4207L.

*Koji Takeda, Fumihiko Hirai, Takeharu Yamanaka, Kenichi Taguchi, Haruko Daga, Junichi Shimizu, Yoshihito Kogure, Tatsuo Kimura, Kaoru Tanaka, Yasuo Iwamoto, Akira Ono, Hidefumi Sasaki, Junya Fukuoka, Kenichi Nishiyama, Takashi Seto, Yukito Ichinose, Kazuhiko Nakagawa, Yoichi Nakanishi, West Japan Oncology Group; Osaka City General Hospital, Osaka, Japan; National Kyushu Cancer Center, Fukuoka, Japan; National Cancer Center Hospital East, Kashiwa, Japan; Aichi Cancer Center Hospital, Nagoya, Japan; Nagoya Medical Center, Nagoya, Japan; Osaka City University, Graduate School of Medicine, Osaka, Japan; Kinki University School of Medicine, Osaka, Japan; Hiroshima City Hospital, Hiroshima, Japan; Shizuoka Cancer Center, Nagaizumicho, Japan; Nagoya City University Graduate School of Medicine, Nagoya, Japan; Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; Kyushu University Hospital, Fukuoka, Japan*

**Background:** Thymic carcinoma (TC) is a rare malignant tumor originated within the thymus gland and is associated with a poor prognosis, differing from thymoma which is the most common type of thymic malignant neoplasm. No results of clinical trials focusing on TC have been reported. This single-arm study evaluated carboplatin and paclitaxel (CbP) in previously untreated patients (pts) with advanced TC. **Methods:** Pts with Masaoka's stage III to IVb TC, ECOG PS 0 to 1, and more than 20 years old were eligible. The study treatment consisted of carboplatin (AUC 6) and paclitaxel (200 mg/m$^2$) every 3 weeks for a maximum of 6 cycles. The primary endpoint was objective response rate (ORR) by extramural assessment. Secondary endpoints included overall survival (OS), progression-free survival (PFS), and safety. All pts were followed-up until 24 months (mo) after last enrollment. Based on the SWOG 2-stage design, the planned sample size of 40 pts was determined to reject the ORR of 20% under the expectation of 40% with a power of 0.85 and a type I error of 0.05. **Results:** From May 2008 to November 2010, 40 pts were enrolled from 21 centers. Of 39 evaluable for analysis, the median age was 62 years (range, 36–84); 23/16 males/females; 3/10/26 with Masaoka's stage III/IVa/IVb; 9/11/19 with squamous cell carcinoma/poorly differentiated neuroendocrine carcinoma/other types. The median number of cycles was 6. There was 1/13 complete/partial responses with an ORR of 36% (95% confidence interval [CI], 21-53%; $P = 0.031$). The median PFS was 8.1 mo (5.4-13.1 mo) while OS did not reach the median value. The 1-year and 2-year survival rates were 85% (95% CI, 69-93%) and 71% (95% CI, 54-83%), respectively. Major adverse event was grade 3-4 neutropenia in 34 pts (87%). Two cases (5%) of grade 3 febrile neutropenia, neuropathy, and arthralgia were observed, respectively. There was no treatment-related death. **Conclusions:** CbP showed higher efficacy in advanced TC as compared with anthracycline-based chemotherapy which is the current standard for the treatment of thymoma. Our results established that CbP, one of the standard treatments for non-small cell lung cancer, also serves as a key chemotherapy regimen for TC. Clinical trial information: UMIN000001358.

**7530 Poster Discussion Session (Board #24), Sat, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM**

# Phase II study of amrubicin (AMR) and carboplatin (CBDCA) for invasive thymoma (IT) and thymic carcinoma (TC): NJLCG0803.

*Yosuke Kawashima, Akira Inoue, Shunichi Sugawara, Masao Harada, Kunihiko Kobayashi, Toshiyuki Kozuki, Shoichi Kuyama, Tomohiro Sakakibara, Makoto Maemondo, Hajime Asahina, Akiko Hisamoto, Taku Nakagawa, Toshihiro Nukiwa; Sendai Kousei Hospital, Sendai, Japan; Tohoku University Hospital, Sendai, Japan; National Hospital Organization Hokkaido Cancer Center, Sapporo, Japan; Saitama Medical University International Medical Center, Saitama, Japan; Department of Thoracic oncology and medicine, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan; Department of Respiratory Medicine, NHO Iwakuni Clinical Center, Iwakuni, Japan; Department of Respiratory Medicine, Miyagi Cancer Center, Natori, Japan; Hokkaido University School of Medicine, Sapporo, Japan; Department of Respiratory Medicine, Okayama University Hospital, Okayama, Japan; Senboku Kumiai Hospital, Daisen, Japan*

**Background:** There has been no standard chemotherapy for advanced thymic malignancies including IT and TC although anthracycline or platinum agents have been commonly used for them. AMR, a new anthracycline agent, was approved for lung cancer in Japan and we had previously conducted some prospective studies of AMR combined with CBDCA for patients with small-cell lung cancer, which revealed this regimen was active with acceptable toxicity. The objective of this study is to evaluate the efficacy and safety of this combination for patients with advanced thymic malignancies. **Methods:** Patients with histologically confirmed thymic malignancies received AMR (35 mg/m2, day1-3) and CBDCA (AUC 4.0, day1) every 3 weeks. Patients who underwent previous chemotherapy received reduced dose of AMR (30 mg/m2). The primary endpoint was overall response rate (ORR), and secondary endpoints were progression-free survival (PFS), overall survival and toxicity profile. Assuming that ORR of 75% and 45% would indicate the potential usefulness while ORR of 50% and 20% would be the lower limit of interest, with alpha = 0.10 and beta = 0.20, for IT patients and TC patients, respectively, 18 IT patients and 16 TC patients were at least required. **Results:** From December 2008 to October 2012, 51 patients (18 IT and 33 TC) were enrolled from 20 institutions in Japan. Patients' characteristics are as follows; male/female 35/16; median age 66 (range 39-78); performance status 0/1 24/27. The ORR and disease control rate were 17% and 89% in IT, and 30% and 85% in TC. Preliminary median PFS was 7.6 months in both groups. Toxicity was generally moderate and no treatment related death was observed. **Conclusions:** This is the largest prospective study of chemotherapy for advanced thymic malignancies. AMR combined with CBDCA was effective for TC patients with acceptable toxicities. Clinical trial information: R000001598.

**7531 General Poster Session (Board #19A), Sat, 8:00 AM-11:45 AM**

## Phase II study of nedaplatin and irinotecan as adjuvant chemotherapy in patients with completely resected non-small cell lung cancer.

*Haruhiro Saito, Shuji Murakami, Tetsuro Kondo, Fumihiro Oshita, Hiroyuki Ito, Haruhiko Nakayama, Kouzo Yamada; Department of Thoracic Oncology, Kanagawa Cancer Center, Yokohama, Japan; Kanagawa Cancer Center, Yokohama, Japan; Kanagawa Cancer Center, Kanagawa, Japan*

**Background:** The aim of this phase II study was to evaluate the feasibility and safety of a nedaplatin and irinotecan combination regimen in the treatment of completely resected non-small cell lung cancer (NSCLC). **Methods:** Patients with completely resected pathologically documented stage IB, II or III NSCLC were treated with nedaplatin and irinotecan. Chemotherapy consisted of 4 cycles of nedaplatin at 50mg/m2 and irinotecan 50mg/m2 on days 1 and 8 every 4 -5 weeks. The primary endpoint of this study was the completion rate of 4 cycles. **Results:** Thirty nine patients were treated, and the patient's demographics were: median age 68 years (range 40-74), gender male (n = 16, 41%)/female (n = 23, 59%), stage IIA (n = 9, 23%), IIB (n = 13, 33%), IIIA (n = 16, 41%), IIIB(n=1,2% ). Thirty six patients (92.3%) received the 4 cycles of the chemotherapy regimen. Among the 3 patients who failed to complete 4 cycles, the reasons for stopping were anaphylaxy (n = 1), G3 infection and diarrhea (n = 2). The main adverse effects were hematological toxicity as well as grade 3/4 neutropenia (which occurred in 36% of the patients). **Conclusions:** Adjuvant chemotherapy with nedaplatin and irinotecan combination regimen has an acceptable toxicity profile, and the majority of patients completed 4 cycles of therapy.

**7532 General Poster Session (Board #19B), Sat, 8:00 AM-11:45 AM**

# Performance of a prognostic genomic signature for early-stage NSCLC in matched fresh frozen and RNA-stabilized tissue.

*Shuguang Huang, Amy L Ewing, Nicholas J Reitze, Arlette H Uihlein, Dakun Wang, Michael J Gabrin, Katherine E. Keating, Jude Mulligan, Claire Wilson, Timothy Davison, Stuart McKenzie, Ming-Sound Tsao, Frances A. Shepherd, Stacey L Brower; Precision Therapeutics, Inc., Pittsburgh, PA; Almac Diagnostics Ltd., Craigavon, Northern Ireland; Department of Pathology, University Health Network, University of Toronto, Toronto, ON, Canada; University Health Network-Princess Margaret Hospital, Toronto, ON, Canada*

**Background:** Recent clinical studies have demonstrated the benefit of adjuvant chemotherapy (ACT) in some early-stage non-small cell lung cancer (NSCLC) patients. A 15-gene signature, developed using fresh frozen (FF) tissue, has been shown to be an independent prognostic marker that identifies high risk patients who may benefit from ACT. Use of this signature in tissue preserved in an RNA stabilization reagent is desired for easier access to tumor tissue in the clinical setting. **Methods:** Matched FF and RNAlater-preserved (RNAL) tissues were obtained from 43 NSCLC patients. Patients provided written consent for the collection of tumor tissue at the time of surgery under an IRB approved protocol. Each tissue sample was split into 2 pieces, creating biological replicates for each tissue format. For each patient, RNA was extracted from 4 tissue pieces (2 FF, 2 RNAL), followed by microarray-based genomic profiling (Affymetrix U133 Plus 2.0). The 15-gene signature was applied to each profile, generating a numerical risk score and a risk category (high, low) using methods previously established (Zhu 2010 J Clin Oncol). The level of agreement was evaluated within biological replicates of each tissue format, as well as between the averaged biological replicates of matched FF and RNAL tissues. **Results:** The concordance in risk category between averaged biological replicates of matched FF and RNAL tissues was 84%, with a Pearson correlation of 0.74. This level of agreement is comparable to the inherent reproducibility of the assay observed within biological replicates of FF tissue, which demonstrated concordance of 79% and Pearson correlation of 0.83. In addition, a statistical in silico simulation was used to demonstrate that if the risk scores in this study had spanned the full dynamic range of the assay while maintaining the same level of inherent reproducibility observed in the current study, the level of concordance would be 89% with a Pearson correlation of 0.93. **Conclusions:** The level of agreement between matched FF and RNAL tissues is not inferior to that seen within FF biological replicates. Therefore, the 15-gene signature maintains its performance when used in RNAlater-preserved NSCLC tissues.

## 7533 General Poster Session (Board #19C), Sat, 8:00 AM-11:45 AM

# Carboplatin versus cisplatin-based adjuvant chemotherapy in elderly patients with stages IB, II, and IIIA non-small cell lung cancer in the community setting.

*Fei Gu, Juan P. Wisnivesky, Grace Mhango, Gary M. Strauss; Tufts Medical Center, Boston, MA; Divisions of General Internal Medicine and Pulmonary and Critical Care Medicine, Mount Sinai School of Medicine, New York, NY; Mount Sinai School of Medicine, New York, NY*

**Background:** It remains controversial whether completely resected elderly NSCLC patients should receive adjuvant chemotherapy (ACT) and with what treatment regimen. We previously reported from a SEER-Medicare analysis of cases diagnosed up to 2005, that carbo-ACT is given much more frequently than cis-ACT and both are associated with improved overall survival (OS). Since randomized ACT trials were published around 2005, an update is necessary to reflect more recent practice patterns. **Methods:** We identified 16,420 patients >65 years in the SEER-Medicare database with resected stage IB-IIIA NSCLC, diagnosed between 1992 and 2007. Among these patients, 1,803 (11%) received platinum-ACT. Propensity score methods and Cox regression analyses were used to assess survival outcomes, as well as to compare carbo- versus cis-based therapy, while controlling for potential confounders. **Results:** Among those receiving platinum-based ACT, of whom 83% received carbo, there was a significant OS survival advantage compared to those receiving no ACT (TABLE). Carbo-ACT is associated with similar OS as compared to cis-ACT. The carbo/paclitaxel doublet was the most commonly used regimen, given to 52%. Chemotherapy-related toxicities requiring hospitalization were comparable between carbo- and cis-ACT groups, except for significantly less dehydration and anemia among those receiving carbo-ACT. **Conclusions:** In community practice reflected in this SEER-Medicare study, a minority of completely resected stage IB-IIIA NSCLC received platinum-based ACT that is associated with improved OS. Carbo-ACT was given in a 5:1 ratio compared to cis-ACT, had comparable OS advantage, and a somewhat more favorable toxicity profile.

**Effect of platinum-based ACT on hazard ratios for OS followed for 5 years with or without propensity score adjustments.**

| | Hazard ratio (95% CI) | |
|---|---|---|
| Adjuvant treatment cohorts | Not adjusted | Propensity score adjusted |
| Platinum vs no ACT | 0.83 (0.78, 0.89) | 0.75 (0.70, 0.81) |
| Carbo vs no ACT | 0.79 (0.74, 0.85) | 0.73 (0.68, 0.78) |
| Cis vs no ACT | 0.82 (0.71, 0.96) | 0.75 (0.64, 0.81) |
| Carbo vs Cis | 1.00 (0.84, 1.20) | 0.99 (0.83, 1.19) |

**7534 General Poster Session (Board #19D), Sat, 8:00 AM-11:45 AM**

# Phase II multicenter clinical trial of isolated lung perfusion (ILuP) with melphalan (MN) in patients (pts) with resectable lung metastases (LM).

*Willem Den Hengst, Jeroen M.H. Hendriks, Bram Balduyck, Inez Rodrigus, Jan Baptist Vermorken, Filip Lardon, Michel I.M. Versteegh, Jerry Braun, Hans Gelderblom, Franz Schramel, Wim-Jan Van Boven, Bart Van Putte, Ozcan Birim, Lex Maat, Paul Van Schil; Antwerp University Hospital, Edegem, Belgium; University of Antwerp, Wilrijk, Belgium; Leiden University Medical Center, Leiden, Netherlands; Department of Clinical Oncology, Leiden University Medical Center, Leiden, Netherlands; St Antonius Hospital, Nieuwegein, Netherlands; Amsterdam Medical Center, Amsterdam, Netherlands; Amphia Hospital, Breda, Netherlands; Erasmus MC, Rotterdam, Netherlands*

**Background:** Five-year overall survival (OS) of pts undergoing surgical resection of LM from colorectal cancer (CRC) and sarcoma remains low [20-50%]. Local recurrence rate is high, even after complete surgical resection [48-66%] (Pastorino et al, 1997). Combined modality therapy is currently evaluated. ILuP allows the delivery of high-dose locoregional chemotherapy without systemic exposure. In a previous phase I study maximum tolerated dose of MN was found to be 45mg at a perfusion temperature of 37°C (Grootenboers et al, 2007). **Methods:** From 2006 to 2011 50 pts, 28 male, median age 57 years [15-76], with LM from CRC [n=30] or sarcoma [n=20] were included in a phase II clinical trial conducted in 4 cardiothoracic surgical centers. In total, 62 ILuP procedures were performed, 12 bilaterally, followed by resection of all palpable LM. Survival was calculated according to the Kaplan-Meier method. **Results:** Operative mortality was 0%, 90-day morbidity was mainly cardiac [grade 3: 2%] and respiratory [grade 3: 29%, grade 4: 2%]. After a median follow-up of 24 months [3-63 mos] 18 pts died, 2 without recurrence. Seven pts [14%] had their initial recurrence in the perfused lung. Initial progressive disease outside the perfused lung occurred in 23 pts [46%]; contralateral, non-perfused lung 10, liver 3, brain 2, primary site 1 and other location 7. OS and disease-free survival (DFS) are shown in table 1. Lung function data showed a decrease in $FEV_1$ and $D_LCO$ of 21.6% and 25.8% after 1 month, and 10.4% and 11.3% after 12 mos, respectively, compared to preoperative values. Long-term quality of life evolution after ILuP and lung metastasectomy was comparable with a standard lung metastasectomy by thoracotomy in one participating center (Balduyck et al, 2012). **Conclusions:** Compared to historical series of LM resection without ILuP favorable results are obtained in terms of local control without long-term adverse effects. These data support the further investigation of ILuP as additional treatment in pts with resectable LM from CRC or sarcoma. Clinical trial information: 2006-002808-34.

| | 3-year OS | 4-year OS | 3-year DFS | 4-year DFS |
|---|---|---|---|---|
| **All patients** | 57±9% | 49±11% | 36±8% | 36±8% |
| **CRC** | 62±13% | 62±13% | 41±11% | 41±11% |
| **Sarcoma** | 48±12% | 31±15% | 27±10% | 27±10% |

**7535 General Poster Session (Board #19E), Sat, 8:00 AM-11:45 AM**

## Lymphovascular invasion as a prognostic indicator in stage I non small cell lung cancer: A systematic review and meta analysis.

*Nathan M Mollberg, Carrie Bennette, Eric Howell, Leah M. Backhus, Mark K. Ferguson; University of Washington, Seattle, WA; University of Chicago Hospital, Chicago, IL*

**Background:** Identification of pathologic features able to predict outcomes in resected stage I non-small cell lung cancer (NSCLC) may help to further stratify patients into risk groups, allowing for further refinement of adjuvant treatment recommendations. We performed a systematic review and meta-analysis to evaluate whether the presence of lymphovacular invasion (LVI) is associated with disease outcome in stage I NSCLC patients. **Methods:** A systematic search of the literature was performed (1990 to December 2012; Medline/Embase) using search terms related to lymphovascular invasion, lung cancer and prognosis. Studies were considered eligible if they reported the outcome of lung cancer in patients with LVI compared to those without. Pooled Hazard Ratios (HR) were estimated with a random effects model. Two different endpoints were independently analyzed: recurrence-free survival (RFS) and overall survival (OS). We analyzed both unadjusted and adjusted effect estimates, for a total of four separate meta-analyses. Several studies presented multiple results (i.e. adjusted and unadjusted and/or recurrence-free and overall survival) and were therefore included in more than one pooled analysis. **Results:** Of 2,878 titles identified, 20 articles met the inclusion criteria. Of these, 5 studies were excluded from the analysis due to duplication of results (n=4) and lack of data to calculate HR (n=1). The unadjusted models consisted of 808 (RFS) and 1675 (OS) patients, while the adjusted models consisted of 1,545 (RFS) and 2,601 (OS). The unadjusted pooled effect of LVI was significantly associated with worse both RFS (HR: 4.71, 95% Confidence Interval (CI): 3.08-7.21), and OS (HR: 3.05, 95% CI: 2.34-3.98). Adjusting for potential confounders yielded the same results with both RFS (HR: 2.49, 95% CI: 1.6-3.89), and OS (HR: 1.80, 95% CI: 1.44-2.25) being significantly worse for patients exhibiting LVI in their pathologic specimens. **Conclusions:** The present study indicates that LVI is an adverse prognostic factor in patients with surgically managed stage I lung cancer. Based on these results, the use of LVI as a stratifying factor in future prospective lung cancer trials seems to be justifiable.

**7536 General Poster Session (Board #19F), Sat, 8:00 AM-11:45 AM**

# Intratumoral gene expression of 5-fluorouracil pharmacokinetics related enzymes in stage I and II non-small cell lung cancer patients treated with uracil-tegaful after surgery.

*Keisuke Eguchi, Tomohiko Abiko, Mitsuo Kohno, Makoto Sawafuji, Hirotoshi Horio, Toshinori Hashizume, Mitsuo Nakayama, Ryoichi Kato, Masafumi Kawamura; Saitama Medical Colledge, Kawagoe General Hospital, Saitama, Japan; Kawasaki Municipal Ida Hospital, Kawasaki, Japan; Keio University Hospital, Tokyo, Japan; Kawasaki Municipal Hospital, Kanagawa, Japan; Tokyo Metropolitan Komagome Hospital, Tokyo, Japan; Saitama Medical University International Medical Center, Saitama, Japan; National Tokyo Medical Center, Tokyo, Japan; Teikyo University, School of Medicine, Tokyo, Japan*

**Background:** It is believed through meta-analysis that the adjuvant chemotherapy with oral administration of uracil-tegafur combination drug (manufactured as UFT) yielded better survival than surgery alone in early stage non-small cell lung cancer patients (NSCLC) in Japan. However, no promising bio-marker, which can predict the benefit of UFT use in NSCLC patients, has been found. This clinical trial was designed to evaluate the relationship between the intratumoral gene expression of the five-fluorouracil pharmacokinetics related enzymes such as thymidylate synthase (TS), dihydropyrimidine dehydrogenase (DPD), orate phosphoribosyltransferase (OPRT) and thymidine phosphorylase (TP), and clinical outcomes in patients to whom UFT was administered for 2 years after surgery. **Methods:** From June 2004 to September 2007, 236 NSCLC patients who underwent complete resection of a pathological stage IA (maximum diameter of 2cm or more), IB and II (according to the 1997 UICC TNM classification) were eligible in this study. Other inclusion criteria were age of 20 to 80 years, ECOG PS of 0 or 1 and feasible oral UFT administration within 8 weeks after surgery. Total RNA was extracted from formalin-fixed lung cancer cell sample obtained with micro-dissection method. Gene expression was examined using quantified fluorescence-based real time revers transcription-polymerase chain reaction assay. **Results:** 131 (63%) patients completed 2 year administration of UFT. 73 (31%) patients had recurrence during 5 years follow-up and 48 (73%) patients among them were treated with chemotherapy including platinum. The 5-year disease free survival (DFS) and overall survival (OS) rates in all patients were 66.7% and 83.7%, respectively. A cox multivariate analysis revealed pathological stage (HR: 0.4463; p=0.034), TS expression status (HR: 0.469; p=0.021) and DPD expression status (HR: 1.956; p=0.048) to be prognostic for DFS but no factors to be prognostic for OS. **Conclusions:** This study suggested that TS and DPD mRNA expression in the tumor were possible prognostic biomarkers for postoperative adjuvant chemotherapy with UFT in stage I-II NSCLC. Clinical trial information: 15-65-1.

**7537 General Poster Session (Board #19G), Sat, 8:00 AM-11:45 AM**

# Survival study of neoadjuvant versus adjuvant chemotherapy with docetaxel combined carboplatin in resectable stage IB to IIIA non-small lung cancer.

*Xue-Ning Yang, Gang Cheng, Xiao-song Ben, Hong-He Luo, Chang-li Wang, Wenzhao Zhong, Di Ge, Gui-bin Qiao, Zheng Wang, Yang Shentu, Jie Yang, Hong hong Yan, Yi Long Wu, Chinese Society of Lung Cancer; Guangdong Lung Cancer Institute, Guangdong General Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China; Guangdong General Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China; Department of Thoracic Surgery,The First Affiliated Hospital of SUN Yat-sen University, Guangzhou, China; Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; Department of Thoracic Surgery, Zhongshan Hospital of Fudan University, Shanghai, China; Department of Chest Surgery,General Hospital of Guangzhou Military Command, Guangzhou, China; Shenzhen People's Hospital, Shenzhen, China; Shandong Provincial Chest Hospital; Shanghai Lung Tumor Clinical Medical Center, Shanghai, China; Department of Thoracic Surgery,The First People s Hospital of Foshan, Foshan, China; Guangdong Lung Cancer Institute, Guangdong General Hospital, Guangzhou, China*

**Background:** Adjuvant chemotherapy is the standard of care for completely resected stage 2-3 non-small cell lung cancer(NSCLC). A few trials suggest neoadjuvant chemotherapy is a promising mode for resectable NSCLC. Indirect comparison meta-analysis of adjuvant versus neoadjuvant therapy showed no difference in survival. This study was conducted to determine whether neoadjuvant chemotherapy or adjuvant chemotherapy prolongs disease-free survival among patients with resectable NSCLC. **Methods:** Patients with clinical stage IB-IIIA NSCLC were eligible. Patients were randomly assigned to 3 cycles of neoadjuvant DC (Docetaxel: 75mg/m2, Carboplatin :AUC=5 on day 1 every 3wk),followed by surgery 3-6 wk after chemotherapy, or surgery followed by 3 cycles of adjuvant DC at the same schedule. The primary end point was 3 years Disease Free Survival(DFS); secondary end points were 3 years Overall Survival rate (OS) and Safety. Planned sample size is 410. **Results:** Between March 2006 and May 2011, 198 patients have been accrued, 97 in the neoadjuvant arm, 101 in the adjuvant arm. The neoadjuvant arm had more patients received chemotherapy( 100% v.s 85.1%, $P<0.001$ ) and received 3 cycles( 91.8% v.s82.6%, $P=0.061$) than adjuvant arm. Both arms are well tolerated to DC chemotherapy. The most common grade 3/4 adverse event is neutropenia (41.2% with neoadjuvant arm v.s 31.7% with adjuvant arm). One chemotherapy related death in adjuvant arm. One patient die of perioperative pulmonary embolism in neoadjuvant arm. No difference in peri-operative complication between two arms. The 3 years DFS was 45% in the neoadjuvant arm and 53% in the adjuvant arm, HR=0.88 (0.58-1.33), $P=0.54$. Median survival has not been reached in both arms. **Conclusions:** Neoadjuvant or adjuvant chemotherapy with docetaxel plus carboplatin in resectable clinical stage IB-IIIA NSCLC is feasible and safe. Preliminary results show similar 3 years DFS in both arms. The OS data has not matured in both arms. Clinical trial information: NCT00321334.

**7538 General Poster Session (Board #19H), Sat, 8:00 AM-11:45 AM**

# Utilization and impact of adjuvant chemotherapy (AC) in surgically resected stages I-III non-small cell lung cancer (NSCLC).

*Christina D. Williams, Ajeet Gajra, Apar Kishor Ganti, Michael J. Kelley; Durham VA Medical Center, Durham, NC; Syracuse VA Medical Center, SUNY Upstate Medical University, Syracuse, NY; University of Nebraska Medical Center, Omaha, NE; Durham VA Medical Center/Duke University Medical Center, Durham, NC*

**Background:** Clinical trials demonstrating improved survival with AC for stages I-III NSCLC are limited in their applicability to broader populations. We sought to describe the pattern of AC use and its correlation with survival in the population-based VA system. **Methods:** We conducted a retrospective analysis of pts with stages I-III NSCLC in the VA Central Cancer Registry. Descriptive statistics were used to examine patterns of AC use over an 8 yr period and to obtain survival rates associated with use of AC. Chi-square was used to compare distributions. **Results:** Among 28,173 pts with stages I-III NSCLC in 2001-2008, 10,043 had surgical resection. The proportion receiving AC was 9% (stage I), 34% (II), and 40% (III). Receipt of AC increased for each stage, with the greatest increase observed in stage II (2001-03: 12%; 2004-05: 41%; 2006-08: 50%). About 90% received a platinum agent; among these carboplatin was most common (77%) but by 2008 43% received cisplatin. For stages II and III in 2001-2003, the 3-year survival rate was similar irrespective of AC use. In latter time periods, survival rates were significantly higher for stage II AC pts (2004-2005: 53 vs 43%, $p=0.03$; 2006-2008: 58 vs 46%, $p=0.001$). Stage III AC pt diagnosed in 2006-2008 had a higher 3-yr survival (52 vs 36%, $p<0.001$). For all stages and years combined, use of cisplatin yielded a better 3-yr survival rate compared to carboplatin (62% vs 55%; $p=0.01$). 3-yr survival for stage I, II, and III, regardless of AC, increased over time (stage I: 60, 64, and 69%; stage II: 44, 47, 52%; stage III: 33, 40, and 44%). The fraction of lung cancer pts diagnosed at each stage during the 3 time periods was not significantly different. **Conclusions:** This retrospective study suggests a significant increase in use of AC for NSCLC in the VA, though half of surgically treated pts with stage II and III did not receive AC in 2006-2008. By univariate analysis, AC use is associated with a significantly better 3-yr survival for resected stage II and III NSCLC and the stage-specific 3-year survival for all pts improved over time in association with increasing use of AC. Cisplatin is associated with better survival compared to carboplatin. Multivariate analysis is planned.

**7539 General Poster Session (Board #20A), Sat, 8:00 AM-11:45 AM**

## Effect of age on impact of adjuvant chemotherapy for resected non-small cell lung cancer.

*Apar Kishor Ganti, Christina D. Williams, Ajeet Gajra, Michael J. Kelley; VA Nebraska-Western Iowa Health Care System, Omaha, NE; Durham VA Medical Center, Durham, NC; Upstate Medical University, Syracuse, NY; Durham VA Medical Center/Duke University Medical Center, Durham, NC*

**Background:** Adjuvant chemotherapy (AC) is considered standard of care in patients with resected stages 2 and 3 non-small cell lung cancer (NSCLC). However data regarding its utility in older patients are sparse. This analysis was conducted to evaluate the role of AC in older patients with early stage NSCLC. **Methods:** We conducted a retrospective analysis of patients with stages 1-3 NSCLC between 2001 and 2008 in the VA Central Cancer Registry. Patients were divided into two groups based on age: $<$70 yrs and $\geq$70 yrs. Descriptive statistics were used to examine patterns of AC use and to obtain survival rates associated with use of AC in the two age groups. Chi-square was used to compare distributions. **Results:** Of the 10,036 patients who underwent surgical resection, 3958 (39.4%) were $\geq$70 yrs, while 6078 were $<$70 yrs old. Overall, 11.2% of older patients (6.3% - stage 1, 21% - stage 2, 26.2% - stage 3) and 22.3% of younger pts (11.6% - stage 1, 41.1% - stage 2, 47.1% - stage 3) received AC. Of the patients who received AC, a greater proportion of younger patients received platinum-based AC (91.8 vs 86.4% vs; p=0.0008). Also, in each stage younger patients had a better 3 yr overall survival (OS) (Stage 1-69.2 vs 58%, stage 2 – 52.8 vs 39.1%, stage 3 – 42.5 vs 33.7%). Younger patients with stages 2 and 3 NSCLC who received AC had improved 3 yr OS (58.8 vs 48.6%; p=0.0009 and 48.8 vs 36.9%; p=0.0002 respectively). There was no difference in 3 yr OS for older patients based on AC when all stages were included. For patients with stages 2 and 3, a larger proportion of younger patients received cisplatin-based AC (11.3 vs 3.5%). Older patients with stages 2 and 3, who received cisplatin-based AC had a better 3 yr OS compared to those who received carboplatin-based AC or no AC (55.3 vs 42.2 vs 35.3% respectively; p=0.01). Similarly cisplatin-based AC had an improved 3 yr OS in younger patients with stages 2 and 3 NSCLC (61.4 vs 52 vs 43.4% respectively; p=0.0001). **Conclusions:** This analysis suggests that older patients do not benefit from AC after resection of stage 1-3 NSCLC to the same degree as younger patients. This differential effect may be due to less common use of cisplatin among older patients. Multivariate analyses are planned.

**7540 General Poster Session (Board #20B), Sat, 8:00 AM-11:45 AM**

# Impact of the presence of EGFR mutation on definitive chemoradiotherapy in patients with locally advanced non-small cell lung cancer: Pattern of relapses and survival analyses in 145 patients.

*Shigehiro Yagishita, Hidehito Horinouchi, Tomoko Taniyama, Shinji Nakamichi, Satoru Kitazono, Hidenori Mizugaki, Shintaro Kanda, Yutaka Fujiwara, Hiroshi Nokihara, Noboru Yamamoto, Minako Sumi, Kouya Shiraishi, Takashi Kohno, Koh Furuta, Koji Tsuta, Tomohide Tamura; Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan; Division of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan; Division of Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan; Division of Genome Biology, National Cancer Center Research Institute, Tokyo, Japan; National Cancer Center Research Institute, Tokyo, Japan; Division of Clinical Laboratories, National Cancer Center Hospital, Tokyo, Japan; Division of Pathology, National Cancer Center Hospital, Tokyo, Japan*

**Background:** EGFR mutational status is an important biomarker in advanced NSCLC patients. However, little is known about the frequency and clinical significance of the presence of EGFR mutation in patients with potentially curable locally advanced NSCLC (LA-NSCLC) eligible for definitive chemoradiotherapy (CRT). **Methods:** Between Jan 2001 and Dec 2010, we conducted analysis for the presence of EGFR mutations, in consecutive NSCLC patients who were eligible for CRT. The response rate (RR), progression-free survival (PFS), 2-year relapse-free rate, first relapse sites, and overall survival were investigated according to the EGFR mutational status. **Results:** A total of 528 patients received CRT at the National Cancer Center Hospital during the study period. Of these, 274 were diagnosed as having non-squamous NSCLC, and sufficient specimens for mutational analyses could be obtained from 145 patients. EGFR mutants (EGFR-mt) were found at a frequency of 18% in these patients. In addition to the well-known characteristics of NSCLC patients carrying EGFR mutations (female, adenocarcinoma, and never/ light smoker), the proportion of cases with smaller (T1/2) primary lesions was higher in patients with EGFR-mt than in those carrying wild-type EGFR (EGFR-wt). EGFR-mt showed a slightly better RR (85.7% vs. 72.9%), but similar median PFS (12.2 m vs. 10.6 m) and 2-year relapse free rates (23.8% vs. 29.2%) as compared to EGFR-wt. Local recurrence as first relapse occurred less frequently in EGFR-mt than in EGFR-wt (6% vs. 20%). After disease progression, a majority of EGFR-mt received EGFR-TKIs (62%), and these patients showed longer post-progression survival and a higher 5 year survival rate (60% vs. 40%) than EGFR-wt. **Conclusions:** Among the LA-NSCLC patients eligible for definitive CRT analyzed, 18% had EGFR- activating mutations. Although definitive CRT was similarly effective in both EGFR-mt and EGFR-wt, slightly better local control rate was noted in EGFR-mt. Treatment with EGFR-TKIs contributed to longer post-progression survival and overall survival in LA-NSCLC patients harboring EGFR mutations.

**7541 General Poster Session (Board #20C), Sat, 8:00 AM-11:45 AM**

# REINFORCE: A randomized trial of resistance training in patients with radically treated respiratory cancer.

*Veerle F Surmont, Bihiyga Salhi, Christel Haenebalcke, Sylvia Perez Bogerd, Delphine M Nguyen Dang, Roos Colman, Vincent Ninane, Karim Y Vermaelen, Thomas Malfait, Georges Van Maele, Eric Derom, Jan P. Van Meerbeeck; Ghent University Hospital, Gent, Belgium; AZ St Jan, Bruges, Belgium; Centre Hospitalier Universitaire Erasme, Brussels, Belgium; Centre Hospitalier Universitaire, Liege, Belgium; Ghent University, Ghent, Belgium; Centre Hospitalier Universitaire St Pierre, Brussels, Belgium; Ghent University Hospital, Ghent, Belgium; University Hospital Antwerp-MOCA, Edegem, Belgium*

**Background:** Limited evidence suggest that patients (pts) with respiratory cancer improve their post-radical treatment (PRT) exercise capacity (EC) and quality of life (QoL) by rehabilitation (REH). Whole body vibration (WBV) is proposed as an alternative to conventional resistance training (CRT). REINFORCE investigates the effect of 2 supervised resistance training programs on functional and maximal EC and QoL, measured by resp. 6 minutes walking distance (6MWD), Wmax and EORTC-QLQ-C30 physical functioning (PF). **Methods:** Consecutive pts with cI-IIIB (N)SCLC or cI-II mesothelioma were evaluated before (M1) and after (M2) completion of either surgery (S) +/- platin-based chemotherapy (PCT) and postop. radiotherapy (RT) or RT +/- PCT, and then randomized to usual care (UC) or 38 sessions of either CRT or WBV. After stratification for COPD, S, PCT and center, 6MWD (primary endpoint), Wmax and PF were measured at M1, M2 and after 12 weeks (w) of REH (M3). Minimal clinical important difference in 6MWD is 54 m, in Wmax 10 Watt and in PF +9 points. Mean changes are compared within and in-between the intention-to-treat intervention groups using linear regression models. **Results:** 70 pts were randomized with balanced M1-characteristics: UC 24; CRT 24; WBV 22; male 73%, median age 62 y(29-79); median BMI 25 kg/m$^2$(16-42); COPD 40%; NSCLC 91%; stage I-II 60%. 48% had S and 6% RT as sole therapy, 46% a combination of S or RT with PCT and/or PORT; pneumectomy in 19%. A median of 28 CRT-sessions (10 – 36) and 23 WBV-sessions (0 – 37) were attended with a median M2-M3 interval of 14 w (9-30). M2-M3 change in 6MWD is 95 m (58-132) in CRT ($p<.0001$), 37m (-1-76) in WBV ($p=0.06$), 1 m(-34-36) in UC and is significantly higher with CRT than with WBV (p value vs. UC 0.0006 and 0.16, resp.) and highest in CRT-pts without COPD (133 m (86-181), $p< 0.0001$). M3 values did not significantly exceed M1 with either intervention. M2-M3 change in Wmax significantly improved with 15 Watt (6-24) in both CRT and WBV($p= 0.002$). M2-M3 PF increased 6 points (-1–14) in CRT ($p= 0.1$) and 8 points (0–16) in WBV ($p=0.04$). **Conclusions:** In pts with respiratory cancer, PRT REH is recommended, with CRT significantly improving functional and maximal EC and WBV increasing maximal EC and PF. Clinical trial information: NCT00752700.

**7542 General Poster Session (Board #20D), Sat, 8:00 AM-11:45 AM**

# Correlation of epidermal growth factor receptor (EGFR) mutation profile with computed tomography (CT) imaging features in lung adenocarcinomas.

*Benjamin F. Chu, Efe Ozkan, Selnur B Erdal, Weiqiang Zhao, Konstantin Shilo, Gregory Alan Otterson; Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, OH; Department of Diagnostic Radiology, The Ohio State University Comprehensive Cancer Center, Columbus, OH; Department of Pathology, The Ohio State University Comprehensive Cancer Center, Columbus, OH*

**Background:** Imaging studies provide essential clinical information for lung cancer diagnosis, treatment and management. Features such as ground glass opacity (GGO) or internal air bronchogram (IAB), while commonly seen in early stage lung cancer, have minimal clinical implication. By examining a cohort at a single institution, we explored the hypothesis that radiographic characteristics correlates with the molecular signatures. **Methods:** Since 2009, our institution has prospectively characterized the EGFR status of all non-squamous lung carcinomas. Our inclusion criteria included tumor size $< 3$ cm and positive EGFR mutation. We randomly selected wild type (WT) patients matched by age and tumor size. The CT imaging of these patients was evaluated by a single radiologist (EO). **Results:** Imaging features were extracted from 20 WT and 19 EGFR-mutated tumors. Of the EGFR-mutated tumors, 7 had the exon 21 L858R point mutation and 12 had in-frame exon 19 deletion. There were 68% (13) solid nodules in EGFR-mutated and 90% (18) in WT tumors. While solid nodule was the primary feature seen in both WT and EGFR-mutated tumors, exon 21 mutation was associated with mixed ground glass/solid nodule (MGGS) ($p = 0.005$). This tendency, however, is not present in the exon 19 mutated tumors. No pure GGO was identified in either EGFR or WT group. IAB was present in 62% (24), pleural attachment (PA) in 87% (34), and spiculated (SP) as opposed to lobulated (LO) nodules in 90% (34) of the tumors, which do not differ significantly among groups. **Conclusions:** Early stage lung adenocarcinomas show a spectrum of imaging features that can be correlated with tumor's genetic mutations. MGGS is a distinct imaging characteristic differentiating exon 19 and exon 21 EGFR-mutated tumors.

| | Exon 19 n=12 (%) p value* | Exon 21 n=7 (%) p value# | Exon 19 and 21 n=19 (%) p value& | Wild type n=20 (%) |
|---|---|---|---|---|
| GGO | 0 | 0 | 0 | 0 |
| MGGS | 1(8) | 5(71) | 6(32) | 2(10) |
| Solid | 11(92) | 2(29 ) | 13(68) | 18(90) |
| | 1 | 0.01≠ 0.005 | 0.127 | |
| IAB | 7(58 ) | 6(86) | 13(68) | 11(55) |
| No IAB | 5(42) | 1(14 ) | 6(32) | 9(45) |
| PA | 10(83) | 6(86) | 16(84) | 17(85) |
| No PA | 2(17) | 1(14) | 3(16) | 3(15) |
| SP | 10(83 ) | 5(71) | 16(84) | 19(95) |
| LO | 2(17) | 2(29) | 3(16) | 1(5) |

* WT and exon 19; # WT and exon 21; & WT and exon 19&21; ≠ p value comparing exon 19 and exon 21.

**7543 General Poster Session (Board #20E), Sat, 8:00 AM-11:45 AM**

## Outcomes of elderly stage I lung cancer patients treated with segmentectomy via video assisted thoracoscopic surgery or open resection.

*Cardinale B. Smith, Grace Mhango, Juan P. Wisnivesky; Division of Hematology and Medical Oncology, The Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY; Mount Sinai School of Medicine, New York, NY; Divisions of General Internal Medicine and Pulmonary and Critical Care Medicine, Mount Sinai School of Medicine, New York, NY*

**Background:** Video-assisted thoracic surgery (VATS) is considered an alternative to open lobectomy for the treatment of non-small cell lung cancer (NSCLC). Limited data is available however, regarding the equivalence of open vs. VATS segmental resections, particularly among elderly patients. In this study, we used population-based data to compare postoperative and oncologic outcomes following open vs. VATS segmentectomy for early NSCLC. **Methods:** We identified all stage I NSCLC patients >65 year treated with VATS or open segmentectomy from the Surveillance, Epidemiology, and End Results registry linked to Medicare claims. We used propensity score methods to control for differences in the baseline characteristics of patients. Overall and lung cancer-specific survival of patients treated with VATS vs. open segmentectomy was compared after adjusting, stratifying, or matching patients based on their propensity score. We performed secondary analyses evaluating perioperative complications, need for intensive care unit (ICU) admission, extended length of stay, and perioperative mortality. These were repeated adjusting for physician characteristics (sociodemographics, specialty, and procedure volume). **Results:** Of the 577 study patients, 27% underwent VATS resection. VATS were mostly performed by high volume surgeons ($p<0.001$). Overall (hazard ratio [HR]: 0.80, 95% CI: 0.60-1.06) and lung cancer-specific (HR: 0.71, 95% CI: 0.45-1.12) survival was similar among treatment groups. VATS-treated patients had lower rates of postoperative complications (odds ratio [OR]: 0.55, 95% confidence interval [CI]: 0.37-0.83), need for ICU admission (OR: 0.18, 95% CI: 0.12-0.28), and decreased length of stay (OR: 0.41, 95% CI: 0.41-0.81) after adjusting for propensity scores. The distribution of all postoperative complications, ICU admission, extended length of stay, and perioperative mortality was not significantly different across groups after adjusting for surgeon characteristics. **Conclusions:** VATS segmentectomy can be safely performed among elderly patients with early stage NSCLC and is associated with equivalent postoperative and long-term oncologic outcomes.

**7544 General Poster Session (Board #20F), Sat, 8:00 AM-11:45 AM**

## Test performance of PET-CT for mediastinal lymph node staging of pulmonary carcinoid tumors.

*Holly Pattenden, Emma Beddow, Michael Dusmet, Andrew G Nicholson, Iyer Swetha, Adrian Marchbank, Amy Greenwood, Douglas West, Priyadharshanan Ariyaratnam, Mahmoud Loubani, Felice Granato, Alan Kirk, Eric Kian Saik Lim, UK Thoracic Surgery Collaborative; Royal Brompton & Harefield Trust, London, United Kingdom; Royal Brompton Hospital, London, United Kingdom; Derriford Hospital, Plymouth, United Kingdom; Bristol Royal Infirmary, Bristol, United Kingdom; Castle Hill Hospital, Hull, United Kingdom; Golden Jubilee National Hospital, Clydebank, United Kingdom*

**Background:** PET-CT is a standard investigation to stage the mediastinum in non-small cell lung cancer when radical management is planned. The clinical utility of PET-CT in carcinoid tumours is uncertain as its test performance at identifying mediastinal lymph node disease in these tumours is as yet undefined with such tumours being rare and FDG avidity often variable or low. We sought to determine the test performance of PET-CT for mediastinal lymph node staging of pulmonary carcinoid tumours. **Methods:** We collated retrospective data from 5 institutions for a consecutive series of patients who underwent thoracic surgery for carcinoid tumours and had preoperative PET-CT staging prior to surgery (with lymph nodal dissection). PET-CT results were compared against the reference standard of pathologic results obtained from lymph node dissection, and test performance reported using sensitivity and specificity. **Results:** From November 1999 to May 2012, a total of 153 patients with a preoperative PET-CT scan from 5 institutions underwent surgery for a carcinoid tumour. The mean age of the patients was 60 (SD 16) and 67 were male (44%). The pathologic sub-type was typical carcinoid in 138 patients (90%) and atypical carcinoid in 15 patients (10%). The mean SUV uptake in the primary tumour was 4.9 (SD 5). Results from lymph node dissection were obtained in 125 patients and the sensitivity and specificity of PET-CT to identify mediastinal lymph node disease was 40% (95% CI 5-85%) and 93% (93-99%) respectively. **Conclusions:** In this largest cohort study to date, our results suggest that PET-CT has a poor sensitivity but good specificity for mediastinal lymph node metastases for pulmonary carcinoid tumours. Therefore lymph node metastases cannot accurately be ruled out in carcinoid tumours with a negative PET-CT. If treatment decisions are based on the N2 status, invasive mediastinal staging should be undertaken in carcinoid tumours.

**7545 General Poster Session (Board #20G), Sat, 8:00 AM-11:45 AM**

# Scoring system predicting overall survival (OS) in patients (Pts) with non-small cell lung cancer (NSCLC).

*Steven E. Schild, Angelina D. Tan, Jason A. Wampfler, Julian R. Molina, Helen J. Ross, Ping Yang, Jeff A. Sloan; Mayo Clinic, Scottsdale, AZ; Mayo Clinic, Rochester, MN*

**Background:** Interpretation of lung cancer clinical trials is complicated by the heterogeneity of the patient population due to disease burden and comorbidities making pre-trial assessment of OS probability challenging. **Methods:** To create and validate a scoring system to estimate OS and improve the quality of future trials, this study evaluated the pretreatment prognostic factors of 2,442 pts with NSCLC. Univariate (UV) and multivariate (MV) Cox models were used to evaluate the prognostic importance of each baseline factor on OS. Those prognostic factors significant on both UV and MV analyses that were used to develop the scoring system included overall quality of life, age, sex, stage, ECOG performance status, the presence of other cancers, and smoking cessation. The score for each factor was determined by dividing the 5-year OS rate (in %) by 10 and summing these scores to form a total score. Multivariate models and the score for each factor were validated using bootstrapping with 1000 iterations from the original samples. **Results:** The score for each factor ranged from 1 to 7 points and the total scores ranged between 23 and 39 points. Higher scores reflected better OS. Categorization of the score was delineated first by clinician expert opinion (see Table) and then by multiple statistically defined empirical cut points. All categorization schemes demonstrated successful prognostic power. The bootstrap method confirmed the reliability of multivariate Cox model and score (Spearman correlation coefficient= 0.45). **Conclusions:** Prognostic factors significantly associated with OS on both UV and MV analysis were used to construct a valid scoring system which can be used to predict survival of NSCLC pts. This scoring system can be used by clinicians in counseling pts and for stratification in future trial design.

**Total score and the corresponding 5-year OS.**

| Total score | N | 5-year OS (%) (95% CL) | Hazard ratio (95% CL) |
|---|---|---|---|
| **23-26** | 49 | 0.0% (0.0%, 0.0%) | 19.29 (13.37,27.83) |
| **27-29** | 209 | 8.3% (2.3%, 14.2%) | 10.86 (8.56,13.76) |
| **30-32** | 423 | 26.1% (20.8%, 31.4%) | 5.81 (4.71,7.16) |
| **33-35** | 733 | 51.3% (46.8%, 55.9%) | 2.57 (2.10,3.15) |

**7546 General Poster Session (Board #20H), Sat, 8:00 AM-11:45 AM**

## Appropriateness of imaging in lung cancer in a national cohort.

*Leah M. Backhus, Farhood Farjah, Thomas K Varghese, Aaron Cheng, Xiao Hua Zhou, Douglas E. Wood, Larry Kessler, Steven B Zeliadt; Veterans Affairs Puget Sound Healthcare System, Seattle, WA; University of Washington, Seattle, WA; Veterans Affairs Puget Sound Health Care System, Seattle, WA*

**Background:** Rising healthcare costs prompt emphasis on quality, appropriate care, and cost containment. Imaging is a source of high healthcare expenditures in cancer. We sought to examine variability of adherence to national guidelines for staging, and appropriateness criteria for imaging for patients with locally advanced lung cancer. **Methods:** Stage IIB, IIIA, or IIIB lung cancer patients were identified from the national VA Central Cancer Registry from 2004-2008 with linkage to VA data and Medicare claims. Imaging was assessed 180 days pre and post diagnosis per National Comprehensive Cancer Network guidelines and American College of Radiology Appropriateness Criteria for Imaging. Multivariate logistic regression with robust variance estimates (adjusting for within-cluster correlation by facility) was used to control for covariates and results reported as adjusted risk differences (95% confidence intervals [CI]). **Results:** Recommended imaging was performed in 69.5% of patients for brain imaging and 51.1% of patients for positron emission tomography (PET). Overutilization, with combined bone scintigraphy and PET (BS/PET), occurred in 19.7% of patients and did not vary over time (15.8% to 19.5% p=0.168). Facilities affiliated with a medical school had a 14.8 (CI -25.2, -4.4) percentage point lower utilization of PET. Facility volume and tumor board availability were not associated with variability. Appropriateness of imaging varied significantly by region. New England had the highest rates of imaging. Relative to New England, brain imaging was lowest in the Great Basin Region with 26.9 (-40.0, -14.0) percentage point decrease. Both recommended PET use and overutilization of BS/PET was lowest in the Mississippi Region with 25.0 (CI -49.3, -0.6) and 11.7 (CI – 23.3, -0.1) percentage point decrease respectively compared to New England. **Conclusions:** A significant proportion of patients do not receive recommended imaging and many undergo excessive imaging for lung cancer. Furthermore, there is substantial regional variation in imaging utilization. These observations are hallmarks of poor quality. A disease-based quality improvement plan aimed at modification via policy and reimbursement initiatives may mitigate poor quality care.

**7547 General Poster Session (Board #21A), Sat, 8:00 AM-11:45 AM**

# Association of miR-141 and miR-200c with time to recurrence (TTR) and overall survival (OS) in resected non-small-cell lung cancer (NSCLC) adenocarcinoma (ADC) patients (p).

*Marc Campayo, Alfons Navarro, Rut Tejero, Maria L Cabanas, Laureano Molins, Ramon M Marrades, Jose Ramirez, Mariano Monzo, Nuria Vinolas; Department of Medical Oncology, Hospital Clinic de Barcelona, Barcelona, Spain; School of Medicine, University of Barcelona, IDIBAPS, Barcelona, Spain; Department of Pathology, CDB, IDIBPAS, Hospital Clinic de Barcelona, Barcelona, Spain; Thoracic Surgery, ICT, IDIBAPS, Hospital Clinic de Barcelona, Barcelona, Spain; Department of Pneumology. ICT. IDIBAPS. Hospital Clinic de Barcelona, Barcelona, Spain; Department of Pathology, CDB, IDIBAPS, Hospital Clinic de Barcelona, Barcelona, Spain; Hospital Clinic de Barcelona, Barcelona, Spain*

**Background:** Surgical resection remains the standard curative treatment for early-stage NSCLC, but nearly 50% of p experience recurrence, highlighting the need for novel diagnostic and therapeutic strategies. Moreover, treatments in NSCLC are often histology-dependent, underlining the need for histology-related markers. MicroRNAs (miRNAs) are promising molecular markers in cancer, with marked differences in expression according to histology. miR-200 family members have been associated in vitro with the regulation of epithelial-mesenchymal transition. We have examined their impact on outcome in resected NSCLC p. **Methods:** We analyzed miRNA expression using TaqMan assays in 160 tumor samples from NSCLC p who had undergone surgical resection and correlated our findings with TTR and OS. **Results:** p characteristics: age, 67 (51-83); 140 male; 96 (60%) stage I, 34 (21.3%) stage II, 30 (18.7%) stage III; 77(48.1%) ADC, 71(44.4%) squamous cell carcinoma (SCC); 16 (9.1%) received adjuvant treatment. With a median follow-up of 28 months (m), 64 p (40%) had relapsed. TTR for the 107 p with high miR-200c was 26.7 m vs 100.2 m for the 52 p with low miR-200c ($P=0.032$). OS for p with high miR-200c was 71.2 m vs. 125 m for p with low miR-200c ($P=0.01$). TTR for 112 p with high miR-141 was 26.7 m vs. 100.2 m for 46 p with low miR-141 ($P=0.06$). OS for p with high miR-141 was 72 m vs. 118 m for p with low miR-141 ($P=0.02$). Interestingly, neither miR-200c nor miR-141 correlated with TTR or OS in SCC p. In contrast, in ADC p, the prognostic value of both miRNAs increased: miR-200c (TTR, $P=0.01$; OS, $P<0.0001$) and miR-141 (TTR, $P=0.003$; OS, $P<0.0001$). This prognostic value was maintained in the subgroup of stage I p: miR-200c (TTR, $P=0.011$; OS, $P<0.001$) and miR-141 (TTR, $P=0.018$; OS, $P<0.001$). In the multivariate analysis, miR-200c and miR-141 emerged as an independent prognostic factor for OS (OR: 3.2, $P=0.006$; OR:2.5, $P=0.02$, respectively) together with age$>65$ (OR: 3.3, $P=0.001$) and stage I (OR: 0.3, $P=0.004$). **Conclusions:** miR-200c and miR-141 expression is associated with TTR and OS in resected ADC but not in SCC NSCLC p.

**7548 General Poster Session (Board #21B), Sat, 8:00 AM-11:45 AM**

## Pulmonary pure ground-glass opacity lesions: Use of computed tomography attenuation for predicting tumor progression.

*Takashi Eguchi, Ryoichi Kondo, Satoshi Kawakami, Mina Matsushita, Tetsu Takeda, Takao Sakaizawa, Yoshiaki Tominaga, Gaku Saito, Masahiro Hashizume, Masayuki Toishi, Takayuki Shiina, Kazuo Yoshida, Jun Amano, Tomonobu Koizumi; Shinshu University, Matsumoto, Japan; Matsumoto Medical Center Chushin Hospital, Matsumoto, Japan*

**Background:** Cases with pure ground-glass opacity (GGO) are increasing with the use of computed tomography (CT). In some cases, pure GGO on follow-up CT may represent tumor enlargement or the presence of solid components. We evaluated the natural progression of pure GGO lesions during a long-term follow-up period of more than 2 years. **Methods:** We retrospectively investigated 95 patients with pure GGO lesions detected between February 2003 and December 2010, in whom these lesions were monitored using CT for more than 2 years. **Results:** The median follow-up period was 64.7 months (range, 24–114 months). During the follow-up period, areas showing GGO increased in size or appeared to have solid components in 49 patients (group 1) and showed no change in 46 patients (group 2). We compared patient characteristics and tumor properties between the 2 groups. Mean CT attenuation values of the tumors differed significantly between groups 1 (-639.9 $\pm$ 88.9 HU) and 2 (-709.2 $\pm$ 60.9 HU). In contrast, no significant differences were noted with regard to age, gender, smoking history, lung cancer history, tumor size, and total numbers of GGO lesions between the 2 groups. The difference in the time to tumor growth according to the initial mean CT attenuation value was estimated using the Kaplan–Meier method. The growth incidence at 114 months for lesions with a mean CT attenuation value of -650 HU or more ($n = 35$) and less than -650 HU ($n = 60$) were estimated to be 96% and 48%, respectively. The difference between the 2 Kaplan–Meier curves was statistically significant ($p < 0.0001$). The usefulness of the mean CT attenuation value in predicting the growth of GGO lesions was evaluated using receiver operating characteristic analysis. The sensitivity and specificity was 63% and 87%, respectively, for a mean CT attenuation cutoff value of -650 HU. The area under the curve was 0.76. **Conclusions:** Many pure GGO lesions have potential for growth as seen during long-term follow-up. CT attenuation is useful in predicting the growth of GGO lesions.

**7549 General Poster Session (Board #21C), Sat, 8:00 AM-11:45 AM**

# Concurrent chemoradiation (CChRT) with bi-weekly docetaxel and cisplatin and thoracic radiotherapy for stage III non-small cell lung cancer (NSCLC): A phase II study from the Galician Lung Cancer Group.

*Joaquin Casal Rubio, EM Brozos, Martin Lázaro Quintela, Sergio Vazquez-Estevez, Jl Firvida, MB Taboada, M Caeiro, JE Castro, Maria Vieito Villar, Clara Senin Estor, MJ Villanueva, Silvia Varela Ferreiro, MC Areses, C Pena, P Calvo, E. Hernandez, N. Martinez, Urbano Anido, Gerardo Huidobro; Complexo Hospitalario Universitario de Vigo, Vigo, Spain; Complexo Hospitalario Universitario de Santiago, Santiago, Spain; Hospital Universitario Lucus Augusti, Lugo, Spain; Complexo Universitario de Ourense, Ourense, Spain; Complexo Universitario de Santiago, Santiago, Spain; Complexo Hospitalario Universitario de Ourense, Ourense, Spain; Hospital Clinico Universitario, Santiago de Compostela, Spain; Complexo Hospitalario Universiotario de Pontevedra, Vigo, Spain*

**Background:** CChRT is recommended as the evidence-based approach for the management of patients (p) with locally advanced stage III NSCLC and a good performance status, although a clearly superior regimen has not been identified. The aim of our study was to evaluate the effectiveness and toxicities of CChRT with bi-weekly docetaxel (D) and cisplatin (C) and thoracic radiotherapy. **Methods:** 50 p with histologically confirmed inoperable locally advanced NSCLC, stage IIIAN2/IIIB (no pleural T4), PS 0-1 and adequate lung function (FEV1 $>$ 1.1, V20 $<$ 25%) were included: one cycle of D 75 mg/m2 on day 1 and C 40 mg/m2 days 1-2 followed at 21 days by CChRT with bi-weekly D 40 mg/m2 and C 40 mg/m2 for four courses, during conformal thoracic radiotherapy (66 Gys, 180 cGy/day). The primary objective was overall survival (OS); secondary objectives were progression free survival (PFS), response rate (RR) and toxicity. Median follow-up: 14,5 months. **Results:** The p characteristics were: mean age 59,1 years (34-75); male/female 44/6; squamous/adeno/large cell carcinoma: 52%/34%/14%; stage IIIAN2 14 p (28%) and stage IIIB 36 p (72%). All p were evaluable for response and toxicity. RR: 4 CR, 36 PR (RR 80%; 95% CI:69-91), 4 SD (8%) and 6 PD (12%). The median PFS was 13 months (95% CI:8-18) and median OS was 19 months (95% CI:14-24). The PFS and OS at 1/2 years were 52%/30% and 79%/40% respectively. A total of 50 cycles of D-C induction chemotherapy were given; main toxicities (NCI-CTC 3.0) per p Grade (g) 1-2/3-4 (%) were as follows: neutropenia 2/16; anemia 12/0; nausea/vomiting 28/2; diarrhea 22/4; there were two episodes of febrile neutropenia. Main toxicities per p in CChRT (D-C doses: 192, 3.8 per p; mean doses RT: 64,6 Gys) were g1-2/3 (%): neutropenia 28/6; anemia 60/0; esophagitis 52/4 and pneumonitis 34/0; there were four episodes of hospitalization: febrile neutropenia, 2 p and g3 esophagitis, 2 p. **Conclusions:** CChRT with bi-weekly docetaxel and cisplatin and thoracic radiotherapy is a feasible treatment option for inoperable locally advanced stage III NSCLC, showing good clinical efficacy and tolerability with acceptable long-term survival.

**7550 General Poster Session (Board #21D), Sat, 8:00 AM-11:45 AM**

## Prognostic significance of α1,6-fucosyltransferase (α1,6-FT) in non-small cell lung cancers (NSCLCs).

*Rio Honma, Ichiro Kinoshita, Eiji Miyoshi, Utano Tomaru, Yoshihiro Matsuno, Yasushi Shimizu, Satoshi Takeuchi, Kichizo Kaga, Naoyuki Taniguchi, Hirotoshi Akita; Department of Medical Oncology, Hokkaido University Graduate School of Medicine, Sapporo, Japan; Department of Molecular Biochemistry and Clinical Investigation, Osaka University Graduate School of Medicine, Suita, Japan; Department of Pathology, Hokkaido University Graduate School of Medicine, Sapporo, Japan; Department of Surgical Pathology, Hokkaido University Hospital, Sapporo, Japan; Department of Cardiovascular and Thoracic Surgery, Hokkaido University Graduate School of Medicine, Sapporo, Japan; Department of Disease Glycomics, Institute of Scientific and Industrial Reserch, Osaka University, Ibaraki, Japan*

**Background:** Lung cancer is one of the leading causes of cancer death throughout the world. A more sophisticated understanding of the pathogenesis and biology of NSCLCs could provide useful information for predicting clinical outcome and individualizing treatment. α1,6-FT is the only one enzyme responsible for the core α1,6-fucosylation of *N*-glycans of glycoproteins, including EGF receptor, TGF-β1 receptor, and integrin α3β1. **Methods:** α1,6-FT expression was studied by immunohistochemistry in a cohort of 129 surgically resected NSCLCs, classified categorically based on the proportion of positively stained cancer cells (high, $> 20\%$; or low, $< 20\%$), and analyzed statistically in relation to various characteristics, including histology, survival and prognosis. **Results:** High and low expression of α1,6-FT was found in 67 and 62 of 129 NSCLCs, respectively. Multivariate logistic regression analysis revealed a significant association between high α1,6-FT expression and non-squamous cell carcinoma (mostly adenocarcinoma), as compared with squamous cell carcinomas (odds ratio, 3.51; $p = 0.008$). Patients with tumors having high α1,6-FT expression had significantly shorter survival time than patients with tumors having low expression in potentially curatively resected NSCLCs ($p = 0.03$) and adenocarcinomas ($p = 0.009$), as well as in pStage I NSCLCs ($p = 0.03$) by the log-rank test. Surprisingly, in pStage I adenocarcinomas, 12 of 23 patients with tumors having high α1,6-FT expression died of lung cancer, although none of 15 patients with tumors having low expression died of lung cancer. High α1,6-FT expression was a significant and independent unfavorable prognostic factor in potentially curatively resected NSCLCs (hazard ratio, 1.81; $p = 0.047$) and adenocarcinomas (hazard ratio 2.39; $p = 0.006$) and in pStage I NSCLCs (hazard ratio 2.55; $p = 0.03$) by Cox's proportional hazards model analysis. **Conclusions:** These results suggest that α1,6-FT may play a pivotal role for the biological characteristics of NSCLCs. α1,6-FT expression is associated with histology of NSCLCs, and may be a new prognostic marker for overall NSCLCs and adenocarcinomas.

**7551 General Poster Session (Board #21E), Sat, 8:00 AM-11:45 AM**

# Reducing futile thoracotomy rates in PET-CT staged non small cell lung cancer: Clinical risk factors from a population-based review.

*Martin Smoragiewicz, Janessa J. Laskin, Don Wilson, Katherine Ramsden, Yongliang Zhai, Cheryl Ho; British Columbia Cancer Agency, Vancouver, BC, Canada; Department of Nuclear Medicine, British Columbia Cancer Agency, Vancouver, BC, Canada; BC Cancer Agency, Vancouver, BC, Canada; University of British Columbia, Department of Statistics, Vancouver, BC, Canada*

**Background:** The use of PET-CT in staging NSCLC reduces futile thoracotomy (FT) rates to approximately 30%. We aimed to identify pre-operative clinical risk factors for FT in patients (pts) staged with PET-CT. **Methods:** The British Columbia Cancer Agency (BCCA) provides care to 4.5 million people. A retrospective chart review was conducted on all pts referred to the BCCA in 2009-2010 who had staging PET-CT and thoracotomy for NSCLC. Exclusion criteria: tri-modality therapy, clinical N2 disease, or cancer within 5 years. FT was defined as benign lung lesion, exploratory thoracotomy, pathologic N2 disease, stage IIIB/IV, or recurrence or death < 1 year of surgery (sx). The FT and non-FT groups were compared with the Fisher test in univariate analysis and logistic regression model multivariate analysis. **Results:** 108 pts met inclusion criteria. Baseline characteristics: male 42%, median age 67 (45-82), ECOG 0-1/+2: 85%/15%, never/former/current smoker 18.5/42.5/39%, weight loss >10% 9%. Disease characteristics: nonsquamous/ squamous histology 72/28%, median primary tumor size 3.2 cm, median SUVmax 10.1, PET + N1 24%. Median time from PET to sx 29 days. 29% pts received adjuvant chemotherapy. Thoracotomy was futile in 27 pts (25%); 14 recurred < 1 yr of sx, 10 pathologic N2 and 1 each incomplete resection, pleural disease at sx, death within 1 yr. On univariate analysis, PET + N1 (odds ratio [OR] 3.77, p 0.008) and primary tumor size > 3.2cm (OR 2.93, p 0.026) were associated with FT. On multivariate analysis, ECOG >1 (OR 4.57, p 0.017), PET + N1 status (OR 4.24, p 0.006) and primary tumor size > 3.2cm (OR 2.87, p 0.039) were associated with FT. Among the 26 pts wth PET + N1, 44% underwent FT; 23% due to N2 disease, 19% relapsed within 1 yr, 4% incomplete sx. 27% had mediastinoscopy or EBUS staging. Among the 82 pts with PET – N1,18% underwent FT; 5% due to N2 disease, 11% relapsed < 1 yr, 2% pleural dx or death < 1 yr. **Conclusions:** Pre-operative ECOG >1, primary tumor size > 3.2 cm and PET + N1 are associated with higher rates of FT in NSCLC. PET + N1 disease corresponds to higher rates of N2 disease and surgical staging may reduce FT in this population. These factors should be taken into consideration to reduce FT rates in NSCLC.

**7552 General Poster Session (Board #21F), Sat, 8:00 AM-11:45 AM**

## Fibroblast growth factor receptor 1 (*FGFR1*) gene copy number gain in adenocarcinoma and squamous cell carcinoma of the lung.

*Ximing Tang, Yuwen Xue, Xinying Su, Nusrat Harun, Yiran Cai, Carmen Behrens, Vassiliki Papadimitrakopoulou, David Blowers, Cesar Moran, Neda Kalhor, David C. Rice, Garry Beran, J. Jack Lee, Elaine Kilgour, Ignacio Ivan Wistuba; The University of Texas MD Anderson Cancer Center, Houston, TX; AstraZeneca Innovation Center China, Shanghai, China; Department of Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; AstraZeneca, Macclesfield, United Kingdom; AstraZeneca, Macclesfield, England; Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX; AstraZeneca, Oncology Innovative Medicines, Macclesfield, United Kingdom*

**Background:** FGFR-1 is a novel target for therapy in non-small cell lung carcinoma (NSCLC). *FGFR1* gene has been shown to be amplified in ~20% of squamous cell carcinomas (SCC) of the lung. The frequency of *FGFR1* copy number gain (CNG) and gene amplification (GA) in lung adenocarcinoma (AC) is unknown, and the clinicopathological and molecular characteristics of the NSCLC tumors with *FGFR1*gene increase have not been fully described. **Methods:** We examined *FGFR1* gene copy number (GCN) by fluorescent in-situ hybridization (FISH) and FGFR1 protein expression by immunohistochemistry in 475 surgically resected NSCLCs (162 SCCs, and 313 ACs) stages I-III in tissue microarrays. Three *FGFR1* FISH categories were identified: a) no CNG; b) CNG, defined as ≥4 gene copies in ≥40% of cells; c) GA, defined as ratio of copies of *FGFR1:CEP8* ≥2 or presence of tight gene clusters in ≥10% of cells. FGFR1 protein expression in the cytoplasm and membrane of tumor cells was quantified using H score. **Results:** *FGFR1* GA was detected only in SCCs (14 cases, 9%). CNG was detected in both SCC (39 cases, 24%) and AC (80 cases, 26%). In AC, significantly higher frequency of CNG was detected in patients with smoking history ($P=0.008$) and in tumors with low differentiated histology ($P=0.0005$). No correlation was detected between *FGFR1* CNG and mutation of *KRAS* and *EGFR* in AC. In SCC, tumors with *FGFR1* CNG/GA had higher cytoplasmic *FGFR1* protein expression than those with no copy changes ($49\pm39$ vs. $26\pm21$, $P<0.001$), and the protein expression correlated with GCN ($R=0.55$; $P<0.001$). In multivariate analysis, patients with stage I/II SCCs having *FGFR1* gene copy ≥6 or GA showed a significantly better overall survival (HR=0.26; 95% CI: 0.08-0.84, $P=0.02$) than patients with <6 gene copy, after adjusting for smoking, gender and tumor size. An increase on *FGFR1*copy number was detected in 8/45 (18%) brain metastasis compared with primary tumors. **Conclusions:** In NSCLC, *FGFR1* GA occurs only is a small subset of SCCs (9%), whereas CNG is a relatively frequent phenomenon in both SCC (24%) and ACs (25%). *FGFR1* copies ≥6 or GA is associated with better outcome in patients with surgically resected stages I/II SCCs of the lung.

**7553 General Poster Session (Board #21G), Sat, 8:00 AM-11:45 AM**

## The potential role of lung cancer screening in lung cancer survivors.

*John M. Varlotto, Nengliang Yao, Rickhesvar Mahraj, Abram Recht, John Charles Flickinger, Chandra Prakash Belani, Jennifer Toth, Michael Reed, Chris Sciamanna, Christopher Gilbert, Suhail M. Ali, Malcolm M. DeCamp; Penn State Hershey Cancer Institute, Hershey, PA; Penn State Hershey Medical Center, Hershey, PA; Beth Israel Deaconess Medical Center, Boston, MA; Presbyterian University Hospital, Pittsburgh, PA; Pennsylvania State University Cardiovascular Institute, Hershey, PA; Lebanon VA Medical Center, Lebanon, PA; Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL*

**Background:** The National Lung Screening Trial demonstrated improved overall survival (OS) and lung cancer specific survival (LCSS) in the 55-74-year-old age group, likely due to finding early-stage lung cancer. Patients with a past history of lung cancer were excluded from this trial. The purpose of investigation is to assess whether there is an increasing frequency of second lung cancers and whether the first primary reduces survival in a proposed screening population with Stage I (tumor size $<$4cm) NSCLC (survivor population, SP) as compared to similar patients presenting with their first lung cancer (new patients, NP). **Methods:** The SEER databases were used to investigate incidence (1973-2009) and OS/LCSS (1998-2009) of secondary lung cancer. Incidence was examined by frequency analysis and trend analysis. A SP was chosen who was originally treated definitively for Stage I-III NSCLC and survived at least four years after diagnosis (N=515). They were compared to NP who were presenting with their first lung cancer (N = 21,040). OS/LCSS in NP and SP with Stage I NSCLC were analyzed by Kaplan-Meier estimation, log-rank tests, and multivariate proportional hazards modeling. **Results:** The annual incidence rate/100,000 for secondary lung cancer has increased almost 5-fold in last 36 years (2.5 in 1973; 12 in 2009; $p<0.001$), more so in male patients. OS was not significantly different between NP and SP after accounting for treatment, tumor, and patient characteristics (male, HR=1.111, p=0.330; female, HR=0.840, p=0.118). Multivariate analyses show that LCSS was significantly better in SP females than for NP females (HR=0.849, p=0.025) but did not differ for males (HR=0.923, p=0.388). In the SP, OS decreased significantly with less aggressive treatment compared to lobectomy as the reference treatment (sub-lobar resection, HR=1.841, p=0.009; radiation, HR=2.351, p=0.002; observation, HR=2.145, p=0.016). Patient and tumor characteristics of the first lung cancer diagnosis were not significantly linked to OS. **Conclusions:** NP and SP diagnosed at Stage I had similar survival rates. The SP group also benefitted from increasingly aggressive treatment. Screening for lung cancer might be of benefit to lung cancer survivors.

**7554 General Poster Session (Board #21H), Sat, 8:00 AM-11:45 AM**

# The role of lymphatic vascular invasion in the prognosis and determination of therapy in surgically resected non-small cell carcinoma of the lung.

*Malcolm M. DeCamp, Adin-Cristian Andrei, Satvik Ramakrishna, Laura Nyshel Medford-Davis, Julia Shelkey, Megan McClean, Abram Recht, John M. Varlotto; Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL; Northwestern Memorial Hospital, Chicago, IL; Feinberg School of Medicine, Northwestern University, Chicago, IL; Ben Taub General Hospital, Houston, TX; Penn State Milton S. Hershey Medical Center, Hershey, PA; Feinberg School of Medicine, Chicago, IL; Beth Israel Deaconess Medical Center, Boston, MA; Penn State Hershey Cancer Institute, Hershey, PA*

**Background:** Lymphatic-vascular invasion (LVI) is not currently considered in staging of non-small cell lung cancer (NSCLC). We assessed the impact of LVI on overall survival (OS), local/distant recurrence (LR/DR) and patterns of recurrence. **Methods:** 869 consecutive patients who underwent a definitive surgical resection ± adjuvant chemotherapy for NSCLC from 2000–2008 were qualified for analysis if they did not receive any adjuvant/neo-adjuvant radiotherapy, had at least three months of follow-up, and did not have a history of other cancers within 5 years. Tumors with LVI (N = 160) were compared to tumors without LVI (N = 705). LR/DR rates at 2,3, and 5 years were calculated by the methods of Kaplan-Meier. Association between LVI and OS and LR/DR were compared in the total population and in a propensity matched population (PS) by factors affecting OS and LR/DR (n=160 matched pairs). **Results:** OS, LR, and DR were significantly worse in patients with LVI in the total population and in the subset of patients matched by propensity score (Table). In the PS-matched pairs, LVI was associated with a greater number of N1 nodes involved, a longer length of stay, higher histologic grade, and higher T-stage. Patterns of local failure (P<.001) but not distant failure (P=.11) differed between patients with and without LVI. Tumors with LVI were 3-fold more likely to recur in ipsilateral mediastinal nodes. In a subset analysis of tumors < 4cm (n=121 PS matched pairs), LVI was also associated with higher LR, DR, a lower OS and a 4-fold risk of mediastinal nodal recurrence. **Conclusions:** Detection of LVI in resected NSCLC predicts aggressive biologic behavior and provides important prognostic information. LVI may help identify high-risk cohorts within discreet TNM stages who could benefit from adjuvant therapies.

| Survival/recurrence factor | 2-year recurrence free or OS (%) | 3-year recurrence free or OS (%) | 5-year recurrence free or OS (%) |
|---|---|---|---|
| OS-no LVI | 89 | 81 | 67 |
| OS-LVI | 69 | 61 | 40 |
| LR-no LVI | 86 | 81 | 71 |
| LR- LVI | 69 | 65 | 54 |
| DR-no LVI | 96 | 95 | 94 |
| DR- LVI | 88 | 85 | 85 |
| OS-no LVI-PS | 86 | 79 | 67 |
| OS-LVI-PS | 70 | 61 | 40 |
| LR-no LVI-PS | 82 | 75 | 68 |
| LR- LVI-PS | 69 | 65 | 55 |
| DR-no LVI-PS | 96 | 96 | 94 |
| DR- LVI-PS | 88 | 86 | 86 |

**7555 General Poster Session (Board #22A), Sat, 8:00 AM-11:45 AM**

## The role of molecular profiling to differentiate multiple lung primary adenocarcinomas from intrapulmonary metastases from a lung primary.

*Mari Mino-Kenudson, Atsushi Miyamoto, Dora Dias-Santagata, Vicente Morales-Oyarvide, Lindsay Ann Bernardo, Amanda Pawlak, Jae Young Han, Diane L. Davies, Michael Lanuti, Eugene J. Mark, Anthony John Iafrate; Department of Pathology, Massachusetts General Hospital, Boston, MA; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; Division of Thoracic Surgery, Massachusetts General Hospital, Boston, MA; Thoracic Oncology, Massachusetts General Hospital Cancer Center, Boston, MA*

**Background:** In the case of patients with multiple lung adenocarcinomas (ADCs) (whether synchronous or metachronous), the distinction of intrapulmonary metastases from independent primaries is clinically important as it impacts staging and thus therapeutic strategy. Currently the distinction is made based principally on histology of the tumor. Molecular profiling is becoming a routine diagnostic procedure for lung cancer to help treatment decision-making. Thus, we sought the role of mutation assays to differentiate multiple primaries from metastases. **Methods:** 45 synchronous and 37 metachronous cases of multiple tumors were obtained at 103 surgeries in 68 patients. Each of the resultant 156 tumors was tested with the SNaPshot multiplex PCR genotyping assay and each case, based on molecular profiling, was classified as synchronous multiple primaries (SP), metachronous primaries (MP), synchronous intrapulmonary metastases (SM), or metachronous metastases (MM). Each case was also classified into 4 groups by a comprehensive histologic analysis. Clinical outcomes were compared between multiple primaries (SP and MP) and metastases (SM and MM) in the molecular and histologic analyses using Log-rank test. **Results:** Based on histology alone, SP were present in 37 cases, MP in 32, SM in 8 and MM in 5. The molecular results were interpreted as SP in 25, MP in 21, SM in 10 and MM in 11. 15 of the 82 cases were non-informative, since no mutations were identified in any lesions. Of the 67 cases harboring mutations, 21 (31%) showed discordant results consisting of 16 with SP or MP by histology and SM or MM by molecular profiling. 5 cases showed the opposite results. Molecular profiling showed a trend toward the 5-year survival of the patients with metastases being shorter than those with multiple primaries (57 months vs. 87 months, $P=0.068$), which was not observed by histology ($P=0.84$). **Conclusions:** Although its performance is limited by non-informative results in 18% of cases of multiple ADCs, SNaPshot profiling for clinical use appears to be useful in determining whether multiple ADCs are primaries or metastases. Thus, it may allow for more accurate staging and optimal therapeutic management.

**7556 General Poster Session (Board #22B), Sat, 8:00 AM-11:45 AM**

## Long-term results of a phase II trial of S-1 and cisplatin with concurrent thoracic radiotherapy for locally advanced non-small cell lung cancer.

*Fumiyoshi Ohyanagi, Nobuyuki Yamamoto, Atsushi Horiike, Takeshi Horai, Takuyo Kozuka, Haruyasu Murakami, Hideyuki Harada, Toshiaki Takahashi, Yukiko Nakamura, Makoto Nishio; Department of Thoracic Medical Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan; Division of Thoracic Oncology, Shizuoka Cancer Center, Nagaizumi-cho, Shizuoka, Japan; Department of Radiation Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan; Division of Thoracic Oncology, Shizuoka Cancer Center, Nagaizumi-chou, Shizuoka, Japan; Division of Radiation Oncology, Shizuoka Cancer Center, Shizuoka, Japan*

**Background:** Concurrent chemoradiotherapy is the standard treatment for unresectable stage III non-small cell lung cancer (NSCLC). S-1 has been shown to be significant efficacious for treating advanced NSCLC. Our previous phase II study reported short-term outcomes of cisplatin (CDDP)/S-1 chemoradiotherapy. Because CDDP/S-1 chemoradiotherapy is considered to have advantages over others in overall survival (OS) and toxicity, we analyzed its long-term outcomes by following up patients included in the phase II study. **Methods:** Forty-eight patients (aged $<$75 years) with unresectable stage III NSCLC were evaluated. They were treated with CDDP (60 mg/m$^2$ on day 1) intravenously and oral S-1 (40 mg/m$^2$ twice daily on days 1–14); this regimen was repeated every 4 weeks for four cycles. A 60-Gy thoracic radiation dose was delivered in 30 fractions beginning on day 2. **Results:** After a median follow-up of 6.3 years (range, 5.7–7.4 years), the median OS was 2.8 years [95% confidence interval (CI); 1.04–4.63 years], and the 3- and 5-year OS rates were 49.7% (95% CI: 35.6%–63.8%) and 33.0% (95% CI: 20.0%–46.6%), respectively. Out of the several variables evaluated as predictors of OS, including gender, age, stage, histology, and performance status (PS), only PS proved to be a statistically significant predictor in both univariate and multivariate analyses. **Conclusions:** CDDP/S-1 concurrent thoracic radiotherapy is clinically feasible and highly efficacious. Despite our relatively small sample size, the benefits of this regimen revealed in this study warrant further research.

**7557 General Poster Session (Board #22C), Sat, 8:00 AM-11:45 AM**

# Does *EGFR* mutation define the histological predominant subtype of lung adenocarcinoma?

*Eri Sugiyama, Koichi Goto, Genichiro Ishii, Tomohiro Haruki, Shingo Matsumoto, Shigeki Umemura, Kiyotaka Yoh, Seiji Niho, Hironobu Ohmatsu, Kanji Nagai, Yuichiro Ohe; Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan; Pathology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, Kashiwa, Japan; National Cancer Center Hospital East, Kashiwa, Japan*

**Background:** In 2011, invasive adenocarcinomas were newly classified into the five predominant subtypes by IASLC/ATS/ERS: lepidic, papillary, acinar, micropapillary, and solid. The purpose of this study is to investigate the correlation between *EGFR*mutation and the histological predominant subtype of lung adenocarcinoma. **Methods:** Among a total of 1,736 patients with lung adenocarcinoma who underwent surgical resection from 2002 to 2011 in National Cancer Center Hospital East, 1,507 were classified into invasive adenocarcinoma. 526 of whom were examined *EGFR* mutation status. Histological predominant subtypes were evaluated at the maximum cut surface of tumors. The *EGFR* mutation analysis was performed by PCR-invader method. Treatment efficacy of *EGFR*-tyrosine kinase inhibitors (TKIs) in 73 relapsed patients with *EGFR*major mutations were also examined. **Results:** 526 adenocarcinomas were consisted of 95 lepidic (18%), 221 papillary (42%), 80 acinar (15%), 9 micropapillary (2%), and 121 solid predominant subtype (23%). *EGFR* mutations were detected in 227 adenocarcinomas (43%), and its frequency in the solid subtype (22%) was significantly less than that of other histological subtypes (lepidic 47%, papillary 53%, and acinar 44%; $P < 0.01$). The proportion of minor mutations, other than exon 21 L858R and exon 19 deletions, were significantly higher in the solid subtype (22%) than that of the others (lepidic 4%, and papillary 12%; $P < 0.01$). In 73 patients with *EGFR* major mutations treated by *EGFR*-TKIs, the response rate was not different between histological subtypes (lepidic 86%, papillary 76%, acinar 89%, and solid 60%). **Conclusions:** The correlation between histological predominant subtypes of lung adenocarcinoma and the presence of *EGFR* mutations or the efficacy of *EGFR*-TKI were not identified in this study. Little is known about the reason why EGFR minor mutations were highly detected in the solid subtype of adenocarcinoma, however it is possibly due to the high frequency of heavy smokers in solid subtype (heavy smoker: solid 67% vs. others 27-44%).

## 7558 General Poster Session (Board #22D), Sat, 8:00 AM-11:45 AM

# Association of germ-line single nucleotide polymorphisms (SNPs) with pathologic response to neoadjuvant cisplatin-based chemotherapy in patients with resectable non-small cell lung cancers.

*Jamie E. Chaft, Sohela Shah, Esther N. Drill, Camelia S. Sima, Vijai Joseph, Ana Virginia Calogeras Dutra-Clarke, Jason Littman, Mark G. Kris, William D. Travis, Naiyer A. Rizvi, Kenneth Offit; Memorial Sloan-Kettering Cancer Center, New York, NY; Clinical Genetics Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY; Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY*

**Background:** Pathologic response to neoadjuvant chemotherapy correlates with survival in resected lung cancers. Predictive biomarkers of response are needed. Tumor-specific biomarkers have been hindered by reproducibility and specimen adequacy. Genome-wide association studies (most in SE Asia) have identified candidate SNPs that correlate with clinical outcomes after cisplatin-based chemotherapy. We evaluated whether these candidate SNPs are predictive of pathologic response to neoadjuvant chemotherapy in a US population. **Methods:** We aimed to correlate SNPs with near complete PR (ncPR) to neoadjuvant cisplatin + docetaxel in patients with resectable lung cancers. ncPR was defined as 90% necrosis, inflammation and fibrosis across serial 1cm sections of the resected tumor. Germline DNA was extracted and 50 candidate SNPs were genotyped by Sequenom Mass ARRAY iPLEX. SNPs were analyzed for correlation with ncPR using recessive (aa vs AA/aA) , dominant (AA vs aa/aA) and log-additive (linear increase in risk with each additional allele) genetic models. In this exploratory dataset, a p-value $<0.1$ was considered worthy of further study. **Results:** 60 patients were treated and had sufficient DNA for analysis. Nine patients had a ncPR. 7 of 50 SNPs (table) correlated with pathologic response in one of the three models. **Conclusions:** Of the candidate SNPs identified from the literature, 7 showed a promising correlation to ncPR to neoadjuvant chemotherapy. This expands upon the experience evaluating SNPs and chemotherapy sensitivity into a North American population. Study of these 7 SNPs is ongoing in our current multimodality trial as a validation cohort. This study was funded by the Lung Cancer Research Foundation.

| | Gene (Chr) | Odds ratio, | 95% Confidence Interval | P value |
|---|---|---|---|---|
| SNP rs# | | Recessive | Dominant | Log-Additive |
| **1209950** | ETS2 (21) | 5.3 (0.9-31.5), 0.06 | | 2.3 (0.9-8.2), 0.07 |
| **2072671** | CDA (1) | 7.4 (1.2-46.9), 0.03 | | |
| **1047768** | ERCC5 (13) | 5.2 (1.1-25.3), 0.04 | | 2.7 (1.0-7.3), 0.04 |
| **9981861** | DSCAM (21) | 4.9 (1.0-23.7), 0.04 | | |
| **1042522** | TP53 (17) | | 0.27 (0.05-1.2), 0.09 | |
| **2279744** | MDM2 (12) | | 0.20 (0.04-0.9), 0.04 | |
| **1051730** | CHRNA3 (15) | | | 4.3 (1.2-15.4), 0.02 |

**7559 General Poster Session (Board #22E), Sat, 8:00 AM-11:45 AM**

# Prognostic impact of *FGFR1* amplification in patients with early-stage resected squamous cell carcinomas of the lung (SQCLC).

*Matthew David Hellmann, Lu Wang, Melissa Wynne, Camelia S. Sima, Mark G. Kris, Andre L. Moreira, Natasha Rekhtman, Paul K. Paik; Memorial Sloan-Kettering Cancer Center, New York, NY; Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY*

**Background:** The spectrum and frequency of oncogenes in squamous cell lung cancers (SQCLCs) has recently been defined. Amplification of fibroblast growth factor receptor 1 (*FGFR1*) occurs in ~20% of SQCLCs; clinical trials of *FGFR1* inhibitors for advanced SQCLCs are ongoing. The frequency, clinicopathologic features, and prognosis of *FGFR1* amplification in early-stage, resected SQCLCs have been reported but with discrepant results (Kim *et al*, J Clin Oncol 2012, Heist *et al*, J Thorac Oncol 2012). **Methods:** A cohort of histopathologically-defined and clinically-annotated resected SQCLCs was tested for *FGFR1* amplification by FISH (Zytovision Dual Color Probe). Amplification was defined by *FGFR1* copy number $\geq$2.2x CEP8 control copy number and was assessed by two evaluators (MW, LW) who were blinded to clinical results. Disease-free survival (DFS) was defined as date of resection until relapse, recurrence, or death, whichever occurred first. We assessed association between *FGFR1*status and clinical features (Fisher's exact test) and DFS (long-rank test). Multivariate DFS analysis was performed using Cox regression analysis. **Results:** 63 resected SQCLCs were evaluated. *FGFR1* amplification was detected in 16 (24%). The median age of the cohort was 70 years (range 48-88). 15 (24%) currently smoked, 47 (75%) former, 1 (1%) never. 7 (11%) received neo-adjuvant therapy. 35 (56%) were stage I, 15 (24%) were stage II, and 13 (20%) were stage IIIA. There was no association between *FGFR1* amplification and age ($p>0.99$), sex ($p>0.99$), smoking status ($p=0.32$), or stage of disease ($p=0.18$). 1-year and median DFS in *FGFR1*-amplified vs non-amplified cases were 86% vs 71% ($p=0.022$) and not reached vs 2.3 yrs (95% CI 1.1-3.4 yrs), respectively. Multivariate analysis (*FGFR1* status, sex, and stage) found *FGFR1*amplification significantly associated with improved DFS (HR 3.2, 95% CI 1.1-9.4). **Conclusions:** In this cohort of resected SQCLCs *FGFR1* amplification was associated with improved outcomes. There was no association between *FGFR1* status and sex, age, smoking status, or stage. *FGFR1* amplification is common in SQCLCs.

**7560 General Poster Session (Board #22F), Sat, 8:00 AM-11:45 AM**

## Human papillomavirus (HPV)-associated early stage non-small cell lung cancer (NSCLC).

*Rathi Narayana Pillai, Camille Ragin, Gabriel Sica, Madhusmita Behera, Zhengjia Chen, Sungjin Kim, William Mayfield, Robert C. Hermann, Nabil F. Saba, Anthony A Gal, Fadlo Raja Khuri, Suresh S. Ramalingam, Taofeek Kunle Owonikoko; The Winship Cancer Institute of Emory University, Atlanta, GA; Fox Chase Cancer Center, Philadelphia, PA; Department of Pathology, Emory University, Atlanta, GA; Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA; WellStar Health System, Marietta, GA; Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA*

**Background:** HPV is an established risk factor for cervical and oropharyngeal cancer. It has been suggested as a potential risk factor for lung cancer based on studies conducted mostly in Asian patients with advanced NSCLC. We characterize potential role of HPV in a North American patient population with early stage NSCLC. **Methods:** We analyzed surgically resected samples of NSCLC patients diagnosed between 2002-2007. HPV status was determined by polymerase chain reaction (PCR) using the INNO-LiPA genotyping Extra Amplification and Genotyping Extra kits, followed by reverse hybridization line probe assay to identify specific HPV serotypes. Differences between HPV+ and HPV- patients were assessed by Chi-square, Fisher's exact, and Wilcoxon rank-sum tests. Survival was estimated by the Kaplan-Meier method and differences between HPV+ and HPV- patients were assessed by Log-rank test. Multivariable logistic regression modeling was employed to select predictors of HPV+ NSCLC. The significance levels were set at 0.05 for all tests. **Results:** Paraffin-embedded tumor samples from 208 patients were analyzed; M/F (49%/51%); stage I: 80%; II: 11%; III: 9%; IV: $<$1%; Caucasians 95.6% and African-Americans (AA) 4.4%. There were 32 (14.9%) HPV+ cases including 10 cases with HPV 16/18. Ethnicity was significantly associated with HPV status (p-value=0.033). AA patients are more likely to be HPV+ (OR: 7.373; p=0.01) and more likely to harbor high risk serotypes 16/18 (OR: 10.8; p=0.05). Regression modeling identified AA ethnicity, adenocarcinoma (ADC) histology and current smoking (parameter estimates of 2.04, -2.34 and -2.82 respectively) as predictors of HPV+ NSCLC. Smoking status and histology showed significant interaction in predicting HPV+ tumors: OR: 0.06; p=0.0023 for smokers with squamous cancer; 2.52; p=0.24 for smokers with ADC and 10.339; p=0.0293 for smokers with adenosquamous cancer. Median disease free survival (NR; p=0.42) and median overall survival (71 months; vs. 55 months) were not significantly different between HPV+ and HPV- patients. **Conclusions:** HPV positivity is observed in 15% of early stage NSCLC with strong association with AA ethnicity, adenosquamous histology and non-smoking status.

**7561 General Poster Session (Board #22G), Sat, 8:00 AM-11:45 AM**

# Multiplex testing of driver mutations in non-small cell lung cancer (NSCLCs) of African-American (AA) patients.

*Shirish M. Gadgeel, Michele L Cote, Ann G. Schwartz, Aliccia Bollig-Fischer, Susan Land, Angie Wenzlaff, Wei Chen, Antoinette J. Wozniak, Ammar Sukari, Laura Mantha, Gerold Bepler; Karmanos Cancer Institute, Wayne State University, Detroit, MI; Wayne State University, Detroit, MI*

**Background:** Recently driver genetic alterations have been identified in NSCLC that can be targeted for therapeutic interventions. Previous reports have suggested that rates of certain mutations may vary according to ethnic background. We conducted multiplex testing of NSCLCs of AA and white patients to assess variability in the mutation rates by race. **Methods:** We identified tumor tissues of 136 AA and 320 white NSCLC patients collected as part of three different institutional review board approved studies. Using the Sequenom MassArray system and a multiplexed panel, we analyzed tumor DNA for 214 oncogenic mutations in 26 genes previously identified in NSCLC. Estimated risk (Odds Ratios (OR)) of any mutation and specific gene mutations among AA patients compared to white patients were calculated after adjusting for age, sex, smoking status and histology (adenocarcinoma versus non-adenocarcinoma). Information on smoking status was unavailable on 46 patients and was not included in calculations of ORs for some genes ($OR^a$). **Results:** The median age at diagnosis was 60 vs 66 years in AA vs white patients; 43% of AA patients and 66% of white patients were males; 69% of AA patients and 52% of white patients had adenocarcinoma; 66% of AA patients and 85% of white patients had stage I/II NSCLC and 10% of AA patients and 6% of white patients were never smokers. 43% of the AA patients and 47% of white patients had at least one mutation detected (OR = 0.78; 0.5-1.2). 19% of AA patients and 6% of white patients had more than 1 mutation detected (OR 2.3; 1.1-4.9). AA patients were more likely to harbor mutations in STK11 (LKB1) (OR=8.4; 3.2-21.8) and NOTCH1 ($OR^a$=8.1; 2.2-30.8), and they were less likely to have MET mutations ($OR^a$= 0.12; 0.02-0.9) then white patients. While not statistically significant, AA had lower prevalence of Kras mutations (OR=0.64, 0.3-1.4) and p53 mutations (OR= 0.82; 0.4-1.6). **Conclusions:** Our analysis of NSCLCs shows that AAs were more likely to have multiple genetic mutations than whites and the mutation profile differs by race.

**7562 General Poster Session (Board #22H), Sat, 8:00 AM-11:45 AM**

# Computer-aided lung cancer screening with CT: A clinically usable nodule detection and assessment system.

*Pechin Lo, Matthew S. Brown, Jonathan Goldin, Eran Barnoy, Hyun J. Kim, Michael F. McNitt-Gray, Denise R. Aberle; Center for Computer Vision and Imaging Biomarkers, University of California, Los Angeles, CA; Center for Computer Vision and Imaging Biomarkers, University of California, Los Angeles, Los Angeles, CA*

**Background:** The National Lung Screening Trial (NLST) recently demonstrated that lung cancer screening with low-dose CT reduces mortality. Current protocols use 4–8 mm nodules as positive screens. While there are some computer-aided nodule detection (CAD) systems currently available, they are rarely used in clinical practice because they generate too many false positives and lack reliable measurement tools. The purpose of this work is to develop a new CAD system to overcome these limitations and evaluate it against an expert panel of radiologists. **Methods:** The CAD system developed for lung nodule detection and measurement incorporates computer vision techniques including intensity thresholding, Euclidean Distance Transformation, and watershed segmentation. Rules pertaining to volume and shape were applied to automatically discriminate between nodules and bronchovascular anatomy. CAD system performance was assessed using 108 consecutive cases from the publically available Lung Imaging Database Consortium (LIDC), in which four radiologists reviewed each case. CT slice thickness ranged from 0.6–3.0 mm. Nodules were included that were: (a) $\geq$ 4mm, and (b) marked by a majority of the LIDC readers, and (c) $\geq$ 4 x CT slice thickness (to ensure adequate spatial resolution). **Results:** 44 of 108 subjects had one or more nodules meeting criteria. Median CAD sensitivity per subject for these 44 cases is reported for all nodules $\geq$ 4mm and the subset of nodules $\geq$ 8mm. The false positive (FP) rate per subject is reported for all 108 cases. The overall concordance correlation coefficient (CCC) between the CAD volume of each nodule and the LIDC reference volume was measured. **Conclusions:** Based on clinical CT screening protocols, a CAD system has been developed with high nodule sensitivity and a much lower false positive rate than previously reported systems. Automated volume measurements show strong agreement with the reference standard, providing a comprehensive detection and assessment workflow for lung cancer screening.

| | Nodules ≥ 4 mm | Nodules ≥ 8mm |
|---|---|---|
| **Median sensitivity % (IQR)** | 100 (37.5) | 100 (8.3) |
| **Median FP rate (IQR)** | 0 (2.0) | 0 (1.0) |
| **Volume CCC [95% CI]** | 0.90 [0.84, 0.93] | 0.87 [0.78, 0.92] |

**7563 General Poster Session (Board #23A), Sat, 8:00 AM-11:45 AM**

# Competing mortality (CM) risk in patients with resected stage I and II non-small cell lung cancer (NSCLC): A Surveillance, Epidemiology, and End Results (SEER) analysis.

*Gayathri Nagaraj, Janakiraman Subramanian, Feng Gao, Siddhartha Devarakonda, Ramaswamy Govindan; Loma Linda University, Loma Linda, CA; Hanna Cancer Associates, Knoxville, TN; Washington University School of Medicine in St. Louis, St. Louis, MO; St. Luke's Hospital, St. Louis, MO*

**Background:** CM risk has been identified as a potential confounder in the interpretation of treatment effects in head and neck cancer (Rose et al. J Clin Oncol. 2011). Lung cancer patients (pts) are at considerable risk for CM due to their advanced age at diagnosis and smoking related chronic diseases. We plan to identify risk factors for CM in pts with early stage NSCLC and develop a statistical model to estimate the effect of CM on power calculation for lung cancer clinical trials. **Methods:** Using SEER registry we identified 32104 pts who had undergone surgical resection with or without radiation for stage I and II NSCLC between 1994 and 2006. The data set was split into two groups: training set (75%) and testing set (25%). Risk factors for lung cancer-specific mortality (LCSM) and CM were identified using training data by Gray's sub-distribution regression of competing risk. Pts from the testing data were then stratified according to CM risk and the impact of this risk on power loss was evaluated. **Results:** The 5-year cumulative incidence of death from lung cancer, other causes and overall mortality was 32.7%, 14.2% and 46.9% respectively. Risk factors for CM were: age (hazard ratio [HR] 1.05), male gender (HR 1.43), divorced (HR 1.30), widowed (HR 1.23) or single (HR 1.29) marital status, squamous (HR 1.40) or not-otherwise-specified (HR 1.22) histology, stage I NSCLC (HR 1.27) and sublobar resection (HR 1.23). The 5-year cumulative incidence of CM in low, mid and high-risk tertiles was 7%, 14% and 21% respectively. Sample size calculations based on all-cause mortality (ACM) result in over-estimation of power as the risk for CM increases. In order to restore the underestimated power in LCSM, 19% and 35% more pts are required in the mid and high CM risk groups respectively (Table). **Conclusions:** Our findings indicate that conventional sample size calculation methods can result in significant loss of power and incorporating CM risk models in power estimation should be considered for clinical trials involving early stage NSCLC pts.

| | 5-year incidence | | | Power | | Adjustment | |
|---|---|---|---|---|---|---|---|
| | LCSM | CM | ACM | ACM | LCSM | N | % |
| Low | 0.29 | 0.07 | 0.36 | 80% | 80% | 0 | |
| Mid | 0.34 | 0.14 | 0.48 | 91% | 86% | 140 | 19% |
| High | 0.37 | 0.21 | 0.58 | 95% | 87% | 250 | 35% |

**7564 General Poster Session (Board #23B), Sat, 8:00 AM-11:45 AM**

# Dose-escalation study of chemoradiotherapy with use of involved-field conformal radiotherapy and accelerated hyperfractionation for stage III non-small cell lung cancer.

*Naruo Yoshimura, Shigeki Mitsuoka, Tatsuo Kimura, Hidenori Tanaka, Tomohiro Suzumura, Misato Nagata, Kanako Umekawa, Toshiyuki Nakai, Masako Hosono Hosono, Takuhito Tada, Kazuto Hirata, Shinzoh Kudoh; Department of Clinical Oncology, Graduate School of Medicine, Osaka City University, Osaka, Japan; Department of Respiratory Medicine, Graduate School of Medicine, Osaka City University, Osaka, Japan; Department of Respiratory Medicine, JR Osaka railway hospital, Osaka, Japan; Department of Medical Oncology, Izumi Municipal Hospital, Osaka, Japan; Department of Radiology, Graduate School of Medicine, Osaka City University, Osaka, Japan; Department of Radiology, Izumi Municipal Hospital, Osaka, Japan*

**Background:** To determine a recommended dose (RD) of chemoradiotherapy with use of involved-field conformal radiotherapy and accelerated hyperfractionation (AHF) for stage III non-small cell lung cancer (NSCLC). **Methods:** Eligible patients had unresectable stage III NSCLC, age of less than 75 years, PS: 0 or 1, V20 of 35% or less. PET was used for staging. Cisplatin (80mg/m$^2$) was administered on day 1 and vinorelbine (20mg/m$^2$) was administered on days 1 and 8 for two cycle. Twice-daily radiation therapy (1.5 Gy per fraction) without elective nodal irradiation started on day 1. Total doses were 60Gy in 40 fractions and 66Gy in 44 fractions at levels 1 and 2 respectively. After concurrent chemoradiotherapy, consolidation chemotherapy regimen was cisplatin (80mg/m$^2$) on day 1 and vinorelbine (20mg/m$^2$) on days 1 and 8 every 4 week for three cycles. The dose-limiting toxicity (DLT) was defined as grade $\geq$ 3 esophagitis, grade 3 neutropenic fever, grade $\geq$ 3 other non-hematologic toxicities and interruption of irradiation for more than 2 weeks. DLT was monitored for 90 days. **Results:** A total of 12 patients were enrolled (6 patients in Level 1, 6 patients in Levels 2). DLTs were noted in 2 patients at Level 1, which were grade 3 esophagitis and grade 3 febrile neutropenia. Radiation dose was escalated up to 66 Gy in 44 fractions (Level 2), and there was no DLT. In principle, Sixty-six Gy in 44 fractions (Level 2) should be the RD. Major toxicities were leucopenia, neutropenia, and anemia. The response rate, the median progression free survival time, and the median overall survival time was 83.3%, 10.4 months, and 36.3 months for all patients, respectively. **Conclusions:** The RD was 66 Gy in 44 fractions (Level 2). The toxicity of this chemoradiothrapy regimen was manageable and efficacy is promising. The efficacy and safety of this regimen should be confirmed in a phase II study. Clinical trial information: UMIN000003769.

**7565 General Poster Session (Board #23C), Sat, 8:00 AM-11:45 AM**

# Impact of environmental tobacco smoke (ETS) on ALK rearrangements in never smokers (NS) with non-small cell lung cancer (NSCLC): Analyses on a prospective multinational ETS registry.

*Akihito Kubo, Masahiko Ando, Ross A. Soo, Tomoya Kawaguchi, Sai-Hong Ignatius Ou, Myung-Ju Ahn; Aichi Medical University School of Medicine, Nagakute, Japan; Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, Nagoya, Japan; National University Health System, Singapore, Singapore; National Hospital Organization Kinki-Chuo Chest Medical Center, Osaka, Japan; Chao Family Comprehensive Cancer Center, Orange, CA; Department of Medicine, Division of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

**Background:** EGFR and ALK are important driver mutations in NS. While we reported the significant association of increased ETS with EGFR mutations in Japanese cohort (Kawaguchi, Clin Cancer Res, 2011), ETS association with ALK has not been reported. **Methods:** ETS exposure on NS with NSCLC was evaluated using the standardized questionnaire including exposure period, place, and duration. Cumulative dose of ETS (CETS) was defined as a sum of the number of the exposure years in childhood and in adulthood, and was treated as a continuous variable or quintile. EGFR mutations and ALK rearrangements were tested by PCR-based detection and fluorescence in situ hybridization, respectively. Multivariate analyses were done using the generalized linear mixed model (GLIMMIX procedure, SAS v9.3). **Results:** From March 2008 to December 2012, 498 NS with NSCLC were registered with the following patient characteristics: ethnicity (nationality) of Asian/ Caucasian/ others, 425 (Japanese 250, Korean 102, Chinese 46, others 2)/ 48/ 25; male/female, 114/384; age <65/>=65, 286/212. EGFR status was wild type 43.6%, exon 19 deletion 25.3%, L858R 21.5% and other mutations 9.6%. ALK status was wild type 52.0%, rearranged 10.6% and unknown 37.3%. Average CETS (years) of NS with EGFR (+), ALK (+) and wild type tumors were 45.4, 26.9 and 37.7, respectively. In multivariate generalized linear mixed model, incidence of activating EGFR mutations, not ALK rearrangements, was significantly associated with the increment of CETS in female, not in male gender. Odds ratios (OR) for EGFR mutations in female (n=384) were 1.084 (95% CI, 1.003-1.171; p=0.0422) for each increment of 10 years in CETS while OR in male (n=114) were not significant (OR 0.890; 95% CI, 0.725-1.093; p=0.2627). OR for ALK rearrangements in female (n=238) and those in male gender (n=74) were 0.930 (0.791-1.094; p=0.3814) and 0.854 (0.620-1.178; p=0.3319). **Conclusions:** Increased ETS exposure was closely associated with EGFR mutations in NS with female gender and NSCLC in the expanded multinational cohort. However, the association of ETS and ALK rearrangements in NS with NSCLC was not significant.

**7566 General Poster Session (Board #23D), Sat, 8:00 AM-11:45 AM**

# Automated tumor size assessment: Consistency of computer measurements with an expert panel.

*Matthew S. Brown, Hyun J. Kim, Pechin Lo, Eran Barnoy, Michael F. McNitt-Gray, Denise R. Aberle, Jonathan Goldin; Center for Computer Vision and Imaging Biomarkers, University of California, Los Angeles, CA; Center for Computer Vision and Imaging Biomarkers, University of California, Los Angeles, Los Angeles, CA*

**Background:** Manual tumor measurements for use in diagnosis and longitudinal assessment suffer from intra- and inter-observer variability. In practice they are also limited to 1-dimensional diameter measurements because manual contouring of 3D tumor boundaries is impractical. In this work we evaluated a fully automated tumor assessment system in the setting of lung nodules on CT by comparing its tumor size and density measurements against independent measurements made by an expert panel of radiologists. **Methods:** A new computer-aided detection (CAD) system has been developed that performs fully automated lung nodule detection and measurement. In order to identify the nodule boundary in 3D the system performs automated intensity thresholding, a Euclidean Distance Transformation, and segmentation based on watersheds. The system computes nodule diameter, volume, and mean density in Hounsfield Units (HU). The automated measurements were evaluated against data from the publically available Lung Imaging Database Consortium (LIDC), where each CT scan was reviewed and annotated (with volumetric tumor contours) by an expert panel of four radiologists. Nodule were included from consecutive subjects in the database that were $\geq$ 4 mm. The CT slice thickness ranged from 0.6 – 3.0 mm. For each nodule measure, the intra-class correlation coefficient (ICC) was computed among the four radiologists and then re-computed with CAD as a fifth observer. **Results:** 51 lung nodules from 44 subjects were analyzed. The ICCs were computed as shown in the table using a log transformation for volume and diameter. All nodule measures have similar ICCs and overlapping confidence intervals (CI). **Conclusions:** A new fully automated CAD system has been developed that provides CT lung nodule measurements that are consistent with an expert panel of radiologists. The automated computer system enables practical 3D tumor assessment and reduces measurement variability, which has implications for longitudinal studies.

| | 4 Radiologists ICC [95%CI] | 4 Radiologists + CAD ICC [95%CI] |
|---|---|---|
| **Volume** | 0.97 [0.96, 0.98] | 0.96 [0.94, 0.98] |
| **Longest diameter** | 0.92 [0.89, 0.96] | 0.91 [0.87, 0.95] |
| **Mean HU density** | 0.73 [0.63, 0.83] | 0.72 [0.62, 0.81] |

**7567 General Poster Session (Board #23E), Sat, 8:00 AM-11:45 AM**

## Prognostic role of MET expression in early stage NSCLC.

*Tom John, Carmel Murone, Khashayar Asadi, Adrienne Morey, Simon Knight, Paul Mitchell; Ludwig Institute for Cancer Research/Austin Health, Melbourne, Australia; Ludwig Institute for Cancer Research, Heidelberg, Australia; Department of Anatomical Pathology, Austin Health, Heidelberg, Australia; SydPath, St. Vincent's Hospital, Sydney, Australia; Austin Hospital, Melbourne, Australia; Joint Austin-Ludwig Oncology Unit, Austin Health, Melbourne, Australia*

**Background:** The MET receptor tyrosine kinase and its ligand are associated with the malignant phenotype. In non-small cell lung cancer (NSCLC) MET expression increases with disease stage and is involved in *de novo* and acquired resistance to tyrosine kinase inhibitors. Despite this, in early stage NSCLC small data series have failed to demonstrate MET expression to be prognostic. We investigated a large cohort of patients who underwent curative surgical resection at our institution to determine whether MET receptor or gene amplification was prognostic. **Methods:** Tissue Microarrays (TMAs) were constructed using 1mm cores of FFPE primary NSCLC tissues in triplicate. TMAs were stained with the SP44 clone (Novus Biologicals) and a H-score calculated based on % cells stained and intensity; (%cellsx1)+(%cellsx2)+(%cellsx3) with a minimum of 0 and maximum of 300. The mean of triplicate values was calculated. MET gene amplification was detected using Ventana's MET DNP probe with ultraView SISH DNP silver detection, performed on Ventana's XT autostainer. DNA was isolated and subjected to mutational profiling using Sequenom's LungCarta panel. **Results:** Data for 508 patients, 352 (69%) male, were available for analysis including 329 pathological node negative (pN0), 67 pN1, 104 pN2 and 8 patients with resected primaries and solitary brain metastases (M1). Most patients were smokers with only 33 (6%) non-smokers. The median MET H-score was 100 and consistent across N0, N1 and N2 patients, although was higher in M1 patients. Median H-scores were significantly higher in adenocarcinoma compared to squamous cell carcinoma (140 vs 91.5, $p<0.0001$). Increased MET expression (H-score$>$100) was seen in 227 (45%) patients and associated with significantly improved overall survival (HR 1.28 95% CI 1.04-1.59; $p=0.023$). In univariate analyses improved survival occurred in all stages and histologies. DNA and multivariate analyses are pending. *MET* gene copy number amplification was detected in 11 cases. **Conclusions:** In contradistinction to advanced NSCLC, increased MET receptor expression is associated with improved survival in a large cohort of early stage lung cancer. Further correlation with mutation status and gene rearrangements will be reported.

**7568 General Poster Session (Board #23F), Sat, 8:00 AM-11:45 AM**

## Genomic rearrangements in lung adenocarcinoma: Lineage relationships between the in situ and invasive components.

*Stephen J Murphy, Dennis A. Wigle, Faye R Harris, Joema Felipe Lima, Sarah H Johnson, Bruce W Eckloff, Charlie T Seto, Michael Asiedu, Tobias Peikert, Ping Yang, Marie-Christine Aubry, George Vasmatzis; Mayo Clinic, Rochester, MN*

**Background:** The molecular events in the initiation and progression of invasive lung adenocarcinoma remain poorly characterized. These tumors are thought to develop through an adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), invasive adenocarcinoma (AD) sequence. The goal of our study was to assess lineage relationships between in situ and invasive components within adenocarcinomas with prominent lepidic growth patterns. **Methods:** Frozen tissue from fourteen lung adenocarcinomas with mixtures of AD together with an adjacent in situ component (AIS), varying in ratio between 40 to 80%, were selected from our Lung Specimen Registry. Laser capture microdissection (LCM) of each component was performed separately for each tumor. Genomic DNA was isolated using a direct in situ whole genome amplification (WGA) methodology, and Next Generation Sequencing performed using an Illumina Mate Pair (MP) library protocol. MP sequence reads were mapped to the human genome and primers spanning the fusion junctions were used in validation PCRs. **Results:** Genomic break points identical and unique to a specific patient were identified between the AIS and AD components in 13 (of 14) cases. The total number of events per case ranged from 4-215, and the number of identical events shared between the AIS and AD components ranged from 30 to 90%. Recurrent genomic breakpoints between cases were also observed, with the 2 most common involving 8q24.3 in 5 cases and FAM19A2 on chromosome 12 in 4 cases. PCR validation of selected genomic alterations confirmed the genomic break points identified from sequencing in both the AIS and AD in all cases. Interestingly, we also observed a limited number of genomic alterations present in a zonal distribution of surrounding normal lung around the tumor mass. **Conclusions:** Our study demonstrates unique chromosomal alterations present in both the AIS and AD components of individual lung tumors with features of lepidic growth. These data provide evidence for lineage relationship and clonal relatedness between the two components, and provide genomic evidence for a model of stepwise progression from AIS to invasive AD in this subset of lung adenocarcinomas.

**7569 General Poster Session (Board #23G), Sat, 8:00 AM-11:45 AM**

# Dual intervention with a lymph node (LN) specimen collection kit and enhanced specimen dissection to improve staging of resectable non-small cell lung cancer (NSCLC).

*Srishti Sareen, Robert A. Ramirez, Ahmed Yasir Javed, Laura Elizabeth Miller, Christopher Wang, Matthew Smeltzer, Alim Khandekar, Glenn P Schoettle, Samuel G Robbins, Jeffrey B Gibson, Bradley Aaron Wolf, Edward T Robbins, Raymond U Osarogiagbon; Boston Baskin Cancer Foundation, Memphis, TN; Boston Baskin Cancer Foundation, Germantown, TN; University of Memphis, Memphis, TN; University of Tennessee Medical Group, Memphis, TN; St. Francis Hospital, Memphis, TN; The Cardiovascular Center, Methodist Germantown Hospital, Germantown, TN; Cardiovascular Surgery Clinic, Memphis, TN; Cardiothoracic Surgery Associates, Memphis, TN; Baptist Cancer Center, Memphis, TN*

**Background:** LN metastasis impairs survival of resectable NSCLC, but routine pathologic nodal staging is suboptimal. We tested the impact of a dual intervention (a surgical specimen collection kit with specific, pre-labeled LN collection cups, to improve intraoperative hilar/mediastinal LN dissection; and a fastidious gross dissection of the resected lung specimen for perihilar/intrapulmonary LNs) on the rate of detection of LN metastasis. **Methods:** We matched dual intervention cases with controls performed with standard surgical specimen collection and pathology examination protocols. Controls were hierarchically matched for extent of resection, laterality, surgeon, pathologist and T-stage. All statistical comparisons were made with Exact Conditional Logistic Regression, to account for the matched case-control design. **Results:** Patient demographic, tumor histology, and size characteristics were similar between the groups. The impact of the dual interventions is shown in the Table. **Conclusions:** The dual interventions significantly increased retrieval of N1 and N2 LNs, the rate of detection of LN metastasis, and nodal up-staging. There were strong trends towards higher aggregate stage and increased adjuvant therapy eligibility. The interventions may improve stage-adjusted survival by improving stage accuracy, and improve aggregate survival by increasing the appropriate use of post-operative adjuvant therapy. A prospective randomized trial to test survival impact of the dual interventions is at an advanced planning phase.

| | Cases, N=100 | Controls, N=100 | P |
|---|---|---|---|
| # LN examined (mean, SD) | 11 (7.9) | 3 (2.9) | <.0001 |
| N1 | 7 (4.1) | 2 (2.6) | <.0001 |
| N2 | 18 (8.9) | 6 (4.1) | <.0001 |
| Total | | | |
| Patients meeting LN # criteria, % | 79 | 13 | <.0001 |
| >10 lymph nodes | 41 | 2 | <.0001 |
| >17 lymph nodes | | | |
| # LN positive (mean, SD) | 1.1 (2.6) | 0.3 (0.9) | <.001 |
| N1 | 0.3 (0.8) | 0.1 (0.4) | .069 |
| N2 | 1.4 (3.0) | 0.5 (1.1) | <.001 |
| Total | | | |
| Nodal stage, % of patients | 65 | 79 | .0486 |
| pN0 | 20 | 12 | .02 |
| pN1 | 15 | 9 | |
| pN2 | 35 | 21 | |
| Any positive LN | | | |
| Aggregate stage, % of patients | 54 | 66 | 0.0629 |
| I | 24 | 20 | |
| II | 22 | 14 | |
| III | | | |
| Eligibility for adjuvant therapy | 51 | 40 | .07 |
| Chemotherapy | 15 | 9 | .24 |
| Radiation therapy | | | |

**7570 General Poster Session (Board #23H), Sat, 8:00 AM-11:45 AM**

# Clinical characteristics of patients with multiple primary lung cancers: Moving beyond the Martini and Melamed criteria.

*Marjorie Glass Zauderer, Alexander Edward Dela Cruz Drilon, Camelia S. Sima, Feiran Lou, David J. Finley, Mark G. Kris; Memorial Sloan-Kettering Cancer Center, New York, NY; Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY*

**Background:** Deciding to operate for lung cancer in patients with a prior lung cancer resection is influenced by the extent of disease at 1st resection and the certainty that the new lesion is a 2nd primary lung cancer. While the Martini and Melamed (M&M) criteria (J Thorac Cardiovasc Surg 1975) guide the decision whether a new lesion represents a 2nd lung cancer, improvements, incorporating detailed clinical and molecular analyses, are needed. **Methods:** From a prospective database, we identified 130 patients who underwent two curative resections from 1995 to 2009 for non-small cell lung cancers. We examined associations between clinical factors and patterns of recurrence/DFS/OS following 2nd surgery. **Results:** Patient characteristics: median age 66; 42% men; and 8% never smokers. See Table for stage, histology, and completeness of resection. DFS and OS were not associated with smoking status, surgical procedure, and histology. Stage at 1st resection was not associated with patterns of recurrence (none vs local vs distant, $p=0.77$), DFS ($p=0.61$), or OS ($p=0.37$). Earlier stage at 2nd resection was associated with improved DFS ($p<0.001$) and OS ($p<0.001$), as well as a trend toward less distant recurrence ($p=0.06$). As many surgeries predated routine genotyping, very few patients (5%) had genotyping from both resections. 38% of 2nd resection stage IA lung cancers recurred distantly. 20% had a third lung cancer and 47% had at least one other malignancy. **Conclusions:** Outcomes after 2nd primary lung cancers are unaffected by the stage of the 1st lung cancer. Pursuit of curative interventions should not be influenced by the stage of the 1st cancer. We need more detailed molecular analysis to help correctly identify new primaries. We also need additional features to help discriminate among those at most risk for another lung cancer vs local recurrence vs distant recurrence.

| | 1st resection N (%)> | 2nd resection N (%) |
|---|---|---|
| **Stage** | | |
| IA | 74 (57) | 90 (69) |
| IB | 31 (24) | 16 (12) |
| IIA | 14 (11) | 7 (5) |
| IIB | 4 (3) | 7 (5) |
| IIIA | 5 (4) | 10 (8) |
| **Histology** | | |
| Adenocarcinoma | 98 (75) | 100 (77) |
| Squamous | 24 (18) | 23 (18) |
| Large cell | 4 (3) | 5 (4) |
| Non-small cell NOS | 4 (3) | 2 (2) |
| **Complete resection** | | |
| R0 | 119 (92) | 121 (93) |
| R1/R2 | 11 (8) | 9 (7) |

**7571 General Poster Session (Board #24A), Sat, 8:00 AM-11:45 AM**

# Outcomes of early stage lung cancer treatments in older patients: A SEER database analysis.

*Alissa S. Marr, Valerie Shostrom, K. M Islam, Apar Kishor Ganti; University of Nebraska Medical Center, Omaha, NE; VA Nebraska-Western Iowa Health Care System, Omaha, NE*

**Background:** Although the majority of lung cancer patients are over the age of 65, there are limited data on outcomes of treatment options for early stage lung cancer in older patients. **Methods:** Treatment and outcome data of stage I and II non-small cell lung cancer (NSCLC) patients were obtained from the Surveillance, Epidemiology and End Results (SEER) database. Treatment modalities included no treatment, surgery, radiation, and a combination of surgery and radiation. Patients were divided based on age groups into <65, 65-75, and >75 years old. Multivariate logistic regression was used to compare the likelihood of survival in the three age groups while controlling for gender and race. **Results:** A total of 10,763 patients diagnosed with stage I and II NSCLC between 1988 and 2007 within the SEER database were analyzed. The age distribution was as follows: <65 (n=3558), 65-75 years (n= 4454), >75 years (n=2751). Patients <65 years of age were more likely than those >75 years of age to be treated with surgery (72.5% vs. 53.5%, respectively; p = <0.0001). Patients >75 years of age were more often treated with radiation alone (23%) or no treatment (18.2%) as compared to those patients <65 (9% and 4.9%, respectively; p = <0.0001). Patients <65 years of age with stage I lung cancer had a statistically significant improved lung cancer-specific 5-year survival with surgery alone as compared to those 65-75 years and >75 years. Lung cancer specific mortality at 5 years was 19%, 26% and 30%, respectively; p= <0.0001. Similar results were seen in stage II patients. When stage I patients received radiation therapy, lung cancer-specific deaths at 5 years were not different between the three groups (66% vs. 63% vs. 66%, respectively; p=0.1263). The 5-year lung cancer- related mortality was lower in younger patients who received no treatment (51% in <65, 56% in 65-75, and 57% in >75 years old; p=0.006). **Conclusions:** Older patients treated surgically for stages I and II NSCLC have a lower lung cancer-specific survival when compared to younger patients. In contrast, there is no difference in lung cancer-specific survival for patients treated with radiation therapy. Hence, careful selection of older patients for surgical therapy of early stage NSCLC is warranted.

**7572 General Poster Session (Board #24B), Sat, 8:00 AM-11:45 AM**

# Identification of actionable mutations in surgically resected tumor specimens from Japanese patients with non-small cell lung cancer by ultra-deep targeted sequencing.

*Yasuhiro Koh, Hirotsugu Kenmotsu, Masakuni Serizawa, Mitsuhiro Isaka, Keita Mori, Hisao Imai, Hiroaki Akamatsu, Akira Ono, Tateaki Naito, Tetsuhiko Taira, Haruyasu Murakami, Toshiaki Takahashi, Masahiro Endo, Takashi Nakajima, Yasuhisa Ohde, Nobuyuki Yamamoto; Division of Drug Discovery and Development, Shizuoka Cancer Center Research Institute, Nagaizumi-chou, Shizuoka, Japan; Division of Thoracic Oncology, Shizuoka Cancer Center, Nagaizumi-cho, Shizuoka, Japan; Division of Thoracic Surgery, Shizuoka Cancer Center, Nagaizumi-cho, Shizuoka, Japan; Clinical Trial Coordination Office, Shizuoka Cancer Center, Nagaizumi-cho, Shizuoka, Japan; Division of Thoracic Oncology, Shizuoka Cancer Center, Nagaizumi-chou, Shizuoka, Japan; Division of Diagnostic Radiology, Shizuoka Cancer Center, Nagaizumi-chou, Shizuoka, Japan; Division of Pathology, Shizuoka Cancer Center, Nagaizumi-chou, Shizuoka, Japan*

**Background:** Detection of tumor genetic alterations is critically needed for lung cancer clinic as well as for the development of molecular targeted therapeutics. Here we report the results of a broad spectrum of genetic alterations identified in Japanese non-small cell lung cancer (NSCLC) patients by ultra-deep targeted sequencing. **Methods:** Highly multiplexed amplicon sequencing was performed using genomic DNA extracted from snap-frozen tumor specimens. TruSeq amplicon cancer panel was used for the detection of somatic mutations in 48 cancer related genes followed by ultra-deep sequencing (Illumina) at an average coverage of approximately 2800x. *ALK*, *ROS1* and *RET* traslocations and *EGFR, MET, PIK3CA, FGFR1* and *FGFR2* amplifications were also detected by multiplex RT-PCR and quantitative PCR, respectively. **Results:** The demographics of 204 consecutive patients enrolled in this prospective study at Shizuoka Cancer Center between July 2011 and November 2012: median age 69 years (range: 38-92); male 66%; never smoker 25.5%; histology: adenocarcinoma 68.6%, squamous cell carcinoma (SQ) 27.0%, others 4.4%; tumor stage: I 53.9%, II 28.4%, III 12.7%, IV 4.9%. *TP53* mutation was most frequently detected (44.4%) in all patients, particularly in SQ (67.9%). Mutations in genes such as *MLH1* (4.9%), *STK11* (6.3%), *CTNNB1* (5.6%), *SMAD4* (1.4%), *VHL1* (1.4%), *PTPN11* (0.7%) and *GNAS* (0.7%) were detected besides major mutations in genes such as *EGFR* (43.0%), *KRAS* (17.6%) and *PIK3CA* (14.1%) in adenocarcinoma. *PIK3CA* (21.4%), *MLH1* (5.4%), *APC* (3.6%), *STK11* (3.6%), *FGFR2* (1.8%) and *VHL* (1.8%) mutations were identified in SQ and notably, 48.2% of SQ patients harbored simultaneous gene mutations, suggesting the genetic complexity of this histology. *FGFR1* amplification was found in 8.9 % of SQ, suggesting lower frequency in Asian population than in Caucasian population. **Conclusions:** We managed to detect a wide range of genetic alterations and identified additional actionable mutations besides popular driver mutations. This approach may facilitate elucidation of detailed molecular characteristics of NSCLC, thereby implementing personalized cancer medicine.

**7573 General Poster Session (Board #24C), Sat, 8:00 AM-11:45 AM**

# Lung adenocarcinoma microRNA-31 expression levels to predict lymph node metastasis and patient survival.

*Tim Lautenschlaeger, Wei Meng, Zhenqing Ye, Ri Cui, James Perry, Alexander Huebner, Vaia Dedousi-Huebner, Volinia Stefano, Nakanishi Hiroshi, Taewan Kim, Sung-Suk Suh, Leona W. Ayers, Patrick Ross, Carlo M Croce, Victor Jin, Arnab Chakravarti; Department of Radiation Medicine, The Ohio State University, Columbus, OH; The Ohio State University, Columbus, OH; Department of Biomedical Informatics, The Ohio State University, Columbus, OH; Department of Molecular Virology, Immunology and Medical Genetics,The Ohio State University, Columbus, OH; Department of Radiation Oncology, The Ohio State University, Columbus, OH; The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH; Department of Molecular Virology, Immunology and Medical Genetics, Comprehensive Cancer Center, The Ohio State University, Columbus, OH; Department of Molecular Virology, Immunology and Medical Genetics, The Ohio State University, Columbus, OH; 3Department of Molecular Virology, Immunology and Medical Genetics, The Ohio State University, Columbus, OH; Department of Pathology, College of Medicine, The Ohio State University, Columbus, OH; Ohio State University, Columbus, OH; Arthur G. James Cancer Center, The Ohio State University, Columbus, OH*

**Background:** In this study we performed genome-wide microRNA-seqencing (miRNA-seq) in lung adenocacinoma (ADC) patient samples and used bioinformatic analyses to identify novel and annotated microRNAs that are differentially expressed between patients with and patients without lymph node metastasis, as well as examining their potential prognostic value. **Methods:** Sixty four frozen tissue specimens from lung ADC patients collected between 2003 and 2012 were obtained through the OSUCCC Tissue Procurement Shared Resource, approved by internal review board (IRB). Total RNA samples were processed and loaded on the Applied Biosystems SOLiD 4 sequencing system for data acquisition. 249 patients from the TCGA lung ADC cohort were used for results validation. Human lung ADC cell lines H23 and H1573 were used for in vitro functional assays. **Results:** We identified several microRNAs that were associated with the presence of lymph node metastasis in primary lung adenocarcinoma tissues using genome-wide miRNA-seq. We confirmed miR-31 to be up-regulated in lung ADC tissues from patients with lymph node metastasis in a separate patient cohort ($p=0.009$, t-test), and to be expressed higher in ADC tissues than in matched normal adjacent lung tissues ($p<0.0001$, paired t-test). MiR-31 was then validated as a marker for lymphnode metastasis in an external validation cohort of 233 lung ADC cases of the TCGA that did not have distant metastasis ($p=0.031$, t-test). In vitro functional assays showed that miR-31 upregulation increases cell migration, invasion, and proliferation. In addition, overexpression of mir-31 increased the expression of markers of epithelial-mesenchymal transition (EMT) and associated with activated ERK1/2 signaling. MiR-31 was a significant predictor of survival in a multivariate Cox regression model even when controlling for tumor stage. In silico analysis showed that low expression of miR-31 was associated with excellent survival for T2N0 patients. **Conclusions:** In summary, we applied microRNA-seq to study microRNomes in lung ADC tissue samples for the first time and identified a microRNA that could predict the presence of lymph node metastasis and survival outcomes in lung ADC patients.

**7574 General Poster Session (Board #24D), Sat, 8:00 AM-11:45 AM**

## Patient-reported symptom burdens in NSCLC patients undergoing proton, 3DCRT, or IMRT.

*Xin Shelley Wang, Zhongxing X. Liao, Ritsuko Komaki, James D. Cox, Daniel Richard Gomez, Raza H Bokhari, Mary L Sailors, Charles S. Cleeland; The University of Texas MD Anderson Cancer Center, Houston, TX*

**Background:** Concurrent chemoradiation (CXRT) for stage III non-small-cell lung cancer (NSCLC) patients is associated with the development of systemic self-reported symptom burden as well as radiation esophagitis (RE). This longitudinal study aims to provide a profile of the symptom burden among 3 radiation techniques concurrently used with chemotherapy: 3-dimensional conformal radiation therapy (3DCRT), intensity- modulated radiation therapy (IMRT) and proton beam therapy (PBT). **Methods:** NSCLC patients (N=164) treated at MD Anderson Cancer Center rated symptoms via the M. D. Anderson Symptom Inventory (MDASI) weekly from pre-therapy up to 20 weeks post-therapy. Descriptive analysis identified major symptom burden, and mixed effect modeling examined change over time in symptom outcomes among the 3 types of CXRT. **Results:** Average total radiation dose was higher (p=.0003) for PBT (N=30, 71.6 Gy) and IMRT (N=67, 66.3 Gy) than for 3DCRT (N=24, 62.1 Gy). Over time, all patients reported a cluster of symptoms that increased as the dose accumulated, including fatigue, drowsiness, pain, difficulty swallowing, poor appetite and sore throat; symptoms generally peaked at week 7-9 and returned to pre-therapy levels at week 13. The IMRT group had significant less-severe sore throat (p=.03), while there were no significant differences in symptom severity among the 3 types of CXRT for the other major symptoms before, during and after CXRT. However, there was a trend of more patients reporting moderate to severe sickness symptoms as a component score (fatigue, pain, sore throat, poor appetite and drowsiness) in the 3DCRT group than in the IMRT or PBT groups at end of CXRT (50% vs. 44%, 31%) and at 13 weeks (53% vs. 23%, 25%). Also, there was a trend of more patients under 3DCRT than IMRT or PBT had moderate to severe sore throat (RE symptom) by end of CXRT (60% vs. 44%, 46%) and no different by 13 weeks (27% vs. 25%, 31%). **Conclusions:** Although clinical studies have reported the toxicities of CXRT, this is the first longitudinal study that compared symptom profiles for NSCLC patients receiving PBT, IMRT and 3DCRT. There is an impression of more severe treatment-related symptoms for 3DCRT (although in lower radiation dose) than IMRT or PBT.

**7575 General Poster Session (Board #24E), Sat, 8:00 AM-11:45 AM**

## A favorable population among clinical stage IIIA-N2 non-small cell lung cancer: The importance of the location of the primary tumor and involved nodes.

*Takeshi Matsunaga, Kenji Suzuki, Kazuya Takamochi, Shiaki Oh; Juntendo University School of Medicine, Tokyo, Japan*

**Background:** The number of station of involved N2 nodes has been considered to be one of the most important prognostic factors for lung cancer. However most reports detailed with not clinical nodal status, but pathological nodal status. We investigated the relationship between prognosis and the location of the primary tumor and involved nodes. **Methods:** A retrospective study was conducted on 1257 patients with primary lung cancer, which was resected between 1996 and 2009. Among them, 79 patients (6.3%) had cN2, c-stage IIIA, pN2 and NSCLC. Mediastinal lymph node with a diameter of 10mm or more in the short axis was diagnosed as metastasis. We defined cN2$\alpha$ as only involvement of upper mediastinal lymph node (UMLN) in main tumor located on upper lobe or as that of lower mediastinal lymph node (LMLN) in main tumor located on lower lobe. And we did cN2$\beta$ as involvement of LMLN in main tumor located on upper lobe with or without metastatic UMLN or as that of UMLN in main tumor located on lower lobe with or without metastatic LMLN. We analyzed preoperative clinical factors and investigated overall and disease-free survival. **Results:** The overall 5-year survival rate was 30.2% and median follow-up was 52.8 months. The disease-free 5-year survival rate was 22.2%. The differences in survival between cN2$\alpha$ and cN2$\beta$ were statistically significant (29.5% vs. 0%, p-value=0.0007), whereas no significant differences was found between cN2 single station and multiple station (23.3% vs. 19.4%, p-value=0.1220). Multivariate analysis with cox's hazard model disclosed that cN2$\alpha$ was independent good disease-free prognostic factor(HR: 0.426, 95%CI: 0.193-0.941). The sensitivity, specificity and positive predictive value for pN2 single station based on cN2 single station were 71.4%, 49.1% and 34.9% (p=0.1269). **Conclusions:** Clinical mediastinal lymph node status based on the location of the primary tumor and involved nodes was an important preoperative prognostic factor. Thus this factor should be taken into consideration for planning and evaluating clinical trials. Another fruit of the study was that clinical single nodal N2 was not always pathological single N2 disease.

**7576 General Poster Session (Board #24F), Sat, 8:00 AM-11:45 AM**

## Reproducible molecular characterization of non-small cell lung cancer from paraffin.

*Matthew Wilkerson, Myla Lai-Goldman, Philip Seth Bernard, Charles M. Perou, David N. Hayes, Juneko E. Grilley-Olson; The University of North Caroline at Chapel Hill, Chapel Hill, NC; Personalized Sci, LLC, Chapel Hill, NC; University of Utah Health Sciences Center, Salt Lake City, UT; The University of North Carolina at Chapel Hill, Chapel Hill, NC; Lineberger Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC*

**Background:** Recommendations exist to aid the clinically relevant non-small cell lung cancer (NSCLC) classification of squamous (SQ) versus adenocarcinoma (AD), including immunohistochemistry (IHC) for TTF1 and p63. We hypothesize that PCR of RNA gene panels may improve the diagnostic accuracy over IHC. **Methods:** A multi-institutional cohort of NSCLC patients was abstracted for use of IHC in clinical practice. RNA was isolated from routine paraffin sections and a 54-gene Histology by gene Expression Predictor (HEP) was implemented to distinguish SQ, AD, and other NSCLC variants. IHC for TTF1 and p63 was obtained on a subset of patients in a standardized manner. To compare the reproducibility of PCR diagnostics to morphologic diagnosis, a subset of samples was processed as matched pairs from the same tumor, in blinded manner. **Results:** 493 clinical samples were analyzed from 419 patients. Pathologists obtained any IHC in 22% of the cases, with TTF1 or p63 in $<$10% of cases. In the subset of cases where standardized TTF1 and p63 was obtained, the stains were un-evaluable or incompletely obtained in 30% for reasons including technical failure, limited sample, and ambiguous staining (i.e positive for both p63 and TTF1); on this same subset, the HEP technical failure rate was 7%. In cases where staining was successful, both IHC and the HEP agreed with the clinical diagnosis at high rates (93 and 91% respectively). In IHC un-evaluable cases, slides were reviewed by up to 7 additional pathologists. In general such cases failed to produce a consensus diagnosis, suggesting that IHC failure indicates a difficult to diagnose case (kappa statistic $<$0.5). As another concordance assessment method, we evaluated a second diagnostic property, reproducibility, by taking paired samples from the same case for blinded review. Strikingly, morphologic review in a blinded manner by pathologist generated low agreement with overall agreement of 65% compared to the HEP agreement of 92%. **Conclusions:** PCR based diagnostics such as the HEP may improve NSCLC diagnostic performance

**7577** **General Poster Session (Board #24G), Sat, 8:00 AM-11:45 AM**

# Has the paradigm changed away from lobectomy for stage I non-small cell lung cancer (NSCLC)? Anatomic segmentectomy: Surgery's answer to image-guided ablation/radiation therapy for the small peripheral lung lesion.

*Matthew J. Schuchert, Joseph J. Wizorek, Daniel Paul Normolle, David O Wilson, Jill Siegfried, Omar Awais, Ghulam Abbas, James D. Luketich, Rodney Jerome Landreneau; Department of Cardiothoracic Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA; Department of Cardiothoracic Surgery; University of Pittsburgh Medical Center, Pittsburgh, PA; University of Pittsburgh, Pittsburgh, PA; University of Pittsburgh Medical Center, Pittsburgh, PA; Department of Pharmacology and Chemical Biology UPMC Endowed Chair for Lung Cancer Research, Hillman Cancer Center, Pittsburgh, PA; University of Pittsburgh Shadyside Medical Center, Pittsburgh, PA*

**Background:** Lobectomy has been the "gold standard" for stage I NSCLC management. Image guided ablation/radiation therapy approaches are now being touted as alternatives to surgery despite concerns regarding diagnosis, pathologic staging, local control, and delayed toxicities. We evaluated the diagnostic utility and oncologic efficacy of lung sparing, anatomic segmentectomy for indeterminate pulmonary nodules and clinical stage I NSCLC. **Methods:** Retrospective review of 1,005 anatomic segmentectomies from 2002-2012 for indeterminate pulmonary nodules and clinical stage I NSCLC. Outcome variables included perioperative data, morbidity and mortality. Survival was assessed with the Kaplan-Maier method. **Results:** Mean age was 66.7 years. Median lesion size was 1.9 cm. VATS was employed in 62.8% of cases. Median operative time and blood loss was 112 minutes and 80 ml, respectively. Median hospital stay was 5 days. Major complications occurred in 12.7%. Thirty-day mortality was 1.0%. Of these, NSCLC was identified in 71.6%, metastases in 8.7%, and other benign conditions in 19.7%. Among patients with clinical stage I NSCLC, clinical: pathological upstaging was seen in 34.5%. Local recurrence rate was 5.2% and five-year freedom from any recurrence was 69%, equivalent to lobectomy in our experience. **Conclusions:** Anatomic segmentectomy is a valuable primary surgical approach today. In this era of competing image-guided ablation modalities, anatomic segmentectomy provides safety, diagnostic accuracy and adherence to oncologic surgical principles including completeness of resection with adequate surgical margins, systematic nodal staging improving pathologic accuracy, and tissue for pharmacogenomic assessment to guide individualized adjuvant therapy.

**7578 General Poster Session (Board #24H), Sat, 8:00 AM-11:45 AM**

## Multi-institutional study of reirradiation with proton beam radiotherapy for non-small cell lung cancer.

*Abigail T. Berman, Christine Agnes Martin, Haibo Lin, Stefan Both, Corey J. Langer, Kristi Varillo, Ramesh Rengan, Stephen M. Hahn, Marcio Fagundes, William F. Hartsell, Charles B. Simone, John Peter Plastaras; Department of Radiation Oncology, Hospital of the University of Pennsylvania, Philadelphia, PA; Hospital of the University of Pennsylvania, Philadelphia, PA; Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; Department of Radiation Oncology, University of Pennsylvania School of Medicine, Philadelphia, PA; University of Pennsylvania, Philadelphia, PA; Procure Proton Therapy Center, Oklahoma City, OK; CDH Proton Center, Warrenville, IL*

**Background:** The management of recurrent non-small cell lung cancer (NSCLC) in the setting of prior radiation (RT) is complex. Proton radiotherapy (PRT) is ideally suited to minimize toxicity by sparing dose to previously-irradiated organs. Herein we report the safety and feasibility of PRT for NSCLC reirradiation. **Methods:** Patients (pts) with recurrent NSCLC in or near their prior RT field were identified in three proton centers. An interval of 3 months was required between original RT course and PRT start. Pts were classified as low volume (LV, clinical target volume [CTV] $\leq$250 cc) or high volume (HV, CTV $>$250 cc). PRT was deemed infeasible if pts were unable to tolerate 15% of fractions or complete all treatments in $<$10 days of estimated end date and without a break $\geq$5 days. **Results:** Between 10/2010-11/2012, 24 pts were reirradiated, with 12 on a prospective trial of PRT for reirradiation. Median age was 69 (51-89). Histologies included squamous cell carcinoma (50%), adenocarcinoma (39%), and other (13%). Stage at initial diagnosis was I (8.3%), II (20.8%), III (50%), IV (12.5%), and unknown (8.3%). All pts were ECOG PS 0-2. Median prior dose was 62.4 Gy (30.6-80); 1 pt had 2 prior RT courses. The majority of pts (63%) were LV (median CTV 75.3, 11.9-236) and 38% were HV (359, 297.8-695.7). Concurrent systemic therapy (platinum-based or erlotinib) was given in 63%. Median PRT dose was 66.6 Gy (36-74). Average mean lung dose was 7.6 and 10.8 Gy and lung volume receiving 5 and 20 Gy was 16 and 24% and 26 and 33% in LV and HV pts, respectively. Follow up was $>$60 days in 17 pts. Overall, 46% of pts were hospitalized. PRT was infeasible in 3/9 HV and 1/15 LV pts. In HV pts, there were 2 grade 5 toxicities (hemoptysis and neutropenic fever). There was 1 in-field and 4 other thoracic recurrences, and 5 and 4 deaths in LV and HV pts, respectively. **Conclusions:** Preliminary results show promising early outcomes and acceptable toxicity in LV pts; due to the toxicity seen in HV pts, additional exclusion criteria were added for NSCLC pts in the ongoing trial. NSCLC reirradiation should continue to be studied in prospective trials to identify pts that may derive clinical benefit. Mature follow up is needed prior to standardizing NSCLC reirradiation with PRT.

**7579 General Poster Session (Board #25A), Sat, 8:00 AM-11:45 AM**

# Total lesion glycolysis (TLG) at baseline FDG-PET/CT compared with maximum standard uptake value ($SUV_{max}$) to predict survival in non-small cell lung cancer (NSCLC).

*Ling Li, Feng-Ming (Spring) Kong, Nan Bi, Jingbo Wang, Pawinee Mahasittiwat, Paul Stanton, Timothy Ritter; Deparment of Radiation Oncology, University of Michigan, Ann Arbor, MI; University of Michigan Department of Radiation Oncology, Ann Arbor, MI; Department of Radiation Oncology, University of Michigan, Ann Arbor, MI; Deparment of Radiation Oncology,University of Michigan, Ann Arbor, MI; Universtiy of Michigan, St.Louis, MO; University of Michigan, Ann Arbor, MI; University of Michigan Medical Center, Ann Arbor, MI*

**Background:** $SUV_{max}$at baseline FDG-PET has been reported as a significant prognostic factor while recent studies suggest that metabolic tumor volume (MTV) may be more important factor in patients with NSCLC. We hypothesized that TLG is a better prognostic factor than either $SUV_{max}$ or MTV alone for overall survival (OS) and progression free survival (PFS) in NSCLC because it integrates both volumetric and biologic activity. **Methods:** The study population included a prospectively recruited cohort of stage I-III NSCLC patients treated with chemoradiation. FDG PET/CT scans were performed within 2 weeks from treatment start. The SUV in the tumor was normalized to that of the background level in the middle of ascending aorta to minimize the confounding effect from inter-scan variation in SUV measurement. MTV was delineated by auto-threshold at 1.5 times background level in the aorta followed by knowledge based manual editing. Mean and maximum SUV normalized to the background level were computed. TLG was calculated as the product of lesion $SUV_{mean}$ and MTV. **Results:** A total of 96 patients with minimum follow-up of 1 year were eligible. The median follow-up among survivors was 30 months. Univariate analysis demonstrated that MTV and TLG were significant factors for both OS and PFS (all $P<0.05$). There was a significant correlation between $SUV_{mean}$ and PFS ($P=0.013$), but there was no significant association between $SUV_{mean}$ and OS. $SUV_{max}$ was not a significant factor for either OS or PFS (all $P>0.05$). Under multivariate Cox regression analysis, MTV (HR= 2.62, $P= 0.003$) and $NSUV_{mean}$ (HR=0.351, $P=0.003$) were significantly associated with PFS; but only TLG was significantly associated with OS (HR=2.14, $P=0.006$)adjusted by of TNM stage and other clinical factors. **Conclusions:** These results support our hypothesis that metabolic tumor volume and biologic average glucose metabolic activity of this volume are more important prognostic factors for overall prognosis than $SUV_{max}$ in NSCLC patients treated with chemoradiation. Should this be validated by independent studies, future clinical trial should take this into consideration for individualized care.

**7580 General Poster Session (Board #25B), Sat, 8:00 AM-11:45 AM**

## Serum miRNA signature to identify a patient's resistance to high-dose radiation therapy for unresectable non-small cell lung cancer.

*Nan Bi, Matthew J Schipper, Paul Stanton, Weili Wang, Feng-Ming (Spring) Kong; Department of Radiation Oncology, University of Michigan, Ann Arbor, MI; University of Michigan, Ann Arbor, MI; University of Michigan Department of Radiation Oncology, Ann Arbor, MI*

**Background:** There is a growing literature on unique profiles of serum micro RNAs (miRNAs) expression to predict clinical outcome of metastatic and early stage non-small cell lung cancer (NSCLC). However, the predictive role of circulating miRNAs in unresectable NSCLC treated with definitive radiation therapy (RT) is unknown. **Methods:** 134 patients with inoperable/unresectable NSCLC treated with definitive RT (18-month minimum follow-up) were eligible. Serum samples were collected prospectively before treatment. 100 patients had enough serum and reliable miRNA profile quality, which were randomly divided into training and validation sets (50 patients each). MiRNA profiling was performed using real-time PCR-based array, containing a panel of 84 miRNAs detectable in human bodily fluids. Spiked-in cel-miR-39 was used for normalization. Stepwise regression Cox model building was used to build a miRNA signature on the training set, which was then assessed on the validation set both alone and with clinical factors. **Results:** The median age was 67 years; 76% were stages III and 79% received chemoradiation; the median physical dose was 70.0 Gy. A serum hsa-miR-885/hsa-miR-7 signature was identified as significant predictors for overall survival (OS) in the training set, which was validated by the validation set ($p=0.02$). After adjustment for GTV Volume and KPS, the only two significant clinical factors in univariate analysis, this signature remained significant ($p=0.04$). In the high-dose RT group ($>70$ Gy, $n=45$), individuals with low-risk had a significantly longer OS than patients with high-risk (70.7 vs. 18.8 months, $p=0.007$); while in the low-dose RT group ($\leq 70$ Gy, $n=55$), no significant association was observed (OS, 22.0 vs. 13.3 months, $p=0.43$). **Conclusions:** Circulating hsa-miR-885/hsa-miR-7 signature may be used as a putative non-invasive biomarker for predicting survival and radiation resistance in unresectable NSCLC, which may potentially help to select patients who will not benefit from high-dose radiation. Independent validation studies are needed to confirm our findings. Clinical trial information: NCT01190527.

**7581 General Poster Session (Board #25C), Sat, 8:00 AM-11:45 AM**

## Genomic characterization and high-throughput therapeutic screening of malignant mesothelioma to reveal novel tumor dependencies.

*Constantine Alifrangis, Josine Quispel Janssen, Hilda de Vries, Laurel Schunselaar, Graham Bignell, Mathew Garnett, Jacques Neefjes, Anton Berns, Paul Baas, Ultan McDermott; University of Cambridge, Cambridge, United Kingdom; NKI-AVL, Amsterdam, Netherlands; Wellcome Trust Sanger Institute, Hinxton, United Kingdom; Wellcome Trust Sanger Institute, Cambridge, United Kingdom; Netherlands Cancer Institute, Amsterdam, Netherlands*

**Background:** Clinical trials of targeted therapeutics in mesothelioma have demonstrated limited efficacy. It has been suggested that combinations of targeted agents may be more effective in this disease, but given the unknown status of tractable oncogenic mutations it has been difficult to ascertain which key signalling nodes drive these tumours that may lend themselves to therapeutic intervention. We therefore aimed to characterise a representative panel of mesothelioma cell lines at the genomic level, and then determine critical "nodes" utilising a high throughput screen of targeted agents. **Methods:** 19 mesothelioma cell lines and 6 mesothelioma primary tumour early passage lines underwent Illumina whole exome sequencing and copy number analysis. In parallel a high throughput screen was performed utilising a panel of targeted therapeutics enabling each mesothelioma to be screened across 48 compounds. Efficacy was confirmed in 3D spheroid culture. **Results:** Exome sequencing of the mesothelioma panel revealed mutations in tumour suppressor genes previously described in mesothelioma including *NF2*, as well as previously unreported mutations in this disease affecting histone modifying genes *MLL2* and *SETD2*. Notably an absence of mutated "driver" oncogenes was observed. High throughput screening demonstrated limited activity for most small molecule inhibitors as single agents. However, despite an absence of mutations in *PIK3CA*or related genes, PI3K/mTORC inhibition had the broadest single agent efficacy. **Conclusions:** We demonstrate that mutations in cell lines are similar to those found in patient-derived tumours implying fidelity at the genomic level. Mesotheliomas harbour multiple mutations in tumour suppressors, but lack commonly tractable oncogenic mutations which may explain poor efficacy seen in clinical trials to date. We further demonstrate that PI3K may represent a critical node therapeutically that may be useful in combinatorial approaches.

## 7582 General Poster Session (Board #26A), Sat, 8:00 AM-11:45 AM

# Multiplexed genetic analysis of malignant pleural mesothelioma and the relationship to clinical outcome.

*Takehito Shukuya, Masakuni Serizawa, Masato Abe, Hiroaki Akamatsu, Takaaki Tokito, Hisao Imai, Akira Ono, Tetsuhiko Taira, Hirotsugu Kenmotsu, Tateaki Naito, Haruyasu Murakami, Toshiaki Takahashi, Masahiro Endo, Takashi Nakajima, Yasuhiro Koh, Nobuyuki Yamamoto; Division of Thoracic Oncology, Shizuoka Cancer Center, Nagaizumi-chou, Shizuoka, Japan; Division of Drug Discovery and Development, Shizuoka Cancer Center Research Institute, Nagaizumi-chou, Shizuoka, Japan; Division of Pathology, Shizuoka Cancer Center, Nagaizumi-chou, Shizuoka, Japan; Division of Thoracic Oncology, Shizuoka Cancer Center, Nagaizumi-cho, Shizuoka, Japan; Division of Diagnostic Radiology, Shizuoka Cancer Center, Nagaizumi-chou, Shizuoka, Japan*

**Background:** Genotype-based stratification is essential to improve cancer treatment. We have developed a multiplexed tumor genotyping panel for detecting gene alterations relevant to molecular targeted therapies. We applied this genotyping panel to malignant pleural mesothelioma (MPM) and evaluate the relationship between clinical outcome and gene alterations. **Methods:** Surgical specimens and tumor biopsies from 40 patients with MPM were collected from 2003 to 2012. Pathological diagnoses were confirmed by immunohistochemistry in addition to HE stain. 37 patients were genotyped with multiplexed tumor genotyping panel developed to assess 9 gene mutations (*EGFR*, *KRAS*, *BRAF*, *PIK3CA*, *NRAS*, *MEK1*, *AKT1*, *PTEN* and *HER2*) and 5 genes amplifications (*EGFR*, *MET*, *PIK3CA*, *FGFR1* and *FGFR2*) using pyrosequencing plus capillary electrophoresis, and qRT-PCR, respectively. Other 3 patients were analyzed by ultra-deep targeted sequencing with next generation sequencer. 5 fusion genes (*EML4-ALK, CD74-ROS1, SLC34A2-ROS1, KIF5B-RET and CCDC6-RET*) were tested in 2 patients with fresh frozen specimens. **Results:** Gene alterations were detected in 6 patients (Table shown below). These patients harboring gene alterations showed poorer survival than the patients in whom gene alterations were not detected (median survival time (MST): 583 vs 164 days, log-lank: p=0.009). Moreover, the patients with PIK3CA amplification/mutation showed poorer survival than the patients without PIK3CA amplification/mutation (MST: 583 vs 103 days, log-lank: p=0.031). **Conclusions:** Gene alterations which could be a target for molecular targeted therapy were detected in MPM. Especially, PIK3CA pathway is a potential target.

| Gender | Age | Histology | PS | Asbestos exposure | Stage | Type of genetic abnormality | Initial therapy | Response to CTx | PFS | OS |
|---|---|---|---|---|---|---|---|---|---|---|
| M | 60 | Sarcomatoid | 1 | Definite | IV | *PIK3CA* amplification | CDDP+PEM | PD | 67 | 144 |
| M | 73 | Epithelioid | 0 | Definite | III | *PIK3CA* amplification | Operation | - | 38 | 62 |
| M | 63 | Epithelioid | 0 | Suspected | I | *PIK3CA* K111R | Operation | - | 162+ | 193+ |
| F | 26 | Sarcomatoid | 2 | Not definite | IV | *KRAS* G12D | CBDCA+PEM | PD | 40 | 50 |
| M | 68 | Sarcomatoid | 0 | Definite | IV | *EGFR* exon 19 deletion | CDDP+PEM | SD | 247 | 393+ |
| M | 63 | NOS | 1 | Suspected | IV | *APC* A1485T, *TP53* R342Q | CDDP+PEM | PD | 30 | 184 |

**7583 General Poster Session (Board #26B), Sat, 8:00 AM-11:45 AM**

# A feasibility study of induction pemetrexed plus cisplatin followed by extrapleural pneumonectomy (EPP) and postoperative hemithoracic radiation (H-RT) for malignant pleural mesothelioma (MPM): First all-Japan trial.

*Fumihiro Tanaka, Seiki Hasegawa, Morihito Okada, Takeharu Yamanaka, Toshinori Soejima, Norihiko Kamikonya, Kazuya Fukuoka, Kohei Yokoi, Takashi Nakano; Deaprtmant of Surgery, University of Occupational and Environmental Health, Kitakyusyu, Japan; Hyogo College of Medicine, Department of Thoracic Surgery, Nishinomiya, Japan; Department of Surgical Oncology, Hiroshima University, Hiroshima, Japan; Research Center for Innovative Oncology, National Cancer Center Hospital East, Kashiwa, Japan; Department of Radiation Oncology, Hyogo Cancer Center, Akashi, Japan; Department of Radiology, Hyogo College of Medicine, Nishinomiya, Japan; Division of Internal Medicine, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan; Division of Thoracic Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan; Division of Respiratory Medicine, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan*

**Background:** The first all Japan multi-institutional trial was conducted to evaluate the feasibility of tri-modality therapy for MPM with support by the Special Coordination Funds for Promoting Science and Technology from the Japanese Ministry of Education, Culture, Sports, Science and Technology, and the first analyses data including macroscopic complete resection (MCR) rate by EPP as well as treatment-related mortality were presented at the ESMO meeting 2011 after completion of planned patient enrollment, and all survival data collection has been completed in January 2013. **Methods:** Major eligibility criteria: a histologically confirmed diagnosis of MPM, including all subtypes clinical T0–3, N0–2, M0 disease considered to be completely resectable; no prior treatment for the disease; age between 20 and 75 years; ECOG performance status of 0 or 1; a predicted postoperative forced expiratory volume in 1 s of $>$1000 ml; and written informed consent. Treatment methods: Induction chemotherapy of pemetrexed 500 mg/m$^2$ plus cisplatin 60 mg/m$^2$ for 3 cycles, followed by EPP and postoperative H-RT (54 Gy). Primary endpoints: MCR rate by EPP and treatment-related mortality for tri-modality therapy. **Results:** A total of 17 institutions in Japan with certified specialists in oncology, surgery and radiation therapy participated in this trial. The study was initiated in May 2008 and patient enrollment was completed in November 2010 with 42 eligible patients. Median age 64.5 (range 43–74), M: F = 39:3, Clinical stage I:II:III = 14:13:15, Histological type epithelial: sarcomatous; biphasic; others = 28: 1: 9: 4. The trial met the primary endpoints with MCR rate of 71% and treatment-related mortality of 9.5%. All survival data to calculate disease-free survival and overall survival at 2 years after EPP have been collected, and results will be presented at the meeting. **Conclusions:** Results of the present trial will be the foundation of treatment strategy for resectable MPM. Clinical trial information: 000001154.

**7584 General Poster Session (Board #26C), Sat, 8:00 AM-11:45 AM**

# Independent validation of progression-free survival rate at 9 and 18 weeks (PFSR-18, PFSR-9) as predictor for overall survival (OS) in patients with malignant pleural mesothelioma (MPM): EORTC 08052 study.

*Baktiar Hasan, Athanasios G. Pallis, Rabab Mohamed Gaafar, Laurent Greillier, Jan P. Van Meerbeeck, Mary O'Brien; European Organisation for Research and Treatment of Cancer Headquarters, Brussels, Belgium; EORTC, Brussels, Belgium; National Cancer Institute, Cairo University, Cairo, Egypt; Assistance Publique, Hôpitaux de Marseille, Université de la Méditerrranée, Marseille, France; Ghent University, Gent, Belgium; The Royal Marsden Hospital NHS Foundation Trust, Sutton, United Kingdom*

**Background:** The increasing incidence and the plateau of current treatment outcomes in MPM necessitates development of new therapeutic approaches. Reliable and meaningful response assessment is difficult in phase II trials thus a primary endpoint based on progression free survival (PFS) rate at certain time point has been proposed (Greillier et al, 2011). EORTC 08052 was a phase II study in MPM where independent validation of PFSR-18 weeks was foreseen. We extend this to PFSR-9. **Methods:** Association of PFS and response with OS was assessed at two distinct time points; 9 and 18 weeks after registration. Landmarks method was used, PFS status (CR/PR/SD vs. PD) and response status (CR/PR vs. PD/SD) were determined at those time points. Cox regression and logrank test were performed and the corresponding c-indexes were calculated. **Results:** Of 82 registered patients, 28.4% achieved CR/PR and 77.8% had disease control (CR/PR/SD) as their best overall response. PFSR-18 and PFSR-9 were both strongly correlated with OS. Patients with no progression at 18 weeks had median OS of 16.9 months compared to 11.9 months in those who progressed at 18 weeks. Hazard ratio [HR] (95 confidence interval [CI]) was 0.46 (0.32-0.67), logrank test was 0.007 and C-index = 0.60. Adjusting for 3 important baseline prognosis factors, histology, performance status and disease stage resulted in PFS-18 as the only significant factor. When 9 weeks landmark was chosen, patients with no progression had median OS of 16.9 months vs. 6.8 months in those who progressed with HR (CI), logrank test and C-index 0.35(0.25-0.49), $< 0.0001$ and 0.66 respectively. When adjusted by 3 important baseline prognosis factors PFS-9 remained the only significant factor. The results also confirmed that response at 18 weeks and 9 weeks was correlated with OS. **Conclusions:** PFSR-18 was strongly correlated and discriminated patients with better OS from the poorer prognosis patients. An earlier endpoint, PFSR-9 was also strongly correlated to OS and had a better discriminating capacity. Previous results on correlation between PFSR-9 and PFSR-18 and OS were independently validated.

**7585 General Poster Session (Board #27A), Sat, 8:00 AM-11:45 AM**

# Platelet counts (PLT) at baseline and on treatment as predictor for progression free survival (PFS) in patients with advanced malignant pleural mesothelioma (MPM): EORTC 08052 study.

*Rabab Mohamed Gaafar, Sanjay Popat, Jan P. Van Meerbeeck, Paul Baas, Dean Fennell, Athanasios G. Pallis, Baktiar Hasan, Mary O'Brien; National Cancer Institute, Cairo University, Cairo, Egypt; The Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom; Ghent University, Gent, Belgium; Netherlands Cancer Institute, Amsterdam, Netherlands; University of Leicester, Leicester, United Kingdom; EORTC, Brussels, Belgium; European Organisation for Research and Treatment of Cancer Headquarters, Brussels, Belgium; The Royal Marsden Hospital NHS Foundation Trust, Sutton, United Kingdom*

**Background:** PLT values at baseline are considered as a negative prognostic factor in several different tumor types (lung, colorectal, renal and endometrial cancer) in both early and advanced disease settings. This is an exploratory analysis of PLT (baseline and changes during treatment) and their value in predicting PFS and overall survival (OS) in patients with stage IV MPM treated with cisplatin/bortezomib in the context of a single-arm phase II trial (EORTC 08052). **Methods:** Patients participating in the clinical trial were chemo-naïve with histological proven MPM and PS 0/1 (cisplatin 75 mg/m$^2$ d1 and bortezomib 1.3 mg/m2 on d1, 4, 8, 11 q3wks). PLT analysis was pre-planned in the protocol and was recorded at baseline and at each cycle. Nadir of change in PLT was recorded at 8 and 18 weeks according to predefined cut off points (median PLT value). The association of the PLT with PFS and OS was analyzed. **Results:** 82 patients from EORTC-08052 study were analyzed with 1394 records of PLT. The cut off point for baseline was median PLT 374x10$^3$/mm$^3$. We confirmed that patients with baseline PLT less than median had longer PFS compared to patients with counts higher than median (median PFS: 5.7 vs. 3.7 months [mo]; HR: 0.55; 95% CI: 0.34-0.88; p: 0.012). There was also a trend towards higher OS for patients with baseline PLT values less than median (median OS: 14.8 vs.10.6 mo; HR: 0.62; 95% CI: 0.38-1.02; p: 0.059). The median decrease of PLT values at 8 wks of treatment was 243 x10$^3$/mm$^3$. Patients with decrease lower than median had higher PFS (median PFS: 7.5 vs. 5.7 mo; HR: 2.2; 95% CI: 1.3-3.8; p: 0.003) and a trend towards higher OS (median OS: 14.9 vs. 10.6 mo; HR: 1.6; 95% CI 1-2.7; p: 0.06). Changes at 18 weeks had no prognostic value. **Conclusions:** Besides low baseline PLT values we observed that a decrease in PLT at 8 weeks (but not 18 weeks) during treatment could predict PFS and to less extent OS. Validation of this observation is planned.

**7586 General Poster Session (Board #27B), Sat, 8:00 AM-11:45 AM**

# A novel microRNA-based treatment approach for malignant pleural mesothelioma.

*Glen Reid, Marcella Pel, Michaela Kirschner, Yuen Yee Cheng, Nancy Mugridge, Jocelyn Weiss, Marissa Williams, Casey Wright, Sonja Klebe, Himanshu Brahmbhatt, Jennifer MacDiarmid, Nico Van Zandwijk; Asbestos Diseases Research Institute, Sydney, Australia; University of Amsterdam, Amsterdam, Netherlands; Asbestos Diseases Research Institute, University of Sydney, Concord, Australia; EnGeneIC, Sydney, Australia; Flinders Medical Centre, Adelaide, Australia; EnGeneIC, Lane Cove West, Australia*

**Background:** Malignant pleural mesothelioma (MPM) is recalcitrant to treatment and new approaches are needed. The microRNA miR-16 has been implicated as a tumor suppressor in a range of cancer types, and restoration of miR-16 expression has been shown to inhibit tumor cell proliferation. The miR-16 status in MPM is largely unknown. **Methods:** MicroRNA expression was analysed by TaqMan-based RT-qPCR in 10 MPM cell lines and 60 tumour specimens consisting of archival blocks from patients undergoing surgery. MicroRNA expression was restored in vitro using mimics corresponding to the sequence of the mature microRNA, and effects on proliferation and target genes were assessed with standard methods. Human xenograft-bearing mice were treated with miR-16 mimics packaged in minicells targeted with EGFR-specific antibodies. **Results:** Expression of miR-16 was consistently down-regulated in MPM cell lines and MPM tumor specimens as were the co-expressed miR-15a and miR-15b. A decrease of 2- to 5-fold in miR-16 expression was found when MPM cell lines were compared with the normal mesothelial cell line MeT-5A. When tumor specimens were compared with normal pleura, the down-regulation of miR-16 was in the order of 10-fold. Using synthetic miR-16 mimics to restore miR-16 expression in MPM cell lines led to time- and dose-dependent growth inhibition in a panel of MPM cell lines but did not affect growth of MeT-5A. Growth inhibition correlated with cell cycle arrest and concordant down-regulation of miR-16 target genes including Bcl-2 and CCND1. In a series of experiments with nude mice bearing MPM (MSTO-H211) xenografts, intravenous administration of miR-16 mimics packaged in minicells led to consistent and dose-dependent inhibition of tumor growth. **Conclusions:** Restoring miR-16 expression represents a novel approach to treatment for MPM. Preparations are being made to test miR-16 packaged in minicells as a new treatment approach for patients with recurrent MPM and NSCLC.

**7587 General Poster Session (Board #27C), Sat, 8:00 AM-11:45 AM**

## A clinical-based risk score for decision making for surgery after induction chemotherapy in malignant pleural mesothelioma patients.

*Isabelle Opitz, Martina Friess, Rolf A. Stahel, Walter Weder; University Hospital Zurich, Zurich, Switzerland; Department of Thoracic Surgery, University Hospital, Zürich, Switzerland*

**Background:** Scoring tools predicting the potential benefit from surgery after induction chemotherapy in mesothelioma patients may influence decision making. Our score is based on 4 clinical variables available before surgery. **Methods:** 128 patients were uniformly treated with cisplatin based induction chemotherapy followed by extrapleural pneumonectomy between 1999 and 2011. Based on clinical experience and survival influencing factors resulting from uni-and multivariate analysis, we designed a risk score. All 4 variables building up the score were available for 59 patients: pre chemotherapy volumetry above 500 ml, non-epithelioid histotype in the diagnostic biopsy, pre chemotherapy CRP value above 30 mg/l and progressive disease after chemotherapy according to modified RECIST criteria. The 5 resulting groups were analyzed for overall survival (OAS) and progression free survival (PFS) using Kaplan-Meier and Cox regression model. **Results:** The score strongly stratified patients into high and low risk groups for shorter OAS (Table) ($p<0.0005$). As to PFS, patients with Score 0 also had significantly longer median PFS (16 months; 95% CI: 12; 20) in comparison to patients with score 3 or higher (6 months; 95% CI: -; -) ($p<0.0005$). In Cox regression analysis the risk factor for shorter OAS and PFS increased correspondingly to our score. **Conclusions:** Our new score based on 4 clinical variables available before surgery identifies patients' subgroups who may benefit from surgery after induction chemotherapy, which will be further assessed prospectively.

| | Total number | Median OAS | 95% CI |
|---|---|---|---|
| **Score 0** | 18 | 34 months | 18; 50 |
| **Score 1** | 25 | 17 months | 9; 25 |
| **Score 2** | 12 | 12 months | 8; 16 |
| **Score 3** | 3 | 4 months | 3; 6 |
| **Score 4** | 1 | 4 months | . |
| **Overall** | 59 | 18 months | 9; 26 |

**7588 General Poster Session (Board #28A), Sat, 8:00 AM-11:45 AM**

# Interim outcome analysis of a prospective phase I trial of surgical resection with intracavitary hyperthermic cisplatin and gemcitabine for patients with resectable malignant pleural mesothelioma.

*William G. Richards, Marcelo C Dasilva, Hannah M. Eisen, Julianne C Barlow, Raphael Bueno, David Sugarbaker; Brigham and Women's Hospital, Boston, MA*

**Background:** We completed a phase I trial of cisplatin and dose-escalated gemcitabine in a hyperthermic intra-operative lavage (IOHC) following extrapleural pneumonectomy (EPP arm) or extended pleurectomy (PD arm). Primary and secondary endpoints including gemcitabine MTD (1000 mg/m2 with 175 mg/m2 cisplatin) and pharmacokinetics, toxicity and mortality were reported (IMIG congress, 9/11-14/2012, abstract IIB.4 [1]). To define phase II indications, we explored patient outcome in comparison to published phase II results of a similar trial using cisplatin IOHC alone following EPP (J Thorac Cardiovasc Surg 2009, 138:405 [2]). **Methods:** The protocol was registered and IRB approved. Informed consent was obtained. Overall survival was calculated from the date of surgery to the date of death or censored at the date of most recent contact. Patients who were treated on the EPP arm at 500 to 1000 mg/m2 gemcitabine dose levels were included, grouped by epithelial (E) or non-epithelial (NE) histological subtype. Median, 1-year and 2-year survival was estimated using Kaplan-Meier methods. **Results:** 141 patients were registered. Median age was 65 (43-85) and 22 (21%) were women. Histology was epithelial (63), biphasic (32), and sarcomatoid (8). Two patients died perioperatively (2%). 59 patients were treated on the EPP arm of which the 27 (13 censored) treated at 500 to 1000 mg/m2 gemcitabine were studied. Qualitative comparison with a prior phase II trial of cisplatin IOHC (ref [2]) suggests incremental survival benefit to adding gemcitabine for patients with epithelial but not non-epithelial tumor histology (Table). **Conclusions:** Patients with epithelial histology tumors who require EPP for macroscopic complete resection appear likely to benefit from the addition of gemcitabine and should be included in a phase II investigation of this combination. Patients with non-epithelial biopsy who require EPP should be considered for other treatment strategies. Clinical trial information: NCT00571298.

| Procedure | Cis $mg/m^2$ | Gem $mg/m^2$ | Histology | N | Median (months) | 1-year (%) | 2-year (%) |
|---|---|---|---|---|---|---|---|
| **EPP** | 175 | 500-1000 | E | 16 | 25.5 | 94 | 70 |
| **EPP[ref 2]** | 225 | None | E | 53 | 17 | ~65 | ~35 |
| **EPP** | 175 | 500-1000 | NE | 11 | 6.8 | 27 | 0 |

**7589 General Poster Session (Board #28B), Sat, 8:00 AM-11:45 AM**

# Prophylactic cranial irradiation in patients ≥ 70 years old with limited stage small cell lung cancer: A Surveillance, Epidemiology, and End Results analysis.

*Bree Ruppert Eaton, David Mitchell Marcus, Sungjin Kim, Zhengjia Chen, Suresh S Ramalingam, Walter J. Curran, Kristin Higgins; Department of Radiation Oncology, Winship Cancer Institute of Emory University, Atlanta, GA; The Winship Cancer Institute of Emory University, Atlanta, GA; Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA*

**Background**: Prophylactic cranial irradiation (PCI) improves survival in patients with limited stage small cell lung cancer (SCLC) who have a complete response to chemotherapy and radiation (RT). Yet in clinical practice, concerns exist regarding PCI-related toxicity and the extent of benefit in elderly patients. This exploratory analysis evaluates the effect of PCI on survival among patients ≥ 70 years old. **Methods:** Using the Surveillance, Epidemiology, and End Results (SEER) database, we identified 4,003 patients ≥70 years old with localized or regional SCLC diagnosed between 1988 and 1997. Patients with no brain RT information (n=974) were excluded. Patients with overall survival (OS) <6 months (n=1103) were also excluded to eliminate patients with an aggressive disease course and minimize selection bias. Survival rates for patients who received brain RT versus no brain RT were estimated by the Kaplan Meier method and compared with the Log-rank test. A Cox proportional hazards model was further fitted to estimate the effect of brain RT on OS after adjusting for age, race, gender, and stage. **Results:** Of the 1926 patients included, the median age was 75 years (range, 70-94). The majority of patients were white (68%) and male (52%). According to SEER Historic Stage A, 68% of patients had regional stage and 32% had localized stage. One-hundred and thirty-eight patients (7.2%) received brain RT. Patients treated with brain RT were younger at diagnosis ($p<0.01$) and more likely to have regional stage disease ($p=0.02$). Five-year OS was 11.6% (95% CI: 6.9-17.6) among patients who received brain RT versus 8.6% (95% CI: 7.32-9.91) among patients who did not ($p=0.03$). Younger age, female gender, white race, and localized stage were also significant factors associated with improved OS. On multi-variable analysis, receipt of brain RT remained an independent predictor of OS (HR 0.825, 95% CI: 0.69-0.98, $p=0.03$). **Conclusions:** The receipt of brain radiotherapy is associated with improved overall survival in patients ≥70 years old with localized or regional stage SCLC, suggesting the benefit of PCI is maintained in the elderly population.

**7590 General Poster Session (Board #28C), Sat, 8:00 AM-11:45 AM**

## Genetic analysis of the separate morphologic components in combined small cell lung cancer.

*Hongyang Lu, Zhiqiang Ling, Qiao-Yuan Cheng, Bo Chen, Ju-Fen Cai, Wang Xiao Jia, Lei Lei, CaiJin Lou, Jing Qin, Wei-Wu Ye, Weimin Mao; Zhejiang Cancer Hospital, Hangzhou, China; Zhejiang Institute for Food and Drug Control, Hangzhou, China; Key Laboratory Diagnosis and Treatment Technology on Thoracic Oncology & Cancer Research Institute, Zhejiang Cancer Hospital, Hangzhou, China*

**Background:** Combined small cell lung cancer (CSCLC) is currently considered a subset of SCLC and have been reported to account for less than 1-3.2% of all SCLCs. Accurate understanding of CSCLCs is of great importance because treatment strategies are significantly different for NSCLC and SCLC. To address molecular features of different components in CSCLC we analyzed mutation status in CSCLC tumor samples in EGFR signal pathway. **Methods:** Seven CSCLC samples were included in direct sequencing for mutation analysis of EGFR, KRAS, PIK3CA, BRAF, and PTEN. **Results:** Mutations were detected in 4 of 7 (57.1%) CSCLC patients. EGFR Exon 18 mutations were identified in two patients among whom the mutation was identified in both adenocarcinoma component and SCLC combined adenocarcinoma component of one patient. The similar situation also happened in another one with PTEN C511T mutations both conventional SCLC component and SCLC combined adenocarcinoma component. Both KRAS and PIK3CA were detected in one SCLC combined adenocarcinoma patient and no mutation in BRAF was identified. **Conclusions:** Our result is consistent with previous work that the individual components of CSCLC are closely related, despite their distinct morphologic appearances.

**7591 General Poster Session (Board #29A), Sat, 8:00 AM-11:45 AM**

# Phase I/IIa study of the novel combination of bendamustine (B) with irinotecan (I) followed by etoposide (E) and carboplatin (C) in untreated patients (Pts) with extensive-stage small cell lung cancer (ESSCLC).

*Daniel Joseph Allendorf, Rodolfo Bordani, Stefan C. Grant, Mansoor N. Saleh, Mary Jerome, Debi Miley, Alan Cantor, Vishnu Reddy, Francisco Robert; University of Alabama at Birmingham, Birmingham, AL; Georgia Cancer Specialists PC, Atlanta, GA; University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL*

**Background:** Standard therapy for ESSCLC consisting of E and a platin drug (Plat) yields a median time to progression (TTP) of 4 months (m) and overall survival (OS) of 9 m. DNA damage from B is repaired by excision repair, akin to Plat. The activity of I, a topoisomerase (Top)-1 inhibitor, leads to increases in Top-2, the target of E. The sequence B+I → E+C was hypothesized to increase TTP by exploiting mitotic catastrophe. **Methods:** This is an open label trial enrolling pts with ESSCLC and evaluable disease. The phase I primary endpoint was to determine the maximum tolerated dose (MTD) of B+I; the phase IIa primary endpoint was TTP after B+I→E+C. Secondary endpoints were objective response rate (ORR) and OS. In the phase I (N=15), cohorts received I (150 mg/m$^2$, d 1) with B at 80, 100, or 120 mg/m$^2$/day (d 1,2) every 3 weeks for 3 cycles. Phase IIa Pts were treated at the recommended dose of B+I for 3 cycles followed by E (100 mg/m$^2$, d 1-3) + C (AUC 6, d 1) for 3 cycles. Restaging was performed after 3 cycles of each regimen. The phase IIa was powered to detect a 30% increase in TTP from 4 to 5.2 m with a of 0.1. The Kaplan-Meier method was used to calculate TTP and OS. Toxicities were evaluated using the NCI CTCAE. **Results:** The MTD of B was not reached. The recommended phase IIa dose of B was 100 mg/m$^2$; dose-escalation was allowed in subsequent cycles of therapy. Dose limiting toxicities were diarrhea, nausea, and vomiting. One treatment-related death from metabolic encephalopathy occurred in the phase IIa. The commonest grade 3/4 hematologic toxicity was neutropenia. Fatigue, nausea, vomiting, and diarrhea were common non-hematologic toxicities. **Conclusions:** B+I is an active regimen in ESSCLC and the treatment sequence B+I→E+C seems to improve the TTP and OS in ESSCLC compared to historic values for E+C. Toxicities were increased compared to historic values for E+C, but were manageable. Correlative studies with pre-treatment assessment of tumor ERCC-1, Top-1, and Top-2 as predictors of response are ongoing. Clinical trial information: NCT00856830.

**Efficacy parameters (N=29).**

| | | |
|---|---|---|
| **Median TTP** | | **6.0 m (95% CI 5.0-7.0)** |
| **Median OS** | 10.0 m (95% CI 8.3-11.7) | |
| **ORR** | 75% | |
| **Median tumor reduction after** | B+I | 65% |
| **E+C** | 73% | |

**7592 General Poster Session (Board #29B), Sat, 8:00 AM-11:45 AM**

## Circulating tumor cells as a prognostic factor in patients with small cell lung cancer.

*Satoshi Igawa, Jiichiro Sasaki, Noriyuki Masuda; Department of Respiratory Medicine, Kitasato University School of Medicine, Sagamihara, Japan; Department of Respiratory Medicine, Kitasato University School of Medicine, Sagamihara, Kanagawa, Japan; Kitasato University School of Medicine, Sagamihara, Japan*

**Background:** Research on the detection of circulating tumor cells (CTCs) in peripheral blood is currently an important field of research. The aim of this study was to evaluate a new method of detecting CTCs in the peripheral blood of small cell lung cancer (SCLC) patients by using the telomerase-specific replication-selective adenovirus OBP-401. **Methods:** We prospectively enrolled 30 consecutive newly diagnosed SCLC patients who were being started on chemotherapy or chemoradiotherapy as the subjects of this study. We collected peripheral blood specimens from the SCLC patients and detected viable CTCs in them after incubation with a telomerase-specific, replication-selective, oncolytic adenoviral agent carrying the green fluorescent protein (GFP) gene. We also investigated whether the CTC count per 7.5 ml of peripheral venous blood was associated with the outcome of SCLC. **Results:** CTCs were detected in 96% of the patients (29 of the 30 patients). The group of 22 patients with a CTC count of $< 2$ before treatment (baseline) had a significantly longer median survival time than the group of 8 patients with a CTC count of $\geq 2$ before treatment (14.8 months and 3.9 months, respectively, $P = 0.001$). The results of a multivariate analysis showed that the baseline CTC count was an independent prognostic factor for survival (hazard ratio $= 5.11$, $P = 0.038$). **Conclusions:** CTCs in the peripheral blood of SCLC patients can be detected by the OBP-401assay, and based on the results of this study the CTC count before treatment appears to be a strong prognostic factor.

**7593 General Poster Session (Board #29C), Sat, 8:00 AM-11:45 AM**

## Small cell lung cancer (SCLC) among patients who are never smokers.

*Anna M. Varghese, Helena Alexandra Yu, Helen H. Won, Camelia S. Sima, Gregory J. Riely, Lee M. Krug, Natasha Rekhtman, Mark G. Kris, Michael F. Berger, Maureen Frances Zakowski, Maria Catherine Pietanza; Memorial Sloan-Kettering Cancer Center, New York, NY; Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY*

**Background:** Although most patients (pts) with SCLC are current or former smokers, SCLC has been reported in pts who are never smokers, most recently in pts with *EGFR*-mutant lung cancers who develop acquired resistance (AR) to EGFR tyrosine kinase inhibitors (TKIs). We describe clinical, pathologic, and molecular characteristics of never-smoking pts with SCLC at diagnosis and in the AR setting. **Methods:** We identified cases through systematic review of pts seen at MSKCC from 2005 – 2012. Smoking history was obtained prospectively. SCLC diagnosis was confirmed by expert pathology review. We collected age, sex, stage, treatment, and survival data. *EGFR*, *KRAS*, *PIK3CA,* and *ALK* testing and next generation sequencing of 279 cancer genes was performed on available samples. **Results:** 2.2% (23/1040, 95% CI 1.5 to 3.3%) of pts with SCLC seen at MSKCC were never smokers: 61% women, median 64 years, 74% extensive stage, and 22% with brain metastases at diagnosis. 83% (19/23) had *de novo* SCLC, whereas only 17% had SCLC as AR to EGFR TKI after treatment for *EGFR*-mutant lung cancers, all of whom had persistent *EGFR* mutation confirmed at resistance. Median survival from SCLC diagnosis is 23 months (95%CI: 11-26) for all pts and 23 months (95% CI: 8–27) for the 19 pts with *de novo* SCLC. Pathologic review demonstrated 19 cases of pure SCLC and 4 mixed histology cases with SCLC and other histologies. Treatment history was available for 15/19 pts with *de novo* SCLC: 53% etoposide-platinum sensitive. *ALK* rearrangement and *KRAS* mutations were identified in 0/5 and 0/10, respectively. One pt with *de novo* mixed SCLC and adenocarcinoma had an *EGFR* mutation and another pt with *de novo* pure SCLC had *EGFR* and *PIK3CA* mutations. Mutations were identified in *p53* and *Rb1* with amplification in *TERT* in 1 sample to date tested with next generation sequencing. **Conclusions:** 2% of pts with SCLC are never smokers. While transformation to SCLC can occur in the setting of AR to EGFR TKI, *de novo* SCLC occurs in the majority of our never smokers with this disease. *EGFR* mutations uniformly exist in SCLC in the AR setting. *EGFR* mutations were rare, and we found no *KRAS* mutations or *ALK* rearrangements. Comprehensive, multiplexed genotyping can aid in providing optimal care and facilitate research in this unique population.

**7594 General Poster Session (Board #29D), Sat, 8:00 AM-11:45 AM**

## Predictive value of BRCA1, ERCC1, ATP7B, PKM2, TOPO-I, TOPO-iia, TOPO-iib, and c-MYC genes in patients with small cell lung cancer (SCLC) who received first-line therapy with cisplatin and etoposide.

*Chara Papadaki, Niki Karachaliou, Eleni Lagoudaki, Maria Trypaki, Maria Sfakianaki, Anastasios Koutsopoulos, Dimitrios Mavroudis, Efstathios Stathopoulos, Vassilis Georgoulias, John Souglakos; Laboratory of Tumor Cell Biology, School of Medicine, University of Crete, Heraklion, Greece; Pangaea Biotech, Laboratory of Translational Oncology, Barcelona, Spain; University General Hospital of Heraklion, Department of Pathology, Heraklion, Greece; University General Hospital of Heraklion, Department of Medical Oncology, Heraklion, Greece*

**Background:** to evaluate the predictive value of genes correlated with cisplatin-etoposide (EP) metabolism or mode of function in patients with SCLC. **Methods:** Tumor samples from 184 patients, with SCLC were analyzed for *ERCCI, BRCA1, ATP7B, TOPOI, TOPOIIA*, *TOPOIIB PKM2* and *C-MYC* mRNA expression by quantitative real-time PCR, from microdissected cells derived from patients' primary tumors. All patients were treated with EP (plus radiotherapy for patients with limited disease-LS) in the department of Medical Oncology of the University Hospital of Heraklion. **Results:** The median age of the patients was 63 years (min-max: 33-78). One hundred-twenty (65%) patients presented with extended stage (ES), LDH was above the UNL in 75 (41%), while ECOG performance status was 0-1 in 131 (71%) of them. Shorter progression free survival (PFS) was observed in patients with LS-SCLC whose tumors expressed high *ERCC1* ($p=0.028$), *PKM2* ($p=0.046$), *TOPO-I* ($p=0.008$), *TOPO-IIA* ($p=0.002$) and *TOPO-IIB* ($p<0.001$) expression. High expression of *ERCC1* ($p=0.014$), *PKM2* ($p=0.026$), *TOPO-IIA* ($p=0.021$) and *TOPO-IIB* ($p=0.019$) was correlated with shortened median overall survival (OS) in LS-SCLC patients. In patients with ES-SCLC, only high *TOPO-IIB* expression was associated with decreased OS ($p=0.035$). The favorable genotype (low expression of *ERCC1*, *PKM2*, *TOPO-IIA* and *TOPO-IIB*) was correlated with significantly improved PFS in both LS-SCLC ($p<0.001$) and ES-SCLC ($p=0.007$) patients as well as with improved OS in the LS-SCLC ($p=0.007$) and ES-SCLC ($p=0.011$) group. Unfavorable genotype was independent predictor of poor PFS (HR: 3.18; $p=0.002$) and OS (HR: 4.35; $p=0.001$) in LS-SCLC as well as for both PFS (HR: 3.14; $p=0.021$) and OS (HR: 3.32; $p=0.019$) in ES-SCLC. **Conclusions:** Single gene's expression analysis as well as the integrated analysis of *ERCC1*, *PKM2, TOPO-IIA* and *TOPO-IIB* may predict treatment outcome in patients with SCLC. The results of our study, if validated prospectively, may help in selecting patients for personalized therapeutic strategies.

**7595 General Poster Session (Board #29E), Sat, 8:00 AM-11:45 AM**

# A multicenter phase III randomized double-blind placebo controlled trial of pravastatin added to first-line standard chemotherapy in patients with small cell lung cancer (SCLC).

*Michael Seckl, Christian Ottensmeier, Michael H. Cullen, Peter Schmid, Lindsay E. James, Christina Wadsworth, Hannah Farrant, Dakshinamoorthy Muthukumar, Joyce Thompson, Susan Harden, Gary William Middleton, Kate Fife, Barbara Crosse, Paul Taylor, Iftekhar Khan; Charing Cross Hospital Trophoblastic Disease Centre, London, United Kingdom; Southampton University Hospitals NHS Foundation Trust, Southampton, United Kingdom; Cancer Centre At the Queen Elizabeth Hospital, Birmingham, United Kingdom; Brighton and Sussex Medical School, University of Sussex, Brighton, United Kingdom; Cancer Research UK & UCL Cancer Trials Centre, London, United Kingdom; Colchester Hospital University NHS Trust, Colchester, United Kingdom; Birmingham Heart of England Foundation Trust, Birmingham, United Kingdom; Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; Royal Surrey County Hospital, Guildford, United Kingdom; Peterborough & Stamford NHS Trust, Peterborough, United Kingdom; Calderdale & Huddersfield NHS Trust, Huddersfield, United Kingdom; University Hospitals of South Manchester, North West Lung Center, Manchester, United Kingdom*

**Background:** Most SCLC patients initially respond to chemotherapy but then relapse and die so new therapies are urgently required. Pre-clinical data shows statins induce growth arrest and apoptosis in SCLC and several other tumour cell types and are additive with chemotherapy. This may in part be due to impaired Ras superfamily function as statins deplete mevalonate, reducing geranylgeranylation and farnesylation of these proteins. We therefore undertook this large pragmatic phase III trial in order to determine if overall survival (OS) was affected by the addition of pravastatin in SCLC. **Methods:** Patients with limited (LD) or extensive (ED) stage SCLC were randomised to pravastatin 40mg OD or placebo for up to 2 years and given standard chemotherapy according to local practice recommended as either cisplatin 60mg/$m^2$ iv or carboplatin AUC 5 or 6 and etoposide 120 mg/$m^2$iv d1 to 3 or 100 mg BD po d2 & 3; max 6 cycles plus radiotherapy as usually given. Patients were excluded if they had used statins within 12 months prior to randomisation. Stratification was: LD vs ED and ECOG 0,1 vs 2,3. Endpoints were: primary - OS; secondary - progression free survival (PFS), local PFS (local control), response rates (RR) and toxicity. **Results:** Between 2007 and 2012, 846 patients were randomised, 422 (49.9.%) received pravastatin and 424 (50.1%) placebo in 93 participating sites in the UK. The median age was 64 years (range 54-69); ECOG performance status: 0: 23%; 1: 54%; 2: 17% and 3: 6%; weight 72.6 kg; LD, 357 (42.2%); ED, 479 (56.6%); 211 (24.9%) had ipsilateral effusion and 201 (23.8%) had ipsilateral SCF lymph nodes; Relative Dose intensity of cisplatin/carboplatin and etoposide was 91.6% (range 80.8 to 99.7), and 94.7% (range 85.7 to 100); 83.4% vs 86.3% completed $>$ 4 cycles of chemotherapy on the pravastatin and placebo arms respectively. Most patients completed 6 cycles of chemotherapy: 263 (62.3%) vs 265 (62.5%) in the pravastatin vs. placebo groups. Updated results showing OS, PFS, local PFS and toxicity will be presented. **Conclusions:** This trial will report on whether pravastatin 40 mg OD added to standard therapy alters the outcome for SCLC patients. Clinical trial information: ISRCTN56306957.

**7596 General Poster Session (Board #29F), Sat, 8:00 AM-11:45 AM**

## Can hippocampus be spared in patients with small cell lung carcinoma (SCLC) during cranial radiation therapy (CRT)?

*Vijayananda Kundapur, Tasha Ellchuk, Shahid Ahmed; Department of Radiation Oncology, Saskatoon Cancer Center, Saskatchewan Cancer Agency, University of Saskatchewan, Saskatoon, SK, Canada; Department of Radiology, University of Saskatchewan, Saskatoon, SK, Canada; Department of Medical Oncology, Saskatoon Cancer Centre, Saskatchewan Cancer Agency, University of Saskatchewan, Saskatoon, SK, Canada*

**Background:** Although CRT is a standard therapy for prevention and treatment of brain metastases (BM) in patients with SCLC, neurocognitive impairment (NI) following therapeutic whole brain radiation treatment (WBRT) or prophylactic cranial irradiation (PCI) is a major problem and can cause impairment in quality of life. A RTOG study is assessing various outcomes by avoiding the hippocampus (AH) during WBRT in different malignancies. The estimated risk of hippocampal avoidance region metastases (HM) in patients with SCLC before & after WBRT/PCI is not known. AH during CRT may delay the onset of NI in such patients. Our study aims to determine risk of HM in patients with SCLC and to assess clinical factors correlate with it. **Methods:** A patients cohort of SCLC diagnosed and treated at the Saskatoon Cancer Center between 2005 and 2012 were followed. All MRI and/or CT scans were independently reviewed by a neuroradiologist. HM was defined as BM within 5 mm of hippocampus. Binary Logistic regression analysis was done to assess correlation between various clinical variables and HM using SPSS. **Results:** 162 patients with SCLC were identified, 60 (37%) have developed BM. The preliminary data of 39/60 patients is presented here. All 39 patients received CRT and 17 patients received upfront chemotherapy. Their median age was 63 yrs (range: 41-82) & M:F was 22:17. 30 (77%) had extensive stage SCLC and 30 (77%) had de novo BM before CRT. A total 198 (range: 1-33) BM were identified among these patients with a mean BM of 6.6 per patient. 4 (13.3%) of 30 patients had HM involvement with mean BM of 1.3 per patient. Median follow up was 13.5 months (range: 1-69). Post-CRT 13 (33%) of 39 patients (4 PCI, 9 WBRT) developed central nervous system (CNS) progression. None of 13 patients with CNS failure following CRT developed HM. Overall 4 (10.2%) of 39 patients developed HM. No clinical factors significantly correlated with HM. **Conclusions:** The preliminary result revealed that overall incidence of HM before and after WBRT/PCI is low. AH in such patients may consider during CRT to avoid NI. The study is ongoing and final analysis will be presented.

**7597 General Poster Session (Board #29G), Sat, 8:00 AM-11:45 AM**

# Oral (O) versus intravenous (IV) etoposide and platinum in the treatment of extensive-stage small cell lung cancer (SCLC).

*Scott Alan Dorroh, Eric R Siegel, Rangaswamy Govindarajan; University of Arkansas for Medical Sciences, Little Rock, AR; Central Arkansas Veterans Healthcare System, Little Rock, AR*

**Background:** Platinum and etoposide chemotherapy is the treatment for patients with SCLC. O etoposide is substituted for IV by many clinicians at twice the dose for bioavailability but the outcome of these subjects has not been studied. To compare the efficacy of O vs. IV etoposide in extensive stage SCLC, a retrospective analysis of subjects treated in the VISN 16 network of 10VA hospitals was undertaken. **Methods:** Subjects with SCLC diagnosed between 10/1/1996 and 9/30/2010 were identified from the VISN-16 tumor registry. Study was limited to extensive disease by excluding those treated with radiation therapy. Chemotherapy details were obtained from the pharmacy data in the VISN 16 database. Overall survival (OS) was computed as the time in months from the first etoposide issue date to the date of death or last contact. Kaplan-Meier methods were used to compute median OS, and etoposide groups were compared via log-rank test. **Results:** 300 subjects were eligible for analysis, with median age 67 yrs (range 45-84). 295 deaths were observed during 2,419 total months of follow-up. The median OS of all subjects was 6.3 months (interquartile range (IQR) 2.0-11 months). In addition to platinum, 153 subjects received only O etoposide, 147 received some form of IV etoposide. The median duration (IQR) of therapy for all subjects was 29 (1-110) days; 23 days for those who received any IV etoposide and 43 days for those who received only oral etoposide. The median OS was 7.6 months for those who received only O etoposide vs. 5.4 months for any IV etoposide ($P<0.0001$). In the latter group, those receiving purely IV etoposide had only 1.5 months' median OS vs. 8.8 months for those receiving both O and IV etoposide ($P<0.0001$). **Conclusions:** Survival of subjects with SCLC treated with O etoposide is comparable to those who received a combination of O and IV therapy. Poor OS for those with only IV therapy may be due to selection bias of poor-performance subjects.

| Etopside (n) | Median OS mos. (range) | P | Etopside (n) | Median no. of days on etoposide | Median OS mos. (range) | P |
|---|---|---|---|---|---|---|
| **Oral 153** | 7.6 (2.7-13) | <0.0001 | Oral only (153) | 43 | 7.6 (2.7-13) | <0.0001 |
| **Any IV 147** | 5.0 (1.5-9.6) | | Oral+ IV (82) | 108 | 8.8 (0.5-11) | |
| | | | IV only (65) | 3 | 1.5(0.5-1.1) | |

**7598 General Poster Session (Board #29H), Sat, 8:00 AM-11:45 AM**

## Advanced pulmonary carcinoid (APC): 20-year experience at Johns Hopkins (JH).

*Patrick M. Forde, Craig M. Hooker, Peter Illei, David S. Ettinger, Charles M. Rudin, Christine L. Hann, Julie R. Brahmer, Ronan Joseph Kelly; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

**Background:** APC is a rare thoracic malignancy with limited prognostic data and a perceived lack of treatment options other than surgical resection. This is the largest series of APC patients (pts) ever reported and contains data on locally advanced and metastatic disease. Here we compare clinical outcomes and treatment responses for typical carcinoid (TC) and atypical carcinoid (AC). **Methods:** This retrospective cohort includes pts referred to JH from 1992 to 2012. Pts were identified using pathology and medical record databases. Information extracted included, pathology, demographics, stage, prior curative resection, time to relapse, chemotherapy/targeted agents and response rate (RR), date of death/last follow-up. Primary outcome was overall survival (OS), defined as time from diagnosis of advanced disease to death from any cause. Secondary endpoint was recurrence-free survival (RFS), defined as time from curative resection to tumor recurrence. OS and RFS were estimated by using the Kaplan-Meier method and log-rank test comparing TC and AC. **Results:** 49 APC pts (30 female/19 male; 32 AC/17 TC) were identified. 25 pts had relapsed after previous curative resection. Median RFS (n=25), was significantly longer for TC vs. AC (119 months (m) vs. 66 m, p=0.008). Median OS was 85m and significantly longer for TC vs. AC (122m vs. 48m, p=0.009). 39 (80%) pts received systemic therapy for APC. RR to first-line chemotherapy was 22% (5/23) with all 5 (3 AC, 2 TC) responses occurring in pts receiving cisplatin/etoposide. First-line somatostatin therapy was given to 11 pts with 1 partial response (PR) (9%) and 10 pts with stable disease (5 AC, 5 TC) for a median 15m. 5 pts received first-line targeted agents including sunitinib and gefitinib however no responses were seen. 50% (2/4 pts) RR occurred to second-line temozolomide/capecitabine An ongoing PR $>$ 6m to everolimus occurred in a heavily pretreated AC pt. **Conclusions:** Both AC and TC may recur many years after resection. This study demonstrates significantly poorer survival for AC in advanced disease. Thoracic oncologists perceive APC as resistant to systemic therapy however here we report that both AC and TC may respond to cisplatin/etoposide, temozolomide/capecitabine and mTOR targeted therapy.

**7599 General Poster Session (Board #30A), Sat, 8:00 AM-11:45 AM**

## Molecular profiling of small cell lung cancers in Japanese patients.

*Kazushige Wakuda, Hirotsugu Kenmotsu, Masakuni Serizawa, Yasuhiro Koh, Mitsuhiro Isaka, Toshiaki Takahashi, Haruyasu Murakami, Tateaki Naito, Tetsuhiko Taira, Takehito Shukuya, Akira Ono, Hiroaki Akamatsu, Hisao Imai, Keita Mori, Masahiro Endo, Takashi Nakajima, Yasuhisa Ohde, Nobuyuki Yamamoto; Division of Thoracic Oncology, Shizuoka Cancer Center, Nagaizumi-cho, Shizuoka, Japan; Division of Drug Discovery and Development, Shizuoka Cancer Center Research Institute, Nagaizumi-chou, Shizuoka, Japan; Division of Thoracic Surgery, Shizuoka Cancer Center, Nagaizumi-cho, Shizuoka, Japan; Clinical Trial Coordination Office, Shizuoka Cancer Center, Nagaizumi-cho, Shizuoka, Japan; Division of Diagnostic Radiology, Shizuoka Cancer Center, Nagaizumi-chou, Shizuoka, Japan; Division of Pathology, Shizuoka Cancer Center, Nagaizumi-chou, Shizuoka, Japan*

**Background:** Molecular abnormalities discovered in the last decade have led to a paradigm shift in the diagnosis and treatment of lung adenocarcinoma. But there have been few reports about molecular profiling of small cell lung cancers (SCLC). We conducted the Shizuoka Lung Cancer Mutation Study to analyze driver mutations in patients with thoracic SCLC malignancies. **Methods:** We collected molecular profiling data of SCLC from the biobanking system in conjunction with the clinic, including the pathology lab, where 23 mutations in 9 genes (*EGFR, KRAS, BRAF, PIK3CA, NRAS, MEK1, AKT1, PTEN* and *HER2), EGFR, MET, PIK3CA, FGFR1* and *FGFR2* amplifications, and *EML4-ALK* translocations were assessed using pyrosequensing plus capillary electrophoresis, qRT-PCR, and RT-PCR, respectively. To evaluate mutation status for SCLC patients, we collected patient characteristics data from medical records. **Results:** Between July 2011 and July 2012, fifty small cell lung cancer patients were assessed in our biobanking system. Patient characteristics were as follows: median age (range) 70 (43 - 82) years; male 82%; smoker 96%; limited disease/extended disease 56/44%; small cell carcinoma/combined small cell carcinoma with adenocarcinoma 94/6%; surgically resected snap-frozen samples 8, formalin-fixed paraffin-embedded samples 40 and pleural effusion 7. We detected driver mutations in 8 cases (16%). Mutations found: *EGFR* 1 (2%), *KRAS* 1 (2%), *PIK3CA* 2 (4%), *AKT1* 1 (2%), *MET* amplification 1 (2%), *PIK3CA* amplification 6 (12%). *EGFR* and *KRAS* mutation were found in combined small cell carcinoma with adenocarcinoma. No significant differences in age, sex, disease extent at diagnosis or smoking status were found between patients with mutations and those without mutations. But serum neuron-specific enolase (NSE) levels were significantly higher in patients without mutations ($p=0.03$). **Conclusions:** In our analysis, driver mutations were found in 16% of SCLC patients and *PIK3CA* amplification seemed to be relatively frequent in SCLC. Our results suggest that PIK3CA might become a target of treatment for SCLC patients.

**7600 General Poster Session (Board #30B), Sat, 8:00 AM-11:45 AM**

# Prospective molecular evaluation of small cell lung cancer (SCLC) utilizing the comprehensive mutation analysis program at Memorial Sloan-Kettering Cancer Center (MSKCC).

*Maria Catherine Pietanza, Anna M. Varghese, Helen H. Won, Lu Wang, Natasha Rekhtman, Lee M. Krug, Paul K. Paik, Gregory J. Riely, Maureen Frances Zakowski, Marc Ladanyi, Michael F. Berger, Mark G. Kris; Memorial Sloan-Kettering Cancer Center, New York, NY*

**Background:** Oncogenic events in adenocarcinoma and squamous cell cancers of the lung are well described. In contrast, the repertoire of possible molecular targets in SCLC is still unclear. Recent studies using next generation sequencing on rare resected SCLC specimens have provided insights into the molecular heterogeneity of this disease. Comprehensive, prospective molecular profiling of patients with SCLC using the small biopsy specimens available in clinical practice has not been performed. **Methods:** Utilizing an IRB-approved protocol to prospectively test SCLC tumors (Small Cell Lung Cancer Mutation Analysis Program, "SC-MAP"), these biopsies are evaluated by: FISH for *FGFR1* and *MET* amplification; immunohistochemistry for MGMT and PTEN loss; point mutation genotyping with Sequenom for *PIK3CA* (and others); and next-generation sequencing with our MSK-IMPACT assay (Integrated Mutation Profiling of Actionable Cancer Targets). MSK-IMPACT uses exon capture followed by massively parallel sequencing to profile all protein-coding exons and select introns of 279 cancer-associated genes, enabling the identification of mutations, indels, and copy number alterations of these genes. We tested the feasibility of this approach in a series of patients with SCLC. We performed next generation sequencing with MSK-IMPACT, with findings confirmed by FISH. **Results:** We identified 11 patients with SCLC with FFPE samples available from both matched normal tissue and small tumor biopsies, including 3 core biopsies and 8 fine needle aspirations. 9/11 patients had adequate tissue for MSK-IMPACT, which revealed recurrent mutations in *Rb1* (N=7) and *p53* (N=7), *FGFR1* amplification (N=2), and *MET* amplification (N=1), using as little as 15 nanograms of DNA. *FGFR1* and *MET* amplification were confirmed by FISH testing. We have initiated this prospective SC-MAP program for our patients with SCLC. **Conclusions:** Comprehensive molecular evaluation of SCLC is feasible on clinically available, small samples. Such analyses will allow us to characterize the molecular diversity of this disease and identify patients who will be candidates for targeted therapies.

## 7601 General Poster Session (Board #30C), Sat, 8:00 AM-11:45 AM

# Development of a SOMAmer (slow off-rate modified aptamer)-based assay to detect NSCLC.

*Noh Jin Park, Dana Root, Xiuqiang Wang, Angelica Diaz, Taraneh Esmailpour, Charlies e Birse, Robert Lagier, Weimin Sun, Robert J. Morrone, Frederic Waldman, Charles m Strom; Quest Diagnostics, San Juan Capistrano, CA; Quest Diagnostics Nichols Institute, San Juan Capistrano, CA; Quest Diagnostics, Celera Corporation, Alameda, CA*

**Background:** Support for low-dose helical computed tomography (CT) screening for lung cancer in a high risk population has emerged from the National Lung Screening Trial (NLST). However, the low specificity of CT raises concerns regarding the cost and potential morbidity associated with resection of benign nodules. Non-invasive lung cancer biomarkers may serve as a useful complement to imaging, providing a simple means to further clarify the diagnosis of suspicious pulmonary nodules. SOMAmer-based chip technology was previously used to identify a panel of serological biomarkers capable of accurately classifying NSCLC. Here we assess the analytical and clinical performance of an automated assay that uses SOMAmer reagents and qPCR to simultaneously quantify a subset of these markers (n=12). **Methods:** Biomarker levels were measured in sera from 43 subjects with stage I-III NSCLC and 63 long-term smoker controls. qPCR results were analyzed by relative ($\Delta\Delta C_T$) quantitation, which uses calibrator serum and a set of normalizers. Linear mixed-effects models were fit to identify key sources of analytical variability (variance components), including plate-to-plate, within-sample, and between sample effects. Clinical performance for distinguishing NSCLC from control sera was established by a random forest predictive model. **Results:** Median within-sample %CV for the 12 markers was 6.7%. Variance components analyses suggest that, on average, 5.7% of the variance for a given biomarker was due to within-sample effects, 5.2% to plate-to-plate effects, and 86.2% to between-sample effects. A 10-marker random forest model exhibited an AUC [95% CI] of 0.915 [0.905, 0.924], classifying NSCLC from control sera with 79% sensitivity and 90% specificity. **Conclusions:** We have developed a highly reproducible automated assay designed for the clinical laboratory. Combining SOMAmer-based protein capture and qPCR-based quantification, the assay monitors the levels of 12 potential lung cancer markers. An algorithm-based model incorporating 10 of these markers showed good accuracy for distinguishing NSCLC from control sera. Further studies are warranted to evaluate the performance of the test in classifying pulmonary nodules.

**7602 General Poster Session (Board #30D), Sat, 8:00 AM-11:45 AM**

# Thymic carcinoma: A cohort study of prognostic factors after surgical resection from the European Society of Thoracic Surgeons database.

*Enrico Ruffini, Frank C. Detterbeck, Dirk Van Raemdonck, Gaetano Rocco, Pascal Alexandre Thomas, Walter Weder, Alessandro Brunelli, Francesco Guerrera, Shaf Keshavjee, Nasser K. Altorki, Jan Schutzner, Alper Toker, Lorenzo Spaggiari, Alex Arame, Eric Kian Saik Lim, Federico Venuta, European Society of Thoracic Surgeons Thymic Group; Thoracic Surgery, University of Torino, Torino, Italy; Yale School of Medicine, New Haven, CT; Thoracic Surgery, University Hospitals Leuven, Leuven, Belgium; National Cancer Institute, Napoli, Italy; Service de Chirurgie Thoracique, Marseille, France; Department of Thoracic Surgery, University Hospital, Zürich, Switzerland; Division of Thoracic Surgery, Ospedali Riuniti Ancona, Ancona, Italy; Department of Thoracic Surgery, Toronto General Hospital, University Health Network, Toronto, ON, Canada; Weill Cornell Medical College, New York, NY; Thoracic Surgery, Teaching Hospital Motol, Prague, Prague, Czech Republic; Thoracic Surgery, Istanbul Medical Centre, Istanbul, Turkey; European Institute of Oncology, Milan, Italy; Hopital Europeen Georges-Pompidou and hopital Laennec, Paris, France; Royal Brompton Hospital, London, United Kingdom; Thoracic Surgery, University of Rome SAPIENZA; Policlinico Umberto I; Fondazione Eleonora Lorilard Spencer Cenci, Rome, Italy*

**Background**: Thymic carcinomas are rare tumors which have recently been separated from thymomas due to their different histologic/clinical characteristics. Most of the current literature is composed of small series spanned over extended time periods **Methods:** The European Society of Thoracic Surgeons (ESTS) developed a retrospective database collecting data on patients with thymic tumors submitted to surgery (1990-2011). Out of 2,265 incident cases, there were 229 thymic carcinomas. Clinical-pathologic characteristics were analyzed including age, gender, stage (Masaoka), histologic subtypes (squamous cell/others), type of resection (complete/incomplete), tumor size, induction and adjuvant therapy (chemotherapy-ChT/radiotherapy-RT), recurrence. Primary outcome was overall survival (OS); secondary outcomes were disease-free survival (DFS) and the cumulative incidence of recurrence. Survival analysis was performed using univariate and multivariate (Cox-shared frailty) competing-risk models. Missing data were analysed using multiple-imputation techniques **Results:** A multidisciplinary approach (surgery, ChT and RT) was used in most patients. Induction therapy was employed in 78 patients (ChT, 53; ChT/RT 23; RT, 2). Adjuvant therapy was employed in 150 patients (ChT, 19; ChT/RT, 72; RT, 59). Complete resection (R0) was achieved in 71% of the patients. Five and 10-year OS were 60% and 35%. Five and 10-year DFS were 62% and 43%. Cumulative incidence of recurrence was 0.25, 0.32 and 0.40 at 3, 5, and 10 years. Independent OS predictors (multivariate analysis) were young age ($p=0.006$), stage I/II (vs. III/IV, $p=0.02$), R0 resection ($p<0.001$), adjuvant therapy (ChT, RT or both) ($p=0.02$). Independent predictor of recurrence (univariate analysis) was tumor size ($p=0.05$). **Conclusions:** In thymic carcinomas submitted to surgical resection, increased age,Masaoka stages III-IV and incomplete resection had a significant impact in worsening survival. Larger tumors had an increased risk of recurrence. The administration of adjuvant ChT or RT was associated with improved overall survival. A multidisciplinary approach to these rare tumors remains essential.

**7603 General Poster Session (Board #30E), Sat, 8:00 AM-11:45 AM**

## Thymic epithelial tumors at University Federico II of Naples: A 30-year experience.

*Carlo Buonerba, Piera Federico, Filomena Calabrese, Margaret Ottaviano, Lucia Nappi, Pasquale Rescigno, Elide Matano, Giuseppe Di Lorenzo, Vincenzo Damiano, Giovannella Palmieri; Department of Clinical Oncology and Endocrinology and Rare Tumors Reference Center Campania Region, University Federico II, Naples, Italy; Department of Clinical Oncology and Endocrinology and Rare Tumors Reference Center Campania Region, University Federico II, Napoli, Italy*

**Background:** According to the 2004 WHO classification, thymic epithelial tumors (TETs) comprise different histologies, including thymomas, thymic carcinoma, typical and atypical carcinoids. Histology classification of TETs has a dramatic impact on the prognosis and therapeutic strategy. We here review all TETs treated at our Institution over the past 30 years. **Methods:** Eligible patients had a pathologically confirmed TET and had at least one access at our Institution. Relevant demographic and clinical data were retrieved. An exploratory analysis was conducted using a step-wise model in patients with completely resected tumors to seek for factors predictive of recurrence after radical surgery. **Results:** One hundred and three patients with TETs were included in this retrospective analysis. Forty-three were female, sixty were male. Median age was 43 years (range 32-58). Forty-three patients had myasthenia gravis. Four had a thymic neuroendrocrine tumor, 19 had a thymic carcinoma, while the remaining had a thymoma. Forty-seven patients were alive at the time of analysis. Median overall survival was 5.85 years (range, 2.58-9.9). In the whole sample population, seventy-six patients had a completely resected tumor with clear pathological margins. In this sub-group of 76 patients (median age: 46, 35-55; 30 females, 46 males), 12 had a thymic carcinoma and 30 patients recurred after radical surgery. At multivariate analysis, which included age, sex, adjuvant chemotherapy, adjuvant radiotherapy, maximum tumor diameter, presence of myasthenia gravis and stage, the only factor significantly predictive of recurrence was tumor histology (odds ratio: 3,8182, 95% CI: 1,03 to 14,1; p = 0.04). **Conclusions:** We showed that patients with thymic carcinomas are at increased risk of recurrence after radical surgery independently on adjuvant chemotherapy/radiotherapy treatment. Additional therapeutic options are required in the adjuvant setting of completely resected thymic carcinomas.

**7604 General Poster Session (Board #30F), Sat, 8:00 AM-11:45 AM**

# Antitumor activity in advanced cancer patients with thymic malignancies enrolled in early clinical drug development program (phase I trials) at Institut Gustave Roussy.

*Myriam Kossai, Boris Duchemann, Caroline Caramella, Celine Boutros, Christophe Massard, Philippe Vielh, Anas Gazzah, Rastislav Bahleda, Eric Angevin, Antoine Hollebecque, Jean-Charles Soria, Benjamin Besse; Institut Gustave Roussy, Villejuif, France*

**Background:** Thymic epithelial neoplasms (TENs) represent a rare entity with poor prognosis and limited systemic treatment options, particularly in advanced stages and/or in thymic carcinomas (TC). The aim of this study was to assess the clinical benefit, the efficacy and toxicities of agents for patients (pts) with a refractory TEN enrolled in Phase I trials. **Methods:** We reviewed retrospectively pts with advanced pretreated TEN enrolled in Phase I trials at the Institut Gustave Roussy (SITEP) between 1994 and 2012. Toxicities were reported and scored according to NCI CTCAE version 3.0. Efficacy was assessed using RECIST version 1.1. **Results:** Twenty-two treated pts were enrolled (14 with TC, 8 with thymomas). The median number of prior systemic therapies was 2 (1-8). The median age was 50 years (range 23-72), and 4 females were treated. Treatment received were mTOR inhibitor (mTORi) in 4 of pts, antiangiogenic agents (AA) in 11 pts, and other targeted therapies in 7 pts. The median follow-up time was 22.1 months (range, 1.25-77.79 months). Autoimmune associated disease (AID) was reported in 6 pts. 18% had grade III/IV toxicity, 54% grade I/II toxicity and no toxic death was reported. AID exacerbated in one patient. One patient experienced a complete response (CR) and 3 a partial response (PR); 16 pts had stable disease (median 6.6 months) and 2 had a progressive disease. Objective response rate (ORR) was 42%, 25.0% for thymoma and 21.4% for TC. The median overall survival was 54.5 months (95% CI 25-75.50 months), 54.5 for thymoma and 62 for TC. The median progression free survival (PFS) was 6.6 months (95% CI 1.35-11.59 months), 5.2 for thymoma and 6.9 for TC. Median PFS was 11.6 months for mTORi, 6.9 for AA, and 6.6 for other targeted therapies. **Conclusions:** Phase I trials appear as a sound therapeutic option in TENs pts progressing after standard treatments. Use of AA and mTORi seem to yield a good clinical response. Novel targeted therapies might be tested setting in a biology-oriented approach rather than a stochastical one. We are currently offering a molecular profiling in our patients (MOSCATO trial NCT01566019) for a better selection of appropriate Phase I trial.

**7605 General Poster Session (Board #30G), Sat, 8:00 AM-11:45 AM**

## A gene signature to determine metastatic behavior in thymic carcinoma.

*Yesim Gokmen-Polar, Robert W. Cook, Jeffrey Wilkinson, Derek Maetzold, John F Stone, Kristen M. Oelschlager, Wei Lu, Ioan Tudor Vladislav, Kenneth Kesler, Patrick J. Loehrer, Sunil S. Badve; Indiana University School of Medicine, Indianapolis, IN; Castle Biosciences Incorporated, Friendswood, TX; St. Joseph's Hospital and Medical Center, Phoenix, AZ; St. Joseph's Hospital and Medical Center, Phoenix, AZ; Castle Biosciences Incorporated, Phoenix, AZ; Indiana University, Indianapolis, IN; Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN*

**Background:** Thymomas and thymic carcinomas (TC) are rare epithelial tumors derived from the thymic gland in the anterior mediastinum. Although all histological types of thymomas, albeit with different frequencies, can give rise to metastases, TC have a more aggressive behavior and metastasize earlier and more frequently than thymomas. We previously developed a prognostic gene signature able to accurately determine metastatic behavior of thymomas (Gökmen-Polar et al. ASCO 2012). The signature is currently used in clinical practice to identify patients at high or low risk for metastatic disease. In the current study, we sought to evaluate the utility of this signature for determining risk from TC tumors. **Methods:** FFPE tissue sections were macrodissected from 35 primary TC. RNA was isolated and RT-PCR was performed to assess the expression of 23 genes (19 test and four reference genes). Predictive modeling was performed using Radial Basis Machine (RBM) software from JMP Genomics (SAS), and survival analysis was done using the Kaplan-Meier method. **Results:** Samples from the TC cohort ranged from stage II through IVB, with a median age of 54 years. 26 samples had evidence of metastatic progression, while nine samples did not. Prediction of metastasis, based upon comparison to the previously developed thymoma training set and using a 19-gene signature, yielded an ROC = 0.66. Independent analysis of the TC cohort with the thymoma 19-gene signature resulted in a predictive model with an ROC = 0.97 (overall accuracy = 87%, sensitivity = 73% and specificity=100%). Further modeling and gene set reduction revealed a separate ten-gene signature able to segregate metastatic from non-metastatic cases with 100% accuracy. All the cases classified as high risk (n= 26) developed metastasis within 5 years while none of the cases categorized as low-risk (n= 9) had any events at 5 years of follow-up. **Conclusions:** A ten-gene signature was established that appears to predict metastatic behavior of TC with a high degree of accuracy; however, validation in an independent cohort is necessary. Our data suggests that the biologic determinants of the clinical course of TC maybe distinct from thymoma and could be used to improve patient management.

**TPS7606 General Poster Session (Board #30H), Sat, 8:00 AM-11:45 AM**

## A multicenter phase II randomized study of customized neoadjuvant therapy versus standard chemotherapy (CT) in non-small cell lung cancer (NSCLC) patients with resectable stage IIIA(N2) disease (CONTEST trial).

*Francesco Grossi, Erika Rijavec, Giulia Barletta, Claudio Sini, Carlo Genova, Maria Giovanna Dal Bello, Giovanni Battista Ratto, Mauro Truini, Domenico Franco Merlo; Lung Cancer Unit, National Institute for Cancer Research, Genova, Italy; Department of Thoracic Surgery, National Institute for Cancer Research, Genova, Italy; Department of Pathology, National Institute for Cancer Research, Genova, Italy; National Institute for Cancer Research, Genoa, Italy*

**Background:** Stage IIIA NSCLC constitutes 30% of all NSCLC patients (pts). The most powerful prognostic factor that has been identified in this stage is clearance of mediastinal lymph nodes and pathologic complete response (pCR). A pCR is obtained in 5-15% of pts with a significant survival prolongation. The identification of molecular biomarkers, such as excision repair cross-complementation 1 (ERCC1), ribonucleotide reductase subunit M1 (RRM1), and thymidylate synthase (TS), may predict response to CT. Similarly, EGFR mutations may predict response to EGFR inhibitors. **Methods:** CONTEST, a multicenter (19 Italian centers), randomized (2:1) 2-arm phase II study, recruits pts with resectable stage IIIA (N2) NSCLC. Pts will be randomized to receive before resection either standard CT with Cisplatin (CDDP) 75 mg/m$^2$ + Docetaxel (Doc) 75 mg/m$^2$ on day (d) 1 q 21 d for 3 cycles (cys) or customized therapy using predetermined values for ERCC1, RRM1, TS, and EGFR mutations. The choices of customized arms are as follows: -EGFR+: Gefitinib 250 mg/d for 8 weeks. -EGFR-/non-squamous (NS)/TS-/ERCC1-: CDDP 75 mg/m$^2$ + Pemetrexed 500 mg/m$^2$ d 1 q 21 d for 3 cys. -EGFR-/squamous (S) or NS TS+/ERCC1-/RRM1+: CDDP 75 mg/m$^2$ + Doc 75 mg/m$^2$ d 1 q 21 d for 3 cys. -EGFR-/S or NS TS+/ERCC1-/RRM1-: CDDP 75 mg/m$^2$ d 1+ Gemcitabine (Gem) 1250 mg/m$^2$ d 1,8 q 21 d for 3 cys. -EGFR-/S or NS TS+/ERCC1+/RRM1+: Doc 75 mg/m$^2$ d 1 + Vinorelbine 20 mg/m$^2$ d 1,8 q 21 d for 3 cys. -EGFR-/S or NS TS+/ERCC1+/RRM1-: Doc 40 mg/m$^2$ y 1, 8 + Gem 1200 mg/m$^2$ d 1,8 q 21 d for 3 cys. The primary end point will be obtained by comparing the pCR in all randomized pts based on treatment arm. Because pCR is a surrogate endpoint and given the expected proportion of pCR's in the control group pc= 5%, the minimal clinically worthwhile effect of this customized treatment is an increase in this proportion to 20%. To detect such an effect at the 0.05 (1-sided) significance level with 80% power, a total of 168 pts will be enrolled. This study is open for accrual; further details can be found on ClinicalTrials.gov (NCT01784549). Funded by Italian Ministry of Health – RF 2009-1530324. Clinical trial information: NCT01784549.

**TPS7607** **General Poster Session (Board #31A), Sat, 8:00 AM-11:45 AM**

## CRS-207 vaccine plus chemotherapy as front-line treatment for subjects with malignant pleural mesothelioma (MPM).

*Raffit Hassan, Scott J. Antonia, John J. Grous, Aimee Murphy, Anish Thomas, Andrew Miller, Thomas Dubensky, Dirk G. Brockstedt; National Cancer Institute, Bethesda, MD; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; Clinical Cancer Rsrch Inc, Phoenix, AZ; Aduro BioTech, Inc., Berkeley, CA; National Institutes of Health, Bethesda, MD*

**Background:** CRS-207 is a live-attenuated *Listeria monocytogenes* (*Lm*) vaccine expressing the tumor-associated antigen mesothelin which is overexpressed in MPM. CRS-207 was well tolerated and induced *Lm*- and mesothelin-specific T cell immunity in a phase 1 study in adults with mesothelin-expressing cancers (Le et al., Clin. Cancer Res. 2012). Preclinical and clinical studies suggest that vaccines and chemotherapies work synergistically and augment anti-tumor effectiveness of subsequent chemotherapies. **Methods:** This phase 1B study is evaluating the safety and induction of mesothelin-specific immune responses by CRS-207 plus chemotherapy with pemetrexed (P) and cisplatin (C) in adults with newly diagnosed, unresectable MPM. Two doses of $1\times10^9$colony forming units (CFU) CRSE207 are administered intravenously two weeks apart followed two weeks later by up to six cycles of P (500 mg/m2) and C (75 mg/m2) given every 3 weeks. Two booster vaccinations of CRS-207 are administered three weeks apart 4 weeks after completing PC. Secondary and exploratory endpoints will assess objective tumor response, time to progression, overall survival and immune correlates. This is one of the first trials to assess the synergy between vaccines and chemotherapy in newly diagnosed patients with MPM. Sponsor: Aduro BioTech, Inc. ClinicalTrials.gov ID: NCT01675765. Clinical trial information: NCT01675765.

**TPS7608 General Poster Session (Board #31B), Sat, 8:00 AM-11:45 AM**

# CA184-156: Randomized, multicenter, double-blind, phase III trial comparing the efficacy of ipilimumab (Ipi) plus etoposide/platinum (EP) versus placebo plus EP in patients (Pts) with newly diagnosed extensive-stage disease small cell lung cancer (ED-SCLC).

*Joachim Von Pawel, Sang-We Kim, David R. Spigel, Christoph Zielinski, Maria Catherine Pietanza, Veerle de Pril, Marc S. Ballas, Martin Reck; Asklepios Hospital Munich-Gauting, Munich, Germany; Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Sarah Cannon Research Institute; Tennessee Oncology, Nashville, TN; Clinical Division of Oncology and Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; Memorial Sloan-Kettering Cancer Center, New York, NY; Bristol-Myers Squibb, Braine-l'Alleud, Belgium; Bristol-Myers Squibb, Wallingford, CT; Department of Thoracic Oncology, Lung Clinic Grosshansdorf, Grosshansdorf, Germany*

**Background:** Phase III studies have not reported improvement for ED-SCLC beyond EP. Moreover, chemotherapeutic response in SCLC is short-lived, with a median survival of 8–12 months and 5-year survival rates ranging from 1%–2%. Ipi, a fully human monoclonal antibody which binds CTLA-4, augments antitumor immune responses and may potentially improve the clinical benefit of EP. A randomized phase II study of Ipi + paclitaxel/carboplatin (PC) in pts with ED-SCLC showed significant improvement in progression-free survival (PFS) [measured by immune-related response criteria (irRC)] over PC in pts receiving phased Ipi + PC; irRC were derived from WHO criteria to better capture response patterns observed with Ipi. Addition of Ipi trended toward prolonged overall survival (OS) and did not exacerbate PC toxicity; immune-related adverse events were managed using protocol-specific guidelines. This global (~227 sites among 34 countries), multicenter phase III study in pts with ED-SCLC (ClinicalTrials.gov identifier NCT01450761) will determine if adding Ipi to EP increases OS vs EP alone. **Methods:** Pts with first-line ED-SCLC and ECOG 0-1 will be eligible; pts with a history of autoimmune disease will be ineligible. Pts will be randomized (1:1 to either Arm A or Arm B) to 2 cycles of EP (etoposide [100 mg/m$^2$, IV on Days 1-3 Q3W] and cisplatin [75 mg/m$^2$, IV] or carboplatin [AUC=5, IV] once Q3W), followed by 4 cycles of blinded study drug (Ipi 10 mg/kg, IV in Arm A or placebo in Arm B, Q3W) with 2 concurrent cycles (during cycles 3-4) of EP and Ipi (6 cycles of total therapy). Eligible pts will receive Ipi maintenance therapy Q12W until disease progression or unacceptable toxicity; pts with a complete response will also be eligible for prophylactic cranial irradiation at investigator's discretion. The primary endpoint is OS; secondary endpoints include OS among pts who receive blinded therapy, immune-related and mWHO PFS, best overall response rate, and duration of response. The trial will also characterize safety, and is estimated to enroll 1100 pts. Clinical trial information: NCT01450761.

**TPS7609 General Poster Session (Board #31C), Sat, 8:00 AM-11:45 AM**

# Cabazitaxel (Cbz) versus topotecan in patients (pts) with small cell lung cancer (SCLC) that has progressed during or after first-line treatment with platinum-based chemotherapy: A randomized phase II study.

*Tracey L. Evans, Joo-Hang Kim, Frances A. Shepherd, Konstantinos N. Syrigos, Katalin Udud, Viacheslav Chubenko, Dariusz Kowalski, James R. Rigas, Gregory Lo, Jaafar Bennouna, Mustapha Chadjaa, Martin Wolf; Perelman Center for Advanced Medicine, Philadelphia, PA; Department of Internal Medicine (Medical Oncology), Yonsei Cancer Research Institute, Yonsei Cancer Center, Seoul, South Korea; Ontario Cancer Institute, Toronto, ON, Canada; Oncology Unit, 3rd Department of Medicine, Athens University School of Medicine, Sotiria General Hospital, Athens, Greece; Korányi National Institute of Pulmonology, Budapest, Hungary; NN Petrov Research Institute of Oncology, St. Petersburg, Russia; Department of Lung Cancer and Chest Tumours, The Maria Sklodowska-Curie Institute of Oncology, Warsaw, Poland; Dartmouth Hitchcock Medical Center, Lebanon, NH; R. S. McLaughlin Durham Regional Cancer Centre, Lakeridge Health, Oshawa, ON, Canada; ICO René Gauducheau, Saint Herblain, France; Sanofi, Vitry-sur-Seine, France; Department of Internal Medicine, Division of Haematology and Oncology, Klinikum Kassel, Kassel, Germany*

**Background:** Approximately 12–15% of pts with lung cancer have SCLC. Although first-line platinum-based chemotherapy regimens may be effective, pts often experience rapid relapse and develop systemic metastases. Median survival after SCLC relapse varies from 13 to 35 weeks. As such, there is a substantial unmet need for more effective second-line treatments. Clinical studies suggest that taxanes are effective in relapsed SCLC, and Cbz, a next-generation taxane, has shown efficacy in the second-line treatment of taxane-resistant tumors (de Bono JS, *et al.* Lancet 2010;376: 1147–54; Pivot X, *et al.* Ann Oncol 2008;19:1547–52). Assessment of Cbz treatment for SCLC is therefore warranted. **Methods:** This is a multinational, open-label Phase II study (NCT01500720) in pts with confirmed, measurable, locally advanced or metastatic SCLC whose disease has progressed during/after first-line platinum-based chemotherapy. Pts aged $\geq$ 18 years with ECOG performance status $\leq$ 1 are eligible, but those with $>$ 1 prior chemotherapy regimen or prior topotecan or taxane use are excluded. Pts are randomized 1:1 to receive IV Cbz 25 mg/m$^2$ (Day 1 Q3W) or IV topotecan 1.5 mg/m$^2$ (Days 1–5 Q3W). Pts are divided into chemo-sensitive and chemo-refractory subgroups, while stratification is based on the presence of brain metastases (yes vs no) and by lactate dehydrogenase plasma concentration ($\leq$ or $>$ upper limit). Pts will be treated until disease progression, unacceptable toxicity or withdrawal of consent. The primary objective is assessment of progression-free survival (PFS). Secondary objectives include assessment of other efficacy endpoints (proportion of pts free of disease progression at 12 weeks, tumor response and overall survival), safety and health-related quality of life. A centralized imaging review process is being used to independently review tumor measurements. Planned enrollment is 172 pts (to provide 80% power for PFS analysis). The first pt was enrolled in March 2012. By December 2012, 91 pts had been randomized in 38 sites. Clinical trial information: NCT01500720.

**TPS7610 General Poster Session (Board #31D), Sat, 8:00 AM-11:45 AM**

# Randomized phase II study of IV topotecan versus CRLX101 in the second-line treatment of recurrent extensive-stage small cell lung cancer (ES-SCLC).

*Thomas A. Hensing, Theodore Karrison, Edward Graeme Garmey, Meliessa G. Hennessy, Ravi Salgia; NorthShore University HealthSystem, Evanston, IL; The University of Chicago Medical Center, Chicago, IL; Cerulean Pharma, Inc., Cambridge, MA; The University of Chicago, Chicago, IL*

**Background:** SCLC remains an area of high unmet medical need with an aggressive clinical course and < 10% 5-year overall survival. In the U.S., topotecan (Hycamtin, GlaxoSmithKline) is the reference standard for treatment of chemotherapy (C)-sensitive (S) relapsed disease but its use remains compromised by toxicity. There currently exists no standard therapy for patients (pts) with C-resistant (R) disease (relapse occurring < 60 days from last C). CRLX101 is a novel cyclodextrin-containing polymer conjugate of camptothecin (CPT) that self-assembles into nanoparticles and delivers sustained levels of active CPT into cancer cells while substantially reducing systemic exposure. In vitro and in vivo data suggest superior activity of CRLX101 compared to approved agents in multiple animal tumor models including SCLC. A monotherapy recommended phase 2 dose of 15 mg/m2 IV every 2 weeks has now been administered to over 150 cancer pts across five ongoing phase 2 clinical trials. **Methods:** This ongoing, randomized phase 2 clinical trial compares the effect on progression free survival (PFS) of 2nd-line treatment with IV CRLX101 (15 mg/m2 on days 1 and 15 every 28 days) to IV topotecan (1.5 mg/m2 on days 1-5 every 21 days) in pts with CS relapsed ES-SCLC. In parallel, the effect of 2nd-line CRLX101 on 3-mo. PFS rate of pts with CR relapsed ES-SCLC will be evaluated. Secondary objectives in both cohorts include evaluation of objective response rates (by RECIST v1.1), overall survival, and safety. In the randomized cohort, 112 pts (56/arm) will be enrolled in order to achieve 90% power to detect an improvement in median PFS from 3 to 5 mos. (HR=0.60). An interim analysis will be performed after 1/2 of expected PFS events have occurred. Pts with CR disease will all receive CRLX101 and the trial will employ a 2-stage design: 14 pts will be enrolled in stage 1 and the study will be terminated if ≤ 3 pts remain progression free at 3 mos. Otherwise, an additional 30 pts will be enrolled and if ³ 15/44 (34%) pts remain progression free at 3 mos., the drug will be considered worthy of further investigation. The first patient on this clinical trial was enrolled on January 30, 2013. Clinical trial information: NCT# is pending.