8000 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Biomarkers (BM) France: Results of routine EGFR, HER2, KRAS, BRAF, PI3KCA mutations detection and EML4-ALK gene fusion assessment on the first 10,000 non-small cell lung cancer (NSCLC) patients (pts).

Fabrice Barlesi, Helene Blons, Michele Beau-Faller, Isabelle Rouquette, L'houcine Ouafik, Jean Mosser, Jean-Philippe Merlio, Pierre Paul Bringuier, Philippe Jonveaux, Cedric Le Marechal, Marc G. Denis, Frederique Madeleine Penault-Llorca, Didier Debieuvre, Jean-Charles Soria, Jacques Cadranel, Julien Mazieres, Pascale Missy, Franck Morin, Frederique Nowak, Gerard Zalcman, Intergroupe Francophone de Cancérologie Thoracique (IFCT); Aix Marseille University, Assistance Publique Hôpitaux de Marseille, Hôpital Nord, Marseille, France; Hôpital Européen Georges Pompidou (HEGP), Assistance Publique Hôpitaux de Paris (APHP), Paris, France; Centre Hospitalier Universitaire Strasbourg, Strasbourg, France; Centre Hospitalier Universitaire Toulouse, Toulouse, France; Laboratoire de Transfert, CHU Nord, Marseille, France; Centre Hospitalier Universitaire, Rennes, France; Service de Biologie des Tumeurs - CHU, Bordeaux, France; Hopital Edouard Herriot, Lyon, France; Centre Hospitalier Universitaire, Nancy, France; Laboratoire de Génétique Moléculaire - CHU Morvan, Brest, France; Nantes University Hospital, Nantes, France; Centre Jean Perrin, Clermont-Ferrand, France; Emile Muller Hospital, Mulhouse, France; Institut Gustave Roussy, Villejuif, France; Service de Pneumologie and GRC-04 Theranoscan, Pierre et Marie Curie Université, Hôpital Tenon, Paris, France; Hôpital Larrey CHU Toulouse, Toulouse, France; Intergroupe Francophone de Cancérologie Thoracique, Paris, France; French National Cancer Institute, Boulogne, France; Caen University Hospital, Caen, France

Background: Personalized medicine is now a reality for advanced NSCLC pts on the basis of routine screening for EGFR mutation and ALK gene fusion assessment. The French NCI (INCa) also decided to additionally fund the routine assessment of 4 additional BM (HER2, KRAS, BRAF, PI3KCA). **Methods:** Starting on April 2012, these BM analyses were prospectively collected into a database head by the IFCT (www.ifct.fr) with 15-20,000 analyses awaited after one year. The physicians prescribing each of these BM analyses were then connected to this database and were asked to regularly complete epidemiological, clinical and therapeutic data for each corresponding patient. **Results:** 10,000 BM analyses were collected and entered into the BM France database at the time of this first analysis (January 2013). On the basis of available data, the patients were mainly male (63.8%), (ex)smokers (83.3%) and stage IV pts (64%). The tumors were mainly adenocarcinomas (76.1%). The samples for BM analysis were collected under bronchoscopy, surgery or transthoracic biopsy in 27.4, 28.1 and 24.2%, respectively. The 10,000 molecular profiles were characterized by 9.4% EGFR (including 0.8% EGFR resistant), 0.9% HER2, 26.9% KRAS, 1.6% BRAF, and 2.6% PI3KCA mutated and 4.0% EML4-ALK fusion genes. Double mutations were seen in 0.9% of the tumors. On January 2013, data on treatment were available for 18.6% of patients among whom 56.9% of patients received a treatment according to their molecular profile (labeled drugs or bio-guided trials). Updated data will be presented during the meeting. **Conclusions:** Biomarkers France is the largest ever conducted biomolecular study on advanced NSCLC patients and provides solid data on the value of a nationwide BM screening policy for NSCLC patients.

8001 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Molecular analysis-directed, international, phase III trial in patients with advanced non-small-cell lung cancer.

Gerold Bepler, Charles C. Williams, Michael J. Schell, Wei Chen, Zhong Zheng, George R. Simon, Shirish M. Gadgeel, Xiuhua Zhao, Fred James Schreiber, Julie R. Brahmer, Alberto Chiappori, Tawee Tanvetyanon, Mary Colleen Pinder, Jhanelle Elaine Gray, Eric B. Haura, Scott J. Antonia, Jurgen R. Fischer; Karmanos Cancer Institute, Wayne State University, Detroit, MI; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; The University of Texas MD Anderson Cancer Center, Houston, TX; Moffitt Cancer Center and Research Institute, Tampa, FL; Watson Clinic, Lakeland, FL; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Klinik Loewenstein, Loewenstein, Germany

Background: ERCC1 (E1) and RRM1 (R1) are predictive markers for platinum agents and gemcitabine (G) respectively. In a phase II trial that utilized E1 and R1 mRNA expression levels for therapeutic decision-making, a response rate of 44%, PFS of 6.6 m, and OS of 13.3 m was achieved. **Methods:** Pts with advanced, chemo-naive NSCLC, PS 0-1, measurable disease, and a FFPE histological or cell block tumor specimen were eligible. E1 and R1 were analyzed by AQUA and categorized as high or low. Pts were randomized 2:1 to arm A, which received G and carboplatin (Cb) for R1/E1 low, docetaxel (D) and Cb for R1 high and E1 low, G and D for R1 low and E1 high, and D and vinorelbine (V) for R1/E1 high, or arm B, which received GC. Pts received up to 6 cycles. Efficacy was assessed every 6-8 weeks until 1 year from treatment initiation. The primary goal was to improve the 6-m PFS from 38% in arm B (median PFS 4.3 m) to 50% in arm A (median PFS 6.0 m). Secondary goals were improvements in OS (8.0 to 12.0 m) and RR (25% to 50%). **Results:** Of 275 eligible pts, 183 randomized to arm A. 56 were assigned to GCb, 26 to DCb, 37 to GD, and 64 to DV, which was not significantly different ($p=.2$) from the expected assignment (30%, 20%, 20%, 30%). In arm B, all 92 pts received GCb. Protein analysis was successful in 91% of pts. The median time from consent to completed gene analysis was 11 days. A tumor rebiopsy for the specific purpose of gene analysis was required in 17% of pts. The 6-m PFS rate and median PFS were 52.0% and 6.1 m in arm A and 56.5% and 6.9 m in arm B ($p = 0.18$). PFS was not significantly different among the treatment groups in arm A ($p = 0.1$). A significant survival advantage was found for pts with low E1 and low R1 in arm B compared to the same group in arm A ($p = 0.02$) although both received GCb therapy. OS and RR were not significantly different between both groups. A comparison between protein and mRNA levels for both genes revealed no significant correlation. **Conclusions:** This demonstrates that gene expression analysis for therapeutic decision making is feasible in newly diagnosed advanced-stage NSCLC pts. A tumor rebiopsy is safe, required in 17%, and acceptable to 89% pts. The survival results are false negative based on the internal control included in the trial. Clinical trial information: NCT00499109.

LBA8002 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Interim analysis of The Spanish Lung Cancer Group (SLCG) BRCA1-RAP80 Expression Customization (BREC) randomized phase III trial of customized therapy in advanced non-small-cell lung cancer (NSCLC) patients (p) (NCT00617656/GECP-BREC)

Teresa Moran, Manuel Cobo, Manuel Domine, Maria Sanchez-Ronco, Isabel Bover, Mariano Provencio, Bartomeu Massuti, Alain Vergnenegre, Guillermo Lopez-Vivanco, Gilles Robinet, Amelia Insa, Margarita Majem, Ramon De Las Penas, María Ángeles Sala, Dolores Isla, Nathalie Baize, Javier Garde, Imane Chaib, Carlos Camps, Rafael Rosell, Spanish Lung Cancer Group; Institut Catala d´Oncologia, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; Hospital Regional Universitario Carlos Haya, Málaga, Spain; Oncology Department and Translational Oncology Division. Hospital Universitario Fundacion Jimenez Diaz, Madrid, Spain; Alcala de Henares University, Madrid, Spain; Son Llatzer University Hospital, Mallorca, Spain; Hospital Puerta de Hierro Majadahonda, Madrid, Spain; Hospital General de Alicante, Alicante, Spain; Cluzeau Hospital, Limoges, France; Hospital Universitario Cruces, Barakaldo, Vizkaia, Spain; University Hospital Morvan, Brest, France; Hospital Clinico Universitario de Valencia, Valencia, Spain; Hospital de Sant Pau, Oncology Service, Barcelona, Spain; Hospital Provincial, Castellon, Spain; University Hospital of Basurto, Bilbao, Spain; Hospital Lozano Blesa, Zaragoza, Spain; Université Hospital Angers, Angers, Spain; Hospital Arnau de Vilanova, Valencia, Spain; Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; Consorcio Hospital General Universitario de Valencia, Valencia, Spain; Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Pangaea Biotech, Cancer Therapeutics Innovation Group, USP Institut Universitari Dexeus, Barcelona, Spain

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LBA8003 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Randomized, open-label, phase III study of pemetrexed plus carboplatin followed by maintenance pemetrexed (Arm A) versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab (Arm B) in patients with advanced nonsquamous (NS) non-small cell lung cancer (NSCLC).

Ralph Zinner, Helen J. Ross, Robert Weaver, Ramaswamy Govindan, Viran R. Holden, Naveed Mahfooz Chowhan, J. Thaddeus Beck, David Michael Waterhouse, Manuel Modiano, Vijay Phooshkooru Rao, Jingyi Liu, Andrew Koustenis, Symantha Melemed, Susan C. Guba, Waldo Feliu Ortuzar, Durisala Desaiah, David R. Spigel, Coleman K. Obasaju; The University of Texas MD Anderson Cancer Center, Houston, TX; Mayo Clinic, Scottsdale, AZ; Florida Cancer Specialists, Tampa, FL; Washington University School of Medicine in St. Louis, St. Louis, MO; St Johns Clinic, Springfield, MO; Cancer Care Center Inc., New Albany, IN; Highlands Oncology Group, Fayetteville, AR; Oncology Hematology Care/SCRI, Cincinnati, OH; Arizona Clinical Research Center and Arizona Oncology, Tucson, AZ; Mid Dakota Clinic, Bismarck, ND; Eli Lilly and Company, Indianapolis, IN; Sarah Cannon Research Institute, Nashville, TN

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8004 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

A phase III study of pemetrexed (Pem) plus carboplatin (Cb) plus bevacizumab (Bev) followed by maintenance pem plus bev versus paclitaxel (Pac) plus cb plus bev followed by maintenance bev in stage IIIb or IV nonsquamous non-small cell lung cancer (NS-NSCLC): Overall and age group results.

Mark A. Socinski, Jyoti D. Patel, Edward B. Garon, Ramaswamy Govindan, Craig H. Reynolds, David R. Spigel, Mark R. Olsen, Jingyi Liu, Susan C. Guba, Philip Bonomi; University of Pittsburgh, Pittsburgh, PA; Northwestern University, Chicago, IL; University of California, Los Angeles, Santa Monica, CA; Washington University School of Medicine in St. Louis, St. Louis, MO; US Oncology Research, Ocala, FL; Sarah Cannon Research Institute, Nashville, TN; Cancer Care Associates, Tulsa, OK; Eli Lilly and Company, Indianapolis, IN; Rush University Medical Center, Chicago, IL

Background: This study compared Pem+Cb+Bev followed by Pem+Bev maintenance (Pem arm) to Pac+Cb+Bev followed by Bev maintenance (Pac arm). The primary endpoint of improved overall survival (OS) for the Pem arm was not met. **Methods:** Advanced NS-NSCLC pts, ECOG PS 0/1, were randomized to 4 cycles of induction Pem+Cb+Bev with folic acid+vitamin B_{12} or Pac+Cb+Bev (Pem 500 mg/m^{2}or Pac 200 mg/m^2; Cb AUC 6; Bev 15 mg/kg) every 3 weeks. Eligible pts received maintenance Pem+Bev or Bev. OS, progression-free survival (PFS), overall response (ORR), and toxicity were evaluated. A hazard ratio (HR) of 0.80 required 676 OS events/900 pts with 2-sided type-I error .05 and at least 80% power for superiority of Pem over Pac arm. Exploratory Cox models estimated treatment HRs with 95% confidence intervals (CIs) for each age subgroup analyzed: ≤ or >65, 70 (prespecified) and ≤ or >75 yrs (not prespecified). **Results:** 939 pts (median age, 64.7) were randomized. Median (m) OS for ITT pem and pac arms was 12.6 vs 13.4 mos (HR 1.00, p=0.949); mPFS was 6.0 vs 5.6 mos (HR 0.83, p=0.012) Subgroup efficacy is shown in the Table; ≤ or >65 data were similar to ITT. Pem pts had significantly more drug-related grade 3/4 thrombocytopenia, anemia (except >75 yrs) and fatigue (except >70 and >75 yrs). Pac pts had significantly more grade 3/4 neutropenia (except >70 and >75 yrs), sensory neuropathy (except >75 yrs) and grade 1/2 alopecia. Results parallel overall safety data. **Conclusions:** OS was not significantly different in any of the age subgroups. PFS was significantly longer in Pem arm overall and for pts ≤70, but was similar for pts >70, >75 yrs. Toxicity profiles differed; subgroup safety data paralleled overall data. Clinical trial information: NCT00762034.

Efficacy endpoint	≤70 Pem n=354 75%	≤70 Pac n=338 72%	>70 Pem n=118 25%	>70 Pac n=129 27.6%	>75 Pem n=52 11.0%	>75 Pac n=55 11.8%
OS (mos)	12.6	14.3	12.7	11.5	11.8	8.9
HR (95% CI)	1.04 (0.88-1.24)		0.90 (0.67-1.21)		0.98 (0.63-1.51)	
P value	0.638		0.484		0.923	
PFS (mos)	6.3	5.6	5.7	5.6	5.4	4.5
HR (95% CI)	0.77 (0.65-0.92)		0.98 (0.73-1.31)		0.82 (0.52-1.30)	
P value	0.003		0.872		0.393	
ORR%	36.4	35.2	27.1	27.1	19.2	23.6

LBA8005 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Randomized proteomic stratified phase III study of second-line erlotinib (E) versus chemotherapy (CT) in patients with inoperable non-small cell lung cancer (PROSE).

Chiara Lazzari, Silvia Novello, Sandro Barni, Michele Aieta, Filippo De Marinis, Tommaso De Pas, Francesco Grossi, Manlio Mencoboni, Alessandra Bearz, Irene Floriani, Valter Torri, Alessandra Bulotta, Julia Grigorieva, Joanna Roder, Claudio Doglioni, Heinrich Roder, Luisella Righi, Silvia Foti, Angela Bachi, Vanesa Gregorc; Department of Oncology, Istituto Scientifico Ospedale San Raffaele, Milan, Italy; University of Turin, Orbassano, Italy; Department of Medical Oncology, Treviglio and Caravaggio Hospital, Treviglio, Italy; Centro Di Riferimento Oncologico DI Basilicata, Rionero in Vulture, Italy; San Camillo-Forlanini Hospital, Rome, Italy; Division of Thoracic Oncology, European Institute of Oncology, Milan, Italy; Lung Cancer Unit, National Institute for Cancer Research, Genova, Italy; Ospedale Villa Scassi, Genova, Italy; IRCCS Centro Rif Oncologico, Pordenone, Italy; Laboratory of Clinical Trials, Oncology Department, Istituto di Ricerche Farmacologiche, Milano, Italy; Oncology Department, Mario Negri Institute, Milan, Italy; Biodesix Inc., Boulder, CO; Biodesix Inc., Broomfield, CO; Department of Pathology, Istituto Scientifico Ospedale San Raffaele, Milan, Italy; Department of Clinical and Biological Sciences-Pathology, San Luigi Hospital, Orbassano, Italy; Laboratory of Proteomics, Istituto Scientifico Ospedale San Raffaele, Milan, Italy

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8006 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Randomized phase III trial of erlotinib (E) versus docetaxel (D) as second- or third-line therapy in patients with advanced non-small cell lung cancer (NSCLC) who have wild-type or mutant epidermal growth factor receptor (EGFR): Docetaxel and Erlotinib Lung Cancer Trial (DELTA).

Yoshio Okano, Masahiko Ando, Kazuhiro Asami, Masaaki Fukuda, Hideyuki Nakagawa, Hidenori Ibata, Toshiyuki Kozuki, Tateo Endo, Atsuhisa Tamura, Mitsuhiro Kamimura, Kazuhiro Sakamoto, Michihiro Yoshimi, Yoshifumi Soejima, Yoshio Tomizawa, Shunichi Isa, Minoru Takada, Hideo Saka, Akihito Kubo, Tomoya Kawaguchi; National Hospital Organization Kochi Hospital, Kochi, Japan; Nagoya University Hospital, Nagoya, Japan; National Hospital Organization Kinki-Chuo Chest Medical Center, Osaka, Japan; National Hospital Organization Nagasaki Medical Center, Nagasaki, Japan; National Hospital Organization Hirosaki Hospital, Hirosaki, Japan; National Hospital Organization Mie Central Medical Center, Mie, Japan; Department of Thoracic oncology and medicine, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan; National Hospital Organization Mito Medical Center, Mito, Japan; National Hospital Organization Tokyo Hospital, Tokyo, Japan; National Hospital Organization Disaster Medical Center, Tokyo, Japan; National Hospital Organization Yokohama Medical Center, Yokohama, Japan; National Hospital Organization Fukuoka East Medical Center, Fukuoka, Japan; National Hospital Organization Ureshino Medical Center, Ureshino, Japan; National Hospital Organization Nishigunma Hospital, Gunma, Japan; Koyo Hospital, Osaka, Japan; Department of Medical Oncology,National Hospital Organization Nagoya Medical Center, Nagoya, Japan; Aichi Medical University School of Medicine, Aichi, Japan

Background: E and D are standard cares for previously treated patients with advanced NSCLC. Although E shows significant clinical benefits over best supportive care in the EGFR wild type tumors, it remains unknown whether E or D is more active against the disease. **Methods:** This is an open-label, multi-center phase III study, sponsored by the Japanese National Hospital Organization. Patients were randomized to E (150 mg, daily), or D (60 mg/m^2, q3w) by the minimization method according to gender, performance status, histology, and institution. The primary endpoint was progression free survival (PFS), and secondary endpoints included overall survival (OS), response rate, safety, and analyses on EGFR wild type tumors. Eligible patients were those with pathologically proven NSCLC with stage IIIB or IV (AJCC version 6) previously treated with one or two chemotherapy regimens including at least one platinum agent, evaluable or measurable disease, and ECOG PS 0-2. Target sample size was calculated to be 280 based on the assumption that E was superior to D in PFS (3.5 months [m] v 2.5 m, α =0.05 [two sided], β =0.80). **Results:** From August 2009 to July 2012, 301 patients were accrued from 41 institutions. In the ITT population, 150 and 151 patients were randomly assigned to E and D, respectively, including respective 109 (73%, E) and 89 (59%, D) with EGFR wild type tumors. Median PFS and OS for E v D were 2.0 m (95% CI: 1.3-2.8) v 3.2 m (2.8-4.0, log-rank p=0.092; HR=1.22, 95% CI: 0.97-1.55), and 14.8 m (9.0-19.4) v 12.2 m (9.0-15.5, p=0.527; HR=0.91, 95% CI: 0.68-1.22), respectively. In the EGFR wild type tumors, PFS and OS for E v D were 1.3 m v 2.9 m (p=0.013; HR =1.44, 95% CI: 1.08-1.92), and 9.0 m v 9.2 m (p=0.914; HR =0.98, 95% CI: 0.69-1.39), respectively. Main grade 3/4 toxicities were rash (13.3% [E] v 0.7% [D]) and leukopenia (5.4% [E] v 62.9% [D]). **Conclusions:** E failed to show better PFS over D. While PFS was significantly longer in D than E in EGFR wild type tumors, the difference did not translate into OS in this pragmatic trial. Clinical trial information: 000002314.

CRA8007 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

A randomized study of ganetespib, a heat shock protein 90 inhibitor, in combination with docetaxel versus docetaxel alone for second-line therapy of lung adenocarcinoma (GALAXY-1).

Suresh S. Ramalingam, Glenwood D. Goss, Zoran Gojko Andric, Igor Bondarenko, Bojan Zaric, Timur Ceric, Elena Vladimir Poddubskaya, Tudor-Eliade Ciuleanu, James F. Spicer, Enriqueta Felip, Vera Hirsh, Christian Manegold, Rafael Rosell, Fadlo Raja Khuri, Vojislav M. Vukovic, Florentina Teofilovici, Iman El-Hariry, Wei Guo, Safi R. Bahcall, Dean Fennell; The Winship Cancer Institute of Emory University, Atlanta, GA; The Ottawa Hospital Cancer Center, Ottawa, ON, Canada; Clinical Hospital Centre Bezanijska Kosa, Beograd, Serbia; Municipal Institution Dnipropetrov, Dnipropetrovsk, Ukraine; University of Novi Sad, Institute for Pulmonary Diseases of Vojvodina, Novi Sad, Serbia; Clinical Center University of Sarajevo, Sarajevo, Bosnia; Unit of Russian Academy of Medical Sciences, Moscow, Russia; Prof. Dr. Ion Chiricuta Institute of Oncology, Department of Medical Oncology, Cluj-Napoca, Romania; King's College London, Guy's Hospital, London, United Kingdom; Thoracic Tumors Group, Vall d'Hebron Institute of Oncology, Barcelona, Spain; McGill University Health Centre, Montreal, QC, Canada; University Medical Center, Mannheim, Germany; Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Pangaea Biotech, Cancer Therapeutics Innovation Group, USP Institut Universitari Dexeus, Barcelona, Spain; Synta Pharmaceuticals, Inc., Lexington, MA; University of Leicester, Leicester, United Kingdom

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8008 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Clinical activity, safety, and biomarkers of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC).

David R. Spigel, Scott N. Gettinger, Leora Horn, Roy S. Herbst, Leena Gandhi, Michael S. Gordon, Cristina Cruz, Paul Conkling, Philippe Alexandre Cassier, Scott J. Antonia, Howard A. Burris, Gregg Daniel Fine, Ahmad Mokatrin, Marcin Kowanetz, Xiaodong Shen, Daniel S. Chen, Jean-Charles Soria; Sarah Cannon Research Institute, Nashville, TN; Yale School of Medicine, New Haven, CT; Vanderbilt University Medical Center, Nashville, TN; Yale University, New Haven, CT; Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA; Pinnacle Oncology Hematology, Scottsdale, AZ; Vall d'Hebron University Hospital, Barcelona, Spain; Virginia Oncology Associates/US Oncology, Norfolk, VA; Centre Léon Bérard, Lyon, France; Moffitt Cancer Center, Tampa, FL; Genentech, Inc., South San Francisco, CA; Genentech Inc., South San Francisco, CA; Institut Gustave Roussy, Villejuif, France

Background: Human lung cancer expresses high levels of PD-L1, which may inhibit anti-cancer immune responses. MPDL3280A, a human monoclonal Ab containing an engineered Fc-domain designed to optimize efficacy and safety, targets PD-L1, blocking PD-L1 from binding its receptors, including PD-1 and B7.1. **Methods:** Pts with squamous or nonsquamous NSCLC received MPDL3280A IV q3w at doses between 1-20 mg/kg in a Ph I expansion study. Pts were treated for up to 1 y. Objective response rate (ORR) was assessed by RECIST v1.1. Reported ORR includes u/cCR and u/cPR. **Results:** As of Jan 10, 2013, 53 NSCLC pts were evaluable for safety and treated at doses of ≤1 (n=2), 10 (n=10), 15 (n=19) and 20 mg/kg (n=22). Pts had a median age of 61 y (range 24-83 y), 98% were PS 0-1, 89% had prior surgery and 55% had prior radiotherapy. 98% of pts received prior systemic therapy. Pts received treatment for a median duration of 106 days (range 1-324) of MPDL3280A. The incidence of all G3/4 AEs, regardless of attribution, was 34%, including pericardial effusion (6%), dehydration (4%), dyspnea (4%) and fatigue (4%). No G3-5 pneumonitis or diarrhea was reported. 37 NSCLC pts enrolled prior to Jul 1, 2012, were evaluable for efficacy. RECIST responses were observed at dose levels between 1 and 20 mg/kg, with all responses ongoing or improving. An ORR of 24% (9/37) was observed in pts with squamous and nonsquamous histologies, including several with rapid tumor shrinkage. Additional pts had delayed responses after apparent radiographic progression (not included in the ORR). The 24-week PFS was 48%. Analysis of biomarker data from archival tumor samples demonstrated a correlation between PD-L1 status and efficacy. Pts who were PD-L1 tumor status–positive showed an ORR of 100% (4/4) and a PD rate of 0% (0/4), while pts who were PD-L1 tumor status–negative showed an ORR of 15% (4/26) and a PD rate of 58% (15/26). Updated data will be presented. **Conclusions:** Treatment with MPDL3280A was well tolerated, with no pneumonitis-related deaths. Rapid and durable responses were observed. PD-L1 tumor status correlated with response to MPDL3280A. Clinical trial information: NCT01375842.

8009 **Clinical Science Symposium, Mon, 9:45 AM-11:15 AM**

Interim results of phase II study BRF113928 of dabrafenib in *BRAF* V600E mutation–positive non-small cell lung cancer (NSCLC) patients.

David Planchard, Julien Mazieres, Gregory J. Riely, Charles M. Rudin, Fabrice Barlesi, Elisabeth A. Quoix, Pierre Jean Souquet, Mark A. Socinski, Julie Switzky, Bo Ma, Vicki L. Goodman, Stanley W. Carson, C. Martin Curtis, Michael R. W. Streit, Bruce E. Johnson; Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France; Hôpital Larrey CHU Toulouse, Toulouse, France; Memorial Sloan-Kettering Cancer Center, New York, NY; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Aix Marseille University, Assistance Publique Hôpitaux de Marseille, Hôpital Nord, Marseille, France; Hôpitaux Universitaires de Strasbourg, Strasbourg, France; Centre Hospitalier Lyon-Sud, Pierre-Bénite, France; University of Pittsburgh, Pittsburgh, PA; GlaxoSmithKline, Collegeville, PA; Dana-Farber Cancer Institute, Boston, MA

Background: Activating *BRAF* V600E mutations in NSCLC are present in $< 2\%$ of tumors, primarily adenocarcinoma. The BRAF inhibitor dabrafenib has demonstrated clinical activity in *BRAF* V600 mutation–positive melanoma. Here we report interim efficacy and safety data obtained in 17 *BRAF* V600E–mutant NSCLC patients enrolled in dabrafenib phase II study BRF113928. **Methods:** Single-arm, 2-stage, phase II study in stage IV *BRAF* V600E mutation–positive NSCLC pts who failed at least 1 line of chemotherapy. Dabrafenib dosed at 150 mg orally twice daily. The primary endpoint was investigator-assessed overall response rate (ORR) per RECIST 1.1 criteria. **Results:** The median age of the 17 pts was 69 years (range, 51-77 years). Most pts (12/17) were male, all were white with adenocarcinoma, and 13 were former smokers. All pts had failed at least 1 line of prior anticancer therapy, and 5 subjects had failed $\geq$ 2. At the time of reporting, 11 pts remain on therapy, and 6 have stopped therapy (5 with PD and 1 due to an AE). Thirteen pts were evaluable for efficacy. The best response for these pts included 7 PRs (5 confirmed PRs), 1 SD, and 4 PD; 1 pt discontinued due to an SAE (hypersensitivity reaction) prior to response assessment (ORR, 54%). The median duration of treatment for all 17 pts is approximately 9 weeks (range, 1-69 weeks). Among the 5 pts with confirmed PRs, duration of response was 29 and 49 weeks for the 2 pts who progressed, while the remaining 3 pts were responding for 6+ to 24+ weeks. The safety of dabrafenib in NSCLC pts appears to be generally consistent with what has been previously observed. The most common AEs were decreased appetite, fatigue, asthenia, dyspnea, and nausea, mostly grade 1 or 2. Five pts (29%) had a grade 3 AE, and 1 pt (6%) had a grade 4 SAE (hemorrhage). **Conclusions:** Dabrafenib shows early antitumor activity in *BRAF* V600E mutation–positive pretreated NSCLC pts, with an ORR of 54% and with the longest duration of response of 49 weeks thus far. Dabrafenib is generally well tolerated, and the study has met the minimum response rate ($\geq$ 3 of first 20 pts) to continue into the second stage. This study represents the first clinical evidence of BRAF as a therapeutic target in NSCLC. Clinical trial information: NCT01336634.

8010 **Clinical Science Symposium, Mon, 9:45 AM-11:15 AM**

Clinical activity of the ALK inhibitor LDK378 in advanced, ALK-positive NSCLC.

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Background: Lung cancers harboring anaplastic lymphoma kinase (*ALK*) gene rearrangements are sensitive to the tyrosine kinase inhibitor (TKI) crizotinib (CRZ), but invariably develop resistance. LDK378 is a novel, more potent ALK TKI than CRZ, with significant antitumor activity in preclinical models. **Methods:** In this multicenter phase I study, 131 patients (pts) with advanced malignancies harboring a genetic alteration in *ALK*, including 123 with *ALK*-rearranged (ALK+) NSCLC (as determined by FISH), were enrolled. LDK378 was administered orally at doses of 50–750 mg once daily. All pts were assessed for PK, response to therapy, and adverse events (AEs). In >20 pts with CRZ-resistant disease, tumor biopsy was performed before LDK378 treatment to identify CRZ resistance mutations. **Results:** As of November 8, 2012, 131 pts had been enrolled (38% male, median age 53 years), including 59 pts in the dose escalation phase, during which the MTD of 750 mg once daily was established, and 72 pts in an expanded cohort at the MTD. Among 88 evaluable NSCLC pts who received LDK378 at 400–750 mg daily, the overall response rate (ORR) was 70%, with 40 confirmed and 22 unconfirmed responses. In the subset of 64 CRZ-resistant pts, the ORR was 73%, with 31 confirmed and 16 unconfirmed responses. As of November 8, 2012 50% of pts with unconfirmed responses were ongoing. Responses were observed in pts with different CRZ resistance mutations as well as in pts without detectable mutation. Responses were also seen in pts with untreated CNS metastases. Among NSCLC pts with confirmed response, median duration of response (DOR) was 7.4 months (95% CI, 6.7 – NR), and 78% had a DOR of ≥6 months. In all 123 NSCLC pts, median PFS was 8.6 months (95% CI, 4.3 – 19.3). The most common AEs were nausea (72%), diarrhea (69%), vomiting (50%), and fatigue (31%). The most common Grade 3/4 AEs were ALT elevation (12%), diarrhea (7%), and AST elevation (6%). **Conclusions:** LDK378 induces durable responses in the majority of pts with advanced, ALK+ NSCLC, including CRZ-resistant pts with and without CRZ resistance mutations. These results suggest that more potent ALK inhibition by LDK378 represents a highly efficacious treatment strategy for ALK+ pts, particularly those who relapse on CRZ. Clinical trial information: NCT01283516.

LBA8011 **Clinical Science Symposium, Mon, 9:45 AM-11:15 AM**

Nintedanib (BIBF 1120) plus docetaxel in NSCLC patients progressing after one prior chemotherapy regimen: Results of Lume-Lung 1, a randomized, double-blind, phase III trial.

Martin Reck, Rolf Kaiser, Anders Mellemgaard, Jean Yves Douillard, Sergey Orlov, Maciej Jerzy Krzakowski, Joachim Von Pawel, Maya Gottfried, Igor Bondarenko, Meilin Liao, Jose Barrueco, Birgit Gaschler-Markefski, Silvia Novello; Department of Thoracic Oncology, Grosshansdorf Hospital, Grosshansdorf, Germany; Boehringer Ingelheim GmbH, Biberach, Germany; Department of Oncology, Herlev University Hospital, Herlev, Denmark; Department of Medical Oncology, Centre René Gauducheau, Nantes, France; Department of Thoracic Oncology, St. Petersburg State Medical University, St. Petersburg, Russia; The Maria Sklodowska-Curie Institute of Oncology, Warsaw, Poland; Pneumology Clinic, Asklepios Fachkliniken Gauting, Munich, Germany; Lung Cancer Unit, Meir Medical Center, Kfar-Saba, Israel; Municipal Institution Dnipropetrov, Dnipropetrovsk, Ukraine; Shandong Provincial Chest Hospital, Shanghai, China; Boehringer Ingelheim GmbH, Ridgefield, CT; Department of Oncology, University of Turin, Turin, Italy

The full, final text of this abstract will be available at abstract.asco.org at 7:30 AM (EDT) on Monday, June 3, 2013, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2013, issue of *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.

8012 Poster Discussion Session (Board #1), Sun, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Exploratory analyses of efficacy and safety of pemetrexed (Pem) plus bevacizumab (Bev) and bev alone as maintenance therapy (MT) in patients (Pts) with stage IIIb or IV nonsquamous non-small cell lung cancer (NS-NSCLC).

Jyoti D. Patel, Edward B. Garon, Ramaswamy Govindan, Craig H. Reynolds, David R. Spigel, Mark R. Olsen, Robert C. Hermann, Jingyi Liu, Susan C. Guba, Eduardo J. Pennella, Coleman K. Obasaju, Philip D. Bonomi, Mark A. Socinski; Feinberg School of Medicine, Northwestern University, Chicago, IL; David Geffen School of Medicine, University of California Los Angeles, Translational Research in Oncology-US Network, Los Angeles, CA; Washington University School of Medicine in St. Louis, St. Louis, MO; US Oncology Research, Ocala, FL; Sarah Cannon Research Institute, Nashville, TN; Cancer Care Associates, Tulsa, OK; Northwest Georgia Oncology Centers, Marietta, GA; Eli Lilly and Company, Indianapolis, IN; Lilly USA, Indianapolis, IN; Rush University Medical Center, Chicago, IL; University of Pittsburgh Cancer Institute, Pittsburgh, PA

Background: In a phase III superiority study, Pem+carboplatin (Cb)+Bev followed by Pem+Bev improved PFS compared with paclitaxel (Pac)+Cb+Bev followed by Bev in NS-NSCLC pts. Superior OS (primary endpoint) was not met. These analyses assessed the efficacy and safety in pts who received MT. **Methods:** Prespecified exploratory analyses were performed in the maintenance population (MP) and timed from the start of induction. Pts ≥18 years with stage IIIB/IV NS-NSCLC (ECOG status 0–1) from the multicenter, randomized, open-label, phase III superiority study were included in the MP if they received at least one dose of MT. For MT, pts received intravenous Pem 500 mg/m^2+Bev 15 mg/kg (n=292) or Bev 15 mg/kg (n=298). OS, PFS, and safety were evaluated. Comparison is made to the intent-to-treat (ITT; Pem=472, Pac=467) or safety population (SP; Pem=442, Pac=443; received at least one dose of one drug). **Results:** Baseline pt and disease characteristics for the ITT and MP were similar between arms. In the ITT/MP population, the median number of cycles was 7/10 (range, 1-41/4–41) in the Pem arm and 6/9 (range, 1-39/5–39) in the Pac arm. In the ITT/MP, OS was 12.6/17.7 months (mos; Pem) and 13.4/15.7 mos (Pac). Survival rates (%) at 12 and 24 mos with Pem (ITT/MP) were 52.7/71.7 and 24.4/34.5; Pac, 54.1/66.5 and 21.2/26.5%. In pts not receiving MT, OS was 4.7 mos (Pem) and 6.1 mos (Pac). PFS (mos) in the ITT/MT was 6.0/8.6 (Pem) and 5.6/6.9 (Pac). In pts not receiving MT, PFS was 2.3 mos and 2.5 mos with Pem and Pac, respectively. From induction, both SP/MP had significantly more grade 3/4 thrombocytopenia, anemia, and fatigue with Pem and neutropenia and sensory neuropathy with Pac ($p \leq 0.001$). During MT only, the difference in grade 3/4 neutropenia rates between arms was no longer significant. **Conclusions:** Improved efficacy outcomes were consistent with previous Pem maintenance and Bev studies and no new toxicities were observed. Clinical trial information: NCT00762034.

8013 Poster Discussion Session (Board #2), Sun, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

65 plus: A randomized phase III trial of pemetrexed and bevacizumab versus pemetrexed, bevacizumab, and carboplatin as first-line treatment for elderly patients with advanced nonsquamous, non-small cell lung cancer (NSCLC).

Wolfgang Schuette, Sylke Nagel, Claus-Peter Schneider, Walburga Engel-Riedel, Christian Schumann, Martin Kohlhaeufl, Monika Serke, Gert Hoeffken, Cornelius Kortsik, Martin Reck; Hospital Martha-Maria Halle-Doelau, Halle, Germany; Central Hospital Bad Berka, Bad Berka, Germany; Cologne Clinics, Merheim Lung Hospital, Cologne, Germany; University Hospital Ulm, Ulm, Germany; Hospital Schillerhoehe Gerlingen, Gerlingen, Germany; Lung Clinic Hemer, Hemer, Germany; Specialty Hospital Coswig, Coswig, Germany; Catholic Hospital Mainz, Mainz, Germany; Lung Clinic Grosshansdorf, Grosshansdorf, Germany

Background: Pemetrexed (P) and bevacizumab (B) are efficacious drugs for treatment of non-squamous NSCLC. In this trial the benefit of combining PB with carboplatin (C) was investigated in elderly patients (pts) ≥ 65 years with NSCLC. **Methods:** In this German multicenter (27 centers), open-label phase III trial pts with stage IIIb/IV non-squamous NSCLC were recruited. Pts were randomized 1:1 to P (500 mg/m^2) + B (7.5 mg/kg) or P+B+C (AUC5) d1 q3 wks for 4 to 6 cycles followed by maintenance therapy with B or P+B. The primary endpoint was progression-free survival (PFS), while secondary endpoints included overall survival (OS), 1-year survival rate, overall response rate (ORR) as well as tolerability (AEs/SAEs). **Results:** 271 pts were enrolled from Sep 2009 to Jan 2012, the ITT population consists of 251 evaluable pts, less than 10 pts are still receiving maintenance therapy. Baseline characteristics were balanced between both treatment groups (PB 118 pts, PBC 133 pts). Median age was 71 years in PB and 72 in PBC. Median PFS time was 4.8 mo in PB and 6.8 mo in PBC. Treatment comparison for ECOG performance status (PS) 0-1 subgroup (PB 112 pts, PBC 126 pts): p=0.0426 (Wilcoxon test), hazard ratio (HR) = 1.31 (95% CI 0.99-1.73). ORR was 31.4% in PB vs. 44.4% in PBC (p=0.0343). Median OS time was 11.6 mo in PB vs. 15.2 mo in PBC. Treatment comparison ECOG PS 0-1: p=0.2050, HR = 1.20 (95% CI 0.85-1.70). 1-year survival rates were 48.2% and 58.8%, respectively. Compared to this the median OS time in the small group of pts with ECOG PS 2 was 11.5 mo in PB vs. 3.8 mo in PBC. AE grade 3/4 and SAE profiles were comparable in both treatment arms, 76 pts (64.4%) with AEs grade 3/4 in PB and 87 pts (65.4%) in PBC, 58 pts (49.2%) with SAEs in PB and 64 pts (48.1%) in PBC. 46 pts (39.0%) in PB vs. 69 pts (51.9%) in PBC received maintenance therapy. **Conclusions:** Combination of PBC demonstrates with a median OS of 15.2 mo a strong efficacy with acceptable toxicity profile for elderly patients. Addition of carboplatin is recommended for eligible patients. However, in patients with ECOG PS 2 the administration of carboplatin must be carefully reviewed. Clinical trial information: NCT00976456.

8014 Poster Discussion Session (Board #3), Sun, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Effect of maintenance bevacizumab (Bev) plus pemetrexed (Pem) after first-line cisplatin/Pem/Bev in advanced nonsquamous non-small cell lung cancer (nsNSCLC) on overall survival (OS) of patients (pts) on the AVAPERL (MO22089) phase III randomized trial.

Achim Rittmeyer, Arnaud Scherpereel, Vera A. Gorbunova, Radj Gervais, Anders Vikström, Christos Chouaid, Antonio Chella, Joo-Hang Kim, Myung-Ju Ahn, Martin Reck, Antonio Pazzola, Heung Tae Kim, Joachim Aerts, Harry J.M. Groen, Claire Morando, Anderson Loundou, Fabrice Barlesi; Lungenfachklinik Immenhausen, Immenhausen, Germany; Centre Hospitalier Universitaire Lille, Lille, France; N. N. Blokhin Cancer Research Center, Russian Academy of Medical Sciences, Moscow, Russia; Centre François Baclesse, Caen, France; Universitetssjukhuset, Linköping, Sweden; Hôpital Saint-Antoine, Paris, France; University Hospita, Pisa, Italy; Department of Internal Medicine (Medical Oncology), Yonsei Cancer Research Institute, Yonsei Cancer Center, Seoul, South Korea; Department of Medicine, Division of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Department of Thoracic Oncology, Lung Clinic Grosshansdorf, Grosshansdorf, Germany; Medical Oncology - Ospedale Civile SS. Annunziata, Sassari, Italy; Center for Lung Cancer, National Cancer Center, Goyang, South Korea; Amphia Hospital, Breda, Netherlands; University Medical Center Groningen, Groningen, Netherlands; Aix Marseille University, Marseille, France; Aix Marseille University, Assistance Publique Hôpitaux de Marseille, Marseille, France

Background: Maintenance monotherapy has been associated with improved survival for NSCLC pts. AVAPERL was designed to evaluate the safety and efficacy of bevacizumab with or without pemetrexed as continuation maintenance treatment and demonstrated improved progression-free survival (PFS) (Barlesi, *JCO* in press). **Methods:** Pts with advanced nsNSCLC received first-line Bev (7.5 mg/kg), cisplatin (75 mg/m^2), and Pem (500 mg/m^2) every 3 weeks (q3w) for 4 cycles. Those non progressing were randomized to maintenance Bev (7.5 mg/kg) +/-Pem (500 mg/m^2) q3w until progressive disease or unacceptable toxicity. The primary end point (PFS) was met. An independent update analysis has been conducted to assess OS. **Results:** A total of 376 pts receive induction treatment; 125 and 128 were randomized to the Bev-alone and Bev+Pem arms, respectively. Induction therapy resulted in confirmed disease control in 71.9% of pts. After a median follow-up of 14.8 months, PFS for the Bev+Pem arm was significantly improved both from induction (10.2 *v* 6.6 m, HR 0.58 [0.45-0.76], p<.0001) and randomization (7.4 *v* 3.7 m, HR 0.57 [0.44-0.75], p<.0001). With 58% of events, OS for the Bev+Pem arm was also improved both from induction (19.8 *v* 15.9 m, HR 0.88 [0.64-1.22], p=.32) and randomization (17.1 *v* 13.2 m, HR 0.87 [0.63-1.21], p=.29). The PFS and OS improvements were comparable across age, PS, smoking status, and response to induction (SD *v*PR/CR) subgroups. No new safety signal was observed during this updated analysis. **Conclusions:** Continuation maintenance with Bev+Pem in an unselected population of nsNSCLC pts who had achieved disease control after induction was associated with an increase by almost 4 months in OS benefit over standard Bev alone. Clinical trial information: NCT00961415.

8015 Poster Discussion Session (Board #4), Sun, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Different-dose docetaxel plus cisplatin as first-line chemotherapy and then maintenance therapy with single-agent docetaxel for advanced non-small cell lung cancer (TFINE study, C-TONG 0904).

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Background: Docetaxel (75 mg/m^2) has been reported as first-line and maintenance treatment for Western population with advanced NSCLC. Different doses of docetaxel (60 mg/m^2) are currently delivered in Asian population. Pharmacogenomics alterations in taxanes disposition in different ethnic groups may explain this difference. TFINE study was to evaluate the efficacy, safety, and tolerability of docetaxel in the maintenance setting, and to identify the preferable dose of docetaxel in Asian population. **Methods:** Previously untreated patients, aged between 18 and 75 years, histologically or cytologically confirmed advanced NSCLC with PS of 0-1 were included. Patients were initially randomized (R1, 1:1) to receive cisplatin (75 mg/m^2) plus docetaxel of 75 mg/m^2 or 60 mg/m^2 for 4 cycles. Patients with disease control after the initial treatment were subsequently randomized (R2, 1:2) to best supportive care (BSC) or maintenance docetaxel of 60 mg/m^2 for up to 6 cycles. Genomic DNA was prospectively collected from all enrolled patients. The primary endpoint was PFS since R2, and the secondary endpoints included ORR, overall survival, and toxicity. This study is registered with ClinicalTrials.gov (NCT01038661). **Results:** This randomized study was undertaken in 15 centers in China. A total of 378 patients were enrolled to R1 and 184 patients (48.7%) were enrolled to R2 (61 vs. 123). Maintenance docetaxel plus BSC significantly prolonged PFS compared with BSC (5.4 months [95% CI 2.8, 7.0] vs. 2.8 months [1.8, 3.1]; $P=0.002$). The difference of ORR during initial chemotherapy was not significant, with 32.4% in the 60 mg-group and 33.7% in 75 mg-group ($P=0.80$).The data concerning the overall survival and toxicity, together with the information of pharmacogenomics alterations, will be presented in the meeting subsequently. **Conclusions:** Maintenance therapy with docetaxel is well tolerated and offers improved PFS in patients with advanced NSCLC.The dose of 60 mg/m^2 of docetaxel demonstrated similar efficacy and better tolerability than that of 75 mg/m^2 and should be preferred in Asian population. Clinical trial information: NCT01038661.

8016 Poster Discussion Session (Board #5), Sun, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

LUX-Lung 6: A randomized, open-label, phase III study of afatinib (A) versus gemcitabine/cisplatin (GC) as first-line treatment for Asian patients (pts) with EGFR mutation-positive (EGFR M+) advanced adenocarcinoma of the lung.

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Background: A is an oral, irreversible, ErbB Family Blocker, blocking signaling from EGFR (ErbB1), HER2 (ErbB2) and ErbB4. A was superior to first-line pemetrexed/cisplatin in a global phase III trial (LUX-Lung 3) in EGFR M+ NSCLC. This study compared the safety and efficacy of first-line A with GC in EGFR M+ Asian pts. **Methods:** The trial was conducted in Asian countries. Following central testing for EGFR mutations (TheraScreen EGFR RGQ PCR kit), 364 pts (stage IIIB/IV, PS 0–1, chemo-naïve) were randomized 2:1 (A: 242; GC: 122) to daily A 40 mg or IV GC (1,000 mg/m^2 D1, 8 + 75 mg/m^{2}q21 days up to 6 cycles). Primary endpoint was PFS by central independent review. **Results:** Baseline characteristics were balanced in both arms: Female (64.0 vs 68.0%), non-smoker (74.8 vs 81.1%), exon 19 deletion (51.2 vs 50.8%), L858R (38.0 vs 37.7%) in A and GC arms, respectively. PFS was significantly prolonged with A compared with GC by independent review (median PFS 11.0 vs 5.6 months, HR=0.28, $p<0.0001$); this finding was consistent across all subgroups. Results from the investigator review were similar: HR=0.26, $p<0.0001$, median 13.7 (A) vs 5.6 months (GC). Objective response (66.9% vs 23.0%, $p<0.0001$) and disease control (92.6% vs 76.2%, $p<0.0001$) rates (ORR/DCR) were significantly higher with A. OS, based on 43% of events shows HR=0.95, p=0.7593. Drug-related AEs of ≥G3 were reported in 36.0% (A) and 60.2% (GC) of pts, the most common of which were rash/acne (14.6%), diarrhea (5.4%) and stomatitis/mucositis (5.4%) with A and neutropenia (17.7%), vomiting (15.9%) and leukopenia (13.3%) with GC. Related AEs led to discontinuation in 5.9% (A) and 39.8% (GC) of pts. Patient reported-outcomes (PROs) showed significantly better control of cancer-related dyspnea, cough and pain with A. **Conclusions:** In EGFR M+ Asian pts, A significantly prolonged PFS with significant improvements in ORR, DCR, PROs. AEs in both arms were as expected, with a more favorable safety profile with A. LUX-Lung 6 is the largest prospective trial in EGFR M+ lung cancer, providing further evidence of superiority of A over standard chemotherapy in this setting. Clinical trial information: NCT01121393.

8017 **Poster Discussion Session (Board #6), Sun, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM**

Explicit and implicit attitudes toward lung cancer (LC) relative to breast cancer (BC).

Joan H. Schiller, Chris J. Bowden, Jennifer Mills, Edward Lang, Holli Dickson, Heidi A Hamann, N. Sriram; The University of Texas Southwestern Medical Center, Dallas, TX; Genentech, Inc., South San Francisco, CA; University of Psychology, Department of Psychology, Charlottesville, VA

Background: Emerging research suggests that LC may be associated with greater levels of stigma, shame and hopelessness compared to other cancers. This study measured explicit, conscious attitudes (EAs) and used the Implicit Association Test (IAT) to assess implicit, unconscious attitudes (IAs) of LC relative to BC. **Methods:** To assess EAs, participants (Ps), [people with cancer (n=243), caregivers (n=677), healthcare providers (HCPs, n=142), and the general public (n=864)] were asked to rate their agreement, on a six-point scale, with statements about how people with LC and BC "do feel" (descriptive attitudes) or "ought to feel" (normative attitudes) about their disease. IAs were measured with three IATs that used LC or BC images with words representing good/bad; hope/despair; or suitable/shameful. An IAT D score indicated the strength of bias against LC relative to BC: >0.65 = strong bias; 0.35-0.65 = moderate bias; 0.15-0.35 = slight bias; -0.15 -+0.15 = no bias, and < -0.15 indicated bias against BC. **Results:** EAs and IAs were substantially more negative towards LC. Most Ps provided more negative ratings for LC than BC for both descriptive (70%vs.8%) and normative statements (56% vs. 3%). Ps had strong negative IAs towards LC compared to BC (bad: 74% vs. 10%; despair: 75% vs. 9%; shame: 67% vs. 17%). These trends were consistent across caregivers, patients, HCPs, and the public. EAs and IAs were uncorrelated. **Conclusions:** Ps had greater explicit and implicit negative bias against LC compared to BC.

	Caregivers	Patients	HCPs	General public
Explicit				
Negative descriptive	75%, 7%, 18%	81%, 7%, 12%	88%, 5%, 7%	74%, 8%, 18%
Negative normative	59%, 3%, 38%	64%, 2%, 34%	65%, 3%, 32%	56%, 3%, 41%
Bad	D=0.43 73%, 12%, 15%	D=0.33 72%, 13%, 15%	D=0.33 63%, 17%, 20.0%	D=0.44 74%, 9%, 17%
Despair	D=0.43 73%, 10%, 17%	D=0.54 76%, 5%, 19%	D=0.44 77%, 13%, 10%	D=0.47 77%, 8%, 15%
Shame	D=0.32 65%, 18%, 17%	D=0.52 82%, 9%, 9%	D=0.41 72%, 11%, 17%	D=0.35 66%, 17%, 17%

Percentage order: LC bias%, BC bias%, No bias%. D=mean IAT score. All comparisons significant with ps<0.001.

8018 Poster Discussion Session (Board #7), Sun, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Response to erlotinib and prognosis for patients with de novo epidermal growth factor receptor (*EGFR*) T790M mutations.

Gregory J. Riely, Helena Alexandra Yu, Maria E. Arcila, Matthew David Hellmann, Marc Ladanyi, Mark G. Kris; Memorial Sloan-Kettering Cancer Center, New York, NY

Background: A secondary mutation in exon 20 of *EGFR*, T790M, is the most common cause of acquired resistance to EGFR tyrosine kinase inhibitors (TKIs) in patients with *EGFR* mutant lung cancers. De novo EGFR T790M mutations in TKI-naïve patients are rare when assessed by standard genotyping methods. The response to EGFR TKIs in patients with de novo EGFR T790M mutations is unknown. **Methods:** Patients with *EGFR*mutations were identified through routine testing, using PCR-based fragment length analysis, mass spectrometry-based genotyping (Sequenom), and Sanger sequencing. Clinical characteristics, progression free survival (PFS) from start of EGFR TKI and overall survival (OS) were obtained from the medical record. **Results:** From 2008-2012, we observed EGFR T790M in 21 tumors from 20 patients who had not previously been treated with an EGFR TKI representing $<2\%$ of all tumors with identified *EGFR* mutations. Two patients are included in reports from the Lung Cancer Mutation Consortium. The median age at lung cancer diagnosis was 57 (range 35-90). 55% presented with stage IV disease. 60% were women. 65% were never-smokers. In all cases, T790M occurred concurrently with another *EGFR* mutation, L858R (76%, 16/21) or exon 19 deletion (24%, 5/21). Compared to a contemporary cohort of 593 patients with *EGFR* mutations, in these patients with de novo EGFR T790M, L858R was more frequent than exon 19 deletion ($p=0.003$). Thirteen patients received erlotinib monotherapy as treatment for metastatic disease. Their response rate (CR+PR) was 9% (1/11, 95% Confidence Interval: 0-40%). SD was observed in 36% (4/11). The median progression-free survival was 3 months and the median overall survival was 16 months. **Conclusions:** De novo EGFR T790M mutations are rare and occur most commonly with EGFR L858R. Overall survival for patients with de novo EGFR T790 mutations is shorter than what is seen in patients with EGFR exon 19 deletions or L858R, and appears more similar to *EGFR* wild-type patients. Response rate to EGFR TKI in these patients is low. EGFR TKI therapy for patients with de novo EGFR T790M appears to have limited objective benefit and should be considered only after standard cytotoxic chemotherapy.

8019 Poster Discussion Session (Board #8), Sun, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

A multicenter effort to identify driver mutations and employ targeted therapy in patients with lung adenocarcinomas: The Lung Cancer Mutation Consortium (LCMC).

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Background: The detection of driver mutations in the *EGFR* and *ALK* genes and targeted therapy has transformed treatment of lung cancer. The LCMC was established in 2009 to assay lung adenocarcinomas for driver genomic alterations in 10 genes and to study and treat patients by their molecular subtypes. **Methods:** The 14-member LCMC enrolled patients with metastatic adenocarcinoma of the lung and tested their tumors in CLIA laboratories for *KRAS, EGFR, HER2, BRAF, PIK3CA, AKT1*, *MEK1*, and *NRAS* mutations using multiplexed assays, and for *ALK* rearrangements and *MET* amplifications using fluorescence in situ hybridization (FISH). **Results:** 1,102 eligible patients were enrolled; 1,007 underwent testing for at least one genomic alteration with 733 undergoing testing for all 10 genes. 600 patients were women (60%) with a median age of 63; 341 were never smokers (34%) and 589 former smokers (58%). A driver alteration was detected in 622 (62%) of the 1,007 with any genotyping, and in 465 (63%) of the 733 fully genotyped cases. Among the tumors with full genotyping, drivers were found as follows: *KRAS* 182 (25%), sensitizing *EGFR* 107 (15%), *ALK* rearrangements 56 (8%), other *EGFR* 43 (6%), two genes 29 (4%), *BRAF* 16 (2%), *HER2* 15 (2%), *PIK3CA* 6 (1%), *MET* amplification 5 (1%), *NRAS* 5 (1%), *MEK1* 1 (<1%), and *AKT1* 0 (0%). Results were used to select targeted therapy or targeted trials in 279 patients with a driver alteration (28% of 1,007 total). Among 938 patients with clinical follow-up and treatment information, 264 with a driver alteration treated with a targeted agent had a median survival of 3.5 years; 313 with a driver who did not receive targeted therapy had a median survival of 2.4 years; while 361 without an identified driver had a median survival of 2.1 years ($p<0.0001$). **Conclusions:** An actionable driver alteration was detected in 62% of tumors from patients with lung adenocarcinomas, leading to use of a targeted therapy in 28%. The patients with an identified driver treated with a targeted agent lived longer than those patients who did not receive targeted therapy. Multiplexed genomic testing can aid physicians in matching patients with targeted treatments and appropriate clinical trials.

8020 Poster Discussion Session (Board #9), Sun, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Clinical next generation sequencing (NGS) to reveal high frequency of alterations to guide targeted therapy in lung cancer patients.

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Background: Cancer genomic profiling via NGS in a clinical setting can reveal additional actionable genomic alterations (GA) in patients with lung cancer (LC) previously tested only by hotspot analysis and leading to unanticipated avenues of targeted treatment. **Methods:** We performed an NGS-based diagnostic test (FoundationOne) to characterize all classes of GA across 3,320 exons of 182 cancer-related genes and 37 introns of 14 genes frequently rearranged in cancer on 386 LC FFPE specimens in a CLIA-certified lab (Foundation Medicine). Specimens included fine needle aspirates, core needle biopsies, and malignant effusions. 95% of cases were NSCLC (367/386). Actionable GAs are defined as those linked to targeted anti-cancer therapies approved or being evaluated in clinical trials. NGS confirmed known hotspot results for *EGFR*, *KRAS* and *EML4:ALK* in 100% of cases. **Results:** Genomic profiles were generated from 364/386 (94%) of lung cancer cases, identifying 1205 GA, averaging 3.31 alterations per tumor (range 0 to 10). 85% of tumors (310) harbored at least one actionable GA, with a mean of 1.79 GA per tumor (range 0 to 6). In 68% of tumors (248), at least one GA was detected that would be missed by current 'hotspot assays'. *ERBB2* harbored base substitutions or indels in 1.3% of cases. *BRAF* and *C-Kit* were altered at frequencies of 2% and 1% respectively. The *mTOR/PI3K* pathway is likely to be activated via alterations in tumor suppressors *STK11* (11%), *NF1* (6%) and *PTEN* (4%), as well as by alterations of *PIK3CA* (10%) and in *AKT1/2/3* (4%), suggesting possible benefit from mTOR/PI3K inhibitors. The Hedgehog pathway (*PTCH1/SMO/SUFU*) was altered in 2% of cases. *ALK* and *RET* were rearranged in 4% and 2% of cases, respectively, with several cases initially diagnosed negative by FISH testing. **Conclusions:** Profiling the tumor genomes of 364 LC patients led to the identification of a series of GA not detectable by hotspot testing that could significantly inform targeted treatment decisions. Moreover, actionable GA appeared in unexpected tumor type, i.e. an *EGFR* mutation in a SCLC, reinforcing the likely utility of clinical cancer genomic profiling for the personalized treatment of LC patients.

8021 Poster Discussion Session (Board #10), Sun, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Detection of EGFR-activating mutations from plasma DNA as a potent predictor of survival outcomes in FASTACT 2: A randomized phase III study on intercalated combination of erlotinib (E) and chemotherapy (C).

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Background: Biomarker analysis of tumor from FASTACT 2 confirmed predictive power of EGFR mut on the benefit of intercalated combination of E and C as 1st line in advanced NSCLC (T. Mok, ESMO 2012). However, only limited tumor were available. Recent development allowed us to detect EGFR mut in cell-free DNA from plasma (pEGFRmut). In this study, we studied the concordance between pEGFRmut and EGFR mut in tumor (tEGFRmut), and the role of pEGFRmut as predictor of PFS and OS. **Methods:** Retrospective EGFR mut testing of FFPET and plasma from FASTACT 2 were performed with two allele-specific PCR assays, cobas EGFR_FFPET test and cobas EGFR_blood test (in development). Both tests are designed to detect EGFR activating mut (exon 19 deletions, L858R, G719X). One FFPET section was used for tissue test and 2-ml plasma was used for blood test. **Results:** Among 268 tumors from 451 enrolled pts, 90% (241/268) were analyzable. 40% (96/241) harbored at least one activating EGFR mut. All 427 plasmas from 451 enrolled pts were analyzable. 32% (136/427) were positive for EGFR activating mut. The concordance of two tests from 224 matched tissue and plasma samples was summarized below. Using tissue as comparator, the sensitivity of plasma test was 76% (68/89) and the specificity of plasma test was 96% (130/135) respectively. Positive and negative predictive values for EGFR activating mut were 93% (68/73) and 86% (130/151) respectively. Median PFS of patients with pEGFRmut treated with intercalated combination versus chemotherapy alone was 13.8 vs. 6.1 m (HR=0.21 $p<0.0001$), and for pEGFR wild-type, 6.7 vs. 6.0 m (HR=0.80, $p=0.06$). Median OS of patients with pEGFRmut treated with intercalated combination versus chemotherapy alone was 32.4 vs. 19.0 m (HR=0.51, $p=0.0035$), and for pEGFR wild-type, 16.1 vs 13.3 m (HR=0.89, $p=0.39$). **Conclusions:** cobas EGFR_*blood test* can be used to reliably detect EGFR mutations in plasma. pEGFRmut is a potent predictor of survival outcomes in FASTACT 2. Clinical trial information: NCT00883779/ MO22201/CTONG0902.

N=224	EGFR mut*(P)	Wild-type† (P)
EGFR mut* (T)	68	21
Wild-type† (T)	5	130

P: plasma; T: tissue; *activating mut positive; †activating mut negative.

8022 Poster Discussion Session (Board #11), Sun, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Patterns of metastasis and survival in patients with PI3K pathway-driven stage IV squamous cell lung cancers (SQCLC).

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Background: The majority of actionable drivers in SQCLCs occur in the PI3K (30%) and FGFR1 (20%) pathways. The biologic behaviors and natural histories of these oncogenic subtypes are not well characterized. **Methods:** As of October 2011, all patients with SQCLCs at MSK have undergone prospective, multiplex testing of their FFPE tumors for *FGFR1* amplification (FISH), *PIK3CA* mutations (Sequenom), PTEN loss (IHC), and *PTEN* mutations (exon sequencing), among others. Patient characteristics, outcomes, and metastatic sites were identified. Survival probabilities were estimated using the Kaplan-Meier method. Group comparisons were performed with log-rank tests and Cox proportional hazards methods. **Results:** 68 stage IV SQCLC patients were analyzed. 39 had tissue sufficient for next-gen sequencing. Genotypes were: *FGFR1* amplified (16%); PTEN loss (24%), *PIK3CA* mutant (7%), *PTEN* mutant (13%). Events were non-overlapping save for 2 cases with *PTEN*nonsense mutations and PTEN loss. The sole significant clinical difference (KPS, age, sex, lines of tx) was sex (women in PI3K group 52% vs. in others 23%, p=0.02). Metastatic patterns vs. other are shown in the Table. Median OS for PI3K vs. other: 10mo (95%CI:6.5-14.3) vs. 14mo (95%CI:9.6-36.7), p=0.02. Median OS for *FGFR1* vs. others: 19mo (95%CI:9-NR) vs. 10mo (95%CI:6.5-14.3), p=0.3. Multivariate analysis for OS: PI3K vs. other, HR death=2.3 (95%CI:1.1-4.8, p=0.03); Age ≥65, HR=1.3 (95%CI:0.6-2.9, p=0.6); KPS≥70, HR=0.5 (95%CI:0.2-1.7, p=0.3); Male sex, HR=0.7 (95%CI:0.3-1.4, p=0.3). **Conclusions:** Patients with stage IV PI3K-aberrant SQCLCs have poorer survival compared to other patients with SQCLCs. Brain metastases occurred exclusively in patients with PI3K-aberrant tumors. These data suggest that PI3K pathway activation confers a distinct biology, and that targeting this in SQCLC patients with brain metastases may be an effective therapeutic strategy.

Site	PI3K	P	FGFR1	P	Other	Total
Brain	6 (24%)	0.002	0 (0%)	0.6	0 (0%)	6 (9%)
Pleura	4 (16%)	0.4	3 (27%)	0.7	9 (28%)	16 (25%)
Liver	4 (16%)	0.4	1 (9%)	1	2 (6%)	7 (10%)
Bone	6 (24%)	0.8	2 (18%)	0.7	10 (31%)	18 (26%)
Lung	12 (48%)	0.8	7 (64%)	0.2	11 (34%)	30 (44%)
Adrenal	2 (8%)	1	1 (9%)	1	4 (13%)	7 (10%)
Pericardium	1 (4%)	1	1 (9%)	0.3	0	2 (3%)

8023 Poster Discussion Session (Board #12), Sun, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

NTRK1 gene fusions as a novel oncogene target in lung cancer.

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Background: The identification and therapeutic targeting of oncogenic drivers in lung adenocarcinoma has led to significant clinical improvements for patients with *EGFR* mutations or *ALK* fusions. However, many lung cancer patients do not yet have an identified oncogenic driver and the discovery of new actionable oncogenic drivers is thus an active area of investigation. **Methods**: Tumor samples from 36 'pan-negative' (*EGFR*, *KRAS*, *ALK*, and *ROS1*) lung adenocarcinoma patients were analyzed using a next generation sequencing (NGS) test performed in a CLIA-certified lab (Foundation Medicine, Cambridge, MA). Fluorescence in situ hybridization (FISH) screening using a novel *NTRK1* break-apart assay was performed on an additional 61 pan-negative samples. Cells expressing the novel *NTRK1* fusions were assayed for transformation and pharmacologic inhibition. **Results**: Two tumor samples were identified with gene fusions containing the kinase domain of TrkA, encoded by *NTRK1*, including one each with an *MPRIP-NTRK1 (M21;N14)* and *CD74-NTRK1 (C8;N12)* fusion. RT-PCR confirmed mRNA expression and identity of the fusion partner and FISH analysis detected split 5'/3' signals corresponding to the *NTRK1* gene. A third sample was identified by FISH analysis. Cloning and expression of *MPRIP*- and *CD74-NTRK1* into NIH3T3 and Ba/F3 cells show constitutive activation of the TrkA kinase domain and transformation. Treatment of cells expressing *NTRK1* fusions with several candidate pan-Trk inhibitors (ARRY-772, -523, and -470) as well as CEP-701 and crizotinib demonstrate decreased phosphorylation of the fusion oncoprotein and inhibition of cell proliferation. Treatment of the index patient harboring the *MPRIP-NTRK1*fusion with crizotinib led to minor transient tumor shrinkage. **Conclusions:** We identified a novel class of oncogenes, *NTRK1* fusions, in lung adenocarcinomas that can be detected by NGS or FISH. Additional studies to determine the frequency and characteristics of *NTRK1* fusions in lung cancer are ongoing. Our findings suggest prospective clinical trials of Trk inhibitors in *NTRK1* fusion positive patients may be warranted. Support: CO Bioscience Discovery and Evaluation Grant and CO Clinical and Translational Sciences Institute Grant.

8024 Poster Discussion Session (Board #13), Sun, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

RET rearrangements detected by FISH in "pan-negative" lung adenocarcinoma.

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Background: *RET* rearrangements have recently been reported in NSCLC and there is pre-clinical evidence that *RET* tyrosine kinase inhibitors (TKIs) block activated *RET* kinase. Efficient and accurate detection of *RET* rearrangements are crucial for the success of *RET* TKIs in clinical trials. *RET* rearrangements have been detected by specialized sequencing techniques with limited applicability to clinical practice. **Methods:** A 3-target FISH probe set was developed to detect *KIF5B-RET* fusions and identify patterns suggestive of *RET* rearrangements with non-*KIF5B* partners. 51 lung adenocarcinomas negative for *EGFR*, *KRAS*, *ALK* and *ROS1* (36 were also negative for 7 other molecular markers) were investigated. Clinical and demographic characteristics were collected. **Results:** Eight patients (15%) had rearrangements in the *RET* gene: 5 with *KIF5B-RET* fusions, 2 with patterns consistent with the *CCDC6-RET* fusion, and 1 with extra copies of single 3'*RET* (loss of 5'*RET*). Atypical FISH patterns were detected both in *RET* + and negative specimens suggesting high genomic instability in the *KIF5B – RET* region. RT-PCR assay determined the exon/fusion variant in 4 cases including 2 patients with K15:R12, 1 with K16:R12 and 1 with C1:R12. Median age at diagnosis was 58.5 in the mutation negative and 63 in the *RET*+ patients. Both cohorts were predominantly male (66% and 56%, respectively), with a majority of never smokers (59 and 89%, respectively), and stage IV disease at diagnosis (72 and 89%, respectively). Two heavily pretreated *RET*+ patients had stable disease at their initial restaging scans following treatment with the *RET* inhibitor vandetanib (radiographic assessment per RECIST 1.1); two others had early radiographic progression with sunitinib. **Conclusions:** The FISH probe proved efficient to detect *RET* rearrangements in lung adenocarcinomas, involving *KIF5B* and non-*KIF5B* partners. Frequency of *RET* rearrangements in this enriched lung adenocarcinoma cohort was considerably higher than reported in unselected cohorts. Further molecular analyses are being performed to increase understanding of the natural history of this new molecular subtype of NSCLC. Support: B J Addario Foundation, NCI P50CA058187, NCI CCSG P30CA046934.

8025 Poster Discussion Session (Board #14), Sun, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Comparison of the characteristics and clinical course of 677 patients with metastatic lung cancers with mutations in KRAS codons 12 and 13.

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Background: Patients (pts) with *KRAS* mutant lung cancers have a shorter survival compared to pts with *KRAS/EGFR* wild type tumors (Johnson et al, Cancer 2012). Whether outcomes for patients with *KRAS* mutant metastatic lung cancers differ by smoking status or specific amino acid substitution is unknown. In order to understand the impact of *KRAS* mutation subtype in the metastatic setting, we analyzed a large cohort of patients with *KRAS* mutant metastatic lung cancer. **Methods:** We identified all pts with *KRAS* mutant metastatic or recurrent lung cancers from Feb 2005 to Aug 2011. *KRAS* mutation type, clinical characteristics, and outcomes from diagnosis were obtained from the medical record. A multivariate cox proportion hazard model was used to identify factors associated with overall survival. **Results:** *KRAS* mutations were identified in 677 pts (53 at codon 13, 624 at codon 12). Median age: 66 (range 31-89), women: 62%, never smokers: 7%. Pts with transition mutations (n=157) were more likely to be never-smokers ($p<0.0001$). There was no difference in outcome for pts with *KRAS* transition versus transversion mutations ($p=1$) or when comparing current/former smokers to never smokers ($p=0.33$). There was no difference in overall survival (OS) when comparing specific amino acid substitutions (G12C=366, G12V=141, G12D=114, G12A=68, G13C=27, G13D=23, G12S=19, G12F=11)($p=0.20$). Pts with *KRAS* codon 13 mutant tumors had inferior OS compared to pts with codon 12 mutant tumors, median 13 months (mo) (95% CI 13-17 mo) and 16 mo (95% CI 9-16 mo), respectively ($p=0.009$). There was no difference in frequency of receiving platinum-based chemotherapy or chemotherapy of any kind between pts with codon 12 and 13 mutant tumors. In a multivariate Cox model which included age, gender and smoking status, *KRAS* codon 13 mutation was associated with worse overall survival than KRAS codon 12 mutation (HR 1.52 95% CI 1.11-2.08 $p=0.008$). **Conclusions:** Among pts with *KRAS* mutant metastatic lung cancers, smoking history, and specific amino acid substitution do not affect outcome. Patients with KRAS codon 13 mutant metastatic lung cancer have shorter survival compared to pts with KRAS codon 12 mutant lung cancer.

8026 Poster Discussion Session (Board #15), Sun, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Two parallel randomized phase II studies of selumetinib (S) and erlotinib (E) in advanced non-small cell lung cancer selected by KRAS mutations.

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Background: KRAS mutations are present in 20% of NSCLC and are associated with primary resistance to erlotinib (E). KRAS mutations result in constitutive activation of the Ras/Raf/MEK/ERK pathway. Selumetinib (S) (AZD6244, ARRY-142886) is a selective and uncompetitive inhibitor of MEK kinase. Preclinical studies demonstrated increased activity in NSCLC cell lines using S+E regardless of KRAS status. **Methods:** Advanced NSCLC patients with progressive disease after platinum based chemotherapy +/- one other treatment were stratified by KRAS status, which was centrally assessed using macrodissection and pyrosequencing for all mutations involving codons 12, 13, and 61. Patients were randomized to receive either the standard of care E or a combination of S+E in KRAS wild type (wt) and S alone or S+E in patients with KRAS mutations. Single agent E and S were administered orally at 150 mg daily and 75 mg twice daily respectively. Combination dosing were S 150 mg every morning and E 100 mg every evening. The primary endpoint for the KRAS wt group was PFS and for the KRAS mutant group objective response rate. **Results:** From March 2010 to January 2013, 79 patients screened; 78 enrolled: KRAS mutant, 39; KRAS wt, 40; M/F (39:39); median age: 64 years (33-84); median WHO PS 1(0-2); 66 former and 13 never smokers; 67 adenocarcinoma, 9 squamous cell. Three patients died of complications prior to first evaluation (1 coronary disease, 1 pulmonary fibrosis, and 1 disease progression) of which none were related to S. Dose reductions occurred in 5% E, 40% S, and 56% E+S. Most grade 3/4 AEs occurred in combination therapy; diarrhea (23%), fatigue (23%) lymphopenia (13%), myositis (10%), dyspnea (10%), rash (7%). Discontinuation due to AEs was 8% all occurring in S+E cohorts. **Conclusions:** This study failed to show improvement of combination therapy over single agent in KRAS wt and mutant patients. Toxicity was increased in the combination arms. Interestingly, the KRAS mutant cohort had longer PFS than KRAS wt patients, although not statistically significant (p=0.11). Clinical trial information: NCT01229150.

	KRAS WT		KRAS MUT	
E	E + S	S	S + E	
n*	19	18	9	30
RR	0	6% (n=1) (p=1.00)	0	7% (n=2) (p=1.00)
Median PFS(m)	2.3	2.1 (p=0.69)	3.9	4.5 (p=0.95)

* 75 patients evaluable.

8027 Poster Discussion Session (Board #16), Sun, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Oral MEK1/MEK2 inhibitor trametinib (GSK1120212) in combination with pemetrexed for *KRAS*-mutant and wild-type (WT) advanced non-small cell lung cancer (NSCLC): A phase I/Ib trial.

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Background: Lung cancer patients with mutated *KRAS* tumors present a treatment challenge. Trametinib + pemetrexed (pem) enhanced growth inhibition and apoptosis compared with either agent alone in lung cancer cell lines with WT or mutated *RAS/RAF*. **Methods:** This 2-part, multiarm, phase I/Ib, open-label study evaluated the safety and efficacy of trametinib plus chemotherapy (NCT01192165). Part 1 determined the recommended phase II dose (RP2D) for trametinib + pem in patients (pts) with advanced solid tumors. In part 2, NSCLC pts were stratified as *KRAS* WT or mutation unknown (WT) or *KRAS*-mutant (KRAS) and were treated with trametinib + pem at the RP2D. Primary study objectives were safety and tolerability; secondary objectives were efficacy and pharmacokinetics (PK). Exploratory mutational profiling was done using circulating-free DNA from plasma and available archival tumor tissue. **Results:** As of January 2013, 42 NSCLC pts (22 WT [82% had $\geq$ 2 prior therapies], 20 KRAS [55% had $\geq$ 2 prior therapies]) have been treated at the trametinib + pem RP2D (1.5 mg + 500 mg/m^2). Nausea, fatigue, and peripheral edema were the 3 most frequent toxicities. 26% of pts reported grade 3-4 hematologic toxicity. Dose reduction occurred in 15 pts (33%), most often for diarrhea, decreased ejection fraction, and fatigue (all 7%). Preliminary PK suggests no drug-drug interaction. In KRAS pts, the best investigator-assessed response (confirmed + unconfirmed) was 3 partial response (PR; RR = 15%) and 10 stable disease (SD; 50%); additionally, 3 pts had $>$ 20% tumor shrinkage. The disease control rate (DCR) was 65%. Final response and progression-free survival (PFS) data will be reported upon maturity. In WT pts, 3 PR (RR = 14%) and 13 SD (59%) were observed (73% DCR); preliminary median PFS was 5.8 months (95% CI, 2.8-6.7 months). Biomarker analyses, including assessment of *KRAS* mutation subtype vs efficacy, are ongoing. **Conclusions:** MEK inhibition with trametinib + pem demonstrates tolerability and clinical activity in both *KRAS*-mutant and WT NSCLC, exceeding expectations for each drug alone and warranting further study. Clinical trial information: NCT01192165.

8028 Poster Discussion Session (Board #17), Sun, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Oral MEK1/MEK2 inhibitor trametinib (GSK1120212) in combination with docetaxel in *KRAS*-mutant and wild-type (WT) advanced non-small cell lung cancer (NSCLC): A phase I/Ib trial.

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Background: *KRAS*-mutant NSCLC, usually reflecting tobacco-related carcinogenesis, represents an unmet medical need in lung cancer therapy. Trametinib plus docetaxel (doc) enhances growth inhibition and apoptosis of NSCLC cell lines in vitro with and without *RAS*/*RAF* mutations when compared with either agent alone. **Methods:** This 2-part, multiarm, phase I/Ib, open-label study evaluated the safety and efficacy of trametinib plus chemotherapy (NCT01192165). Part 1 determined the recommended phase II dose (RP2D) for trametinib+doc in patients (pts) with advanced solid tumors. In part 2, NSCLC pts were stratified as *KRAS* WT or mutation unknown (WT) or *KRAS*-mutant (KRAS) and were treated with trametinib + doc at the RP2D. Primary study objectives were safety and tolerability; secondary objectives were efficacy and pharmacokinetics (PK). Exploratory mutational profiling was done using circulating-free DNA from plasma and available archival tumor tissue. **Results:** As of January 2013, 46 NSCLC pts (24 WT [67% had $\geq$ 2 prior therapies] and 22 KRAS [41% had $\geq$ 2 prior therapies]) have been treated at the trametinib + doc RP2D (2.0 mg + 75 mg/m^2 + growth factors). Diarrhea, fatigue, asthenia, and nausea were the 4 most frequent toxicities. Dose reduction occurred in 10 pts (22%), mostly for diarrhea, fatigue, mucositis, neutropenia, and skin fissures (all 4%). Preliminary PK suggests no drug-drug interaction. In KRAS pts, the best investigator-assessed response (confirmed + unconfirmed) was 3 partial response (PR; RR = 17%) and 8 stable disease (SD; 44%); additionally, 4 pts had $>$ 20% tumor shrinkage. The current disease control rate (DCR) is 61%; 4 pts have not had postbaseline scans. In WT pts, 5 PR (RR=21%) and 11 SD (46%) were observed (67% DCR). Final response and progression-free survival data will be reported upon maturity. Biomarker analyses, including assessment of *KRAS* mutation subtype vs efficacy, are ongoing. **Conclusions:** MEK inhibition with trametinib + doc (+ growth factors) demonstrates tolerability and clinical activity in both *KRAS*-mutant and WT NSCLC, exceeding expectations for each drug alone and warranting further study. Clinical trial information: NCT01192165.

8029 Poster Discussion Session (Board #18), Sun, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

MEK114653: A randomized, multicenter, phase II study to assess efficacy and safety of trametinib (T) compared with docetaxel (D) in *KRAS*-mutant advanced non–small cell lung cancer (NSCLC).

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Background: *KRAS* mutations are detected in 25% of NSCLC, and there are no approved targeted therapies for this subset of NSCLC. D, an approved second-line treatment for NSCLC, has a response rate of $< 10\%$. T is a reversible, highly selective allosteric inhibitor of MEK1/2 activation and kinase activity. This phase II trial (NCT01362296) evaluated the efficacy of T vs D in pts with advanced *KRAS*-mutant NSCLC who had received prior platinum-based chemotherapy. **Methods:** Pts were randomized 2:1 to T (2 mg QD) or D (75 mg/m^2 IV every 3 weeks) and stratified by type of mutational status and gender. Crossover to the other arm after progressive disease was allowed. Primary endpoint was PFS in pts with *KRAS*-mutant NSCLC (modified ITT; mITT). Secondary endpoints were OS, ORR, duration of response, and safety. PFS and OS were compared using a stratified log-rank test. The trial was stopped early for futility at a planned interim analysis; 92 PFS events were reported at the time of study termination. **Results:** Between September 2011 and July 2012, 134 pts were randomized to T (89) or D (45); 129 pts had *KRAS*-mutant NSCLC. Mean age was 61.4 y and 53% were male. In the mITT, 61/86 pts (71%) on T and 31/43 (72%) on D had a PFS event. HR for PFS was 1.14 (95% CI, 0.75-1.75; $P = .5197$) with a median PFS of 11.7 vs 11.4 wk for T vs D. ORR was 12% for T (10/86) and for D (5/43). With 27 (31%) deaths on T and 15 (35%) on D, HR for OS was 0.97 (95% CI, 0.52-1.83; $P = .934$). Five fatal SAEs were reported during treatment with T but none with D; 1 unspecified death was considered related to T. Frequent AEs reported with T were rash (59%), diarrhea (47%), nausea (34%), hypertension (34%), and dyspnea (33%). Grade 3/4 AEs with T were hypertension (16%/0), dyspnea (7%/3%), rash (6%/3%), diarrhea (6%/0), and asthenia (6%/0). Rate of treatment related SAEs was 15% with T and 12% with D. **Conclusions:** T did not improve PFS in pts with *KRAS*-mutation–positive NSCLC compared with D. However, an ORR of 12% for T in *KRAS*-mutant NSCLC suggests that an effort to better identify responsive mutations is warranted. The safety profile did not favor T, but is, in general, consistent with the overall T safety profile. Clinical trial information: NCT01362296.

8030 Poster Discussion Session (Board #19), Sun, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Survival and long-term follow-up of the phase I trial of nivolumab (Anti-PD-1; BMS-936558; ONO-4538) in patients (pts) with previously treated advanced non-small cell lung cancer (NSCLC).

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Background: The immune checkpoint receptor programmed death-1 (PD-1) negatively regulates T-cell activation. Nivolumab, a PD-1 receptor blocking antibody, was evaluated in a phase 1 study in pts with various tumors including NSCLC (Topalian et al, NEJM 2012;366:2443). **Methods:** Pts with ≥1 prior chemotherapy regimen received nivolumab (1-10 mg/kg IV Q2W) for ≤12 cycles (4 doses/8W cycle) or until discontinuation criteria were met. We report initial overall survival (OS) and updated safety and response data for NSCLC pts. **Results:** 127 pts evaluable for safety received nivolumab at 1, 3, or 10 mg/kg as of July 2012. Common drug-related AEs were decreased appetite (9%), anemia (8%), diarrhea, nausea, and pruritus (7% each). The most common G3/4 AEs were fatigue, pneumonitis, and elevated AST (2% each). Two drug-related deaths from pneumonitis occurred early in the trial and led to increased monitoring without further deaths from pneumonitis. Median OS (mOS) across all dose cohorts was 9.2 mo and 9.6 mo for squamous (sq) and non-sq NSCLC, respectively. mOS was not reached at the 3 mg/kg dose (phase 3 dose) for either histology. Sustained OS was observed, with 44%/ 41% and 44%/ 17% of pts (sq/non-sq) alive at 1 and 2 years, respectively (Table). Prolonged ORs occurred in both histologies (Table). **Conclusions:** In this long-term follow-up of a phase I trial, nivolumab had an acceptable safety profile and showed an encouraging sustained OS benefit across histologies in previously treated advanced NSCLC. Follow-up through a Feb 2013 data cut (≥1 yr follow-up for all pts) will be provided at presentation. Clinical trial information: NCT00730639.

Dose, mg/kg	ORR n/N (%)	mOS Mo (95% CI)
All NSCLC pts	20/122 (16)	9.6 (7.4-13.7)
All Non-sq	11/73 (15)	9.6 (5.3-13.7)
1	1/18 (<6)	9.2 (5.3-NR)
3	5/18 (28)	NR (5.2-NR)
10	5/37 (14)	7.2 (4.6-10.1)
All Sq	9/48 (19)	9.2 (7.6- NR)
1	0/13 (0)	8.3 (3.2-NR)
3	4/15 (27)	NR (6.7-NR)
10	5/20 (25)	10.5 (8.6-NR)
OS rate[a],% (95% CI), pt at risk, n		
	Sq	Non-Sq
1 Yr	44 (27-61), 8	41 (28-53), 16
2 Yr	44 (27-61), 3	17 (0-42), 1

[a]Across doses. OS estimates after 1 Yr reflect heavy censoring and shorter follow-up for pts enrolling in the later portion of the study. NR = not reached.

8031 Poster Discussion Session (Board #20), Sun, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

First-in-human dose-finding study of the ALK/EGFR inhibitor AP26113 in patients with advanced malignancies: Updated results.

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Background: AP26113 is a novel tyrosine kinase inhibitor (TKI) that potently inhibits mutant activated forms of anaplastic lymphoma kinase (ALK+) and epidermal growth factor receptor (EGFRm), and TKI-resistant forms including L1196M (ALK) and T790M (EGFR). AP26113 does not inhibit native EGFR. **Methods**: The dose finding phase (3+3 design) of this phase I/II open-label, multicenter study is ongoing in pts with advanced malignancies (except leukemia) refractory to available therapies or for whom no standard treatment exists. Initial dosing is orally once daily. **Results**: As of 14 Jan 2013, 44 pts were enrolled: 30 mg n=3, 60 mg n=3, 90 mg n=8, 120 mg n=8, 180 mg n=11, 240 mg n=9, 300 mg n=2; 64% female, median age 60 yrs; diagnoses: non-small cell lung cancer (NSCLC, n=37), other (n=7). 26 pts discontinued: 18 disease progression, 6 adverse event (AE), 2 deaths (sudden death, hypoxia; both possibly related). Most common AEs: nausea (45%), fatigue (39%), diarrhea (27%); most common grade 3/4 treatment-related AE: diarrhea (5%). 2 dose limiting toxicities observed: grade 3 ALT increase, 240 mg; grade 4 dyspnea, 300 mg. Doses $<$300 mg are being explored further. 21 pts had ALK+ history (18 NSCLC, 3 other). Among 18 evaluable ALK+ pts, 10 responded. 15 ALK+ pts had 0 (n=3) or 1 (n=12) prior ALK TKI (crizotinib); of these, 2/3 and 8/12 pts (67%) responded, including 2 complete responses. The longest response is 40 wks (ongoing). 4 of 5 ALK+ pts with untreated or progressing CNS lesions at baseline and with follow-up scans had evidence of radiographic improvement in CNS, including 1 pt resistant to crizotinib and LDK378 (overall response = stable disease). 16 pts had EGFRm history (15 NSCLC, 1 SCLC); 14 pts had $\geq$1 prior EGFR TKI. Of 12 EGFRm pts with a follow-up scan, 1 pt (prior erlotinib) responded at 120 mg (duration 21 wks, ongoing), 6 pts had stable disease (2 ongoing, duration 7-31 wks). **Conclusions**: AP26113 has promising anti-tumor activity in ALK+ pts, with initial evidence of activity in EGFRm pts, and is generally well tolerated. Phase II will begin after the recommended phase II dose is determined, with 4 cohorts: crizotinib-naïve NSCLC; crizotinib-resistant NSCLC; EGFR TKI-resistant NSCLC; other tumors. NCT01449461. Clinical trial information: NCT01449461.

8032 Poster Discussion Session (Board #21), Sun, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Efficacy and safety of crizotinib in patients with advanced *ROS1*-rearranged non-small cell lung cancer (NSCLC).

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Background: *ROS1* receptor tyrosine kinase rearrangements define a subset of NSCLC sensitive to the small-molecule tyrosine kinase inhibitor crizotinib, approved multinationally for the treatment of advanced *ALK*-positive NSCLC. Updated efficacy and safety data are presented for crizotinib in patients with advanced *ROS1*-rearranged NSCLC. **Methods:** *ROS1* status was determined by break-apart FISH assays, and patients were enrolled into an expansion cohort of an ongoing phase 1 crizotinib study (NCT00585195). Patients received crizotinib 250 mg BID. Responses were assessed using RECIST v1.0. The disease control rate (DCR; % stable disease [SD] + partial response [PR] + complete response [CR]) was evaluated at weeks 8 and 16. **Results:** At the data cut-off, 33 patients with *ROS1*-positive NSCLC had enrolled, and 31 had received crizotinib, with 25 evaluable for response. Median age was 51 years (range 31–72), 79% of patients were never-smokers and 97% had adenocarcinoma histology. The median number of prior treatments for advanced disease was 1 (range 0–7). The objective response rate (ORR) was 56% (95% CI: 24.4–65.1), with 2 CRs, 12 PRs and 8 SDs. 8-week and 16-week DCRs were 76% and 60%, respectively. Median PFS has not been reached, with ~60% of patients still in follow-up for PFS; 6-month PFS probability was 71% (95% CI: 45.6–86.0). Median treatment duration was 24 weeks (range 2.3–112), and 24 patients were on treatment at the data cut-off; 5 patients died (all disease-related). 91% of patients had treatment-related adverse events (AEs): most commonly visual impairment (82%), nausea (36%) and diarrhea (33%). Most AEs were grade 1 in severity. Peripheral edema and elevated transaminases were also reported, similar to the previous experience of crizotinib. There were no treatment-related serious AEs or treatment-related permanent discontinuations. Accrual of patients with *ROS1*-positive NSCLC is ongoing. **Conclusions:** As observed in *ALK*-positive NSCLC, crizotinib had dramatic antitumor activity with a high ORR (56%) in patients with *ROS1*-positive NSCLC and a generally tolerable and manageable AE profile. These findings indicate that crizotinib is an effective therapy for advanced *ROS1*-positive NSCLC. Clinical trial information: NCT00585195.

8033 Poster Discussion Session (Board #22), Sun, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

A phase I/II study with a highly selective ALK inhibitor CH5424802 in ALK-positive non-small cell lung cancer (NSCLC) patients: Updated safety and efficacy results from AF-001JP.

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Background: Anaplastic lymphoma kinase (ALK) is a constitutively activated tyrosine kinase in a subset of NSCLC with ALK fusion gene derived from chromosomal rearrangement. Previously, CH5424802, a highly selective, second-generation ALK inhibitor, has demonstrated clinically meaningful antitumor activity and a favorable toxicity profile (ESMO 2012). Here we report the updated results of this study. **Methods:** Patients (Pts) with ALK-positive NSCLC and no prior ALK inhibitor therapy were treated with CH5424802 at 300 mg bid until progressive disease or intolerable toxicity to investigate the efficacy and safety. **Results:** As of the cut-off date of Dec. 14, 2012, 58 pts have been treated with CH5424802: median age 49.5 years, M/F 25/33, ECOG PS 0/1 26/32, never-smoker 60.3%, $\geq$2 prior chemotherapy regimens 62%. Among the 46 pts in phase II part of this study, the overall response rate was 93.5% (95% CI: 82.1%, 98.6%) with 2 CRs and 41 PRs. Tumor shrinkage by 30% (PR) was achieved quickly with 65% occurring within 3 weeks of treatment and 87% within 6 weeks. With a median follow-up period of 12.6 months, 47/58 pts (40/46 pts in phase II part) were still on study treatment, and the median treatment duration has passed 10.3 months. The major treatment-related AEs were dysgeusia (21/58, 36%), rash, AST increased, blood bilirubin increased (19/58, 33% each), constipation and blood creatinine increased (17/58, 29% each), mostly grade 1-2. The major treatment-related grade 3 AEs were neutrophil count decreased (4/58, 7%). No grade 4 or fatal AEs were observed. Treatment-related visual disorders, vomiting and nausea were rare and mild. **Conclusions:** In patients with ALK-positive NSCLC but naïve to any ALK inhibitor therapy, treatment with CH5424802 demonstrated generally mild toxicity and lead to high response rate of 93.5% and durable treatment beyond 10 months, expecting that treatment duration can be longer than that of crizotinib. CH5424802 is therefore a promising new ALK inhibitor for NSCLC. Clinical trial information: JapicCTI-101264.

8034 Poster Discussion Session (Board #23), Sun, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Lume-lung 2: A multicenter, randomized, double-blind, phase III study of nintedanib plus pemetrexed versus placebo plus pemetrexed in patients with advanced nonsquamous non-small cell lung cancer (NSCLC) after failure of first-line chemotherapy.

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Background: Nintedanib (N) is an oral inhibitor of VEGFR, FGFR, and PDGFR. This global phase 3 study investigated the safety and efficacy of N + pemetrexed (PEM) vs placebo (P) + PEM in patients (pts) with advanced, non-squamous NSCLC previously treated with chemotherapy. **Methods:** Pts were randomized 1:1 to N 200 mg po bid + PEM 500 mg/m^2 iv q21d (n=353, Arm A) or P + PEM (n=360, Arm B). Continuation until PD or unacceptable toxicity with N, P, PEM, or a combination was permitted. 1° endpoint was centrally reviewed PFS. The null hypothesis was tested on the ITT population after 394 events had occurred (two sided α=5%). 2° endpoints included OS, investigator-assessed PFS, response rate (RR), safety, and QoL. **Results:** Baseline pt characteristics were balanced between Arm A vs B (median age 59 y, female 45–42%, ECOG PS 1 62-61%, adenocarcinoma 95–93%, prior bevacizumab 8%). Based on a planned DMC futility analysis of investigator-assessed PFS, enrolment was halted after randomizing 713/1300 planned pts (no safety issues identified). Ongoing pts were unblinded and follow-up continued per protocol. Subsequent ITT analysis of the 1° endpoint (centrally reviewed PFS) favored Arm A vs B (median 4.4 vs 3.6 mo, HR 0.83 [95% CI: 0.7–0.99], p=0.04). Disease control was also significantly improved in N-treated pts (61 vs 53%, odds ratio 1.37, p=0.039). No difference in OS (HR 1.03) or RR (9%) was found. Exploratory analyses identified time since start of 1st-line therapy as a predictive marker of improved outcome with N + PEM (ASCO 2013). There was no increase in SAEs or G5 AEs with N + PEM. Addition of N to PEM resulted in a higher incidence of ≥G3 elevated ALT (23 vs 7%), elevated AST (12 vs 2%), and diarrhea (3 vs 1%), but no difference in ≥G3 hypertension, bleeding, thrombosis, mucositis, or neuropathy. **Conclusions:** The 1° endpoint was met even though the study was stopped prematurely. Treatment with N + PEM significantly improved centrally reviewed PFS vs P + PEM in pts with advanced non-squamous NSCLC previously treated with chemotherapy, and had a manageable safety profile. Clinical trial information: NCT00806819.

8035 Poster Discussion Session (Board #24), Sun, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

Randomized phase II trial of NGR-hTNF in combination with standard chemotherapy in previously untreated non-small cell lung cancer (NSCLC).

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Background: NGR-hTNF, a selective antivascular agent, induces at low dose an initial vascular normalization that greatly enhances the intratumoral chemotherapy uptake, with synergistic effects that were noted especially in combination with cisplatin and gemcitabine. **Methods:** Chemo-naive patients (pts) with advanced NSCLC were stratified by histology (nonsquamous or squamous) and PS (0 or 1) and randomly assigned to receive cisplatin 80 mg/m^2/d1 plus either pemetrexed 500 mg/m^2/d1 (nonsquamous) or gemcitabine 1,250 mg/m^2/d1+8 (squamous) every 3 weeks (q3w) for 6 cycles, with (arm A) or without (arm B) NGR-hTNF given at 0.8 μg/m^2/d1/q3w until progression. Progression-free survival (PFS) was primary aim (1-β=80%, 1-sided α=10%, n=102). Secondary aims comprised adverse events (AEs), response rate (RR), and overall survival (OS). **Results:** Baseline characteristics in arm A (n=62) vs B (n=59) were: median age: 62 vs 63 years; men: 37 vs 39; PS 1: 23 vs 23; squamous: 18 v 17; smokers: 41 vs 43. For the nonsquamous stratum, 299 cycles were given in arm A (mean 7.0; range 1-20) and 192 in arm B (4.8; 1-6), while for the squamous stratum, 113 in arm A (6.7; 1-31) and 52 in arm B (3.5; 1-6). Rates of grade 3/4 AEs were similar (arm A vs B): neutropenia 13% vs 18%, anaemia 7% vs 4% and fatigue 7% vs 11%. No grade 3/4 AEs related to NGR-hTNF or bleeding/pulmonary hemorrhage events were reported in the squamous subset. With median follow-up time of 24.2 months, median PFS (5.8 vs 5.6 months; HR=0.92), RR (25% vs 21%) and 1-year OS (53% vs 53%) were similar between the two treatment arms. However, by predefined analysis in the squamous stratum, median PFS was 5.6 months for arm A and 4.3 months for arm B (hazard ratio, HR=0.75) and median OS was 14.2 months for arm A and 9.7 months for arm B (HR=0.49; p=0.07). In pts with squamous histology, RR was 38% for arm A and 27% for arm B (odds ratio=1.6), while the median changes in tumor size on treatment from baseline to 2nd, 4th and 6th cycle for arm A vs B were -32% vs -20%, -41% vs -19%, and -42% vs -14%, respectively. **Conclusions:** Clinical tolerability and benefit were noted in squamous NSCLC with NGR-hTNF plus cisplatin and gemcitabine, which deserve further investigation. Clinical trial information: NCT00994097.

8036 Poster Discussion Session (Board #25), Sun, 8:00 AM-12:00 PM and 11:30 AM-12:30 PM

A phase II study of HSP90 inhibitor AUY922 and erlotinib (E) for patients (pts) with EGFR-mutant lung cancer and acquired resistance (AR) to EGFR tyrosine kinase inhibitors (EGFR TKIs).

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Background: AUY922 is a synthetic HSP90 inhibitor that degrades client onco-proteins including EGFR. Preclinical studies demonstrate HSP90 inhibitors are effective agents against models of AR in EGFR-mutant lung cancer cell lines and xenografts harboring the "gatekeeper" mutation EGFR T790M. Pts with EGFR mutations who develop AR often continue E with 2nd-line therapies to avoid "disease flare" associated with discontinuing TKI. This phase II study combines AUY922 and E for the treatment of pts with EGFR-mutant lung cancer and RECIST-progression on 1st-line EGFR TKIs. **Methods:** Eligible pts had EGFR mutations and developed AR (Jackman, *JCO* 2010) after treatment with EGFR TKIs. Pts underwent tumor biopsies after developing AR and prior to study entry. Pts received AUY922 70 mg/m^2 IV weekly and E 150 mg oral daily in 28-day cycles. Response assessment occurred at 4 weeks (wks), 8 wks, and every 8 wks thereafter. The primary objective was overall response rate (ORR, CR+PR) at 8 wks. A Simon mini-max design determined sample size (stage I: 16 pts ($\geq$2 responses needed to proceed to stage II), stage II: 9 pts; α=10%, β=10%, p0=10%, p1=30%). Tumor tissue from re-biopsy at study entry was analyzed for EGFR T790M. **Results:** Sixteen pts have been treated (10 women, median age 58 [range 47-76]). The median time on EGFR-TKI prior to the development of AR was 12 mo (range 2-42 mo). Seven pts had EGFR T790M confirmed by tumor re-biopsy. ORR was 2/16 (13%, 95% CI 2-37%). Both pts with PR had EGFR T790M. Four other pts had stable disease for at least 8 wks, two remain on study after more than 12 wks. Adverse events reported in $\geq$20% of pts were diarrhea, fatigue, myalgias, nausea, and transient flashing lights or night blindness. One pt each experienced grade 3 diarrhea and cardiac abnormalities. **Conclusions:** AUY922 and E is a well-tolerated regimen for pts with EGFR-mutant lung cancer and AR to EGFR TKIs. Two pts remain on study and 9 additional pts will be accrued in stage II; final response rate and survival outcomes will be reported. Supported by Novartis, Inc. Clinical trial information: NCT01259089.

8037 General Poster Session (Board #32A), Sat, 8:00 AM-11:45 AM

Combination chemotherapy with irinotecan and cisplatin (IP) for advanced large-cell neuroendocrine carcinoma (LCNEC) of the lung: A multicenter phase II study.

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Background: LCNEC and small cell lung cancer (SCLC) are recognized as high-grade neuroendocrine carcinoma of the lung. A differential diagnosis between LCNEC and SCLC using a tiny biopsy specimen is frequently difficult. Consequently, prospective clinical trials examining chemotherapy for advanced LCNEC have seldom been reported. We conducted a phase II study of combination chemotherapy with IP in patients (pts) with advanced LCNEC. **Methods:** The eligibility criteria included a chemotherapy-naïve status, a histological diagnosis of advanced LCNEC, an age of 20-75 years, and an ECOG PS of 0-1. Pts received I (60 mg/m^2, days 1, 8, and 15) and P (60 mg/m^2, day 1) every 4 weeks for up to 4 cycles. The primary endpoint was the response rate (RR). The sample size was determined to be 44, with a one-sided alpha of 0.1, a beta of 0.2, and expected and threshold values for the primary endpoint of 50% and 30%. **Results:** 44 pts from 11 institutes were enrolled between Jan 2005 and Nov 2011. The median age was 62.5 years; 21 pts had a PS of 0, and 35 pts were male. 5 pts had stage IIIB, 28 had stage IV, and 11 had recurrences after surgical resection. The RR was 54.5% (95% CI, 38.8-69.6). Grade 3 or 4 neutropenia was observed in 24 pts, but only 3 pts experienced febrile neutropenia. Other toxicities were mild and manageable. The median progression-free survival (PFS) was 5.9 months (95%CI, 5.5-6.3), and the median survival time (MST) was 15.1 months (95%CI, 11.2-19.0). Pathological specimens for a pre-planned central review were available for 41 pts. 30 pts were diagnosed as having LCNEC, whereas 10 pts were diagnosed as having SCLC, and 1 patient was diagnosed as having non-SCLC with a neuroendocrine morphology. Subgroup analyses were shown in the Table. **Conclusions:** Combination chemotherapy with IP was active in pts with advanced LCNEC, but the RR and the overall survival period in pts with LCNEC seemed to be inferior to those in pts with SCLC. Clinical trial information: UMIN000004796.

	Central pathological review (n=40)		
	LCNEC (n=30)	SCLC (n=10)	P
RR (%) (95%CI)	46.7 (28.3-65.7)	80 (44.4-97.5)	0.0823
Median PFS (months) (95%CI)	5.8 (3.8-7.8)	6.2 (5.2-7.2)	0.382
MST (months) (95%CI)	12.6 (9.3-16.0)	17.3 (11.2-23.3)	0.047

8038 General Poster Session (Board #32B), Sat, 8:00 AM-11:45 AM

A randomized phase II trial comparing continuation maintenance therapy with pemetrexed and switch maintenance therapy with docetaxel after first-line therapy with carboplatin and pemetrexed in patients with advanced nonsquamous non-small cell lung cancer.

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Background: Emerging evidence suggests that maintenance chemotherapy could prolong survival in patients with advanced non-small-cell lung cancer (NSCLC), whereas the optimal treatment strategy remains controversial. **Methods:** We conducted a randomized phase II study to compare the efficacy and safety of continuation maintenance with pemetrexed (500 mg/m^2) and switch maintenance with docetaxel (60 mg/m^2) in patients with non-squamous NSCLC who achieved disease control after first-line chemotherapy with four cycles of carboplatin (AUC 6) and pemetrexed (500 mg/m^2). **Results:** Eighty-five patients participated in the study, and 26 and 25 patients were randomized to the pemetrexed and the docetaxel maintenance therapies, respectively. The docetaxel group showed a trend toward longer progression-free survival (median 8.2 months, 95% CI; 3.9-12.2 months) compared with the pemetrexed group (median 4.1 months, 95% CI; 3.0-6.1 months), but not significantly (log-rank $p=0.084$). Grade 3/4 hematologic toxicity was significantly more frequent in the docetaxel group (80%) than the pemetrexed group (20%, $p<0.0001$). **Conclusions:** Continuation maintenance with pemetrexed after induction therapy with carboplatin and pemetrexed may be an efficacious treatment with less toxicity. In contrast, switch maintenance with docetaxel frequently causes severe hematologic toxicity but may be more efficacious. Further studies are warranted to evaluate the risks and benefits of maintenance therapies. Clinical trial information: 000004075.

8039 General Poster Session (Board #32C), Sat, 8:00 AM-11:45 AM

An analysis of the prevalence of *HER2* and *KRAS* mutations, and ALK rearrangements and clinical outcomes in Cancer and Leukemia Group B [CALGB (Alliance)] trial 30406 in advanced non-small cell lung cancer (NSCLC).

Tom Stinchcombe, Lynette M. Sholl, Xiaofei F. Wang, Lin Gu, Mark A. Socinski, Scott J. Rodig, Marzia Capelletti, Jeffrey Crawford, Martin J. Edelman, Miguel Angel Villalona-Calero, Robert Arthur Kratzke, Everett E. Vokes, Vincent A. Miller, Pasi Antero Janne, Alliance; The University of North Carolina at Chapel Hill, Chapel Hill, NC; Dana-Farber Cancer Institute/Brigham and Women's Hospital, Boston, MA; Cancer and Leukemia Group B Statistical Center, Durham, NC; University of Pittsburgh Medical Center, UPMC Cancer Pavilion, Pittsburgh, PA; Department of Pathology, Division of Hematopathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Duke University Medical Center, Durham, NC; University of Maryland, Marlene and Stewart Greenebaum Cancer Center, Baltimore, MD; The Ohio State University Wexner Medical Center, Columbus, OH; University of Minnesota, Minneapolis, MN; The University of Chicago Medicine and Biological Sciences, Chicago, IL; Foundation Medicine, Inc., Cambridge, MA

Background: CALGB (Alliance) 30406 was a randomized phase II trial that investigated erlotinib alone or in combination with carboplatin and paclitaxel in patients (pts) with a never or light smoking history with advanced NSCLC. Tissue collection was mandatory. **Methods:** Between August 2005 and April 2009 188 pts were enrolled. Tumor specimens were assessed using ALK immunohistiochemistry (IHC; clone D5F3; Cell Signaling); *KRAS* and *HER2* mutations were tested. **Results:** The rate of mutations was: *KRAS* 10% (17/164), *HER2* 2% (3/164), and ALK + 7% (8/114). Given the small numbers of *KRAS*, *HER2* and ALK positives, the analysis combines data from both arms. Pts with ALK + compared to ALK- NSCLC had an inferior ORR and PFS (Table). No statistically significant differences in ORR, PFS, OS between pts with *KRAS* or *HER2* mutant and wild-type NSCLC were observed. In multivariate analysis pts with ALK+ compared to ALK- tumors experienced a statistically significant worse PFS (HR=2.67, p=0.0114) but not OS (HR=1.48, p=0.3217). One pt was identified as having an *EGFR* exon 21 mutation and ALK +; the pt experienced a best response of progressive disease, a PFS of 2.9 months, and OS of 17.4 months. **Conclusions:** (1) Pts with ALK+ compared to ALK- NSCLC have a lower ORR, worse PFS, but not OS with erlotinib alone or with carboplatin and paclitaxel. (2) The prevalence *ALK*+, *KRAS* and *HER2* mutations observed was 7%, 10% and 2%, respectively. Clinical trial information: 00126581.

	ORR (%) (95% CI)	PFS (months) (95% CI)	OS (months) (95% CI)
ALK (n=114)			
Positive (n=8)	0 (0 – 36.9)	2.2 (0.6 – 6.6)	12.9 (0.9 – 26.1)
Negative (n=106)	38.7 (29.4 – 48.7)	6.3 (5.0 – 8.0)	20.7 (15.0 – 27.8)
2-sided p value*	0.0491	0.0039	0.1948
KRAS (n=164)			
MUT (n=17)	29.4 (10.3 – 56.0)	4.0 (2.8 – 12.4)	18.0 (7.7 – 39.9)
WT (n=147)	42.2 (34.1 – 50.6)	6.7 (5.3 – 8.0)	23.8 (18.7 – 27.9)
2-sided p value*	0.4359	0.1318	0.4615
HER2 (n=164)			
MUT (n=3)	0 (0 – 70.8)	4.2 (1.2 – 9.7)	17.5 (2.9 – 27.8)
WT (n=161)	41.6 (33.9 – 49.6)	6.6 (5.0 – 7.4)	23.7 (18.4 – 27.8)
2-sided p value*	0.2706	0.2732	0.1911

* P values of testing ORR difference between positive vs. negative/MUT vs. WT are from Fisher's exact tests, while those for PFS and OS are from log-rank tests.

8040 General Poster Session (Board #32D), Sat, 8:00 AM-11:45 AM

Clinical trial risk reduction in non-small cell lung cancer though the use of biomarkers and receptor-targeted therapies.

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Background: We analyzed the risk of clinical trial failure duringnon-small cell lung cancer (NSCLC) drug development between 1998 and 2012. **Methods:** NSCLC drug development was investigated using trial disclosures from publically available resources. Compounds were excluded from the analysis if they began phase I clinical testing before 1998 and if they did not use treatment relevant endpoints. Analysis was conducted in regards to treatment indication, compound classification and mechanism of action. Costs of clinical drug development for advanced NSCLC were calculated using industry data and assumptions, a 9% yearly discount rate and assuming a clinical trial length of 2.5 years for phase I trials, 4 years for phase II trials, 5 years for phase III trials and an average of 5 phase I trials, 7 phase II trials, and 4 phase III trials per approved drug. All funding costs are in US dollars (USD). **Results:** 2,407 clinical trials met search criteria. 676 trials and 199 unique compounds met our inclusion criteria. The likelihood, or cumulative clinical trial success rate, that a new drug would pass all phases of clinical testing and be approved was found to be 11%, which is less than the expected industry aggregate rates (16.5%). The success of phase III trials was found to be the biggest obstacle for drug approval with a success rate of only 28%. Biomarker-guided targeted therapies (with a success rate of 62%) and receptor targeted therapies (with a success rate of 31%) were found to have the highest likelihood of success in clinical trials. The risk-adjusted cost for NSCLC clinical drug development was calculated to be 1.89 billion US dollars. Use of biomarkers decreased drug development cost by 26% to 1.4 billion US dollars. Potential savings may be even higher if fewer clinical trials are required for successful development. **Conclusions:** Physicians that enroll patients in NSCLC trials should prioritize their participation in clinical trial programs that involve either a biomarker or receptor targeted therapy, which appear to carry the best chances for a successful treatment response. Given the high adjusted cost of clinical testing alone in NSCLC, efforts to mitigate the risk of trial failure need to explore these factors more fully.

8041 General Poster Session (Board #32E), Sat, 8:00 AM-11:45 AM

Effect of primary tumor size in patients with metastatic non-small cell lung cancer (NSCLC).

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Background: Primary tumor size is a known prognostic factor for patients with early stage NSCLC treated with either surgery or radiation therapy. Although tumor volume has been associated with outcomes in patients with metastatic disease, it is labor intensive and rarely reported outside of a clinical trial. Since the primary tumor size is more commonly described, we evaluated its prognostic impact in patients with metastatic disease. **Methods:** The SEER was searched for patients with stage M1b NSCLC, with known tumor (T), lymph node (N) status, and diagnosed between 2004 and 2008. Patients with T0 and malignant pleural effusion were excluded. Tumor size is reported as the largest diameter and was subdivided into S1 (0.1-3 cm), S2 (3.1-5 cm), S3 (5.1-7 cm) and S4 (7.1-20 cm), roughly corresponding to T1, T2a, T2b and T3. Overall survival (OS) was estimated by the Kaplan-Meier method, while the hazard ratios (HR) were estimated and compared by Cox proportional hazard models. **Results:** Tumor size was available in 21879 (84.4%) out of 25919 patients with complete TNM staging. The frequencies of S1, S2, S3 and S4 were 33.4%, 33.8%, 17.1% and 13.7% respectively. 1-year OS rates for S1 to S4 were 34%, 27.9%, 24.0% and 19.0% respectively. Primary tumor size was an independent predictor for OS after adjustment for age, gender, race, histology, T and N status ($p < 0.0001$). The decreased OS from each subsequent category of tumor size was statistically significant in both univariate and multivariable analyses (Table). **Conclusions:** Primary tumor size is readily available and represents a significant prognostic factor for survival in patients with stage M1b NSCLC, independently of T and N status.

Comparisons	Univariate analysis Hazard ratio (95% CI), p value	Multivariable analysis Hazard ratio (95% CI), p value
S1 vs S2	0.84 (0.81-0.87), $p < 0.0001$	0.89 (0.85-0.93), $p < 0.0001$
S2 vs S3	0.89 (0.85-0.93) $p < 0.0001$	0.90 (0.87-0.94), $p < 0.0001$
S3 vs S4	0.85 (0.81-0.90), $p < 0.0001$	0.87 (0.83-0.92), $p < 0.0001$
S1 vs S4	0.65 (0.62-0.67), $p < 0.0001$	0.70 (0.67-0.74), $p < 0.0001$

8042 General Poster Session (Board #32F), Sat, 8:00 AM-11:45 AM

A phase II trial comparing pemetrexed with gefitinib as the second-line treatment of nonsquamous NSCLC patients with wild-type EGFR (CTONG0806).

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Background: Pemetrexed or gefitinib is one of the standard second-line treatments for advanced non-squamousNSCLC in East Asia. The CTONG 0806 a multi-center, randomized, controlled, open-label phase II trial was designed to explore the efficacy of pemetrexed versus gefitinib as the second-line treatment in advanced NSCLC patients without EGFR mutation. **Methods:** The patients with locally advanced or metastatic, non-squamous NSCLC previously treated with platinum-based chemotherapy and no EGFR mutation in exons 18-21 were enrolled. Patients were 1:1 randomized to receive either gefitinib 250 mg per oral every day (G arm) or pemetrexed 500 mg/m^2 iv day 1 with vitamin B12 and folic acid supplement every 21 days (P arm) until disease progression, unacceptable toxicity, or discontinuation of treatment due to other reason. The primary endpoint was progression-free survival (PFS). The secondary endpoints were 4-month and 6-month progression-free survival rate, overall survival (OS), objective response rate (ORR), quality of life using the FACT-L questionnaire and safety, EGFR and K-ras mutation status were evaluated and correlated with outcomes. **Results:** From Feb. 2009 to Aug. 2012, 157 evaluable patients were randomized (81 cases in G arm and 76 in P arm). Baseline age, gender, and ECOG performance status were balanced between arms. The primary endpoint of PFS was met with 1.6 months for G arm versus 4.8 months for P arm, the HR is 0.51 (95% CI 0.36~0.73, P$<$0.001). Overall response rates were 14.7 % and 13.3 % (P$=$0.814) and DCR were 32.0% and 61.3% (P$<$0.001) for G arm and P arm, respectively. OS data were not yet mature. More skin rash and diarrhoea were seen in G arm, but more fatigue and ALT increased in P arm. CTCAE grade 3 or 4 of AEs was 12.3% in G arm and 32.9% in P arm (p$=$0.002). The further analyses of efficacy evaluated by IRR and biomarkers analysis will be presented on the ground. **Conclusions:** CTONG0806 is the first trial to show significant improvements in PFS and DCR with pemetrexed compared with gefitinib in second-line setting for advanced NSCLC with EGFR wild type. Patients with EGFR wild type did not benefit from EGFR TKI gefitinb in second-line setting. Clinical trial information: NCT00891579.

8043 General Poster Session (Board #32G), Sat, 8:00 AM-11:45 AM

Prospective randomised phase II trial of oral vinorelbine (NVBo) and cisplatin (P) or pemetrexed (Pem) and P in first-line metastatic or locally advanced non-small cell lung cancer (M or LA NSCLC) with nonsquamous (Non SCC) histological type. NAVoTRIAL01: Final results.

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Background: NVBo+P is considered as a standard treatment in M or LA NSCLC. The recent approval of Pem+P as front line chemotherapy (CT) for non SCC demonstrates that today, histology could become a "new guidance" to treat patients (pts). The importance of histological types was highlighted in a phase III trial (Scagliotti. *JCO* 2008). Moreover, the higher chemosensitivity of non SCC is recognised and reported with other chemotherapies (Ardizzoni. *JNCI* 2007). In GLOB 3 study, NVBo+P also showed better survival in adenocarcinoma (11.7m) than in SCC (8.9m) (Tan. *Ann Oncol*. 2009). This trial was set up to assess the efficacy of NVBo+P (Arm A) and Pem+P (Arm B) for pts with Non SCC histological type, evaluated in terms of Disease Control Rate (DCR) (SD+PR+CR). **Methods:** Pts were randomised to receive q3w NVBo 80 mg/m² D1D8 (60 at Cycle 1) + P 80 mg/m² D1 (Arm A) or Pem 500 mg/m² + P 75 mg/m² D1 (Arm B). After 4 cycles of combination, pts with DCR received single agent NVBo (Arm A) or PEM (Arm B) as maintenance until progression or toxicity. Pts were randomised on a 2/1 basis and stratified according to stage (IIIB - IV - relapse), non SCC confirmed by histology or cytology, gender, smoking status and centre. **Results:** From 11/09 to 02/11, 153 pts were randomised to Arm A (102 pts) or Arm B (51 pts). DCR after combination and maintenance was 75.0% (95% CI, 65.3 to 83.1) in Arm A and 76.5% (95% CI, 62.5 to 87.2) in Arm B. Median PFS was 4.2 (95% CI, 3.6 to 4.7) and 4.3 months (95% CI, 3.8 to 5.6) in Arm A and Arm B, respectively. Median OS was 10.2 months (95% CI, 7.8 to 11.9) and 10.8 months (95% CI, 7.0 to16.4) in Arm A and Arm B, respectively. During the combination period grade 3/4 neutropenia was 44.0% in Arm A and 18.3% in Arm B but febrile neutropenia was 2% in both arms; grade 3/4 thrombopenia was 0% and 6% in Arm A and Arm B, respectively. **Conclusions:** Even if the current results should be confirmed in a phase III study, the choice of a platinum-based doublet with oral vinorelbine as front-line chemotherapy could be a useful alternative in non SCC. Clinical trial information: 2009-012001-19.

8044 General Poster Session (Board #32H), Sat, 8:00 AM-11:45 AM

Serum and tumor biomarkers to predict outcome in the eLung trial, a multicenter, randomized phase IIb study of standard platinum doublets (PD) plus cetuximab (CET) as first-line treatment of advanced non-small cell lung cancer (NSCLC).

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Background: The eLung trial randomized chemotherapy naïve advanced NSCLC patients (pts) to 1 of 3 PD and concurrent CET followed by CET maintenance until progression, stratified by non-squamous (NSQ) and squamous (SQ) histology. Primary outcome results were reported (ESMO, Schwartzberg 2012). Pre-treatment tumor tissue and serum samples were prospectively collected. **Methods:** Tumor samples were analyzed for H-score (graded 0-300), calculated by the intensity and number of cells expressing EGFR by IHC; a score of >200 was considered high (Pirker 2011). Mutation analysis of EGFR and KRAS was performed by PCR. The VeriStrat multivariate serum protein test was performed on available serum samples assigning good and poor classifications (Taguchi 2007). **Results:** Of 601 pts enrolled on the trial, 378 consented to blood/tissue or both. The available tissue (N=210) and serum subsets (N=203) had similar demographics and survival outcome to the full trial set. Results for biomarkers/cohorts in the Table demonstrate that VeriStrat was highly significant for OS in all pts and NSQ, while H-score and EGFR mutations were significant only in NSQ. In adjusted Cox analysis VeriStrat was an independent predictor for OS, HR=.665, p=.026; H-score was not. **Conclusions:** VeriStrat classification significantly correlated with survival outcome in all pts treated with PD and CET and the NSQ subset; tissue biomarkers correlated in NSQ only. Further evaluation of these markers is warranted.

Biomarker	N	OS, median, months	OS, 95% CI, months	Log-rank p
All patients				
H-score high	40	10.0	5.3-16.2	.334
H-score low	170	9.4	7.5-10.7	
VeriStrat good	142	10.9	9.5-12.9	<.0001
VeriStrat poor	61	6.4	4.0-9.0	
NSQ subgroup				
H-score high	17	30.6	6.2-35.1	.033
H-score low	108	9.6	6.4-11.7	
VeriStrat good	99	11.4	9.0-14.9	.001
VeriStrat poor	28	6.4	3.6-12.1	
K-RAS mutated	42	11.1	6.4-20.0	.998
K-RAS WT	88	10.5	7.0-13.2	
EGFR mutated	12	30.6	12.8-undef.	.010
EGFR WT	117	10.4	6.3-11.7	
SQ subgroup				
H-score high	23	5.6	3.6-9.1	.322
H-score low	62	8.3	6.0-10.7	
VeriStrat good	43	10.0	7.1-12.9	.059
VeriStrat poor	53	6.4	3.6-9.0	

8045 General Poster Session (Board #33A), Sat, 8:00 AM-11:45 AM

Retrospective evaluation of RET biomarker status and outcome to vandetanib in four phase III randomized NSCLC trials.

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Background: The prevalence of the tumorigenic *KIF5B:RET* fusion gene in NSCLC tumors has been estimated at 0.2–6% (Jiu *et al* 2012; Lipson *et al* 2012). We retrospectively analyzed tumor samples from 4 Phase III NSCLC trials of vandetanib, a TKI that selectively targets RET, VEGFR and EGFR signaling, to determine the prevalence of *RET* fusions and other RET biomarkers, and any potential association with outcome to vandetanib (V). **Methods:** The studies evaluated were ZODIAC (NCT00312377; docetaxel ± V 100mg), ZEAL (NCT00418886; pemetrexed ± V 100mg), ZEPHYR (NCT00404924; V 300mg vs placebo) and ZEST (NCT00364351; V 300mg vs erlotinib). RET biomarkers evaluated included *RET* fusions (including *KIF5B:RET*) and *RET* gene copy number (assessed by a 4-probe FISH assay), as well as RET protein expression (by IHC). **Results:** Of 4089 patients randomized across the 4 studies, 1291 and 1234 had tumor samples available for FISH and IHC analysis, respectively, with evaluable data obtained for 944 and 1102. *RET* fusions (in >10% of tumor cells) were detected in 7 of 944 samples (vandetanib, n=3; comparator, n=4), at a prevalence of 0.7% (95% CI, 0.3–1.5%). None of the 3 vandetanib-treated *RET* fusion-positive patients had an objective RECIST response, although there was radiologic evidence of tumor shrinkage in 2. Overall, 2.8% (n=26) of samples had *RET* amplification (innumerable *RET* clusters, or ≥7 copies in >10% tumor cells), 8.1% (n=76) had lower *RET* gene copy number gain (4–6 copies in ≥40% tumor cells) and 8.3% (n=92) were RET expression positive (signal intensity ++ or +++ in >10% of tumor cells). There was no difference in ORR between vandetanib and comparator for the *RET* amplification-positive subset (both 8.3% [1/12]), the *RET* copy number gain subset (9.8% [4/41] vs 9.1% [3/33], respectively) or the RET protein expression-positive subset (15.2% [7/46] and 13.6% [6/44], respectively). **Conclusions:** The prevalence of *RET* fusions was estimated at 0.7%. There were too few vandetanib-treated patients with *RET* fusions to make any firm conclusion regarding association with efficacy. Evidence from the other RET biomarkers tested suggested that these do not infer a differential advantage in patients treated with vandetanib. Clinical trial information: NCT00312377; NCT00418886; NCT00404924.

8046 General Poster Session (Board #33B), Sat, 8:00 AM-11:45 AM

Association between baseline tumor dimensions and survival in advanced non-small cell lung cancer (NSCLC).

Daniel H. Ahn, Suzanne Eleanor Dahlberg, Alan Sandler, Michael C. Perry, Joan H. Schiller, Julie R. Brahmer, David H. Johnson, David E. Gerber, Eastern Cooperative Oncology Group; The University of Texas Southwestern Medical Center, Dallas, TX; Dana-Farber Cancer Institute, Boston, MA; Knight Cancer Institute, Oregon Health and Science University, Portland, OR; Ellis Fischel Cancer Center, University of Missouri, Columbia, MO; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; UT Southwestern Medical Center, Dallas, TX

Background: It is not known to what extent radiographic tumor burden is associated with survival in patients with advanced NSCLC. The purpose of this study is to assess whether baseline tumor dimensions are associated with patient survival in advanced NSCLC. **Methods:** Data were derived from the Eastern Cooperative Oncology Group (ECOG) 4599 trial of carboplatin-paclitaxel (CP) ± bevacizumab (B) for advanced nonsquamous NSCLC. Associations between the Response Evaluation Criteria in Solid Tumors (RECIST) baseline sum longest diameter (BSLD) and progression-free survival (PFS) and overall survival (OS) were evaluated using univariate and multivariable Cox regression models. **Results:** 759 of 850 patients (89%) enrolled in E4599 had measurable disease and were included in the analysis. 76% of patients were age $<$ 70 years, 46% were female, and 86% were white. Median number of target lesions was 2; median BSLD was 7.5 cm. In univariate Cox models, BSLD predicted OS (HR 1.41; $P<0.001$) and had a trend toward association with PFS (HR 1.14; $P=0.08$). OS was 12.6 months (mos) for BSLD $<$ 7.5 cm, compared to 9.5 mos for BSLD $\geq$ 7.5 cm. This association persisted across both treatment groups (CP: median OS 11.5 vs 8.5 mos; CP+B: median OS 14.1 vs 10.7 mos), when BSLD was categorized according to quartile (median OS: 13.3, 11.5, 11.6, and 8.3 mos; $P<0.001$), and in a multivariable model controlling for prognostic factors and the presence and site of extrathoracic disease (OS HR 1.24; $P=0.01$). **Conclusions:** Radiographic disease burden, as determined by RECIST BSLD, is associated with survival in the E4599 trial. If validated in other populations, this parameter merits consideration in the stratification of patients for clinical trials and may provide important prognostic information for patients and clinicians.

8047 **General Poster Session (Board #33C), Sat, 8:00 AM-11:45 AM**

Occurrence of HER2 amplification in EGFR-mutant lung adenocarcinoma with acquired resistence to EGFR-TKIs.

Giuseppe Altavilla, Carmela Arrigo, Chiara Tomasello, Mariacarmela Santarpia, Patrizia Mondello, Sara Benecchi, Vincenzo Pitini; Medical Oncology University of Messina, Messina, Italy; Medical Oncology, Messina, Italy

Background: Patients with EGFR-mutant lung adenocarcinoma develop progression of disease on TKIs therapy after a median of 12 months;this acquired resistance is mainly due to a secondary mutation in EGFR (T790 M) in about 50% of patients, amplification of MET in 15%, PIK3CA mutations in 5%, an unknown mechanism in almost 30% and a SCLC transformation in some pts. Recently, Takezawa and colleagues pointed out that HER2 amplification is a mechanism of acquired resistance to EGFR inhibition in EGFR-mutant lung cancers without EGFR T790M mutation. To aid in identification and treatment of these patients we examined a cohort of patients whose cancers were assessed with tumor biopsies at multiple times before and after their treatment with TKIs. **Methods:** 41 lung adenocarcinomas pts. (20 male, 21 female, median age 55 years) with EGFR mutations at 19 or 21 exons received TKIs as first line of treatment. 31 pts. (75%) showed a clinical response and relapsed after a mTTP of 12 months. At the time of relapse a new biopsy was performed, histologic samples were reviewed to re-confirm the diagnosis, EGFR, MET and HER-2 amplification were identified by FISH, while EGFR mutations have been tested by DNA sequencing. **Results:** At the time that drug resistence was acquired all 31 pts. retained their original activating EGFR mutations, 16 pts. developed EGFR T790M resistance mutation with pronunced EGFR amplification in 5, 4 pts. developed MET amplification, 3 pts. were found to have a diagnosis of small cell lung cancer. HER2 amplification was observed in four pts. (13%), with dramatic progression and a median OS of 5 months after treatment with CDDP + pemetrexed. Notably all 4 cases were EGFR T790M negative. **Conclusions:** Among pts. with acquired resistence to EGFR TKIs the presence of HER2 amplification defines a clinical subset with a more adverse prognosis and rapid progression. Interestingly, recent data suggest that afatinib combined with cetuximab could have promising activity in pts. with acquired resistance due to HER2 amplification.

8048 General Poster Session (Board #33D), Sat, 8:00 AM-11:45 AM

Exploratory analysis of angiotensin converting enzyme (ACE) and aldosterone (Ald) serum levels as prognostic and predictive biomarkers on the NCIC CTG BR24 trial.

Jair Bar, Keyue Ding, Huijun Zhao, Scott Andrew Laurie, Lei Han, Frances A. Shepherd, Christina L. Addison, Glenwood D. Goss, Jim Dimitroulakos, Penelope Ann Bradbury; Sheba Medical Center, Tel HaShomer, Israel; NCIC Clinical Trials Group, Kingston, ON, Canada; Ottawa Hospital Research Institute, Ottawa, ON, Canada; Ottawa Hospital Cancer Centre, Ottawa, ON, Canada; NCIC Clinical Trials Group, Queen's University, Kingston, ON, Canada; Princess Margaret Hospital, Toronto, ON, Canada; Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada; The Ottawa Hospital Cancer Center, Ottawa, ON, Canada

Background: Benefit from angiogenesis inhibitors (AI) has been linked to high blood pressure. One of the main determinants of blood pressure is the renin-angiotensin axis. We undertook an exploratory, retrospective analysis of ACE and Ald serum levels on specimens banked during the conduct of the BR24 study. The aim was to evaluate these markers for their prognostic significance and their predictive value regarding Cediranib (Ced) treatment. **Methods:** The NCIC CTG BR24 study randomized advanced non-small cell lung cancer patients (pts) to carboplatin and paclitaxel (CP) +/- Ced. ACE and Ald serum levels were retrospectively tested on baseline samples using commercial ELISA kits. A graphic method, differentiating treatment effect by the range of marker, was used to determine cutoff points (*JCO* 2010, 28: 5247). Exploratory analyses were performed to correlate biomarkers levels with pts characteristics and overall survival (OS). Association between categorical variables was assessed by Chi-square test or Fisher's exact test; time to event correlation with biomarkers was tested using a Cox regression model. Potential confounding factors including medications were integrated into the statistical model. **Results:** Biomarker data was available in 226 of 296 randomized pts. The tested pts vs. all the randomized pts were more likely to have a lower performance status (PS, p=0.03), a normal LDH (p=0.05) and to be ever-smokers (p=0.015). The determined cutoffs were ACE: 115ng/ml and Ald: 250 pg/ml. High ACE was associated with a better PS (p=0.03). High ACE levels were prognostic for longer OS (adjusted HR 0.52 [95%C.I. 0.29-0.92], p=0.025). High ACE pts had no OS benefit (HR 1.27 [95% C.I. 0.78–2.08], p=0.34), while low ACE predicted OS benefit from the addition of Ced to CP (HR 0.64 [95%CI 0.42-0.97], p=0.03). Interaction p value=0.03; this remained significant after adjustment in multivariate analyses. Ald levels were neither prognostic nor predictive. **Conclusions:** This exploratory analysis suggests high ACE serum levels maybe prognostic for better OS, while low ACE may predict benefit from Ced when added to CP.

8049 **General Poster Session (Board #33E), Sat, 8:00 AM-11:45 AM**

Predictors of survival for younger patients (pts) less than 50 years of age with non-small cell lung cancer (NSCLC): A California Cancer Registry (CCR) analysis.

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Background: Lung cancer is often seen in older pts, with a median age at diagnosis of 70 years (yrs). Epidemiology and outcomes are reportedly different among younger NSCLC pts (< 50 yrs). We hypothesized that these pts have longer cause-specific survival (CSS) and that baseline clinical features prognostic for CSS would be identified. **Methods:** NSCLC pts in the CCR diagnosed between 1/98 through 12/09 were included. The primary outcome was CSS. Hazard ratios (HR) for CSS were calculated using Cox Proportional Hazards (PH) models for all ages & for pts <50 years, adjusted for baseline variables. **Results:** We identified 132,671 lung cancer pts: 114,451 (86.3%) had NSCLC. 6,389 (5.6%) were < 50 yrs (median, 46 yrs). Demographics: White (3,557, 56%); Histology: AdenoCA (AC) (3,406, 53%), Squamous (781, 12%), BAC (291, 4.6%); Stage IV (3,655, 57%). Fewer pts < 50 yrs were diagnosed in later yrs: from 37% in '98-'01 to 29% in '06-'09. Results of Cox PH models for all ages and < 50 years are shown. **Conclusions:** The relative proportion of pts < 50 yrs has declined by 22% over the past decade. Age < 50 years was an independent predictor of improved CSS (HR 0.83, p<0.001). In younger pts, AC histology was not prognostic for CSS (versus squamous) despite known differences in clinical and biologic behavior between subtypes.Importantly, clinical variables strongly prognostic for CSS were identified in pts < 50 yrs.

	All pts		Pts < 50 yrs of age	
Selected clinical variables*	HR	P value	HR	P value
Female	0.86	<0.001	0.84	<0.001
Age < 50	0.83	<0.001		N/A
Rural	0.99	0.375	1.09	0.166
Stage				
II	1.75	<0.001	1.94	<0.001
III	2.24	<0.001	2.49	<0.001
IV	3.51	<0.001	4.37	<0.001
Primary treatment				
Surgery	0.22	<0.001	0.23	<0.001
ChemoRT	0.53	<0.001	0.53	<0.001
Year of diagnosis				
2002-05	0.91	<0.001	0.89	<0.001
2006-09	0.82	<0.001	0.73	<0.001
Socioeconomic status (SES)				
Mid (3)	0.96	<0.001	0.95	0.173
High (4,5)	0.90	<0.001	0.83	<0.001
Histology				
AC	0.93	<0.001	0.99	0.788
NOS	1.03	0.0049	1.04	0.497
BAC	0.66	<0.001	0.86	0.112
Large cell	1.1	<0.001	1.09	0.312

* Referent groups: Male, Age >/= 50, Urban, Stage I, No treatment, 1998-2001, Lowest SES (1,2), and Squamous.

8050 General Poster Session (Board #33F), Sat, 8:00 AM-11:45 AM

Success and failure rates of tumor genotyping techniques in routine pathologic samples with non-small cell lung cancer.

Paul A VanderLaan, Norihiro Yamaguchi, Erik Folch, Michael S Kent, Sidharta P Gangadharan, Adnan Majid, Michael Goldstein, Mark Huberman, Daniel Botelho Costa; Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA

Background: Identification of somatic molecular alterrations in NSCLC has become evidence-based practice. The success and failure rate of using commercially-available tumor genotyping techniques in routine day-to-day NSCLC pathology samples is not well described. We sought to evaluate the success and failure rate of *EGFR* mutation, *KRAS* mutation and *ALK* FISH. **Methods:** Clinicopathologic data, tumor genotype success and failure rates were retrospectively compiled and analyzed from 381 patient-tumor samples sent for routine tumor genotype in clinical practice. **Results:** Mean age was 65, 61.2% women, 75.9% white, 27.8% never-smokers, 73.8% had advanced NSCLC and 86.1% adenocarcinoma histology. Tumor tissue was obtained from surgical biopsies in 48.8%, core biopsies in 17.9% and as cell blocks from aspirates/fluid in 33.3%. Anatomic sites for tissue collection included lung (49.3%), lymph nodes (22.3%), pleura (11.8%), bone (6.0%), brain (6.0%), among others. In the 207 tumors in which the three tests were ordered concurrently, the success rate for *EGFR* was 92.3%, for *KRAS* 91.8% and for *ALK* FISH 89.9%. The highest failure rates were observed when the tissue was obtained from core biopsies (30.8%, 20.5% and 30.8% for *EGFR*, *KRAS* and *ALK* tests, respectively) and bone specimens (23.1%, 15.4% and 23.1% for *EGFR*, *KRAS* and *ALK* tests, respectively). In specimens obtained from bone, the failure rate was significantly higher in non-surgical than surgical specimens (40% vs 0%, $p=0.024$ for *EGFR*) and decalcified than non-decalcified samples (60% vs 5.5%, $p=0.021$ for *EGFR*). **Conclusions:** The success rate of multiple tumor genomic analyses techniques for *EGFR*, *KRAS* and *ALK* gene abnormalities using routine lung cancer tissue samples was ~90%. The highest failure rates occurred in tumors obtained from core biopsies and in bone samples from core biopsies with decalcification; specimens that may need to be scrutinized before submission to molecular studies. Tumor genotype techniques are feasible in most other samples obtained with current tumor acquisition methods, and therefore expansion of routine tumor genotype into the care of patients with NSCLC may not require special tissue acquisition or manipulation.

8051^ General Poster Session (Board #33G), Sat, 8:00 AM-11:45 AM

A randomized open-label phase II study evaluating antitumor activity of the survivin antisense oligonucleotide LY2181308 (LY) in combination with docetaxel (DO) for second-line treatment of patients with non-small cell lung cancer (NSCLC) using change in tumor size (CTS).

Denis Charles Talbot, Fiona Helen Blackhall, Dariusz Kowalski, Rodryg Ramlau, Gerold Bepler, Francesco Grossi, Christian A. Lerchenmuller, Mary Colleen Pinder, Jorg Mezger, Sarah Danson, Sophie Callies, Valerie Andre, Mayukh Das, Michael M. F. Lahn, Ronald B. Natale; Department of Oncology, Oxford University Hospitals Trust, Churchill Hospital, Oxford, United Kingdom; Manchester Lung Cancer Group, Manchester University and Christie Hospital, Manchester, United Kingdom; Memorial Cancer Centre of Oncology and Institute Department of Lung Cancer and Chest Tumours, Warsaw, Poland; Poznan University of Medical Sciences, Wielkopolskie Centrum Pulmonologii i Torakochirurgii, Poznan, Poland; Karmanos Cancer Institute, Wayne State University, Detroit, MI; Lung Cancer Unit, National Institute for Cancer Research, Genova, Italy; Gemeinschaftspraxis für Hämatologie und Onkologie, Münster, Germany; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; St. Vincentius-Kliniken, Karlsruhe, Germany; Sheffield Experimental Cancer Medicine Centre, Academic Unit of Clinical Oncology, University of Sheffield, Weston Park Hospital, Sheffield, United Kingdom; Global PK/PD Department, Eli Lilly and Company, Erl Wood, United Kingdom; Global Statistical Sciences, Eli Lilly and Company, Erl Wood, United Kingdom; Eli Lilly and Company, Basingstoke, United Kingdom; Division of Early Phase Oncology Clinical Investigation, Eli Lilly and Company, Indianapolis, IN; Cedars-Sinai Outpatient Cancer Center, Los Angeles, CA

Background: Resistance to chemotherapy in progressive NSCLC is associated with overexpression of antiapoptotic proteins including survivin. Down-regulation of survivin can sensitize NSCLC to DO in vitro and in xenograft studies. On the basis of preclinical/phase I results we examined antitumor activity of DO+LY compared with DO alone. **Methods:** Key eligibility criteria: ECOG PS 0-1, stage IIIB/IV NSCLC all histologies, progression after first-line platinum regimen. Patients randomized (N=180) 2:1 to receive DO+LY (LY 750 mg IV loading ×3, Q1W maintenance) or DO alone (75 mg/m^2 D1Q3W) until progression/toxicities. Antitumor activity was compared using CTS from baseline to end of cycle (C) 2 in each arm. This analysis, which uses tumor measurements as a continuous variable rather than a categorical endpoint based on RECIST, increases statistical efficiency and enables early assessment of clinical benefit. Secondary objectives included assessment of toxicity, PK, PFS and OS. **Results:** 114 patients received study drug and were included in the analyses. Baseline patient demographics were similar. No statistically significant difference in mean CTS ratio at C2 or in PFS was observed between the 2 arms: CTS was 1.07 with LY+DO (SD, 0.28) and 1.04 with DO (SD, 0.28); median PFS was 2.83 mo (95% CI, 1.84–3.65) with LY+DO and 3.35 mo (95% CI, 2.69–4.57) with DO (log-rank p=0.191). However, Cox regression revealed CTS to be a statistically significant factor for PFS: decreased CTS was associated with increased PFS (HR 0.45; 95% CI, 0.30–0.68, p=0.0001). Median OS was 7.9 mo (90% CI, 6.6–9.7) with LY+DO and 8.8 mo (90% CI, 5.7–13.8) with DO (log-rank p=0.481). There were no differences in toxicities or other secondary parameters. Incidence of grade III/IV toxicities was similar in both arms and was consistent with the known profile of LY+DO as was the PK profile. **Conclusions:** Addition of LY to DO did not improve the antitumor activity of DO. CTS appears to be a useful endpoint in phase II studies and should be considered further as an endpoint for early decision-making. Clinical trial information: NCT01107444.

8052 General Poster Session (Board #33H), Sat, 8:00 AM-11:45 AM

Molecular marker assessments for epidermal growth factor receptor (EGFR) expression by immunohistochemistry (IHC) and histoscore (H-score) in the phase III SELECT trial.

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Background: SELECT was a phase III study that investigated whether the addition of cetuximab (C) to pemetrexed (P) improved outcome in previously treated patients (pts) with recurrent or progressive non-small cell lung cancer (NSCLC). Clinical results have been reported previously and demonstrated that adding C to P did not improve progression-free survival (PFS) or overall survival (OS). H-score has been reported to be a potential predictor of outcome for C therapy. Prespecified biomarker analyses, including EGFR IHC and H-score, are reported here. **Methods:** EGFRexpression in tumor tissue was not required for eligibility; however, tissue was collected and analyzed for EGFR expression by IHC using standard methods. In addition, H-score evaluation was performed by trained central pathologists and correlated with clinical outcome using a predefined cutoff for "low" and "high" of <200 and ≥ 200, respectively. **Results:** A total of 449 (IHC) and 406 (H-score) pt specimens were evaluable. Demographics for pts with tissue available for EGFR analysis were similar to the overall population. For IHC+ pts (n=396), median PFS for C+P was 3.02 months (95% CI, 2.76–3.45) compared with 2.99 months (95% CI, 2.63–4.14) for P (HR, 1.02 [95% CI, 0.83–1.24]; p=.86). For pts with low H-score (N=99 [C+P] and N=111 [P]), median PFS was 2.7 months (95% CI, 1.8–3.2) with C+P and 3.1 months (95% CI, 2.6–4.1) with P (HR, 1.11 [95% CI, 0.84–1.46]; P=.48); median OS was 6.7 months (95% CI, 5.3–8.6) with C+P and 6.6 months (95% CI, 4.7–9.2) with P (HR, 0.96 [95% CI, 0.72–1.27]; P=.76). Among pts with high H-scores (N=101 [C+P] and N= 95 [P]), median PFS was 3.2 months (95% CI, 2.7–4.6) with C+P and 3.7 months (95% CI, 1.7–4.5) with P (HR, 1.02 [95% CI, 0.77–1.37]; P=.86); median OS was 7.7 months (95% CI, 6.5–10.9) with C+P and 8.0 months (95% CI, 7.0–9.1) with P (HR, 1.17 [95% CI, 0.86–1.57]; P=.32). **Conclusions:** EGFR H-score was not predictive of benefit for the addition of C to P in this population of pts with NSCLC. There was also no treatment effect in the IHC+ group. Clinical trial information: NCT00095199.

8053 General Poster Session (Board #34A), Sat, 8:00 AM-11:45 AM

Nimotuzumab plus chemotherapy versus chemotherapy alone in advanced non-small cell lung cancer: A phase II, open-label, multicenter, randomized study.

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Background: To evaluate the safety and efficacy of nimotuzumab in combination with chemotherapy (docetaxel and carboplatin) versus chemotherapy alone in stage IIIB/IV non-small cell lung cancer (NSCLC) patients. **Methods:** This multicenter, open-label, phase II study, randomized 110 patients to receive nimotuzumab plus chemotherapy (nimotuzumab group) or chemotherapy alone (control group), and comprised concomitant, maintenance, and follow-up phases. Nimotuzumab (200 mg) was administered once weekly for 13 weeks during the first 2 phases with 4 cycles of chemotherapy; docetaxel (75 mg/m^2) and carboplatin (area under the curve [AUC] = 5 mg/ml*min), every 3 weeks for a maximum of 4 cycles during the concomitant phase. The primary endpoint was objective response rate (ORR; sum of complete response [CR] and partial response [PR]). Secondary endpoints, overall survival (OS), and progression-free survival (PFS) were estimated using Kaplan-Meier method. Efficacy was evaluated on the intent-to-treat (ITT) and efficacy-evaluable (EE) sets. Safety was assessed from adverse events (AEs) and serious adverse events (SAEs) data. **Results:** ORR was significantly higher in the nimotuzumab group than in the control group in the ITT (54% vs. 34.5%; P=0.04) population. CR and PR were achieved in 3.6% and 50% patients, respectively, in the nimotuzumab group, and in 4% and 30.9% patients, respectively, in the control group. No significant differences in median PFS and OS were observed. Safety profiles were comparable between the 2 groups. **Conclusions:** Nimotuzumab plus chemotherapy significantly improved ORR as compared to chemotherapy alone; the combination was safe and well tolerated in stage IIIB/IV NSCLC patients.

8054 **General Poster Session (Board #34B), Sat, 8:00 AM-11:45 AM**

A comparison of bronchofiberscopic (BFS) washing cytology (BWC) and formalin-fixed paraffin-embedded tissue (PPFE) in the analysis of EGFR mutations in advanced non-small cell lung cancer (NSCLC).

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Background: In the treatment of advanced NSCLC, EGFR mutation status is one of the most predictive factors for the efficacy of EGFR tyrosine kinase inhibitors, and the evaluation of EGFR mutation status using the PPFE has been widely used for this analysis throughout the world. However, whether BWC can be used as an alternative for PPFE in the analysis of EGFR mutations is unknown. The largest study evaluating these 2 methods included only around 20 samples. Therefore, in the current study, we compared the freeze stock solution of BWC with PPFE for the determination of EGFR mutation status in a large sample set. **Methods:** In diagnostic BFS examinations, after curetting or brushing and biopsy to target lesions, subsequent bronchial washing by saline was performed. Thereafter, the saline fluid in which the forceps were washed and the bronchial washing fluid were mixed in a sterilized tube and were immediately frozen in a -20°C freezer. EGFR mutation testing for both BWC and PPFE was performed using high-sensitivity PCR (BML, PCR-Invader). **Results:** A total of 440 BFS examinations were performed from Aug 2010 to Nov 2011 in our hospital. The BWCs of 268 suspected cases of lung cancer were successfully obtained. Of these, 51 cases that were pathologically confirmed as adenocarcinoma based on both BWC and PPFE were analyzed in this study. EGFR mutations were identified in 25 cases, while the remaining 26 cases had wild-type EGFR. In 49 of 51 cases, the results of EGFR mutation status were the same for BWC and PPFE, and the concordance rate was 96%. In one case, an exon-18 mutation was detected only by BWC. In another case an exon-21 mutation was detected only by PPFE. In 24 of 25 cases of EGFR mutation, the mutation site was the same in both samples. The kappa coefficient was 0.92. **Conclusions:** This is the largest genetic study to date demonstrating a head-to-head comparison of BWC and PPFE for the evaluation of EGFR mutations. Both methods showed high reliability and concordance using high-sensitivity PCR. BWC is considered a simple, rapid method and represents an effective alternative for PPFE in EGFR mutation testing.

8055 General Poster Session (Board #34C), Sat, 8:00 AM-11:45 AM

BIM deletion polymorphism to predict systemic treatment outcome in advanced non-small cell lung cancer.

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Background: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) and chemotherapies are treatments for EGFR mutant non-small cell lung cancer (NSCLC) patients. We explored the predictive factors for progression-free survival (PFS) and overall survival (OS) on first-line EGFR-TKIs and second-line chemotherapies in NSCLC patients. **Methods:** One hundred and six chemonaïve NSCLC patients who received first line gefitinib in a phase II study were prospectively followed until death. Clinical and molecular biomakers were correlated with PFS and OS. **Results:** The OS and PFS of first-line gefitinib treatment were 19.4 (95% CI 15.6-23.3) months and 7.4 (95% CI 6.7-8.1) months, respectively. Sixty-nine patients (65%) received subsequent second-line chemotherapy. Median PFS and OS of second-line chemotherapy were 5.7 (95% CI 4.8-6.6) and 15.1 (95% CI 10.5-20.2) months. Bcl-2-like protein 11 (also named as BIM) deletion polymorphism was found in 17 out of 101 (16.8%) patients tested. The median PFS from first-line gefitinib in patients carrying normal BIM and deletion polymorphism were 8.1 months and 3.6 months, respectively ($p<0.001$), and the median OS were 22.1 months and 14.1 months, respectively ($p=0.041$); in 44 patients with common EGFR mutations (del 19 or L858R), the PFS for patients carrying normal BIM and deletion polymorphism were 9.6 months and 7.4 months, respectively ($p=0.034$). A multivariate analysis suggested that BIM deletion polymorphism and EGFR mutational status were independent predictors for gefitinib PFS (hazard ratio 2.83, $p=0.001$, and 0.63, $p=0.03$, respectively). **Conclusions:** BIM deletion polymorphism predicts shorter PFS in EGFR mutation NSCLC patients treated with first line gefitinib.

8056 General Poster Session (Board #34D), Sat, 8:00 AM-11:45 AM

Safety and efficacy of nintedanib (BIBF 1120) plus pemetrexed in Japanese patients with advanced or recurrent non-small cell lung cancer (NSCLC): A phase I study.

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Background: Nintedanib (N) is a potent, orally bio-available triple angiokinase inhibitor that targets VEGFRs, PDGFRs and FGFRs, as well as RET and Flt3. The open-label phase I part of this phase I/II study was designed to determine the maximum tolerated dose (MTD) of N when combined with standard-dose pemetrexed (PEM), and to investigate safety and efficacy in Japanese patients (pts) with advanced/recurrent NSCLC. **Methods:** Eligible pts had histologically/cytologically confirmed stage IIIB/IV or recurrent NSCLC (any histology) after failure of first-line chemotherapy. Pts received PEM 500 mg/m^2 iv on day 1 followed by N twice daily (bid) po on days 2–21 every 21 days using a standard 3+3 design. N was started at 100 mg bid and escalated to 200 mg bid in 50 mg bid intervals. Pts received ≥4 cycles of combination therapy with an option of continuing with single-agent N until disease progression or undue adverse events (AEs). Primary endpoints were MTD, defined as the highest dose at which incidence of dose-limiting toxicities (DLTs) was <33.3%, and safety. DLTs were defined as grade 3 non-hematologic or grade 4 hematologic AEs. Secondary endpoints included objective tumor response and pharmacokinetics (PKs). **Results:** 18 pts (14 male) were treated: 3 at N 100 mg bid, 6 at N 150 mg bid, and 9 at N 200 mg bid. DLTs were observed in 0/3, 1/6, and 2/9 pts in each cohort, respectively; 2 of these pts had liver enzyme elevations. The MTD for N (plus PEM) was 200 mg bid. The most common drug-related AEs were increased GGT, increased AST, decreased appetite, and diarrhea. Grade 3 AEs included neutropenia (22.2%), increased AST, increased ALT, and lymphopenia (each 11.1%); no pts experienced grade 4/5 AEs. Two pts (11.1%) achieved a partial response and 12 (66.7%) had stable disease. At the MTD, N exposure after PEM administration was similar to that seen with N monotherapy in a previous Japanese study. Co-administration of N did not affect the PKs of PEM. **Conclusions:** The combination of N and standard-dose PEM had a manageable safety profile and showed promising signs of efficacy in previously treated Japanese pts with advanced/recurrent NSCLC. As in Caucasian pts, the MTD of N was 200 mg bid. Clinical trial information: NCT00979576.

8057 General Poster Session (Board #34E), Sat, 8:00 AM-11:45 AM

Phase II study of metronomic chemotherapy (MC) with bevacizumab (B) in patients (Pts) with advanced (Adv) nonsquamous non-small cell lung cancer (NS-NSCLC).

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Background: Targeting vascular endothelial growth factor (VEGF) has shown modest improvement in pts with adv NS-NSCLC. The incorporation into MC regimens of antiangiogenic agents has been shown to further enhance efficacy in preclinical models. The goal of this pilot study was to achieve a 30% improvement in the 6.4 months (M) progression-free survival (PFS) observed in ECOG 4599. **Methods:** Untreated pts with stage 4 NS-NSCLC, PS 0-1 and measurable disease were treated with a 4-week (W) cycle of paclitaxel (80mg/m^2 D1, 8, 15), gemcitabine (G) (200-300mg/m^2 D1, 8, 15) and B (10mg/m^2 D1, 15) for 6 cycles. Pts without progressive disease or significant toxicity (Tx) received maintenance B every 2 w. Primary endpoint:PFS. Secondary endpoints: ORR, OS, Tx and biomarker (BM) correlation. Blood samples for angiogenic (VEGF, sVEGFR2, BFGF, PLGF, PDGFα, Ang-2, IL-8, E-Selectin, ICAM-1, TGFβ-1, SDF-1α, endocan) and antiangiogenic (Thrombospondin-1, Ang-1) bm were collected at different intervals in 21 pts. Response assessment (RECIST) was performed every 8 w. **Results:** 33 evaluable pts were enrolled. Pt characteristics: median age 59 yrs (37-76), 60% female, 70% $>$ 5% weight loss, 24% never/light smokers, 48% genetic testing (mut EGFR-4; ALK(+)-1), and 9% brain mets. Efficacy parameters are shown in the table. 24 pts had an OR (CR-1, PR-23) and 6 pts had stable disease. No significant differences were observed in the efficacy parameters between former smokers vs. never/light smokers. Worst hematologic and non-hematologic Tx: gr 3 neutropenia (N=1); gr 3/4 nausea/vomiting (N=1); gr 3/4 fatigue (N=2); ischemic colitis (N=1); cerebral ischemia (N=1); gr 3/4 pneumonitis [related to G] (N=2); gr 3/4 proteinuria (N=3), and no gr 3/4 hypertension. **Conclusions:** While conclusions are limited by the size of the trial, the results are consistent with the hypothesis that the addition of B to MC may result in enhanced anti-angiogenic effect and clinical benefits in adv NS-NSCLC. Analysis of prognostic or predictive bm of angiogenesis will be presented. Clinical trial information: NCT00655850.

Clinical outcome		
ORR	73%	(95% CI 0.57-0.87)
Median PFS	9M	(95% CI 7-10)
Median OS	30M	(95% CI 18-37)
1-yr survival	74%	
2-yr survival	55%	

8058 General Poster Session (Board #34F), Sat, 8:00 AM-11:45 AM

Prospective observational cohort study of second-line chemotherapy administration after first-line platinum-based chemotherapy for patients with advanced NSCLC in Japan (SAPPHIRE study).

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Background: Maintenance therapy after first-line platinum-based chemotherapy (first-CT) is reported to be beneficial to patients with advanced non-small cell lung cancer (NSCLC). However, its impact on overall survival appears to be marginal or negligible, if those without maintenance receive active second-line chemotherapy (second-CT), which is initiated at disease progression. The purpose of this study is to investigate the proportion of second-CT administration after first-CT for patients with advanced NSCLC. **Methods:** From April 2010 to September 2011, 865 patients with advanced NSCLC who were initiated on first-CT at 30 institutions in Japan were enrolled in this prospective observational study. Baseline characteristics, regimens and responses to first-CT, whether or not they received second-CT, and if not, reasons for non-administration were recorded. This report describes from patients with at least 6 months of follow up. This study was supported by the Public Health Research Center Foundation CSPOR. **Results:** A total of 865 eligible patients with advanced NSCLC provided patient characteristics and details of first-CT. Of all patients, 70% had adenocarcinoma, 20% had squamous cell carcinoma, and 10% were positive for the EGFR mutation. At this data cut off, 225 patients were excluded from the analysis due to disease progression and loss of follow-up during first-CT, and 194 (22%) patients received maintenance therapy after first-CT. Among the 508 patients who were followed up for at least 6 months, 131 patients (26%) could not receive second-CT; the reasons were as follows: declined PS, 79 (60%); patient refusal, 28 (21%); death of any cause, 6 (5%); others, 18 (14%). **Conclusions:** Preliminary results of this large observational study in Japan suggested that around 20% of patients missed an opportunity to receive appropriate second-CT despite the follow-up of advanced NSCLC patients after first-CT. Further investigation is needed to elucidate the selection criteria of patients that may benefit the most from maintenance therapy, not second-CT at disease progression.

8059 General Poster Session (Board #34G), Sat, 8:00 AM-11:45 AM

Final overall survival (OS) results of a noncomparative phase II study of bevacizumab (B) plus first-line chemotherapy or second-line erlotinib (E) in nonsquamous NSCLC (ns-NSCLC) patients with asymptomatic untreated brain metastases (BM) (BRAIN).

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Background: The non-comparative BRAIN study (NCT00800202) is the first trial to evaluate efficacy/acceptable safety of B in pts with ns-NSCLC and untreated BM. We report final efficacy/safety results. **Methods:** Eligible pts (stage IV ns-NSCLC; PS 0–1; untreated, asymptomatic BM ineligible for surgery/radiosurgery) received until unacceptable toxicity/disease progression: 1st-line B ≤6 cycles (15mg/kg q3w) plus carboplatin (AUC 6 q3w) and paclitaxel (200mg/m^2 q3w; B+CP; n=67); or 2nd-line B plus E (150mg/day; B+E; n=24). Primary endpoint is 6-month progression-free survival (PFS). Six-weekly assessments included mandatory brain MRI. The trial could be halted if there were >3 (B+CP) or >2 (B+E) brain hemorrhages (ICH). **Results:** Baseline (BL) characteristics are reported. With a median follow-up of 16.3 (B+CP) and 11.8 months (B+E), efficacy data are summarized. Adverse events (AE) were comparable with those in previous trials of B. Only 1 grade ≥3 bleeding AE (grade 3, extracranial site; B+E) and only one ICH event (grade 1, resolved; B+CP) occurred. Most frequent cause for B withdrawal was progression: intracranial only in 20.9% (B+CP) and 16% (B+E); extracranial only in 50.7% (B+CP) and 54.2 % (B+E). **Conclusions:** The finalBRAIN results demonstrate promising efficacy and acceptable safety of B with 1st-line chemotherapy or 2nd-line E in ns-NSCLC pts with asymptomatic untreated BM. Clinical trial information: NCT00800202.

		B+CP	B+E
		n=67	n=24
BL characteristics			
Male, n (%)		46 (68.7)	11 (45.8)
Median age, years (range)		61.0 (40–79)	54.0 (34–70)
ECOG PS 0, n (%)		37 (55.2)	13 (54.2)
WHO histology, n (%)	Adenocarcinoma	59 (88.1)	23 (95.8)
Never smokers, n (%)		14 (20.9)	3 (12.5)
Clinical outcomes (95% CI)			
6-month PFS,[a] %		56.5 (43.8–67.4)	58.0 (36.0–74.8)
Median PFS, months		6.7 (5.7–7.1)	6.3 (2.5–8.4)
Median OS, months		16.0 (12.0–21.0)	12.0 (8.9–20.2)
ORR,[b]%		62.7 (50.0–74.2)	12.5 (2.7–32.4)
RR,[b] %	Intracranial BM	61.2 (48.5–72.9)	20.8 (7.1–42.2)
	Extracranial lesions	64.2 (51.5–75.5)	12.5 (2.7–32.4)

[a] Met pre-defined endpoint (lower 95% CI B+CP>30%, B+E>15%; point estimate B+CP>50%, B+E>35%). [b] Unconfirmed response.

8061 General Poster Session (Board #35A), Sat, 8:00 AM-11:45 AM

LUX-Lung 6: Patient-reported outcomes (PROs) from a randomized open-label, phase III study in first-line advanced NSCLC patients (pts) harboring epidermal growth factor receptor (EGFR) mutations.

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Background: Afatinib (A) is an oral, irreversible, ErbB Family Blocker, blocking signaling from EGFR (ErbB1), human epidermal growth factor receptor 2 (HER2; ErbB2) and ErbB4. In LUX-Lung 6, A was significantly better than gemcitabine/cisplatin (GC) in terms of progression free survival (PFS) and tumor response, with a more favorable safety profile. Here, we report the PRO results. **Methods:** 364 pts were randomized (2:1) to receive A or GC. PROs were measured using EORTC questionnaires QLQ-C30/LC13 at baseline and q3w until progression. Changes of $\geq$10 points (scale 0–100) were considered clinically significant. Analyses of cough, dyspnea and pain were prespecified. Time to deterioration (1st 10-point worsening from baseline) was analyzed using a stratified log-rank test. Percentage improved/worsened by $\geq$10 points or stable was determined. Mean scores over time were estimated using longitudinal (mixed-effects growth curve) models. **Results:** Compliance on treatment with questionnaires was $>$90%. Baseline symptom burden was low (cough: 35; dyspnea: 25; pain: 24). Compared with GC, therapy with A significantly delayed time to deterioration for cough (HR=0.45; p=0.0001), dyspnea (HR=0.54; p$<$0.0001) and pain (HR=0.70; p=0.03). A higher proportion of A-treated pts had $\geq$10-point improvements in cough (76% vs 55%; p=0.0003), dyspnea (71% vs 48%; p$<$0.0001) and pain (64% vs 47%; p=0.003) compared with GC, particularly among pts with baseline symptoms. Mean scores over time for cough, dyspnea and pain also significantly favored A. Consistent with their safety profiles, a significantly higher proportion of A-treated pts had worsening of diarrhea, sore mouth and dysphagia, while fatigue, nausea, and vomiting were significantly worse with GC. Overall, therapy with A significantly improved global health-related quality of life (HRQoL; p$<$0.0001), physical (p$<$0.0001), role (p=0.01) and social (p$<$0.001) functioning compared with GC. **Conclusions:** In LUX-Lung 6, prolongation of PFS with A was associated with significantly better HRQoL and significantly longer control of lung cancer-related symptoms compared with GC. Clinical trial information: NCT01121393.

8062 General Poster Session (Board #35B), Sat, 8:00 AM-11:45 AM

First-line carboplatin, pemetrexed, and panitumumab in patients with advanced nonsquamous *KRAS* wild type (WT) non-small cell lung cancer (NSCLC).

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Background: *KRAS* WT colorectal cancer (CRC) is responsive to the EGFR inhibitors panitumumab (P) and cetuximab. Phase III data suggest a small, but statistically significant overall survival (OS) advantage with cetuximab + chemotherapy in *KRAS* unselected NSCLC (Pirker, *Lancet* 2009); and phase I data suggest P alone has activity in non-CRC tumors including NSCLC (Weiner, *Clin Ca Res*. 2008). This single-arm phase II trial examined the safety and efficacy of P in combination with carboplatin (C) and pemetrexed (Pem) in patients (pts) with advanced non-squamous *KRAS* WT NSCLC. The addition of P was hypothesized to improve the median time-to-progression (TTP) from 3.6 months (mos) (historical) to 5.4 mos (1-sided α .10, 80% power). **Methods:** Pts with previously untreated, unresectable stage IIIB/IV non squamous *KRAS* WT NSCLC received P 9 mg/kg, Pem 500 mg/m^2, and C AUC=6 IV day 1 every 21 days for 6 cycles, followed by P and Pem maintenance every 21 days until progressive disease or unacceptable toxicity. Responses were evaluated every 2 cycles per RECIST 1.1. *KRAS* mutation testing was performed centrally (DxS kit). Tissue was also collected for EGFR FISH testing. **Results:** 60 pts were enrolled; median age, 65 years; 58% female, ECOG PS 0-1 (98%), and prior adjuvant chemotherapy (10%). Median number of cycles was 5 (range 1-22). At a median follow-up of 8.7 mos, the median TTP was 6.2 mos (95% CI: 3.7, 9.5), PFS 6.2 mos (95% CI 3.0, 9.0), 1 year OS 65.5% (95% CI 44.8%, 80%). 23 pts (38%) had partial responses (PR); the disease control rate (PR + proportion with stable disease) was 68%. Treatment-related toxicity (TRT) included (all grades) nausea (38%), fatigue (30%), rash (30%), and mucositis (23%). Severe (grade 3/4) TRT in $>$ 2 pts included: thrombocytopenia (11%), neutropenia (7%), and dehydration (5%). There were no treatment-related deaths. *EGFR* mutation and FISH analyses will be presented. **Conclusions:** The addition of panitumumab to carboplatin and pemetrexed in the first-line treatment of advanced *KRAS* WT NSCLC was safe and well-tolerated; the median TTP of 6.2 mos met the primary endpoint. Definitive assessment of the value of panitumumab in this setting requires a randomized trial. Clinical trial information: NCT01042288.

8063 General Poster Session (Board #35C), Sat, 8:00 AM-11:45 AM

Phase II study of afatinib, an irreversible ErbB family blocker, in demographically and genotypically defined non-small cell lung cancer (NSCLC) patients.

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Background: EGFR mutation+ (M+) NSCLC pts have an improved response to EGFR TKIs vs non-M+ pts. Data on EGFR FISH+ (gene amplified) and HER2 M+ pts are, however, limited. Afatinib is an irreversible ErbB Family Blocker with efficacy in Ph II/III trials in EGFR M+ NSCLC. This exploratory, open-label trial assessed afatinib in 3 genotypically and demographically defined NSCLC groups. **Methods:** Never/ex-smokers with stage IIIB/IV lung adenocarcinoma with EGFR M+ tumors who had failed prior EGFR TKIs, HER2 M+ tumors independent of prior therapy, or EGFR FISH+ tumors who received ≤3 prior chemotherapies were enrolled. Afatinib 50 mg qd was administered until disease progression or intolerable adverse events. Tumor assessments (RECIST 1.0) were performed every 8 wks. Pts who progressed on afatinib but experienced clinical benefit could continue treatment with afatinib 40 mg qd + paclitaxel 80 mg/m^2 qw on days 1, 8 and 15 every 28-day cycle. Primary endpoint: Confirmed objective response. **Results:** 41 pts were treated: 63% female; median age 63 yrs; 68% never smokers; 32% ex-smokers. 33 pts received afatinib monotherapy only; 8 pts received afatinib followed by afatinib/paclitaxel combination therapy. 78% (n=32) of pts were EGFR M+, 5% (n=2) were EGFR FISH+ and 17% (n=7) were HER2 M+. For afatinib monotherapy, 1 confirmed partial response (PR) was observed (EGFR FISH+), stable disease (SD) was seen in 5/7 HER2 M+, 2/2 EGFR FISH+ and 17/32 EGFR M+ pts, and overall disease control (DC) rate was 59% (n=24); mean duration of DC was 26 wks.Median PFS was 16 wks (17 wks in HER2 M+ pts). Of 8 afatinib/paclitaxel-treated pts, 1 had a confirmed PR and 2 had SD; median PFS was 7 wks. Most frequently reported drug-related AEs in afatinib monotherapy pts were diarrhea (n=39; grade ≥3 n=13), rash/acne (n=33; grade ≥3 n=4) and stomatitis (n=19; grade ≥3 n=2). In the combination arm these were diarrhea (n=4; grade ≥3 n=1) and nausea (n=3; grade ≥3 n=0). **Conclusions:** Efficacy of afatinib in EGFR M+ NSCLC pts has been established in previous trials. Novel activity of afatinib in HER2 M+ and EGFR FISH+ NSCLC pts has been demonstrated here, with a manageable safety profile of afatinib in the overall population. Clinical trial information: NCT00730925.

8064 General Poster Session (Board #35D), Sat, 8:00 AM-11:45 AM

Phase II study of gefitinib and inserted cisplatin plus docetaxel as a first-line treatment for advanced non-small cell lung cancer haboring an epidermal growth factor receptor activating mutation.

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Background: Gefitinib yields a longer progression-free survival (PFS) period than platinum–doublet chemotherapy as a first–line treatment for patients with advanced non–small–cell lung cancer (NSCLC) harboring an epidermal growth factor receptor (EGFR) activating mutation, but most patients develop resistance against gefitinib after the initial response. We hypothesized that the insertion of platinum–doublet chemotherapy during the initial response could prevent the emergence of acquired resistance and prolong survival, compared with gefitinib alone. **Methods:** We performed a phase II study of the following first–line treatment for patients with advanced NSCLC with EGFR mutation. Gefitinib (250 mg) was administrated on days 1–56. After a two–week rest, three cycles of cisplatin (80 mg/m^2) and docetaxel (60 mg/m^2) were administered on days 71, 92, and 113. Gefitinib was re–started on day 134 and was continued until progression. The primary endpoint was the two–year PFS rate. The sample size was estimated at 33, and this treatment was considered worthy for further development if more than 11 of the 33 patients who started treatment had a 2–year PFS. **Results:** Thirty–three Japanese patients were enrolled. Twenty–five patients could re–start gefitinib, 12 achieved a PFS period of over 2 years, and 9 continued to receive the protocol treatment without experiencing progression. The 1–, 2–, and 3–year estimated PFS rates were 59.4%, 37.5%, and 33.8%, respectively, and the median PFS time was 19.2 months. The 1–, 2–, and 3–year estimated survival rates were 90.0%, 82.9%, and 62.4%, respectively, and the median survival time had not been reached at the time of analysis. Treatment–related deaths and unexpected severe toxicities were not seen. **Conclusions:** Our results indicated that first–line treatment consisting of gefitinib and inserted cisplatin plus docetaxel is promising for patients with advanced NSCLC with EGFR mutation. A phase III study of this treatment compared with gefitinib alone is warranted. Clinical trial information: 000001738.

8065 General Poster Session (Board #35E), Sat, 8:00 AM-11:45 AM

Rebiopsy in TKI-resistance: A retrospective analysis.

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Background: EGFR-TKI provides a clinical benefit in patients with EGFR-mutated NSCLC with median progression-free survival (PFS) of 12 months. Several resistance mechanisms (e.g. T790M mutation) have been described, however data are sparse. We analysed EGFR-mutation spectra in NSCLC patients with acquired resistance to TKI. **Methods:** Biopsies from patients with EGFR-mutation or TKI-response>24 weeks with both pre- and post TKI biopsy available were retrospectively analysed. Information was collected from the medical record. Response to TKI-treatment was assessed according to RECIST. PFS after TKI-treatment was calculated with a Kaplan-Meier curve. **Results:** 63 patients were included for analysis. Pre- and post TKI biopsy results are described in the Table. 32 patients received 1 (38%), 2 (10%) or 3 (3%) lines of chemotherapy before start of TKI and 18 patients received 1 (13%), 2 (11%), 3 (3%), or 5 (2%) lines of therapy after TKI treatment. Median PFS on TKI-treatment was 12,3 months (range: 1,4 – 43,2). Objective response rate was 61,9%. 47,6% of patients developed the T790M mutation. One patient developed transformation to SCLC with the original exon 19 deletion. One patient with pre-TKI an exon 18 + exon 21 mutation was found to have a KRAS-mutation post-TKI. **Conclusions:** In this cohort, frequency of development of T790M mutation was consistent with earlier reports. Transformation to SCLC occurred less than described earlier. Two patients did not retain their original mutation. Surprisingly, one patient developed a KRAS mutation: a second primary tumor is not excluded in this case. Rebiopsy in TKI-resistance provides important information on dynamic tumour characteristics and has management implications in certain patients.

Pre- versus post-TKI biopsy results.

		Post-TKI											
		EGFR exon19	EGFR exon21	T790M + exon 19	T790M + exon 21	EGFR exon 20	Exon 18 + exon 20	SCLC + Exon 19	KRAS	No malignant cells	No mutation	Mutation analysis not possible	Total
	EGFR exon19	13	0	17	0	1	0	1	0	2	2	0	36
	EGFR exon21	0	5	0	3	0	0	0	0	0	0	0	8
Pre-TKI	EGFR mutation NOS	0	0	1	2	0	0	0	0	0	0	0	3
	Exon 18 + exon 20	0	0	0	0	0	1	0	0	0	0	0	1
	Exon 18 + exon 21	0	0	0	0	0	0	0	1	0	0	0	1
	T790M + exon 21	0	0	0	1	0	0	0	0	0	0	0	1
	No mutation	0	0	0	0	0	0	0	0	1	1	1	3
	Mutation analysis not possible	0	0	1	0	0	0	0	0	0	0	0	1
	No mutation-analysis performed	3	0	4	1	0	0	0	0	0	1	0	9
Total		16	5	23	7	1	1	1	1	3	4	1	63

8066 General Poster Session (Board #35F), Sat, 8:00 AM-11:45 AM

Randomized phase III trial of gemcitabine and cisplatin versus gemcitabine alone in patients with advanced non-small cell lung cancer (NSCLC) and a performance status (PS) 2: CAPPA-2 study.

Alessandro Morabito, Vittorio Gebbia, Saverio Cinieri, Maria Grazia Viganò, Roberto Bianco, Santi Barbera, Luigi Cavanna, Filippo De Marinis, Vincenzo Montesarchio, Raffaele Costanzo, Claudia Sandomenico, Agnese Montanino, Gianfranco Mancuso, Angelo Nacci, Pasqualina Giordano, Gennaro Daniele, Cesare Gridelli, Gaetano Rocco, Ciro Gallo, Massimo Di Maio; National Cancer Institute, G.Pascale Foundation, Napoli, Italy; Casa di Cura "La Maddalena", Palermo, Italy; Medical Oncology & Breast Unit, Senatore Antonio Perrino Hospital, Brindisi, Italy; Department of Oncology, Istituto Scientifico San Raffaele, Milan, Italy; Dipartimento di Endocrinologia ed Oncologia Molecolare e Clinica, Università di Napoli Federico II, Napoli, Italy; Mariano Santo Hospital, Cosenza, Italy; Piacenza Hospital, Piacenza, Italy; San Camillo-Forlanini Hospital, Rome, Italy; AORN-Osoedali dei Colli, Napoli, Italy; National Cancer Institute, Napoli, Italy; Medical Oncology and Breast Unit, Antonio Perrino Hospital, Brindisi, Italy; Clinical Trials Unit, National Cancer Institute, Napoli, Italy; SG Moscati Hospital, Avellino, Italy; Medical Statistics, Department of Medicine and Public Health, Second University, Napoli, Italy

Background: Platinum-based chemotherapy (CT) is the standard treatment for patients (pts) with advanced NSCLC, but the evidence of its efficacy among ECOG PS2 pts is weak, because these pts are usually excluded from clinical trials; concern exists about tolerability and feasibility of standard CT in these pts. No prospective randomized trial has tested the addition of cisplatin to single-agent CT in pts with advanced NSCLC and PS2. **Methods:** CAPPA-2 was a multicentre, randomized phase III study for first-line treatment of PS2 pts with advanced NSCLC. Patients, aged 18-70, were eligible if they had stage IV or IIIB with malignant pleural effusion or metastatic supraclavicular nodes (TNM VI ed.) and adequate organ function. Patients in standard arm received gemcitabine 1,200 mg/m^2 dd1 and 8.Patients in experimental arm received cispaltin 60 mg/m^2 d1 plus gemcitabine 1,000 mg/m^2 dd1 and 8. All treatments were repeated q3w, up to 4 cycles, unless disease progression or unacceptable toxicity. Primary endpoint was overall survival (OS). To have 80% power of detecting hazard ratio (HR) 0.71, corresponding to an increase in median OS from 4.8 to 6.8 months, 285 deaths were required. **Results:** The study was stopped in June 2012 after the enrolment of 57 pts, due to the slow accrual and the report of positive results from a similar study. Median OS was 3.0 months with single-agent gemcitabine and 5.9 months with cisplatin + gemcitabine (HR 0.52, 95% CI 0.28-0.98, p=0.039). Combination CT produced longer PFS (median 1.7 vs. 3.3 months, HR 0.49, 95% CI 0.27-0.89, p=0.017) and higher response rate (4% vs. 18%, p=0.19), without substantial increase in toxicity. **Conclusions:** Addition of cisplatin to single-agent gemcitabine improves survival as first-line treatment of PS2 patients with advanced NSCLC. Clinical trial information: NCT00526643.

8067 **General Poster Session (Board #35G), Sat, 8:00 AM-11:45 AM**

Screening for *RET* and *ROS1* fusions in an enriched cohort of pan-negative never-smokers with advanced lung adenocarcinomas to identify patients for treatment in targeted therapy trials.

Alexander Edward Dela Cruz Drilon, Lu Wang, Adnan Hasanovic, Philippe Joubert, Mark G. Kris, Gregory J. Riely, Marc Ladanyi, Naiyer A. Rizvi; Memorial Sloan-Kettering Cancer Center, New York, NY; Lenox Hill Hospital, New York, NY

Background: *RET* and *ROS1* fusions have been identified pre-clinically as drivers of tumor growth in lung adenocarcinomas. In addition, based on response to crizotinib in *ROS1*-positive tumors and emerging data on RET inhibition in some tumors, these fusions represent druggable targets. While each occurs in 1-2% of unselected patients, a screening paradigm based on testing never-smokers whose tumors have no known oncogenic mutations or fusions may enrich identification for ongoing clinical trials. **Methods:** Patients with a never-smoking history (<100 lifetime cigarettes) and advanced pan-negative lung adenocarcinomas (absence of mutations in *EGFR, KRAS, NRAS, BRAF, HER2, PIK3CA, MEK1,* and *AKT,* and *ALK* fusions) were selected for testing. Screening for *RET* and *ROS1* fusions was performed in real-time via dual-probe FISH breakapart assays, RT-PCR, and next-generation sequencing in selected cases. We enrolled patients onto a phase II trial of cabozantinib for *RET* fusion-positive lung cancers (NCT01639508) and, as part of the Lung Cancer Mutation Consortium (LCMC), a phase I trial of crizotinib for *ROS1*-positive lung cancers (NCT00585195). **Results:** Thirty five (n=35) never-smokers with advanced pan-negative lung adenocarcinomas were identified. A *RET* or *ROS1* fusion was found in 31% [n=10/32, 95% CI, 15-47%] of patients. *RET* and *ROS1* fusions were found in 15% [n=5/34, 95% CI, 3% - 27%] and 15% [n=5/33, 95% CI, 2%-27%] of patients, respectively. 1 patient had a novel *TRIM33-RET* fusion. 3 of 5 patients with *RET* fusion-positive tumors were eligible for treatment with cabozantinib, 2 of which had partial responses to therapy. 1 of 5 patients with *ROS1* fusion-positive tumors was treated on-protocol with crizotinib and achieved a partial response. **Conclusions:** 31% of never-smokers with pan-negative advanced lung adenocarcinomas harbor a gene fusion involving either *RET* or *ROS1*. Until multiplexed mutation and fusion testing is routinely available, targeting this population for screening represents an interim enrichment strategy for patient identification and enrollment on clinical trials where responses are already being documented.

8068 General Poster Session (Board #35H), Sat, 8:00 AM-11:45 AM

Final efficacy and safety results of pemetrexed (pem) continuation maintenance (mtc) therapy in the elderly from the PARAMOUNT phase III study.

Cesare Gridelli, Michael Thomas, Kumar Prabhash, Claude El Kouri, Fiona Helen Blackhall, Frederique Bustin, Belen San Antonio, Annamaria Zimmermann, Nadia Chouaki, Carla Visseren-Grul, Luis Paz-Ares; SG Moscati Hospital, Avellino, Italy; Thoraxklinik am Universitätsklinikum Heidelberg, Heidelberg, Germany; Tata Memorial Hospital, Mumbai, India; Centre Catherine De Sienne, Nantes, France; The Christie National Health Services Foundation Trust, Manchester, United Kingdom; Centre Hospitalier Regional de la Citadelle, Liege, Belgium; Eli Lilly and Company, Madrid, Spain; Eli Lilly and Company, Indianapolis, IN; Eli Lilly and Company, Suresnes Hauts de Seine, France; Eli Lilly and Company, Houten, Netherlands; University Hospital Virgen del Rocio, Seville, Spain

Background: The PARAMOUNT phase III trial showed that mtc pem after pem-cisplatin induction was well tolerated and effective for patients (pts) with advanced nonsquamous NSCLC. Here we present the final OS and safety data from this study in elderly (≥70 yrs) vs. non-elderly (<70 yrs) pts. **Methods**: In this double-blind study, 539 pts with a PS of 0/1 were randomized (2:1, stratified for stage, PS and induction response) to receive mtc pem (n=359, 500 mg/m^2, day 1, 21 day cycle) or placebo (plc) (n=180). The study was powered for PFS (previously reported) and key secondary OS. Subgroup analyses were done for pts ≥70 yrs and <70 yrs. **Results**: Subgroups (≥70: n=92, 17%; <70: n=447, 83%) had similar baseline characteristics except for PS and sex (elderly, PS 0/1: 22%/77%, M/F: 66%/34%; non-elderly, PS 0/1: 34%/65%, M/F: 56%/44%). The median ages were 73 yrs (≥70) and 60 yrs (<70). The mean cycles received for pts ≥70 were 7.4 (range 1-36, dose intensity (DI) 91%) for pem and 4.5 for plc, and for pts <70 were 8.0 (range 1-44, DI 94%) for pem and 5.1 for plc. The OS HRs (pem vs. plc) were 0.89 (95% CI: 0.55-1.4) for ≥70 yrs and 0.75 (95% CI: 0.60-0.95, p=0.015) for<70 yrs. The median OS (95% CI) (≥70) was 13.7 mo (10.4-19.4) for pem and 12.1 mo (8.4-16.9) for plc; the median OS (95%CI) (<70) was 13.9 mo (12.5-16.1) for pem and 10.8 mo (9.5-12.9) for plc. The 1 and 2 yr OS rates (95% CI) for the elderly were 60% (45-71%) and 34% (21-47%) for pem vs. 52% (36-66%) and 28% (15-43%) for plc, respectively. For non-elderly pts, the 1 and 2 yr OS rates were 58% (52-63%) and 31% (26-37%) for pem vs. 43% (35-52%) and 19% (13-27%) for plc, respectively. The Table shows a subset of drug-related AEs. **Conclusions**: Continuation mtc pem had comparable survival and toxicity profiles in the ≥70 and <70 yrs subgroups. However, Gr 3/4 anemia and neutropenia were numerically higher for pts ≥70 yrs. Clinical trial information: NCT00789373.

CTCAEs.

All mtc cycles	≥70 yrs						<70 yrs					
Event (%)	Gr 1		Gr 2		Gr 3/4		Gr 1		Gr 2		Gr 3/4	
	pem	plc	pem	plc	pem	plc	pem	plc	pem	plc	pem	plc
Fatigue	8	5	15	5	6	5	9	6	9	5	5	0
Anemia	8	5	10	8	12	0	4	0	10	2	6	0.7
Neutropenia	6	0	8	0	17	0	1	0	3	0.7	4	0
Renal*	4	5	6	0	0	0	3	0.7	4	0.7	1	0
Rash	0	3	0	0	0	0	**3**	2	0.7	0	0	0
Edema	6	3	4	0	0	0	4	4	4	0	0	0

* Creatinine, GFR, renal failure, and genitourinary-other.

8069 General Poster Session (Board #36A), Sat, 8:00 AM-11:45 AM

Impact of aggressive therapy in patients with non-small cell lung carcinoma presenting with brain-only oligometastatic disease.

Phillip J. Gray, David Sher, Beow Y. Yeap, Sarah K Cryer, Raymond H. Mak, Stephanie E. Weiss, Brian Michael Alexander, David Michael Jackman; Harvard Radiation Oncology Program, Boston, MA; Rush University Medical Center, Chicago, IL; Massachusetts General Hospital, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, MA; Fox Chase Cancer Center, Philadelphia, PA; Dana-Farber Cancer Institute/Brigham and Women's Hospital, Boston, MA

Background: Optimal therapy for patients with non-small cell lung carcinoma (NSCLC) presenting with synchronous brain metastases as their only metastatic site is not well defined. We investigated whether aggressive therapy directed to the primary site or whole-brain radiotherapy (WBRT) were associated with improved outcomes in this subset of patients. **Methods:** We conducted a retrospective analysis of patients seen at the Dana-Farber Cancer Institute between 1/2000 and 1/2011. Patients with NSCLC, 1-4 synchronous brain metastases and no other sites of metastatic disease confirmed by CT or PET scan were included. Patients with poor performance status were excluded. Aggressive thoracic therapy (ATT) was defined as surgical resection of the primary disease or radiotherapy to a dose of greater than 45 Gy. A Cox proportional hazards model was used to analyze effects on survival and a competing risks model was constructed to analyze the risk of recurrence in the brain. **Results:** 66 patients met the study criteria. Median follow-up for survivors was 32.3 months. Excluding the metastatic disease, 9 patients had stage I disease, 10 stage II and 47 stage III. 38 patients received ATT. Patients receiving ATT were significantly younger (median age 55 vs. 60.5 years) but otherwise had a similar distribution of sex, performance status and number of brain metastases. Receipt of ATT was associated with significantly prolonged overall survival (OS) (median 26.8 vs. 10.9 months; $p<0.001$). Actuarial 5-year survival was 28% for those who received ATT vs. 0%. ATT remained significantly associated with OS after controlling for age, stage, performance status and receipt of WBRT (HR 0.42, $p=0.016$). On multivariate analysis, receipt of ATT (HR 3.14, $p=0.048$) and WBRT (HR 0.10, $p=0.005$) were the only factors predictive of first failure in the brain. Receipt of initial WBRT did not improve OS. **Conclusions:** Patients with NSCLC presenting with synchronous brain-only metastases may still benefit from aggressive therapy directed to the thoracic primary site. Use of WBRT for this subgroup does not improve OS but significantly reduces future brain recurrences.

8070 **General Poster Session (Board #36B), Sat, 8:00 AM-11:45 AM**

Whole-exome sequencing in tumor samples from sequenom-wild-type, ALK negative stage IV lung adenocarcinoma (ADC) patients (p).

Enriqueta Felip, Ginevra Caratu, Daniel Silberschmidt, Pablo Martinez, Alex Martinez Marti, Susana Cedres, Nuria Murtra-Garrell, Alejandro Navarro-Mendivil, Ludmila Prudkin, Jose Jimenez, Pilar de la Morena, Mercedes Canela, Paolo Nuciforo, Hector G. Palmer, Ana Vivancos; Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; Cancer Genomics Group, Vall d'Hebron Institute of Oncology, Barcelona, Spain; Molecular Pathology Laboratory, Vall d'Hebron Institute of Oncology, Barcelona, Spain; Thoracic Surgery Department, Vall d'Hebron University Hospital, Barcelona, Spain; Stem Cells and Cancer Laboratory, Vall d'Hebron Institute of Oncology, Barcelona, Spain

Background: The majority of lung ADC tumors are characterized by specific genetic features with KRAS mutations (mut) seen in 20-30%, EGFR mut in 15%, EML4-ALK translocations in 5%, and ERBB2 mut in 2%, among others. Some of these genetic alterations are already being used for selecting targeted therapies. However, identification of additional genomic alterations is required. **Methods:** In the present ongoing study we perform whole-exome sequencing in paraffin-embedded tumor samples from OncoCarta v1.0 panel wild-type (no mut in hotspots of KRAS, EGFR, ERBB2, AKT1, BRAF, PIK3CA genes) and ALK negative (by FISH) stage IV ADC lung cancer p, and in their matched normal tissue samples. **Results:** To date, a total of 7 tumors and matched normal tissues have been successfully analyzed. We have detected mut in previously identified ADC genes, such as ERBB2, CTNNB1, TP53, SMAD4 or APC. Interestingly, mut were found in genes belonging to the proposed new cancer hallmark 'epigenetic and RNA regulation', such as BRD3, EPC1, PHF1 in almost every p included in our study. Regarding alterations that could be considered relevant for lung tumor pathogenesis/growth or as potential targets for treatment therapies, we were able to identify candidates in 4 of the 7 p. In one p, a case of a transmembrane domain ERBB2mut in exon 20 (p.E770delinsEAYVM) not previously detected by the OncoCarta v1.0 panel (that interrogates L755P, G776S/L/V/C, A775_G776insYVMA, P780_Y781insGSP, S779_P780insVGS mut) was found. In another p, three somatic mut in the BRCA1/2 genes were detected. Additionally, one p had an ALK point mut (p.P336K), for which no functional information is available, together with an APC mutation. In the remaining p, a non-hotspot mutation (although previously detected in a colorectal tumor) was found in CTNNB1. **Conclusions:** In this limited experience of whole-exome sequencing of a subgroup of stage IV lung ADC p, potentially targetable alterations not formerly detected by other techniques were found. We believe that genomic approaches to detecting alterations may be useful in clinical practice and will hopefully provide assistance in making treatment decisions.

8071 General Poster Session (Board #36C), Sat, 8:00 AM-11:45 AM

First-line pemetrexed plus cisplatin followed by maintenance pemetrexed versus carboplatin-paclitaxel plus bevacizumab followed by maintenance bevacizumab (ERACLE) in advanced nonsquamous NSCLC: A quality-of-life-oriented, multicenter randomized phase III trial of the GOIM (Gruppo Oncologico Italia Meridionale).

Domenico Galetta, Salvatore Pisconti, Saverio Cinieri, Vittorio Gebbia, Alessandro Morabito, Nicolo Borsellino, Evaristo Maiello, Antonio Febbraro, Annamaria Catino, Pietro Rizzo, Michele Montrone, Giovanni Simone, Vito Lorusso, Daniele Rizzi, Giovanni L. Pappagallo, Giuseppe Colucci; National Cancer Research Center Giovanni Paolo II, Bari, Italy; Medica Oncology Division S. Giuseppe Moscati Hospital, Taranto, Italy; Medical Oncology & Breast Unit, Senatore Antonio Perrino Hospital, Brindisi, Italy; Casa di Cura "La Maddalena", Palermo, Italy; National Cancer Institute, Napoli, Italy; Medical Oncology Unit - Buccheri La Ferla Fatebenefratelli Hospital, Palermo, Italy; IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy; Fatebenefratelli Hospital, Benevento, Italy; Medical Oncology Department National Cancer Research Centre Giovanni Paolo II, Bari, Italy; Medical Oncology & Breast Unit, Brindisi, Italy; Medical Oncology Division San Giuseppe Moscati Hospital, Taranto, Italy; National Cancer Institute, Bari, Italy; Data Management "Giovanni Paolo II" Oncology Institute, Bari, Italy; Azienda ULSS 13, Mirano, Italy; National Cancer Institute of Bari, Bari, Italy

Background: In absence of oncogenic driver chemotherapy (CT) for advanced non-squamous non-small cell lung cancer (NS-NSCLC) remains palliative with similar efficacy and survival among different regimens. Histotype, maintenance therapy (m) and quality of life (QoL) have been explored to improve patients (pts) outcome. ERACLE trial (NCT01303926), a QoL-oriented phase III trial was designed to compare the QoL for two CT regimens. **Methods:** Pts with stage IIIB/IV NS-NSCLC (ECOG 0/1) were randomized (1:1) to receive first-line CT. ARM A received 6 cycles of Cisplatin (C) (75 mg/m^2) - Pemetrexed (P) (500 mg/m^2) q3w, followed by mP (500 mg/m^2) while ARM B received Carboplatin (Cb) AUC 6 - Paclitaxel (T) 200 mg/m^{2}plus Bevacizumab (Be) 15 mg/kg q3w for 6 cycles and mBe 15 mg/kg. Both treatments were administered until progression, unacceptable toxicity or death. Stratification was based on Study Centre and disease stage. Co-Primary endpoints were EQ5D Index (EQ5D-I) and EQ5D-VAS (Euro-QoL questionnaire) at 12 weeks during m. Secondary endpoints were QoL over time, activity and safety of CT arms. A sample of 49 pts per arm (not progressed during initial CT and during m therapy for at least 12 weeks) will have 91% chance to have 12-point Minimal Interesting Difference (MID) between arms for EQ5D-VAS, and 87% chance to find 0.137 MID between arms for EQ5D-I. It is assumed that about 20% of pts in both arms experienced a PD before to evaluate primary endpoint. The study sample was then increased to 118. **Results:** From 1/2011 to 3/2012, 118 pts were randomized to CP (n=60) or CbTBe (n=58). Baseline demographics were well balanced across arms; overall 74% male, 79% PS 0 and 94% stage IV. Treatment differences (mean change from baseline), EQ5D-VAS = 1.82 (95%CI -8.60 to 12.24; P=0.73), EQ5D-I = 0.15 (95%CI 0.01 to 0.29), favoured arm A. **Conclusions:** CP-mP showed better (over the MID) health profile (EQ5D-I) at 12 weeks as compared to CbBe-mBe. EQ5D-VAS didn't find any significant difference between treatment arms. Clinical trial information: NCT01303926.

8072 General Poster Session (Board #36D), Sat, 8:00 AM-11:45 AM

A phase I study of nivolumab (anti-PD-1; BMS-936558, ONO-4538) plus platinum-based doublet chemotherapy (PT-doublet) in chemotherapy-naive non-small cell lung cancer (NSCLC) patients (pts).

Naiyer A. Rizvi, Scott J. Antonia, Laura Quan Man Chow, Julie R. Brahmer, Rosalyn A. Juergens, Hossein Borghaei, Frances A. Shepherd, Scott Andrew Laurie, David E. Gerber, Jonathan Wade Goldman, Yun Shen, Christopher Harbison, Suresh Alaparthy, Allen C. Chen, Scott N. Gettinger; Memorial Sloan-Kettering Cancer Center, New York, NY; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; University of Washington, Seattle, WA; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Juravinski Cancer Centre, McMaster University, Hamilton, ON, Canada; Fox Chase Cancer Center, Philadelphia, PA; Princess Margaret Hospital, Toronto, ON, Canada; Ottawa Hospital Cancer Centre, Ottawa, ON, Canada; UT Southwestern Medical Center, Dallas, TX; University of California, Los Angeles, Los Angeles, CA; Bristol-Myers Squibb, Princeton, NJ; Yale School of Medicine, New Haven, CT

Background: A phase I study ofnivolumab (a PD-1 receptor blocking Ab) demonstrated durable responses and a tolerable safety profile in NSCLC pts who failed ≥1 chemotherapy regimen. We report an interim analysis of a phase I study with nivolumab + PT-doublets in chemotherapy-naive advanced NSCLC pts. **Methods:** Stage IIIB/IV NSCLC pts were randomized by histology ≥9 wk prior to data lock (Dec 2012) to: A) nivolumab/gemcitabine/cisplatin; B) nivolumab/pemetrexed/cisplatin; or C) nivolumab/carboplatin/paclitaxel according to a phase I dose de-escalation design to assess the toxicities and incidence of DLTs in the first 6 wk of dosing. Nivolumab doses were started at 10 mg/kg IV Q3W and given until progression. PT-doublet was given for 4 cycles at standard dosing. At a tolerable dose, cohorts were expanded up to 20 pts. **Results:** 43 pts were treated with nivolumab + PT-doublet: Arm A, n=12 squamous (sq); Arm B, n=15 (non-sq); and Arm C, n=16 (3 sq + 13 non-sq). No DLTs were seen across arms. Gr 3-4 regimen-related AEs were 49% across arms, and 25%, 47%, and 69% for Arms A, B, and C, respectively. Select Gr 3-4 toxicities reported included: pneumonitis, rash, nephritis, and colitis (Table). 3 pts had Gr 3 pneumonitis and were addressed with management algorithms (dose discontinuation and immune-modulating therapies). 2 pts fully resolved, however 1 resolved pt subsequently died from *Aspergillus* pneumonia. 1 pt died of disease progression with unresolved pneumonitis (autopsy confirmed). Total/Confirmed ORRs (RECIST 1.1) were 43/33%, 40/33%, and 31/31% in Arms A, B, and C, respectively. **Conclusions:** No DLTs were seen with 10 mg/kg nivolumab combined with PT-doublets; maintenance treatment is ongoing. Similar to monotherapy, select nivolumab related toxicities can be addressed with management algorithms. Safety, durability, and confirmation of responses will be updated based on a 2013 data analysis, including a 5 mg/kg nivolumab dose cohort. Clinical trial information: NCT01454102.

	Select Gr 3-4 toxicities, n (%)				Gr 3-4 regimen-related AEs, n (%)
	Pneumonitis	Rash	Nephritis	Colitis	
Arm A	1 (8)	0	0	0	3 (25)
Arm B	2 (13)	0	1 (7)	1 (7)	7 (47)
Arm C	0	2 (13)	0	0	11 (69)
All arms	3 (7)	2 (5)	1 (2)	1 (2)	21 (49)

8073 **General Poster Session (Board #36E), Sat, 8:00 AM-11:45 AM**

Efficacy and safety of paclitaxel and carboplatin with bevacizumab for the first-line treatment of patients with nonsquamous non-small cell lung cancer (NSCLC): Analyses based on age in the phase III PointBreak and E4599 trials.

Corey J. Langer, Mark A. Socinski, Jyoti D. Patel, Alan Sandler, Joan H. Schiller, Larry Leon, Shailaja Uttamsingh, Suresh S. Ramalingam; Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; University of Pittsburgh Medical Center, UPMC Cancer Pavilion, Pittsburgh, PA; Feinberg School of Medicine, Northwestern University, Chicago, IL; Knight Cancer Institute, Oregon Health and Science University, Portland, OR; Harold C. Simmons Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX; Genentech, Inc., South San Francisco, CA; The Winship Cancer Institute of Emory University, Atlanta, GA

Background: A post hoc analysis of NSCLC (pts) ≥70 y in the pivotal E4599 trial found increased adverse events (AEs) and numerically decreased survival benefit associated with bevacizumab (BEV) vs pts <70 y. We evaluated the efficacy and safety of BEV by age in pts in a pooled dataset from the E4599 and PointBreak (PB) trials. **Methods:** Pts randomized to the PC (paclitaxel and carboplatin) + BEV arms of E4599 and PB received P 200 mg/m^2, C AUC 6, and BEV 15 mg/kg q3w for 6 (E4599) or 4 (PB) cycles; 1 pt in PB received 6 cycles. Eligible pts received maintenance BEV q3w until disease progression or unacceptable toxicity. Overall survival (OS), progression-free survival (PFS), and safety were assessed in pts grouped according to age (<65 y, 65–75 y, 70–75 y, <75 y, and ≥75 y). Pt-level data from the PC + BEV arms of E4599 and PB were pooled and compared with data from pts in the PC-alone arm of E4599. **Results:** PB and E4599 randomized 467 pts and 434 pts to PC + BEV, respectively. Baseline characteristics were balanced between age groups. OS and PFS hazard ratios (HRs) and increases in grade ≥3 AEs for the pooled pt cohort relative to E4599 PC-alone arm are shown (Table). Outcomes were similar in pts <70 y and ≥70 y, and data from the pooled population were similar to those seen in each individual trial (data not shown). **Conclusions:** In a pooled exploratory analysis of pt data from E4599 and PB, the statistically significant benefit associated with the addition of BEV to PC appeared consistent across all age groups <75y. Pts ≥75 y receiving BEV had a higher incidence of grade ≥3 AEs relative to PC alone with no statistically significant survival benefit, although an increase in grade ≥3 AEs was observed in all age groups. Clinical trial information: NCT00762034 and NCT00021060.

PB + E4599	<65 y n=735	65–75 y n=453	70–75 y n=203	<75 y n=1188	≥75 y n=157
HR for OS	0.75	0.80	0.68	0.78	1.05
95% CI	0.62–0.89	0.64–1.00	0.48–0.96	0.68–0.89	0.70–1.57
P	<.01	.05	.03	<.01	.83
HR for PFS	0.71	0.62	0.57	0.69	0.95
95% CI	0.60–0.85	0.49–0.78	0.40–0.81	0.60–0.79	0.62–1.44
P	<.01	<.01	<.01	<.01	.80
E4599	n=499	n=277	n=129	n=776	n=102
Δ Grade ≥3 AEs,[a] %	13	21	23	15	25
P	<.01	<.01	<.01	<.01	<.01

[a] Relative to PC-alone arm.

8074 General Poster Session (Board #36F), Sat, 8:00 AM-11:45 AM

A phase II trial of second-line erlotinib in combination with stereotactic body radiation therapy (SBRT) for patients with metastatic non-small cell lung cancer (NSCLC).

Puneeth Iyengar, Brian D. Kavanagh, Irma Smith, Chul Ahn, David E. Gerber, Johnathan Dowell, Randall S. Hughes, Ramzi Abdulrahman, D. Ross Camidge, Laurie E. Gaspar, Robert Charles Doebele, Paul A. Bunn, Hak Choy, Robert D. Timmerman; UT Southwestern Medical Center, Dallas, TX; University of Colorado Cancer Center, Denver, CO; Harold C. Simmons Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX; The University of Texas Southwestern Medical Center, Dallas, TX; University of Texas Southwestern, Dallas, TX; University of Colorado Cancer Center, Aurora, CO

Background: Stage IV NSCLC patients who progress through first-line therapy have poor progression-free survival (PFS) and overall survival (OS), most commonly failing in existing sites of gross disease after systemic therapy. Cytoreduction with SBRT may aid systemic agents in prolonging survival. We decided to test this hypothesis in a multi-institutional phase II study with SBRT and erlotinib. **Methods**: Stage IV NSCLC patients with $\leq$ 6 sites of extracranial disease who failed first-line systemic therapy were eligible to receive SBRT to all sites of clinically apparent disease, utilizing equipotent fractionation schemes based on location of disease and risk of toxicity to critical normal structures, and erlotinib given daily (150 mg OD) until disease progression. Frequent SBRT fractionation schemes used included 33 Gy in 11 Gy fractions and 40 Gy in 8 Gy fractions. Safety and clinical endpoints were evaluated. **Results**: 23 patients (12 M: 11 F) with a median age of 67 (56-86) were enrolled in this trial with median follow-up of 14.7 months. All patients progressed through platinum-based chemotherapy, 14 with paclitaxel and 7 with pemetrexed as part of the doublet regimen. 20/23 patients received SBRT to 3 or fewer sites. Lung parenchyma and mediastinal lymph nodes represented most common sites of irradiation. Median PFS was 10.7 months and median OS was 20.8 months.A majority of patients progressed in new sites with only 4 patients failing locally. Most distant failures manifested in the liver. Only one grade 3 toxicity, pneumonitis, was radiation-related. The trial commenced before molecular profiling became standard; 5/10 patient tumors tested, however, had EGFR alterations by IHC/FISH, 0/10 were positive for an *EGFR* mutation. **Conclusions:** Use of SBRT with erlotinib for unselected stage IV NSCLC patients as a second-line therapy was well tolerated and resulted in significant PFS and OS, substantially greater than historical values for patients who only received second-line systemic agents. Debulking gross disease with local therapy results in a median PFS of nearly a year with patients relapsing most commonly in new rather than existing sites. Clinical trial information: NCT00547105.

8075 General Poster Session (Board #36G), Sat, 8:00 AM-11:45 AM

Phase I study of ridaforolimus with cetuximab for patients with advanced non-small cell lung cancer (NSCLC), colorectal cancer, and head and neck cancer.

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Background: mTOR inhibition may overcome PI3K/AKT pathway mediated resistance to anti-EGFR therapy. We performed a phase I study to determine the dose-limiting toxicity (DLT) of ridaforolimus, an investigational oral mTOR inhibitor, in combination with the anti-EGFR antibody cetuximab. **Methods:** Patients with advanced NSCLC, colorectal cancer, and head and neck cancer that progressed after at least 1 prior regimen for metastatic disease were eligible. ECOG performance status 0-1. Patients with previously treated brain metastases that were stable for >3 months were eligible. Wild-type K-RAS was required in colon cancer. All patients received cetuximab 400 mg/m^2 week 1 followed by 250 mg/m^2 weekly. Three dose levels of ridaforolimus were planned: 20mg, 30mg, and 40mg daily, 5 days each week, on a 28-day cycle. **Results:** 12 patients were entered with NSCLC (n=7), colon cancer (n=4), and head and neck cancer (n=1). The median age was 58 (42-69). The median number of prior regimens for metastatic disease, by disease type, was NSCLC (n=3), colorectal (n=4), head & neck (n=4). Three patients completed the first dose level without DLT. Two of 3 patients at dose level 2 had dose-limiting mucositis. The first dose level was then expanded with six additional patients with NSCLC without any further dose-limiting toxicities. The recommended phase II dose of ridaforolimus is 20 mg daily, 5 days a week, in combination with cetuximab. Response and prolonged stable disease was demonstrated in NSCLC. **Conclusions:** The DLT of the combination of ridaforolimus and cetuximab is mucositis. The activity observed in heavily pretreated patients with NSCLC suggests that the combination of an mTOR inhibitor with an EGFR antibody merits further investigation in NSCLC. Clinical trial information: NCT01212627.

8076 General Poster Session (Board #36H), Sat, 8:00 AM-11:45 AM

Prognostic impact of tumor (T) and lymph node (N) status in patients with metastatic non-small-cell lung cancer (NSCLC).

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Background: Although commonly reported in databases and clinical trials, T and N status do not affect the final stage or overall treatment plan for patients with metastatic NSCLC. Since there is limited data on the impact of T and N status on outcomes in this population, we conducted a Surveillance, Epidemiology, and End Results (SEER) study to address this question. **Methods:** The SEER database was searched for patients with stage M1b NSCLC, with known T and N status, diagnosed between 2004 and 2008. Patients with T0 and malignant pleural effusion were excluded. Overall survival (OS) was estimated by the Kaplan-Meier method, while the hazard ratios (HR) were estimated and compared using Cox proportional hazard models. **Results:** Among the 25,919 patients included, the frequencies of T1, T2, T3, and T4 were 15.8%, 28.2%, 33.6% and 22.4% respectively, whereas N0, N1, N2, and N3 were observed in 28.0%, 9.3%, 47.1% and 15.6% respectively. One-year OS ranged from 21.1% in T4 to 35.8% in T1, and 23.1% in N2 to 33.2% in N0 disease (Table). Both T and N were also identified as independent predictors for OS in multivariable analysis adjusted for age, gender, race, and histology. **Conclusions:** Both T and N status are important clinical prognostic factors that should be taken into consideration when evaluating patients with metastatic NSCLC. If confirmed in prospective studies, clinical trials and analyses of either clinical or molecular prognostic factors in the future may need to be adjusted according to the complete TNM staging.

Prognostic impact of T and N status in patients with metastatic NSCLC.

Stage	1-year OS	Univariable analysis	Multivariable analysis
		Hazard ratio (95% CI), p value	Hazard ratio (95% CI), p value
T1	35.8%	0.678 (0.649-0.707), $p < 0.0001$	0.708 (0.678 - 0.739), $p < 0.0001$
T2	28.2%	0.809 (0.780-0.838), $p < 0.0001$	0.824 (0.795 - 0.854), $p < 0.0001$
T3	25.4%	0.876 (0.847-0.907), $p < 0.0001$	0.886 (0.856 - 0.917), $p < 0.0001$
T4	21.1%	1	1
N0	33.2%	0.824 (0.791-0.858), $p < 0.0001$	0.810 (0.778 - 0.844), $p < 0.0001$
N1	29.4%	0.902 (0.856-0.951), $p = 0.0001$	0.908 (0.861 - 0.957), $p = 0.0003$
N2	23.1%	1.065 (1.026-1.105), $p = 0.0008$	1.049 (1.011 - 1.089), $p = 0.0113$
N3	25.3%	1	1

8077 **General Poster Session (Board #37A), Sat, 8:00 AM-11:45 AM**

The spectrum of genomic alterations in young adult non-small cell lung cancer (NSCLC).

Geoffrey R. Oxnard, Jennifer C. Heng, Stacy L. Mach, Peter C. Lo, Mohit Butaney, David Michael Jackman, Pasi A. Janne; Dana-Farber Cancer Institute, Boston, MA

Background: Identification of targetable genomic alterations in patients (pts) with NSCLC can have a profound impact on treatment and clinical outcomes. Given the complexity and cost of comprehensive genomic testing, clinical characteristics enriching for targetable genomic alterations are of interest. We hypothesized that young adults with NSCLC would have a higher prevalence of targetable genomics alterations compared to the general NSCLC population. **Methods**: An institutional database of pts with NSCLC was reviewed in an IRB-approved fashion to identify subjects with age < 40 at diagnosis. Clinical characteristics and risk factors were reviewed. Tumor genotyping for alterations in *EGFR*, *KRAS*, *ALK*, *BRAF*, *HER2*, and *ROS1*was pursued as part of an institution-wide genomics protocol. Targeted next-generation sequencing (NGS) of wild-type cases is underway. **Results**: From 2032 subjects with NSCLC, we identified 70 diagnosed at an age < 40 (3.4%). Pt characteristics: median age 35 (range 20-39); 63% never-smokers, 33% with $\geq$10 pack-years; 74% adeno, 9% squam, 14% undifferentiated, 3% neuroendocrine; 19% had a family history of lung cancer; 61% stage IV at diagnosis. Median survival from date of advanced disease was 15.8 months. Genotyping was performed on 51 pts with adeno or undifferentiated histology: 14 with *EGFR* mutations (27%), 5 with *KRAS* mutations (10%), 8 with ALK rearrangements (16%), 0 with *BRAF* mutations, 1 with a *HER2* insertion (2%), 1 with a *ROS1* rearrangement (2%). Compared to a reference prevalence from the Lung Cancer Mutation Consortium (Kris et al, ASCO, 2011), *KRAS* mutations were less common ($p=0.01$) and *ALK* rearrangements were more common ($p<0.01$). NGS of 2 cases to date has identified one pt with a novel 21 base-pair insertion mutation in *FGFR2*, not present in germline tissue. **Conclusions**: 47% (CI: 33%-60%) of pts diagnosed with NSCLC under age 40 harbor a targetable alteration in *EGFR*, *ALK*, *HER2*, or *ROS1*. These patients may be enriched for targetable genotypes and deserving of a unique treatment approach, and additionally represent an attractive population for genomic discovery.Supported in part by the Bonnie J. Addario Lung Cancer Foundation and the Conquer Cancer Foundation of ASCO.

8078 General Poster Session (Board #37B), Sat, 8:00 AM-11:45 AM

Progression patterns at RECIST PD during EGFR-TKIs in advanced NSCLC patients harboring *EGFR* mutation.

Tatsuya Yoshida, Kiyotaka Yoh, Koichi Goto, Shingo Matsumoto, Shigeki Umemura, Seiji Niho, Hironobu Ohmatsu, Yuichiro Ohe; Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan; National Cancer Center Hospital East, Kashiwa, Japan

Background: The progression patterns at RECIST PD during EGFR-TKIs in advanced NSCLC patients harboring *EGFR* mutation are clinically heterogeneous. The aim of this study is to evaluate progression patterns at RECIST PD during EGFR-TKIs in advanced NSCLC patients harboring *EGFR* mutation. **Methods:** From 2008 to 2012, 160 consecutive patients with advanced NSCLC harboring *EGFR* mutation were treated with EGFR-TKIs (erlotinib or gefitinib) at our institution. Among these patients, 104 patients who experienced RECIST PD assessed by radiologic findings were retrospectively evaluated for initial response on EGFR-TKIs, progression sites, focus of progression (solitary lesion or multiple lesions), patients status at RECIST PD, and post progression survival (PPS) from RECIST PD. **Results:** In 104 patients, 96 (92%) patients had *EGFR* major mutation (Exon 19 deletion and L858R), and 49 (47%) received EGFR-TKIs as first-line. The overall response rate and median progression free survival on EGFR-TKIs was 69 % and 8.2 months. At the time of RECIST PD, 44 (42%) patients had symptomatic, and 60 (58%) had asymptomatic. The progression sites were isolated CNS in 17 (16%) patients, isolated bone in 7 (7%), isolated pulmonary in 13 (12%), systemic in 67 (65%) patients. In the focus of progression, 24 (23%) patients have solitary lesion, and 80 (77%) have multiple lesions. After RECIST PD, 40 (38%) patients continued EGFR-TKIs, 25 (24%) were switched to cytotoxic agents, and 39 (38%) had best supportive care. 10 (10%) patients received local radiotherapy for isolated progression site (brain 6; bone 3; lung 1) and 8 of these patients continued EGFR-TKIs. The median PPS from RECIST PD was 10.6 months. Multivariate analysis identified that asymptomatic or solitary progression lesion at RECIST PD were associated with significantly longer PPS (asymptomatic: HR 0.34, 95% CI 0.19-0.58, $P<0.001$; solitary progression lesion: HR 0.39, 95% CI 0.16-83, $P=0.013$). **Conclusions:** The progression patterns at RECIST PD during EGFR-TKIs in advanced NSCLC patients harboring *EGFR* mutation have widely diversity. Further investigation for association between progression patterns at RECIST PD and clinical outcome after RECIST PD is warranted.

8079 **General Poster Session (Board #37C), Sat, 8:00 AM-11:45 AM**

Differences in mutation patterns of diagnostic versus post-chemotherapy samples in patients with metastatic non-small cell lung cancer (NSCLC).

William Nassib William, Heidi S. Erickson, Caimiao Wei, Nana Hanson, Ximing Tang, Jaime Rodriguez, Neda Kalhor, J. Jack Lee, Waun Ki Hong, Edward S. Kim, Ignacio Ivan Wistuba; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Thoracic / Head and Neck Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX; Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX; Carolinas Healthcare System, Charlotte, NC

Background: Many clinical trials in metastatic NSCLC patients who failed first-line chemotherapy have utilized pre-treatment, diagnostic tissues for marker assessment. BATTLE was a randomized, biopsy-driven clinical study in patients with metastatic NSCLC previously treated with systemic therapy. Fresh biopsies were obtained at the time of enrollment for biomarker evaluation. We hypothesized that molecular abnormalities found at the time of enrolment in BATTLE would differ from baseline, pre-chemotherapy, diagnostic tissue. **Methods**: We isolated DNA (SPRI-TE-based DNA recovery and cleanup methodology) from 82 matched pre-chemotherapy and BATTLE formalin-fixed paraffin-embedded specimens. Mutations were assessed by MALDI-TOF MS (MassArray, Sequenom Inc) using a lung cancer panel of 16 genes/140 assays (AKT1, BRAF, CTNNB1, EGFR, ERBB2, FGFR3, HRAS, KRAS, MEK1, MEK2, MET, NRAS, PIK3CA, PIK3R1, PTEN, and STK11) and were compared between pre-chemotherapy versus BATTLE samples. **Results**: Mutations were identified in 25 pre-chemotherapy samples (14 K-RAS, 5 EGFR, 3 PIK3CA, 1 STK11, 1 PTEN, 1 HRAS, 1 CTNNB1). Conversely, 29 BATTLE samples had at least one mutation (14 K-RAS, 7 EGFR, 5 PIK3CA, 2 STK11, 1 PTEN, 1 HRAS, 1 CTNNB1). For the matched pair analysis, 46 patients had wild-type tumors both in pre-chemotherapy and BATTLE samples. 11 patients had wild-type tumors in pre-chemotherapy samples, but had a mutation identified in BATTLE samples (4 K-RAS, 4 EGFR, 2 PIK3CA, 1 STK11). 7 patients had a mutation in pre-chemotherapy samples, but no mutations in BATTLE samples (4 K-RAS, 2 EGFR, 1 HRAS). The remaining 18 patients had mutations in both the pre-chemotherapy and BATTLE samples; of these, 2 had different mutations in the paired samples (both within the same genes, 1 KRAS, 1 PIK3CA). Overall, there was a 24% gene mutation discordance rate between pre-chemotherapy and BATTLE samples. **Conclusions**: Profiling of fresh biopsies may more accurately reflect molecular abnormalities present in the tumor at the time of initiation of salvage therapy, underscoring the importance of real time tissue collection in biomarker-driven studies in this setting (V Foundation, DoD).

8080 General Poster Session (Board #37D), Sat, 8:00 AM-11:45 AM

Erlotinib after initial platinum-doublet chemotherapy in patients with epidermal growth factor receptor (*EGFR*) wild-type (WT) non-small cell lung cancer (NSCLC): Results of a combined patient-level analysis of the BR.21 and SATURN trials.

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Background: Two double-blind, prospective, randomized, placebo-controlled trials demonstrated survival benefit in unselected populations with advanced NSCLC in the 2nd/3rd line (BR.21) and maintenance setting (SATURN). The efficacy of erlotinib in patients with *EGFR* WT NSCLC has been questioned. We examined the impact of erlotinib vs placebo in confirmed *EGFR* WT patients in both studies. **Methods:** Combined re-analysis of progression-free survival (PFS) (from date of randomization to investigator-assessed progression or death from any cause), and overall survival (OS) (from date of randomization to death from any cause) in patients with known WT *EGFR*. PFS and OS were estimated by Kaplan-Meier curves and compared by 2-sided log-rank test. Cox proportional hazards model was used to estimate hazard ratios (HR) adjusted for potential confounders. Sensitivity analyses assessed comparability of patients with known and unknown *EGFR* mutation status to determine generalizability of the two study populations. **Results:** 74% of the BR.21 population (n=150) and 89% of the SATURN population (n=388) with known *EGFR* mutation status had WT *EGFR*. PFS and OS for individual and combined analyses are shown (Table). Adjusting for non-randomized therapy after study therapy discontinuation, HR for OS was 0.74 (0.61–0.91); $p<0.01$. Baseline characteristics were similar for patients with known and unknown *EGFR* status, suggesting generalizability of the *EGFR* WT data. Erlotinib benefit was sustained in all clinical subsets. **Conclusions:** Erlotinib provided a consistent and significant improvement in survival for patients with *EGFR* WT NSCLC in both studies, individually and in combination. The benefit of erlotinib does not appear to be limited to patients with activating *EGFR* mutations.

Median survival, mo	BR.21 (n=150)	SATURN (n=388)	Combined (n=538)
PFS, erlotinib vs control	2.2 vs 1.8	2.8 vs 2.0	
HR	0.55	0.76	0.72
95% CI	0.37–0.81	0.62–0.94	0.60–0.87
P value	<0.01	0.02	<0.01
OS, erlotinib vs control	8.1 vs 3.4	11.3 vs 10.2	
HR	0.68	0.72	0.71
95% CI	0.45–1.02	0.57–0.91	0.58–0.87
P value	0.14	0.02	0.04

8081 General Poster Session (Board #37E), Sat, 8:00 AM-11:45 AM

Comparison of two chemotherapy regimens in non-small cell lung cancer patients relapsing after surgery and peri-operative chemotherapy (IFCT-0702 study).

Denis Moro-Sibilot, Clarisse Audigier-Valette, Patrick Merle, Elisabeth A. Quoix, Pierre Jean Souquet, Fabrice Barlesi, Christos Chouaid, Oliver Molinier, Armelle Lavole, Julien Mazieres, Laurence Baudrin, Franck Morin, Gerard Zalcman, Intergroupe Francophone de Cancérologie Thoracique (IFCT); Thoracic Oncology unit CHU Grenoble, Inserm U823, Grenoble, France; Service de Pneumologie - CH Toulon, Toulon, France; Centre Hospitalier Universitaire Clermont-Ferrand, Clermont-Ferrand, France; Hôpitaux Universitaires de Strasbourg, Strasbourg, France; Centre Hospitalier Lyon-Sud, Pierre-Bénite, France; Aix Marseille University, Assistance Publique Hôpitaux de Marseille, Hôpital Nord, Marseille, France; Hôpital Saint-Antoine, UPMC University, Paris, France; Le Mans Regional Hospital, Le Mans, France; Hôpital Tenon, AP-HP and Faculté de Médecine Pierre et Marie Curie, Université Paris VI, Paris, France; Hôpital Larrey CHU Toulouse, Toulouse, France; Intergroupe Francophone de Cancérologie Thoracique, Paris, France; Caen University Hospital, Caen, France

Background: To evaluate the benefit of adding cisplatin or carboplatin (P) to docetaxel (D) chemotherapy (CT) in patients with the first metastatic relapse after perioperative chemotherapy and surgery. **Methods:** Patients (Pts) with histologically or cytologically confirmed inoperable non-small cell-lung cancer not eligible for curative radiotherapy (local or metastatic relapse), disease progression after perioperative chemotherapy and surgery and PS 0-1. Pts were randomized to D 75 mg/m² combined with cisplatin 75 mg/m² or carboplatin AUC5 every 3 weeks (Arm A) or alone (Arm B). The primary endpoint was progression-free survival (PFS). **Results:** Due to low accrual the trial was interrupted after inclusion of 88 patients. From November 2007 to August 2012, 68 males and 20 females, median age (range) 61 (41-75), ECOG PS 0/1/ 49%/50%, squamous histology 39%, Arm A and Arm B 44 patients each, were enrolled. Interval from last cycle of perioperative CT ou last cycle of adjuvant CT was $\geq$ 12 months in 69% of pts. 79.5% of patients received DP full treatment. A non-statistically significant increase in PFS favoring combined CT was observed with a HR of 0.73 (95% CI: 0.46-1.15; p = 0.18), median PFS 8 months vs 5.6. Objective response rate was increased in the P-containing arm; $p < 10^{-4}$). However, overall survival was not improved by the addition of P to D; the HR for death was 0.90 (95% CI: 0.55-1.48; p = 0.68) median OS 15.9 months vs 12.4 months. Overall grade 3/4 toxicity was observed in 36 pts (DP) vs 30 (D) : neutropenia (32 pts vs 26), febrile neutropenia (8 vs 3), non-hematological toxicities (18 vs 6). **Conclusions:** PFS and OS weresurprisingly longer than expected in this cohort of NSCLC patients with metastasis, and comparable with that observed in historical cohorts of NSCLC treated in first-line. DP resulted in a non significant 27% reduction of hazard of progression as compared to D alone. A reduced statistical power related to a slow and insufficient accrual may explain this lack of significance. Considering survival data and toxicity profile, we suggest that these patients behave like first-line patients and may probably be treated accordingly with a platinum-based doublet. Clinical trial information: NCT00535275.

8083 General Poster Session (Board #37G), Sat, 8:00 AM-11:45 AM

A retrospective analysis of the prevalence of *EGFR* or *KRAS* mutations in patients (pts) with crizotinib-naïve and crizotinib-resistant, ALK-positive non-small cell lung cancer (NSCLC).

Justin F. Gainor, Anna M. Varghese, Sai-Hong Ignatius Ou, Sheheryar Kabraji, Mark M Awad, Ryohei Katayama, Amanda Pawlak, Mari Mino-Kenudson, Beow Y. Yeap, Gregory J. Riely, Anthony John Iafrate, Maria E. Arcila, Marc Ladanyi, Jeffrey A. Engelman, Dora Dias-Santagata, Alice Tsang Shaw; Massachusetts General Hospital, Boston, MA; Memorial Sloan-Kettering Cancer Center, New York, NY; Chao Family Comprehensive Cancer Center, Orange, CA; Department of Pathology, Massachusetts General Hospital, Boston, MA

Background: Anaplastic lymphoma kinase (*ALK*) gene rearrangements define a distinct molecular subset of NSCLC. Recently, several studies have reported that ALK+ pts occasionally harbor concomitant mutations in other oncogenic drivers. **Methods:** We retrospectively analyzed tumor genotyping data from 1,683 pts with NSCLC seen at 3 U.S. centers from 2009 – 2012 to determine rates of overlapping alterations in *EGFR*, *KRAS* and *ALK*. Mutations in *EGFR* and *KRAS* were mainly identified using the SNaPshot multiplexed assay (>95% of cases). ALK FISH was performed in all cases. To determine if this prevalence is impacted by crizotinib, we also updated our earlier analysis (Katayama et al., *Sci Transl Med*, 2012) of a series of repeat biopsy specimens from 34 crizotinib-resistant, ALK+ pts. Resistant specimens were examined using ALK FISH, SNaPshot, and direct sequencing of the ALK tyrosine kinase domain (TKD). **Results:** Screening identified 301 (17.8%) *EGFR* mutations, 465 (27.6%) *KRAS* mutations, and 75 (4.4%) *ALK* rearrangements. *EGFR* mutations and *ALK* rearrangements were mutually exclusive. 4 pts with *KRAS* mutations also had abnormal ALK FISH patterns, involving isolated 5' green probes (3/4 cases) and an isolated 3' red probe that was unusually small (1/4 cases). Sufficient tissue was available for confirmatory ALK immunohistochemistry (clone 5A4, Novacastra, UK) in 3 of these cases, all of which were negative for ALK expression. Among pts with ALK+ NSCLC and acquired crizotinib resistance, repeat biopsy specimens remained *ALK* fusion positive in 28/28 (100%) cases. Secondary mutations in the *ALK* TKD (1151Tins, L1196M, G1202R, S1206Y, and G1269A) were identified in 7/34 (20.6%) cases. L1196M was the most common secondary mutation (3/34, 8.8% cases). *ALK* gene amplification was present in 3/28 (10.71%) pts. No *EGFR* or *KRAS* mutations were identified in 23 crizotinib-resistant, ALK+ pts with sufficient tissue for testing. **Conclusions:** Functional *ALK* rearrangements were mutually exclusive with *EGFR* and *KRAS* mutations in a large Western patient population. This lack of overlap was also observed in ALK+ pts with acquired resistance to crizotinib.

8084 General Poster Session (Board #37H), Sat, 8:00 AM-11:45 AM

Phase I study of peptide vaccine targeting indeolamine 2,3 dioxygenase in metastatic lung cancer patients.

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Background: To investigate the targeting of indeolamine 2,3 dioxygenase (IDO) enzyme by a synthetic peptide vaccine for patients with metastatic non small-cell lung cancer (NSCLC). **Methods:** We treated15 HLA-A2 positive patients with stage III-IV NSCLC and disease stabilization (SD) after standard chemotherapy. Patients were treated every second week (induction) for three months, and thereafter monthly until progression (maintenance) with imiquimod ointment and vaccine (100 μg IDO5 peptide sequence ALLEIASCL mixed with 900 μL montanide) administered subcutaneously. Primary end point was toxicity. Clinical benefit and immune monitoring were assessed. **Results:** Patient characteristics: mean age (63, range 51-71), sex (F=8,M=7), PS(0=9,1=6), histology (adenocarcinoma=93%), previously anti-neoplastic treatments (1st line=100%, 2nd =40% and 3rd=27% of patients). No grade 3-4 CTCAE toxicity was observed. Median PFS was 5.2 months and median OS 2.1 years. Long-lasting disease stabilization (SD≥8.5 months) was demonstrated in 7 patients (47%). Patients demonstrated significant improved OS (P=0.02) when compared to the untreated group of excluded HLA-A2 negative NSCLC patients. IDO expression was frequently detected in tumour biopsies by immune-histochemistry staining. Immune induction of IDO specific CD8 T-cells were demonstrated by IFN-y Elispot and Tetramer staining. Immune correlates of T-lymphocyte subsets were performed by flow cytometry. HPLC analyses of Trp/Kyn ratio suggested stabilization or decrease of IDO activity in 11/15 (73%) of the patients. **Conclusions:** The vaccine was safe and well-tolerated with no grade 3/4 toxicity occurring. Long-lasting SD was seen in 47% of the patients demonstrating a median OS of 2.1 year. IHC demonstrated frequent IDO activity in NSCLC tumour biopsies, and blocking of IDO activity was indicated by Kyn/Trp ratio measurements. Clinical trial information: NCT01219348.

8085 General Poster Session (Board #38A), Sat, 8:00 AM-11:45 AM

Incidence, characteristics, and survival of patients with *EGFR*-mutant lung cancers with *EGFR T790M* at diagnosis identified in the lung cancer mutation consortium (LCMC).

Mark G. Kris, Geoffrey R. Oxnard, Bruce E. Johnson, Lynne D Berry, Heidi Chen, David J. Kwiatkowski, Anthony John Iafrate, Ignacio Ivan Wistuba, Wilbur A. Franklin, Dara Aisner, Lecia V. Sequist, Fadlo Raja Khuri, Edward B. Garon, William Pao, Charles M. Rudin, Joan H. Schiller, Eric B. Haura, John D. Minna, Paul A. Bunn; Memorial Sloan-Kettering Cancer Center, New York, NY; Dana-Farber Cancer Institute, Boston, MA; Vanderbilt University, Nashville, TN; Vanderbilt-Ingram Cancer Center, Nashville, TN; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Colorado Denver, Denver, CO; University of Colorado School of Medicine, Aurora, CO; Massachusetts General Hospital, Boston, MA; The Winship Cancer Institute of Emory University, Atlanta, GA; University of California, Los Angeles, Santa Monica, CA; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; The University of Texas Southwestern Medical Center, Dallas, TX; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; University of Colorado Cancer Center, Aurora, CO

Background: Somatic *T790M* mutations are detected in 62% of *EGFR*-mutant lung cancers with acquired resistance to EGFR TKIs, and have rarely been identified in the tumor at diagnosis and/or within the germline DNA. Multiplexed genotyping by the LCMC permitted us to evaluate the incidence of *T790M* at diagnosis, co-mutations, and survival of patients with this driver. **Methods:** The 14 member LCMC prospectively tested tumors of patients with lung adenocarcinomas in CLIA laboratories for mutations in *EGFR* and 9 other genes. We assayed *T790M*by Sequenom, Snapshot, or Sanger sequencing. Germline DNA was not collected. **Results:** In the 987 tumors tested, 209 had mutations in *EGFR* alone: 25 *T790M* (2.5%) , 157 sensitizing *EGFR* mutations (exon 19 del, *L858R*, *L861Q*, *G719X*) without *T790M*, 23 exon 20 ins, 4 other mutations. 13 additional cases harbored mutations in *EGFR* and another driver; 2 with both *T790M* and *PIK3CA*. In each of the 27 *EGFR*-mutant cases with *T790M*, a coincident *EGFR* mutation was detected (18 exon 19 del, 9 *L858R*, 1 exon 20 ins). *EGFR T790M* was found more often than *EGFR* exon 20 ins or mutations in *HER2 (1.9%)*, *BRAF (1.6%)*, or *PIK3CA (0.7%)*. Patients with *T790M*: 77% women, 81% never smokers, median age 55 (range 38-79), stage IV at diagnosis 81%, PS 0/1 100%. Characteristics did not differ from persons with sensitizing mutations and no *T790M*. Median survival from the diagnosis of metastatic disease for patients with *EGFR*-mutant lung cancers was 3.5 yrs with *T790M*and 4.0 yrs without (p=0.926). **Conclusions:** *T790M* mutations were detected at diagnosis in 3% of adenocarcinomas and always coincident with another *EGFR* mutation. Cases with *T790M* represent 13% of all cases of *EGFR*-mutant lung cancer. Characteristics and survival for patients with *EGFR*- mutant lung cancers with *T790M* at diagnosis were similar to individuals with sensitizing mutations and no *T790M*. The observed incidence of *T790M* exceeded that of the other actionable targets *HER2, BRAF*, and *PIK3CA*. Trials should study this unique population identified by routine multiplexed genotyping. Supported by 1RC2CA148394-01 and the National Lung Cancer Partnership. Clinical trial information: NCT01014286.

8086 General Poster Session (Board #38B), Sat, 8:00 AM-11:45 AM

Translational research (TR) results from pointbreak: A randomized, open-label, phase III study of pemetrexed (Pem)+carboplatin (Cb)+bevacizumab (Bev) followed by maintenance pem+bev (Pem Arm) versus paclitaxel (Pac)+cb+bev followed by maintenance bev (Pac Arm) in patients (pts) with stage IIIB or IV nonsquamous non-small cell lung cancer (ns-NSCLC).

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Background: Results of PointBreak were previously reported. Correlative tissue TR results are presented. **Methods:** Of 939 pts in the intent-to-treat population (ITT), 211 (22.5%) signed TR consent forms and had evaluable samples. Specimens were analyzed for: Epidermal Growth Factor Receptor (EGFR) mutations by polymerase chain reaction (n=132); thyroid transcription factor-1 (TTF-1) (n=205), thymidylate synthase (TS) (n=189), and folate receptor-alpha (FR-α) (n=180) by immunohistochemistry (IHC) (H-scores range, 0-300). H scores were dichotomized based on positive (>0)/negative (=0) cutpoint. Adjusted Cox/logistic regression determined correlations between overall survival (OS), progression-free survival (PFS), response rate (RR), and dichotomous IHC markers. A 2-sided test with $\alpha = 0.05$ and 0.1 evaluated treatment and interaction effects, respectively. **Results:** Median (m) OS and mPFS were similar in the ITT and TR populations for both arms. 11/132 (8.3%) pts had activating EGFR mutations. For TS or FR-α, no significant between-arm differences in OS, PFS and RR were seen. 139/205 (67.8%) pts had positive TTF-1 (TTF-1+). TTF-1+ pts, compared with TTF-1-, independent of treatment, had significantly longer mOS (14.9 vs 8.7 mos, HR 0.48, p<0.001), mPFS (6.9 vs 4.5 mos, HR 0.62, p=0.006), and higher RR (38.9% vs 19.7%, OR 2.68, p=0.008). For TTF-1+ pts, compared with Pac arm, Pem arm had longer mOS (17.6 vs 12.8 mos, HR=0.7, p=0.08; interaction p=0.12) and mPFS (7.3 vs 5.8 mos, HR=0.78, p=0.20; interaction p=0.261); although not statistically significant. **Conclusions:** The number of pts with EGFR mutations was too small to draw conclusions. No significant between-arm differences for TS and FR-α were seen. Longer survival in TTF-1+ pts suggests TTF-1 expression is prognostic. Additional studies will be needed to better understand trends favoring pem for survival among TTF-1+ pts and other prognostic and/or predictive relationships of these markers. Clinical trial information: NCT00762034.

8087 General Poster Session (Board #38C), Sat, 8:00 AM-11:45 AM

Prediction of survival outcomes in NSCLC using a new PRO index from the LCSS (Lung Cancer Symptom Scale): Results of a 622-patient prospective trial.

Richard J. Gralla, Patricia J Hollen, Sumitra Thongprasert, Hoon-Kyo Kim, Te-Chun Hsia, Shi Yuankai, Nina Kohn, Martin Lesser; Albert Einstein College of Medicine, Jacobi Medical Center, Bronx, NY; University of Virginia, Charlottesville, VA; Maharaj Nakorn Chiang Mai Hospital, Chiang Mai, Thailand; St. Vincent's Hospital, Suwon, South Korea; China Medical University, Taichung, Taiwan; Chinese Academy of Medical Sciences, Beijing, China; Feinstein Institute for Medical Research, Manhasset, NY

Background: Accurate and easy prediction of survival at the onset of treatment for all patients is required for appropriate trial design and personalization of patient (pt) monitoring. No pt reported factor is routinely used for these purposes, as performance status (PS) is not pt rated. **Methods:** This prospective study, the AP-QL lung trial, enlisted 622 pts receiving initial docetaxel-based chemotherapy (80% with cisplatin or carboplatin) and correlated patient reported outcomes (PROs) from an electronic version of the LCSS (eLCSS-QL) every 3 weeks with survival outcomes. The eLCSS-QL requires $<$ 3 minutes. **Results:** Baseline PROs and survival data were available for 96% of pts. Pts: 70% male; 65% adenoca; medians: KPS $=$ 90; ECOG $=$ 1 (27% ECOG 0); Stages: IV (72%), IIIB (28%). Survival: 12.8 months median; 52%, 1 year. Survival results were analyzed for differences for those living less than or greater than the median for each NSCLC symptom and LCSS global factor. For symptoms such as pain, dyspnea, or appetite, survival differences above and below the median varied from 2.5 to 4 months. Unlike individual symptoms which are found only in subsets of pts, LCSS pt-reported global items (symptom distress, activity level, and quality of life) each apply to all pts. Median survival differences above (positive factor) or below (negative factor) medians for each global item varied by 4 months ($p < 0.003$). An index was created using the number of negative factors, 0 to 3, based on survival less than the median for each of these 3 factors (Table). **Conclusions:** Several large and highly significant survival differences can be predicted by this simple LCSS HRQL-PRO Index, if assessed prior to chemotherapy. This index identifies more accurate survival differences than PS, can assist better trial design and analysis, and can aid in personalizing patient monitoring based on individual likelihood of risk and benefit. The results illustrate the strong correlations of PROs with survival.

# of negative PRO factors	% of patients	Median survival (months)	Survival: 1 year	Survival: 2 year
0	29%	16 (p = .0003, 0 vs 3 factors)	64%	36%
1,2	44%	13 (p = .007, 1 vs 3 factors)	54%	30%
3	27%	9	38%	13%

8088^ General Poster Session (Board #38D), Sat, 8:00 AM-11:45 AM

Phase I and pharmacodynamic study of the histone deacetylase (HDAC) inhibitor romidepsin plus erlotinib in previously treated advanced non-small cell lung cancer (NSCLC).

David E. Gerber, Rachael Skelton, Ying Dong, Laurin Loudat, Jonathan Dowell, David A. Boothman, Venetia Sarode, Wei Zhang, Yang Xie, Adi Gazdar, Eugene P. Frenkel, Joan H. Schiller; Harold C. Simmons Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX; Harold C. Simmons Cancer Center, Univesity of Texas Southwestern Medical Center, Dallas, TX

Background: Preclinical studies have demonstrated anti-tumor efficacy of the combination of the HDAC inhibitor romidepsin plus erlotinib in NSCLC models insensitive to erlotinib monotherapy (eg, *KRAS* mutation, *EGFR* resistance mutation, *EGFR* wild type). **Methods:** This phase I study evaluated safety, pharmacodynamics, and preliminary activity of romidepsin (8-10 mg/m^2) given IV days 1, 8, and 15 every 28 days plus erlotinib 150 mg PO daily in previously treated advanced NSCLC. In Cycle 1, erlotinib was initiated on Day 3, permitting pharmacodynamic analysis of romidepsin alone and in combination. **Results:** As of January 31, 2013, 15 patients (pts) have been treated: median age 60 years; 7 F, 8 M; all former or current smokers; 6 had prior erlotinib exposure; 8 adenocarcinoma, 6 squamous, 1 large cell; 5 *EGFR* wild type 1 *KRAS* mutation, 9 unknown mutation status. Most common related AEs regardless of grade were nausea (87%), vomiting (73%), fatigue (60%), diarrhea and rash (both 53%), and decreased appetite (47%). Grade 3-4 AEs (all grade 3) included nausea and vomiting (both 20%); decreased appetite, diarrhea, fatigue (each 13%). Dose-limiting nausea and vomiting occurred at romidepsin 10 mg/m^2 level despite aggressive antiemetic prophylaxis and treatment. At romidepsin 8 mg/m^2, related grade 3 AEs included fatigue (n=1) and diarrhea (n=1), with no grade 3 nausea or vomiting. 9 pts were evaluable by RECIST; best response SD (n=6), PD (n=3). Median PFS was 3.3 months (range 1.4-16.5 months). At romidepsin 8 mg/m^2, PFS range 2.0-16.5 months. At both dose levels, romidepsin inhibited HDAC activity and increased histone H3 and H4 acetylation status in peripheral blood mononuclear cells. Romidepsin also inhibited EGFR phosphorylation and, in 60% of pts, MAPK phosphorylation in skin biopsies. **Conclusions:** Romidepsin 8 mg/m^2 plus erlotinib appears well tolerated, has encouraging evidence of disease control, and exhibits effects on relevant molecular targets in an unselected advanced NSCLC population. Further studies are underway. Clinical trial information: NCT01302808.

8089 **General Poster Session (Board #38E), Sat, 8:00 AM-11:45 AM**

Multitargeted antiangiogenic tyrosine kinase inhibitors in advanced non-small cell lung cancer: A meta-analysis of randomized controlled trials.

Wenhua Liang, Li Zhang; Cancer Center, Sun Yat-Sen University, Guangzhou, China; Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Novel multitargeted antiangiogenic tyrosine kinase inhibitors (MATKIs) have showed promising advantages in combination with chemotherapy or as monotherapy in treatments of advanced non-small cell lung cancer (NSCLC). Since the efficacy and safety of these small molecules have been evaluated by several phase II/III randomized controlled trials (RCTs), we seek to summarize the current evidences by performing a meta-analysis. **Methods:** PubMed, EMBASE, the Cochrane Library as well as the ASCO and ESMO databases were searched for eligible literatures. We defined the experimental arm as MATKI-containing group while the control arm as MATKI-free group. The endpoints being evaluated included overall survival (OS), progression free survival (PFS), objective response rate (ORR) and disease control rate (DCR), as well as adverse events (AEs). Pooled hazard ratios (HRs) for survival outcomes and odds ratio (ORs) for dichotomous data, with 95% confidence intervals (CI) were calculated using REVMAN 5.0. Subgroup analysis was conducted according to each agent respectively. **Results:** Five agents (vandetanib, sunitinib, cediranib, sorafenib, motesanib) with comparable data could be analyzed. Fifteen phase II/III RCTs that involved a total of 8854 participants were included. Compared to MATKI-free group, MATKI-containing group was associated with significant longer PFS (HR 0.824, 95% CI 0.759 to 0.895, $P<0.001$), superior ORR (OR 1.27, 95% CI 1.13 to 1.42, $P<0.0001$) and DCR (OR 1.14, 95% CI 1.04 to 1.25, $P=0.006$). However, although some improvement in OS was observed, the benefit did not reach statistical significance (HR 0.962, 95% CI 0.912 to 1.015, $P=0.157$). In terms of subgroup results, sorafinib was revealed to yield no improvement in all endpoints. The specific AEs in patients who received these agents were rash, diarrhea and hypertension. **Conclusions:** Regimens consisting of multitargeted antiangiogenic TKIs were superior to those without these agents in terms of tumor response and PFS in patients with advanced NSCLC. However, no significant benefits in OS were observed. In addition, sorafinib seemed to has no substantial efficacy for NSCLC patients.

8090 General Poster Session (Board #38F), Sat, 8:00 AM-11:45 AM

Patterns of second-line chemotherapy and its effect on survival in patients treated within the Veterans Health Administration (VHA).

Rafael Santana-Davila, Danielle M. File, Carlos Eduardo Arce-Lara, Michael J. Kelley, Christina D. Williams, Jeffrey C. Whittle; Medical College of Wisconsin, Milwaukee, WI; Durham VA Medical Center/Duke University Medical Center, Durham, NC; Durham VA Medical Center, Durham, NC; Medical College of Wisconsin; Milwaukee VA Medical Center, Milwaukee, WI

Background: Second-line chemotherapy (2-L) improves overall survival (OS) in patients with metastatic NSCLC. In 2004, erlotinib and pemetrexed were approved as 2-L agents. In this study we analyze the utilization of anti-cancer agents and survival for patients with NSCLC who received 2-L treatment within the VHA. **Methods**: We identified from the VA Central Cancer Registry incident cases of metastatic NSCLC diagnosed between 2001 and 2008. We included patients who received their 1st cycle of chemotherapy within 120 days of diagnosis. A chemotherapy regimen included all chemotherapy agents prescribed during the next 28 days. We defined a subsequent line of therapy when a new agent was started after a period of more than the initial 28 days since the last drug. We divided our cohort into two based on whether they were diagnosed or treated before August of 2004 (the date pemetrexed was approved). **Results**: 5,893 patients fulfilled our eligibility criteria and were included for analysis. 2,200 patients were diagnosed before 2004 and 3,693 after. 2-L was administered in 35% (n=2052) of patients overall. Veterans diagnosed after 2004 were more frequently prescribed 2-L compared to those diagnosed earlier (30.2 vs. 37.6%, $p<0.001$). The most commonly prescribed agent in the earlier period was docetaxel in 43% (n=226) followed by gemcitabine in 22% (n=115). In contrast for patients treated after 2004 the most common agents were pemetrexed in 28% (n=421) followed by erlotinib in 27% (n=418). In this period docetaxel and gemcitabine was prescribed in 19 and 10% of cases respectively. Time from diagnosis to the start of 2-L was shorter in patients treated before 2004 (median 3.6 months (IQR 2.3-6.9) vs. 4.9 (IQR 2.6-8.2) $p<0.001$). Third-line chemotherapy was administered more frequently in those patients treated after 2004 (26 vs. 5.9%, $p<0.001$). There was no difference in survival between the two periods (Median OS 5.8 vs. 5.6 months in patients treated after 2004$p=0.73$) **Conclusions**: Since 2004 with the introduction of two new agents, which were widely adopted, patients are more likely to receive 2-L for NSCLC. In the last decade there has been no improvement in OS for patients treated with 2-L.

8091 General Poster Session (Board #38G), Sat, 8:00 AM-11:45 AM

KRAS subset analysis from randomized phase II trials of erlotinib versus erlotinib plus sorafenib or pazopanib in refractory non-small cell lung cancer (NSCLC).

David Michael Waterhouse, Dawn Michelle Stults, Davey B. Daniel, Paula L. Griner, F Anthony Greco, Howard A. Burris, John D. Hainsworth, David R. Spigel; Oncology Hematology Care/SCRI, Cincinnati, OH; Sarah Cannon Research Institute, Nashville, TN; Tennessee Oncology, PLLC/SCRI, Nashville, TN; Sarah Cannon Research Institute; Tennessee Oncology, Nashville, TN

Background: *KRAS* mutations are among the most common genetic alterations in NSCLC; however no targeted therapies have been approved to benefit this lung cancer subset. Between 2/2008 and 2/2011 our center conducted two consecutive multicenter randomized phase II trials in patients (pts) with refractory NSCLC comparing erlotinib/placebo versus erlotinib + either sorafenib or pazopanib, both oral multikinase inhibitors (Spigel et al, JCO 2011; Chicago MSTO 2012). Progression-free survival (PFS) was improved with the multikinase regimens in the *EGFR* wild-type (WT) subsets, but not in the overall populations. An unplanned analysis of the combined *KRAS* subset data is the subject of this report. **Methods:** Eligibility criteria for both trials included: stage IIIB/IV NSCLC; 1 to 2 prior regimens; ECOG performance status 0–2; measurable disease. PFS was the primary endpoint of each trial. Treatment groups included: erlotinib/placebo (N=121), erlotinib/sorafenib (N=112), and erlotinib/pazopanib (N=127). 168 pts (47%) in these three groups had sufficient tumor specimens for *KRAS* analysis. **Results:** The PFS and OS results based on *KRAS* results are shown in the Table below. **Conclusions:** Patients in whom the *KRAS* mutation status was known achieved a significantly longer PFS with erlotinib and a multikinase inhibitor than with erlotinib alone. Although this unplanned combined analysis has several limitations, the greater PFS and OS benefits in pts with *KRAS* mutations warrant further study. Clinical trial information: NCT00600015; NCT01027598.

	Erlotinib + TKI	Median PFS months (95%CI)	HR	Erlotinib + placebo	Median PFS months (95%CI)	P value
***KRAS* mutant**	28 pts	2.60 (2.23, 3.65)	0.2	18 pts	1.64(0.92, 1.68)	0.0001
***KRAS* WT**	76 pts	3.25 (2.13, 4.04)	0.62	46 pts	1.83 (1.74, 2.46)	0.02
	Erlotinib + TKI	Median OS months (95%CI)	HR	Erlotinib + placebo	Median OS months (95%CI)	P value
***KRAS* mutant**	28 pts	5.29 (3.15, 11.33)	0.53	18 pts	3.63(1.25, 5.85)	0.06
***KRAS* WT**	76 pts	8.11(6.77, 9.86)	0.91	46 pts	7.16(4.30, 6.77)	0.68

8092 General Poster Session (Board #38H), Sat, 8:00 AM-11:45 AM

Overcoming barriers in incorporating evaluation of quality of life (QL) and symptoms by using the ePRO version of the LCSS (eLCSS-QL) in a large-scale multinational NSCLC trial (AP-QL Trial).

Sumitra Thongprasert, Richard J. Gralla, Patricia J Hollen, Hoon-Kyo Kim, Te-Chun Hsia, Shi Yuankai, Karenza M. Alexis, Nina Kohn, Martin Lesser; Maharaj Nakorn Chiang Mai Hospital, Chiang Mai, Thailand; Albert Einstein College of Medicine, Jacobi Medical Center, Bronx, NY; University of Virginia, Charlottesville, VA; St. Vincent's Hospital, Suwon, South Korea; China Medical University, Taichung, Taiwan; Chinese Academy of Medical Sciences, Beijing, China; Feinstein Institute for Medical Research, Manhasset, NY

Background: Survival and QL improvements are primary treatment goals in advanced NSCLC. Few trials evaluate both of these major endpoints well: typically only a minority of patients (pts) have QL followed over time, preventing such data from assisting in key decisions concerning the effectiveness and value of treatment. To overcome barriers, we used a computer-assisted version of the validated LCSS measure and tested this prospectively in a large study. Prior trials indicated that the eLCSS-QL requires only 2 minutes to complete the pt version and is highly acceptable. **Methods:** 622 pts received initial docetaxel (D)-based chemo, at 65 sites in 9 Asian countries. 70% male; 65% adenocarcinoma; median: KPS = 90; ECOG = 1 (27% ECOG 0). Stages: IV (72%), IIIB (28%). 84% had > two major symptoms. 80% had combination chemo with cisplatin (52%) or carboplatin (28%). Computer skills were low in 73%. eLCSS-QL was completed every 3 weeks at the clinic. We also surveyed 98 physicians (MD) and nurses (RN) treating these pts regarding communication, usefulness and acceptability of the eLCSS-QL. **Results:** 97% of pts completed the eLCSS-QL at baseline; 90% completed follow-up evaluations. Over 90% found the eLCSS-QL easy to use, acceptable to complete at each visit; >80% reported increased awareness of symptoms; making it easier to speak with MDs / RNs. 1% refused eLCSS-QL completion. Of MDs/RNs: >90% found the eLCSS-QL easy to use and increased symptom awareness; >80% reported improved communication, enhanced satisfaction with the pt visit, and recommend its use. Nearly 90% of MDs reported they could identify benefit from chemo earlier; 76% would order fewer imaging tests and 80% said the eLCSS-QL could save time. Major response rate 37%; median survivals: 13.9 months (D + cisplatin), 12.7 months (D + carboplatin). **Conclusions:** Patients, MDs, RNs all found the eLCSS-QL to be highly acceptable and easy to use with 90% of pts doing repeated QL measures. This large prospective trial demonstrates the potential for QL / symptom evaluation to aid in decision making and to guide appropriate use of chemotherapy and imaging while enhancing staff and pt satisfaction.

8093 **General Poster Session (Board #39A), Sat, 8:00 AM-11:45 AM**

First-in-human dose escalation study of LY2875358 (LY), a bivalent MET antibody, as monotherapy and in combination with erlotinib (E) in patients with advanced cancer.

Jonathan Wade Goldman, Lee S. Rosen, Alain Patrick Algazi, Patricia Kellie Turner, Volker Wacheck, Jay Tuttle, James E Wooldridge, Michaela S. Banck; David Geffen School of Medicine at University of California, Los Angeles, Santa Monica, CA; University of California, San Francisco, San Francisco, CA; Eli Lilly and Company, Indianapolis, IN; Mayo Clinic, Rochester, MN

Background: Activation of the hepatocyte growth factor (HGF)/MET receptor pathway promotes tumor growth, invasion and dissemination. LY is a humanized IgG4 monoclonal bivalent antibody against MET which inhibits ligand dependent- and ligand independent activation of MET. Based on preclinical results, we examined LY alone in patients with advanced solid tumors and LY+E in advanced NSCLC patients. **Methods:** LY monotherapy was administered 20-2,000 mg Q2W IV to 23 patients with advanced solid tumors. Combination therapy with 700-2,000 mg Q2W IV of LY and E (150 mg QD) was completed in 14 patients with advanced NSCLC. The primary objective was to determine a recommended phase II dose (RPTD) for LY and LY+E. Secondary objectives included assessment of toxicity, PK, PD (including MET extracelluar domain and HGF), and antitumor activity. **Results:** LY and LY+E were well tolerated. No dose-limiting toxicities, serious adverse events, or ≥ Grade 3 adverse events (AEs) possibly related to LY have been observed. The most frequent (≥5% of patients) AEs possibly related to LY2875358 monotherapy were nausea (8.7 %), vomiting (8.7%), and diarrhea (8.7%). The most frequent (≥10% of patient) grade 1 or 2 adverse event possibly related to LY2875358 in patients treated with LY+E were fatigue (21.4%) and anorexia (14.3%). Durable PR according to RECIST were observed for LY (n=1) and LY+E (n=2 out of 13 evaluable patients; both PR patients positive for MET protein expression). **Conclusions:** LY appears to be safe when administered as single agent and in combination with E up to 2,000 mg Q2W IV. The RPTD of LY is 750 mg Q2W IV for monotherapy and in combination with E based on PK/PD data. Clinical trial information: NTC 01287546.

8094 General Poster Session (Board #39B), Sat, 8:00 AM-11:45 AM

Potential chemo-sensitization effect of tergenpumatucel-L immunotherapy in treated patients with advanced non-small cell lung cancer (NSCLC).

John Charles Morris, Gabriela R. Rossi, Nancy Harold, Lucinda Tennant, William Jay Ramsey, Nicholas N. Vahanian, Charles J. Link; University of Cincinnati, Cincinnati, OH; NewLink Genetics, Ames, IA; National Cancer Institute, Bethesda, MD

Background: Lung cancer is the leading cause of cancer-related mortality. Tumor progression after initial chemotherapy has a poor prognosis. A major obstacle is chemo-resistance, thus targeted therapies that enhance cancer cell sensitivity to chemotherapeutic agents with limited toxicities are needed. We report that tergenpumatucel-L (HyperAcute-Lung immunotherapy, HAL) shows signs of chemo-sensitization to follow-up treatment after progression in immunized patients. This drug exploits a potent innate immune mechanism that normally functions to destroy cells expressing a common xenoantigen (αGal). HAL immunotherapy consists of injecting patients with genetically modified allogeneic NSCLC cells bearing αGal moieties on their cell surface. **Methods:** This phase II study included 28 patients with metastatic or recurrent NSCLC, age $\geq$18, ECOG PS $\leq$2, $\leq$2 prior systemic therapies. Trial objectives were response rate, safety and immunogenicity. Patients received 300 x 10^6HAL cells q2wks x 8 doses. Adverse events were assessed using CTCAE v3. Immunogenicity was assessed by changes in serum anti-αGal titers and IFN-γ response. Patients progressing on study trial (n=16) received follow up chemotherapy. Response was evaluated using RECIST criteria. **Results:** Twenty-eight (28) patients were evaluable for response and 16 progressing patients received salvage chemotherapy. Median overall survival (OS) was 11.3 months (95% CI 3.8-21.9). Eight of 28 patients demonstrated stable disease (SD) $\geq$16 wks including one patient that progressed and later regressed to survive $>$50 months. Fifty six percent (9/16) of the progressing patients receiving follow up chemotherapy showed a response. Five (31%) achieved a PR and 25% (4/16) had SD after initial progression during the trial suggesting a chemo-sensitization effect of tergenpumatucel-L. **Conclusions:** HAL immunotherapy is safe and feasible. The median OS compared favorably to that reported in patients receiving 2nd line chemotherapy for relapsed or advanced NSCLC. The potential chemo-sensitization effect of tergenpumatucel-L is highly encouraging and currently being studied in a phase IIB/III trial. Clinical trial information: NCT00073398.

8095 General Poster Session (Board #39C), Sat, 8:00 AM-11:45 AM

Randomized, blinded, placebo-controlled phase II trial of docetaxel and bavituximab as second-line therapy in locally advanced or metastatic non-squamous non-small cell lung cancer.

Mikhail Shtivelband, David R. Spigel, David E. Gerber, Minish Mahendra Jain, Olga V. Ponomarova, Davit Giorgadze, Joseph Shan, Kerstin B. Menander, Chandra Prakash Belani; Ironwood Cancer and Research Centers, Chandler, AZ; Sarah Cannon Research Institute; Tennessee Oncology, Nashville, TN; UT Southwestern Medical Center, Dallas, TX; Ruby Hall Clinic, Pune, India; R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology, Kiev, Ukraine; Chemotherapy and Immunotherapy Clinic, Tbilisi, Georgia; Peregrine Pharmaceuticals, Inc., Tustin, CA; Penn State Hershey Cancer Institute, Hershey, PA

Background: Bavituximab (B) is a monoclonal antibody against phosphatidylserine (PS) with a selective tumor vascular-directed immune response. The purpose of this trial is to evaluate the efficacy and safety of B or placebo (P) combined with docetaxel (D) in patients with locally advanced or metastatic non-squamous NSCLC. **Methods:** Patients were randomized 1:1:1 to receive 75 mg/m^2 of D every 21 days for up to 6 cycles combined with weekly blinded infusions of P, 1mg/kg B or 3 mg/kg B until disease progression or unacceptable toxicity. Primary efficacy endpoint was overall response rate (ORR). Secondary endpoints included progression free survival (PFS) and overall survival (OS). Safety was evaluated by adverse events (AEs), vital signs, CBC, biochemistry, urinalysis, coagulation, ECG. Post study unblinding, a PK substudy revealed vial coding discrepancies in the P and 1 mg/kg vials. As a result, data from these two groups were pooled to form the control (C) arm in the analysis. **Results:** Forty-one patients were entered into the 3mg/kg B+D arm and 80 into the control arm. No significant differences were seen in age, gender, ethnicity or disease stage. ECOG 2 was 13% in C and 24% in 3 mg/kg B+D arms. At this analysis, 54% death events have been reported in 3 mg/kg B+D and 71% in C arm. ORR is 17.1%/13.8% and median PFS is 4.5/3.3 months for 3 mg/kg B+D/C. Median OS is 11.7 months for 3 mg/kg B+D and 7.3 months for C. The safety profile for 3 mg/kg B+D was similar to that of C in severity and frequency. No other safety signal was identified. **Conclusions:** This randomized, placebo-controlled phase 2 trial demonstrated a positive trend favoring 3 mg/kg B+D in ORR, PFS and OS. 3 mg/kg B in combination with D was well tolerated and is the planned dose forPhase 3. Clinical trial information: NCT01138163.

8096 General Poster Session (Board #39D), Sat, 8:00 AM-11:45 AM

Canadian ALK (CALK): A pan-Canadian multicenter study to optimize and standardize ALK immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) for *ALK* gene rearrangements.

Ming Sound Tsao, Kenneth Craddock, Guilherme Brandao, Zhaolin Xu, Wenda Greer, Yasushi Yatabe, Diana Ionescu, Sungmi Jung, Ronald F Carter, Aly Karsan, Anna Bojarski, Harmanjatinder S. Sekhon, Gilbert Bigras, Jean Deschenes, Roula Albadine, Melania Pintilie, Jean-Claude Cutz, Danh Tran-Thanh, Emina Torlakovic, Christian Couture; Department of Pathology, University Health Network, University of Toronto, Toronto, ON, Canada; Department of Pathology, University Health Network, Toronto, ON, Canada; Jewish General Hospital, McGill University, Montreal, QC, Canada; Queen Elizabeth II Health Sciences Centre and Dalhousie University, Halifax, NS, Canada; Department of Pathology and Molecular Diagnostics, Aichi Cancer Center Hospital, Nagoya, Japan; Department of Pathology, BC Cancer Agency, Vancouver, BC, Canada; Department of Pathology, McGill University Health Sciences Centre, Montreal, QC, Canada; McMaster University Health Sciences Centre, Hamilton, ON, Canada; Department of Pathology, BC Cancer Agency and University of British Columbia, Vancouver, BC, Canada; Health Sciences North, Sudbury, ON, Canada; Department of Pathology, The Ottawa Hospital and University of Ottawa, Ottawa, ON, Canada; Cross Cancer Institute, Edmonton, AB, Canada; Department of Pathology, Centre Hospitalier De L'universite De Montreal, Montreal, QC, Canada; University Health Network-Princess Margaret Hospital, Toronto, ON, Canada; Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada; Laval Hospital, Sainte-Foy, QC, Canada

Background: *ALK* gene rearrangement (ALK+) has been found in 3-5% of advanced non-small cell lung cancer patients. FISH is considered the "gold standard" for identification of ALK+ tumors, but its cost-effectiveness and adoption as a screening assay has been debated. Recent reports suggested that ALK IHC may serve as an alternative screening or possibly a diagnostic method. In this context, CALK was initiated to assess the feasibility of implementing ALK IHC and/or FISH assays across Canadian hospitals. **Methods:** FISH-confirmed 22 ALK+ and 6 ALK- tumors were used as study samples. Unstained sections and scanned images of HE-stained slides from each tumor block were distributed to participating centres. IHC protocols with best signal to noise ratio using the 5A4 (Novocastra) or ALK-1 (Dako) antibodies were developed for various auto-stainers and implemented to suit the existing conditions of the participating centres. A common FISH protocol using the *ALK* break-apart probe (Abbott Molecular, Chicago, IL) was developed based on published reports. H-score was used to assess IHC. FISH signals were scored in 100 tumor cells/case by 2-3 pre-trained persons. A second round IHC study using newly distributed slides was completed by 8 centres. **Results:** Independent IHC scores from 12 centres and FISH scores from 11 centres were collected and analysed. The intraclass correlation coefficients (ICC) between centres for IHC and FISH were 0.84 and 0.68, respectively. Following the analysis of initial IHC results, a second round study resulted in improved ICC of 0.94. One of 23 tumors revealed IHC-/FISH+ discrepancy, with the FISH revealing unusual signal configurations that suggested an atypical rearrangement. However, the sensitivity and specificity of FISH results across centres using the 15 aberrant signals cut-off ranged from 86.7-100% and 100%, respectively. **Conclusions:** Standardization across multiple centres for ALK testing by IHC and FISH can be achieved. IHC detected all FISH+ ALK tumors, except for one discrepant case with atypical FISH finding of unknown clinical implication. The study was supported by a Pfizer Canada grant.

8097 **General Poster Session (Board #39E), Sat, 8:00 AM-11:45 AM**

Randomized phase II study of pharmacodynamic separation (PDS) of pemetrexed (Pem) and erlotinib (Erl) versus pem alone in patients (pts) with advanced non-small cell lung cancer (NSCLC).

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Background: Preclinical and phase I studies showed that PDS optimizes cytotoxicity of concurrent EGFR inhibitors and chemotherapy. We conducted a randomized phase II trial to assess relative efficacy of Pem alone (Arm A) versus Pem +Erl on a PDS dose-schedule (Arm B) as 2nd-line therapy in pts with advanced NSCLC (NCT00950365). **Methods:** Eligible pts were randomized 2:1 (Arm B: A), stratified by sex, smoking history, and performance status (0/1 vs 2). Accrual was restricted to non-squamous histology in 2009. Treatment: Arm A – Pem 500 mg/m^{2}IV on day 1; Arm B – Pem + Erl 150 mg po QD on days 2-17. 1 cycle = 3 weeks. Primary endpoint was progression-free survival (PFS). 50 pts in Arm B were needed to detect an increase in median PFS from ~3 to 4.5 months. **Results:** 83 pts were entered. Age: 63 yo. Female: 42 (53%). Smoking ≥15PY: 58 (72%). Nonsquamous: 78 (99%). The primary endpoint of the study was met: Efficacy results from 79 eligible pts showed 1.6-fold longer PFS in Arm B (4.6 m) compared to Arm A (2.8 m). Although the study was not designed to directly compare two arms, p value was 0.052. Toxicity: G3/4 Hem (A/B): 8(30%)/12(23%); Neutropenia with infection (A/B): 0/3(6%). G3/4 Non-Hem (A/B): skin rash: 0/3(6%); diarrhea: 0/2(4%); joint pain: 1(4%)/6(11.5%). Treatment related death (A/B): 0/1. Interstitial lung disease (A/B): 0/1. **Conclusions:** PDS of Pem and Erl is well tolerated and has promising clinical activity in 2nd-line non-squamous NSCLC. Ongoing correlative studies aim to identify a subgroup of patients who might benefit most from this treatment, which will guide the design of a confirmatory phase III study. (UL1 RR024146, P30CA093373, Lilly, Astellas) Clinical trial information: NCT00950365.

	All eligible pts (n=79)		All evaluable pts (n=75)			
Treatment arm	Median PFS: mo (95% CI)	Median OS: mo (95% CI)	ORR % (95% CI)	DCR 3m (95% CI)	DCR 6M (95% CI)	DCR 12M (95% CI)
A: Pem (N=27)	2.79 (1.74-4.64)	8.25 (4.70-11.84)	12% (0%-25%)	48% (28%-68%)	28% (10%-46%)	8% (0%-19%)
B: Pem + Erl (N=52)	4.57 (3.55-5.85)	9.67 (6.77-16.04)	28% (16%-40%)	70% (57%-83%)	38% (25%-51%)	18% (7%-29%)
Fold (p-value)	1.6 (0.052*)	1.2 (0.16*)	2.8 (0.15#)	1.6 (0.08#)	1.4 (0.45#)	2.3 (0.32#)

* Log-rank; #Fisher's exact test.

8098 General Poster Session (Board #39F), Sat, 8:00 AM-11:45 AM

High-dose erlotinib for refractory leptomeningeal metastases (LM) after failure of standard dose EGFR-TKIs.

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Background: EGFR-TKIs, gefitinib and erlotinib can demonstrate dramatic and durable response in patients with *EGFR*-mutant non-small cell lung cancer. Approximately one-third of patients develop central nervous system (CNS) metastases, including leptomeningeal metastases (LM) after initial response to EGFR-TKIs. Pharmacokinetic failure due to insufficient penetration of EGFR-TKIs is suggested as a cause of CNS failure. Therefore, high-dose EGFR-TKIs are considered reasonable therapeutic options for refractory CNS metastases after failure of standard dose EGFR-TKIs, but there is little present evidence of high-dose EGFR-TKI's efficacy and tolerability. **Methods**: Between 2007 and 2012, we screened 279 patients harboring *EGFR* sensitive mutations, and identified 31 patients with LM. Ten of 31 patients received high-dose erlotinib, and the other 21 underwent only standard dose EGFR-TKIs (gefitinib and/or erlotinib). In these 10 patients, erlotinib was administered at 200 mg on alternating days (n=2), 300 mg on alternating days (n=6), 300 mg every 3 days (n=1), or 600 mg every 4 days (n=1). We retrospectively investigated the efficacy and tolerability of high-dose erlotinib. Additionally, survivals from the diagnosis of LM to death were compared in patients with or without high-dose erlotinib. **Results**: Regarding high-dose erlotinib, five of 10 patients were radiologically evaluable, and partial response was observed in 60% (3/5), stable disease in 20% (1/5), and progressive diasease 20% (1/5). Median time to CNS progression was 3.4 months (range, 0.3-6.6 months). Improvement of neurological symptoms was observed in 9 (90%) of 10 patients. No severe adverse events ($\geq$ grade 3) associated with high-dose erlotinib were confirmed. Median survival from the diagnosis of LM in patients with high-dose erlotinib was 6.5 months (95% CI: 2.5-12.3 months), and that in those without was 5.8 months (95% CI: 1.1-7.8 months) ($p = 0.51$). **Conclusions**: The efficacy and tolerability of high-dose erlotinib were suggested for refractory LM. It can be a therapeutic option in patients after failure of standard dose erlotinib. Optimal dose and schedule are unclear, and further investigations are warranted.

8099 **General Poster Session (Board #39G), Sat, 8:00 AM-11:45 AM**

Detection of ROS1 translocations in triple-negative lung adenocarcinomas.

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Background: After *ALK* (anaplastic lymphoma kinase) rearrangements, *ROS1* (c-ros oncogene 1, located at 6q22) translocations were recently shown to define a new molecular subgroup in non-small cell lung cancers (NSCLC). These translocations, activating a proto-oncogene with a tyrosine kinase domain, are also targeted by the MET and ALK crizotinib. *ROS1* rearrangements are found in only 1.2-1.7% NSCLCs, but seemingly only in triple negative (EGFR and KRAS non-mutated and ALK non-rearranged) adenocarcinomas and preferentially in non- or light smokers. **Methods:** 60 triple negative non- or light-smoking patients with lung adenocarcinoma were screened for *ROS1* rearrangements by fluorescent in situ hybridization (FISH). Two commercially available break-apart FISH probe kits containing a mixture of two probes hybridizing on each side of the ROS1 locus, one located in a centromeric (3') position, and the other one in a telomeric (5') position relative to the *ROS1* gene were used. *ROS1* fusions were therefore detected without any preconception on the fusion partner, as multiple fusion partners have been described. At least 100 nuclei were screened, and a tumor was considered positive if it contained more than 15% rearranged nuclei. **Results:** Forty-nine of the 60 tumors were interpretable. Four (8.2%) of theses 49 tumors were *ROS1* rearranged by FISH. Only one of the positive cases showed a "classical" split rearrangement pattern (one fusion, one green and one red signal in more than 15% of nuclei), whereas the three other tumors showed a variant pattern, with a deletion of the telomeric probe, located in a 5' position relative to the *ROS1* gene locus, indicating the presence of a fusion partner upstream of the *ROS1* gene. The four positive cases were all at an advanced stage (3 or 4), but did not display any common architectural feature. **Conclusions:** The prevalence of *ROS1* positivity in our selected population was far superior (8.2%) to that of a non-selected NSCLC population, suggesting that this type of screening may be more effective (faster and more cost-worthy) to detect *ROS1* positive tumors.

8100 General Poster Session (Board #39H), Sat, 8:00 AM-11:45 AM

A French multicentric and prospective validation study for ALK translocation diagnosis in lung adenocarcinomas.

Sylvie Lantuejoul, Isabelle Rouquette, Hugues Begueret, Helene Blons, Frederique Penault-Llorca, Marie-Christine Copin, Martine Antoine, Paul Hofman, Jean-Philippe Merlio, Anne McLeer Florin, Francoise Galateau-Salle, Jean-Michel Vignaud, Stéphane Garcia, Francoise Thivolet, Mojgan Shisheboran-Devouassoux, Marie Brevet, Veronique Hofman, Audrey Mansuet-Lupo, Claire Danel; Université J. Fourier, CHU Grenoble, Inserm U823, Grenoble, France; Centre Hospitalier Universitaire Toulouse, Toulouse, France; Centre Hospitalier Universitaire Haut-Levêque, Bordeaux, France; Hôpital Européen Georges Pompidou (HEGP), Assistance Publique Hôpitaux de Paris (APHP), Paris, France; Centre Jean Perrin/ERTICa EA 4677, Clermont-Ferrand, France; Centre Hospitalier Régional Universitaire Lille, Lille, France; Tenon University Hospital, Paris, France; Biobank LPCE, Pasteur Hospital, Nice University, Nice, France; Service de Biologie des Tumeurs - CHU, Bordeaux, France; Université Joseph Fourier - CHU Grenoble, Grenoble, France; Pathology Department, Caen Universtiy Hospital, Caen, France; Centre Hospitalier Universitaire de Nancy, Nancy, France; Hôpital Nord service d'Anatomie et Cytologie Pathologiques, Marseille, France; Hôpital Louis Pradel, Bron, France; Hôpital de la Croix Rousse, Lyon, France; Centre Hospitalier Universitaire Edouard Herriot, Lyon, France; Laboratory of Clinical and Experimental Pathology, Nice, France; Hôtel Dieu, Paris, France; Hôpital Bichat, Paris, France

Background: *ALK* rearrangements occur in nearly 5% of NSCLC and lead to a permanent ALK protein activation, targeted by a small molecule, the crizotinib. To date, FISH (Fluorescent In situ Hybridization) is considered as the gold standard to identify ALK abnormalities, but dual testing and pre-screening by immunohistochemistry have been proposed. **Methods:** The purpose of the study was to compare immunohistochemistry (IHC) using 5A4 and D5F3 Abs, with FISH and quantitative RT-PCR in a series of 500 surgical specimens, collected within one year from 15 French Thoracic Pathology Departments and INCa genetic platforms. Our study was deliberately enriched in ALK positive cases and clinicopathological data were recorded. **Results:** Among the 459 cases included to date, 340 were both FISH and IHC ALK negative, and 85 were ALK FISH and IHC positive. Fifteen cases were FISH neg/IHC pos, but with low staining scores; 12 cases were FISH pos/IHC neg, most provided by two centers. Seven cases were non interpretable by FISH, but 5 were ALK IHC positive. Regarding RTqPCR, nearly 50% of ALK positive cases presented a variant 1, 30% a variant 3a/b, and less than 5%, variants 2 or 7; 20%were negative or non interpretable. Discordant cases will be further discussed according to the crizotinib response. ALK positive patients were more frequently women (65 vs 42%) and younger than ALK negative patients (mean age 59 vs 64yrs); 72% were non or light smokers, whereas 75% of ALK negative patients were smokers (mean of 41PY). Histologically, most ALK positive and negative tumors presented a solid or acinar predominant architecture and were P63 negative. However, ALK positive tumors were more frequently TTF1 positive (91 vs 76%). **Conclusions:** 5A4 or D5F3 immunohistochemistry is a reliable and easy technique for routine diagnosis of ALK abnormalities, while FISH and RT-qPCR still dependent on pre-analytic conditions and technical expertise. However, in case of a suggestive clinical presentation, double testing with FISH remains the safer testing option as false negative IHC cases exist.

8101 General Poster Session (Board #40A), Sat, 8:00 AM-11:45 AM

Clinical features of patients with lung adenocarcinomas harboring BRAF V600E mutations.

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Background: To investigate the prevalence, distribution, and prognostic role of activating BRAF mutations in Chinese patients with lung adenocarcinomas (ADCs). **Methods:** This retrospective study included 192 lung ADCs (97 males 50.5%, 95 females 49.5%). BRAF gene mutations were screened using AmoyDx BRAF V600E mutations detection kit. Mutations of EGFR and KRAS gene were also analyzed. **Results:** BRAF mutations were present in 8(4.17%) lung ADCs patients. V600E mutations were significantly more prevalent in females (6 of 96; 6.25%) than in males (2 of 97; 2.06%), as indicated by multivariate logistic regression analysis. Other clinocopathologic parameters, including age, smoking history, and tumor stage, were not significantly associated with V600E BRAF mutations. V600E-mutated tumors were not associated with different progression-free and overall survival rates comparing with non V600E-mutated tumors in this study. The frequency of EGFR and KRAS mutations in all patients were 42.7%(82/192) and 8.3%(16/192), respectivelyBRAF and EGFR were concomitantly mutated in three tumors. All tumors with BRAF mutations were found to be negative for KRAS mutations. **Conclusions:** We report for the first time to our knowledge that V600E BRAF mutation has high concomitant occurrence rate with EGFR mutations in Chinese lung ADCs patients. BRAF mutations were found to be independently associated only with female gender.

8102 General Poster Session (Board #40B), Sat, 8:00 AM-11:45 AM

A phase I/II study combining dasatinib (D) and erlotinib (E) in non-small cell lung cancer.

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Background: In preclinical models, combining EGFR and Src inhibition has been shown to have at least additive and possibly synergistic effects. In this phase I/II (phI/II) trial, we combined EGFR inhibitor E with D, a multi-targeted tyrosine kinase inhibitor with activity against Src. Primary endpoint of PhI was to determine maximum tolerated dose (MTD) of the combination of E and D; primary endpoint of PhII was progression free survival (PFS) at 12 weeks. **Methods:** In preclinical models, combining EGFR and Src inhibition has been shown to have at least additive and possibly synergistic effects. In this phase I/II (phI/II) trial, we combined EGFR inhibitor E with D, a multi-targeted tyrosine kinase inhibitor with activity against Src. Primary endpoint of PhI was to determine maximum tolerated dose (MTD) of the combination of E and D; primary endpoint of PhII was progression free survival (PFS) at 12 weeks. **Results:** 53 pts were enrolled between 2/09 and 4/12. 6 were not eligible. Of the 47 eligible pts (12 in PhI, 35 in PhII): median (range) age was 62 yrs (44-88), 26 pts (45%) were female. 6 pts in PhI and all 35 pts in PhII had NSCLC: adeno 25 pts, squamous 11, NSCLC NOS 5. Other tumor types enrolled in PhI: head and neck cancer (2), adenoid cystic carcinoma (1), mesothelioma (2), small cell lung cancer (1). 47% of pts were chemo-naïve. 8 pts had activating EGFR mutations (6 exon 19 deletions, 2 L858R mutations). The PhI starting dose E150/D100 was not well tolerated as 2 of 3 pts experienced grade 3 hypophosphatemia as a dose limiting toxicity. MTD was found to be E150/D70. 11% achieved PR and 44% SD. All observed responders had EGFR mutations. 9 pts (19%) stopped treatment early and were unevaluable. Median time on treatment was 43 days (range 1-262). Median time on treatment for the 8 pts with activating EGFR mutations was 144 days. **Conclusions:** Combination of E and D is safe and feasible in NSCLC, with MTD E 150 mg PO daily and D 70 mg PO daily. Rate of PR and SD were 11%,and 44%, respectively. Biomarker and pharmacokinetic studies will be reported. Clinical trial information: NCT00826449.

8103 General Poster Session (Board #40C), Sat, 8:00 AM-11:45 AM

Prognostic value of ECOG performance status in lung cancer assessed by patients and physicians.

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Background: Physician-reported Eastern Cooperative Oncology Group (ECOG) performance status (MD-PS) is a reliable prognostic factor of overall survival (OS) and has a major influence on treatment decisions. MD-PS is also used to quantify cancer patients' general well-being and activities of daily life. The extent and prognostic importance of disagreements between MD-PS and cancer patients' self-reported ECOG PS (Pt-PS) have not been adequately evaluated. **Methods:** Four hundred and sixty consecutive patients with lung cancer (LC) were referred to the Dept. of Oncology at Herlev University Hospital, Denmark, from February 1 2012 to January 31 2013. Three hundred and forty-seven (75%) of these patients were enrolled in a prospective, longitudinal, LC biomarker study, "LUCAS". Patients assessed their own Pt-PS in a questionnaire at first visit. Treating physicians scored the MD-PS at first visit. **Results:** Fifty-four (16%) LUCAS patients had missing PS data (39 no Pt-PS; 14 no MD-PS; 1 neither). LUCAS patients were significantly younger than the total LC population (mean age, 68.1 vs. 71.1; t-test: $p < 0.01$). The MD-PS and Pt-PS were distributed differently in the LUCAS cohort: PS=0 (121 vs. 76), PS=1 (147 vs. 145), PS=2 (39 vs. 54), PS=3 (25 vs. 30), PS=4 (0 vs. 2) (X^2 test: $p < 0.01$). In 170 (58%) cases the physician and patient were in concordance. In 24 (8%) cases the MD-PS scored the patient in poorer PS compared to the Pt-PS. In 99 (34%) cases the MD-PS scored the patient in better PS than the Pt-PS. In 11 (4%) cases the physician scored a PS value more than 1 different from the patient; all were towards a better PS. The median OS in the total cohort (460 patients) was 9.7 months. MD-PS and Pt-PS were both effective in predicting OS. For patients with MD-PS = 0, a poorer Pt-PS did not significantly predict worse outcome. However, for patients with MD-PS = 1, there was a trend (HR 1.98, $p = 0.08$; log rank test) towards worse outcome if Pt-PS was > 1. **Conclusions:** Oncologists and patients frequently disagree regarding PS. The physicians tend to note a better PS score than the patients. The differences between MD-PS and Pt-PS could influence the prognostic value. It may be beneficial in clinical practice to involve patients in PS assessments.

8104 General Poster Session (Board #40D), Sat, 8:00 AM-11:45 AM

A phase I/II trial combining erlotinib with gamma secretase inhibitor RO4929097 in advanced non-small cell lung cancer (NSCLC).

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Background: All NSCLC patients treated with erlotinib (E) eventually develop resistance. Both the epithelial-mesenchymal transition (EMT) and cancer stem cells may contribute to resistance to E. The Notch pathway plays a key role in maintaining stem cell viability and in EMT. Gamma secretase inhibitors such as RO4929097 (R) inhibit Notch activity by preventing cleavage of Notch to its active form. In this CTEP-sponsored study, primary endpoint of phase I was to determine maximum tolerated dose (MTD) of the combination of E and R; primary endpoint of phase II was response rate. **Methods:** Eligible pts had incurable NSCLC, measurable disease, ECOG PS 0-1, and adequate laboratory parameters. There were no limits on prior therapy. All pts were required to have a tumor biopsy. Patients received E PO daily on a continuous schedule and R PO daily on days 1-3, 8-10, and 14-17 of a 21 day cycle. Dose cohorts (E/R both in mg) were as follows: 100 /20, 150/20, 150/30, 150/45. Imaging was performed every 6 weeks. Patients could remain on therapy until progression. **Results:** 21 pts were enrolled between 9/2010 and 3/2012. 5 were not eligible and did not receive treatment. For the 16 treated pts: median age was 61 yrs (40-75), 7 (44%) were male, 14 (88%) had adenocarcinoma. All pts had received prior chemotherapy (1-8 regimens); 7 (44%) had prior E. 3 pts had known EGFR mutations; 2 pts had KRAS mutations. Time on therapy ranged from 20 to 248 days. Median PFS was 42 days. Pts with prior progression on E had a median PFS of 64 days. 1 pt (6%) had a partial response, 4 (19%) had stable disease at 6 weeks. Median overall survival is 6.5 months (1.3 to 24.5+ months). Observed dose-limiting toxicity was hypophosphatemia in 1 pt in 150/45 cohort. Other toxicities included rash, neuropathic pain and nausea. MTD was determined to be 150/45. The study was halted early, after completion of the phase I cohort, as production of R was discontinued by the manufacturer. 12 pts (75%) have adequate tumor tissue for analyses. Biomarker studies are pending. **Conclusions:** Combination of R and E is safe and feasible in pts with NSCLC. Though development of R has been discontinued, other drugs targeting the Notch pathway are in development (NCI R21CA153017). Clinical trial information: NCT01193881.

8105 General Poster Session (Board #40E), Sat, 8:00 AM-11:45 AM

Subgroup analysis of crizotinib versus either pemetrexed (PEM) or docetaxel (DOC) in the phase III study (PROFILE 1007) of advanced *ALK*-positive non-small cell lung cancer (NSCLC).

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Background: PROFILE 1007 compared the efficacy and safety of crizotinib with that of standard-of-care chemotherapy in patients with *ALK*+ NSCLC. Although the study was not designed for formal assessment of patient outcomes on crizotinib vs. PEM or crizotinib vs. DOC, due to later interest, we performed retrospective efficacy and safety analyses of patient subgroups treated with crizotinib or each chemotherapy individually. **Methods:** Patients with stage IIIB/IV *ALK*+ NSCLC previously treated with 1 prior platinum-based regimen were randomized to receive crizotinib 250 mg PO BID or chemotherapy (PEM 500 mg/m^2 or DOC 75 mg/m^2, IV q3 wk). Patients with progressive disease on chemotherapy were offered crizotinib treatment in a separate study. In these subgroup analyses, PFS and ORR based on independent radiologic review, and safety were evaluated. **Results:** Of 347 patients randomized, 172 received crizotinib, 99 PEM, 72 DOC, and 4 no treatment. At data cutoff (Mar 2012), 85 crizotinib patients, 21 PEM patients, and 7 DOC patients were receiving treatment. Median treatment duration was longer in the crizotinib arm (7.1 mo) than in either the PEM (4.1 mo) or DOC (2.1 mo) treatment subgroups. Median PFS was significantly longer on crizotinib (7.7 mo) than on either PEM (4.2 mo; HR, 0.59; P=0.0004) or DOC (2.6 mo; HR, 0.30; P<0.0001). 1-year PFS rates were 31% on crizotinib, 16% on PEM, and 6% on DOC. The ORR on crizotinib (66%) was significantly higher than on either PEM (29%; risk ratio, 2.31; P<0.0001) or DOC (7%; risk ratio, 9.65; P<0.0001). The most common all-causality adverse events with crizotinib were diarrhea (60%), vision disorder (60%), and nausea (55%); with PEM, nausea (38%), fatigue (36%), and decreased appetite (26%); and with DOC, alopecia (47%), neutropenia (43%), and nausea (36%). **Conclusions:** Crizotinib's superior efficacy over chemotherapy, with a distinct but generally tolerable and manageable side effect profile in patients with advanced *ALK*+ NSCLC, was also observed in separate comparisons with either PEM or DOC. In patients receiving chemotherapy, median PFS, 1-year PFS rates, and ORR were all numerically higher on PEM than on DOC. Clinical trial information: NCT00932893.

8106 General Poster Session (Board #40F), Sat, 8:00 AM-11:45 AM

Exploratory biomarker analyses from ECOG 4508: Three-arm randomized phase II study of carboplatin (C) and paclitaxel (P) in combination with cetuximab (CET), IMC-A12, or both for advanced non-small cell lung cancer (NSCLC) patients (pts).

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Background: ECOG 4508 was a phase II study that randomized advanced NSCLC pts that were not candidates for bevacizumab to receive: C + P iv on day 1 every 3 wks with either CET iv weekly (arm A, n=39), IMC-A12 iv every 2 wks (arm B, n=42), or both (arm C, n=48). The study was closed prematurely due to safety concerns after 129 eligible pts were treated. The study failed to meet its primary objective (Hanna et al ASCO 2012). **Methods:** Tumor samples were analyzed by immunohistochemistry (IHC; EGFR, IGF-1R and IGF-2R expression), fluorescent in-situ hybridization (FISH; EGFR gene copy number) and DNA sequencing (EGFR, KRAS gene mutations). Time-to-event distributions were estimated using the Kaplan-Meier method, and differences were tested using the logrank test. Cox proportional hazards models were fitted to estimate hazard ratios. **Results:** Histology: 38% squamous cell, 39% adenocarcinoma, 2% BAC, 5% NOS and 6% other. OS was similar in EGFR FISH+ (Colorado classification system, n=30/70, 43%) vs EGFR FISH- pts (57%), (9.5 mos vs 8.6 mos, HR=0.62, p=0.08). For EGFR FISH+ pts, there was no difference in outcomes with CET (n=19, OS=9.7 mos, PFS=4.1 mos) vs no CET (n=11, OS=9.5 mos, PFS=5.5 mos). EGFR and KRAS mutations were detected in 6% (5/80) and 22% (6/27) of the pts respectively, but sample sizes were not large enough for robust testing. EGFR and IGFR IHC hybrid (H) scores were assessed on 98/102 available samples (Arm A=29, Arm B=34, Arm C=35). Median H scores (and range): IGF-1R: 190 (30-390), IGF-2R: 145 (20-350), EGFR membrane and cytoplasm: 190 (0-380) and EGFR membrane only: 160 (0-390). With IGF-1R and IGF-2R H score > 200, there was no association with OS (HR 1.3, p=0.26; HR 1.4, p=0.28) or PFS (HR=1.1, p=0.67; HR=1.2, p=0.56), adjusted for whether or not IMCA12 was received. Similarly, no associations with OS or PFS were seen with EGFR membrane H score > 200, adjusted for CET administration (OS HR=0.89, p=0.64; PFS HR 1.1, p=0.62). **Conclusions:** There was no correlation between EGFR FISH or H score and outcomes with CET. IGF-1R and IGF-2R expression was not predictive of favorable outcome with IMC-A12. Clinical trial information: NCI-2011-01976.

8107 General Poster Session (Board #40G), Sat, 8:00 AM-11:45 AM

A phase Ib safety and tolerability study of a pan class I PI3K inhibitor buparlisib (BKM120) and gefitinib (gef) in EGFR TKI-resistant NSCLC.

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Background: Overcoming EGFR TKI resistance (R) is a major clinical challenge; reported mechanisms include EGFR T790M mutation (mt), MET amplification (amp) and PIK3CA mt. As the PI3K pathway is a central convergent signaling node, we hypothesized that addition of buparlisib (BKM) could overcome EGFR TKI-R. **Methods:** Patients (pt) resistant to EGFR TKI (Jackman JCO 2010) were enrolled to determine safety, tolerability, pharmacokinetics (PK) and pharmacodynamics of BKM-gef. Using a "3+3" design, escalating doses of BKM were added to pt progressing on gef (Gp A). Pt not on gef preceding enrolment received a 2 wk run in (Gp B). Given the favorable CNS penetration of BKM, a CNS gp with brain metastases only was included. Pt had pretreatment biopsies and sequential PET-CT scans (baseline & d28). **Results:** 15 pt have been treated at 3 dose levels: BKM 80 mg/d (n=6), 100 mg/d (n=6), 80 mg 5d on 2d off (5/2, n=3), with gef 250 mg/d. Gp A (n=9, 1 CNS), B (n=6, 1 CNS), F:M (9:6), median age 63 (47-73) and majority >3 lines of therapy. DLT was G3 diarrhea observed in 2/6 pt at BKM100. Common adverse events (AE, all grades) include rash (80%), diarrhea (73%), fatigue (60%), anorexia (47%), mucositis (40%). Notably, 40% of pt had late (beyond DLT period) G3 toxicities such as rash and diarrhea. MTD is BKM 80/d and gef 250/d. To improve the overall safety profile, an intermittent schedule of BKM80 5/2 was also found to be feasible. In gp B, PET-CT done after 2 wk run-in of gef, 3/4 evaluable pt demonstrated reduction in SUV_{max} of which 1 had PR. With addition of BKM, reduction in SUV_{max} (>25%) was seen in 4/10 pt (gp A & B). Median PFS 2.8 m (95%CI 2.3 – 8.1), two pt in CNS gp had PFS of 2.8 and 10.7 m. Molecular analyses revealed 6/12 (50%) harbored T790M mt, 2/5 (40%) MET amp, 0/12 PI3KCA mt. In gp A, 4/9 pt (2 T790M; 1 MET amp) had clinical responses, including slight tumor shrinkage and reduced pleural effusion, but required dose reductions due to AE. PK profiles are being analyzed. **Conclusions:** MTD is gef 250-BKM 80/d. Antitumor activity has been observed with addition of BKM in EGFR TKI-R pt. In view of late toxicities and long t½ of BKM, exploring alternative schedules is warranted. A dose expansion cohort at MTD is currently ongoing. Clinical trial information: NCT01570296.

8108 General Poster Session (Board #40H), Sat, 8:00 AM-11:45 AM

Impact of crizotinib on patient-reported symptoms and quality of life (QOL) compared with single-agent chemotherapy in a phase III study of advanced *ALK+* non-small cell lung cancer (NSCLC).

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Background: PROFILE 1007 compared the efficacy and safety of the ALK inhibitor crizotinib (N=172) with that of standard-of-care chemotherapy (pemetrexed [PEM; N=99] or docetaxel [DOC; N=72]) in patients with advanced *ALK+* NSCLC. The primary endpoint was progression-free survival. The main objective of our present post-hoc analyses was to compare patient-reported outcomes in the crizotinib arm with those of the DOC and PEM subgroups in the chemotherapy arm. **Methods:** Patient-reported outcomes were assessed at baseline, on day 1 of each cycle, and at the end of treatment using EORTC QLQ-C30 and lung cancer module QLQ-LC13. Higher scores (range 0−100) indicate higher symptom severity or better functioning/QOL. Time to deterioration (TTD) was defined as time from randomization to the earliest time with a ≥10-point increase from baseline for pain in chest, dyspnea, or cough and was compared between groups using an unstratified log-rank test. Repeated measures mixed-effects analyses were performed to compare change from baseline scores, with no adjustment for multiple comparisons. **Results:** Completion rates at baseline were ≥90% in each group and scores were well balanced. Crizotinib treatment was associated with a significantly longer TTD compared with PEM (median, 5.6 vs. 1.9 mo; HR, 0.66; 95% CI, 0.48−0.92; P=0.013) or DOC (median, 5.6 vs. 0.9 mo; HR, 0.37; 95% CI, 0.26−0.54; P<0.0001). A significantly greater improvement from baseline was observed with crizotinib compared with either the PEM or DOC subgroups for global QOL (P<0.01), cough (P<0.001), dyspnea (P<0.0001), pain in arm or shoulder (P<0.0001), pain in chest (P<0.0001), pain in other parts (P<0.01), fatigue (P<0.05), insomnia (P<0.05), and pain (P<0.0001). A significantly greater improvement was also observed with crizotinib compared with DOC for functioning (P<0.05), alopecia (P<0.0001), and hemoptysis (P<0.0001). **Conclusions:** Crizotinib treatment showed a significantly greater improvement from baseline in key patient-reported lung cancer symptoms and global QOL compared with DOC and PEM, in addition to improved efficacy previously reported. Clinical trial information: NCT00932893.

8109 General Poster Session (Board #41A), Sat, 8:00 AM-11:45 AM

Dynamic changes in circulating tumor cell levels as a prognostic marker in stage IV non-small cell lung cancer.

Anders Carlsson, Lyudmila Bazhenova, Anand Kolatkar, Madelyn Luttgen, Kelly Bethel, Jorge J. Nieva, Peter Kuhn; The Scripps Research Institute, La Jolla, CA; UC San Diego Moores Cancer Center, La Jolla, CA; Scripps Research Institute, La Jolla, CA; Billings Clinic Cancer Center, Billings, MT

Background: We have previously reported the performance of our immuno-enrichment free HighEDefinition CTC (HDECTC) assay in the enumeration and characterization of circulating tumor cells (CTCs) in lung cancer patients. In the HD-CTC assay, nucleated cells are fluorescently labeled and imaged using automated microscopy. CTCs are defined as morphologically distinct, cytokeratin positive, CD45 negative cells. Here, we investigate further how CTCs numbers and physical properties relate to prognosis in NSCLC patients. **Methods:** The HD-CTC assay was applied for CTC enumeration in 362 blood samples collected longitudinally from 81 Stage IV NSCLC patients. Blood was collected at time 0, 3 weeks, and every 3 months thereafter. The collection protocol was restarted at disease progression, resulting in a sample number ranging between one and 12 samples per patient. **Results:** Eighty-one patients were enrolled, with 41 patients in 1^{st} line therapy, 11 in 2^{nd}, 17 in 3^{rd}, 7 in 4^{th}, 3 in 5^{th} and 2 in 6^{th} line therapy. Average age was 63, range 33 to 90; male to female ratio was 1:1.19. Eighty-six percent of patients had CTCs in at least one blood sample; CTC counts ranged from 0 to 885 CTCs/ml with a mean of 23.5 CTCs/ml across all samples. While no correlation was found between the absolute CTC concentration and survival, it was observed that for the 26 patients that had samples collected both at the start and during firstEline chemotherapy, an increase in CTC level between the two time points was significantly associated with longer survival ($p < 0.001$). **Conclusions:** As detected with our assay, it is the change in CTC level upon entering 1^{st} line chemotherapy and not the absolute CTC concentration that carries prognostic information. This observation highlights not only the importance of CTCs as prognostic biomarkers, but also that of access to serially collected specimens. The latter is here made possible only by the fact that the HDECTC assay samples tumor cells from peripheral blood.

8110 General Poster Session (Board #41B), Sat, 8:00 AM-11:45 AM

Differential activity of afatinib (AFAT), cetuximab (CET), and erlotinib (E) in a patient-derived xenograft (PDX) model of acquired E resistance.

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Background: The UC Davis - Jackson Labs Consortium has established a PDX resource of over 50 NSCLC models (12 EGFR mutant) for experimental therapeutics and personalized medicine, using the NSG mouse. Here we report on a unique PDX model, LG703, derived from a patient at time of acquired E resistance. This tumor harbors EGFR L858R with no T790M mutation, high MET and very high EGFR protein expression. The patient is in remission following treatment with AFAT-CET. In this model, we investigated the respective contribution of CET and AFAT relative to E on tumor growth and signal transduction. **Methods:** Individual mice implanted with LG703 tumor fragments were randomized to E (50 mg/kg qd po), AFAT (20 mg/kg qd po), CET (10 mg/kg twice weekly iv), AFAT-CET, or vehicle control (n per arm = 12) for 3 weeks followed by a 75-day monitoring period. Changes in signal transduction mediators and RTKs were assessed after 6 and 24h treatment exposures using kinase arrays (R&D systems) and immunoblotting. **Results:** AFAT, CET and AFAT-CET resulted in complete tumor response (CR) during the 21-day treatment period; whereas E resulted in temporary growth delay. After cessation of treatment, E-treated mice progressed rapidly and AFAT-treated mice progressed within 2 weeks. Mice treated with CET or AFAT-CET remained in complete remission. At 6h, E and AFAT significantly ($>$70%) reduced EGFR phosphorylation as well as that of AKT1, AKT2, ERK1, p38a, RSK1 and p70S6K. At 24h, E-treated tumors had returned to baseline-like states for all factors, AFAT showed an intermediate response, and CET, alone or with AFAT, achieved the greatest inhibition of pEGFR with sustained inhibition of all downstream effectors. **Conclusions:** In the LG703 PDX model, CET and AFAT+CET resulted in CRs, mirroring the patient's response to similar therapy, associated with sustained inhibition of pEGFR and multiple downstream signaling factors. In contrast, E exhibited only temporary growth delay associated with transient inhibition of EGFR pathway factors. These experiments demonstrate the potential of this PDX resource to assess new therapeutic strategies in models representing individual patients. Supported by BJALCF.

8111 General Poster Session (Board #41C), Sat, 8:00 AM-11:45 AM

Randomized phase II study of pemetrexed plus carboplatin followed by pemetrexed versus paclitaxel plus carboplatin followed by pemetrexed in advanced nonsquamous, non-small cell lung cancer (LOGIK 0904).

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Background: PARAMOUNT study confirmed the improvement of overall survival with continuation maintenance chemotherapy with pemetrexed (PEM) compared with placebo after 4 cycles of cisplatin plus PEM induction chemotherapy recently. JMEN study also showed the usefulness of switch maintenance with PEM after 4 cycles of platinum doublet without PEM. In this study, we conducted the randomized phase II study comparing switch or continuation maintenance chemotherapy with PEM after standard doublet regimen. **Methods:** Histologically/cytologically confirmed stage IIIb or IV non-squamous NSCLC patients with mesurable disease, ECOG PS 0-1, age over 20 years and adequate organ function were eligible for the study. Randomization was stratified by gender and stage of disease. Patients received 3 cycles of PEM 500 mg/m^2 plus CB AUC6 (Arm 1) or PAC 200 mg/m^2 plus CB AUC6 (Arm 2). All patients with non-PD after induction chemotherapy continued PEM 500 mg/m^2 until PD. Primary endopoint is progression-free survival (PFS). **Results:** 140 pts were enrolled and assigned to Arm 1 or Arm 2 randomly. The clinical data of 132 pts were used as full analysis set (median age 64.5 yrs (42-83), 85 male, 120 stage IV, 58 PS0, 127 adenocarcinoma, 46 never smoker). 42 pts had prior treatment including 9 sugery, 1 adjuvant chemotherapy, 24 radiotherapy and 8 others. In both arms, 50% of pts entered into the maintenance treatment with PEM after completion of 3 cycles induction chemotherapy. The median PFS was 92 days in Arm 1 and 143 days in Arm 2, respectively. Cox-proportinal Hazard ratio was 0.827, and 95% HR confidential interval was 0.563-1.248. Stratified Log-Rank test showed no significant difference in both arms. **Conclusions:** There was no significant difference for PFS in PEM plus CB follwed by PEM and PAC plus CB followed by PEM. Clinical trial information: 000005008.

8112 General Poster Session (Board #41D), Sat, 8:00 AM-11:45 AM

SORAVE: Sorafenib and everolimus for treatment of patients with relapsed solid tumors and with KRAS mutated NSCLC—A phase I study.

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Background: Dual inhibition of signaling pathways interfering with cell proliferation and angiogenesis may increase anti-tumor efficacy. Sorafenib and mTOR inhibitors showed preliminary activity in KRAS mutated NSCLC. **Methods:** In the dose escalation part patients with relapsed solid tumors were treated with escalating doses of everolimus from 2.5-10.0 mg daily p.o. in a 14 days run-in phase followed by the combination with a fixed dose of sorafenib 400 mg bid p.o. Extension phase is currently recruiting patients with KRAS mutated NSCLC. The KRAS mutation status was determined by PCR based high resolution melting curve analysis (HRM) on DNA extracted from FFPE material and validated using Sanger sequencing. The HRM has now been replaced by a multiplex PCR. Pharmacokinetic (PK) analyses are performed during run-in and during the combination. Treatment outcome is validated with CT scans on day 57. **Results:** (I) In the dose escalation part, 19 patients were recruited. The dose limiting toxicity (DLT) was not reached. At everolimus dose level of 10 mg/day, increased rates of grade 3 thrombocytopenia (3 patients), leukocytopenia (2 patients) and anaemia (2 patients) occurred after the DLT interval of 29 days. Based on these observations, the dose level of 7.5 mg/day everolimus in combination with 400 mg sorafenib bid was defined as a maximal tolerated dose. The AUC and C_{max} values of everolimus at all dose levels were comparable on days 5 and 14. On day 29, AUC and $C_{max}$of everolimus showed a 20 - 40% reduction when co-administered with sorafenib. The best treatment outcome was stable disease in 11 patients. Median PFS and OS were 3.7 and 5.5 months, respectively. (II) The extension phase in KRAS mutated NSCLC is currently ongoing. Nine patients have been recruited so far. The CT response at day 57 compared to the baseline of 4 evaluable patients is ranging from -22% to +5% in the sum of the longest diameter of all targeted lesions. **Conclusions:** Treatment with the combination of 7.5 mg everolimus p.o. daily and 400 mg sorafenib p.o. bid is safe and feasible. Current results of an extension phase in KRAS mutated NSCLC patients show preliminary clinical activity in this patient group with an unfavorable prognosis. Clinical trial information: NCT00933777.

8113 General Poster Session (Board #41E), Sat, 8:00 AM-11:45 AM

Clinical implications of routine testing for epidermal growth factor receptor (EGFR) mutations in patients with nonsquamous non-small cell lung cancer (NSCLC).

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Background: EGFR mutation (Mut) testing is recommended for all patients (pts) with advanced NSCLC to identify pts who may benefit from front-line EGFR tyrosine kinase inhibitor (TKI) therapy. In July 2010 the Cleveland Clinic initiated reflex EGFR testing of all new diagnoses of nonsquamous NSCLC, prior to which testing was done only by physician request. A retrospective study was designed to review how this change affected clinical practice in a large academic health center. **Methods**: All pts with NSCLC that had EGFR Mut testing performed at the Cleveland Clinic from 07/2009 to 02/2012 were included (n=287). Pt characteristics, tumor histology and stage, Mut status, treatments, and pt outcomes were collected from electronic medical records. Special attention was given to pts with EGFR Mut+ who received erlotinib (E). Data were analyzed using Fisher's exact, chi-square and the Wilcoxon rank-sum tests. **Results**: See Table. **Conclusions**: Automatic EGFR mutation testing, recommended in an ASCO provisional clinical opinion in April 2011, was feasible in a large academic center and significantly shortened the time between diagnosis and EGFR status becoming available to guide treatment decisions. Although not statistically significant due to the small sample size, there were positive trends towards increased first line usage of E in pts with EGFR Mut+, better performance status, lower rates of E discontinuation due to toxicity, and higher response rate to E in the automatic testing group. There was no difference in overall survival between the two groups.

			MD request	Automatic	P value
All pt characteristics	Pt No. (%)		132 (46%)	155 (54%)	
	Age at Dx (range)		65 (29-87)	68 (27-90)	
	Male (%)		59 (45%)	76 (49%)	
	Stage IIIB/IV at Dx (%)		64 (49%)	58 (39%)	0.03
	Time from Dx to EGFR testing (range) (months)		2.6 (0.1-92.5)	0.5 (0-51.2)	<0.001
	Testing turnaround time (range) (days)		12 (3-33)	5 (2-25)	<0.001
	EGFR Mut+ (%)		28 (21%)	20 (13%)	0.08
Outcomes of EGFR Mut+ pts treated with E	Pt No.		21	10	
	Line of therapy using E	1	10 (48%)	6 (60%)	0.7
		2	10 (48%)	4 (40%)	
		3	1 (4%)	0	
	PS	0	7 (33%)	7 (70%)	0.18
		1	13 (62%)	2 (20%)	
		2	1(5%)	1 (10%)	
	Discontinue E due to toxicity (%)		6 (28%)	0	0.14
	Response CR/PR (%)		9 (45%)	8 (80%)	0.12

8114 General Poster Session (Board #41F), Sat, 8:00 AM-11:45 AM

Erlotinib beyond progression study: Randomized phase II study comparing chemotherapy plus erlotinib with chemotherapy alone in EGFR tyrosine kinase inhibitor (TKI)-responsive, non-small cell lung cancer (NSCLC) that subsequently progresses.

Balazs Halmos, Nathan A. Pennell, Gregory Alan Otterson, Shirish M. Gadgeel, Tarek Mekhail, Michael Robert Snell, J. Phillip Kuebler, Pingfu Fu, Neelesh Sharma, Afshin Dowlati; New York-Presbyterian Hospital, Columbia University, New York, NY; Cleveland Clinic Taussig Cancer Institute and Case Comprehensive Cancer Center, Cleveland, OH; Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, OH; Karmanos Cancer Institute, Wayne State University, Detroit, MI; Florida Hospital Cancer Institute, Orlando, FL; MetroHealth Medical Center, Cleveland, OH; Columbia Oncology Associates, Columbus, OH; Case Comprehensive Cancer Center, University Hospital of Cleveland Medical Center, Cleveland, OH; University Hospitals Seidman Cancer Center, Case Comprehensive Cancer Center, Cleveland, OH; University Hospitals Seidman Cancer Center, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH

Background: In EGFR-TKI responsive NSCLC, at progression only some tumor clones might carry resistance mechanisms. This provides a rationale for maintenance therapy with TKIs on progression and is supported by "tumor flares" noted in patients taken off of TKI therapy. **Methods:** Randomized, phase II study of chemotherapy (pemetrexed or docetaxel) versus chemotherapy plus erlotinib (ERL) in patients with progressive NSCLC following clinical benefit from erlotinib for $>$ 12 weeks. In Arm A Pemetrexed or Docetaxel were given at standard doses every 3 weeks to a maximum of 8 cycles. In Arm B chemotherapy was given with ERL at 150 mg oral daily dose on days 2-19 of each cycle. The primary endpoint was that continuation ERL in this patient population could extend PFS by 50%, from 3 to 4.5 months. The original enrollment goal was 39 pts per arm to allow 80% power to detect such a difference. **Results:** 46 patients were randomized (Arm A: 24; Arm B: 22). Early termination was due to slow enrollment. Patient characteristics were well balanced except for more females on Arm A ($p=0.075$). The median PFS on Arm A was 5.4 months and for Arm B was 4.6 months ($p=0.569$). The median overall survival (OS) on Arm A was 18.7 months and for Arm B 14.7 months ($p=0.295$). Multiple Cox regression analysis showed an impact of female gender on OS (HR 0.1) but not PFS (HR=0.49). EGFR status was available on 39/46 patients. 17 patients in Arm A and 14 Arm B were mutation positive. In analyzing mutation + only patients, no difference in PFS ($p=0.332$) or OS ($p=0.346$) was seen amongst the 2 groups. In the mutation + patients the 6 months PFS for Arm A was 39% and for Arm B was 32%. More toxicity was seen on Arm B as compared to Arm A. Irrespective of causal attribution, 1 grade 5 event occurred on Arm A as opposed to 2 events on Arm B. A total of 7 grade 3/4 events occurred on Arm A while 24 occurred on Arm B. **Conclusions:** No benefit was seen with the continuation of ERL in addition to chemotherapy as compared to chemotherapy alone in patients who had previously benefited from ERL but then showed progression. The combination arm showed significantly more toxicity. Clinical trial information: NCT00660816.

8115 General Poster Session (Board #41G), Sat, 8:00 AM-11:45 AM

DDR2 mutations in lung cancer in adenocarcinoma and squamous cell carcinoma and association with MET activation.

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Background: The discoidin domain receptor tyrosine kinase 2 (*DDR2*) gene is mutated in a small subset of squamous cell carcinomas (SQCAs) of the lung. Targeting of DDR2 with the inhibitor dasatinib inhibits *DDR2*-mutated cell line growth and is being investigated in clinical trials for treatment of *DDR2*-mutated lung tumors. We investigated the frequency and type of *DDR2* mutations and their association with other targetable growth factor pathway alterations in non-small cell lung carcinoma (NSCLC). **Methods:** DNA was extracted from macro-dissected FFPE sections of 105 advanced stage lung carcinomas. Next-generation sequencing was performed using a 36-amplicon panel including the coding regions of *DDR2* and exons 11 and 15 of *BRAF*. *DDR2* mutations were confirmed by bidirectional Sanger sequencing. Lung tumors were classified using a standard immunohistochemistry panel. MET pathway activation was assessed with immunohistochemistry using an activation-specific phospho-antibody (pMET, Try1234/1235). *MET* amplification and *ALK* rearrangement were assessed using FISH. Mutational analysis for *EGFR* (exon 18-21), *PIK3CA* (exons 9 and 20), and *KRAS*(exons 1-2) was performed using PCR-based DNA sequencing. **Results:** Heterozygous *DDR2* point mutations were identified in 7/105 (6.7%) NSCLCs, including 3/29 (10.3%) SQCAs and 4/69 (5.8%) ACAs, but not in neuroendocrine/large cell carcinomas (0/7). *DDR2* mutations were scattered throughout the gene, with 4 present in the discoidin domain and 3 in the kinase domain. MET pathway activation, seen in 25% of *DDR2*-unmutated cases, was found in 3/6 (50%) *DDR2*-mutated cases, including 1 SQCA with high-level *MET* gene amplification. *DDR2* mutations were mutually exclusive with *BRAF* or *EGFR* mutation or *ALK* rearrangement, with 1 *KRAS*-mutated case. **Conclusions:** *DDR2* mutations occur in lung carcinomas with a range of histologic features and in association with MET activation. Dual targeting of the MET and DDR2 kinases in such cases may warrant further investigation.

8116 General Poster Session (Board #41H), Sat, 8:00 AM-11:45 AM

Pulsed dosing of erlotinib for central nervous system (CNS) progression in EGFR-mutant non-small cell lung cancer (NSCLC).

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Background: Lung cancer is the most common cause of CNS metastases. Options for CNS progression are limited, particularly with leptomeningeal metastases (LM). High dose EGFR-TKIs have been used in this setting. This is a retrospective series of our experience with pulsed high dose erlotinib for these patients. **Methods:** Eligible pts with EGFR-mutant NSCLC were identified through our institutions' databases and had received pulsed high dose erlotinib for CNS progression. Patients had received erlotinib 1000-1500 mg once weekly. The primary endpoint was CNS response; secondary endpoints included toxicity, systemic response, CNS progression-free survival, and overall survival. **Results:** Between 10/2010 – 10/2012, 10 eligible pts received pulsed dose erlotinib for CNS progression. The median age was 60 yrs; 8/10 were female, 7/10 were never-smokers, with a median of 2 pack-years. All pts had lung adenocarcinoma, and 9/10 had received prior EGFR-TKI. Median duration of prior TKI was 19 months. 6 received prior erlotinib, 1 received prior dacomitinib, and 2 received prior erlotinib followed by dacomitinib. The overall CNS response rate was 10% (1/10); 2 others achieved CNS stability. Median overall survival was 1.7 months (range 0.6 – 7.0). There was no clear correlation between outcomes and underlying EGFR genotype; type, duration, or dose of prior EGFR-TKI; or extent of CNS involvement. **Conclusions:** While there has been evidence of higher penetration of EGFR-TKI's into cerebrospinal fluid with pulsed high doses of EGFR-TKI's, the clinical efficacy of this strategy remains limited.

Baseline EGFR genotype	Prior EGFR-TKI	Extent of CNS disease	Prior WBRT	Best CNS response	Time to CNS progression, months
Exon 19 del	E>D	BM, LM	Y	PD	0.6
Exon 19 del	E	BM, LM	Y	PD	2.6
L858R	E>D	BM, LM	N	PR	7.0
L858R, T790M	E	BM, LM	Y	SD	3.7+
Exon 19 del	E	BM	Y	PD	1.8
L858R	E	LM	Y	SD	4.5+
Exon 19 del	E	BM, LM	Y	PD	0.8
L858R	E	BM	Y	PD	1.4
Exon 19 del	D	LM	Y	PD	1.7
Exon 19 del	None	BM, LM	Y	PD	0.7

Abbreviations: WBRT, whole brain radiation therapy; E, erlotinib; D, dacomitinib; BM, brain metastasis; LM, leptomeningeal metastasis; PR, partial response; SD, stable disease; PD, progressive disease.

TPS8117 General Poster Session (Board #42A), Sat, 8:00 AM-11:45 AM

CA184-104: Randomized, multicenter, double-blind, phase III trial comparing the efficacy of ipilimumab (Ipi) with paclitaxel/carboplatin (PC) versus placebo with PC in patients (pts) with stage IV/recurrent non-small cell lung cancer (NSCLC) of squamous histology.

Martin Reck, Pablo Gonzalez-Mella, Myung-Ju Ahn, Hassan H. Ghazal, Claus-Peter Schneider, Jacek Jassem, Haolan Lu, Diane Opatt McDowell, Pieter E. Postmus; Department of Thoracic Oncology, Lung Clinic Grosshansdorf, Grosshansdorf, Germany; Instituto Oncológico, Viña del Mar, Chile; Department of Medicine, Division of Hematology-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Kentucky Cancer Clinic, Hazard, KY; Department of Pneumology, Zentralklinik Bad Berka, Bad Berka, Germany; Department of Oncology and Radiotherapy, Medical University of GdÃ¡nsk, GdÃ¡nsk, Poland; Bristol-Myers Squibb, Wallingford, CT; Department of Pulmonary Diseases, VU University Medical Center, Amsterdam, Netherlands

Background: Improved outcomes for squamous, advanced NSCLC—beyond standard platinum doublets—have not been demonstrated. Data suggestive of response to immune therapies in squamous NSCLC support investigation in this subtype. Ipi, a fully human monoclonal antibody which binds CTLA-4, augments antitumor immune responses. Ipi improved overall survival (OS) in advanced melanoma, with side effects managed using product-specific treatment guidelines. A randomized phase II study of phased Ipi/PC (Ipi started after 2 cycles of PC) in pts with stage IV NSCLC showed significant improvement in progression-free survival (PFS), as measured by mWHO or immune-related response criteria (irRC), with a trend toward prolonged OS, over chemotherapy alone; irRC were derived from WHO criteria to better capture response patterns observed with Ipi. Improvement in PFS and OS appeared greater in tumors of squamous histology. Ipi did not exacerbate PC toxicity, and immune-related adverse events were managed using protocol-specific guidelines. This global (~253 sites among 34 countries) phase III trial (ClinicalTrials.gov identifier NCT01285609) is investigating whether phased Ipi/PC will prolong OS in first-line pts with squamous NSCLC. **Methods:** Stage IV/recurrent squamous NSCLC with ECOG 0-1 will be included; pts with CNS metastases or history of autoimmune disease will be excluded. Pts are randomized to 2 cycles of PC (175 mg/m^2 and AUC=6, respectively; IV), followed by 4 cycles of study drug (Ipi in Arm A, placebo in Arm B; IV) with 4 additional cycles of PC (total 6 cycles). Pts without progressive disease (PD) after induction receive maintenance therapy with blinded study drug Q12W until PD per mWHO. The study will enroll an estimated 920 pts, randomized 1:1 between arms. The primary endpoint is OS; secondary endpoints include OS among pts who receive blinded therapy, PFS, and best overall response rate. Safety is an exploratory objective of the trial. Clinical trial information: NCT01285609.

TPS8118 General Poster Session (Board #42B), Sat, 8:00 AM-11:45 AM

BATTLE-2 program: A biomarker-integrated targeted therapy study in previously treated patients with advanced non-small cell lung cancer (NSCLC).

Vassiliki Papadimitrakopoulou, Ignacio Ivan Wistuba, J. Jack Lee, Anne S. Tsao, Neda Kalhor, Frank V. Fossella, John Heymach, Christine M Alden, Scott N. Gettinger, Kevin R. Coombes, Pierre Saintigny, Ximing Tang, Emily Duffield, Julie Boyer, Suzanne E Davis, Garth Powis, David J. Mauro, Eric H. Rubin, Waun Ki Hong, Roy S. Herbst; Department of Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX; Yale University, New Haven, CT; Yale Cancer Center, New Haven, CT; Merck & Co, Inc, North Wales, PA; Merck Sharp & Dohme, North Wales, PA

Background: New strategies incorporating a personalized medicine approach for NSCLC treatment are increasingly explored and were pioneered in the prospective, biomarker-driven clinical program titled Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE-1) (Kim et al *Cancer Discov* 2011;1:44). Effective therapeutic strategies for mutant *KRAS* and other biomarkers of resistance in refractory NSCLC remain an unmet medical need. The BATTLE-2 clinical study is using EGFR, PI3K/AKT and MEK inhibitors and is designed to identify biomarkers for optimal patient selection for these therapies, with a long-term goal to significantly improve the survival of NCSLC patients (pts) (ClinicalTrials.gov NCT01248247). **Methods**: This is a four-arm, open-label, multi-center, biopsy-driven, adaptive randomization, phase II clinical trial in refractory NSCLC pts (failed at least 1 prior line of therapy). After a study-entry tumor biopsy, pts are adaptively randomized, based on KRAS status, to 4 trial arms: erlotinib, erlotinib plus the AKT inhibitor MK-2206, MK-2206 plus the MEK inhibitor selumetinib, and sorafenib. The primary objective is 8-week disease control rate (DCR). Baseline tumor testing includes *KRAS* and *EGFR* mutations and *EML4/ALK* translocation, the latter two being exclusion criteria. The trial is conducted in 2 stages. In Stage 1, 200 evaluable pts are adaptively randomized (AR) based on observed 8-week DCR and *KRAS* status while predictive biomarkers are being developed. In Stage 2, the AR model is refined to include the most predictive biomarkers tested in Stage 1, with subsequent Stage 2 AR based on the new algorithm, to a total of 400 evaluable pts. Selection of Stage 2 single and/or composite markers ("signatures") follows a rigorous, internally and externally reviewed statistical analysis. All Stage 1 and 2 randomization biomarker assays are CLIA-certified. 219 pts have been enrolled and 124 pts randomized. 100 pts are evaluable for the 8-week DCR endpoint. Accrual updates, demographics, and further details will be presented at the meeting. Supported by NCI R01CA155196-01A1. Clinical trial information: NCT01248247.

TPS8119 General Poster Session (Board #42C), Sat, 8:00 AM-11:45 AM

A phase II single-arm study of LDK378 in patients with ALK-activated (ALK+) non-small cell lung cancer (NSCLC) previously treated with chemotherapy and crizotinib (CRZ).

Alice Tsang Shaw, Tony Mok, David R. Spigel, Makoto Nishio, Enriqueta Felip, Daniel Shao-Weng Tan, M. Rosario Garcia-Campelo, Harry J.M. Groen, Shaker R. Dakhil, Eric Scott Schaefer, Nicholas John Farrell, Rick E. Blakesley, Alexander Weir, Mirta Ristic, Giovanni Selvaggi, Giorgio Scagliotti; Massachusetts General Hospital Cancer Center, Boston, MA; The Chinese University of Hong Kong, Hong Kong, China; Sarah Cannon Research Institute; Tennessee Oncology, Nashville, TN; Department of Thoracic Medical Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan; Thoracic Tumors Group, Vall d'Hebron Institute of Oncology, Barcelona, Spain; National Cancer Center Singapore, Singapore, Singapore; Complexo Hospitalario A Coruña, A Coruña, Spain; University Medical Center Groningen, Groningen, Netherlands; Cancer Center of Kansas, Wichita, KS; Highlands Oncology Group, Fayetteville, AZ; Associates in Oncology and Hemotology, Rockville, MD; Novartis Pharmaceuticals, East Hanover, NJ; Novartis Pharma AG, Basel, Switzerland; University of Turin, Orbassano, Italy

Background: NSCLC harboring anaplastic lymphoma kinase (*ALK*) gene rearrangements (2–8% of cases) are sensitive to CRZ, the only approved ALK inhibitor, but invariably develop resistance. There are currently no standard ALK-targeted treatments for CRZ-resistant ALK+ NSCLC. LDK378 is a novel, oral ALK inhibitor with 20-fold greater potency than CRZ in enzymatic assays. In an ongoing phase I trial, LDK378 has demonstrated substantial clinical activity in patients (pts) with ALK+ NSCLC whose disease has failed CRZ. At a dose ≥400 mg (45 pts), the overall response rate (ORR) was 80%, with 47% confirmed responses (data cutoff August 31, 2012). Nausea, vomiting, diarrhea and fatigue were the main toxicities. The recommended phase II dose is 750 mg daily. **Methods**: This phase II multicenter, open label, single-arm study (CLDK378A2201) is designed to evaluate the efficacy and safety of oral LDK378 750 mg once-daily in pts with ALK+ (by FDA-approved FISH test) advanced NSCLC. Pts must have received cytotoxic chemotherapy (1–3 lines, including 1 platinum doublet) and progressed on CRZ as the last therapy prior to study entry. Pts with ECOG PS 0–2 and stable CNS metastases are eligible. LDK378 may be continued beyond RECIST-defined PD if there is evidence of clinical benefit. The primary objective is to assess the antitumor activity of LDK378 in terms of ORR by investigator assessment (using RECIST v1.1). Secondary/exploratory objectives include evaluating response endpoints (duration of response, time to response and ORR by independent radiological review), PFS, OS, safety, PK, and impact on patient-reported outcomes. The primary analysis will occur when all pts have completed 6 cycles or discontinued treatment earlier. The study design (137 pts) provides 90% power to test a null hypothesis of ORR ≤25% vs. a target ORR of ≥38%: if ≥45 responses are observed (estimated ORR 33%), the null hypothesis will be rejected at a one-sided significance level of 0.025. The study is recruiting in 67 sites from 14 countries across Europe, Asia and North America. As of February 5, 2013, 7 pts have been enrolled. ClinicalTrials-.gov identifier NCT01685060. Clinical trial information: NCT01685060.

TPS8120 **General Poster Session (Board #42D), Sat, 8:00 AM-11:45 AM**

Double-blind randomized phase II trial of carboplatin and pemetrexed with or without OGX-427 in patients with previously untreated stage IV non-squamous non-small-cell lung cancer (NSCLC): The Spruce Clinical Trial.

David R. Spigel, Howard A. Burris, F Anthony Greco, John D. Hainsworth; Sarah Cannon Research Institute; Tennessee Oncology, Nashville, TN

Background: OGXE427 is an antisense oligonucleotide (ASO) designed to bind to Hsp27 (heat shock protein 27) mRNA, resulting in the inhibition of production of Hsp27 protein. Hsp27 is over-expressed in many cancers including lung, prostate, breast, and bladder. Increased expression has been associated with inhibition of chemotherapy-induced apoptosis, increased tumor cytoprotection, and the development of treatment resistance. OGX-427 is an inhibitor of Hsp27 that effectively targets and down-regulates Hsp27 mRNA and has been shown to increase apoptosis, inhibit tumor growth, and sensitize cells to various chemotherapy regimens in a variety of malignancies. Based on this preclinical data, addition of an Hsp27 inhibitor to standard chemotherapy may improve the efficacy of treatment. In this randomized phase II study, OGX-427 will be added to a standard carboplatin/pemetrexed regimen, with the goal of improving progression-free survival when compared to carboplatin and pemetrexed alone in the first-line treatment of non-squamous NSCLC patients. **Methods:** A total of 155 patients will be randomized in a 1:1 ratio. Randomization will be stratified by histology (adenocarcinoma vs. large cell carcinoma) and smoking status (smoker vs. non-smoker). Treatment will include a loading dose period with OGX-427 600 mg or placebo. On day one of each 21 day cycle, patients will receive OGX-427 1000 mg or placebo, pemetrexed 500 mg/m^2, and carboplatin AUC 6, all administered IV. On days 8 and 15, OGX-427 or placebo will also be administered. Key eligibility criteria include; untreated recurrent or stage IV predominantly non- squamous NSCLC, measureable disease by RECIST v 1.1, ECOG PS 0 or 1, adequate organ function, and no known CNS disease. Serum Hsp27 levels will be assessed at screening, baseline and during treatment. In addition, archival tissues will be collected and assessed for PTEN (protein expression by IHC) and a panel of gene mutations for correlative analyses.

TPS8121 **General Poster Session (Board #42E), Sat, 8:00 AM-11:45 AM**

A phase III comparative study of nivolumab (anti-PD-1; BMS-963558; ONO-4538) versus docetaxel in patients (pts) with previously treated advanced/metastatic nonsquamous non-small-cell lung cancer (NSCLC).

Scott N. Gettinger, Julie R. Brahmer, Naiyer A. Rizvi, Neal Ready, Laura Quan Man Chow, Scott J. Antonia, Marc E. Buyse, Jacek Jassem, Friedrich Graf Finckenstein, Lucio Crinò, Thomas James Lynch; Yale Cancer Center, New Haven, CT; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Memorial Sloan-Kettering Cancer Center, New York, NY; Duke University Medical Center, Durham, NC; University of Washington, Seattle, WA; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; International Drug Development Institute, Louvain la Neuve, Belgium; Medical University of Gdańsk, Gdańsk, Poland; Bristol-Myers Squibb, Princeton, NJ; Azienda Ospedaliera di Perugia, Perugia, Italy

Background: Lung cancer is the leading cause of cancer mortality globally. Non-squamous NSCLC represents up to 75% of NSCLC cases with most pts diagnosed with advanced disease, which progresses rapidly following failure of 1st-line platinum-based doublet (Pt-doublet) chemotherapy. Benefit from current therapies has reached a plateau with median overall survival (OS) for late stage NSCLC pts of 10-12 months. Standard 2nd-line therapy (single-agent chemotherapy; eg. docetaxel) results in OS of 8 months. Expression of programmed death-1 (PD-1), an immune checkpoint receptor that negatively regulates T-cell activation, is associated with poor prognosis in NSCLC. Nivolumab, a PD-1 receptor blocking antibody, prevents activation of PD-1 by its known ligands, PD-L1 and PD-L2, and demonstrated durable antitumor activity in NSCLC pts in a phase 1 study (Topalian ST, et al. *N Engl J Med* 2012). We present a phase III study comparing OS benefit of nivolumab vs docetaxel in pts with metastatic/recurrent non-squamous NSCLC. **Methods**: In this study, 574 pts will be randomized 1:1 to receive nivolumab 3 mg/kg IV q 2 weeks (wks) or docetaxel 75 mg/m^2 q 3 wks until disease progression or unacceptable toxicity. Pts will include those having progressed during/after Pt-doublet ± bevacizumab (bev) for advanced disease as well as pts with EGFR-mutant or ALK-rearranged NSCLC who have progressed following treatment with a tyrosine kinase inhibitor (TKI) and a Pt-doublet ± bev. Prior maintenance therapy with erlotinib, pemetrexed and/or bev is allowed. Pts will be stratified by prior use of maintenance therapy and receipt of 1 vs 2 (Pt doublet and TKI) prior lines of therapy. Response will be assessed (modified RECIST 1.1) at 9 wks following treatment initiation and every 6 wks thereafter until disease progression. The primary objective is to compare the OS of nivolumab vs docetaxel treated pts. Secondary objectives include comparison of objective response rates, progression-free survival and disease related symptom progression, and evaluation of clinical benefit of nivolumab vs docetaxel in PD-L1+ vs PD-L1- tumor subgroups. Clinical trial information: NCT01673867.

TPS8122 **General Poster Session (Board #42F), Sat, 8:00 AM-11:45 AM**

A phase III comparative study of nivolumab (anti-PD-1; BMS-936558; ONO-4538) versus docetaxel in patients with previously treated advanced or metastatic squamous cell non-small cell lung cancer (NSCLC).

Hossein Borghaei, Thomas James Lynch, Naiyer A. Rizvi, Laura Quan Man Chow, Robert Reilly, Lucio Crinò, Marc E. Buyse, Rana Ezzeddine, Brian Joseph Lestini, Julie R. Brahmer; Fox Chase Cancer Center, Philadelphia, PA; Yale School of Medicine, New Haven, CT; Memorial Sloan-Kettering Cancer Center, New York, NY; University of Washington, Seattle, WA; St Mary Medical Center, Langhorne, PA; Azienda Ospedaliera di Perugia, Perugia, Italy; International Drug Development Institute, Louvain la Neuve, Belgium; Bristol-Myers Squibb, Wallingford, CT; Bristol-Myers Squibb, Princeton, NJ; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD

Background: NSCLC is the leading cause of cancer death worldwide, exceeding breast, colon and prostate cancer combined. Most patients (pts) are diagnosed with advanced/recurrent disease. NSCLC therapies have incrementally improved overall survival (OS), but benefit has reached a plateau (median OS for late stage pts is just 1 yr). Squamous cell carcinoma (SCC) represents one quarter of NSCLC cases and has limited treatment options. Pemetrexed and bevacizumab are not approved in SCC, and molecularly targeted therapies have limited application. Single-agent chemotherapy is standard of care following progression with platinum-based doublet chemotherapy (Pt-doublet), resulting in median OS of approximately 7 months. Immune checkpoint blockade in NSCLC may promote tumor regression by reversing tumor-induced immunosuppression and restoring the antitumor immune response. Programmed death-1 (PD-1), an immune checkpoint receptor that negatively regulates T-cell activation, is upregulated in tumor infiltrating lymphocytes; expression of its ligand PD-L1 has been associated with poor prognosis in NSCLC. Nivolumab, a PD-1 receptor blocking antibody, showed encouraging antitumor activity in SCC pts in a phase 1 study, with objective responses (ORs) in 4 pts (27%) and stable disease ≥24 weeks in 1 pt (7%) (3 mg/kg; n=15) (Gettinger S et al; ESMO 2012 [Abstr 1237PD]). We describe an ongoing open-label phase 3 study to compare the clinical benefit of nivolumab vs docetaxel in advanced/metastatic SCC pts following failure of Pt-doublet. **Methods:** A total of 264 pts will be randomized 1:1 to nivolumab monotherapy 3 mg/kg IV every 2 weeks or docetaxel 75 mg/m^2 every 3 weeks until disease progression or unacceptable toxicity. Pts will be stratified by prior paclitaxel use and geographic region. Tumor response will be assessed using modified RECIST 1.1. The co-primary objectives are OR rate and OS. Secondary objectives include progression free survival, clinical benefit in PD ligand 1 (PD-L1+) and PD-L1– subgroups (archived tissue required for entry), durability of and time to OR, and pt proportion with symptom improvement. Clinical trial information: NCT01642004.

TPS8123 **General Poster Session (Board #42G), Sat, 8:00 AM-11:45 AM**

Phase III randomized, open label study (ARCHER 1050) of first-line dacomitinib (D) versus gefitinib (G) for advanced (adv) non-small cell lung cancer (NSCLC) in patients (pts) with epidermal growth factor receptor (*EGFR*) activating mutation(s).

Tony Mok, Kazuhiko Nakagawa, Rafael Rosell, Yi Long Wu, Carl Trygstad, Robert L. Capizzi, Min Young Lee, Fumito Tsuji, Robert DeBenedetto, Zelanna Goldberg, Tao Wang, Jane Q. Liang, Stephen P. Letrent, Joseph P. O'Connell, Vladan Antic; Prince of Wales Hospital, Shatin, Hong Kong; Kinki University Faculty of Medicine, Higashi-Osaka City, Japan; Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Pangaea Biotech, Cancer Therapeutics Innovation Group, USP Institut Universitari Dexeus, Barcelona, Spain; Guangdong Lung Cancer Institute, Guangdong General Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China; SFJ Pharmaceuticals, Inc., Pleasanton, CA; SFJ Pharmaceutical, Inc., Singapore, Singapore; SFJ Pharmaceutical, Inc., Osaka, Japan; Pfizer Oncology, La Jolla, CA; Pfizer Oncology, Groton, CT; Pfizer Oncology, New York, NY; Pfizer AG, Zurich, Switzerland

Background: D is an orally available, potent and selective irreversible small molecule inhibitor of all catalytically active members of the HER (human epidermal growth factor receptor) family tyrosine kinases that has shown activity in preclinical studies on *EGFR* mutant cell lines, including those resistant to G. In a phase II trial of NSCLC pts who received 1st-line D, 75.6% of 45 pts with confirmed *EGFR* exon 19 or 21 sensitizing mutations (m) experienced a partial response (PR). The median progression-free survival (PFS) was 18.2 mo, and the PFS rate at 1 yr was 76.5% (preliminary data; Mok et al APLCC 2012). **Methods:** Based on the phase II data, a phase III randomized, open label trial (ARCHER 1050; NCT01774721) was designed to compare the efficacy of 1st line D with G in pts with adv *EGFR* m-positive NSCLC. Eligible pts (N=440) have pathologically confirmed stage IIIB/IV NSCLC with at least one activating *EGFR* m, either exon 19 deletion or exon 21 *L858R* m. Concurrent m in exon 20 *T790M* is permitted. Pts must have radiologically measurable disease, ECOG PS 0–1 and no prior systemic therapy. Pts will be randomized (1:1) to receive D 45 mg or G 250 mg orally once daily. The primary endpoint is PFS by Independent Radiologic Review. Secondary endpoints include PFS by investigator assessment, overall survival (OS), OS at 30 mo, best overall response, duration of response, and safety and tolerability. Pt-reported outcomes (HRQoL and disease/treatment-related symptoms) were also assessed. Randomization will be stratified by race (Japanese vs mainland Chinese vs other East Asian vs nonEEast Asian), and *EGFR* m status (exon 19 deletion vs exon 21 *L858R* m). A minimum of 268 PFS events is required for 90% power to detect a PFS improvement of ≥50% in D vs G recipients using the intent-to-treat (ITT) analysis population (HR ≤0.667). A significant (0.025 significance level) 1-sided stratified log-rank test for PFS at the final PFS analysis will be indicative of a positive study outcome. An interim analysis is planned to assess safety and whether early discontinuation of the trial is required for futility. Clinical trial information: NCT01774721.

TPS8124 **General Poster Session (Board #42H), Sat, 8:00 AM-11:45 AM**

Randomized phase II study of neratinib with or without temsirolimus in patients (pts) with non-small cell lung cancer (NSCLC) carrying *HER2*-activating mutations.

Leena Gandhi, Jean-Charles Soria, Richard Bryce, Benjamin Besse; Dana-Farber Cancer Institute, Boston, MA; Institut Gustave Roussy, Villejuif, France; Puma Biotechnology, Los Angeles, CA

Background: Recent advances in NSCLC have highlighted the importance of identifying mutations in driver oncogenes (eg *EGFR*, *ALK*) and the use of targeted agents to treat genetically-defined pt populations. HER2 (ERBB2) is a member of the ERBB receptor tyrosine kinase (TK) family which, once activated, stimulates several downstream effector pathways including PI3K, MAPK and JAK/STAT. Activating *HER2* mutations are documented in approx 2–4% of pts with NSCLC and occur independently of *EGFR, KRAS, NRAS* and *BRAF* mutations. The efficacy of single-agent neratinib in *HER2*-mutated NSCLC is currently unknown; however, in vivo studies suggest that dual inhibition with an irreversible TK inhibitor (TKI) and an mTOR inhibitor is a promising therapeutic approach for *HER2*-mutated NSCLC [Perera et al. PNAS 2009]. This concept has been supported recently by a phase I study of neratinib, an irreversible pan-ERBB TKI, plus temsirolimus, which showed tumor regression in 5/6 evaluable pts with *HER2*-mutated NSCLC [Gandhi et al. WCLC, Amsterdam, Netherlands, 2011]. **Methods:** This international, randomized, open-label phase II study includes pts with previously treated stage IIIB/IV NSCLC and *HER2*-activating mutations. Pts are randomized 1:1 to oral neratinib 240mg od continuously ± IV temsirolimus 8mg/w (dose escalation to 15mg/w after one 4w cycle if tolerated). The addition of temsirolimus is permitted in pts assigned to neratinib monotherapy after progression. Tumor evaluations will be conducted every 8w. The primary endpoint is overall response rate (RECIST 1.1). Secondary endpoints are: clinical benefit rate; response duration; progression-free and overall survival; safety; health outcomes. Exploratory analyses include: correlative studies between tumor and plasma biomarkers and outcomes; pharmacokinetics. The trial has an optimal 2-stage design. Sample size (13–52 pts/arm) is based on a null response rate of 0.09, an alternative response rate of 0.25, power of 80% and 0.05 type I error rate. Both arms will be compared independently against historical controls. Enrollment is scheduled to open in March 2013. EudraCT identifier: 2012-004743-68. Clinical trial information: 2012-004743-68.

TPS8125 **General Poster Session (Board #43A), Sat, 8:00 AM-11:45 AM**

A randomized, open-label phase II study of single-agent vintafolide versus vintafolide plus docetaxel versus docetaxel alone in second-line NSCLC patients with all target lesions expressing folate-receptor (TARGET).

Martin J. Edelman, Hong Ma, Wendy Perez, Alex A. Adjei, Nasser Hanna; University of Maryland, Marlene and Stewart Greenebaum Cancer Center, Baltimore, MD; Endocyte, Inc., West Lafayette, IN; Roswell Park Cancer Institute, Buffalo, NY; Simon Cancer Center, Indiana University School of Medicine, Indianapolis, IN

Background: Folate receptor (FR) is frequently overexpressed in NSCLC and is a potential biomarker for therapy selection. Vintafolide (EC145) is designed to target FR expressing cells and consists of folate linked to desacetylvinblastinehydrazide. The FR targeted imaging agent, ^{99m}Tc-etarfolatide (EC20), consists of folate coupled to technetium and identifies lesions that overexpress FR which may respond to vintafolide treatment. A phase II study of single-agent vintafolide in heavily pre-treated lung adenocarcinoma patients (pts) showed promising activity in clinical benefit response (50% vs. 14.3%) and overall survival (OS, 47.2 wks vs. 14.9 wks), in pts whose target lesions all expressed FR [FR (100%)] vs pts whose target lesions were not all FR positive (Edelman et al, *JTO* 2012:7:1618-21). This trial assesses the benefit of vintafolide as second-line therapy in NSCLC FR (100%) pts. **Methods:** This is a randomized, open-label phase II study of vintafolide vs. vintafolide + docetaxel vs. docetaxel in second line NSCLC FR (100%) pts (NCT01577654). Key eligibility criteria include: cytologic or histologic diagnosis of NSCLC, 1 prior systemic therapy for advanced disease, and PS 0-1. At baseline, pts undergo ^{99m}Tc-etarfolatide imaging to detect FR-positive lesions. FR (100%) pts are randomized 1:1:1 to vintafolide, vintafolide + docetaxel, or docetaxel. Vintafolide (2.5 mg) is administered on d 1, 4, 8, and 11 of a 3-wk cycle. Docetaxel (75 mg/m^2) is given on d 1 of a 3-wk cycle. Treatment continues until disease progression or unacceptable toxicity. Pts receiving vintafolide + docetaxel who discontinue docetaxel due to toxicity may continue vintafolide alone. Disease status is evaluated by RECIST v1.1 criteria every 6 wks and adverse events are monitored throughout. The primary objective of this study compares PFS between the docetaxel control arm and each experimental arm with the goal of demonstrating a hazard ratio of $\leq$0.67 favoring the experimental arms. Secondary objectives include response rate, disease control rate, OS, and safety/tolerability. Enrollment to the study is ongoing. Clinical trial information: NCT01577654.

TPS8126 **General Poster Session (Board #43B), Sat, 8:00 AM-11:45 AM**

GALAXY-2 trial: A randomized phase III study of ganetespib in combination with docetaxel versus docetaxel alone in patients with advanced non-small cell lung adenocarcinoma.

Dean Anthony Fennell, Glenwood D. Goss, Mark A. Socinski, Kazuhiko Nakagawa, Joan H. Schiller, Philip Bonomi, Vera Hirsh, Karen Kelly, James F. Spicer, Rafael Rosell, Bojan Zaric, Tudor-Eliade Ciuleanu, Vojislav M. Vukovic, Florentina Teofilovici, Iman El-Hariry, Wei Guo, Suresh S. Ramalingam; University of Leicester, Leicester, United Kingdom; The Ottawa Hospital Cancer Center, Ottawa, ON, Canada; University of Pittsburgh, Pittsburgh, PA; Kinki University Faculty of Medicine, Higashi-Osaka City, Japan; The University of Texas Southwestern Medical Center, Dallas, TX; Rush University Medical Center, Chicago, IL; McGill University Health Centre, Montreal, QC, Canada; Division of Hematology and Oncology, UC Davis Comprehensive Cancer Center, Sacramento, CA; King's College London, Guy's Hospital, London, United Kingdom; Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Barcelona, Spain; University of Novi Sad, Institute for Pulmonary Diseases of Vojvodina, Novi Sad, Serbia; Prof. Dr. Ion Chiricuta Institute of Oncology, Department of Medical Oncology, Cluj-Napoca, Romania; Synta Pharmaceuticals, Inc., Lexington, MA; The Winship Cancer Institute of Emory University, Atlanta, GA

Background: Hsp90 is a molecular chaperone recognized as a key facilitator of cancer cell growth and survival. Ganetespib is a resorcinolic Hsp90 inhibitor that has shown single-agent activity in patients with lung, breast, and other cancers after progression on standard treatments. Ganetespib in combination with docetaxel induces synergistic efficacy in human non-small-cell lung carcinoma (NSCLC) tumor xenografts. Ganetespib is well tolerated and has not shown severe liver or common ocular toxicities reported for other Hsp90 inhibitors. Transient diarrhea is the most common adverse event, and is manageable with appropriate supportive care. A large randomized study of ganetespib in combination with docetaxel in advanced NSCLC patients (GALAXY-1 Trial) is ongoing. Preliminary results indicate good tolerability of the combination, and improvement in efficacy, including OS. **Methods:** GALAXY-2 is a randomized (1:1), international, open-label phase III study enrolling patients who received and progressed on one prior systemic therapy for advanced NSCLC of adenocarcinoma histology. Patients (N=500) are prospectively stratified for ECOG PS, total LDH, and best response to first-line therapy. The primary endpoint is OS. Key secondary endpoints include: OS in 3 subpopulations (mKRAS and elevated LDH and LDH5); PFS, ORR, DCR, DOT, and DOR. Patients in the control arm are treated with docetaxel 75 mg/m^2 on Day 1 of a 3-week cycle. In the combination arm, ganetespib 150 mg/m^2 is given on Day 1 with 75 mg/m^2 docetaxel, and ganetespib 150 mg/m^2 alone is given on Day 15 of each 3-week cycle. Two interim analyses for OS will be performed. Tumor tissue and blood samples will be collected for planned translational studies.