non-small cell lung cancer, metastatic

A RANDOMIZED PHASE 2 STUDY OF ERLOTINIB PLUS PEMETREXED VS ERLOTINIB OR PEMETREXED ALONE AS SECOND-LINE TREATMENT FOR NEVER-SMOKER PATIENTS WITH NON-SQUAMOUS ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

D.H. Lee¹, J.S. Lee², S.W. Kim¹, J. Rodrigues Pereira³, B. Han¹, X.Q. Song⁴, J. Wang⁵, H.-K. Kim⁶, T. P. Sahoo⁶, R. Digumarti⁷, X. Wang⁸, S. Altug⁹, M. Orlando¹¹

¹Asan Medical Center, Seoul, KOREA, ²Grupo de Asistencia Médica, Sao Paulo, BRAZIL, ³Shanghai Chest Hospital, Shanghai, CHINA, ⁴Affiliated Cancer Hospital of Guangxi Medical University, Nan Ning, CHINA, ⁵Beijing Tumor Hospital, Beijing, CHINA, ⁶St. Vincent Hospital, Suwon, KOREA, ⁷Chirayu Medical College and Hospital, Bhopal, INDIA, ⁸Eli Lilly and Company, Shanghai, CHINA, ⁹Eli Lilly and Company, Buenos Aires, ARGENTINA

Methods: From Nov 2007 to Jul 2010, never-smoker NSCLC, ECOG Performance Status (PS) ≤ 2 pts who had failed 1 prior chemotherapy regimen were enrolled and randomized to either: E 150 mg daily, P 500 mg/m² day 1, or P 500 mg/m² day 1 plus E 150 mg daily on days 2 to 14 of a 21-day cycle, continued until discontinuation criteria were met. The primary endpoint of progression-free survival (PFS) was analyzed using a sequential approach. A multivariate Cox model was used to perform a global comparison across the 3 arms with pairwise comparisons between treatments using contrasts within the model. If the global null hypothesis was rejected at a 2-sided 0.2 significance level (SL), then 2 pairwise comparisons of E + P vs E or P were conducted. Statistical significance was claimed if both pairwise and global null hypotheses were rejected at a 2-sided 0.05 SL.

Results: A total of 240 non-squamous pts (Male, 34.6%; East Asian, 55.4%; ECOG PS 0-1, 92.9%) were included. A statistically significant difference in PFS was found across the 3 arms (global p = 0.003); with E + P significantly better than both single agents (HR (95% CI) for E + P vs E was 0.57 (0.40, 0.81), p = 0.002; for E + P vs P was 0.58 (0.39, 0.85), p = 0.005). Median PFS (95% CI) was 7.4 months (4.4, 12.9) in E + P, 3.8 (2.7, 6.3) in E and 4.4 (3.0, 6.8) in P. PFS analyses showed a higher number of pts with ≥1 TEAE with CTCAE grade 3/4 toxicity in E + P (n = 45; 60.0%) than in P (n = 10; 28.9%) or E (n = 22; 12.0%), the majority being neutropenia, anemia, rash and diarrhea.

Conclusions: Erlotinib + Pemetrexed significantly improved PFS compared to either agent alone in this clinically selected population, E + P had more toxicity, but was clinically manageable. Further analysis of the EGFR mutational status will help to understand and predict which pts will benefit most from this approach.

Disclosure: X. Wang: I am employee of Eli Lilly and Company. S. Altug: I am employed by and hold stock in Eli Lilly & Company. All other authors have declared no conflicts of interest.

BIOMARKER ANALYSES AND OVERALL SURVIVAL (OS) FROM THE RANDOMIZED, PLACEBO-CONTROLLED, PHASE 3, FASTACT-2 STUDY OF INTERCALATED ERLOTINIB WITH FIRST-LINE CHEMOTHERAPY IN ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC)

T.S.K. Mok¹, J.S. Lee², L. Zhang³, C. Yu⁴, S. Thongprasert⁵, G.E.I. Ladreba⁶, V. Simmernnimmith⁷, M.I. Truman⁸, B. Klughammer⁹, Y. Wu¹⁰

¹Department of Clinical Oncology, Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, HONG KONG, ²Research Institute and Hospital, National Cancer Center, Goyang, KOREA, ³Medical Oncology, Sun Yat-Sen University Cancer Center, Guangzhou, CHINA, ⁴Department of Internal Medicine, National Taiwan University Hospital, Taipei, TAIWAN, ⁵Faculty of Medicine, Chiang Mai University, Chiang Mai, THAILAND, ⁶Department of Pulmonary Medicine, Lung Center of the Philippines, Quezon City, PHILIPPINES, ⁷Department of Medicine, Siriraj Hospital, Mahidol University, Bangkok, THAILAND, ⁸Department of Biometrics, F. Hoffmann-La Roche Ltd., Sydney, AUSTRALIA, ⁹Pharmaceutical Division, F. Hoffmann-La Roche Ltd., Basel, SWITZERLAND, ¹⁰Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, CHINA

Methods: FASTACT-2 is a randomized, placebo-controlled, phase 3 study in first-line advanced NSCLC, which met its primary endpoint of significantly prolonged PFS with intercalated erlotinib and chemotherapy: median 7.6 vs 6.0 months; HR = 0.57; p < 0.0001 (Mok et al. ASCO 2012). We report OS results and correlations of biomarkers with PFS for this study.

Results: OS data are not fully mature yet (45.1% and 52.4% of pts in GC-E and GC-P arms with event, respectively; in Oct 2011), but a trend towards prolonged OS with GC-E vs GC-P was observed: HR = 0.78 (95% CI 0.60-1.02); p = 0.0868; median 18.3 vs 14.9 months. Updated OS data with June 2012 cut-off will be presented. A total of 283/451 pts (62.7%) provided samples for biomarker analyses. The table shows correlations with PFS for the overall biomarker populations and the EGFR wild-type (WT) subgroup.

Conclusions: As expected, the EGFR mutation-positive (Mut+) subgroup had the strongest PFS benefit with intercalated erlotinib and first-line chemotherapy. ERCC1 IHC+ status was also associated with longer PFS with GC-E vs GC-P, even in pts with known EGFR WT status.

Background: AR to reversible epidermal growth factor receptor (EGFR)-specific tyrosine kinase inhibitors (TKIs) in EGFR mutant (mt) NSCLC is associated with an exon 20 EGFR T790M mutation in ~50% of cases. The targeted combination of afatinib (A), a potent ErbB Family Blocker, and cetuximab (C), induced nearly complete regression in T790M transgenic murine models. Following determination of the maximum tolerated dose, early clinical data suggest that the recommended dose combination of A/C is tolerable, with encouraging activity in AR cases (Janjigian Y. J Clin Oncol 2011; 29 (suppl); abstr 7525). Here, we report safety and efficacy data from an expanded cohort in AR NSCLC.

Methods: Pts with EGFR mt advanced NSCLC – progressive on erlotinib or gefitinib – transitioned directly (interval minimum 3 months) to oral daily A 40 mg and intravenous, bi-weekly C 500 mg/m2. Tumour biopsy after AR, prior to study therapy, was mandated by protocol. Efficacy endpoints included objective response (OR) and progression-free survival (PFS) with imaging at week 4, 12 and every 8 weeks thereafter.

Results: To date, 100 eligible pts have been treated (median duration 4.1 months, range 1–14 months). EGFR del 19 and L858R mt were present in 63% and 31% of pts, and EGFR T790M mt in 53% of pts. Adverse events included rash (Grade 1/2: 65%; Grade 3: 12%) and diarrhea (Grade 1/2: 63%; Grade 3: 6%). Ninety pts were evaluable for efficacy; rate of disease control was 94% and probability of PFS at 3, 6 and 12 months was 70%, 65% and 53%, similar in both T790M+ (38%) and T790M- (47%) tumours; the median PFS was 4.7 months and the median duration of response was 7.7 months.

Conclusions: Afatinib/cetuximab shows encouraging clinical efficacy in pts with AR to erlotinib or gefitinib, demonstrating that many EGFR mt NSCLCs continue to respond to ErbB signalling for survival. Efforts to elucidate the underlying mechanisms are ongoing, and updated clinical data will be presented. Further studies are planned to establish the potential role of this targeted combination in the treatment of EGFR mt NSCLC.


**Dacomitinib (PF-00299804), an Irreversible Pan-Her Tyrosine Kinase Inhibitor (TKI), for First-Line Treatment of EGFR-Mutant or HER2-Mutant or -Amplified Lung Cancers**


1Thoracic Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, UNITED STATES OF AMERICA, 2Oncology, Pfizer, San Diego, CA, UNITED STATES OF AMERICA, 3Thoracic Oncology, Dana-Farber Cancer Institute, Boston, Boston, UNITED STATES OF AMERICA, 4Thoracic Oncology, Seoul National University Hospital, Seoul, KOREA, 5Thoracic/Head and Neck Oncology, University of Washington/Seattle Cancer care Alliance, Seattle, UNITED STATES OF AMERICA, 6Department of Clinical Oncology, Chinese University of Hong Kong Prince of Wales Hospital, Shatin, Hong Kong, CHINA, 7Oncology, Pfizer, New York, NY, UNITED STATES OF AMERICA, 8Chao Family Comprehensive Cancer Center, University of California Irvine Medical Center, University of California Irvine, Irvine, Orange, CA, UNITED STATES OF AMERICA, 9Translational Oncology, Pfizer Inc, Groton, CT, UNITED STATES OF AMERICA, 10Oncology, Pfizer (China) Research and Development Co. Ltd., Shanghai, CHINA

Background: Dacomitinib irreversibly inhibits EGFR, HER2 and HER4, and showed superior activity vs. reversible EGFR TKI in EGFR mutant lung cancer models, including resistant forms. This open-label Phase II study evaluates dacomitinib in patients with EGFR-mutant or HER2-amplified or -mutant advanced NSCLCs.

Methods: Patients had stage IIIb/IV adenocarcinoma, no prior systemic treatment (EGFR cohort), had smoked <10 pack years (none within 15 years of enrolment) or had known EGFR mutation. Patients with HER2 amplifications or mutations, could have had any number of prior lines of therapy. Patients received dacomitinib orally once daily continuously at 45 mg, or 30 mg with the option to escalate to 45 mg; evaluation was every 28 days. Endpoints included progression-free survival (PFS) at 4 months (PFS4M, primary); PFS, partial response (PR) rate; and safety.

Results: 89 patients were enrolled and dosed in the EGFR cohort; 46 had EGFR mutation in exons 19 (n = 25) or 21 (n = 21) and 32 (70%) were female. 34/46 evaluable patients with EGFR exon 19 or 21 mutations had a PR (PR rate = 74%, 95% CI: 59–86; exon 19 = 72%; exon 21 = 76%). Preliminary PFS were similar for exons 19 and 21. Preliminary PFS4M was 96% (95% CI: 84–99), preliminary PFS rate at 12 months was 74% (95% CI: 59–85) and preliminary median PFS was 17 months (95% CI: 13–24). Median duration of tx was 14 months. To date, 17 patients have been dosed in the HER2 cohort (3 with amplification). For 16 patients with response data, there are 2 PR (1 confirmed), both with HER2 mutation. 5 patients had SD as their best response. Common side effects included dermatitis acriform (grade 3/4 = 16.9%/0) and diarrhea (13.5%/0). 5 patients in total discontinued therapy due to drug-related toxicity.

Conclusions: 7/4% of patients with EGFR exon 19 or 21 mutant lung cancers experienced PRs with 1st-line dacomitinib; preliminary PFS rate was 74% at 1 year; preliminary median PFS was 17 months; PR rates and preliminary PFS were similar for patients with HER2 mutations; further study in these patient populations. There are early signs of activity of dacomitinib in targeting HER2 in advanced NSCLCs and recruitment continues.

LUNG-LUNG 3: SYMPTOM AND HEALTH-RELATED QUALITY OF LIFE RESULTS FROM A RANDOMIZED PHASE III STUDY IN 1ST-LINE ADVANCED NSCLC PATIENTS HARBOURING EGFR MUTATIONS

L.V. Sequist1, M. Schuler2, N. Yamamoto3, K.J. O’Byrne4, V. Hirsh1, T.S. Kim5, J. Lungershausen6, M. Shahidi7, M. Palmer8, J.C. Yang9
1Medicine, Massachusetts General Hospital, Boston, MA, UNITED STATES OF AMERICA, 2Medicine, West German Cancer Center, University Duisburg-Essen, Essen, GERMANY, 3Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, JAPAN, 4Oncology, St James’s Hospital, Dublin, IRELAND, 5Oncology, McGill University Health Centre, Montreal, QC, CANADA, 6Department of Clinical Oncology, The Chinese University of Hong Kong, Shatin, Hong Kong, CHINA, 7Health Economics, Boehringer Ingelheim, Ingelheim, GERMANY, 8Clinical Research / Management, Boehringer Ingelheim, Bracknell, UNITED KINGDOM, 9Statistics, Keele University, Keele, UNITED KINGDOM, 10Oncology, National Taiwan University Hospital, Taipei, TAIWAN

Background: Afatinib (A) is an oral, irreversible ErbB family blocker. LUNG-Lung 3 compared A with cisplatin/pemetrexed (CP) in patients with EGFR mutation positive lung adenocarcinoma. The primary analysis demonstrated significant improvements in progression-free survival (PFS), with a median PFS of 11.1 months for A and 6.9 months for CP (HR = 0.58; p = 0.0004). Here, we present patient-reported Health-related Quality of Life (HRQoL) data.

Methods: 345 patients were randomized (2:1) to receive A or CP. Symptoms and HRQoL were measured using EORTC questionnaires (QLQ-C30/LC13) at baseline and q3w until progression. Changes of ≥10 points were considered clinically significant. Analyses of cough, dyspnea and pain symptoms were pre-specified.

Results: Compliance with questionnaires was >85% over time and all patients had low baseline symptom burden. Compared to CP, therapy with A significantly delayed time to deterioration for cough (HR = 0.68; p = 0.0145); results for pain trended toward A (HR = 0.82; p = 0.1913). A higher proportion of A-treated patients had ≥10 point improvements in cough (67% vs 60%; p = 0.2444), dyspnea (64% vs 50%; p = 0.0103) and pain (59% vs 48%; p = 0.0513), compared to CP, particularly among patients with baseline symptoms. Mean scores over time for cough and dyspnea also significantly favoured A. Consistent with the safety profile of A, a higher proportion of A-treated patients had significant worsening of symptoms of diarrhoea, sore mouth and dysphagia compared to CP. Reported fatigue, nausea, and vomiting were significantly worse on CP. Overall, therapy with A improved global HRQoL, physical, role and cognitive functioning compared to CP (p < 0.05).

Conclusion: In LUNG-Lung 3, prolongation of PFS on A was associated with significant HRQoL improvement and delay of deterioration of lung cancer related symptoms compared to CP.

Disclosure: L.V. Sequist: Paid consultancy/advisory relationship with: Boehringer Ingelheim, Daiichi Sankyo, Merrimack, Clovis and Celgene; Research funding from: Boehringer Ingelheim, M. Schuler: Paid consultancy/advisory relationship with: Boehringer Ingelheim, Lilly Oncology; Honoraria from: Boehringer Ingelheim, Lilly Oncology; Research funding from: Boehringer Ingelheim, Lilly Oncology; Travel support from: Lilly. K.J. O’Byrne: Paid consultancy/advisory relationship with: Boehringer Ingelheim, Lilly Oncology; Honoraria from: Boehringer Ingelheim, Lilly Oncology; Research funding from: Boehringer Ingelheim; Travel support from: Lilly. J.C. Yang: Honoraria from the Boehringer Ingelheim Advisory Board. T.S. Kim: Paid consultancy/advisory relationship with and compensation from: AstraZeneca, Roche, Eli Lilly, Merck Serono, Eisai, BMS, BeGenex, Aveo, Pfizer, Taiho, Boehringer Ingelheim; Research funding from: AstraZeneca. J. Lungershausen: Employee of Boehringer Ingelheim, M. Shahidi: Employee of Boehringer Ingelheim, M. Palmer: Consulting fee, honorarium, travel support, fees for reviews, and payment for writing or reviewing the manuscript via N Zer0 1 Ltd; Board membership of N Zero 1 Ltd and consultancy, travel/accommodation/meeting costs unrelated to activities listed. J.C. Yang: James Chi-hsin Yang has received honorarium for speech and advisory roles from AstraZeneca, Roche, Pfizer, OSI. He was the advisor for Boehringer Ingelheim and Eli Lilly without payment. All other authors have declared no conflicts of interest.
LUNG CANCER HARBORING HER2 MUTATION: EPIDEMIOLOGICAL CHARACTERISTICS AND THERAPEUTIC PERSPECTIVES

J. Mazieres1, S. Peters2, A. Cortot3, B. Besse3, F. Barlesi4, M. Beau-Faller5, T. Urban6, D. Moro-Sibilot7, J. Mialet1, O. Gautschi8
1Department of Pneumology, CHU Toulouse - Hôpital Larrey, Toulouse, FRANCE. 2Oncology, Centre Hospitalier Universitaire Vaudois - CHUV, Lausanne, SWITZERLAND. 3Pneumology, CHU Lille, Lille, FRANCE. 4Thoracic Group, INSERM U981, Institut Gustave Roussy, Villejuif, FRANCE. 5Service d’Oncologie Multidisciplinaire et Innovations Thérapeutiques, Hôpital Nord, Marseille, FRANCE. 6Hôpitaux Universitaires de Strasbourg et INSERM U892, Hôpital De Hautepierre, Laboratory for Biochimie et de Biologie Moleculaire, Strasbourg Cedex, EIM Laboratoire de Biochimie et de Biologie Moleculaire, Hôpitaux Universitaires de Strasbourg et INSERM U892 Hôpital de Hautepierre, Strasbourg, FRANCE. 7Oncology Department, CHU Anger, Angers, FRANCE. 8Cancerologie, Hôpital A. Michallon - CHU Grenoble, Grenoble, FRANCE. 9Medizinische Onkologie, Luzerner Kantonsspital, Luzern, SWITZERLAND.

Introduction: HER2 oncogene is a member of the EGF family, encoding a transmembrane receptor that drives and regulates cell proliferation. HER2 mutations are identified in about 2% of non small cell lung cancer (NSCLC), mainly located in exon 20, and appear to be critical for lung cancer carcinogenesis. Very scarce data are available to define a clinical profile of the patients harboring HER2 mutated NSCLC. We aimed to study clinicopathological characteristics and therapeutic outcomes of patients harboring HER2 mutation in a large European series.

Methods: PROLINE 1005 is an ongoing global, multicenter, open-label, single-arm, phase II study evaluating the safety and efficacy of crizotinib (250 mg BID in 3-week cycles) in previously treated patients with advanced ALK-positive NSCLC. Patient-reported outcomes (PROs) were assessed as secondary endpoints using the European Organisation for Research and Treatment of Cancer questionnaires (EORTC QLQ-C30 and lung cancer module ((QLQ-LC13) at baseline. Day 1 of each cycle and at end of treatment. Functioning, symptoms and global QOL were assessed and scored on scales of 0–100. Higher scores indicate higher symptom severity or higher functioning. Change from baseline was assessed for statistical and clinical significance (defined as ≥10-point change from baseline).

Results: As of Jan 2012, 901 patients were evaluable for safety and 797 (88%) of these patients had completed the entire questionnaire at baseline. The majority of patients was female (57%), never smokers (66%), and had adenocarcinoma (92%), with a median age of 52 years. A clinically meaningful (≥10-point) improvement from baseline was observed early and maintained in patient-reported symptoms of cancer symptoms and global QOL.

Discussion: All authors have declared no conflicts of interest.

Disclosure: A. Reisman is an employee of Pfizer and receives stock. All other authors have declared no conflicts of interest.
**Background:** Quality of life (QOL) should be an explicit priority throughout the course of care for patients with advanced non-small-cell lung cancer (NSCLC). Docetaxel plus cisplatin (DP) is the only third-generation regimen that has demonstrated statistically significant improvements in overall survival and QOL by a head-to-head comparison with a second-generation regimen (vinorelbine plus cisplatin) in patients with advanced NSCLC. S-1 plus cisplatin (SP) has shown activity and good tolerability in phase II settings.

**Method:** Patients with previously untreated stage IIIB or IV NSCLC, an ECOG PS of 0-1 and adequate organ functions were randomly assigned to receive either oral S-1 80 mg/m²/day (40 mg/m² b.i.d.) on days 1 to 21 plus cisplatin 60 mg/m² on day 8 every 5 weeks or docetaxel 60 mg/m² on day 1 plus cisplatin 80 mg/m² on day 1 every 3 weeks, both up to 6 cycles. The primary endpoint was overall survival (OS). A non-inferiority study design was employed; the upper confidence interval (CI) limit of the hazard ratio (HR) was <1.322. Secondary endpoints included progression-free survival (PFS), response, safety, and QOL.

**Results:** From April 2007 through December 2008, 608 patients were randomly assigned to SP (n = 303) or DP (n = 305) at 66 sites in Japan. Patient demographics were well balanced between the two groups. Two interim analyses were preplanned. At the final analysis, a total of 480 deaths had occurred. The primary endpoint was met. OS in the SP arm was non-inferior to that in the DP arm (median survival, 16.1 vs. 17.1 months, respectively; HR = 1.013; 96.4% confidence interval, 0.837-1.227). PFS was 4.9 months in the SP arm and 5.2 months in the DP arm. The rates of febrile neutropenia (7.4% vs. 1.0%), grade 3/4 neutropenia (73.4% vs. 22.9%), grade 3/4 infection (14.5% vs. 5.3%), and grade 1/2 alopecia (59.3% vs. 12.3%) were significantly lower in the SP arm than in the DP arm. In terms of physical functioning and global functioning on the EORTC QLQ-C30 and lung cancer module (LC-13), QOL was worse in the DP arm (repeated measures ANOVA: p < 0.01).

**Conclusion:** S-1 plus cisplatin is a standard first-line chemotherapeutic regimen for advanced NSCLC.

**Disclosure:** M. Nishio: HONORARIA: Chugai Pharma. K. Kobayashi: HONORARIA: a royal payment for lectature speech from Taiho Pharmaceutical Company. M. Takeuchi: CONSULTANT OR ADVISORY ROLE; Taiho. All other authors have declared no conflicts of interest.

---

**Background:** RANDOMIZED PHASE III TRIAL OF S-1 PLUS CISPLATIN VERSUS DOCETAXEL PLUS CISPLATIN FOR ADVANCED NON-SMALL-CELL LUNG CANCER (TOGO7001)

H. Sakai1, A. Gemma2, K. Kubota3, M. Nishio4, H. Okamoto5, A. Inoue6, H. Tsuibo6, K. Kobayashi1, M. Takeuchi1, S. Kudoh1

1Thoracic Oncology, Saitama Cancer Center, Saitama, JAPAN, 2Internal Medicine, Nippon Medical School, Tokyo, JAPAN, 3Thoracic Oncology Center, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, JAPAN, 4Department of Respiratory Medicine, Yokohama Municipal Citizen’s Hospital, Yokohama, JAPAN, 5Department of Respiratory Medicine, Tohoku University, Sendai, JAPAN, 6Clinical Oncology, KRK Sapporo Medical Center, Sapporo, JAPAN, 7Respiratory Medicine, Saitama International Medical Center, Saitama, JAPAN, 8Biostatistics and Pharmaceutical Medicine, Kitasato University School of Pharmacy, Tokyo, JAPAN, 9Respiratory Medicine, Fukujuji Hospital, Tokyo, JAPAN

**Results:** Placebo (PLB) FOLLOWING INDUCTION TREATMENT FINAL OVERALL SURVIVAL (OS) FOR THE PHASE III STUDY OF PEMETREXED (P) VERSUS PLACEBO (PLB) FOLLOWING INDUCTION TREATMENT WITH PEM plus CISPLATIN (C) FOR ADVANCED NON-SQUAMOUS (NS) NON-SMALL CELL LUNG CANCER (NSCLC)

M. Reck1, L. Paz-Ares2, F. De Marinis3, O. Molinier4, T. Prasad Sahoo5, E. Lasich1, W. John6, A. Zimmermann7, C.M. Visseren-Grul8, C. Gridelli9

1Thoracic Oncology, Hospital Grosshansdorf, Grosshansdorf, GERMANY, 2Instituto de Biomedicina De Sevilla, University Hospital Virgen del Rocío, Sevilla, SPAIN, 3Pulmonary Oncological First Unit, Azienda Ospedaliera S. Camillo Forlanini, Rome, ITALY, 4Oncology, Le Mans Regional Hospital, Le Mans, FRANCE, 5Oncology, Jeeahahnal Nehru Cancer Hospital and Research Center, Bhopal, INDIA, 6Oncology, Ambulantes Krebszentrum Hamburg, Hamburg, GERMANY, 7Oncology, Eli Lilly and Company, Indianapolis, UNITED STATES OF AMERICA, 8Oncology Europe, Eli Lilly, PA Houten, NETHERLANDS, 9Medical Oncology, UO Oncologia Medica’S.G. Moscati Hospital’, Avellino, ITALY

**Background:** PARAMOUNT demonstrated that pem continuation maintenance significantly reduced the risk of disease progression (HR = 0.62) and death (HR = 0.78) versus plb in patients (pts) with advanced NS NSCLC. Preplanned subgroup analyses by baseline characteristics revealed the OS results were consistent, with benefit seen across all subgroups. Here we present descriptive subgroup analyses of the final OS data.

**Methods:** 939 pts received induction therapy (4 cycles pem 500 mg/m² and cis 75 mg/m² on day 1 of 21-day cycles), after which 539 pts who had not progressed and had an ECOC performance status (PS) of 0/1 were randomized (2:1) to maintenance pem (500 mg/m², on day 1 of 21-day cycles) or plb until disease progression. All pts received vitamin B12, folate acid, and dexamethasone.

**Results:** Pt characteristics were well balanced between arms. The table summarizes baseline characteristics for pts on the pem arm surviving 6-24 months after randomization. Characteristics of pts surviving for longer periods were comparable to those of pts surviving shorter periods, suggesting OS benefit for all subgroups of pts on maintenance therapy. PS, a known prognostic factor, was the only baseline characteristic associated with improved OS. On the pem arm, the percentage of pts with an induction response of complete/partial (CR/PR) versus stable disease (SD) was consistent over time. An additional analysis showed no correlation between the percent of tumor shrinkage with final OS (rho <0.1), showing that tumor response to induction is not an indicator of OS.

**Conclusions:** In PARAMOUNT, the OS benefit was seen across all subgroups. Other than PS, no baseline or clinical parameter clearly identifies a subgroup more likely to benefit. Maintenance treatment decisions should be made on an individual basis.

**Disclosure:** M. Reck: Have served as an adviser or consultant to Eli Lilly and Company. L. Paz-Ares: Have served as an adviser or consultant to Eli Lilly and Company. O. Molinier: Have served as an adviser or consultant to Eli Lilly and Company. W. John: Employed by and own stock in Eli Lilly and Company. A. Zimmermann: Employed by and own stock in Eli Lilly and Company. C. Gridelli: Have served as an adviser or consultant to Eli Lilly and Company. All other authors have declared no conflicts of interest.
Background: BO21015 (NCT007000180) is a phase II, randomized, multicentre study exploring correlation between biomarkers (BMs) and best overall response (BOR) to bevacizumab with carboplatin/gemcitabine (CG) or carboplatin/paclitaxel (CP) in chemonaïve patients with advanced/recurrent NSCLC. Efficacy, safety and correlation of 7 baseline (BL) plasma BM (bFGF, E-selectin, ICAM, PLGF, VEGFA, VEGFR-1 and VEGFR-2) with BOR and progression-free survival (PFS) have been reported. This abstract presents BM analysis for tumour tissue, plasma time course and clinical outcome.

Methods: 303 eligible patients were randomized 1:1 to receive bevacizumab 7.5 mg/kg or 15 mg/kg until disease progression (PD) or unacceptable toxicity (with 6 cycles of CG or CP, at investigators’ discretion). Consented patients provided blood and tumour samples for BM analysis. Pre-specified exploratory analyses examined correlation between BL plasma BM and overall survival (OS) and changes in plasma BM levels from BL to peak BM levels at cycles 2, 4 and 6. Plasma BM levels were measured by ELISA. IHC analyses of 5 tumour BMs (VEGFR-1, MVD, VEGFA, VEGFR-2 and NRPI) were assessed for correlation with BOR, PFS and OS, and with BL plasma BM levels.

Results: Further exploratory analyses adjusting for BL prognostic factors and accounting for multiple testing showed a correlation of high BL VEGFA levels and high VEGFR1 expression and VEGFA plasma BL (p = 0.025, 0.26). No significant correlation was seen between tumour BM level and BOR, PFS or OS.

Conclusions: Exploratory analysis showed high plasma BM VEGFA significantly correlated with shorter OS, consistent with previously reported data on PFS. No other BL plasma BMs correlated with OS. BL plasma VEGFA levels correlated with tumour VEGFR1 expression. None of the investigated tumour BMs significantly correlated with clinical outcome. 1 Mok et al. ESMO 2011

Disclosure: M. Reck: Attended advisory boards for Roche, Lilly, BMS, AstraZeneca and Daiichi Sankyo and AstraZeneca. V.A. Gorbunova: Attended advisory boards with Novartis and Daiichi Sankyo. Received honoraria for lectures from Roche, Lilly, Daiichi Sankyo and AstraZeneca. V.A. Gorbunova: Currently employed by Roche/Genevent. V. Archer: Currently employed by Roche. T.S.K. Mok: Advisory boards for Roche, AstraZeneca, Pfizer and Takeda. C. Pallaud: Owns stock in Roche. Currently employed by Roche. S.J. Scherer: Currently employed by Roche/Genevent. V. Archer: Currently employed by Roche. T.S.K. Mok: Advisory boards for AstraZeneca, Roche, Eli Lilly, Merck, Biogen, Eisai, BMS, BiGene, AVEO, Pfizer, Taiho, BI, GSK, Biologicals. On the IASLC board of directors. Received research funding from AstraZeneca. Employed by The Chinese University of Hong Kong. All other authors have declared no conflicts of interest.

1237PD

CLINICAL ACTIVITY AND SAFETY OF ANTI-PROGRAMMED DEATH-1 (PD-1) (BMS-936558/MDX-1106/ONO-4538) IN PATIENTS (PTS) WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)


1Thoracic Oncology, Yale University School of Medicine, New Haven, CT, UNITED STATES OF AMERICA, 2Thoracic Oncology Program, Vanderbilt-Ingram Cancer Center, Nashville, TN, UNITED STATES OF AMERICA, 3Thoracic Oncology, H. Lee Moffitt Cancer Research & Biologics, Tampa, FL, UNITED STATES OF AMERICA, 4Oncology, Sarah Cannon Research Institute/ Tennessse Oncology PLLC, Nashville, TN, UNITED STATES OF AMERICA, 5Oncology, Dana-Farber Cancer Institute, Boston, MA, UNITED STATES OF AMERICA, 6Oncology, Massachusetts General Hospital Cancer Center, Boston, MA, UNITED STATES OF AMERICA, 7Discovery Medicine-CLINICAL Oncology, Bristol-Myers Squibb, Princeton, NJ, UNITED STATES OF AMERICA, 8Biostatistics and Data Management, Bristol-Myers Squibb, Princeton, NJ, UNITED STATES OF AMERICA, 9Discovery Medicine, Immunooncology, Bristol-Myers Squibb, Princeton, NJ, UNITED STATES OF AMERICA, 10Medelona Program, Sidney Kimmel Cancer Center at Johns Hopkins University, Baltimore, MD, UNITED STATES OF AMERICA

Purpose: BMS-936558 is a fully human monoclonal antibody that blocks the PD-1 co-inhibitory receptor expressed by activated T cells. We report here the activity and safety of BMS-936558 in pretreated pts with advanced NSCLC, a tumor not previously considered responsive to immunotherapy.

Methods: BMS-936558 was administered IV q2wk to pts with various solid tumors at 1 – 10 mg/kg during dose escalation and/or cohort expansion. Pts with advanced NSCLC previously treated with at least 1 prior line of therapy were eligible. Pts received up to 12 cycles (4 doses/cycle) of treatment or until unacceptable toxicity, confirmed progressive disease, or complete response. Clinical activity was assessed by RECIST v1.0.

Results: As of Feb 24, 2012, 122 NSCLC pts had received BMS-936558 at n = 31, 3 (n = 33), or 10 mg/kg (n = 58). ECOC performance status was ≤1 for 117/122 pts. 67/122 pts had received ≥3 prior therapies. Median duration of therapy was 12 weeks (range 2 – 101.3 wks). Common drug-related AEs in NSCLC pts were fatigue (18%), decreased appetite (10%), anemia (8%), and nausea (7%). The incidence of grade 3–4 related AEs was 8%. There were 2 drug-related deaths from pneumonitis. Of 76 evaluable pts, 14 had a partial response (PR) (Table); all 14 were treated ≥24 wk, and 8 had responses ≥24 wk. 5 pts had stable disease (SD) lasting ≥24 wk. Additionally, 3 pts had a persistent decrease in target lesion tumor burden in the presence of new lesions and were not categorized as responders.

Conclusions: BMS-936558 had an acceptable risk: benefit profile in previously treated, advanced NSCLC. Activity in squamous NSCLC was particularly intriguing. Additional long-term follow-up data will be reported.

<table>
<thead>
<tr>
<th>Dose, mg/kg</th>
<th>No. pts*</th>
<th>ORR, No. pts (%) [95% CI]</th>
<th>PFSR at 24 wks, % [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18</td>
<td>1 (0.6 [0.1 – 2.7])</td>
<td>16 [0 – 34]</td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>6 (32) [13 – 57]</td>
<td>41 [18 – 64]</td>
</tr>
<tr>
<td>10</td>
<td>39</td>
<td>7 (18) [8 – 34]</td>
<td>24 [11 – 38]</td>
</tr>
<tr>
<td>All</td>
<td>76b</td>
<td>14 (18) [11 – 29]</td>
<td>26 [16 – 36]</td>
</tr>
<tr>
<td>All-Nonsquamous</td>
<td>56</td>
<td>7 (13) [5 – 24]</td>
<td>22 [11 – 34]</td>
</tr>
<tr>
<td>All-Squamous</td>
<td>18</td>
<td>6 (33) [13 – 59]</td>
<td>33 [12 – 53]</td>
</tr>
</tbody>
</table>

*Response-evaluable pts dosed by 07/01/2011 1Includes 2 pts with unknown histology, 1 with PR ORR = objective response rate ([CR + PR] / n) × 100; PFSR = progression-free survival rate

Disclosure: L. Horn: Consultant or Advisory Role: OSI/Astellas (myself, uncompensated). D. Spigel: Consultant or Advisory Role: Bristol-Myers Squibb (myself, uncompensated). L.V. Sequist: Consultant or Advisory Role: Clovis, Celgene,
### ACTIVE SPECIFIC IMMUNOTHERAPY WITH RACOTUMOMAB IN THE TREATMENT OF ADVANCED NS-NSCLC

**A. Macie1, S. Altomaro2, E. Sarti9teben3, C. Viada4, I. Mendoza6, P.P. Guerra4, R.E. Gómez5, M.L. Ardigo5, A.M. Vázquez1, R. Pérez1, Markusovszky Hospital Oncoradiology, Szombathely, HUNGARY, 5Department of Internal Medicine, National Taiwan University Hospital, Taipei, TAIWAN, R.E. Gómez5, M.L. Ardigo5, A.M. Vázquez1, R. Pérez1**

**Background:** Gangliosides, especially NeuGc-GM3, are an attractive target for cancer immunotherapy. They do not express in normal human cells but are overexpressed in several solid tumors including NSCLC and are involved in tumor development and growth. Racotumomab is therapeutic vaccine which induces a cellular and humoral immune response against NeuGc-GM3 expressed in tumors. Phase I and II trials in melanoma, breast and lung cancer have shown the low toxicity and high immunogenicity of racotumomab.

**Methods:** Multicenter, randomized, placebo controlled, double blind clinical trial in patients with advanced (IIIB and IV) NSCLC who had an ECOG status ≤ 2 and had achieved partial or complete response or disease stabilization after completion of onco-specific treatment. 176 patients were randomized 1:1 to placebo or racotumomab. Immunotherapy was administered every 14 days (induction period, 5 doses in total), followed by 1 dose every 28 days (maintenance period) until patient refusal or worsening of ECOG status.

**Results:** Safety: The most common adverse events were mild reactions at the injection site (pain and itching). No differences were observed between both groups. Overall Survival (OS): Intent to Treat Analysis (ITT): Survival since inclusion was 15.7 months (mean) and 8.3 months (median) in the racotumomab arm and 10.6 months (mean) and 6.3 months (median) in the placebo arm (log rank test, p = 0.02). OS rate (%) at 12 and 24 months was 38 % and 17 % in the racotumomab arm and 24 % and 8 % in the placebo arm. Per Protocol Population Analysis (PPP): Includes patients who received ≥ 5 doses of racotumomab/placebo (135/174 patients, 77% of the patient population). Survival since inclusion was 18.9 months (mean) and 10.9 (median) in the racotumomab arm and 11.4 months (mean) and 6.9 months (median) in the placebo arm (log rank test, p = 0.002). OS rate (%) at 12 and 24 months: 48 % and 22 % in the racotumomab arm and 28 % and 8 % in the placebo arm.

**Conclusions:** Immunization with racotumomab is safe. There is an OS benefit for racotumomab, both in the ITT and PPP analyses. Survival benefit appears to be increased when the patient’s clinical condition allows completion of the induction Period of vaccination.

**Disclosure:** R.E. Gómez: Is a full time employee at Elea Laboratories. M.L. Ardigo: Is a full time employee at Elea Laboratories. All other authors have declared no conflicts of interest.

### CIRCULATING ENDOTHELIAL CELL MARKERS AS MARKERS OF RESPONSE TO BEVACIZUMAB/CARBOPLATIN/PACLITAXEL (B + CP) OR BEVACIZUMAB/ERLOTINIB (B + E) IN ADVANCED NON-SQUAMOUS NON-CELL LUNG CANCER (NS-NSCLC)

**F. Farace1, S. Le Moulec2, J. Mazieres3, H. Senelert4, E. Dantis5, A. Mandroszyk6, X. Quantin7, H. Berard8, B. Besse9, 1Laboratory of Translational Research, Institut Gustave Roussy, Villejuif, FRANCE, 2Department of Oncology, Hôpital d’Instruction des Armées du Val-de-Grâce, Paris, FRANCE, 3Department of Thoracic Oncology, Hôpital De Larrey, Toulouse, FRANCE, 4Department of Medical Oncology, Institut de Cancérologie de l’Ouest Site René Gauducheau, Nantes, FRANCE, 5Department of Medical Oncology, CLCC Oscar Lambret, Lille, FRANCE, 6Department of Medical Oncology, Institut Paoli Calmettes, Marseille, FRANCE, 7Department of Thoracic Oncology, Hôpital Arnaud de Villeneuve, CHU de Montpellier, Montpellier, FRANCE, 8Department of Thoracic Oncology, Hôpital d’Instruction des Armées Sainte Anne, Toulon, FRANCE, 9Department of Medicine, Institute Gustave Roussy, Villejuif, FRANCE**

**Background:** The phase II, open-label BRAIN study (ML21823; NCT00800202) is the first to assess the efficacy/safety of bevacizumab combined with chemotherapy in patients (pts) with ns-NSCLC and untreated CNS metastases. Investigation of CEC, CEP or CTC levels as potential markers of response to bevacizumab was undertaken.

**Methods:** In the B + CP arm, blood samples were taken before treatment on day 1 (d1) of cycle 1 (C1) (and 6 hrs after C1 + 6h) treatment at one centre only, and on d1 of C2 and C3, i.e. 4 samples in total. Samples were taken for the B + E arm on d1 of C1, C2 and C3 (3 samples total). CEC and CTC levels were measured with CellSearch (Immunicon, Veridex). CEP were measured using four-colour flow cytometry after enrichment of progenitor cells using Miltenyi Biotec EPC enumeration and enrichment kit. Cut-offs were 15 cells/4mL for CEC, 2 cells/7.5mL for CTC and 15 cells/7.5mL for CEP. For the treatment period and prognosis factors, no CEC were associated with significantly higher risk of hyperefiion.

**Conclusions:** One SNP was associated with increased risk of progression/death, CEC levels were increased at C1 + 6h, possibly reflecting the antivascular effect of bevacizumab. Initially 1 dose was administered every 14 days (induction period, 5 doses in total), followed by 1 dose every 28 days (maintenance period) until patient refusal or worsening of ECOG status.

**Disclosure:** C. Pallau: Own stock in and currently employed by F. Hoffmann-La Roche. J. Reck: Attended advisory boards for Roche, BMS and AstraZeneca. D. Peters: Employment or Leadership Role: Bristol-Myers Squibb (employment, myself, compensated). Stock Ownership: Bristol-Myers Squibb (myself). G. Kollia: Employment or Leadership Role: Bristol-Myers Squibb (employment, myself, compensated). All other authors have declared no conflicts of interest.

### CLINICAL GENOTYPING AND EFFICACY OUTCOMES: EXPLORATORY BIOMARKER DATA FROM THE PHASE II ABIGAIL STUDY OF 1ST-LINE BEVACIZUMAB + CHEMOTHERAPY IN NON-SQUAMOUS NON-CELL LUNG CANCER (NS-NSCLC)

**C. Palou1, M. Reck2, E. Luhas3, B. Szirma4, C. Yu5, O. Burdawa6, S. Orto6, S.J. Scherer8, V. Archer9, T.S.K. Mok10, 1Department of Medical Oncology, Institut Gustave Roussy, Villejuif, FRANCE, 2Department of Thoracic Oncology, Hôpital De Larrey, Toulouse, FRANCE, 3Department of Medical Oncology, Institut de Cancérologie de l’Ouest Site René Gauducheau, Nantes, FRANCE, 4Department of Medical Oncology, CLCC Oscar Lambret, Lille, FRANCE, 5Department of Medical Oncology, Institut Paoli Calmettes, Marseille, FRANCE, 6Department of Thoracic Oncology, Hôpital Arnaud de Villeneuve, CHU de Montpellier, Montpellier, FRANCE, 7Department of Medical Oncology, Hôpital d’Instruction des Armées Sainte Anne, Toulon, FRANCE, 8Department of Medicine, Institute Gustave Roussy, Villejuif, FRANCE, 9Department of Thoracic Oncology, Hôpital d’Instruction des Armées Sainte Anne, Toulon, FRANCE, 10Department of Clinical Oncology, Hôpital Hôpital de la Timone, Marseille, FRANCE**

**Background:** One SNP was associated with increased risk of progression/death, while 3 others were associated with increased BOR. However, adjustment for multiple testing would no longer result in statistically significant p-values. SNPs analysed in this study have been previously reported as showing potential predictive value in other studies: VEGFA SNPs in breast cancer (E2100) and NSCLC (E4599); VEGFR1 SNP in pancreatic cancer (AVITA). More exploratory analyses from this and other trials of bevacizumab may provide further insight.

**Disclosure:** C. Pallau: Own stock in and currently employed by F. Hoffmann-La Roche. J. Reck: Attended advisory boards for Roche, BMS and AstraZeneca. D. Peters: Employment or Leadership Role: Bristol-Myers Squibb (employment, myself, compensated). Stock Ownership: Bristol-Myers Squibb (myself). G. Kollia: Employment or Leadership Role: Bristol-Myers Squibb (employment, myself, compensated). All other authors have declared no conflicts of interest.

---

The text above is a summary of research findings related to cancer immunotherapy and biomarker analysis in lung cancer patients. The abstracts highlight the clinical applications of specific treatments and the potential for genetic markers in predicting treatment response. The studies cover a range of topics from immunotherapy to genetic profiling, each with detailed methodologies and outcomes.
A PLASMA PROTEOMIC SIGNATURE PREDICTS OUTCOMES IN A PHASE 3 STUDY OF GEMCITABINE (G) + CISPLATIN (C) ± SORAFENIB IN FIRST LINE STAGE IIIB OR IV NSCLC

J.F. Vansteenkiste1, L. Paz-Ares1, T.O.G. Eisen1, D. Heigener4, W. Eberhardt6, M. Thomas1, C. Zhou1, A. Santoro2, C. Lathia3, H. Roder1

1Respiratory Oncology Unit (Pulmonology), University Hospital Gasthuisberg, Leuven, BELGIUM, 2Instituto de Investigaciones Biomédicas de Sevilla, University Hospital Virgen del Rocío, Sevilla, SPAIN, 3Oncology, University of Cambridge, Addenbrooke’s Hospital, Cambridge, UNITED KINGDOM, 4Medical Oncology, Krankenhaus Großhadern, Grosshadern, GERMANY, 5Department of Medical Oncology, West German Cancer Center, University Hospital Essen, Essen, GERMANY, 6Department of Thoracic Oncology, University of Heidelberg, Heidelberg, GERMANY, 7Lung Cancer Institute, Shanghai Pulmonary Hospital, Shanghai, CHINA, 8Medical Oncology, Istituto Clinico Humanitas, Rozzano, MILAN, 9Clinical Sciences, Bayer HealthCare Pharmaceuticals, Montville, NJ, UNITED STATES OF AMERICA, 10Research and Development, Biodesix, Inc, Boulder, CO, UNITED STATES OF AMERICA

Introduction: Previously presented results from NExUS, a Phase 3 study of sorafenib in combination with G + C (GC) vs placebo + GC in first line NSCLC patients, showed no improvement in overall survival (OS) and a small statistically significant improvement in progression free survival (PFS) for sorafenib + GC. VentiStrat® (V), a proteomic test using Matrix Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry (MALDI-TOF MS), was used in the present study to classify baseline plasma samples from NExUS patients into V Good (VG) and V Poor (VP) categories based on a pre-specified 8-peak mass spectral signature. The overall objective was to determine if V status was predictive of sorafenib + GC clinical activity.

Methods: Patients with Stage IIIIB or IV NSCLC, ECOG PS 0 or 1, were randomized 1:1 to receive G (1250 mg/m2 on Days 1 and 8) and C (75 mg/m2 on Day 1) for up to six 21-day cycles, in combination with sorafenib 400 mg bid or placebo. V status was determined for 403 of 774 non-squamous patients. Analyses were performed blinded to clinical outcomes. PFS was compared between treatment arms within VP and VG groups. Hazard ratios (HR) and Kaplan-Meier curves were evaluated and multivariate analyses performed.

Results: Consistent with previous reports, approximately 30% of subjects had VP status. PFS and HRs in treatment arms in patients with and without assigned V status were similar. VG status was associated with a longer PFS in placebo + GC patients (HR = 0.51, log-rank p < 0.001). There was a statistically significant interaction between treatment and V status in PFS, whereby relative to placebo + GC, sorafenib + GC showed an improvement in PFS in patients with VG status (HR = 0.63, log-rank p = 0.019) but not in patients with VG status (HR = 1.06, log-rank p = 0.628). V treatment interaction remained significant in multivariate analysis adjusting for demographics and known risk factors (p = 0.019). Analyses of OS data are ongoing.

Conclusions: VG status is associated with a better prognosis in first line NSCLC patients treated with placebo + GC. VG is also predictive, with VP patients receiving sorafenib + GC showing improved PFS compared to placebo + GC.

Disclosure: H. Senellart: Financial Interest: Advisory Board. E. Dansin: Attended advisory boards for Roche, Lilly and Boehringer-Ingelheim. B. Besse: Received consulting fees from Bayer, Pfizer, Roche, AstraZeneca, GSK, and has received research funding from AstraZeneca. G. Roder: Received consulting fees and honoraria from Bayer, Pfizer, Roche, Esai, and has received research funding from Astellas, GSK, Pfizer, Bayer. W. Eberhardt: Wiltfred E. E. Eberhardt has received honoraria from Bayer, Roche, Astrazeneca, Pfizer, Boehringer Ingelheim, Sanofiaventis, Novartis, BMS, GSK, Imclone, Eli Lilly, and Pierre Fabre. M. Thomas: Michael Thomas has received consulting fees from Bayer Healthcare, Life. C. Lathia: Chetan Lathia is an employee of Bayer HealthCare Pharmaceuticals. H. Roder: Heinrich Roder is a founder and stockholder of Bayer Biosciences, Inc. Other all authors have declared no conflicts of interest.

References: 1. Shimagi, Y. Nakainishi, Y. Nakagawa, I. Tsuchi, N. Takahashi, S. Hishimoto, N. Nemoto

1Respiratory Medicine, Nihon University School of Medicine, Tokyo, JAPAN, 2Pathology, Nihon University School of Medicine, Tokyo, JAPAN, 3Respiratory Medicine, Nihon University School of Medicine, Tokyo, JAPAN, 4Medical Oncology, Istituto Clinico Humanitas, Rozzano, MILAN, 5Clinical Sciences, Bayer HealthCare Pharmaceuticals, Montville, NJ, UNITED STATES OF AMERICA, 6Research and Development, Biodesix, Inc, Boulder, CO, UNITED STATES OF AMERICA

Background: Combination cisplatin plus pemetrexed (PMT) and carboplatin plus paclitaxel or paclitaxel plus bevacizumab are standard first-line chemotherapies for advanced non-small cell lung cancer (NSCLC). However, it is unclear whether a PMT-based regimen is superior to a carboplatin-based regimen or whether taxane-based regimen should be selected for patients with advanced NSCLC. Thymidylate synthase (TS) is an important enzyme in DNA synthesis and influences sensitivity to several anti-cancer drugs. The purpose of this study is to determine whether TS expression affects the therapeutic efficacy of PMT or taxane.
Disclosure: Clinical variables, like stage and performance status (PS), have predictive and prognostic values in advanced NSCLC pts treated with chemotherapy, but not on an individual basis. As a secondary aim of a prospective study, we assessed the predictive (for response) and prognostic (for survival) values of miRNA expression in NSCLC pts treated by C (60 mg/m² D1) and V (25 mg/m², D1 + 8) in 1st line chemotherapy.

Methods: During the diagnostic bronchoscopy, a tumour biopsy was lysed into Tripure Isolation Reagent (Roche Diagnostics) on ice, snap frozen and stored at -80°C. miRNA expression was assessed using TaqMan® Low Density Arrays (756 human miR array, Applied Biosystems) and normalized using the delta delta Ct method to RNU48 (SNORD48) Ct value for every sample. Survival was measured from the registration date and response by WHO criteria.

Results: From 180 pts screened between 04/2009 and 11/2011, 38 pts were eligible including 27 males, 26 pts with Karnofsky PS of 80-100, 20 adenocarcinomas and 30 stage IV. Seventeen partial responses (43%) were observed. After stepwise selection, a two miRNA (miR-149 and miR-375) predictive signature for response to C (AUC 0.90, sensitivity 88%, negative predictive value 96%) which was related to progression-free survival (medians 12 and 17 months, respectively, p = 0.037). Using a linear combination of the miRNA Ct values with Cox’s regression coefficients as weights, a prognostic score for survival including 4 miRNA (miR-200c, miR-29c and miR-124) was identified. The signature distinguished pts with good (n = 18) and poor (n = 20) prognosis with median survival of 47.5 months (95% CI 29.8-52.4) and 15.5 months (95% CI 9.1-22.8), respectively (p <0.001; hazard ratio 21.1, 95% CI 4.7-94.9).

Conclusions: miRNA signatures are predictive of response and are prognostic for survival in patients with NSCLC treated with cisplatin-vinorelbine in 1st line. The validation of these results in an independent cohort, taking in consideration conventional prognostic factors, is ongoing.

Disclosure: All authors have declared no conflicts of interest.

Identification of Microrna (miRNA) Signatures for Response and Survival in Non-Small Cell Lung Cancer (NSCLC) Patients (pts) Treated with Cisplatin-Vinorelbine (Cv): a EcwP Study

Background: The identification of predictors of efficacy of chemotherapy in NSCLC could help in the selection of patients who are more likely to benefit from a particular scheme of treatment and, thus, could improve treatment outcomes.

Methods: A total of 117 patients with NSCLC and genomic DNA was isolated from the peripheral blood nucleated cells. Polymorphisms were examined the role of several polymorphisms in DNA repair and DNA synthesis genes as pharmacogenetic markers in the outcome of NSCLC patients.

Results: The germline polymorphisms studied were excision repair cross-complementing-1 (ERCC1) Asn118Asn, xeroderma pigmentosum group D (XPD) Lys74Gln, thymidylate synthase (TS) Val108Ile, and methylenetetrahydrofolate reductase (MTHFR) C677T, A1298C. Progression-free survival (PFS) and overall survival (OS) were evaluated according to each genotype.

Results: 103 patients with stage III-IV NSCLC (47% adenocarcinoma, 41% squamous cell carcinoma, 12% NSO) receiving platinum-based chemotherapy were eligible. A total of 14 patients with stage III I/II were excluded. The median PFS was significantly longer in patients with C/T or T/T genotypes in codon 118 in ERCC1: 13 months (m) and 10 m, respectively, as compared to 6 m for the C/C patients (p = 0.034). Patients with ERCC1 C/T or T/T genotypes had a trend to longer median OS (20 m) than those C/C (10.5 m; p = 0.1). Subgroup analysis revealed that ERCC1 C/T or T/T genotypes were associated with increased PFS in male (p = 0.005), smokers (p = 0.036) and age <70 years (p = 0.012). Patients with A/A or A/C genotypes in codon 751 in XPD had a trend to longer median OS than those C/C (p = 0.09). No differences in median PFS were observed. No association between TS and MTHFR polymorphisms and outcome was found in overall population.

Conclusions: ERCC1 C/T or T/T genotype in codon 118 might be useful for predicting the outcome of NSCLC patients treated with platinum-based chemotherapy specially in male, smokers and age <70 subgroups.

Disclosure: All authors have declared no conflicts of interest.

Effect of Germline Polymorphisms of DNA Repair Genes on Chemotherapy Outcome in Advanced Non-Small Cell Lung Cancer (NSCLC) Patients

Background: Vascular endothelial growth factor (VEGF)-mediated angiogenesis plays an important role in NSCLC pathogenesis. RAM is a fully human IgG1 monoclonal antibody that inhibits VEGF receptor-2 (VEGFR-2) binding and signaling. This study investigates RAM in combination with first-line platinum-based chemotherapy in advanced NSCLC.

Methods: NSQ pts with Stage IV NSCLC, ECOG PS ≤2, adequate hematologic, hepatic and renal function were randomized to either Arm A: pemetrexed + carboplatin/cisplatin or Arm B: RAM + pemetrexed + carboplatin/cisplatin, once every 3 weeks. The primary analysis will be when 103 progression-free survival (PFS) events are observed in NSQ pts. This pre-planned interim analysis was performed when 61 NSQ PFS events were observed. Other interim endpoints: objective response rate, disease control rate (DCR), and safety.

Results: Arm A (n = 71) median (medn) age 64, 63% male (M), 37% female (F), ECOC PS 0-1 / 2 (91.6% / 5.6%), Arm B (n = 69) median age 64, 52% M, 48% F, ECOC PS 0-1 / 2 (89.9% / 7.2%).

Interim efficacy analyses

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Arm A (N = 71) n (%)</th>
<th>Arm B (N = 69) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS Events Censored</td>
<td>32 (35) / 48 (43) (3.8, 5.7)</td>
<td>24 (35) / 45 (6.5) (6.3, 5.7)</td>
</tr>
<tr>
<td>Median (months) 90% CI</td>
<td>14 (13-17) / 17 (15-25)</td>
<td>10 (9-12) / 12 (10-20)</td>
</tr>
<tr>
<td>Best Response PR SD DCR (SD + PR)</td>
<td>26 (26) / 35 (35) (51.72)</td>
<td>30 (34) / 40 (60) (68.8)</td>
</tr>
</tbody>
</table>

Nonhematologic adverse events (AEs) were fatigue (61%; 17% Grade(G)3), nausea (55%; 7% G3), vomiting (36%; 4% G3), constipation (30%; 1% G3), hypertension (HTN) (6%; 1% G3), proteinuria (4%; 0% G3), on Arm A; fatigue (63%; 12% G3), nausea (51%; 10% G3), vomiting (33%; 8% G3), constipation (27%; 0 G3), HTN (19%; 10% G3), proteinuria (5%; 0% G3) on Arm B. Hematologic AEs were anemia (A) (55%; 16% G3), neutropenia (N) (23%; 16% G3), thrombocytopenia (T) (23%; 12% G3) on Arm A; A (39%; 8% G3), N (33%; 13% G3), T (31%; 15% G3) on Arm B.

Conclusions: Based on interim analyses of PFS and acceptable tolerability and safety, RAM may provide clinical benefit in combination with first-line platinum-based chemotherapy in NSQ NSCLC. Enrollment of pts in squamous Arms C and D is ongoing.

Disclosure: R. Doelebe: Research funding: ImClone Systems, Eli Lilly & Co., Pfizer Inc. Honoraria: Boehringer Ingelheim, Abbott Laboratories, Pfizer Inc. Stock: Ariad (< $10,000). M. Reck: Honoraria for Lectures: Lilly, Hoffman-La Roche, AstraZeneca, Daiichi-Sankyo Advisory Board (compensated); Lilly, Hoffmann-La Roche, AstraZeneca, Daiichi-Sangyo, Pfizer, Merck, BMS. S. Verma: Advisory Board and honoraria from Eli Lilly. S. Yurasov: I am employed by Eli Lilly and own Lilly stock. D.R. Camidge: Advisory role and honoraria: ImClone Research Funding; Eli Lilly. All other authors have declared no conflicts of interest.
Roche, received honorarium from Pfizer, and honorarium from Speaker + pac/carb, and was less well tolerated in pts with advanced non-squamous NSCLC. Axitinib + pac/carb did not improve efficacy compared with bevacizumab neutropenia (31% vs 27%). Neutropenia was the most common grade 3/4 AE in both 42%), decreased appetite (43% vs 22%), fatigue (34% vs 39%), nausea (36% vs 32%), and mo for the axitinib and bevacizumab arms, respectively. Common treatment-emergent were 29.3% (18.1 1.12, 95% CI 0.74 0.74–1.12, 95% CI 0.37–1.54). Objective response rates (95% CI)– 56.8) and duration of response was 4.4 and 7.5) in the 7.5)–7.0) in the 7.5)–7.0). Other AEs were common and included (G3) 1.9/ 3.0, pain 3.8/6.0, Respiratory disorders 0/4.0, deep vein thrombosis (G3) 0/2.0, pulmonary embolism(G4)/2.0). During Maintenance: anemia 5.0/4.1, leucopenia 2.8/10.2, neutropenia 11.0/20.4, febrile neutro 3.8/0, fatigue (G3) 3.8/0, stomatitis (G3) 1.9/3.0, pain 3.8/6.0, Respiratory disorders 0/4.0, deep vein thrombosis (G3)/ 2.0). Deaths potentially related to CT 2/1. Conclusions: NC and PC had similar efficacy. In the present economic context, the acquisition cost of the two platinum based doublets should be considered in the treatment decision making of pts with advanced NSCC NSCLC.

Disclosure: S. Malassé: Statistician of the study Employment for the sponsor. F. Biville-Hedouin: Medical Project Manager of the study Employment for the sponsor. All other authors have declared no conflicts of interest.

1247P

**RANDOMISED PHASE II TRIAL OF ORAL VINORELBINE (N) AND CISPLATIN (P) OR PEMETREXED AND C (PC) IN FIRST LINE ADVANCED NON SQUAMOUS (NSCC) NON SMALL CELL LUNG CANCER (NSCLC) PATIENTS (PTS). NAVOTRIAL01: FINAL RESULTS**


**Background:** Axitinib is a potent and selective second-generation inhibitor of vascular endothelial growth factor receptors 1, 2, and 3, with promising single-agent activity in advanced NSCLC. This study evaluated the efficacy and safety of axitinib + pac/carb vs bevacizumab + pac/carb in advanced non-squamous NSCLC.

**Methods:** Pts with stage IIIIB with pleural effusion or stage IV non-squamous NSCLC without prior systemic therapy (except adjuvant therapy >12 mo prior to enrolment) were stratified by prior adjuvant therapy and gender, and randomised 1:1 to receive axitinib (5 mg twice daily) or bevacizumab (15 mg/kg every 3 wks [q3w]) plus pac/carb (200mg/m²/AUC 6 mg/L x min q3w). The primary endpoint was progression-free survival from randomisation (PFS).

**Results:** Pt baseline characteristics in the axitinib (n = 58) and bevacizumab (n = 60) arms were well balanced: 38% were female, 31% vs 30% were current smokers, respectively. Median PFS (95% confidence interval [CI]) was 5.7 mo (4.1–7.5) in the axitinib vs 6.1 mo (4.2–8.7) in the bevacizumab arms (hazard ratio [HR] 1.09, 95% CI 0.68–1.76; 1-sided stratified P = 0.64). Median overall survival (95% CI) was 10.6 mo (7.5–16.4) and 13.3 mo (10.4–17.6), respectively, in the axitinib vs bevacizumab arms (HR 1.12, 95% CI 0.74–1.69; 1-sided stratified P = 0.70). Objective response rates (95% CI) were 29.3% (18.1–42.7) and 43.3% (30.6–56.8) and duration of response was 4.4 and 7.0 mo for axitinib and bevacizumab arms, respectively. Common treatment-emergent all-causeality adverse events (AEs) with axitinib + pac/carb vs bevacizumab + pac/carb, respectively, were diarrhoea (47% vs 34%), alopecia (36% vs 46%), hypertension (43% vs 42%), decreased appetite (43% vs 22%), fatigue (34% vs 39%), nausea (36% vs 32%), and neutropenia (31% vs 27%). Neutropenia was the most common grade 3/4 AE in both treatment arms. More pts in the axitinib arm discontinued treatment due to AEs than in the bevacizumab arm (41% vs 31%), respectively.

**Conclusions:** Axitinib + pac/carb did not improve efficacy compared with bevacizumab + pac/carb, and was less well tolerated in pts with advanced non-squamous NSCLC.

**Disclosure:** C. Twelves: I am an advisor to member for Pfizer and Genentech/ Roche, received honorarium from Pfizer, and honorarium from Speaker’s Bureau from Genentech/Roche. S. Popat: I am a consultant for Roche and Pfizer and received honoraria from Roche and Pfizer. P. Bycott: I am a full-time employee of Pfizer Inc and own Pfizer stock. I am a former employee of Pfizer and own Pfizer stock. P. De Bisi: I am a consultant for Pfizer and Genentech and received grants/research support from Pfizer and Genentech. All other authors have declared no conflicts of interest.

**1249P**

**FINAL RESULTS OF A RANDOMIZED, DOUBLE-BLIND PHASE II STUDY TO COMPARE NILOTICYN (N) PLUS ORAL VINORELBINE (NVBO) PLUS CISPLATIN (C) WITH PLACEBO (P) PLUS NVBO PLUS C IN PATIENTS (PTS) WITH STAGE IIIIB/IV NON-SMALL CELL LUNG CANCER (NSCLC)**


**Background:** Nilotinib (NVBO) is a selective, irreversible, oral, highly selective, inhibitors of KIT and PDGFRA. Nilotinib remains active against imatinib-resistant KIT and PDGFRA mutations, including T670I, and has been shown to be active in patients with metastatic KIT-positive GIST, chronic myelogenous leukemia, and myelodysplastic syndrome. The primary objective of this study was to compare the efficacy and safety of NVBO plus cisplatin (NVBO+C) vs cisplatin alone (C) in patients with advanced, non-small cell lung cancer (NSCLC).

**Methods:** This study was a Phase II, randomized, double-blind, placebo-controlled study conducted at 64 sites in the United States and Canada. The primary endpoint was overall survival (OS) with a secondary endpoint of progression-free survival (PFS). Secondary endpoints included quality of life, adverse events, and quality of death.

**Results:** From 10/07 to 05/10, 68 pts were randomized to the N-arm (35 pts) or placebo (33 pts). Median OS was 10.6 mo (95% CI 7.8–12.1) in the N-arm vs 10.8 mo (95% CI 7.0–14.5) in the placebo arm. The median PFS was 4.2 mo (95% CI 3.6–4.7) in the N-arm vs 4.4 mo (95% CI 3.2–5.6) in the placebo arm. The overall response rate (ORR) was 24% (95% CI 16.0–33.6) in the N-arm vs 31% (95% CI 19.1–45.9) in the placebo arm. The median time to progression (TTP) was 5.6 mo (95% CI 4.6–6.7) in the N-arm vs 5.9 mo (95% CI 4.7–6.2) in the placebo arm. The median duration of response (DOR) was 4.4 mo (95% CI 3.2–5.6) in the N-arm vs 4.3 mo (95% CI 3.1–5.5) in the placebo arm. The median number of cycles was 4 in the N-arm vs 4 in the placebo arm. The median number of drug-related adverse events (AEs) was 14 (95% CI 12–16) in the N-arm vs 15 (95% CI 13–17) in the placebo arm. The most common grade 3/4 AEs were neutropenia (26% vs 18%, respectively) and fatigue (2% vs 2%, respectively). The most common grade 3/4 non-hematologic AEs were diarrhea (47% vs 34%), alopecia (36% vs 46%), hypertension (43% vs 42%), decreased appetite (43% vs 22%), and fatigue (34% vs 39%). Neutropenia (31% vs 27%) and neutropenia (31% vs 27%) were the most common grade 3/4 AE in both treatment arms. More pts in the axitinib arm discontinued treatment due to AEs than in the bevacizumab arm (41% vs 31%), respectively.

**Conclusions:** Axitinib + pac/carb did not improve efficacy compared with bevacizumab + pac/carb, and was less well tolerated in pts with advanced non-squamous NSCLC.

**Disclosure:** C. Twelves: I am an advisor to member for Pfizer and Genentech/ Roche, received honorarium from Pfizer, and honorarium from Speaker’s Bureau from Genentech/Roche. S. Popat: I am a consultant for Roche and Pfizer and received honoraria from Roche and Pfizer. P. Bycott: I am a full-time employee of Pfizer Inc and own Pfizer stock. I am a former employee of Pfizer and own Pfizer stock. P. De Bisi: I am a consultant for Pfizer and Genentech and received grants/research support from Pfizer and Genentech. All other authors have declared no conflicts of interest.
Conclusions: This randomized phase 2 trial of ombrabulin combined with a platinum-taxane regimen did not meet the primary endpoint of improving PFS compared with Pbo in the first-line treatment of metastatic NSCLC. Study sponsored by Sanofi.


1251P
FRONT-LINE CHEMOTHERAPY WITH OR WITHOUT NGR-HTNF IN NON-SMALL CELL LUNG CANCER (NSCLC)

V. Gregoor,1 N. Zlombo2, F. Grossi3, T. De Pas4, F. Pietrantoni5, M. Giovannini6, G. Massoni7, A. Bulotta1, A. Lambiase1, C. Bordignon5
1Oncology, IRCCS San Raffaele, Milano, ITALY, 2Department of Oncology, IRCCS Fondazione Istituto Nazionale dei Tumori, Milan, ITALY, 3Lung Cancer Unit, Istituto Nazionale per la Ricerca sul Cancro, Genova, ITALY, 4Unit of Respiratory Tract and Sarcomas, Istituto Europeo di Oncologia, Milan, ITALY, 5Clinical Development, MoleMed, Milan, ITALY

Background: NGR-HTNF (an-gly-asn-human tumor necrosis factor α) is a selective vascular targeting agent able to improve intratumoral chemotherapy uptake.

Methods: After stratification by histology (non squamous or squamous) and PS (0 or 1), previously untreated patients (pts) with advanced NSCLC were randomly assigned to receive cisplatin 80 mg/m2/d1 plus either pemetrexed 500 mg/m2/d1 (non-squamous) or gemcitabine 1250 mg/m2/d1 plus cisplatin 100 mg/m2/d1 (squamous). The primary endpoint was progression-free survival (PFS).

Results: Baseline characteristics in arm A (n = 61) vs B (n = 58): median age 62 ± 63 years; male 36 vs 38; PS 0 ± 1; squamous vs nonsquamous (78% vs 22%); nonsmokers 19 vs 14; EGFR mutations 5 vs 5. For the squamous non-squamous, 25% were cycles given in A (mean 6.9; range 1-18) and 192 in B (4.8; 1-6), while for the squamous stratum, 95 in A (63.1-124.0) and 49 in B (35.1; 1-6). The rates of grade 3 to 4 AEs were comparable in arm A v B: neutropenia 14% v 17% and fatigue 7% v 11%. Neither grade 3 to 4 AEs related to NGR-HTNF nor bleeding in pts with squamous histology were noted. With a median follow-up of 16.4 months for all pts, median PFS was 5.8 ± 5.6 months, 1-year OS rate was 58% ± 56%, and RR was 35% ± 21% in arm A v B, respectively. For the nonsquamous stratum, trends toward higher 6-month PFS rates for arm A v B were noted in pts with PS 1 (65% vs 33%), nonsmoking history (59% vs 33%), younger age (64% vs 30%), and EGFR mutations (75% vs 25%). Similarly, in these pts the 1-year OS rates were: PS 1 (65% vs 33%), nonsmoking history (59% vs 33%), younger age (64% vs 30%), and EGFR mutations (75% vs 25%). For the squamous stratum, median PFS was 5.6 ± 4.3 months (HR = 0.71) and median OS was 14.2 ± 10.2 months (HR = 0.54) for arm A v B, respectively. In these pts, RR was 36% for arm A and 29% for arm B, while median changes from baseline in target tumor size after 2, 4, and 6 cycles were -27%, -39%, and -33%, respectively for arm A and -18%, -22%, and -14%, respectively for arm B.

Conclusion: NGR-HTNF can be safely given with standard chemotherapy and may have therapeutic potential in squamous NSCLC.

Disclosure: A. Lambiase: Employment - MoleMed. C. Bordignon: Employment - MoleMed. All other authors have declared no conflicts of interest.

1252P
ACTIVITY OF AFATINIB IN UNCOMMON EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATIONS IN LUX-LUNG 3, A PHASE III TRIAL OF AFATINIB OR CISPLATIN/PEMETREXED IN EGFR MUTATION-POSITIVE LUNG CANCER

J.C. Yang1, M. Schuler2, N. Yamamoto3, K.J. O’Byrne4, V. Harsh5, T.S.K. Mok6, D. Massiey7, V. Zazulina1, M. Shahidi7, L.V. Sequist2
1Oncology, National Taiwan University Hospital, Taipei, TAIWAN, 2Medicine, West German Cancer Center, University Duisburg-Essen, Essen, GERMANY, 3Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, JAPAN, 4Oncology, St James’s Hospital, Dublin, IRELAND, 5Oncology, McGill University Health Centre, Montreal, QC, CANADA, 6Clinical Oncology, The Chinese University of Hong Kong, Hong Kong, CHINA, 7Statistics, Boehringer Ingelheim, Bracknell, UNITED KINGDOM, 8Clinical Research / Management, Boehringer Ingelheim, Bracknell, UNITED KINGDOM, 9Medicine, Massachusetts General Hospital, Boston, MA, UNITED STATES OF AMERICA

Background: Afatinib (A) is an irreversible ErbB family blocker of EGFR (Erbb1), HER2 (Erbb2) and ErbB4 with in vitro activity against activating and resistant EGFR mutations. LUX-Lung 3 demonstrated superiority of A vs cisplatin/pemetrexed (CP)

Downloaded from https://academic.oup.com/annonc/article-abstract/23/suppl_9/ix400/218620 by guest on 20 August 2018
In 345 treatment-naïve pts with EGFR mutation-positive NSCLC, median progression-free survival (PFS) 11.1 vs 6.9 mo, HR 0.58, *p = 0.0004 (ITT cohort) and 13.6 vs 6.9 mo, HR = 0.47, *p = 0.0001 for pts with common (Del19/L858R) mutations (n = 308). Here we present data from pts with uncommon EGFR mutations, detected by central EGFR screening assay (Thracegen29).

**Methods:** All pts (n = 345) were stratified according to mutation (Del19, L858R, other) and randomized 2:1 to oral A 40 mg daily or IV CP (75 mg/m2 + 500 mg/m2 q21 days up to 6 cycles). Other mutations were categorized into 5 groups: T790M, G129X, S768I, gefitinib TBP, exon 20 insertions, L816V (A3, CP3), S768L (A3, CP0). Baseline imbalances between the A and CP arms were noted for smoking status (never smoker 65% vs 82%, respectively) and presence of brain (27% vs 0%) and liver metastases (27% vs 18%). Of 32 pts with target lesions, 19/23 on A and 8/9 on CP had measurable shrinkage. The small size of the uncommon mutation cohort, its molecular heterogeneity and numeric imbalances within genetic subgroups limited formal statistical analyses. Tumour response and prolonged PFS were noted in A-treated pts with L858R + T790M (1PR, 11.0 mo); 3SD, 9.6+ mo, 8.5 mo and 6.7 mo); L861Q (ISD, 8.5 mo); G129X (1PR, 10.8 mo); S768L + L858R (1PR, 13.8+ mo); S768L (1PR, 19.2+ mo).

**Conclusions:** RECIST responses and prolonged disease control were observed in pts with most types of uncommon EGFR mutations. The efficacy of A in uncommon EGFR mutations should be explored in larger cohorts in future studies.

**Disclosure:** JC. Yang: James Chih-Hsin Yang has received honorarium for speech and advisory roles from AstraZeneca, Roche, Pfizer, OSI. He was the advisor for Boehringer Ingelheim and Eli Lilly without payment. M. Schuler: Paid consultancy/ advisory relationship with: Boehringer Ingelheim; Research funding from: Boehringer Ingelheim; Travel support from: Lilly, K. O’Byrne: Paid consultancy/advisory relationship with: Boehringer Ingelheim, Lilly Oncology; Honoraria from Boehringer Ingelheim, Lilly Oncology; Research funding from Boehringer Ingelheim; Other remuneration from Boehringer Ingelheim, Lilly Oncology: V. Hirsh: Honoraria from the Boehringer Ingelheim Advisory Board. T.S.K. Mok: Paid consultancy/advisory relationship with and honoraria from: AstraZeneca, Roche, Eli Lilly, Merck Serono, Eisai, BMS, BeGene, Aveo, Pfizer, Taiko; Boehringer Ingelheim: Research funding from: AstraZeneca, D. Massey: Employee of Boehringer Ingelheim. V. Zazulina: Employee of Boehringer Ingelheim. L.V. Sequist: Paid consultancy/advisory relationship with: Boehringer Ingelheim, Daichi-Sankyo, Merrimack, Clovis and Celgene; Research funding from: Boehringer Ingelheim. All other authors have declared no conflicts of interest.

---

**125SP DOES GEFITINIB RE-CHALLENGE OR TREATMENT BEYOND PROGRESSION (TBP) PROLONG SURVIVAL OF NSCLC PATIENTS? – REAL WORLD EVIDENCE FROM GEFITINIB TREATMENT RESPONDERS**


1Department of Thoracic Oncology, National Hospital Organization Toneyama National Hospital, Toyonaka, JAPAN
2Department of Thoracic Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, JAPAN
3Biostatistics and Epidemiology, Yokohama City University Medical Center, Yokohama, JAPAN
4Department of Thoracic Oncology, Osaka Police Hospital, Osaka-City, JAPAN
5Department of Thoracic Oncology, Osaka University Graduate School of Medicine, Suita, JAPAN

**Background:** After gefitinib was approved in July 2002, several patients have experienced long-term survival in the clinical setting. However, it is not yet clear which factor of treatment strategy is contributing to the long-term survival.

**Methods:** We extracted information from medical records of advanced NSCLC patients with the following inclusion criteria: 1) Japanese patients who were diagnosed by October 2010 and treated with gefitinib after July 2002; 2) performance status (PS) 0-2; 3) PR, CR, or long SD (6 months or more) by gefitinib. 4) Patients who had not received curative surgical operation or radiation therapy. The primary objective was to evaluate the effects of treatment histories on Overall Survival (OS).

**Results:** We conducted a Dynamic Treatment Regimen Analysis (DTRA) to identify the key treatment strategy contributing to long-term survival. DTRA included multiple clinical factors (sex, age, stage, histology, PS, smoking) and time-dependent clinical factors (PS, pretreatment).

**Results:** A total of 335 NSCLC patient details were extracted. The mean age was 64.8 years and 90.3% had adenocarcinoma histology. Sixty five patients experienced gefitinib re-challenge and 93 patients experienced gefitinib Treatment Beyond Progression (TBP). There was a statistical difference in OS between gefitinib re-challenge group and non re-challenge group (median OS was 1272 days vs 774 days; *p = 0.0001), Comparison of gefitinib TBP group and non TBP group also showed statistical difference (median OS was 1016 days vs 797 days; *p = 0.035). Next, a cox regression model to investigate potential factors showed that "gefitinib re-challenge" was a factor which significantly contributed to long-term OS (HR: 0.515, 95%CI: 0.363-0.731; *p = 0.0002) whereas "gefitinib TBP" was not (HR: 0.787, 95%CI: 0.571-1.083; *p = 0.1427). We confirmed this result using DTRA, The DTRA strongly supported the significant contribution of the gefitinib re-challenge treatment strategy to longer OS time.

**Conclusion:** This retrospective cohort that gefitinib re-administration may have a significant impact on OS in long surviving patients who experienced response to gefitinib.

**Disclosure:** All authors have declared no conflicts of interest.
**1258P** POPULATION BASED EVALUATION OF CHEMOTHERAPY USE AFTER FIRST LINE GEFITINIB IN EPIDEMIOLOGICAL GROWTH FACTOR RECEPTOR (EGFR) MUTATION POSITIVE ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

C. Mariano1, I. Bosde2, D. Ionescu3, A. Karsan4, S. Sun5, N. Murray6, B. Melosky7, J. Laskin8, C. He9

1Medical Oncology, British Columbia Cancer Agency, Vancouver, BC, CANADA.
2Cancer Genetics, British Columbia Cancer Agency, Vancouver, CANADA.
3Pathology, British Columbia Cancer Agency, Vancouver, CANADA.

**Introduction:** The IPASS trial demonstrated superior progression free survival for Asian, light/never smoking, advanced, adenocarcinoma patients treated with first line Gefitinib compared to carboplatin/paclitaxel, of which 59% of those tested were EGFR mutation positive (MUT+) 1. In IPASS 39% of Gefitinib treated patients went on to receive platin based therapy. We hypothesize that in a population-based setting fewer patients receive second line platin based chemotherapy.

**Methods:** The Iressa Alliance Program provided standardized EGFR mutation testing and appropriate access to Gefitinib to all patients in British Columbia (population 4.5 million) with advanced, non squamous NSCLC. EGFR mutation testing was limited to the most common mutations: exon 19 and 21. We retrospectively analyzed clinical, pathologic and outcomes for all patients tested in this program between March 2010 and June 2011.

**Results:** A total of 548 patients were referred for testing and 107 (19%) patients were MUT+. Baseline characteristics of MUT- and MUT+; median age 67.65, male 41%/31%, Asian 15%/51%, smoking status: never smoker 21%/58%, stage IV 90%/84.5%. OS survival was 10.9 versus 14.9 months (p = 0.0001). In MUT+ patients treated with first line Gefitinib average duration of therapy was 312 days. 5% of patients continued on Gefitinib after radiographic progression of disease. Gefitinib treated patients progress at the same rate of analysis; 15% of patients received Gefitinib only, 33% platin based doublet, 10% other chemotherapy and 42% no further treatment. Five patients received 3rd line therapy.

**Conclusions:** This North American population based study shows similar efficacy of Gefitinib in MUT+ patients compared to the IPASS trial. Clinicians often continued Gefitinib past progression, likely due to ongoing clinical benefit. Contrary to our hypothesis, delivery of second line chemotherapy was feasible in a significant proportion of Gefitinib treated patients, similar to results seen in clinical trials. MUT+ patients have a better prognosis and this may contribute to their ability to receive further therapy.

**Disclosure:** All authors have declared no conflicts of interest.

**1258P** LONG-TERM SURVIVORS IN NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS WITH EPIDEMIOLOGICAL GROWTH FACTOR RECEPTOR (EGFR) MUTATIONS: DATA FROM A RANDOMIZED PHASE III STUDY COMPARING GEFITINIB WITH CARBOPLATIN PLUS PACLITAXEL (NEJ002)

Y. Minegishi1, K. Kobayashi2, M. Masamoto3, A. Inoue4, S. Sugawara5, S. Oizumi6, K. Hagiwara7, T. Nakawa5, S. Monta8, A. Gemma9

1Internal Medicine, Division of Pulmonary Medicine, Infectious Diseases, and Oncology, Nippon Medical School, Tokyo, JAPAN.
2Respiratory Medicine, Saitama International Medical Center, Saitama, JAPAN.
3Department of Respiratory Medicine, Miyagi Cancer Center, Natori, JAPAN.
4Department of Respiratory Medicine, Tohoku University, Sendai, JAPAN.
5Department of Respiratory Medicine, Saitama Kousei Hospital, Saitama, JAPAN.
6First Department of Medicine, Hokkaido University School of Medicine, Sapporo, JAPAN.
7Department of Respiratory Medicine, Saitama Medical University, Saitama, JAPAN.
8Medical Commissioner, South Miyagi Medical Center, Miyagi, JAPAN.
9Internal Medicine, Nippon Medical School, Tokyo, JAPAN.

**Background:** In the NEJ002 study comparing first-line gefitinib to a standard-chemotherapy of carboplatin plus paclitaxel for advanced NSCLC patients with tumors harboring sensitive EGFR mutations, progression-free survival was significantly longer in the gefitinib group compared with the standard-chemotherapy group. However, as 98% of the patients in whom first-line carboplatin-paclitaxel failed crossed over to gefitinib therapy, the overall survival was similar between the two groups. The 2.5-year survival rate of both groups in NEJ002 were very good at about 50%. In order to clarify the factors which contribute to the long-term survival of NSCLC patients with mutated EGFR, we evaluated any correlation between demographic factors and overall survival outcome in 230 patients enrolled in NEJ002.

**Methods:** The analysis was performed independently from our previous reports. A total of 226 patients who received EGFR-tyrosine kinase inhibitors (TKI) and had survival confirmation were analyzed. Fourteen factors were evaluated using the cause-specific survival (CSS) and multi-variate analyses were conducted by Cox's proportional hazard model.

**Results:** Four prognostic factors were identified by univariate analysis: base-line performance status (PS), existence of the distant metastasis, response to standard-chemotherapy and EGFR-TKI (P < 0.05). There were no significant differences among age, sex, smoking status, histologic type, clinical stage, EGFR mutation type and the assigned treatment groups. Three independent prognostic factors were identified by multivariate analysis: PS 1 (hazard ratio 1.64: 95% CI 1.14-2.36) and stable disease or progressive disease as response to standard-chemotherapy [HR 2.29: 95% CI 1.31-4.02] and to EGFR-TKI [HR 3.18: 95% CI 1.20-4.00].

**Conclusion:** Baseline PS, responses to standard chemotherapy and response to EGFR-TKI were significant factors on the prognosis of NSCLC with sensitive EGFR mutations. Using updated survival data, a logistic regression analysis for long survivors (more than 3 years) will be presented.

**Disclosure:** A. Inoue: I was paid lecture fees from AstraZeneca. S. Oizumi: I was paid an honorarium (AstraZeneca). K. Hagiwara: I was paid honoraria from AstraZeneca. A. Gemma: I (my department) received grant for basic science research from AstraZeneca as a chief of department. All other authors have declared no conflicts of interest.

**1258P** INFLUENCE OF SMOKING STATUS ON RESPONSE TO EGFR TKI – A RETROSPECTIVE ANALYSIS OF REFLEX EGFR MUTATION TESTING IN ASIAN PATIENTS WITH ADVANCED LUNG ADENOCARCINOMAS

A. Jain1, S.L. Koo2, K.S. Chan3, Q.S. Ng1, N.M. Chau1, M.K. Ang1, L. Oon1, W. T. Lim4, E.H. Tan5, D.S.W. Tan6

1Department of Medical Oncology, National Cancer Centre Singapore, Singapore, SINGAPORE.
2Department of Pathology, Singapore General Hospital, Singapore, SINGAPORE.
3Department of Medical Oncology, National Cancer Center, Singapore, SINGAPORE.

**Introduction:** Although the role of EGFR mutations (m) is established in predicting response to EGFR TKI, there is little data on the impact of smoking on m subtype and treatment outcomes. We hypothesized that m spectra differ between never-smokers (NS) and those with a smoking history (ex-smokers or current smokers) (SM), and that SM may have poorer outcomes to EGFR TKI.

**Methods:** All cases that had undergone reflex EGFR mt testing between 6/10 – 3/12 were reviewed for smoking status, performance status, patient demographics and type of EGFR mt. In patients who were treated with EGFR TKI, progression free survival (PFS) and 1-year overall survival (OS) was determined.

**Results:** 742 patients (MF 384:358) were identified of which 342 (46.1%) were EGFR mt+ Majority were females 64.6% (n = 221), SNS 15.197) while males comprised 35.4% (n = 121, SNS 54.66). Mts in order of frequency: Exon (Ex) 19 deletions (del) (52.3%), L858R 33.9%, Ex 20 insertion (ins)/duplication (4.9%), G719X (4.1%), L861Q (1.8%), T790M (1.2%), and Exon 19 ins (0.3%). In patients with known smoking status and mt status, (n = 332), median age was 63 years in both NS (n = 261) and SM (n = 71). There was no significant difference in location of mt (Ex 18, 19, 20 and 21, p = 0.991), or the type of mt (Ex19 deletions vs. point mutations, p = 0.723). When we reviewed the clinical outcomes of 127 TKI naive patients (NS n = 103, SM n = 24) receiving gefitinib or erlotinib monotherapy with at least 6 months of follow up, median PFS was 11.9 months (m) and OS at 1 year was 73.5%. In subgroup analysis, PFS for NS vs. SM was 11.9 and 14.7 m (p = 0.855) and 1 year OS 75.3% vs. 65.7% (p = 0.683).

**Conclusion:** EGFR mutations occur in 46% of patients in Singapore, of which one fifth of patients had significant smoking history. Contrary to our hypothesis, the EGFR mt spectra and clinical outcomes is similar in NS vs. SM underscoreing the importance of reflex testing in a population where mt prevalence is high.

**Disclosure:** All authors have declared no conflicts of interest.

**1258P** GEFITINIB (G) AND PEMETREXED (PEM) AS A FIRST LINE TREATMENT IN PATIENTS WITH EGFR MUTANT ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC): A PHASE II STUDY

N. Yoshimura1, K. Matsuura1, S. Mitsuoka1, K. Asai1, Y. Tochino1, T. Kimura1, M. Nakai1, T. Mitsuakari1, K. Hirate1, S. Kudoh1

1Department of Respiratory Medicine, Osaka City University Medical School, Osaka, JAPAN.
2Pharmacetical Department, Osaka City University Medical School, Osaka, JAPAN.

**Background:** G is the key drug for patient (pts) with NSCLC harboring mutations of EGFR as a first line treatment. However, they have disease progression in most cases. PEs and G are reported to have a schedule-depended cytotoxic synergism.

**Objectives:** We evaluated the efficacy and safety of G and PEM as a first line chemotherapy in pts with NSCLC harboring mutations of EGFR.

**Methods:** Eligibilities were histologically or cytologically proven non-squamous NSCLC with EGFR active mutation, chemotherapy naive, measurable lesion, ECOG PS 0-1, adequate organ function, LVEF > 50%. Eligible pts were informed consent. G (250mg/body) was administered on days 2-16 and PEM (500mg/m2) was administered on day 1. This combination was repeated every 3 weeks until progressive disease (PD). Primary endpoint was overall response rate
(ORR) and secondary endpoints were toxicities, disease control rate (DCR), progression free survival (PFS), and overall survival (OS). The planned sample size was 28 pts.

Results: From March 2010 to May 2012, 20 pts were enrolled and eligible: males/females 10/10; median age 66 (range 59-75); PS 0/2 2/18; stage III/IV 1/19; adenos/others 20/0. Nineteen pts were eligible for efficacy and toxicity; a total of 226 cycles (median 12 cycles, range 1-27) was given. Major grade 3/4 toxicities were neutropenia, leucopenia, liver dysfunction and infection, respectively. There was no treatment-related death. ORR was 68.8%, and DCR was 100%. Median PFS is 18.2 months and median OS is not reached.

Conclusions: This combination showed longer median PFS and acceptable toxicity. Randomized trial of PEM + G compare with G alone is warranted.

Disclosure: All authors have declared no conflicts of interest.

1259P GEFITINIB FOR NON-SMALL CELL LUNG CANCER (NSCLC) WITH MINOR EGFR MUTATIONS: A RETROSPECTIVE STUDY FROM THE NORTH EAST JAPAN STUDY GROUP (NEJ)

S. Watanabe1, H. Yoshizawa1, M. Maemondo2, A. Inoue2, S. Sugawara2, H. Tsuboi3, M. Harada4, Y. Ishi1, K. Higawara5, K. Kobayashi6
1Bioscience Medical Research Center, Nigata University Medical and Dental Hospital, Nigata-City, JAPAN, 2Department of Respiratory Medicine, Miyagi Cancer Center, Natori, JAPAN, 3Department of Respiratory Medicine, Tohoku University, Sendai, JAPAN, 4Department of Respiratory Medicine, Sendai Kousei Hospital, Sendai, JAPAN, 5Clinical Oncology, KFR Sapporo Medical Center, Sapporo, JAPAN, 6Department of Pulmonary Oncology, National Hospital Organization Hokkaido Cancer Center, Sapporo, JAPAN, 7Department of Respiratory Medicine and Clinical Immunology, Dokyko Medical University School of Medicine, Mttsu, JAPAN, 8Department of Respiratory Medicine, Satanna Medical University, Satanna, JAPAN, 9Respiratory Medicine, Saitama International Medical Center, Satanna, JAPAN

Background: In NSCLC, the sensitive mutations of epidermal growth factor receptor (EGFR), such as exon 19 deletion and L858R point mutation, are predictors of response to EGFR tyrosine kinase inhibitors (TKIs). However, it is still uncertain whether minor EGFR mutations are associated with sensitivity to EGFR-TKIs. In this study, we retrospectively evaluated the outcomes of patients who were treated with gefitinib in a NEJ002 study performed.

Materials and methods: Retrospective review of 221 EGFR mutated (exon 19 deletion, L858R, G719X and L861Q) patients who were treated with gefitinib in a NEJ002 study was performed. We identified 7 patients with G719X and 3 patients with L861Q.

Results: Among 10 patients harboring minor EGFR mutations (G719X or L861Q), 5 patients were treated with gefitinib as the 1st line treatment, and 5 patients were treated with carboplatin/paclitaxel as the 1st line chemotherapy, and then received gefitinib as the 2nd line treatment. Only 2 patients showed PR, 4 achieved SD, and 4 had PD with gefitinib treatment. The overall response rate was 20% and the disease control rate was 60%. The overall survival (OS) from enrollment was significantly shorter in patients with minor mutations (median OS, 12 months (95% CI 5.8-24.1) compared to those who were treated with gefitinib (median OS, 22.8 months (95% CI 9.9 - 41.8)).

Conclusions: Our results indicate that NSCLC patients with G719X or L861Q minor EGFR mutations are less responsive to gefitinib than those with 19 deletion or L858R.

Disclosure: All authors have declared no conflicts of interest.

1260P A PHASE II STUDY OF ERLOTINIB AS FIRST-LINE TREATMENT IN JAPANESE ADVANCED NSCLC PATIENTS HARBORING EGFR MUTATIONS

A. Hiroki1, M. Nishio1, K. Goto2, N. Yamamoto3, K. Chikamori4, M. Maemondo5, T. Hida5, N. Katakami4, T. Tamura6
1Thoracic Oncology Center, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Koto-ku, Tokyo, JAPAN, 2Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, JAPAN, 3Division of Internal Medicine, Thoracic Oncology, National Cancer Center Hospital East, Chuo-ku, Tokyo, JAPAN, 4Oncology Medicine, National Hospital Organization, Yamaguchi - Ube Medical Center, Ube, JAPAN, 5Department of Respiratory Medicine, Miyagi Cancer Center, Natori, JAPAN, 6Department of Thoracic Oncology, Aichi Cancer Center Hospital, Nagoya, JAPAN

Background: Several studies of EGFR TKIs have shown a benefit in response and progression-free survival (PFS) for NSCLC patients harboring EGFR mutations in the first-line setting. This is the first prospective study to investigate erlotinib for the first-line treatment of NSCLC patients harboring EGFR mutations in Japanese patients.

Methods: We undertook the single-arm phase II study at 25 centers. Eligible patients were adults (over 20 years) with advanced or recurrent NSCLC harboring EGFR mutations (Exon 19 deletions (19del) or Exon 21 L858R mutation) with no prior chemotherapy for NSCLC. The primary endpoint was progression-free survival (PFS) and the secondary endpoints were ORR, disease control rate (DCR), overall survival (OS), and response duration.

Results: Between April 8 and October 6 2010, 103 patients were enrolled. All patients were administered erlotinib and included in the safety analysis. One patient was excluded from efficacy analysis, because of the deviation of GEP. Thus 102 patients were analyzed in the efficacy analysis. At Data cut-off (Sep 1, 2011), median PFS assessed by Independent Review Committee was 11.8 months [95% CI 9.7- not reached]. The updated median PFS incorporated with follow up assessments will be obtained in August 2012. The most common adverse events were rash and diarrhea in 82.5% and 80.6% respectively, with Grade 3 was 13.6% and 1.0% respectively, and there were no Grade 4/rash and diarrhea. Six treatment-related ILD like events were reported by investigators, and of which two were fatal. ORR was 78.4%, DCR was 95.1%, and response duration was 11.1 months [95% CI 9.4- not reached]. OS data is immature at this time (only ten deaths events). Median PFS in 50 patients with 19del was 12.5 months, in 50 patients with L858R was 11.0 months, and two patients with L858R/T790M was 3.8months.

Conclusion: This study showed a promising efficacy and safety profile of erlotinib in Japanese advanced NSCLC patients harboring EGFR mutations.


1261P ERLOTINIB AS NEOADJUVANT TREATMENT IN PATIENTS WITH IIIA-N2 NON-SMALL CELL LUNG CANCER(NSCLC) WITH ACTIVATING EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATION (NCT01217619, ESTERN)

B. Hay, L. Xiong, R. Li, J. Sun, Y. Lou, Y. Zhang
Department of Pulmonary Medicine, Shanghai Chest Hospital affiliated to Shanghai Jiaotong University, Shanghai, CHINA

Background: Patients with stage IIIA N2 NSCLC have poor outcomes with 5-year survival rate of approximately 15% after treatment with surgical resection or chemoradiotherapy. Tyrosine kinase inhibitor monotherapy have been demonstrated a significant improvement in tumor response rate and progression free survival as the first line treatment for metastatic NSCLC patients with activating EGFR mutation. The objective of this trial is to explore the efficacy and safety profile of erlotinib as neoadjuvant treatment in patients of stage IIIA-N2 NSCLC with activating EGFR mutation.

Material and methods: This is a single arm, one center, phase II study of erlotinib as neoadjuvant treatment in patients with Endobronchial Ultrasound (EBUS) confirmed stage IIIA-N2 NSCLC with activating EGFR mutation in exon 19 or 21. The primary endpoint is to evaluate radical resection rate. A total of 44 patients will be enrolled. Major inclusion criteria: IIA-N2 NSCLC Patients with pathologically confirmed ipsilateral mediastinal metastasis by EBUS. The biopsy specimen shows activating EGFR mutation in exon 19 or 21.

Treatmen schedule: All the recruitment patients will be treated by erlotinib 150mg orally per day for 56 days for neoadjuvant period. Patients will be assessed by Chest CT for the efficacy evaluation in day 29 and right after day 56. All the post-operative patients will receive standard adjuvant treatment which will be decided by the investigator.

Current enrollment: 48 patients have been screened, and 7 patients met the inclusion criteria and were enrolled. 2 patients are still on neoadjuvant treatment, 5 patients have completed the neoadjuvant therapy, and RECIST evaluation showed partial response in 2 patients, disease progression in 2 patients, and disease stable in 1 patient. Due to active hepatitis and technical infeasibility, 2 patients with PR didn’t receive surgery, only one SD patient received R0 surgery.

Disclosure: All authors have declared no conflicts of interest.
Introduction: Our aim in this study was to explore the potential association of epidermal growth factor receptor (EGFR) with characteristics of tumor spread in patients with pulmonary adenocarcinoma. Clinical implication of EGFR mutational status on brain metastasis was also evaluated in surgically treated patients.

Methods: We analyzed clinical data on 317 patients who were tested for EGFR mutation and who underwent brain MRI at diagnosis between October 2005 and December 2011. The relationship between EGFR mutation status and clinical and functional characteristics were analyzed. Initial metastatic disease was stratified according to brain metastases and their association with EGFR mutations was evaluated using multivariable logistic regression.

Results: Of the 317 patients, 139 patients (43.8%) harbored EGFR mutations. EGFR mutational status was more commonly found in patients with early nodal stage (71.9% versus 28.1%, adjusted OR = 1.90, p = 0.003) and distant metastases (54.0% versus 46.0%, adjusted OR = 2.05, p = 0.011). Further analysis showed that EGFR mutations were more likely to be detected in brain metastases (64.7% versus 35.3%, p = 0.005), whereas their association with noncervical metastases was not significant (55.4% versus 44.6%, p = 0.960). Children, sup. EGFR receptor status on patients treated with surgical resection showed that EGFR mutation status was a poor prognostic factor for brain metastasis (HR = 5.94, 95% CI = 1.08-16.28, p = 0.039) after adjustment of pathologic N stage.

Conclusions: In this study, EGFR mutation status was significantly associated with early nodal and distant metastasis, in the patients with pulmonary adenocarcinoma. The current study also suggests the preference of brain metastases in mutant EGFR tumors at initial presentation and after curative resection.

Disclosure: All authors have declared no conflicts of interest.

IMPACT OF EPIDERMAL GROWTH FACTOR RECEPTOR-TYROSINE KINASE INHIBITOR TREATMENT IN ADVANCED NON-SMALL CELL LUNG CANCER: A META-ANALYSIS

C.K. Lee1, C. Brown2, R. Grala3, V. Hirsh4, A. Inoue5, V. Gibs6, C.J. Yang7
1NHCC Clinical Trials Centre, University of Sydney, Sydney, NSW, Australia, 2Clinical Trials, NHCC Clinical Trials Centre, University of Sydney, Sydney, Australia, 3Department of Medicine, Hofstra University School of Medicine, New York, United States of America, 4Oncology, McGill University Health Centre, Montreal, QC, Canada, 5Department of Respiratory Medicine, Tohoku University, Sendai, Japan, 6Biostatistics and Research Methodology, NHCC Clinical Trials Centre, University of Sydney, Sydney, Australia, 7Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan

Background: Previous meta-analyses have reported that epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) improves progression-free survival (PFS) in patients with advanced non-small cell lung cancer (NSCLC) harboring EGFR mutation. We examined the influence of EGFR-TKI on PFS and overall survival (OS) in those with (EGFR+) and without mutation (EGFR-).

Methods: We included published and unpublished randomised trials of advanced NSCLC that compared EGFR-TKI monotherapy or combination EGFR-TKI chemotherapy with chemotherapy or placebo. We used published hazard ratios (HR) if available, or derived treatment estimates from other survival data. We investigated treatment effects in different regimens.

Results: We identified 20 eligible trials investigating EGFR-TKI in front-line (n = 12), second or subsequent (n = 5), and maintenance (n = 3) treatment, with EGFR status known in 3198 (23%) patients. Overall, HR for EGFR+ over control for PFS were (EGFR+) 0.37 (95% CI, 0.31 to 0.43), (EGFR-) 1.01 (95% CI, 0.92 to 1.12; p = 0.67). EGFR mutation is predictive of PFS benefit with EGFR-TKI in all settings: front-line HR (EGFR+) 0.39, p < 0.005, HR (EGFR-) 1.07, p = 0.27, interaction p = 0.001; second or subsequent lines HR (EGFR+) 0.38, p < 0.01, HR (EGFR-) 1.12, p = 0.007; interaction P = 0.003; maintenance HR (EGFR+) 0.15, p < 0.001, HR (EGFR-) 0.81, p = 0.02, interaction p = 0.02. There was no difference in OS for patients treated with EGFR-TKI or control in these subgroups of patients: HR (EGFR+) 0.95, p = 0.21; HR (EGFR-) 0.95, p = 0.29.

Conclusions: In this meta-analysis, treatment with EGFR-TKI was found to significantly delay disease progression in EGFR+ patients; however, no impact on OS was identified. EGFR mutation is a predictive biomarker of PFS benefit with EGFR-TKI treatment in all settings. These findings support assessment for EGFR mutation before initiation of EGFR-TKI treatment and that EGFR-TKI should be considered as front-line therapy in EGFR+ patients with advanced NSCLC.

Disclosure: R. Gralla: Consultant or advisory role for Boehringer Ingelheim. V. Hirsh: Advisory role for Boehringer Ingelheim. A. Inoue: Received lecture fees and research grants from AstraZeneca. C.J. Yang: Advisory roles for Boehringer Ingelheim, AstraZeneca, Roche and OSI, and have received honoraria from AstraZeneca, Roche and OSI. All other authors have declared no conflicts of interest.

IS THERE A BENEFIT ON SURVIVAL OF TYROSINE-KINASE INHIBITORS VS CHEMOTHERAPY IN FIRST LINE IN MUTATED EGFR PATIENTS WITH ADVANCED NON-SMALL CELL CANCER (NSCLC)? A META-ANALYSIS

G. De Quez1, B. Uzzan2, K. Chouahnia1, P. Nicolas3, L. Zetek1, M. Paller4
1Oncologie, Hôpital Avicenne, Bobigny, France, 2Pharmacologie, Hôpital Avicenne, Bobigny, France

Background: Tyrosine-Kinase Inhibitors (TKIs) markedly improve Progression Free Survival (PFS) of advanced NSCLC patients mutated for Epidermal Growth Factor Receptor (EGFR). Results on Overall Survival (OS) are more questionable. Therefore, we performed a publication-based meta-analysis to further assess this issue.

Disclosure: All authors have declared no conflicts of interest.

META-ANALYSIS ADVANCED NON-SMALL CELL LUNG CANCER: A TREATMENT IN RECEPTOR-TYROSINE KINASE INHIBITORS VERSUS CHEMOTHERAPY IN FIRST LINE IN SPANISH WORLD07 DATABASE

J. de Castro1, D. Isla Casado2, M. Provençol Pulía3, M. Mejani Tarruelia4, N. Vinolas Segarra5, E. Felippa6, A. Artal Cortesa7, V. Hirsh8, A. Inoue9, V. Gebski10, C.J. Yang11
1Oncology, Hospital Universitario Puerta de Hierro Majadahonda, Majadahonda, Spain, 2Oncology Service, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain, 3Medical Oncology, Hospital Universitario Puerta de Hierro Majadahonda, Majadahonda, Spain, 4Medical Oncology, Hospital de La Santa Creu i Sant Pau, Barcelona, Spain, 5Medical Oncology, Hospital Clinic y Provincial de Barcelona, Barcelona, Spain, 6Oncología Médica, Vall d’Hebron University Hospital Institut d’Oncologia, Barcelona, Spain, 7Servicio de Oncología Médica, Hospital Miguel Servet, Zaragoza, Spain, 8Medical Oncology, Complejo Hospitalario Universitario de A Coruña, La Coruña, Spain, 9Oncology, Fundación Jiménez Díaz, Madrid, Spain, 10Medical Oncology, Hospital Ramon y Cajal, Madrid, Spain

Background: Lung cancer in never-smoker appears to be a distinct entity from lung cancer in smoker, with specific molecular characteristics and potential different treatment. Several factors like hormonal, environmental, genetic, pre-existing lung diseases, and virus, may play etiological role, and an in-depth understanding of them is needed. So, new clinicopathologic aspects of never-smoking WLC should be very important to know the biology of this tumor disease.

Methods: Information has been extracted from WORLD07 database, a prospective, from 32 Spanish centers, epidemiologic female-specific lung cancer e-database performed by ICAPEM, an association to research WLC.

Results: From October 2007 to October 2011, 539 newly diagnosed never-smoking WLC were included in World07 database (39.3% of 1371 patients). P characteristics are: median age 71.1 years (range: 22-91). Previous history of cancer (%): 13(breast, lung, cervix: 41.4,5.7,2.9). Gynecological features: median age of menarche 13y, Postmenopausal 88.9%, median age of menopause 49y. Median age of first child 26.4y Children: 91.2% (median: 2.3). Oral contraceptive: 11.9%. HRT: 5.2%. Tobacco exposure: Second-hand smokers: 40%, work-exposure 17.1%, home-exposure 88.8%. Obesity: 16.3%. Familiar history of cancer: 39.9% (lung cancer 29.8%).Lung cancer histology (%): adenocarcinoma/BAC/squamous/large cell/SCLC others: 69.2/6.8/5.7/5.0/3.8/3.8. EGFR mutated p (268 p analized): 55.5%, exon 19/75.4, exon 21/24.6. Overall survival: median 27 months (m), 1/2-y(%) 74.8/55.2; stage IV NSCLC: median 20.5m, 1/2-y(%) 67/46; EGFR mutated p: median 27.3m, 1/2-y(%) 74.8/55.2; stage IV NSCLC(1 line):median age 65.7y, stage IV NSCLC(>1 line):median age 61.7y, stage IV NSCLC(1 line):median age 67.5y, stage IV NSCLC(>1 line):median age 62.9y.

Conclusions: Never-smoking WLC represents 39% of Spanish World07 database. The high incidence of adenocarcinoma histology (69.2%) and EGFR mutated tumors suggests a different clinical and genetic profiling and recommend a different treatment approach for this group of patients.

Disclosure: All authors have declared no conflicts of interest.
Selection. ALK+ was not a favorable prognostic factor, although disease stage and smoking history may influence OS in ALK+ NSCLC.


A LARGE RETROSPECTIVE ANALYSIS OF PEMETREXED (PEM) ACTIVITY IN PATIENTS (PTS) WITH ALK-POSITIVE (ALK+) NON- Small Cell Lung Cancer (NSCLC) PRIOR TO CRIZOTINIB (CRIZ) TREATMENT


1S. Luigi Hospital, University of Turin, Turin, ITALY, 2Department of Internal Medicine, Seoul National University Hospital, Seoul, KOREA, 3Cancer Center, Massachusetts General Hospital, Boston, MA, UNITED STATES OF AMERICA, 4Cancer Centre, University of California at Irvine, Irvine, CA, UNITED STATES OF AMERICA, 5Medical Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, UNITED STATES OF AMERICA, 6Thoracic Oncology, Yale University School of Medicine, New Haven, CT, UNITED STATES OF AMERICA, 7Department of Medicine, Institute Gustave Roussy, Villejuif, FRANCE, 8Research and Development, Pfizer Oncology, La Jolla, CA, UNITED STATES OF AMERICA, 9Medical Oncology, Pfizer Oncology, New York, NY, UNITED STATES OF AMERICA

Background: Retrospective small cohort studies evaluating multiple lines of therapy suggest ALK+ NSCLC may be particularly sensitive to PEM treatment.

Methods: PROFILE 1005 (NCT00932451; Pfizer) is a large phase II multinational, single-arm study of CRIZ in previously treated ALK+ NSCLC. We retrospectively assessed overall response rate (ORR) and time to progression (TTP; 1st dose to objective progression) in pts who received PEM-based regimens prior to CRIZ in the 1st-line (1L) and 2nd-line (2L) settings. ORR to CRIZ post-PEM-based regimens was assessed.

Results: Of the 901 ALK+ pts enrolled as of Jan 2012, 711 (79%) received prior PEM (single-agent or combination; any line advanced/metastatic) with an ORR to PEM of 19%. Pts who received 1L PEM combinations (n = 308) were predominately of young age (median 53 y; 82% <65 y); never/former smokers (96%); with good PS (82% ECOG <2) and had adenocarcinoma (95%). ORR to 1L PEM combinations was 24% (95% CI: 20, 29) and median TTP was 6.3 months (95% CI: 5.8, 7.0). These patients subsequently achieved higher ORR with ≥2L CRIZ (39%; 95% CI: 34, 45). Pts who received 2L single-agent PEM (n = 141) had similar demographic characteristics to those who received 1L PEM-based regimens (median age, 50 y; 84%; <65 y; 95% never/former smokers; 82% ECOG <2; 93% adenocarcinoma). ORR to 2L single-agent PEM was 14% (95% CI: 9, 21) and median TTP was 5.4 months (95% CI: 4, 6.5). These patients subsequently achieved higher ORR with CRIZ in ≥2L (48%; 95% CI: 40, 57).

Conclusion: This retrospective analysis of a large data set reports lower ORR and shorter TTP with PEM than that reported in smaller retrospective cohorts of ALK+ NSCLC. This analysis and previous reports observed a tendency towards a higher ORR and/or better ORR or TTP with 1L and 2L PEM-based regimens in ALK+ NSCLC than in unselected populations, which may not be specifically related to ALK status but to clinical characteristics such as younger age, adenocarcinoma histology or a higher sensitivity to cytotoxic agents in never-smokers.

Disclosure: G. Scagliotti: Honoraria received from Pfizer, Eli Lilly, Roche and AstraZeneca and Novartis. S. I. Ou: Advisory relationship with Pfizer and Genentech. Received honoraria from Pfizer, Genentech and Lilly. Received research funding from Pfizer, G. J. Reley: Advisory relationship with Chugui, Ariad, Daiichi-sankyo. Received research funding from AstraZeneca and Novartis. D. W. Kim: Advisory relationship with Pfizer and Genentech. Received research funding from Pfizer, Genentech and Lilly. Received research funding from Pfizer, G. J. Reley: Advisory relationship with Chugui, Ariad, Daiichi, Tragara, Foundation Medicine, Boehringer-Ingehl and Novartis. Received research funding from Pfizer, Bristol-Myers Squibb, Chugui, GlaxoSmithKline, Novartis and Infinity. B. Besse: Received research funding from Pfizer, K. Wilder: Employed by Pfizer as a Senior Director and has stock ownership with Pfizer. Y. Tang: Employed by Pfizer as a Manager and has stock ownership with Pfizer. C. H. Bartlett: Employed by Pfizer as a Senior Director, Medical Affairs Lead and has stock ownership with Pfizer. All other authors have declared no conflicts of interest.
Background: Crizotinib is a potent, small-molecule ALK inhibitor with a high response rate in advanced ALK-positive NSCLC. In early phase studies, patients (pts) commonly reported mild visual disturbances. Here we characterize such visual effects with objective and subjective measures in an ongoing phase II study (PROFILE 1005).

Methods: Previously treated pts with advanced ALK-positive NSCLC received crizotinib 250 mg BID. Ophthalmological examinations, comprising best corrected visual acuity (BCVA), biomicroscopy, and fundoscopy, were performed at screening and after a visual effect event was reported, except for a subset of pts in France, where examinations were done every 4 cycles. In addition, on day 1 of each cycle, pts completed the Visual Symptom Assessment Questionnaire (VSAQ) that assessed the presence, frequency, timing, duration, and severity of visual effects and their impact on activities of daily living (ADL).

Results: As of Jan 2012, 901 pts had enrolled in PROFILE 1005; 21–27% were evaluable for ophthalmological examinations (visual acuity: 193/901; biomicroscopy: 239/901; fundoscopy: 239/901). There were no changes in BCVA, conjunctiva, cornea, anterior chamber, iris, lens, or fundus attributable to crizotinib. The most frequently reported ophthalmological finding was worsening of cataracts (right eye: 9%; left eye: 10%), which was also unlikely related to crizotinib. Visual effects as identified by the VSAQ were reported by 65% of pts (405/622) at cycle 2 (C2), 58% at C3 (323/558), 55% at C4 (257/468), and 51% at C5 (203/397). The most common were appearance of flashing lights, streamers/strings/floaters, and overlapping shadows. Most pts reported each event as lasting ≤1 min (C2: 63%; C3: 68%; C4: 72%; C5: 75%), occurring mostly in the morning (46–59%) and/or evening (70–74%). The majority of pts reported that visual effects were not at all or a little bothersome, with no or minimal impact on ADL. Similar results were observed in the French pt subset.

Conclusions: There were no objective ophthalmological changes associated with the visual effects on crizotinib. Pt-reported visual effects were frequent, but transient, with no or minimal impact on ADL.

Background: In the phase III SATURN study, maintenance erlotinib significantly prolonged progression-free survival (PFS) vs placebo in patients (pts) with advanced non-small-cell lung cancer (NSCLC) and non-progressive disease after first-line chemotherapy (Capuzzo et al, Lancet Oncol 2010). Epidermal growth factor receptor (EGFR) expression analysis by immunohistochemistry (IHC) found no significant difference in PFS (p = 0.63) or overall survival (OS; p = 0.52) with erlotinib by EGFR IHC status (Brugger et al, J Clin Oncol 2011). Recently, Pirker et al. (Lancet Oncol 2012) presented data on EGFR expression as a predictor of OS for patients (pts) with advanced NSCLC and non-progressive disease after first-line chemotherapy plus cetuximab in the phase III FLEX study, using a novel method (H-score) to assign EGFR IHC status. We used this method to reassess samples from the SATURN study.

Methods: The H-score method assigns an IHC score to each pt on a continuous scale of 0–300, based on the percentage of cells at different staining intensities (Pirker et al, Lancet Oncol 2012). As per this method, the outcome-based discriminatory threshold IHC H-score for our analysis was set at 200 and existing OS (wild-type [WT] or mutant [Mut]). Treatment outcome was analyzed further in FLEX study EGFR expression groups according to EGFR mutation status.

Results: The original EGFR IHC analysis used samples from 370 and 372 pts in the erlotinib and placebo arms, respectively. This analysis examined existing samples from 351 and 361 pts in the erlotinib and placebo arms, respectively. PFS and OS according to EGFR IHC by different methods are shown in the Table.

Conclusions: Rel-scoring of EGFR IHC status in SATURN by H-score found similar benefit of erlotinib treatment in PFS or OS for subsets with high or low EGFR expression, in overall or EGFR WT populations.

Disclosure: W. Brugger: Financial Interest: Advisory Board. F. Capuzzo: Financial Interest: Advisory board, F. Hoffmann-La Roche Ltd. I. Bara: Employed by F. Hoffmann-La Roche Ltd. B. Klughammer: Stock Ownership: F. Hoffmann-La Roche Ltd Employed by F. Hoffmann-La Roche Ltd. All other authors have declared no conflicts of interest.

Note: HR < 1 is in favour of erlotinib

Table: 1271P

<table>
<thead>
<tr>
<th>SATURN protocol-defined EGFR IHC+</th>
<th>SATURN protocol-defined EGFR IHC+</th>
<th>EGFR IHC by H-score ≥ 200 (high)</th>
<th>EGFR IHC by H-score &lt; 200 (low)</th>
<th>EGFR IHC by H-score ≥ 10%</th>
<th>EGFR IHC by H-score &lt; 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>p = 0.0001</td>
<td>0.69 (0.58–0.82) log-rank p = 0.1768</td>
<td>0.77 (0.51–1.14) log-rank p = 0.591</td>
<td>0.68 (0.53–0.86) log-rank p = 0.0010</td>
<td>0.76 (0.62–0.93) log-rank p = 0.0076</td>
</tr>
<tr>
<td>OS</td>
<td>p = 0.0063</td>
<td>0.77 (0.64–0.93) log-rank p = 0.0063</td>
<td>0.91 (0.59–1.38) log-rank p = 0.08</td>
<td>0.80 (0.62–1.05) log-rank p = 0.0199</td>
<td>0.70 (0.64–0.91) log-rank p = 0.0063</td>
</tr>
<tr>
<td>n (EGFR WT)</td>
<td>n = 170 placebo: 157</td>
<td>0.69 (0.58–0.82) log-rank p = 0.1146</td>
<td>0.77 (0.53–1.05) log-rank p = 0.1168</td>
<td>0.69 (0.51–0.95) log-rank p = 0.188</td>
<td>0.69 (0.53–0.95) log-rank p = 0.0964</td>
</tr>
</tbody>
</table>

PFS in WT: n = 0.0003 | 0.76 (0.63–0.99) log-rank p = 0.65 (0.37–1.13) log-rank p = 0.82 (0.58–1.29) log-rank p = 0.0010 | 0.69 (0.51–0.95) log-rank p = 0.0188 | 0.76 (0.55–1.05) log-rank p = 0.1568 | 0.76 (0.55–1.05) log-rank p = 0.0964 |

OS in WT: n = 0.0004 | 0.76 (0.60–0.99) log-rank p = 0.64 (0.35–1.20) log-rank p = 0.1608 | 0.76 (0.55–1.05) log-rank p = 0.1568 | 0.76 (0.55–1.05) log-rank p = 0.0964 |

Note: HR < 1 is in favour of erlotinib
MERCK SERONO: Advisor, speaker in symposia, research grant PFIZER: Advisor ROCHE/GENENTECH: Advisor, speaker in symposia. R. Piker: The author declares the following: Honoraria for Advisory Board and speaker’s fee from AstraZeneca, Boehringer Ingelheim (Merck Serono and Roche). J. Byrne: The author declares: Payment from Merck Serono in relation to a protocol writing committee and advisory boards and travel costs in related to attendance. Honoraria from Merck Serono associated with presentation of data at satellite/company symposia. K.M. Kerr: Keith Kerr has acted on Advisory Boards and has received speaker’s fees from Merck Serono. He has had similar roles with Astra Zeneca, Roche, Eli Lilly, Daichi Sankyo, Pfizer, Boehringer Ingelheim and Glaxo Smith Klein. S. Störek: The author has been involved in sponsored research by Merck KGaA. I. Celik: The author is an employee of Merck KGaA and declares stock ownership in this company. E.A. Shepherd: Honorarium from Merck KGaA for presentation at Scientific, Industry-sponsored Satellite Symposium. Provided compensated consultation services to Merck KGaA.

Background: EGFR-mutant NSCLC patients (pts) ultimately overcome resistance to EGFR tyrosine kinase inhibitors (TKIs). Among resistant mechanisms, somatic EGFR T790M mutation is the most frequent and account 50% of tumors. Previous data suggest that tumors with acquired T790M at post-progression biopsy specimen may have a more favorable prognosis and indolent progression. However, tumor re-biopsies at progression sites are scarce in NSCLC patients and blood samples are a non-invasive method that may help to identify resistant mechanisms.

Material and methods: Pts with advanced NSCLC harboring EGFR mutations (Exon 19 and 21) and acquired resistance to EGFR tyrosine kinase inhibitors (TKIs) were eligible. All pts where included in a phase II trial (TARZO) and treated with erlotinib 150 mg PO daily plus oral vorinostat 400 mg QD on days 1–7 and 15–21 in a 28-day cycle. Blood samples were required at study entry. We aim to determine the feasibility and incidence of T790M resistant mutation from plasma DNA from patients by mutation from cell free circulating DNA from patients using a 5 nucleotide PCR assay (TaqMan assay) with a FAM MGB-labeled probe for the wild-type and a VIC MGB-labeled probe for the mutant sequence in the presence of a protein nucleic acid (PNA) clamp, which was designed to inhibit the amplification of the wild-type allele (Pangaea Biotech SL patent).

Results: Twenty-five pts were included in the trial. From those, nineteen plasma nucleic acid (PNA) clamp, which was designed to inhibit the amplification of the

Disclosure: All authors have declared no conflicts of interest.
SECOND-LINE ERLOTINIB THERAPY IN ELDERLY PATIENTS WITH ADVANCED NON-SMALL-CELL LUNG CANCER: IFCT-0501 RANDOMISED, PHASE 3 TRIAL

E. Quoix1, V. Westeel2, J. Oster3, E. Pichon4, J. Daubuis5, D. Debieuvre6, L. Blaudin7, F. Morin8, B. Milleron9, G. Zalcman10

1Pneumologie, HUS, Strasbourg, FRANCE, 2Pneumologie, CHU, Besançon, FRANCE, 3Pneumologie, CH, Colmar, FRANCE, 4Pneumologie, CHU, Tours, FRANCE, 5Pneumologie, CH, Mont-de-Marsan, FRANCE, 6Pneumologie, General Hospital, Mulhouse, FRANCE, 7Biostatistics, IFCT, Paris, FRANCE, 8IFCT, PARIS, FRANCE, 9Pneumologie, AP-HP Hôpital Tenon, PARIS, FRANCE, 10Pneumologie, CHU, Caen, FRANCE

Background: The IFCT-0501 randomised, phase 3 trial showed a significant survival benefit for the experimental arm using carboplatin-weekly paclitaxel doublet chemotherapy (Arm B) versus vinorelbine or gemcitabine monotherapy (Arm A), in elderly patients with advanced NSCLC (Quoix et al, Lancet 2011; 378:1079-88). In case of progression or toxicity, second-line (2nd) treatment with erlotinib was administrated in both arms. Here we report the results of this 2nd-line therapy.

Methods: Patients aged 70 to 89 years, with locally advanced or metastatic NSCLC, received erlotinib 150 mg daily as 2nd-line treatment until disease progression or excessive toxicity.

Results: Among 443 patients who completed first-line chemotherapy, 292 received 2nd-line erlotinib, at the same proportion in both arms (A: 64%; B: 67%; p = 0.46). Median duration of erlotinib treatment was not different according to first-line treatment arm, 2.01 and 2.24 months for arm A and arm B, respectively. Ability to receive 2nd-line treatment was significantly associated with performance status (0 vs. 2-3), weight loss (≥5% vs. <5%), MMS (<23 vs. ≥23) and ADL (<6 vs. ≥6) scores, and stage (III vs. IV), but not with age (<80 vs. ≥80), sex or histology (squamous vs. non squamous). Response evaluated after 2 months of erlotinib was: CR: 1 (0.33%), PR: 25 (8.77%) and SD: 63 (22.1%). From the Day 1 of erlotinib administration, median overall survival was 4 and 6.8 months in arm A and B, respectively, with a 1-yr survival rate of 26.4% and 33.7%, respectively (p = 0.08). Progression-Free Survival was 2.2 and 2.6 months, respectively (p = 0.36). Grade 3/4/5 toxicity was 19.9/1/0%.

Conclusions: In elderly patients with advanced NSCLC, administration of 2nd-line erlotinib is feasible, well tolerated, with a response rate comparable to that observed in previous trials, and maintained the survival advantage obtained with first-line carboplatin-weekly paclitaxel (NCT002598415).

Disclosure: S. Wojtowicz-Praga: Dr. Wojtowicz-Praga is an employee of and holds stock options in Roche/Genentech. L. Leon: Dr. Leon is an employee of and holds stock options in Roche/Genentech.
Conclusions: These data from SAiL along with previously presented data from ARIES suggest that cumulative exp to post-IP BV is associated with incremental increases in OS for NSCLC pts.

Disclosure: N. Thatcher: Dr. Thatcher is a member of the Roche advisory board and has received speaker fees from Roche. P. Garrido Lopez: Dr. Garrido Lopez is a member of the Roche advisory board. N. Pavlakis: Dr. Pavlakis has received speaker honoraria and travel grants from Roche, and has participated in Roche Advisory Boards. J. Laskin: Dr. Laskin is a member of the Canadian National Ad Board for lung cancer for Astra Zeneca, BI, and Eli Lilly and has received research funding from Roche, Boehringer Ingelheim, and Eli Lilly. E. Dansim: Dr. Dansim is a member of the Roche advisory board. F. Griesinger: Dr. Griesinger is a member of national and international advisory boards of Roche and has received honoraria for presentations at meetings. L. Leon: Dr. Leon is an employee of and holds stock options in Roche/Genentech. D. Dalal: Dr. Dalal is an employee of and holds stock options in Roche/Genentech. P. Perez-Moreno: Dr. Perez-Moreno is an employee of and holds stock options in F. Hoffman LaRoche. L. Crino: Dr. Crino received honoraria from Roche as a speaker in a scientific symposium.

### 127OP

**CUMULATIVE EXPOSURE TO BEVACIZUMAB (BV) AFTER DISEASE PROGRESSION (PD) CORRELATES WITH SURVIVAL IN NON-SMALL CELL LUNG CANCER (NSCLC): A TIME-DEPENDENT ANALYSIS OF THE ARIES OBSERVATIONAL COHORT STUDY**

T.J. Lynch1, M. Jahanzeb1, D.R. Spigel2, A. Wozniak4, L. Leon5, S. Fish5, E. Li6, D. Dalal6, M.P. Kosty7

1Yale School of Medicine, Yale Comprehensive Cancer Center, New Haven, UNITED STATES OF AMERICA, 2University of Miami, Miller School of Medicine, Sylvester Comprehensive Cancer Center, Deerfield Beach, FL, UNITED STATES OF AMERICA, 3lung Cancer Research Program, Sarah Cannon Research Institute, Nashville, TN, UNITED STATES OF AMERICA, 4Department of Hematology- Oncology, Wayne State University, Detroit, MI, UNITED STATES OF AMERICA, 5Biostatistics, Genentech, Inc., South San Francisco, CA, UNITED STATES OF AMERICA, 6In Medical Affairs, Genentech, Inc., South San Francisco, CA, UNITED STATES OF AMERICA, 7Department of Oncology, Scripps Clinic, La Jolla, CA, UNITED STATES OF AMERICA

**Background:** Duration of BV use appears to contribute to treatment (tx) efficacy in some cancers (eq. ovarian). A phase 3 mCRPC trial met its 1st end pt of improved postprogression overall survival (ppOS) when continuing BV with chemotherapy (CT) into 2nd-line (2L) tx. A phase 2 study showed a trend for OS benefit when adding BV to CT in CT-naive 2L NSCLC (HR 0.71; 95% CI 0.41-1.21) (Herbst JCO 2007). This analysis evaluated whether BV exposure (exp) after PD correlates with ppOS in NSCLC.

**Methods:** ARIES 1st-line (1L) BV-treated NSCLC patients (pts) who survived 1st PD were included. ppOS equaled the time from 1st PD to any-cause death. BV exp, over follow-up, equaled the cumulative days of BV from 1st PD. A time-dependent Cox regression model was fitted to assess the effect of cumulative BV exp on ppOS, while controlling for potential time-dependent and fixed confounders. A landmark sensitivity analysis, also adjusting for confounders, compared ppOS in pts treated with BV beyond PD (BBP) and pts treated otherwise (No BBP) ≥50 days after PD.

**Results:** As of 09/2011, of 1607 enrolled 1L pts, 1461 (74%) had 1st PD. Characteristics (n = 1461) were: 48% had 1st PD within 6 mos, 52% male, 31% ≥70 y, 13% never smokers, and 13% ECOG status ≥2. The median ppOS for all pts with 1st PD was 6 mos (95% CI 3.6-6.7). Among pts with any BV tx, the mean cumulative BV exp was 116 days (range, 2-1140). Across follow-up, the HRs for ppOS decreased by ~4% for each additional 21-day interval of cumulative exp (Table). Cumulative BV duration was associated with improved ppOS (P = .0001). The landmark analysis also showed that BBP was independently associated with higher ppOS (BV vs BBP: HR, 0.75; 95% CI, 0.65-0.86). A cycle is calculated as 21 days of cumulative exposure after PD. * Eg. n = 55 patients were continuously dosed through approximately day 126 (cycle 6) after PD.

**Conclusion:** This is the first report to evaluate erlotinib efficacy in Japanese NSCLC patients with wt-EGFR and to find a biomarker that predicts the efficacy of erlotinib except EGFR gene mutation.

**Disclosure:** T.J. Lynch: Dr. Lynch is on the Infinity Pharmaceuticals board of directors, consults for Merck, Boehringer-Ingelheim and Astex, and holds a patent on EGFR testing from Partners Healthcare. M. Jahanzeb: Dr. Jahanzeb is a consultant/advisor for Genentech. D.R. Spigel: Dr. Spigel is an unpaid advisor/ consultant to Genentech. A. Wozniak: Dr. Wozniak has received honoraria and research support from Genentech and research funding from Eli Lilly. L. Leon: Dr. Leon is an employee of and holds stock options in Roche/Genentech. S. Fish: Dr. Fish is an employee of and holds stock options in Roche/Genentech. E.D. Flick: Dr. Flick is an employee of and holds stock options in Roche/Genentech. D. Dalal: Dr. Dalal is an employee of and holds stock options in Roche/Genentech. M.P. Kosty: Dr. Kosty has participated in the Genentech Speakers Bureau.

**Background:** Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have dramatically improved clinical outcome in NSCLC harboring EGFR gene mutation. On the other hand, survival benefit from erlotinib was revealed even in the NSCLC patients with wild type (wt) EGFR gene by subset analyses of several phase III trials. Additionally, smoking status was identified as one of predictive factors of erlotinib efficacy. This study aimed to evaluate the efficacy of erlotinib in Japanese NSCLC patients with wt-EGFR and to find a biomarker that predicts the efficacy of erlotinib except EGFR gene mutation.

**Methods:** The primary endpoint was an objective response rate. Secondary endpoints included disease control rate, overall survival, safety, and a biomarker finding. Advanced NSCLC patients without EGFR gene mutation who had received one to three prior chemotherapy regimens and who had never or light smoked were eligible in this study. EGFR gene status was evaluated by the PNA-LNA PCR clamp method. Erlotinib was administered daily (150mg/day) until disease progression or unacceptable toxicities.

**Results:** Forty seven patients were enrolled between March 2010 and November 2011. One patient was excluded for evaluation because having activating EGFR mutation. Efficacy and safety were evaluated among 46 patients. Best responses were PR 7 (15.2%), SD 12 (26.1%), PD 26 (46.4%), and NE 1 (2.2%). Response rate and disease control rate were 15.2% (95%CI: 4.9-25.5%) and 41.3 % (95%CI 27.1-55.5%) respectively. Median PFS was 15.5 months and 5 (11%) cases received erlotinib for more than 6 months. Grade 3 or 4 adverse events were anorexia (4), skin rash (2), neutropenia (1), leukopenia (1), anemia (2), elevation of AST/ALT (1), rectal ulcer (1), and cerebral infarction (1).Two patients suffered grade 3 interstitial lung disease.

**Conclusion:** This is the first report to evaluate erlotinib efficacy in NSCLC selected by EGFR mutation negative and smoking status. This study elucidated that erlotinib has appreciable effect on some EGFR-wild cases without severe toxicities. Finding of predictive marker became more important. Biomarker analysis is ongoing.

**Disclosure:** M. Maemondo: M. Maemondo received honoraria for lecture fees from Chugai. All other authors have declared no conflicts of interest.
1281P MAINTENANCE THERAPY FOR NONQUAMOUS NON-SMALL CELL LUNG CANCER (NSQNSCLC): PATIENT-REPORTED SYMPTOMS, PERFORMANCE STATUS (PS) AND EFFICACY

C. Obasaju1, L. Bowman1, P. Wang2, W. Shen2, K.B. Winfree1, E.N. Smyth1, M. Boyer1, W. John2, P. Bialy1
1Oncology, Eli Lilly and Company, Indianapolis, IN, UNITED STATES OF AMERICA, 2Global Health Outcomes, Eli Lilly and Company, Indianapolis, IN, UNITED STATES OF AMERICA, 3Global Statistics, Eli Lilly and Company, Indianapolis, IN, UNITED STATES OF AMERICA, 4Cancer Institute, Perin State Milton S. Hershey Medical Center, Hershey, PA, UNITED STATES OF AMERICA

Purpose: Cuielena et al. (2009) showed that pemtrexed (Pem) maintenance therapy is well-tolerated and offers significantly superior overall survival (OS) and progression-free survival (PFS) versus (vs) placebo (pbo) in patients (pts) with advanced nsqNSCLC. This retrospective analysis assessed the effect of maintenance therapy on OS and PFS by baseline patient-reported symptom burden and PS.

Methods: Data from 481 nonquamous pts were analyzed. Symptom burden of 464 pts was captured with baseline values of the Lung Cancer Symptom Scale (LCSS), which includes 6 disease-specific symptom items (anorexia, fatigue, cough, dyspnea, pain, hemoptysis), each ranging from 0 (no symptoms) to 100 (worst symptoms). Average symptom burden index (ASBI) is the mean of the 6 items. Symptom subgroups were defined by ASBI: low symptom burden (LSB; ASBI < 25) and high symptom burden (HSB; ASBI ≥ 25). Multivariate Cox models were used to evaluate the maintenance treatment effect within ASBI subgroups adjusting for 9 demographic/c clinical (DC) factors, including ECOG PS and stage of disease. Similarly, maintenance treatment effects within PS 0, 1 subgroups were evaluated.

Results: Controlling for PS and other DC factors, pts with LSB (n = 333) and HSB (n = 131) who received maintenance therapy had improved PFS vs pbo: 5.1 vs 3.9 months (mos) [hazard ratio (HR) 0.49, p < 0.001] for LSB and 3.7 vs 1.9 mos (HR 0.50, p = 0.003) for HSB. LSB pts had improved OS vs pbo (median OS 17.5 vs 11.0 mos, HR 0.65, p = 0.001), but HSB pts did not (median OS 11.8 vs 10.6 mos, HR 1.02, p = 0.92). PS was associated with patient-reported symptoms. PS 0 pts had lower mean LCSS scores than PS 1 pts for fatigue, pain, and ASBI (each p < 0.05). PS subgroup results are similar to the symptom-burden analysis: improved PFS in PS 0, 1 pts and improved OS in PS 0 pts.

Conclusion: NLsNSCLC pts with LSB and HSB at the end of induction therapy experienced significant improvements in PFS with maintenance therapy. This translated into improved OS for LSB pts. These data suggest that maintenance therapy, rather than a break in treatment or “chemo holiday,” is an appropriate treatment strategy for NSqNSCLC pts at successful completion of induction therapy.

Disclosure: All authors have declared no conflicts of interest.

1282P A COMPARATIVE STUDY OF EPIDERMAL GROWTH FACTOR RECEPTOR TYROSINE KINASE INHIBITOR IN TREATMENT OF PATIENTS WITH BRAIN METASTASIS FROM NON-SMALL CELL LUNG CANCER

L. Zhang1, L. Ca½, J. Zhu1
1Thoracic Surgery, Sun Yat-Sen University Cancer Center, Guangzhou, CHINA, 2Radio-Oncology, Sun Yat-Sen University Cancer Center, Guangzhou, CHINA

Purpose: Brain metastasis (BM) presents 20-25% of patients with non-small cell lung cancer (NSCLC). Whole brain radiation therapy (WBRT) is considered as standard therapy along with stereotactic radiosurgery (SRS), or surgical resection (SR) or chemotherapy (CXT). Median survival time ranged from 6.5-10 months for conventional therapy. In this study, we purposed to compare the outcomes of conventional therapy (CVT) combined with or without epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) in the treatment for patients with BM from NSCLC.

Methods: A total of 275 NSCLC patients with BM were treated sequentially between Jan, 1999 and Nov, 2011 according to our institutional protocol. Of these 275 patients, 97 (35%) underwent EGFR-TKI combined with CVT (TKI + CVT) and 178 (65%) underwent CVT. All patients received WBRT. Both treatment groups were similar with regard to age, sex, smoking status, histological subtype, number and size of BM lesions, extracranial lesions and intracranial symptoms.

Results: Median overall survivals (MOS), median progress free survivals (MPFS), median progress free survivals of intracranial lesions (MPFSI) and median progress free survivals of extracranial lesions (MPFSE) were 28.2 (95% CI:22.3-34.1) and 13.7 (95% CI:11.4-15.9) months, 10.9 (95% CI:8.4-13.4) and 6.7 (95% CI:5.1-8.4) months, 18.7 (95% CI:12.6-24.8) and 10.3 (95% CI:8.4-12.3) months, 11.1(95% CI:9.1-13.1) and 7.9 (95% CI:6.2-9.5) months for TKI + CTV and CTV groups, respectively. With TKI + CTV group, improved outcome was found to be significantly associated with no lymph node metastasis (P = 0.001) and adverse drug reaction (ADR) (P = 0.001) for MOS, MPFS, MPFSE and MPFSI. With CVT group, improved outcome could be associated with age <65yrs (P = 0.038), never smoking (P = 0.047), number of BM lesions <3 (P = 0.018), maximum diameter of lesion <3cm (P = 0.018), no extracranial lesions (P = 0.001), and no lymph node metastasis (P = 0.001). On multivariate analysis for TKI + CTV group, age (P = 0.023), smoking status (P = 0.004), extracranial lesions (P = 0.022), N staging (P = 0.002) and ADR (P = 0.005) retained statistical significance.

Conclusion: Patients with NSCLC and brain metastasis might benefit from treatment of EGFR-TKI in combination with conventional therapy.

Disclosure: All authors have declared no conflicts of interest.

1283P MULTIMODAL STRATEGY MAY IMPROVE SURVIVAL IN NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS (PT) WITH BRAIN METASTASES (BM)

M. Chabret Houd1, C. Le Pechoux1, E. Lanoy1, B. Bouz1, B. Bessey1, B. Roussi1, V. Krou1, F. Villain, FRANCE, 2Radiation, Gustave Roussy Institute, between April 2002 and April 2010. Inclusion criteria were: NSCLC histology, BM and WBRT performed in our institution. Synchronous diagnosis of BM was defined as a delay less than 3 month between NSCLC and BM diagnoses. OS from time of

Disclosure: All authors have declared no conflicts of interest.

Background: BM occur in approximately 50% of all lung cancer. Local treatment of BM consist of whole brain radiation therapy (WBRT), stereotactic radiation surgery (SRS) and or surgical resection. Median overall survival (OS) remain poor: ranges observed in previous study were 4.8-13 months (mos), 2.8-6 and 2-4 m for RPA I, II and III. We evaluated the long-term outcome of NSCLC pts with BM treated by WBRT at least.

Methods: We conducted a retrospective analysis of pts treated at the Gustave Roussy Institute, between April 2002 and April 2010. Inclusion criteria were: NSCLC histology, BM and WBRT performed in our institution. Synchronous diagnosis of BM was defined as a delay less than 3 month between NSCLC and BM diagnoses. OS from time of

Disclosure: All authors have declared no conflicts of interest.

Results: Baseline characteristics were well balanced in these predominantly elderly NSCLC pts (median = 77 yrs, range 42-91). Among all pts, the hazard ratios (HRs) were 0.94 (95% CI 0.81-1.10, P = 0.46) for OS. Pts receiving erlotinib had a better
Oncology, National Hospital Organization Toneyama National Hospital, Toyonaka, JAPAN
5Integrated Oncology, Institute of Biomedical Research and Innovation Hospital, Kobe, JAPAN, 6Department of Thoracic Respiratory Medicine, Keio University School of Medicine, Tokyo, JAPAN

Background: Incidence of elderly patients with advanced non-small cell lung cancer (NSCLC) is increasing, however the treatment for elderly patients is still waiting for the best answer. Although several studies had suggested the advantage of chemotherapy with platinum doublet for elderly patients with advanced NSCLC (e.g. Quesq E, et al., The Lancet 378, 2011), the application of platinum doublet to the elderly is still controversial. To evaluate the efficacy and tolerability of combination chemotherapy with biweekly carboplatin (CBDCa) and paclitaxel (PTXx) for elderly patients with advanced NSCLC, we conducted a multicenter non-randomized open label phase II trial.

Methods: Eligibility criteria were as follows; histologically proven NSCLC, aged 70 years and older, ECOG Performance Status (PS) of 0 to 2, clinical stage IIIb and IV, chemotherapy naive, and adequate organ function. Patients received CBDCa (AUC = 2.5) and PTX (90 mg/m2) on day 1 and 15 every 4-week for up to 6 cycles, until disease progression or intolerable toxicity. The primary endpoint was ORR, and the secondary endpoints were PFS, OS and tolerability.

Results: 60 patients (median age 78 years old, range 70-85) were enrolled. 45 patients were male and 45 were 65 to 70 years. OS PS 0/1/2 were 19/20/4 respectively. The median number of treatment cycle was 3 (1-6). CR/PR/SD/PD were 0/6/38/7.84/3.3% as the best response, giving an ORR of 28.9 % and DCR of 66.7%. Median PFS and OS were 5.3 months (95% CI: 3.1-7.5) and 26.7 months (95% CI: 18.2-31.5), respectively. Grade 3/4 hematomatous toxicities were neutropenia (27%), leucopenia (15%) and anemia (8%). Grade 3 non-hematological toxicities were mucositis reaction (2%), anorexia (3%), infection (10%), thrombosis (2%), fatigue (3%), diarrhea (2%) and gastrointestinal bleeding (3%). Although no grade 4 non-hematological toxicity was observed, one patient died probably due to treatment-related interstitial pneumonitis. The adverse events were relatively mild and manageable.

Conclusions: The combination of biweekly CBDCa (AUC = 2.5) and PTX (90 mg/m2) was effective and well tolerated for elderly patients with advanced NSCLC. (This study was registered at UMIN 000001328)

Disclosure: All authors have declared no conflicts of interest.

NSCLC diagnosis and time of BM diagnosis were estimated using Kaplan-Meier method. Association between delayed WBRT, after at least 2 cycles of chemotherapy (CT) or not, and death was evaluated using multivariable Cox proportional hazards model adjusted by gender, smoking status, histology, and RPA score.

Results: We included 175 consecutive pts: 61% were male, median age was 57 years [range = 27-79], 68% had adenocarcinoma, 15% were never smoked. At first diagnosis of NSCLC, the TNM 2009 stage was mainly IV (68%) and III (21%). 42 % of BM were synchronous and 58% were metachronous. No extracranial disease was observed in 34%, and more than three lesions in 41%. Karnofsky index was >= 70% in 79% of pts. The RPA class was good-I in 13 pts and poor-III in 37 pts. Radical surgery was performed in 23 pts (16%) while 8 pts (6.4%) received SRS. 70% had CT with a median nrb of 1 line [6-1], 31% were treated with anti EGFR therapy. Median OS from NSCLC diagnosis was 18 (95%CI = [15;20]) months. Median OS from BM diagnosis was 9 (95%CI = [7;6,160]) for the whole population, 43 m for RPA class I, 10 m for class II and 2 m for class III. In 26% of the pts, WBRT was delayed and delayed selected WBRT was not associated with survival in multivariable analysis (HR = 1.24 95%CI:0.85-1.80).

Conclusions: Our results suggest that in NSCLC with BM, RPA class II could be easily treated with systemic therapy, with then long survival, selected RPA class III may benefit WBRT and systemic treatment. ALK and EGFR status will be presented.

Disclosure: All authors have declared no conflicts of interest.

Background: VEGF-mediated angiogenesis contributes to NSCLC pathogenesis. RAM is a recombinant human mAb that binds the extracellular domain of the vascular endothelial growth factor receptor 2 (VEGFR-2) and inhibits cancer growth in diverse preclinical models.

Methods: Pts with advanced NSCLC (Stage IIIb not suitable for locoregional therapy or Stage IV) were eligible. Squamous histology and treated brain metastases were allowed. Exclusion criteria included prior bevacizumab, blood vessel invasion, intratumor cavitation, and recent gross hemoptysis. Pts received RAM 10 mg/kg, paclitaxel 200 mg/m2, and carboplatin AUC 6 on Day 1 of a 3-week cycle for up to 6 cycles, followed by maintenance RAM. The primary endpoint was PFS at 6 months (m); secondary/exploratory endpoints were safety, ORR, OS rate at 1 year, PK/PD profiles, and immunogenicity.

Results: 40 pts were treated (15m:25f; median age 60; 39 nonsquamous / 1 squamous); all had discontinued. 39 pts were evaluable for response. 22 of 40 treated pts had an objective response (1 CR, 21 PR; ORR = 55%). 14 pts had a best response of SD. Median PFS was 7.85 m (95% CI: 5.49 m-9.86 m), and the PFS rate at 6 m was 62.5% (90% CI: 48.3%-75.3%); the 1-year survival rate was 74.6% (95% CI: 57.9%-85.4%). 34 of 40 pts (85%) reported an AE at least possibly related to RAM; the most common were fatigue (15%), peripheral neuropathy (33%), nausea (28%), myalgia (23%), and epistaxis (23%). Related AEs of Gr 3 were reported for 15 pts; the most common were neutropenia (5 pts), thrombocytopenia (4 pts), fatigue, febrile neutropenia (3 pts each); peripheral neuropathy and pulmonary embolism (1 pt each). There were 5 pts with a total of 6 Gr 4 related events: febrile neutropenia, pulmonary embolism (2 pts each), neutropenia and thrombocytopenia (1 pt each).

Conclusions: RAM in combination with paclitaxel and carboplatin shows promising efficacy based on the overall disease control rate (CR + PR + SD) reaching 90% and PFS rate at 6 m of 62.5%, and is well tolerated by patients with NSCLC.

Disclosure: D.R. Camidge: I have received research funding from Eli Lilly and Company and honoraria from ImClone Systems. R.C. Doebele: Research Funding: ImClone Systems, Eli Lilly & Co., Pfizer Inc. Honoraria: Boehringer Ingelheim,
Abbott Laboratories, Pfizer Inc Stock: Ariola (<$10,000). M. Ballas: I now have an employment position at Bristol Myers Squibb (BMS), own <10% stock of BMS, and have received honoraria from Eli Lilly/ImClone. My wife owns stock of <10% of Abbott and <10% Novartis and used to be employed by both. T. Jahan: I have received additional research funding from Eli Lilly & Co. for other trials, as well as research funding from Morphophet, Pfizer, and Genentech. I have no speaker or consultant income to disclose. S. Yurasov: Employed by ImClone/Eli Lilly; own Lilly stock. All other authors have declared no conflicts of interest.

1288P

EFFICACY OF THE IRREVERSIBLE EGFR-HR2 DUAL INHIBITOR AFATINIB IN PRETREATED LUNG ADENOCARCINOMA

L. Landi,1, D. Galetti,1, C. Bennati,1, F. Curi,1, R. Chiari,1, G. Metro,1, M. D’Arco,1, A. Marchetti,1, F. Capuzzo,2, L. Ciminà1

1Oncology, Istituto Toscano Tumori, Livorno, ITALY; 2Oncologia Medica, Istituto Tumori Giovanni Paolo II, Bari, ITALY

Background: Although lung adenocarcinoma harboring activating Epidermal Growth Factor Receptor (EGFR) mutations respond dramatically to reversible EGFR tyrosine kinase inhibitors (TKI), all patients (pts) inevitably develop acquired resistance. Afatinib, an irreversible EGFR-HR2 dual inhibitor, demonstrated some activity in Non-Small-Cell Lung Cancer (NSCLC) pts progressing after at least 3 months of EGFR-TKI therapy.

Materials and methods: We analyzed 44 advanced lung adenocarcinoma pts resistant to EGFR-TKI according to criteria used in the LUX-Lung 1 trial (Miller VA, Lancer Oncol 2012) and treated with Afatinib at the daily dose of 40-50 mg in three Italian centers. The drug was given as compassionate use.

Results: Pts included had a median age of 61.6 yr, the majority was female (N = 23/52%), never/former smoker (N = 41/93%), with good PS (0-1; N = 37/84%) and pretreated with > 3 therapy lines (N = 36/81%). EGFR status was assessed in all cases and 35 pts (80%) harbored a mutation in exon 18 (N = 3/6,6%), in exon 19 (N = 19/54,3%), in exon 20 (T790M; N = 2/5,7%) and in exon 21 (N = 11/31,4%). Among the 42 pts evaluable for toxicity, 58% had skin rash (G3 = 4.7%) and 18% diarrhea (G3 = 2.3%). Among the 35 pts evaluable for efficacy, response rate (RR) was 11%, disease control rate (DCR) RR+ stable disease was 65%, median progression free survival and overall survival were 3.5 months and 4.8 months respectively. EGFR resulted mutated in 3 of 4 responders including 1 pt with T790M mutation. In 4 pts in which tumor biopsy was repeated before starting Afatinib therapy only 1 pt had T790M mutation, with no evidence of response.

Conclusions: In “real life” experience Afatinib showed encouraging activity in pretreated NSCLC with manageable toxicity profile.

Disclosure: All authors have declared no conflicts of interest.

1289P

TREATMENTS AND OUTCOME OF NSCLC PATIENTS WHO RECEIVE GEFITINIB FOR MORE THAN THREE YEARS

K. Otsuka1, N. Katakami2, A. Hata2, R. Kaji2, S. Fujita2, K. Nagata1, A. Nakagawa1, R. Tachikawa1, K. Otsuka1, K. Tomii1

1Respiratory Medicine, Kobe City Medical Center, General Hospital, Kobe, JAPAN; 2Integrated Oncology, Institute of Biomedical Research and Innovation Hospital, Kobe, JAPAN

Background: Non-small cell lung cancer (NSCLC) patients harboring epidermal growth factor receptor (EGFR) mutation initially respond well to gefitinib, but most of them revealed acquired resistance after approximately 10 months. However, some patients can obtain clinical benefit from gefitinib for several years. Little is known of them revealed acquired resistance after approximately 10 months. However, some NSCLC patients with EGFR mutation.

Methods: Between July 2002 and September 2011, 18 NSCLC patients received gefitinib for more than three years. We retrospectively evaluated patient characteristics, treatment strategy, prescription period, progression-free survival (PFS), and overall survival (OS) from gefitinib initiation.

Results: Median age was 71 (range: 50-87), male/female = 3/15, All of them had adenocarcinoma, performance status (PS) 0 or 1 / 2 = 17/1, smoking status: never/former =13/5, previous treatment regimen:0/1/2 = 5/8/5, EGFR mutation status: mutated/wild-type/unknown = 7/3/8, mutation site: exon 19 (deletion) / exon 21 (L858R)others = 4/2/1, stage: recurrence/stage IV = 10/8. Five patients still continue gefitinib without disease progression (PD). Among 13 patients with PD, 4 switched to another regimen. 2 received local treatments (metastectomy and stereotactic body radiation therapy) for progressive primary site, 7 continued gefitinib in spite of progressive disease status, and 3 of 7 continued gefitinib with radiotherapy to progressive metastatic sites (brain and bone). Median prescription period, PFS, and OS from gefitinib initiation were 54.0 months (95% confidence interval [CI]: 47.8, 61.7 months), 47.9 months (95%CI: 36.4, 74.9 months), and 80.2 months (95%CI: 62.0, undeterminable months), respectively.

Conclusions: In patients receiving gefitinib over 3 years, median survival was notably over 80 months. Even after PD, multidimensional personalized therapy with continuous gefitinib administration and/or additional local treatment may prolong survival of some NSCLC patients with EGFR mutation.

Disclosure: All authors have declared no conflicts of interest.

1290P

PHASE I TRIAL OF IRREVERSIBLE PAN-ERBB INHIBITOR DACOMITINIB (DAC) IN COMBINATION WITH ALK/MET INHIBITOR CRIZOTINIB (CRIZ) IN PREVIOUSLY TREATED ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC)

P.A. Janné,1 A.T. Shavi,2 G. Giaccone3, D.R. Camidge,4 S.M. Shreeve5, Z. Goldberg,6 Y. Tang,7 B. Solomon8

1Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA, UNITED STATES OF AMERICA; 2Cancer Center, Massachusetts General Hospital, Boston, MA, UNITED STATES OF AMERICA; 3Head, Thoracic Oncology Section, National Cancer Institute, Bethesda, MD, UNITED STATES OF AMERICA; 4Thoracic Oncology, University of Colorado Cancer Center, Aurora, CO, UNITED STATES OF AMERICA; 5Research and Development, Pfizer Oncology, La Jolla, CA, UNITED STATES OF AMERICA; 6Research and Development, Pfizer Oncology, La Jolla, CA, UNITED STATES OF AMERICA; 7Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, AUSTRALIA

Objectives: EGFR T790M and MET amplification are acquired resistance mechanisms to erlotinib and gefitinib. We evaluated the feasibility of combining dac to criz to overcome this resistance.

Methods: Dose escalation was followed by an expansion phase comprising two planned cohorts: A) dac/criz and B) dac followed by dac/criz at progression. Biopsy at study entry was mandatory in the dose expansion cohorts. Dose escalation phase included patients (pts) with advanced NSCLC who had progressed after ≥1 line of chemotherapy or targeted therapy. Expansion phase included pts who had developed acquired resistance to the first generation EGFR tyrosine kinase inhibitors (TKI) erlotinib or gefitinib. Dose escalation of both agents continued until dose limiting toxicity (DLT). Endpoints included safety, best overall objective response rate (ORR), progression free survival, and biomarkers in tumor and blood that are potentially predictive for antitumor activity.

Results: Currently, 30 NSCLC pts have enrolled and are evaluable for safety (dose escalation: 25; expansion: 5). Characteristics: M/F: 13/17; mean age: 57; ECOCO PS 0/1/2 = 7/21/2; Caucasian/Asian: 26/4; never/former smokers: 11/19; prior therapies 1/2 > 3/7/9/14; prior EGFR TKI/crizotinib: 28/5; EGFR mutant/WT: 17/3, ALK-positive (ALK+): 5; ALK-negative: 25; prior EGFR TKI/crizotinib: 28/5; EGFR mutant/WT: 17/3; ALK-positive (ALK+): 5; HER2-positive: 1. DLTs were mucositis (n = 1/6) at dac 30 mg qd/criz 250 mg bid, diarrhea (n = 1/6) at dac 45 mg qd/criz 250 mg bid, and nausea (n = 1/6) at dac 45 mg qd/criz 250 mg qd. The dose used for the expansion phase was dac/criz: 30mg qd/200mg bid. 28 pts were evaluable for response: 2 unconfirmed partial responses (1 EGFR/ALK WT; 1 ALK+), 14 stable disease, 6 progressive disease and 6 indeterminate. Dose escalation is ongoing in both cohorts.

Conclusions: Dac and criz can be combined with a manageable toxicity profile. Clinical activity has been observed in erlotinib, gefitinib and crizotinib treated pts. Dose escalation and correlation with predictive tumor biomarkers including EGFR T790M and MET amplification is underway.

Disclosure: P.A. Janné: Advisory relationship with Boehringer-Ingleheim, Roche, Genentech, Abbott, AstraZeneca, Pfizer, Sanofi and Teva Other remuneration received from LabCorp. A.T. Shavi: Advisory relationship with Pfizer, Astard, Chugai, Novartis and Daiichi-sankyo. Received research funding from AstraZeneca and Novartis. D.R. Camidge: Advisory relationship with Pfizer Honoraria received from Pfizer. S.M. Shreeve: Employed as a Director by Pfizer and has stock ownership with Pfizer. Z. Goldberg: Employed as a Medical Director by Pfizer and has stock ownership with Pfizer. Y. Tang: Employed as a Manager by Pfizer and has stock ownership with Pfizer. B. Solomon: Advisory relationship with Pfizer Received research funding from Pfizer. All other authors have declared no conflicts of interest.
Background: c-Met expression is common in NSCLC tumors and has been implicated in the development of resistance to EGFR inhibitors. Criz is an ALK and MET/HER2 receptor tyrosine kinase inhibitor (TKI). In pre-clinical studies, combining criz with an EGFR inhibitor enhanced anti-tumor activity in NSCLC cell lines that were sensitive or resistant to EGFR inhibition. The phase I portion of a phase I/II study (A8081002; NCT00965731) investigated the combination of E (EGFR TKI) and criz in pts with advanced NSCLC.

Methods: Pts had advanced NSCLC, 1 or 2 prior chemotherapy regimens, and no prior MET-directed therapy. Endpoints included maximum tolerated dose (MTD) determination, safety, and pharmacokinetics (PK). Pts received E 100 mg QD for >27 days before adding criz 150 or 200 mg BID (150 + 200 and 150 + 100, respectively).

Results: As of March 15th 2012, 27 pts had started therapy. Median (range) duration of combination therapy in 150 + 200 (n = 19) was 7 weeks (0.1-28.0); for 200 + 100 (n = 7) was 6.9 weeks (1.9-77.6). Five pts had dose-limiting toxicities (grade [G] 2 or G3) that were manageable and consistent with the known safety profile. Common toxicities reported included G1 or G2 severity. Common TRAEs were diarrhea (73%), rash (62%) and fatigue (46%). Six pts discontinued therapy due to TRAEs (150 + 100: G3 diarrhea, G4 dehydration; and at 200 + 100: G3 dry eye and rash). The most frequent reported TRAEs were rash (46%) and diarrhea (41%). Median time with criz was comparable to 150 mg BID (7 weeks, 95% CI: 6.9-9.7) was 6.9 weeks (1.9-77.6). Five pts had dose-limiting toxicities (G2 or G3) that were manageable and consistent with the known safety profile. Common toxicities reported included G1 or G2 severity. Common TRAEs were diarrhea (73%), rash (62%) and fatigue (46%). Six pts discontinued therapy due to TRAEs (150 + 100: G3 diarrhea, G4 dehydration; and at 200 + 100: G3 dry eye and rash). The most frequent reported TRAEs were rash (46%) and diarrhea (41%). Median time with criz was comparable to 150 mg BID (7 weeks, 95% CI: 6.9-9.7) was 6.9 weeks (1.9-77.6). Five pts had dose-limiting toxicities (grade [G] 2 or G3) that were manageable and consistent with the known safety profile. Common toxicities reported included G1 or G2 severity. Common TRAEs were diarrhea (73%), rash (62%) and fatigue (46%). Six pts discontinued therapy due to TRAEs (150 + 100: G3 diarrhea, G4 dehydration; and at 200 + 100: G3 dry eye and rash). The most frequent reported TRAEs were rash (46%) and diarrhea (41%). Median time with criz was comparable to 150 mg BID (7 weeks, 95% CI: 6.9-9.7).

Conclusions: E plus criz at the MTD was well tolerated, with no unexpected AEs, and showed signs of activity in a pre-treated population. E 100 mg QD plus criz 150 mg BID was defined as MTD. Prescription: S. I. Ou. Advisory relationship with Pfizer and Genentech (both compensated). Received honoraria from Pfizer, Genentech and Lilly. Research funding from Pfizer. K. Eaton: Research funding from Pfizer. A. Argiris: Advisory relationship with Pfizer. Received honoraria from Pfizer. Research funding from Pfizer. G. Ottensoer: Received honoraria from Genentech and Abraxis/Celgene. Research funding from Genentech, Abraxis/Celgene, Pfizer, Tragara, Pharmacyclics, OSI and GSK. F. Robert: Research funding to the University of Alabama at Birmingham. N. Brega: Employed by Pfizer as a Director. Hold Pfizer stock. T. Usari: Employed by Pfizer as a statistician. Holds Pfizer stock. W. Tan: Employed by Pfizer. Holds Pfizer stock. All other authors have declared no conflicts of interest.
DEFINITIVE THORACIC CHEMORADIOThERAPY IN NON-SMALL CELL LUNG CANCER PATIENTS WITH SOLITARY BRAIN METASTASIS

C. Parlik1, O.C. Guker1, O. Ozcylik2
1Department of Radiation Oncology, Basvent University Adana Medical Faculty, Adana, TURKEY; 2Medical Oncology, Basvent University Faculty of Medicine/Adana Uygulama Ve Arastirma Mor., Adana, TURKEY

Background: The aim of the study was to evaluate the impact of definitive thoracic chemoradiotherapy on outcomes in non-small cell lung cancer (NSCLC) patients with solitary brain metastases.

Materials and methods: Fifty four medically fit NSCLC patients with isolated BM were retrospectively evaluated. Patients were staged with PET-CT besides conventional staging tools. TRT to a total dose of 66 Gy in 2 Gy fx was delivered with 2 cycles of concomitant cisplatin-based chemotherapy (CT) following surgery + 30 Gy whole-brain RT (WBRT) (n=18), 30 Gy WBRT + 15 Gy boost (n=22), or 30 Gy WBRT + stereotactic radiosurgery (SRS) (n=14) for their BM. Response evaluation was done according to EORTC RECIST criteria.

Results: Pretreatment patients characteristics were as given in Table 1. Overall the treatment was well-tolerated and all patients received planned TRT and 2 cycles of CT. A median follow-up of 15.2 months (4.4-42.3), median overall, locoregional progression free and progression free survivals were 12.2, 8.5 and 5.9 months.

Univariate analyses revealed that patients receiving WBRT + SRS for BM (P < 0.001), performance status of ECOG 0-1 (P < 0.001), older than median age of 50 (p:0.031) no weight loss (p:0.001) had better survival. Multivariate analysis based on these factors demonstrated that all factors except age retained their independent prognostic values (p <0.05 for each).

Conclusion: Results of this study demonstrated that definitive T-CRT following WBRT + SRS for BM could improve poor prognosis in NSCLC patients with solitary BM. However, to make a firm conclusion, these findings should be validated by further prospective studies with larger cohorts.

Pre-treatment patients characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Surgery + WBRT</th>
<th>WBRT + BOOST</th>
<th>WBRT + SRS</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>52.3 (33-68)</td>
<td>50.4 (32-66)</td>
<td>48.3 (38-62)</td>
<td>0.57</td>
</tr>
<tr>
<td>Sex [N, %]</td>
<td>11 (20.4) 7 (13.0)</td>
<td>14 (25.9) 8 (14.8)</td>
<td>10 (18.5) 4 (7.4)</td>
<td>0.82</td>
</tr>
<tr>
<td>Female Male</td>
<td>11 (20.4) 7 (13.0)</td>
<td>14 (25.9) 8 (14.8)</td>
<td>10 (18.5) 4 (7.4)</td>
<td>0.82</td>
</tr>
<tr>
<td>Performance status</td>
<td>14 (25.9) 4 (7.4)</td>
<td>11 (20.4) 7 (13.0)</td>
<td>11 (20.4) 3 (5.6)</td>
<td>0.25</td>
</tr>
<tr>
<td>Histology [N, %]</td>
<td>11 (20.4) 7 (13.0)</td>
<td>14 (25.9) 8 (14.8)</td>
<td>5 (9.3) 9 (16.7)</td>
<td>0.22</td>
</tr>
<tr>
<td>Squamous cell</td>
<td>Adenocarcinoma</td>
<td>T Stage T1 T2 T3</td>
<td>3 (5.6) 4 (7.4)</td>
<td>3 (5.6) 4 (7.4)</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>(9.3) 6 (11.1)</td>
<td>(5.6) 12 (22.2)</td>
<td>(13.0) 3 (5.7)</td>
</tr>
<tr>
<td></td>
<td>N Stage N0 N1 N2</td>
<td>6 (11.1) 5 (9.3)</td>
<td>3 (5.6) 7 (13.0)</td>
<td>2 (3.7) 3 (5.7)</td>
</tr>
<tr>
<td></td>
<td>N3</td>
<td>3 (5.6) 1 (1.9)</td>
<td>(9.3) 8 (14.8)</td>
<td>(13.0) 3 (5.6)</td>
</tr>
<tr>
<td>≥5% weight loss</td>
<td>9 (16.7) 9 (16.7)</td>
<td>12 (22.2) 10</td>
<td>5 (9.3) 7 (16.7)</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Disclosure: All authors have declared no conflicts of interest.

ROLE OF CT-GUIDED LUNG BIOPSY IN THE ERA OF PERSONALIZED MEDICINE — AN EFFECTIVE AND SAFE TISSUE ACQUISITION FOR SPECIFIC SUBYPTING AND MOLECULAR DIAGNOSIS OF NON-SMALL CELL LUNG CANCER

S. Heiße1, C. Chung2, S. Lin3
1Division of Pulmonary Medicine, Department of Internal Medicine, Taipei Medical University Hospital, Taipei, Taipei, TAIWAN; 2Department of Pathology, Taipei Medical University Hospital, Taipei, Taipei, TAIWAN

Purpose: Recent several phase III clinical trials have demonstrated that determination of histological subtypes and molecular genotypes of non-small cell lung cancer (NSCLC) is very crucial in personalized medicine. One of the most debated in this issue is how to achieve optimal tumor samples. We sought to examine the efficacy, safety of computed tomography (CT)-guided lung biopsy and the suitability of the obtained tumor samples for epidermal growth factor receptor (EGFR) mutational testing.

Patients and methods: Clinicopathological data of 305 consecutive patients undergoing CT-guided core biopsies for lung lesions were retrospectively reviewed for the period between January 2007 and December 2011 under the approval of institutional review board. Additionally, 128 residual tumor tissues were examined for the suitability, efficacy and results of EGFR mutation analysis.

Results: Among a total 321 CT-guided lung biopsies, 93% provided adequate tissues for histological analyses, with 72% as malignancy and 26% as benign diagnoses. The sensitivity and specificity of malignancy diagnosis were 92% and 100%, respectively. As to the complications, the rates of procedure-related immediate and delayed pneumothorax, hemoptysis and mortality were 28%, 10%, 3%, and none, respectively. Only 6% (20/321) of lung biopsies led to pneumothorax needing a chest tube-guided air drainage, significantly associated with the number of biopsy cuts (OR = 3.12, 95% CI = 1.39-7.03, p = 0.006). Of 203 diagnoses as NSCLC category, up to 91% were specifically subtyped as adenocarcinoma (79%) and squamous cell carcinoma (12%), and the remaining were not otherwise specified (9%). In total, 128 residual tumor tissues with diagnosis of NSCLC were submitted for EGFR mutational testing under the clinicians’ request, and 126 (98.4%) were eligible after pathologist’s review. Conclusive results of EGFR tests were achieved in 124 (98.4%) of 126 identified samples, indicating 63% with EGFR exon 18-21 mutations.

Conclusion: We demonstrate that CT-guided lung biopsy provides adequate tissues for histological analyses with high sensitivity and specificity of malignancy diagnosis, and for subtyping NSCLC and EGFR molecular testing; its complications are limited and manageable.

Disclosure: All authors have declared no conflicts of interest.

EVALUATION OF WHITE BLOOD CELL GROWTH FACTOR (WBCGF) USE IN METASTATIC NON-SMAL CELL LUNG CANCER (NSCLC) PATIENTS

J.R. Hoverman1, S. Sheth, M. Clayton, J. Garay, R. Beveridge
1The Level I Pathways Task Force, The US Oncology Network/McKesson Specialty Health, The Woodlands, TX, UNITED STATES OF AMERICA

Background: Data suggest that chemotherapy regimens administered to NSCLC patients in the metastatic setting is not typically associated with febrile neutropenia rates of 20% or greater, therefore, use of WBCGF in this setting should be minimal. National guidelines recommend reduction of chemotherapy dosing in these patients. Our objective was to evaluate the current US Oncology

Downloaded from https://academic.oup.com/annonc/article-abstract/23/suppl_9/ix400/218620 by guest on 20 August 2018
Network utilization of WBCGF in the metastatic setting to determine current practice and associated costs in this palliative chemotherapy setting.

Methods: We retrospectively identified metastatic NSCLC patients between 7/2006 and 6/2011 using the US Oncology Network EHR database (KnowMed). Secondary diagnoses and clinical trials were excluded. Chemotherapy and WBCGF utilization was determined by the number of patients assigned to a 1st or 2nd (and beyond) line of therapy (LOT) during the study period.

Results: During this timeframe, 10,374 patients (female: 44%; median age 67) diagnosed with metastatic NSCLC were identified. Of these, 3284 patients received WBCGF with chemotherapy; where, 2825 patients (33%) were administered 1st LOT and 459 patients (27%) were administered 2nd LOT. When reviewing the chemotherapy regimens assigned (regardless of WBCGF administration), the most commonly utilized regimens were: Carboplatin + Paclitaxel +/- Bevacizumab, Pemetrexed containing regimens, Docetaxel containing regimens, Gemcitabine containing regimens, and Vinorelbine. The average estimated cost for these chemotherapy regimens (Medicare Allowable 1Q2012) is $2589/cycle; the average estimated cost of WBCGF usage in the metastatic setting was $1889/dose (Medicare Allowable 1Q2012).

Conclusion: The American Society of Clinical Oncology has recently identified two opportunities to reduce the cost of care without adversely affecting outcomes (i.e., ineffective chemotherapy at the end of life; the use of WBCGF in palliative chemotherapy where dose reduction is an option). These insights in this study of NSCLC. These data indicate there is an opportunity to address 40% of the drug costs of NSCLC by the judicious use of protocols using dose reduction as a strategy.

Disclosure: J.R. Howerman: I am a medical director for Innoment Oncology. R. Beveridge: I am EVP, Medical Director for McKesson Specialty Health. All other authors have declared no conflicts of interest.

**1298P** ANALYSIS OF ERLOTINIB-RELATED SKIN TOXICITIES FROM JAPANESE POST-MARKETING SURVEILLANCE (POLARSTAR) IN 9,909 NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS (PTS)

Y. Kiyohara1, N. Yamazaki2, A. Seki3, M. Fukuko4

1Department of Dermatology, Shizuoka Cancer Center, Nagazumi, Shizuoka, JAPAN, 2Department of Dermatologic Oncology, National Cancer Center Hospital, Tsukiji, Chuo-ku, Tokyo, JAPAN, 3Pharmacovigilance Department, CHUGAI PHARMACEUTICAL CO., LTD., Muromachi, Chuo-ku, Tokyo, JAPAN, 4Medical Oncology, Iizumi Municipal Hospital/Cancer Center, Iizumi, CITY, JAPAN

Background: Skin toxicities (rash) are the most common adverse reaction associated with erlotinib. Most cases of rash are mild or moderate using appropriate rash management (RM). RM is very important for keeping good QOL during erlotinib treatment. Though steroids are commonly used as RM, the precise efficacy and the appropriate way of administration have not yet been fully established. Establishment of appropriate management of rash is necessary to continue erlotinib treatment for obtaining maximum benefit. In this surveillance, we analyzed RM clinical practice from 9,909 NSCLC pts.

Methods: From Dec 2007 to Oct 2009, all recurrent/advanced NSCLC pts in Japan treated with erlotinib were enrolled into this surveillance. The observation period was 12 months and all adverse events were collected. Erlotinib related rash, interventions for the symptoms and outcomes of the interventions were analyzed.

Results: A total of 9,909 pts were evaluated. Rash was occurred in 67.4% (6674) pts. Grade 1 / 2 / 3 rash was observed (26.8%, 32.4%, and 7.2%). Frequency and the median time to onset from erlotinib administration to per each acneiform rash, dry skin, and paronychia were 60.9%, 9.0 days, 7.4, 16.0 days, and 8.6%, 34.0 days, respectively. The most common RM was steroids in 75.0% of acneiform rash. In the patients who were treated with steroids for their acneiform rash, more than 75% of them started steroids within 4 days from onset date. Median time from steroids start to recovery in pts whose steroids were started after 0-1 days / 2-6 days / 7-13 days / 14-20 days / 21 days or later from rash observed were 35.0 days / 39.0 days/ 40.0 days/ 64.0 days/ 103.5 days, respectively. In the patients who are initiated from steroids within 4 days from onset date. Median time from steroids start to recovery in pts whose steroids were started after 0-1 days / 2-6 days / 7-13 days / 14-20 days / 21 days or later from rash observed were 35.0 days / 39.0 days/ 40.0 days/ 64.0 days/ 103.5 days, respectively. The most common RM was steroids in 75.0% of acneiform rash. In the patients who were initiated from steroids within 4 days from onset day. On the other hand, Median time to recovery from rash onset was 40.0 days in the pts who were initiated with steroids of strong or strongest potency.

Conclusion: Earlier initiation of management for rash with more than strong topical steroids achieves faster improvement.

Disclosure: Y. Kiyohara: Chugai, Takeda, Merck Serono,Bristol-Myers Squibb, GlaxoSmithKline/advisory board, N. Yamazaki: Chugai, Takeda, Merck Serono, Bristol-Myers Squibb, GlaxoSmithKline/advisory board, A. Seki: corporate-sponsored research. All other authors have declared no conflicts of interest.
Disclosure: B. Besse: Received grants from Roche. H. Senellart: Attended advisory boards. F. Barlesi: Attended advisory boards for Roche. Received research funding from Roche. E. Dansin: Attended advisory boards for Roche, Lilly and Boehringer-Ingelheim. M. Perel: Attended advisory boards for Roche, Pfizer, Lilly and Boehringer-Ingelheim. D. Moro-Sibilot: Attended advisory boards for Roche, Pfizer and Lilly. Received research funding from Roche, Pfizer, Lilly, Astra Zeneca and BIF. Substantive Relationships with Roche, Pfizer, Lilly, Astra Zeneca and BIF. All other authors have declared no conflicts of interest.

**1300P**

**HIGH EXPRESSION OF BAP1 IS BIOMARKER OF BETTER PROGNOSTIC IN ADVANCED NON–SMALL CELL LUNG CANCER PATIENTS**

Y. Zuo1, Z. Shen2

1Department of Respiration Medicine, Lianshu People’s Hospital, Lianshu, Jiangsu, CHINA, 2Department of Oncology, Shanghai 6th People’s Hospital, Shanghai Jiao Tong University, Shanghai, CHINA

Background: Non small cell lung cancer (NSCLC) is the leading worldwide source of cancer-related deaths. Although some drugs targeting EGFR mutations were developed, most of advanced NSCLC is still incurable. New targets for anticancer drugs are demanded. SRCA1-associated protein-1 (BAP1) is a component of the ubiquitin proteasome system (UPS). The UPS has emerged as a potential target for anticancer drugs. The expression of BAP1 protein in patients with NSCLC has not been reported to date.

Methods: Here, we assessed BAP1 expression by Western blot in 103 cases patients with advanced NSCLC to investigate the impact of BAP1 on survival.

Results: Our data revealed 49 (47.5%) patients were classified as high expression of BAP1. Squamous cell carcinomas were more likely to be BAP1 high expressers compared to adenocarcinomas (55.8% vs. 32.3%, p = 0.001). High BAP1 expression was associated with lymph node metastasis (p = 0.008) as well as remote metastasis (p = 0.012) and was not associated with other clinical or pathological characteristics. In Kaplan-Meier survival analysis showed that patients with high BAP1 expression had a longer median survival compared to lower expressers (23.2 vs. 14.7 months, p = 0.021) especially in the subset of squamous tumors (27.3 vs. 13.1 months, p = 0.013). Multivariate analysis revealed that high BAP1 expression was an independent lower risk for all 103 patients (HR = 0.61, 95% CI 0.32-0.71, p = 0.003).

Conclusions: BAP1 may be a useful prognostic factor of NSCLC patients and potential target for anticancer drugs.

Disclosure: All authors have declared no conflicts of interest.

**1301P**

**FINAL ANALYSIS OF RANDOMIZED PHASE II TRIAL OF CARBOPLATIN COMBINED WITH WEEKLY PACLITAXEL (CP) AND DOCETAXEL ALONE (D) IN ELDERLY PATIENTS (PTS) WITH ADVANCED NON–SMALL CELL LUNG CANCER (NSCLC): NJLGC 0801**

T. Harada1, M. Maemondo2, S. Sugawara3, A. Inoue4, K. Usui5, M. Ando6, T. Morita7, Y. Ma8, A. Gennia9, T. Nukiwa10

1Center for Respiratory Diseases, Hokkaido Social Insurance Hospital, Sapporo, JAPAN, 2Department of Respiratory Medicine, Miyagi Cancer Center, Natori, JAPAN, 3Department of Respiratory Medicine, Sendai Kousei Hospital, Sendai, JAPAN, 4Department of Respiratory Medicine, Tohoku University, Sendai, JAPAN, 5Division of Respiratory Medicine, NTT Medical Center Tokyo, Tokyo, JAPAN, 6Division of Respiratory Medicine, Teikyo University School of Medicine, Ibaraki, JAPAN, 7Division of Respiratory Medicine, Iwate Prefectural Central Hospital, Morioka, JAPAN, 8Internal Medicine, Nippon Medical School, Tokyo, JAPAN, 9President, South Miyagi Medical Center, Miyagi, JAPAN

Background: Standard first-line chemotherapy for elderly NSCLC pts has been considered as a monotherapy with vinorelbine or gemcitabine. D has been considered as an alternative option for this population in Japan (WITOG9904, ICO 2006). Meanwhile, we have shown the high efficacy of CP for elderly pts (NJLGC0403, Oncol Ann 2010). Thus we compared the two regimens to select a proper candidate for future phase III trial.

Methods: Eligible pts were aged 70 years or older with newly diagnosed stage IIIIB/IV NSCLC; ECOG performance status 0-1; adequate organ function; written informed consent. Pts were randomized to receive carboplatin (AUC 6) on day 1 and paclitaxel (70mg/m2 on day 1, 8, and 15) every 3 weeks for 4 weeks or D (60mg/m2 on day 1) every 3 weeks. The primary endpoint was overall response rate (ORR), and secondary endpoints were progression-free survival (PFS), overall survival, and toxicity profile. Assuming that ORR of 40% would be potential usefulness while ORR of 20% would be the lower limit of interest, 40 pts in each arm were required if expect 10% loss to follow up.

Results: Between July 2006 and September 2010, 84 pts were enrolled and 41 pts in CP arm and 42 pts in D arm were eligible (median age, 76 years; 75% male; 72% stage IV). Median treatment cycle was 4 in each arm (CP, range 1-6; D, range 1-8). ORRs were 54% (95%CI: 39-69%) and 24% (95%CI: 11-37%) in the CP and D arm, respectively. With a median follow-up of 27.6 months, median PFS were 6.6 and 3.5 months in the CP and D arm, respectively (P = 0.0005) and median survival time were 14.3 and 13.8 months in the CP and D arm, respectively (P = 0.24). Grade 3 or severer toxicities were as follows: neutropenia (CP: 56% and D: 7%), anemia (CP: 15% and D: 7%), thrombocytopenia (CP: 10% and D: 0%), infection (CP: 20% and D: 25%). One treatment-related death due to neutropenia, pneumonia, and lethal arrhythmia occurred in D arm.

Conclusions: The platinum doublet CP achieved higher activity with less toxicity profile for elderly pts with advanced NSCLC compared to monotherapy with D. The superiority of CP to the monotherapy in this trial is consistent with results of recent IFCT-0501 trial (Lancet 2011).

Disclosure: M. Maemondo: Makoto Maemondo receives honoraria from Sanofi. S. Sugawara: Shunichi Sugawara receives honoraria from Sanofi. A. Inoue: Akira Inoue receives honoraria from Sanofi. All other authors have declared no conflicts of interest.

**1302P**

**CLINICAL IMPACT OF PRESENCE AND TYPE OF KRAS MUTATION IN A POPULATION OF EGFR WILD TYPE (WT) ADVANCED NON–SMALL CELL LUNG CANCER (NSCLC) PATIENTS (PTS) TREATED WITH PLATINUM-BASED CHEMOTHERAPY: A RETROSPECTIVE ANALYSIS**

G. Metro1, S. Duranti2, V. De Angelis1, R. Chiari1, C. Bennis1, M.F. Currà1, D. Galliarielli2, V. Ludovini1, V. Minotti1, L. Cirino2

1Medical Oncology, Santa Maria della Misericordia Hospital, Perugia, ITALY, 2Medical Oncology, Regina Elena National Cancer Institute, Roma, ITALY

Background: In this retrospective analysis we assessed whether KRAS mutation would affect the clinical outcome of EGFR WT advanced NSCLC pts treated with a first-line platinum-based chemotherapy. Moreover, the effect of specific mutant KRAS was evaluated.

Methods: One hundred and ninety-five EGFR WT, advanced NSCLC pts were included in the analysis. Study pts were treated at the Medical Oncology of the Perugia Hospital from Jan 2005 to March 2012. EGFR (exons 18 to 21) and KRAS (codons 12, 13 and 61) genes were amplified by nested PCR and sequenced in both sense and antisense directions.

Results: Median age was 60 years (29-81); 181 pts (92.8%) were PS 0 or 1; 155 pts (79.4%) belonged to the non-squamous subtype and 39 pts (20.0%) were never-smokers. Treatment was as follows: platinum + a third generation agent in 103 pts (52.8%); platinum + pemetrexed in 81 pts (41.6%); platinum-based doublet + bevacizumab in 11 pts (5.6%). Seventy-five pts (38.4%) were KRAS mutant (MUT), of which 60 pts at codon 12 (COD 12 MUT), 12 pts at codon 13 (COD 13 MUT) and 3 pts at codon 61 (COD 61 MUT). The most common amino acid changes found were: Gly12Cys (29 pts), Gly12Val (11 pts) and Gly13Cys (10 pts). In the whole study population, 69 pts (33.3%) responded to treatment and 62 pts (31.7%) achieved stable disease, for a disease control rate of 67.0%. At a median follow-up of 14 months (2-102), median progression-free survival (PFS) and overall survival (OS) were 6.2 and 21.6 months, respectively. When analyzed according to KRAS mutation status, a significantly shorter PFS was noted for the EGFR WT/KRAS MUT subgroup (n = 75) compared with the EGFR WT/KRAS WT population (n = 120) [5.1 vs 6.6 months, respectively, P = 0.02; HR = 1.43 (95% CI, 1.05 to 1.95)]. Similarly, a significant difference was observed between the two groups in terms of OS [137 vs 26.1 months, respectively, P = 0.02; HR = 1.56 (95% CI, 1.06 to 2.30)]. In the EGFR WT/KRAS MUT subgroup, OS for COD 12 MUT, COD 13 MUT and COD 61 MUT was 17.2, 10.2 and 8.0 months, respectively, P = 0.17. Multivariate analysis for PFS and OS confirmed that KRAS mutation was an independent predictor of poorer survival (PFS), overall survival, and toxicity profile.

Conclusions: EGFR WT/KRAS MUT pts appear to experience a less favorable prognosis compared with the EGFR WT/KRAS WT genotype, with a significant difference in clinical outcome according to the mutant codon of KRAS.

Disclosure: All authors have declared no conflicts of interest.
**1303P** COST EFFECTIVENESS OF PEMETREXED/CISPLATIN (Pem/cis) IN THE TREATMENT OF ADVANCED, NON-SQUAMOUS, NON-SMALL CELL LUNG CANCER (NSQNSCLC) PATIENTS

K.B. Winfree1, M. Shah2, P. Peterson3, S. Gruschkus2, M. Eaddy2, M. Green2

1Global Health Outcomes Oncology, Eli Lilly and Company, Indianapolis, UNITED STATES OF AMERICA,
2Oncology, Xcenda AmersourceBergen Consulting Services, Palm Harbor, FL, UNITED STATES OF AMERICA,
3Oncology Statistics, Eli Lilly and Company, Indianapolis, IN, UNITED STATES OF AMERICA

**Purpose:** Pem/cis is indicated for 1st line therapy in patients (pts) with advanced, nsqNSCLC. Data from community practices provide an opportunity to evaluate the cost effectiveness (CE) of Pem/cis relative to other 1st line regimens.

**Methods:** Advanced nsqNSCLC pts receiving 1st line therapy with Pem/cis, carboplatin/paclitaxel + bevacizumab (C/P + B), or carboplatin/paclitaxel (C/P) from 2006–2009 were identified through EMRs of 20 large US community oncology practices. Pts were matched by stage, ECOG performance status (PS), gender, age, and index year. Progression-free survival (PFS) / overall survival (OS) were calculated and treatment effect was assessed via Kaplan-Meier and Cox regression analyses. Costs included chemotherapy, supportive care, and medical services. To evaluate CE, differences in costs/survival were calculated. Bootstrapping was used to estimate 95% confidence intervals (CIs) for mean differences and probability of falling within quadrants of CE plane.

**Results:** Each comparison had 78 matched pairs. Mean age was 64.1, 59.0% were male and 78.2% had PS = 0/1. Median PFS for pts treated with Pem/cis (128 days) was significantly longer than those treated with C/P + B (112 days; P = 0.007) or C/P (105 days; P = 0.004). Pts treated with Pem/cis had higher median OS, however not significant. Analyses of costs/PFS and costs/OS revealed greater effectiveness with less cost for Pem/cis compared to C/P + B (Tables).

**Conclusions:** Pts treated with Pem/cis experienced a significant PFS benefit and a trending OS benefit compared to C/P + B and C/P pts. Compared to C/P + B, Pem/cis yielded greater effectiveness with less cost.

**Disclosure:** K.B. Winfree: I am an employee of and have stock ownership in Eli Lilly and Company. M. Shah: Eli Lilly and Company sponsored this research study. P. Peterson: I am an employee of and have stock ownership in Eli Lilly and Company. S. Gruschkus: Eli Lilly and Company sponsored this research study. M. Eaddy: Eli Lilly and Company sponsored this research study. M. Green: On 3/16/12 I served as moderator for a Lilly Global Adv Board per my employment with Xcenda. Consistent with Lilly rules, the payments made to Xcenda for services will appear on the Lilly website delineating payments to physicians for services to Lilly.

---

**1304P** CHARACTERISTICS OF 982 LUNG CANCER PATIENTS IN SERBIA ACCORDING TO THE WHO/IASLC CLASSIFICATION OF LUNG CANCERS AND SUBSEQUENT TREATMENT – AVATAR EPIDEMIOLOGY STUDY

D. Jovanovic1, N. Secer2, Z. Murzezn2, M. Rancic, V. Kacar-Kukic1, M. Velenovic2, A. Tepavac3, E. Budicin1, Z.G. Andric2, N. Vukobradovic Djoric3

1Institute of Lung Diseases, Clinical Center of Serbia, Belgrade, SERBIA, 2Clinic for Pulmonary Oncology - Department for Chemotherapy, Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica, SERBIA, 3Medical Oncology, KBC Bezanjicka Kosa, Belgrade, SERBIA, 4Clinic for Pulmonary Oncology, Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica, SERBIA, 5Medical, Roche, Belgrade, SERBIA

**Introduction/background:** The purpose of this prospective study, conducted over 3 months period, was to analyse demographic and clinicopathological features of lung cancer patients in Serbia, and subsequent treatment approach as well.

**Material and methods:** The data on lung cancer patients were collected based on specific questionnaire at 4 major centers in Serbia. An analysis of demographic and clinical/ histological features with subsequent treatment was performed in 982 patients (aged over 19 years).

**Results:** Male to female ratio 709 (72%): 273 (28%), 46% aged ≥ 60 years. Majority were current smokers (68%) and ex-smokers (21%), 11% non-smokers. NSCLC was diagnosed in 80% (789), and SCLC in 19 %. Among NSCLC patients, 71.6 % had stage IIIb and IV. Most common histological subtype was adenocarcinoma (46%), squamous cell carcinoma - 44%, large cell - 4% and the rest NOS and rare subtypes. Neoadjuvant therapy was applied in 8%, 19% were operated: 64% of them received adjuvant chemotherapy; Most common adjuvant regimens were PE (65%) and platinum/gemcitabine (30%). First line chemotherapy was applied in 91% of stage IIIb and IV NSCLC patients: platinum/etoposide-51% and platinum/gemcitabine-45% were most frequently applied. EOCG PS 0 and 1, was noted in 92%. Second line chemotherapy was given to 27% of patients who received 1st line therapy. Most common 2nd line regimens were platinum/gemcitabine (35%), platinum/taxanes (18%), platinum/vinorelbine (13%) and taxanes monotherapy (12.5%). Only 8% received pemetrexed or erlotinib. Almost all 2nd line treated patients (93%) had good ECOG PS 0 and 1. Third line chemotherapy was applied in 22% of those who received 2nd line.

**Conclusions:** This is the largest series of lung cancer patients in Serbia, analyzed by both, patient characteristics and therapy regimens. Compared with previous similar analysis from 2009, it can be concluded the number of NSCLC patients is increasing, especially in stage IIIb and IV (1.5% per year). Adenocarcinoma rate is also increasing (41% in 2009 vs 45% in 2011). Regarding treatment, we can conclude there is no major progress in treatment options in Serbia.

**Disclosure:** All authors have declared no conflicts of interest.

---

**1305P** FACTORS PREDICTING BRAIN METASTASES IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

S. Hsieh1, C. Chung1, H.E. Liu2

1Division of Pulmonary Medicine, Department of Internal Medicine, Taipei Medical University Hospital, Taipei, TAIWAN, 2Division of Hematology and Oncology, Department of Internal Medicine, Department of Medicine, Wanfang Hospital, Taipei Medical University, Taipei, TAIWAN

**Purpose:** Brain metastases (BM), a common complication of non-small cell lung cancer (NSCLC), usually lead to a poor prognosis. Recent advances in BM therapy modestly prolong the survival after BM diagnosis in a subset of patients. Selection of treatment modalities for BM is based largely on the number of BM, BM-related symptoms and patient’s functional performance status. Therefore, early dection of BM in high-risk patients is crucial. In this study, we sough to elucidate the factors predicting BM.

**Methods and patients:** Medical records of patients with stage 1-4 NSCLC were retrospectively reviewed for the period between January 2006 and December 2011 under the approval of the joint institutional review board. Clinical demographic data,
histology, stage of disease, presence of BM, survival were collected and analyzed. A multivariate logistic regression model was used to identify the predictors of BM.

Results: Among 596 NSCLC patients with a mean follow-up time of 12.5±12.5 months and a mortality rate of 62% at the last follow up, 187 (31%) experienced BM during their disease course. The accumulative incidence of BM was higher in patients with adenocarcinoma (ADC) than those with squamous cell carcinoma (SCC) (36% vs 13%, p < 0.001). On multivariate analysis, female, age ≥ 60 years, ADC and stage IIIb/IV were significantly associated with BM (OR = 1.67, 95% CI = 1.06-2.63, p = 0.025; OR = 1.9, 95% CI = 1.28-2.78, p = 0.001, and OR = 2.67, 95% CI = 1.35-5.26, p = 0.017, and OR = 3.94, 95% CI = 2.15-7.13, p < 0.001, respectively). The incidence of BM in stage IIIb/IV NSCLC patients was 36% and varied from 14% to 59% in patients with or without identified risk factors. Specifically, ADC patients with age less than 60 years were more likely to experience BM than the elder with SCC (OR = 5.46, 95% CI = 2.79-10.71, p < 0.001). Additionally, prolonged survival after diagnosis of lung cancer heightened the risk of BM; its incidence was 42%, 54% and 64% in patients who survived longer than 3, 12 and 24 months, respectively.

Conclusion: We find that gender, age and histological subtype are independent factors predicting BM in NSCLC patients and suggest identification of patients at high risks for BM might help detect BM earlier and facilitate the design of clinical trials aimed at the prevention of BM.

Disclosure: All authors have declared no conflicts of interest.

INITIAL REPORT OF COHORT STUDY IN PATIENTS WITH NON-SMALL-CELL LUNG CANCER (NSCLC) WHO WERE TREATED WITH 1ST- LINE PLATINUM-BASED CHEMOTHERAPY (SAPPHIRE STUDY)

Y. Naito1, K. Kishi2, K. Yoshi3, Y. Goto4, Y. Ohashi5, H. Kunitoh6
1Dept. of Hematology and Medical Oncology, National Cancer Center Hospital East, Kashiwa, JAPAN, 2Dept. of Respiratory Medicine, Toranomon Hospital, Tokyo, JAPAN, 3Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, JAPAN, 4Department of Respiratory Medicine, Graduate School of Medicine, University of Tokyo, Tokyo, JAPAN, 5Department of Biostatistics, School of Public Health, University of Tokyo, Tokyo, JAPAN, 6Department of Respiratory Medicine, Mitsu Memorial Hospital, Tokyo, JAPAN

Background: Although 2nd-line chemotherapy comprises the standard of care for NSCLC, not every patient could receive one. How many and why did they miss the opportunity are not fully investigated.

Methods: We prospectively registered consecutive patients with NSCLC treated with platinum-based 1st-line therapy from April 2010 to September 2011 from 30 institutions in Japan. Baseline characteristics, regimens and responses for the 1st-line therapy, whether the patients received 2nd-line chemotherapy or not, and if not treated, the reason was recorded. This study was supported by the Public Health Research Center Foundation CSPOR.

Results: A total of 866 patients were registered. Patient characteristics were: median age, 65 (24-80); female patients, 27.5%; ECOG PS 0 or 1, 91.6%; adenocarcinoma, 69.6%; squamous cell carcinoma, 20.1%; never smoker, 20.1%; EGFR activating mutation positive, 10.2%. Maintenance chemotherapy was administered to 28.9% of patients whose disease did not progress during the course of 1st-line chemotherapy. Among 592 patients with at least 6 months of follow-up, 193 were excluded (129 PD during the course of 1st-line chemotherapy, 20 ongoing 1st-line chemotherapy, and 44 others). The remaining 399 patients were analyzed with regard to administration of 2nd-line chemotherapy. A total of 135 patients (33.8%) did not receive 2nd-line chemotherapy, and the reasons were: without disease progression, 42 (31.1%); declined PS, 55 (40.7%); patient refusal, 20 (14.8%); death of any cause, 5 (3.7%). Therefore, approximately 20% of patients missed their opportunity to receive appropriate 2nd-line chemotherapy during follow-up period after completion of effective 1st-line therapy.

Conclusion: This is the largest prospective observational study exploring the proportion and the reasons for NSCLC patients not receiving 2nd-line chemotherapies. Further investigations to identify predictive factors for ‘missing the opportunity for 2nd-line chemotherapy’ are underway.

Disclosure: All authors have declared no conflicts of interest.

EFFECTIVENESS OF ERLOTINIB TREATMENT IN K-RAS WILD TYPE LUNG ADENOCARCINOMAS – RESULTS OF A HUNGARIAN OBSERVATIONAL COHORT STUDY (MOTIVATE)

G. Ostoros1, V. Sárosi2, G. Losonczi3, J. Strauss4, E. Toina5, L. Molnár6
1Department VIII, National Körányi Institute of Pulmonology, Budapest, HUNGARY, 21st Department of Internal Medicine Pulmonology Department, University of Pecs, Pecs, HUNGARY, 3Department of Pulmonology, Semmelweis University, Budapest, HUNGARY, 4Department VI., National Körányi Institute of Pulmonology, Budapest, HUNGARY, 52nd Department, Pest County Institution of Pulmonology, Törökáblint, HUNGARY, 6Pulmonology Department, Borsod County Szent Ferenc Hospital, Miskolc, HUNGARY

Background: Erlotinib as a targeted therapy is a highly potent inhibitor of epidermal growth factor receptor tyrosine-kinase activity. K-RAS mutations are found in 25-35% of lung adenocarcinomas, and these mutations may be predictive of resistance to treatment with erlotinib. The aim of our analysis was to investigate prospectively the efficacy and safety of second and third line erlotinib treatment in advanced lung adenocarcinoma excluding the K-RAS mutation positive cases.

Materials and methods: This observational study was conducted in 27 Hungarian sites. Enrolled patients were treated with erlotinib. Analyzed patients have historically or cytologically verified, advanced (IIIb/IV), K-RAS (codon-12, codon-13) mutation negative lung adenocarcinoma, refractory to at least one prior chemotherapy. Primary endpoint was progression-free survival. Secondary endpoints were best tumor response rate according to RECIST, overall survival and safety.

Results: 327 patients’ data were analyzed, who were enrolled between February 2008 and December 2010. The study closure date was 31. December 2011. Baseline patients’ characteristics: median age: 60,3 years; male: 50,2%; stage: III/B: 31,1%, IV: 68,9%; smoking status: former/current/never smoker: 39,1/2,8/31,9, ECOG PS: 0/ 1/2: 35,9/51,8/11,2%. Best tumor response: CT/PR/SD/PD were achieved: 0,9/ 16,2/41,9/24,5 % of all patients. The disease control rate was 70,48% in patients for whom the best response data were available. The median progression-free survival (PFS) was 3,27 months. The median overall survival was 14,1 months. For ECOG PS 0-1 patients, the median OS was 16,1 months and the median PFS was 3,47 months, while median OS of 2,5 and median PFS of 1,9 months were detected for ECOG PS 2-3 patients.

Conclusions: Our results confirm the favorable efficacy of erlotinib in K-RAS mutation negative lung adenocarcinoma with an OS of 14,1 months in this real-life setting. A remarkable, 16,1 months median OS was identified in patients with ECOG PS 0-1 receiving erlotinib.

Disclosure: G. Ostoros: corporate-sponsored research; investigator in company-sponsored (Roche) trials. All other authors have declared no conflicts of interest.

PKM2 EXPRESSION MAY PREDICT CHEMOSENSITIVITY TO CISPLATIN-BASED CHEMOTHERAPY IN METASTATIC NON-SMALL-CELL LUNG CANCER (NSCLC)

C. Papadaki1, M. Stakianakis2, E. Lagoudaki3, G. Giaours4, E. Tsakalaki5, M. Trypiski6, S. Pitsikas6, A. Koumoudi7, V. Georgoulas7, I. Sougklos8
1Laboratory of Tumor Cell Biology, School of Medicine, University of Crete, Heraklion, GREECE, 2Laboratory of Pathology, School of Medicine, University of Crete, Heraklion, GREECE, 3Medical Oncology, University Hospital of Heraklion, Heraklion, GREECE, 4Medical Oncology, University General Hospital of Heraklion, Heraklion, GREECE

Background: Tumor cells have been shown to express exclusively the embryonic M2 isofrom of pyruvate kinase (PKM2). Overexpression of PKM2 has been correlated with cisplatin resistance in cell lines and xenograft models. We evaluated the predictive significance of PKM2 in pathologic stage IV NSCLC.

Methods: PKM2 mRNA expression was analysed by RT-qPCR in microdissected FFPE primary tumors from 305 NSCLC patients (148 as training and 157 as experimental set) treated with front-line cisplatin-based chemotherapy and 85 patients treated with a non-platinum doublet (as validation set).
Results: The patients’ characteristics were all typical for metastatic NSCLC (median age 61 years, 86% males, 64% adenocarcinomas and 28% squamous cell carcinomas, ECOG PS 0-1: 83%). PKM2 was successfully amplified in all specimens. Progression Free Survival (PFS) was significantly lower in patients with overexpression of PKM2 (4.9 vs. 6.4 months for high and low expression, respectively, p = 0.028) in the training set and the results were confirmed in the experimental set (3.7 vs. 5.9 months, p = 0.006). Similarly, median overall survival (mOS) was significantly decreased in patients with upregulation of PKM2 (10.1 vs. 17.0 months in the training set (p = 0.001) and 8.3 vs 16.8 months in the experimental sets (p = 0.003), for high and low expression, respectively. In contrast, there was no statistical difference in terms of PFS (5.6 vs 5.9 months, p = 0.431) and mOS (9.8 vs. 10.1 months, p = 0.512) between low and high PKM2 expression in the validation set.

Multivariate analysis revealed that PKM2 high mRNA expression could be emerged as an independent factor associated with decreased PFS (training set: HR = 1.6, p = 0.02; experimental set: HR = 2.1, p = 0.013) and mOS (training set: HR = 1.9 , p = 0.02; experimental set: HR = 2.6, p = 0.001), but not in the validation set (PFS: HR = 1.1, p = 0.627; mOS: HR = 0.96, p = 0.495).

Conclusions: These results indicate that the PKM2 mRNA expression may be used as a predictive factor for sensitivity to cisplatin-based chemotherapy.

Disclosure: All authors have declared no conflicts of interest.

|130OP| ROLE OF THE HEDGEHOG PATHWAY IN MEDIATING RESISTANCE TO ANTI-EGFR TYRISONE KINASE INHIBITORS IN NON SMALL CELL LUNG CANCER

F. Morgillo, C.M. Della Corte, G. Martini, A. Manzo, V. Gambardella, D. Vitagliano, E. Martinelli, T. Troiani, F. Ciardiello Medical Oncology, Second University of Naples, Naples, ITALY

In recent years, the management of non small lung cancer (NSCLC) has been moving towards molecular-guided treatment, and the best example of this new approach is the use of EGFR tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib. The clinical benefit observed with EGFR-TKIs in NSCLC is limited to a subset of patients, and the development of resistance, even in responders, is sooner or later observed. Several studies have provided new insights into the molecular basis of EGFR inhibitors resistance. Recently our group demonstrated the acquisition of a mesenchymal phenotype in an in vitro model of NSCLC cell lines with acquired resistance to anti-EGFR TKIs. Among the various molecular pathways, the Hedgehog (Hh) signaling pathway has emerged as an important mediator of carcinogenesis and cancer metastases. The objective of this research is to investigate the role of Hh signaling pathway in human NSCLC cell models of constitutive or acquired resistance to EGFR-TKIs. To investigate the expression profile of Hh signaling components in our panel of sensitive and resistant NSCLC cell lines, we performed analysis of mRNA and protein levels of Shh, Gli1 and Smo by using semiquantitative PCR and Western blot analysis. The experiment showed a strong expression of sonic Hh and Gli1 in NSCLC cell lines resistant to EGFR TKIs. In addition, PTCH mRNA levels resulted increased in TKI-resistant cell lines. This is of relevance, because PTCH gene itself is a target gene of Gli1 transcriptional activity and its levels indicates an activation of Hh signaling in such cells. Treatment with cyclopamine, a Smo inhibitor, strongly inhibited the proliferation of resistant NSCLC cell lines. Furthermore, treatment with cyclopamine blocked the invasive and migratory behavior of resistant cells. Of interest, the inhibition of Smo and Hh signaling pathway was accompanied by an inhibition of MET and MAPK phosphorylation. Our study should provide the opportunity to better understand the role of Hh pathway in mediating resistance to anti-EGFR TKIs and to design new strategies to be easily transferred into clinical practice.

Disclosure: All authors have declared no conflicts of interest.

|131OP| PROGNOSTIC IMPACT OF SERUM CYFRA 21-1 IN ADVANCED LUNG ADENOCARCINOMA

A. Oro1, T. Takahashi1, H. Akamatsu1, T. Taira1, T. Shukuya1, H. Kenmotsu1, T. Nakao1, H. Mihara1, N. Endo1, N. Yamamoto1

1Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, JAPAN
2Division of Diagnostic Radiology, Shizuoka Cancer Center, Shizuoka, JAPAN

Background: Serum CYFRA 21-1 is one of the most important serum markers in diagnosing non-small cell lung cancer (NSCLC), especially squamous-cell carcinoma. It is not known whether pretreatment serum CYFRA 21-1 values (PCV) have prognostic implications in advanced lung adenocarcinoma. The aim of this study was to evaluate the prognostic implications of PCV in advanced lung adenocarcinoma.

Material and methods: Out of 424 newly diagnosed lung cancer patients (pts) at our institution during the period April 2008- June 2010, we retrospectively reviewed 284 consecutive pts who were diagnosed with advanced lung adenocarcinoma and had been treated with systemic chemotherapy. Survival was estimated using the Kaplan-Meier method. A log-rank test was performed to test the significance of differences in the overall survival among the groups. A multivariate analysis using the Cox proportional hazards model was used to establish the association between various prognostic factors and survival.

Results: One hundred twenty one pts (43%) had activating EGFR mutations (Mt+) and 63 pts (57%) had EGFR wild type (Mt-). The median follow-up time was 29.7 months (range: 2.8-75.7 months). In univariate analysis, gender (male/ female), ECOG performance status (PS) (0/2-3, 4), PCV (< 2.2ng/ml, >2.2ng/ml), EGFR mutation (Mt+ / Mt-), and smoking history (yes/ no) were favorable prognostic factors (p< 0.01, p=0.001, p=0.008, p=0.0008, p=0.0007, respectively) for survival. However, age (> 65 vs. <=65 years) was not a significant prognostic factor (p= 0.512) in the validation set. Furthermore, patients with Mt+ and CYFRA < 2.2ng/ml (n = 70) had a better prognosis than those with Mt- and CYFRA > 2.2ng/ml (n = 48) (median survival time [MST]: 52.4 vs. 21.0 months, p< 0.0001), and those with Mt- and CYFRA < 2.2ng/ml (n = 78) had a better prognosis than Mt- and CYFRA > 2.2ng/ml (n = 86) (MST: 24.1 vs. 10.2 months, p< 0.0001).

Conclusions: PCV should be regarded as a potential independent prognostic factor in both Mt+ and Mt- advanced lung adenocarcinoma.

Disclosure: All authors have declared no conflicts of interest.

|1311P| MOLECULAR GENOTYPING WITH HIGH-THROUGHPUT METHOD, ONCOMAP V4.0 FOR SMALL BIOPSIES SAMPLES IN NEWLY DIAGNOSED ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS

C.H. Maeng1, M.A. Ahn4, K. Park1, S.J. Lee1, H.A. Jung1, W. Chang1, S. Park1, MK. Chae1, Y.S. Kim1, J.Y. Hong1

1Division of Hematology/Oncology, Department of Medicine, Sungkyunkwan University School of Medicine, Seoul, KOREA, 2Department of Internal Medicine, Hematology, Oncology, Samsung Medical Center Sungkyunkwan University, School of Medicine, Seoul, KOREA, 3Medicine, Samsung Medical Center, Seoul, KOREA, 4Hematology-Oncology, Samsung Medical Center, SEOUL, KOREA

Introduction: With the introduction of molecular targeted agents, mutational analysis of cancer tissue became mainstay of treatment decision making in oncology field. Since lung cancer has the complex and diverse somatic mutations, extensive and fast genetic profiling such as high-throughput molecular genotyping is needed. Given the difficulty in acquisition of adequate tumor tissues for high-throughput molecular genotyping in advanced non-small cell lung cancer (NSCLC), fast and efficient method for detecting various genetic alterations with small biopsy is also required.

Methods and materials: We analyzed tissue specimens obtained from total 64 patients (one specimen per one patient) who were pathologically confirmed with advanced NSCLC. Oncomap v4, a mass-spectrometry based assay, was used to interrogate 471 oncogenic mutations in 41 commonly mutated genes. All of the tumor specimens were prepared from fresh frozen tissue obtained by endobronchial ultrasound or radiologic intervention-guided biopsy core.

Results: In total, we have detected any mutations in 66% of patients (42 out of 64 patients). There were total 59 hotspot mutations out of 64 specimens tested. The most frequent mutation was TP53 mutation (n = 25, 39.1%), followed by EGFR (n = 16, 25.0%), KRAS (n = 8, 12.5%), ALK (n = 7, 10.9%), BRAF (n = 3, 4.7%), EGFR (n = 3, 4.7%), ERBB2 (n = 2, 3.1%), and one case of ABL1 (1.6%) and HRAS (1.6%), respectively. The rate or types of mutation detected are comparable to the results of previous literatures or database such as COSMIC data. Approximately 7-10 days were required to complete primary profiling and assay validation. Among 16 patients who were shown to be positive for EGFR mutation by Oncomap, 3 patients were negative for the mutation test by direct sequencing method. Two patients of positive ERBB2 mutation had very short duration of response to erlotinib (25 days and 26 days, respectively).

Conclusions: These results suggest that molecular genotyping using high-throughput technology such as Oncomap v4 is feasible even with small biopsied specimens from advanced NSCLC patients. This platform can be useful for clinicians to make treatment decision based on molecular genotyping in daily clinical practice.

Disclosure: All authors have declared no conflicts of interest.

|1312| ABDERRANT ALK1 MRNA EXPRESSION PATTERNS ARE ASSOCIATED WITH POOR PROGNOSIS IN NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS

V. Kotoulou, M. Bobos, S. Lakis, K. Papadopoulos, S. Levva, D. Repana, V. Karavellas, E. Santantias, P. Kosmidis, G. Fountzilas

Data Office, Hellenic Cooperative Oncology Group (HECOG), Athens, GREECE

Background:–aim: ALK1 (ALK) translocation is a rare event in NSCLC, which more often seem to harbor aberrant ALK gene copies. Herein, we investigated the still undefined impact of ALK gene copies and of ALK mRNA expression on NSCLC patient outcome.
Disclosure: All authors have declared no conflicts of interest.

13115

PROGNOSTIC SIGNIFICANCE OF EGFR, HER-2, CEA ON CIRCULATING TUMOUR CELLS (CTC) IN PATIENTS WITH METASTATIC NON-SMALL-CELL LUNG CANCER (NSCLC)

C. Loretelli1, E. Galizia2, M. Scartozzi1, R. Giampieri1, D. Gagliardini1, C. Brugà1, S. C. Cellerino1
1Clinica di Oncologia Medica, AOU Ospedali Riuniti Ancona Università Politecnica delle Marche, Ancona, ITALY, 2Oncologia Medica, Ospedale “E. Profili”, Fabbriano, ITALY

Purpose: We aimed to assess the role of CTCs in providing prognostic information of mNSCLC patients receiving chemotherapy.

Patients and methods: In this single-center prospective study, blood samples for CTCs analysis were obtained from patients with previously untreated mNSCLC. CTCs were measured using an epithelial cell adhesion molecule-based immunomagnetic bead enrichment for cells expressing epithelial cell adhesion molecule (EpCAM) was performed, followed by multi-marker quantitative real-time PCR of a panel of marker genes: EGFR, HER-2, CEA.

Results: We analysed 45 patients with mNSCLC: 24 adenocarcinoma, 8 squamous cell carcinoma and 13 poorly differentiated. EGFR, HER-2 and CEA expression were found in CTCs of respectively 12, 5 and 11 patients. Globally, 31 patients (68.9%) progressed during treatment, whereas disease control (i.e. patients with partial/complete response or stable disease) was achieved in 14 patients (31.1%). EGFR expression was detected in 11/31 patients with disease progression (35.5%) and in only 1 out of 14 patients with disease controlled (7.1%) (p = 0.07). HER-2 expression was detected in 3/31 patients with disease progression (9.7%) and in 2/14 patients with disease controlled (14.3%) (p = 0.64). CEA expression was detected in 10/31 patients with disease progression (32.3%) and in 1/14 patients with disease controlled (7.1%) (p = 0.13). Only EGFR expression in CTCs showed a correlation with clinical outcome, expressed by progression free survival (PFS). Patients with and without EGFR expression in CTCs were homogeneous for clinical characteristics. PFS was 2.8 ± 2.3 months (p = 0.03) respectively for patients without and with EGFR expression.

Conclusion: CTCs are detectable in patients with mNSCLC and could show novel prognostic factor for this disease. Further validation is warranted before routine clinical application.

Disclosure: All authors have declared no conflicts of interest.

13114

ASSESSMENT OF THE PREDICTIVE/PROGNOSTIC VALUE OF THE MYELOID-DERIVED SUPPRESSOR CELLS (MDSC) AND REGULATORY T CELLS (TREGS) IN NON-SMALL CELL LUNG CANCER (NSCLC), PRELIMINARY RESULTS

E.K. Vetsila1, E. Skaldalak1, A. Koutulak1, D. Mavroudis2, V. Georgoulis2, A. Kotsiaris3
1Laboratory of Tumor Cell Biology, University of Crete, School of Medicine, Heraklion, GREECE, 2Medical Oncology, University Hospital of Heraklion, Heraklion, GREECE

Background: The circulating MDSCs and Tregs in cancer patients suppress immune system. This study is investigating the expression of the MDSCs and Tregs in the peripheral blood of NSCLC patients and their correlation with the clinical outcome of the 1st line chemotherapy.

Methods: 62 chemotherapy naive patients (57 males) with stage IIIB/IV NSCLC have been enrolled in this study, so far, median age 67. Peripheral blood was collected prior to treatment. 19 healthy, aged-matched donors (12 males) were used as controls. The distinct MDSC subpopulations (A (monocytic): CD11b+CD14+CD15-CD33+CD16−HLA-DR−; B (monocytic): CD11b+CD14+CD15−CD16−HLA-DR− and C (granocytic): CD11b+CD14−CD15+CD33−CD16−HLA-DR−), CD4+ Tregs (CD4+CD25+CD127low FoxP3+CD39+CD13+) and CD8+ Tregs (CD3+CD8+CD25−CD45RO+CD15+CD69FoxP3+CD39+) were determined by flow cytometry. A comparison of the overall survival (OS) and the progression-free survival (PFS) according to the frequency of the MDSC and Treg was performed (high expression defined as the percentage of cells above the 75% percentile of the controls).

Results: The levels of Tregs prior to treatment did not differ from the controls. Patients with progression (PD) during the 1st line treatment had significantly elevated percentage of CD4+ (24.6 ± 8.5) and CD8+ (0.7 ± 0.2) Tregs at baseline compared to those with no PD (3.7 ± 1.8, p = 0.04; 0.1 ± 0.05, p = 0.03, respectively). In contrast, MDSCs were significantly increased (A: 3.8 ± 10.7; B: 2.5 ± 0.5 and C: 10.8 ± 2.3) in patients compared to controls (0.8 ± 0.4, p = 0.001; 0.5 ± 0.2, p = 0.01, and 2.7 ± 1.3, p = 0.05, respectively) but that difference was not associated with response to treatment. Patients with normal CD8+ Tregs levels at baseline had higher OS and PFS compared to those with high levels (13.2 mo vs 7.9 mo, p = 0.02 and 13.1 mo vs 3.7 mo, p = 0.003, respectively).

Conclusion: The MDSCs are elevated in NSCLC. The increased expression of CD4+ and CD8+ Tregs could be a potential predictive/prognostic biomarker. The study is still opened to accrual and more mature data will be presented at the meeting.

Disclosure: All authors have declared no conflicts of interest.

13116

CYTOLOGY SAMPLES (S) FOR EGFR AND KRAS MUTATION (MUT) TESTING IN NON-SMALL-CELL LUNG CANCER (NSCLC), EXPERIENCE FROM A SINGLE INSTITUTION

T. Moran Bueno1, E. Castella Fernandez2, M. Temo Garcia1, C. Boges Sanchez3, C. Gueralt Herrero1, M. Perez Cano1, D. Naranjo Hansen1, F. Andreo Garcia3, L. Capdevila Riera1, R. Rosell1
1Medical Oncology Department, Catalan Institute of Oncology Badalona, Hospital Universitari Germans Trias i Pujol, Badalona, SPAIN, 2Pathology Department, Hospital Universitari Germans Trias i Pujol, Badalona, SPAIN, 3Pulmonology Department, Hospital Universitari Germans Trias i Pujol, Badalona, SPAIN

Background: Targeted therapy has yielded impressive clinical outcomes in advanced NSCLC. For molecular testing, cytology samples are not commonly used since the tumor content is less likely to be adequate. At IEO-Badalona, Hospital Germans Trias i Pujol we have used cytology specimens when biopsies are not available. We describe the general results when using cytology specimens in NSCLC to detect EGFR and KRAS mut.

Methods: From January 2007 to February 2012, 227 cytology samples from patients with NSCLC were collected at the Department of Pathology as cell blocks or fresh specimens extended over an appropriate slide (MembraneSlide 1.0 PEN, Zeiss*). Tumor cells (8-150) were captured by laser microdissection. DNA sequencing for
EGFR mut at exons 18, 19, 21, and KRAS mut at codons 12 and 13 and allelic discrimination technique for EGFR mut at exon 20 were performed at Molecular Biology Laboratory (ICO-Badalona).

**Results:** EGFR mut were tested in 227 s. The overall output was 86.3% (15 not evaluable, 8 insufficient issue, 4 no tumor cells, 4 not done). EGFR mut were detected in 8.81% (20/227). KRAS mut were tested in 41 s with results in 33, 80.5% (2 not evaluable, 3 insufficient tumor cells 1 no tumor and 2 not done). KRAS mut were positive in 14.6% (6/41). The output for cell block was 83.3% (124/148) and testing was not possible in 24 s (11 not evaluable, 6 insufficient tumor cells, 4 not tumor and 3 not done). The output for fresh specimens was 91.1% (72/79) and was not possible in 7 s (4 not evaluable, 2 insufficient tumor cells and 1 not done).

**Conclusions:** Our results support the use of cytology samples for EGFR and KRAS molecular testing in NSCLC when biopsy specimens are not available. Both fresh specimens and cytology blocks have been used and are suitable for molecular testing.

**Disclosure:** All authors have declared no conflicts of interest.

**1316 FEASIBILITY AND USEFULNESS OF DETERMINING EGFR AND KRAS MUTATIONS IN CYTOLOGICAL SAMPLES AND CNB OF NSCLC USING AN AUTOMATED REAL-TIME PCR SYSTEM**

M.D. Lozano1, T. Labiano1, M. Monttariana1, J.J. Echeveste1, A. Gurpide2, J.L. Pérez - Gracia2, F. Sneath3, T. Ramos3, J. Zuleika4, S. Martin Algarra2

1Pathology, University of Navarra, Pamplona, SPAIN, 2Clinical Oncology, Clinica Universitaria de Navarra, Pamplona, SPAIN, 3Roche Molecular System, Roche Molecular System, Pleasanton, UNITED STATES OF AMERICA, 4Roche Diagnostics, Barcelona, SPAIN, 5Pulmonary Medicine, Clinica Universidad de Navarra, Pamplona, SPAIN

**Background:** EGFR and KRAS gene mutations guide treatment selection in non-small cell lung cancer (NSCLC) patients. About 70%–80% of these patients are diagnosed at advanced stage, and mutational analysis has to be performed in small samples: core needle biopsy (CNB) and fine needle aspiration (FNA) cytology. Cobsa® EGFR Mutation Test has been CE-IVD marked for the detection of 41 mutations in formalin-fixed-paraffin-embedded (FFPE) NSCLC specimens. No validation studies have been performed using cytological samples. Determining the feasibility of cobsa® test on such samples is an important step to extend the benefits of molecular targeted therapy.

**Methods:** EGFR and KRAS mutations were studied in 64 non-selected samples from NSCLC patients: 31 CNB and 33 FNA. DNA was extracted directly from stained smears in FNA samples and from 4-micron sections in CNB. All samples contained at least 50% of tumor cells. All cases were studied using the cobsa® test, and FNA samples were also analyzed by direct sequencing. DNA was extracted using the cobsa® DNA Sample Preparation Kit. DNA concentration and DNA ratio of sample absorbance at 260/280nm (A260/280) were registered. U Mann Whitney test was used.

**Results:** CNB diagnosis was: 23 SqCC, 6 AC, 1 BAC, and 1 NSCLC-NOS. FNA diagnosis was: 26 AC, 3 SqCC, 1 BAC, 1 LCC, and 2 NSCLC-NOS. Mean DNA concentration from CNB was 23.07ng/ul ± 20.99, and from FNA samples 12.41ng/ul ± 20.04 (p < 0.001). However A260/280 was 1.61 ± 0.26 and 1.71 ± 0.55 respectively (p = 0.666). Mutational analysis results from all 31 CNB and from 19 FNA cases are shown in Table 1. Sanger sequencing in all FNA cases rendered concordant results. Updated results will be presented.

**Conclusions:** Assessment of EGFR and KRAS mutations in FNA and CNB samples using cobsa® EGFR and KRAS test is feasible and reliable. Quality of DNA (A260/280) using cobsa® DNA Sample Preparation Kit in FNA samples is similar to those from CNB. Molecular results from FNA samples using cobsa® test and direct sequencing are concordant, though cobsa® tests are simpler, faster and easier to use.

**Disclosure:** All authors have declared no conflicts of interest.

---

**1318 FREQUENCY AND SPECTRUM OF EGFR MUTATIONS IN MOROCCAN LUNG ADENOCARCINOMA PATIENTS**

I. Elghissassi1, H. Inhaurou2, A. Bouki3, Y. Bensouda1, H. Mrabti1, H. Erinani1

1Medical Oncology, Institut National d’Oncologie Sidi Mohamed Ben Abdellah, Rabat, MOROCCO, 2Medical Oncology, National Institute of Oncology, Rabat, MOROCCO

**Background:** EGFR mutations reported in lung cancer are potential therapeutic targets leading to improved response with tyrosine kinase inhibitors (TKI). The frequency of EGFR mutations is ethnicity-dependent with a higher proportion in Asian populations (30%) than in Caucasians (10-15%). Furthermore, exon 19 mutation is associated with better response to EGFR-TKI compared to exon 21 mutation. The aim of this study was to report the frequency and spectrum of EGFR mutations in unselected group of Moroccan lung adenocarcinoma patients.

**Methods:** We summarized the result of the EGFR mutation analysis in exons 18-21 for 83 patients performed from November 2010 to march 2012 in three laboratories in Rabat. Mutation detection techniques were PCR amplification and sequencing.

**Results:** The overall frequency of the EGFR mutation was 22%. It was more frequent in female patients (58%) than in male ones (5%). Mutations were mainly detected in the exon 19 (67%) followed by exon 21 (17%) and exon 20 (11%).

**Conclusion:** Some one fifth of Moroccan lung adenocarcinoma tumors harbor EGFR mutations. This mutation frequency is higher than that found in Caucasians but lower than in Asian population. The high rate of exon 19 mutation in Moroccan population may result in a higher frequency of response to TKI.

**Disclosure:** All authors have declared no conflicts of interest.

---

**1319 THE ROLE OF EPITHELIAL-MESENCHYMAL TRANSITION AND IGF-1R EXPRESSION IN PREDICTION OF GEFITINIB ACTIVITY AS THE SECOND-LINE TREATMENT FOR ADVANCED NON-SMALL CELL LUNG CANCER**

W. Zhang, B. Chen

Oncology, Guangzhou General Hospital of Guangzhou Military Command, Guangzhou, Guangzhou, CHINA

We retrospectively analyzed the relationship of EMT, IGF-1R and gefitinib efficacy in 53 NSCLC patients who accepted gefitinib as the second-line treatment. Compared with EMT (+), EMT (-) showed a higher ORR in both EGFR mutation subgroup (50.0% vs. 28.6%) and EGFR wild-type subgroup (20.0% vs. 4.5%), and a longer MST in EGFR wild-type subgroup (6 months vs. 3 months, P = 0.014). IGF-1R (+) showed a higher ORR tendency than IGF-1R (-) in EGFR mutation patients (54.6% vs. 30.0%) and EGFR wild-type patients (18.2% vs. 48.8%). EMT and IGF-1R are correlated with the efficacy of gefitinib as the second-line therapy for NSCLC, especially in patients with wild-type EGFR.

**Disclosure:** All authors have declared no conflicts of interest.

---

**1320 PERIODIC MEASUREMENT OF N-TELOPEPTIDES OF TYPE I COLLAGEN IN SERUM (sNTx) FOR EARLY DIAGNOSIS OF BONE METASTASIS IN PATIENTS WITH LUNG CANCER**


1Department of Clinical Oncology, Osaka City General Hospital, Osaka, JAPAN, 2Thoracic Malignancy, Osaka Prefectural Hospital Organization Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Hapabeno-City, JAPAN, 3Clinical Oncology, Osaka City General Hospital, Osaka, JAPAN

**Background:** The bone resorption biomarker sNTx has been previously shown to add value as an aid in the diagnosis of bone metastasis in patients with lung cancer. The objective of this prospective study was to determine if periodic sNTx measurements could lead to early diagnosis of bone metastasis in patients with lung cancer.

**Methods:** Patients with newly diagnosed organ-confined lung cancer were enrolled. sNTx values were determined once each month using the OSTEOMARKTM serum NTx assay (Alere Medical).

**Disclosure:** All authors have declared no conflicts of interest.

---

**Table 1. FNA and CNB Results for EGFR and KRAS Mutations**

<table>
<thead>
<tr>
<th></th>
<th>FNA</th>
<th>CNB</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>WT</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>EXON 19 DEL</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>EXON 20 INS</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>KRAS</td>
<td>WT</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>12/13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUTATED</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>INVALID</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions:** Assessment of EGFR and KRAS mutations in FNA and CNB samples using cobsa® EGFR and KRAS mut at exons 18, 19, and 21, and allelic discrimination technique for EGFR mut at exon 20 were performed at Molecular Biology Laboratory (ICO-Badalona). EGFR mut were tested in 227 s. The overall output was 86.3% (15 not evaluable, 8 insufficient issue, 4 no tumor cells, 4 not done). EGFR mut were detected in 8.81% (20/227). KRAS mut were tested in 41 s with results in 33, 80.5% (2 not evaluable, 3 insufficient tumor cells 1 no tumor and 2 not done). KRAS mut were positive in 14.6% (6/41). The output for cell block was 83.3% (124/148) and testing was not possible in 24 s (11 not evaluable, 6 insufficient tumor cells, 4 not tumor and 3 not done). The output for fresh specimens was 91.1% (72/79) and was not possible in 7 s (4 not evaluable, 2 insufficient tumor cells and 1 not done).

**Conclusions:** Our results support the use of cytology samples for EGFR and KRAS molecular testing in NSCLC when biopsy specimens are not available. Both fresh specimens and cytology blocks have been used and are suitable for molecular testing.

**Disclosure:** All authors have declared no conflicts of interest.
months for 12 months. All patients were required to provide written informed consent.

Results: Forty patients were enrolled between June and December 2010. One patient withdrew early and was excluded from analysis. The mean +/− 1 SD baseline level of sNTx was 17.5 +/− 4.6 nM BCE/L. Five patients developed bone metastasis (characterized by bone scintigraphy) during the study period. The level of sNTx in subjects with bone metastasis was slightly increased (21.6 +/− 3.2 nM BCE/L), however, in these patients, there was no statistically significant difference between sNTx values at baseline (18.2 +/− 4.2 nM BCE/L) and when metastasis was diagnosed. (p = 0.176). When a cut-off value of sNTx was set to 22.0 nM BCE/L, the sensitivity and the specificity of detection of bone metastasis were 80.0% and 41.2%, respectively.

Discussion: Although patients who are elderly, those with poor PS, and those who had a history of previous chemotherapy showed a trend towards a worse outcome, the patient characteristics were not significantly related to the rate of bone metastasis development. A cut-off value of sNTx was 17.5 +/− 4.4 nM BCE/L. Zero percent and 55.0% of the patients with sNTx values lower than 17.5 nM BCE/L developed bone metastasis and disease progression, respectively. No statistically significant difference was found when comparing the incidence of bone metastasis and disease progression with different age, PS, and smoking status. The use of sNTx as a tool for early detection of bone metastasis and disease progression may be cost-effective in clinical practice.

Disclosure: All authors have declared no conflicts of interest.

1321 USEFULNESS OF SERIAL MEASUREMENT OF SERUM N-TELLOPEPTIDES OF TYPE I COLLAGEN (sNTx) IN PATIENTS WITH NON-SMALL CELL LUNG CANCER WHO DEVELOPED BONE METASTASIS: A PROSPECTIVE STUDY


1Department of Thoracic Malignancy, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Osaka, JAPAN, 2Clinical Oncology, Osaka City General Hospital, Osaka, Osaka, JAPAN, 3Department of Clinical Oncology, Osaka City General Hospital, Osaka, JAPAN, 4Thoracic Malignancy, Osaka Prefectural Hospital Organization Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Hattakino-City, JAPAN

Background: The bone resorption biomarkers urinary NTx (uNTx) and serum NTx (sNTx) have been shown to aid in the diagnosis of bone metastasis in patients with lung cancer. Patients with metastatic bone disease from lung cancer (MBDLC) are often treated with zoledronic acid. Zoledronic acid reduces the levels of bone resorption biomarkers and also the risk of skeletal adverse events in patients with MBDLC. We studied the effects of treatments including zoledronic acid on levels of sNTx during disease progression.

Methods: Patients with MBDLC at the initial diagnosis were entered into this study. sNTx was measured once a month using the sNTx assay OSTEOMARK seru NTX (Alere Medical). MBDLC was characterized by monthly physical examination and by bone scintigraphy every 3 months for 12 months. All patients were required to provide written informed consent.

Results: Twenty patients were enrolled between June and December 2010. The mean +/− 1 SD of the sNTx concentrations was 19.8 +/− 5.8 nM BCE/L at baseline. In the 16 patients receiving zoledronic acid, the levels of sNTx showed a significant decrease in the first month of treatment (baseline: 21.3 +/− 5.5 nM BCE/L; one month later: 13.6 +/− 2.7 nM BCE/L; p < 0.01). During follow-up period, 12 of the patients treated with zoledronic acid experienced worsening MBDLC or had died from lung cancer, and there were statistically significant differences in the levels of sNTx at baseline (19.7 +/− 4.4 nM BCE/L) and at the lowest levels after the administration of zoledronic acid (11.5 +/− 2.73 nM BCE/L) and at the point of measurable disease progression or death (13.0 +/− 2.57 nM BCE/L).

Conclusion: Serial measurements of sNTx in patients with MBDLC treated with zoledronic acid might predict disease progression of bone metastasis. Administration of zoledronic acid significantly decreased the level of sNTx from baseline within one month and maintained the level of sNTx lower than baseline during study periods.

Disclosure: All authors have declared no conflicts of interest.

1322 PREDICTIVE BIOMARKERS IN NSCLC PATIENTS TREATED WITH ERLOTINIB AFTER CHEMOTHERAPY: EGFR EXPRESSION OR MUTATIONS?

A. Inno1, E. Maci2, M. Martini2, V. Arena2, V.P. Di Noia1, G. Schinari1, L. M. Laffocea1, A. Cassiano1, C. Pozzo2, C. Barone1

1Oncologia Medica, Università Cattolica del Sacro Cuore, Roma, ITALY, 2Istituto di Patologia, Università Cattolica del Sacro Cuore, Roma, ITALY

Introduction: Retrospective subgroup analysis from randomized trials did not show a significant association between activating EGFR mutations and benefit from erlotinib in patients with NSCLC previously treated with chemotherapy, so whether EGFR mutational status should be used as a tool to select patients for erlotinib in the second-line setting is debatable. Novel predictive biomarkers would be helpful to choose the most appropriate therapeutic strategy.

Methods: We correlated retrospectively the mutational status of EGFR and KRAS and also the IHC expression of EGFR, cMET, IGF1R and HER2, with the outcome of 51 patients with metastatic NSCLC treated with erlotinib as second or third-line at our institution from 2009 to 2012.

Results: EGFR and KRAS activating mutations were mutually exclusive and were found in 5 and 7 patients. IHC score for EGFR, IGF1R, cMET and HER2 was 3+ in 11, 8, 7 and 1 patients, respectively. RR was 20% and 13% and PFS was 9 and 2 months for EGFR mutant and wild-type patients, respectively, but this difference was not statistically significant. Similarly, KRAS mutational status did not significantly affect the outcome, although none of KRAS mutant patients achieved an objective response. RR and PFS were not related to IGF1R and cMET expression. Nine out of 11 patients (81.8%) with the EGFR overexpression responded to treatment, compared with 13 out of 40 patients (32.5%) with a lower EGFR level. EGFR overexpression was also associated with a longer PFS (8 vs 2 months, p = 0.05). Interestingly, in our study the outcome of patients was not affected by gender, performance status, histology or smoking history.

Conclusion: cMET and IGF1R were not related to the efficacy of erlotinib as second or third-line treatment for metastatic NSCLC patients. No conclusions can be drawn about HER2 since only one case of overexpression was found. EGFR mutations are associated with a longer PFS, even if not significantly. The IHC expression of EGFR seems to be predictive of a better outcome, whereas KRAS mutations may represent a mechanism of resistance. Given the limitations of our study, however, those findings should be confirmed within prospective clinical trials.

Disclosure: A. Inno: Speaker at educational meetings sponsored by Merk-Serono and Amgen. All other authors have declared no conflicts of interest.

1324 ANALYSIS OF EML4-ALK POSITIVE NON-SMALL CELL LUNG CANCER WITH ADVANCED STAGE

J. Park1, C. Kondo1, J. Shinmizu1, Y. Hori1, K. Yoshida1, Y. Yatabe2, T. Mitsudomi3, T. Hida1

1Department of Thoracic Oncology, Aichi Cancer Center Hospital, Nagoya, JAPAN, 2Thoracic Oncology, Aichi Cancer Center, Nagoya, JAPAN, 3Department of Pathology and Molecular Diagnostics, Aichi Cancer Center, Nagoya, JAPAN, 4Department of Thoracic Surgery, Kinki University Faculty of Medicine, Osaka, JAPAN

Background: The purpose of this study is to investigate the clinical characteristics and the efficacy of the cytotoxic chemotherapy in the first and second line setting in EML4-ALK positive NSCLC with advanced stage.
Methods: EML4-ALK fusion was screened with RT-PCR and immunohistochemistry. When positive results were obtained with either method, gene rearrangement of ALK was confirmed with fluorescent in-situ hybridization. Clinical features and the efficacy of chemotherapy were evaluated retrospectively.

Results: We evaluated 20 EML4-ALK positive patients with advanced stage. Seventeen (85%) of 20 had stage IV disease. Nine cases were male, and 11 were female. The mean ages were 46.3 years (range 26-79). Most of their CT findings demonstrated mass or nodule in primary sites, while 2 cases showed air-space consolidation. In patients with stage IV the most common sites of metastasis at the first onset were bone (47%), followed by pleura (35.2%), liver (29.4%), and lung (23.5%). In 13 cases of which were evaluable in the first line setting, 7 (53.8%) had a partial response (PR), 4 (30.8%) had stable disease (SD), and 2 (15.4%) had progressive disease (PD). Among 10 evaluable cases in the second line setting, 2 (20%) had a PR, 5 (50%) had SD, and 3 had PD (30%). Two patients who had a PR were both treated by oral ALK inhibitor (crizotinib). One case had no response to crizotinib. Within the 7 patients who were treated by cytotoxic agents, none had marked clinical response. Five patients (71.4%) had SD, 2 patients had PD (28.6%) on single cytotoxic drug.

Conclusions: Our study suggests that the EML4-ALK positive patients may show relatively favorable response to cytotoxic drug in the first line setting, but low response in the second line setting. These data could be helpful for further clinical trials including EML4-ALK patients.

Disclosure: T. Mitsudomi: Dr. Mitsudomi has received lecture fees from AstraZeneca and Chugai, and he is a member of advisory boards of Pfizer and Boehringer-Ingelheim. All other authors have declared no conflicts of interest.

1326 Phase II trial of carboplatin and pemetrexed as first-line chemotherapy for non-squamous non-small cell lung cancer and correlation between the efficacy/toxicity and genetic polymorphisms associated with pemetrexed metabolism: Hokkaido lung cancer clinical study group trial (HOT) 0902

1Department of Respiratory Medicine, National Hospital Organization Asahikawa Medical Center, Asahikawa, JAPAN, 2Department of Pulmonary Medicine, Fukushima Medical University Hospital, Fukushima, JAPAN, 3Center for Respiratory Diseases, Hokkaido Social Insurance Hospital, Sapporo, JAPAN, 4Department of Pulmonary Disease, National Hospital Organization Hokkaido Cancer Center, Sapporo, JAPAN, 5First Department of Medicine, Hokkaido P.W. F.A.C Oshiro-Kosei General Hospital, Oshiro, JAPAN, 6First Department of Medicine, Hokkaido University School of Medicine, Sapporo, JAPAN, 7Department of Medical Oncology and Respiratory Medicine, KFJ Sapporo Medical Center, Sapporo, JAPAN, 8Department of Medical Oncology, Hokkaido University Graduate School of Medicine, Sapporo, JAPAN

Background: The importance of biomarkers is increasing in individualized treatment strategy for cancer patients (pts). We evaluated the efficacy and safety of carboplatin (CBDCA) and pemetrexed (PEM) in Japanese pts with non-squamous non-small cell lung cancer (NSCLC), and single nucleotide polymorphisms (SNPs) associated with PEM metabolism were also analyzed to investigate their relationship with efficacy or toxicity.

Patients and methods: Eligible pts had a performance status 0 or 1, aged from 20 to 74 years, chemotherapy-naive stage III/IV non-squamous NSCLC, and adequate organ function. Pts received CBDCA at a dose targeting an area under the concentration-time curve of 5 and 500 mg/m² PEM every 3 weeks. More than 3 cycles was considered as completion of treatment. Peripheral blood was drawn for SNPs analyses of thymidylate synthase gene (TS) and methylenetetrahydrofolate reductase gene (MTHFR) in pts with consent for the biomarker study.

Results: Forty-one pts (28 men, 13 women; median age 63 years, range 43 - 73), with 39 adenocarcinomas and 2 large cell carcinomas, were enrolled and SNPs were analyzed in 37 pts. The median follow-up time was 16.1 months and the median number of treatment cycle was 4 (range 1 - 6). The completion rate was 80.5% (33 pts). All pts were assessable for response; the overall response rate (RR) was 36.6% and disease control rate (DCR) was 85.4%. Median progression-free survival (PFS) and overall survival (OS) were 4.8 months (138 days: 95%CI; 107-168) and 16.1 months (485 days: 95%CI; 180-766), respectively. Grade 3 or 4 hematologic toxicities included anemia (34.1%), neutropenia (29.3%), leukopenia (19.5%) and thrombocytopenia (17.1%). Grade 3 or 4 non-hematologic toxicities included anorexia (7.3%) and nausea (4.9%). No treatment-related death was observed. Although the SNPs had no relation to PFS, OS, RR nor hematologic toxicity, the variable number of tandem repeat (VNTR) of the TS significantly correlated with anemia (p = 0.047) and thrombocytopenia (p = 0.038).

Conclusion: The efficacy of this regimen seems even better than previously reported, and with acceptable toxicities. VNTR of the TS has the possibility of being a predictive factor of anemia and thrombocytopenia for this regimen.

Disclosure: All authors have declared no conflicts of interest.

1327 A phase II trial of cisplatin-docetaxel-bevacizumab induction chemotherapy followed by bevacizumab and pemetrexed maintenance therapy in patients with non-squamous cell lung carcinoma: Okayama lung cancer study group trial 0903

A. Nishiyama1, H. Yoshisaka2, K. Kunimasa3, K. Hotta1, N. Nogami1, T. Kozuki1, S. Hattori1, N. Takigawa2, M. Tanimoto3, K. Kiura2
1Respiratory, Kurashiki Central Hospital, Kurashiki, JAPAN, 2Department of Respiratory Medicine, Okayama University Hospital, Okayama, JAPAN, 3Respiratory, NHO Shikoku Cancer Center, Matsuyama, JAPAN, 4Dept of Thoracic Oncology, NHO Shikoku Cancer Center, Matsuyama, JAPAN, 5Respiratory, Chugoku Central Hospital, Hukuyama, JAPAN, 6Internal Medicine, Kawasaki-Hospital, Okayama, JAPAN

Background: Addition of bevacizumab (BEV) to platinum-based doublet yields a significant but only modest survival advantage. Recently, in the PARAMOUNT trial

Disclosure: All authors have declared no conflicts of interest.
Penetrated (PEM) maintenance therapy produced a high magnitude of PFS improvement. The OLCSG 0903 phase 2 trial investigated efficacy and safety of cisplatin (CDDP)-docetaxel (DOC)-BEV induction therapy followed by BEV-PEM maintenance therapy in patients with advanced nonsquamous non-small cell lung carcinoma.

Methods: In this trial, 40 patients with good PS (0 or 1) participated in the induction phase, specified as four cycles of induction CDDP (80 mg/m²), DOC (60 mg/m²) and BEV (15 mg/kg) on day 1 of a 21-day cycle. Patients who had not progressed during CDDP-DOC induction received maintenance BEV (15 mg/kg) and PEM (500 mg/m²) on day 1 of a 21-day cycle until disease progression. The primary endpoint was PFS, and the secondary endpoints included toxicity, OS and response rate.

Results: Patient characteristics were as follows: median age: 62 years; 78% male; 100% Japanese; 30% PS 0, 73% stage IV; and 70% adenocarcinoma. At the time of this analysis, 23pts (58%) discontinued the treatment, and the proportion of discontinuations to AEs was 35% (8/23). The principal toxicity was myelosuppression (grade 4 hematological: 20 patients [50%]), and grade 3/4 febrile neutropenia was observed in 10 (25%) despite no treatment-related deaths. The observed response rate and disease control rate (% patients with CR/PD/SD) was 82.5% and 97.5%, respectively. However, the median PFS was 10.2 months, and the 6-month PFS rate was 63.2% (95% confidence interval: 44.9-76.9%).

Conclusions: CDDP-DOC induction followed by BEV-PEM maintenance seems an effective and moderately tolerated treatment for patients with advanced nonsquamous non-small cell lung carcinoma.


1329
META-ANALYSIS OF RELATIONSHIP BETWEEN SKIN RASH AND OUTCOME IN NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS TREATED WITH ERLOTINIB (E) AND GEFITINIB (G)

Medical Oncology Division, Azienda Ospedaliera Treviso-Caravaggio, Treviglio, ITALY

Introduction: Dermatological toxicity in the form of acniform rash is a common event in NSCLC patients being treated with anti-EGFR TKIs. An association between clinical benefit by EGFR-targeted therapy and development of this form of skin toxicity has been noted. The objective of this meta-analysis was to assess the predictive value of skin rash for outcome in patients with NSCLC treated with E or G.

Materials and methods: Prospective clinical trials or retrospective case series with reported survival (OS), progression (PFS/TTP) and response rate (RR) as a function of skin rash were searched in PubMed until January 2012. The selected studies have to include adult patients with histologically confirmed NSCLC treated with G or E, alone or in combination with other approved agents. Hazard ratios with 95% confidence intervals (HRs) for PFS/TTP and OS and risk ratios (RRs) for response rate in patients with rash were pooled in a meta-analysis.

Results: Twenty-four publications were included in this meta-analysis (17 prospective trials and 7 retrospective case series) for a total of 3632 patients. For the primary endpoint (OS) the occurrence of skin rash was significantly associated to reduced risk of death in patients treated with E or G (HR 0.39, p < 0.0001). The HR for progression with skin rash was significant too (HR 0.50, p < 0.0001). Skin rash was also a significant predictor of activity with a RR of 1.89 (p < 0.0001) for patients with toxicity compared to patients with no or mild grade toxicity. In particular response rate ranged between 7% for patients with no rash to 42% for patients with more severe rash. The results are similar for both the drugs.

Conclusion: A predictive factor as cutaneous rash that can be objectively evaluated during the course of the disease treatment could be useful in NSCLC to decide early the course of treatment and to shift to another line of treatment. The occurrence of skin rash during treatment with anti-EGFR TKIs for NSCLC represents a significant strong predictor of efficacy of these drugs.

Disclosure: All authors have declared no conflicts of interest.

1330
A MULTICENTER, RANDOMIZED PHASE II STUDY OF V (VINORELBINE)/C (CISPLATIN)/B (BEVACIZUMAB) FOLLOWED BY D (DOCETAXEL)/G (GEFITINIB)/B VERSUS D /C/B AS A FIRST-LINE THERAPY FOR ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (NSCLC)

MedicOnco, Hellenic Oncology Research Group (HORG), Athens, GREECE

Background: The combination of D/G has shown equal activity compared to the platinum-based doublets, which is considered the cornerstone for the treatment of NSCLC, with a more favorable toxicity profile. Sequential therapy with four active drugs, including C, was recently investigated and attributed a favorable response rate (Pallis A, et al; Lung Cancer 2006 52(2): 165-71). Incorporation of B to the standard platinum-based regimen improved its clinical outcome. The efficacy of sequential four drug treatment in combination with B was compared to the standard non-platinum-based regimen combined with B.

Methods: Seventy-seven treatment-naive patients with unresetable stage IIIIB and IV non-squamous NSCLC were randomized to receive V 60 mg/m² PO on day 1 and 8, C 80mg/m² IV on day 1 and B 15 mg/kg IV on day 1, for 3 cycles followed by D 75 mg/m² IV, G 1100 mg/m² IV and B 15 mg/kg IV, all on day 1 (Arm A) or D 75 mg/m² IV, C 80mg/m² IV and B 15 mg/kg IV on day 1. The cycles were repeated every 3 weeks for a total of 6 cycles. The primary endpoint was response rate (RR) and the secondary endpoints overall survival (OS) and progression free survival (PFS).

Results: Thirty-nine patients were randomized to arm B (control) and 38 patients to the sequential arm. The overall RR was 36.8% and 46.2% in arm A and B, respectively (p = 0.49). There were 3 complete responses, one in arm A. Median PFS was 5.77 and 5.53 months in arm A and B, respectively (p = 0.368). Median OS was 16.9 and 10.9, respectively (p = 0.39). The estimated 1 and 2-year survival for arm A versus B were 64.1% and 35% versus 48.4% and 24%, respectively. No difference in the toxicity profile was observed between the 2 arms, although more cycle-delays were observed in the experimental arm (29.5 versus 12.2; p = 0.001).

Conclusion: Sequential treatment with four active drugs is feasible and safe. The combination attributes encouraging results compared to the standard platinum-based regimen.

Disclosure: All authors have declared no conflicts of interest.

1331
COMPARISON OF SURVIVAL IN PATIENTS WITH ADVANCED LUNG ADENOCARCINOMA TREATED BEFORE AND AFTER GEFITINIB APPROVAL IN CHINA

Y. Shi1, Y. Liu2, X. Hao1, J. Li, X. Hu1, Y. Wang2, Z. Wang2, H. Wang2, X. Han1, X. Zhang1
1Oncology, Cancer Hospital-China Academy of Medical Sciences, Beijing, CHINA, 2Medical Oncology, Cancer Hospital-Chao Yang District BeijingCAMS and PUMC, Beijing, CHINA

Objective: This study compared the overall survival (OS) between advanced lung adenocarcinoma patients of before and after gefitinib approval in China.

Methods: The clinical data of 558 advanced lung adenocarcinoma patients who ever received palliative chemotherapy were retrospectively analyzed. According to a matched-pair case-control study design, 255 patients of before gefitinib approval who only received palliative chemotherapy and 255 patients of after gefitinib approval who received gefitinib treatment were matched by age, sex and smoking history.
Results: The median survival time (MST) of 510 advanced lung adenocarcinoma patients from the date of first-line palliative therapy was 22.8 months. MST was significantly longer among the patients treated with gefitinib after gefitinib approval compared with the patients treated before gefitinib approval (33.5 vs. 14.1 months, p < 0.001). Multivariate analysis showed that the independent prognostic factors to significantly improve OS of 510 patients included gefitinib treatment (hazard ratio 0.175, P=0.001), age > 60 years, non-smoker, no hepatitis metastasis and receiving ≥ 3 prior cytotoxic chemotherapy regimens. Patients after gefitinib approval showed significantly longer OS in almost all clinical factors subgroups (p < 0.001) including age, sex, smoking history, EGOG PS 0-1, tumor stage, sites of metastasis including lung, pleural, bone, brain, adrenal gland and liver and numbers of prior cytotoxic chemotherapy regimens, except EGOG PS ≥2 subgroup (p = 0.096). Multivariate analysis showed that non-smoker, receiving ≥3 prior cytotoxic chemotherapy regimens and EGFR mutation were associated with longer OS of 250 patients after gefitinib approval.

Conclusion: Gefitinib treatment significantly improved the survival of the patients with advanced lung adenocarcinoma in China.

Disclosure: All authors have declared no conflicts of interest.

QUALITY OF LIFE ANALYSIS IN THE GALAXY TRIALTM (NCT01348126): A RANDOMIZED PHASE III/III STUDY OF GANETESPIB (STA-9090) IN COMBINATION WITH DOCETAXEL VERSUS DOCETAXEL ALONE IN PATIENTS WITH STAGE IIIIB OR IV NSCLC

Z.G. Andric1, L. Hasefi2, I. D. Harly2, V. Vukovic3, F. Teofillović4, W. Guo5, S. Mucareli6, R. Bradley7, T. Čerić7

1Medical Oncology, KBC Beznjinska Kosa, Novi Beograd, SERBIA
2Pneumology- Budniva 2, Fakultet Nemocnice Na Bulovce, Praha, CZECH REPUBLIC
3Oncology, Synta Pharmaceuticals, Lexington, MA, UNITED STATES OF AMERICA
4Oncology, Synta Pharmaceuticals Corp., Lexington, MA, UNITED STATES OF AMERICA
5Oncology, Synta Pharmaceuticals, Lexington, MD, UNITED STATES OF AMERICA
6Oncology, Synta Pharmaceuticals, Lexington, MA, UNITED STATES OF AMERICA
7Oncology, Hellenic Oncology Research Group (HORG), Athens, GREECE

Background: Inhibition of Hsp90, a key molecular chaperone required for activation and function of many oncproteins, can lead to cancer cell death. Ganetespib is an Hsp90 inhibitor that has shown single agent activity in patients with NSCLC, breast and gastric cancers. Combination therapy in 2nd line NSCLC has been hampered by inferior results compared to single agent activity. In a phase II/III study, ganetespib plus docetaxel showed evidence of improved quality of life (QoL) in advanced NSCLC patients. This randomized trial compared ganetespib (G) + docetaxel (D) to D in 2nd line advanced NSCLC patients.

Methods: This randomized trial compared ganetespib (G) + docetaxel (D) to D in 2nd line advanced NSCLC patients. The primary endpoints included disease control rate, overall survival and patient-reported outcomes as measured by the QoL Questionnaire using the EORTC QLQ-C30. The questionnaire was completed at 3 time points through the study: at baseline, at weeks 6 and 12 of study treatment. The impact of G on pain, fatigue, and dyspnea were explored. Changes from baseline were calculated at each time point for each domain or symptom.

Results: Approximately 160 of the 300 planned patients were enrolled by early May. Baseline characteristics were balanced. The overall safety profile of the combination is comparable to D arm. QoL in patients treated with D + G was not negatively impacted compared with those receiving D alone. Analysis of the symptom scale showed a trend towards improvement for pain, fatigue, and appetite loss. There was a marked improvement in dyspnea scale with G + D compared to D. As expected, the functional status was stable and didn’t demonstrate significant difference in the QoL deterioration between the 2 treatment arms.

Conclusions: The addition of ganetespib to docetaxel has no negative impact on QoL as assessed by EORTC QLQ-C30.

Disclosure: All authors have declared no conflicts of interest.
received docetaxel (75mg/m² IV), cisplatin (80 mg/m² IV) and bevacizumab (15 mg/kg IV) in cycles of 21 days. Patients did not receive maintenance bevacizumab.

Results: All patients were eligible for response. Complete and partial responses were achieved in two (4.2%) and 14 (29.2%) patients, respectively (overall response rate: 33.3%; 95% CI = [20.0%-46.7%]) whereas stable disease was documented in 14 patients. The median PFS was 4, 4 months (95% CI: 1.32-7.48) and the median OS 13.27 (95% CI: 9.72-16.81). Treatment-related grade 3 or 4 hematologic adverse events were leucopenia, neutropenia, and anemia in 8.4%, 18.7%, and 2.1% of the patients, respectively. Three (6.3%) patients developed grade 2-4 febrile neutropenia and one (2.1%) patient (2.1%) died because of sepsis due to bowel perforation.

Conclusions: The DCV regimen is an active regimen with manageable toxicity when administered as front line treatment in patients with advanced non-squamous NSCLC and merits to be further investigated.

Disclosure: All authors have declared no conflicts of interest.

1336 CLINICAL MODES OF EGFR TYROSINE KINASE INHIBITOR FAILURE AND SUBSEQUENT MANAGEMENT IN ADVANCED NON-SMALL CELL LUNG CANCER

H. Chen, J. Yang, H. Yan, X. Zhang, Z. Wu, Y. Wu
Guangdong Lung Cancer Institute, Guangdong General Hospital (GGH) & Guangdong Academy of Medical Sciences, Guangzhou, CHINA

Context: The diversity of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) failure in advanced non-small cell lung cancer (NSCLC) has been reported sporadically, but there is no published overview of EGFR-TKI failure modes, which could hinder the appropriate management for patients with distinct failure modes.

Objectives: This study mainly aimed to classify the diversity of TKI failure, and to investigate the usefulness of clinical modes in subsequent management and prognosis.

Patients and methods: The retrospective study accrued 227 Chinese advanced NSCLC patients with EGFR-TKI failure. One-hundred and twenty consecutive clinical trial patients were enrolled as the training set to establish a clinical model based on clinical factors. Another 107 routine patients were enrolled as the validating set according to a Bayes discriminant analysis. EGFR mutations and c-MET amplification were analyzed. Kaplan-Meier survival analysis was used to test the differences of prognosis and subsequent management in clinical modes.

Results: The duration of disease control, symptom improvement, and evolution of tumor burden were verified as feasible grouping variables. A correct grouping rate achieved 84.1%. The cohort was classified into three groups, as follows: 130 patients with dramatic progression, 42 with gradual progression, and 55 with local progression. Progression-free survivals (PFSs) for the dramatic progression, gradual progression, and local progression groups were 9.3, 12.9, and 9.2 months, respectively (P = 0.037). Overall survivals for the four groups (OSs) were 17.1, 39.4, and 23.1 months, respectively (P = 0.001). TKI continuation was superior to switching chemotherapy in a subsequent setting for gradual progression (39.4 vs. 17.8 months, P = 0.02). The difference of EGFR mutations or c-MET amplification among the three groups was not significant.

Conclusions: Clinical modes of EGFR-TKI failure could favor strategies for subsequent treatment and predicting a survival benefit in advanced NSCLC.

Disclosure: All authors have declared no conflicts of interest.

1337 NP CHEMOTHERAPY PLUS ENDOSTAR COMPARED WITH NP ALONE AS FIRST-LINE THERAPY IN STAGE III/B/IV NON-SMALL CELL LUNG CANCER: A RETROSPECTIVE STUDY

M. Zhao1, H. Deng1, B. Jin1, P. Yu1, Y. Luo1, X. Xu1, Y. Teng1, Q. Guan1, Y. Liu1
1Medical Oncology, The First Hospital of China Medical University, Shenyang, CHINA, 2Department of Medical Oncology, The First Hospital, China Medical University, Shenyang, CHINA

Purpose: Recombinant human endostatin is a novel inhibitor of tumor angiogenesis. Previous studies have indicated that Recombinant human endostatin (endostar) plus vinorelbine-cisplatin chemotherapy could improve objective response rates (ORRs) and time to progression (TTP) of advanced non-small cell lung cancer (NSCLC) patients with decreased toxicity. The purpose of this study was to retrospectively compare the efficacy and safety of NP chemotherapy plus endostar or NP alone as first-line therapy in stage III/B/IV non-small cell lung cancer.

Methods: We reviewed the records of 65 previously untreated Chinese patients with stage III/B/IV NSCLC who were treated with NP chemotherapy plus endostar or NP alone between January 2005 and December 2010 at The First Hospital of China Medical University. Vinorelbine (25mg/m²) was administered on days 1 and 8, cisplatin(75mg/m²) was administered on day 1, and endostar (7.5mg/m²) was administered on day 1-14. Treatments were repeated every 3 weeks for a maximum of 6 cycles. The best tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1). The adverse events were defined by WHO-CTC 3.0 criteria. Univariate and multivariate analyses were performed using the SPSS 20.0 software.

Results: The median age of patients was 58 years (range, 34-77 years). Our main results are as follows: Addition of endostar to standard NP significantly reduced the risks of disease progression and death. The median progression-free survival of the NP plus endostar group and NP group were 7.4 months and 5.5 months (P = 0.042). The median overall survival of the NP plus endostar group and NP group were 16.6 months and 12.6 months (P = 0.004). There was no statistical difference in objective response rates and disease control rates between the two groups. The incidence of grade 3/4 hematologic adverse events was higher in NP plus endostar group (48.5% vs 21.9%, P = 0.025) but tolerable.

Conclusion: This study demonstrated that the addition of endostar to the NP regimen is effective in treating patients with advanced NSCLC with an acceptable increase in hematologic toxicity in previously untreated patients with stage III/B/IV non-small cell lung cancer.

Disclosure: All authors have declared no conflicts of interest.

1339 IMPACT OF EGFR MUTATION STATUS ON CLINICAL BENEFIT FROM BIBW 2992 IN PATIENTS (PTS) WITH ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC) PROGRESSING AFTER CHEMOTHERAPY (CTX) AND ERLOTINIB (E) OR Gefitinib (G) – A SINGLE CENTER EXPERIENCE

J. Köhler1, K. Worm2, T.C. Gauler1, M. Hoiczyk1, D. Theegarten2, W. Eberhardt1, J. Henze1, F. Breitenbuecher1, K.W. Schmid2, M. Schuler3
1Department of Medical Oncology, West German Cancer Center, University Hospital Essen, Essen, GERMANY, 2Department of Pathology, West German Cancer Center, University Hospital Essen, Essen, GERMANY

Background: The reversible EGFR tyrosine kinase inhibitors E and G are effective treatments for advanced NSCLC, but most pts acquire resistance. Currently, the...
benefit from sustained EGFR blockade during subsequent salvage therapy is unclear. Docetaxel as a second-line treatment provides better PFS and OS for advanced NSCLC patients through comparing the efficacy, toxicities and therapeutic schema. Background: Docetaxel has been approved as a second-line therapy for advanced non-squamous NSCLC patients. The objective of the study was to provide real-world data of docetaxel regimen as second-line treatment in Chinese NSCLC patients through comparing the efficacy, toxicities and therapeutic schema. Methods: 1220 advanced NSCLC patients who had received docetaxel regimen as second-line treatment from nationwide 47 clinical centers in China from April 2009 to October 2010 were analyzed. The primary end point was overall survival (OS). Progression-free survival (PFS), response, toxicities and therapeutic models of docetaxel were assessed as secondary end points. Survival analysis was evaluated by Kaplan-Meier method. Single factor analysis and the COX regression model were performed to analyze the relationship between the influential factors and the prognosis of disease. Results: Docetaxel as second-line treatment for NSCLC associated with high response rate (RR) of 29.7%, median PFS of 8.2 months, median OS of 16.1 months. TNM staging (IV vs non-IV, P = 0.0270) and docetaxel regimen (docetaxel-based combinations vs docetaxel alone, P < 0.0001) were the prognostic factors for the studied group. The hematologic toxicity was the main adverse effect for docetaxel regimen. The most common grade III/IV adverse events were febrile neutropenia (4.3%), leucopenia (9.3%), neutropenia (11.6%), thrombocytopenia (0.6%), anemia (0.3%), nausea (1.6%), vomiting (1.6%), and alopecia (5.2%) in the total group. OS (608/1220, 49.8%) patients were treated with docetaxel alone, and 612 (612/1220, 50.2%) with docetaxel-based combinations. Compared with docetaxel alone regimen, docetaxel-based combinations better prolonged the PFS (9.0m vs 7.1m, P < 0.0001) and OS (296.6m vs 14.3m, P < 0.0001) for advanced NSCLC. The toxicity of combination therapy was significantly higher in terms of hematologic (P = 0.0197) and non-hematologic adverse events (P = 0.0322) compared with docetaxel alone. Conclusions: Docetaxel as a second-line treatment provides better PFS and OS for Chinese NSCLC patients. The hematologic toxicity is the main adverse effect for docetaxel regimen. Owing to the limitation of registry study, further studies are warranted to confirm these findings. Disclosure: All authors have declared no conflicts of interest.

1341

DOCETAXEL REGIMEN AS SECOND-LINE TREATMENT FOR PRETREATED ADVANCED NSCLC PATIENTS - A LARGE-SCALE, MULTICENTER, UNCONTROLLED, REGISTRY STUDY IN CHINA

S. Lui1, Y. L. Wu2, Y. Z. Wang1, X. Song1, L. Q. Jia4, G. Y. Chen3, T. Sun5, K. Li6, M. Ouyang2, H. Zhao1

1Shanghai Lung Tumor Clinical Center, Shanghai Chest Hospital, Shanghai, CHINA, 2Department of Clinical Oncology, Guangdong General Hospital (GGH) & Guangdong Academy of Medical Sciences, guangzhou, CHINA, 3Department of Medical Oncology, Peking Union Medical College Hospital, Beijing, CHINA, 42nd Department of Respiratory Diseases, Shanxi Cancer Hospital, TAIYUAN, CHINA, 5Oncology Department of Integrative Medicine, China Janpan Friendship Hospital, Beijing, China, 6Department of Medical Oncology, Hefongiang Lung Cancer Hospital, Harbin, CHINA, 7Department of Medical Oncology, Liaoning Cancer Hospital, Shenyang, CHINA, 8Department of Medical Oncology, Jiangsu Province Hospital, Nanjing, CHINA, 9Department of Thoracic Surgery, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, CHINA, 10Department of Medical Oncology, The 301 Military Hospital, Beijing, China

Background: Docetaxel has been approved as a second-line therapy for advanced non-squamous NSCLC patients. The objective of the study was to provide real-world data of docetaxel regimen as second-line treatment in Chinese NSCLC patients through comparing the efficacy, toxicities and therapeutic schema. Methods: 1220 advanced NSCLC patients who had received docetaxel regimen as second-line treatment from nationwide 47 clinical centers in China from April 2009 to October 2010 were analyzed. The primary end point was overall survival (OS). Progression-free survival (PFS), response, toxicities and therapeutic models of docetaxel were assessed as secondary end points. Survival analysis was evaluated by Kaplan-Meier method. Single factor analysis and the COX regression model were performed to analyze the relationship between the influential factors and the prognosis of disease. Results: Docetaxel as second-line treatment for NSCLC associated with high response rate (RR) of 29.7%, median PFS of 8.2 months, median OS of 16.1 months. TNM staging (IV vs non-IV, P = 0.0270) and docetaxel regimen (docetaxel-based combinations vs docetaxel alone, P < 0.0001) were the prognostic factors for the studied group. The hematologic toxicity was the main adverse effect for docetaxel regimen. The most common grade III/IV adverse events were febrile neutropenia (4.3%), leucopenia (9.3%), neutropenia (11.6%), thrombocytopenia (0.6%), anemia (0.3%), nausea (1.6%), vomiting (1.6%), and alopecia (5.2%) in the total group. OS (608/1220, 49.8%) patients were treated with docetaxel alone, and 612 (612/1220, 50.2%) with docetaxel-based combinations. Compared with docetaxel alone regimen, docetaxel-based combinations better prolonged the PFS (9.0m vs 7.1m, P < 0.0001) and OS (296.6m vs 14.3m, P < 0.0001) for advanced NSCLC. The toxicity of combination therapy was significantly higher in terms of hematologic (P = 0.0197) and non-hematologic adverse events (P = 0.0322) compared with docetaxel alone. Conclusions: Docetaxel as a second-line treatment provides better PFS and OS for Chinese NSCLC patients. The hematologic toxicity is the main adverse effect for docetaxel regimen. Owing to the limitation of registry study, further studies are warranted to confirm these findings. Disclosure: All authors have declared no conflicts of interest.

1342

ERLOTINIB (ERL) VERSUS Pemetrexed (MTA) AS SECOND-LINE TREATMENT FOR NON-SQUAMOUS NON- Small Cell Lung Cancer (NSNSCLC): EFFICACY AND SAFETY DATA

J. Zugazagoitia1, J. Puente1, S. Hernandez2, J.L. Gonzalez-Larriba1, J. Sanz2, A. Manzano5, E. Diaz-Rubio1

1Medical Oncology, Hospital Clinico San Carlos, Madrid, Spain, 2Pulmonology, Hospital Clinico San Carlos, Madrid, Spain

Background: A recently published study shows that ERL and chemotherapy (MTA/ docetaxel) offer similar efficacy outcomes in pretreated patients (p) with advanced NSCLC, and a direct comparison of ERL versus MTA in a prospective, randomized phase III trial also shows equivalent efficacy. However, both studies were conducted before the treatment-by-histology interaction effect was observed for MTA and p were not prospectively selected based on histology. Moreover, both studies included p considered optimal candidates for randomized trials, not always representative of the entire patient population. Material and methods: P with advanced nNSCLC treated with ERL (150 mg/p.o.) or MTA (500 mg/m2 on d1, every 3 weeks) as 2nd-line treatment were included in the study. This single-centre, retrospective, observational study was conducted to...
compare the efficacy and safety of ERL versus MTA in non-selected p with nNSCLC who have progressed after 1st-line chemotherapy in a clinical practice scenario.

Results: From 2006-2011, 67 p fulfilled eligibility criteria, ERL (n = 32) and MTA (n = 35). Baseline characteristics ERL/MTA: median age 67.65 yrs.; male 69/80%; smokers 34/40%; PS ≥ 2 22/26%; adenocarcinoma 91/71%; stage IV 77%; EGFR mutation positive 19/3%. No difference in terms of OS, 8.9 m (ERL) vs 7.1 months (MTA) (p = 0.551). Statistically significant differences were recorded for PFS, 3.5 (ERL) and 2.3 months (MTA) (p = 0.002) and a relative reduction in risk of progression of 53.5% for ERL vs MTA (p = 0.005). SLP differences remained statistically significant when adjusting for EGFR mutation status, histology, primary response to 1st-line treatment and location of metastatic sites. OS showed a non-statistically significant difference after adjusting for each variable. The DCR was 46% in the ERL and 31% in the MTA arm (p = 0.46). There was more grade 3-4 hematologic toxicity, anemia (8.5%), thrombopenia (11.4%) and neutropenia (5.7%), in the MTA arm, and skin rash (9.3%) and diarrhea (6.2%) in the ERL arm.

Conclusions: These results in real-life setting suggest that ERL offers similar efficacy outcomes as MTA for p with nNSCLC, with less and easier manageable toxicity.

Disclosure: All authors have declared no conflicts of interest.

MULTICENTER SURVEY FOR MANAGEMENT BEYOND PROGRESSION DISEASE WITH GEFTINIB IN NON-SMALL CELL LUNG CANCER

T. Sawada, Y. Futamura, J. Shiridoh, Y. Ohno, S. Shigeaki Satoh, O. Ohtsuki, K. Morise, Y. Hasegawa

1Cancer Center, Gifu Municipal Hospital, Gifu, JAPAN, 2Respiratory Medicine, Ogaki Municipal Hospital, Ogaki, JAPAN, 3Respiratory Medicine, Gifu University, Gifu, JAPAN, 4Medical Oncology, Nagoya City University, Nagoya, JAPAN, 5Respiratory Medicine, Me University, Tsu, JAPAN, 6Respiratory Medicine, Nagoya University, Nagoya, JAPAN, 7Respiratory Medicine, Nagoya University Graduate School of Medicine, Nagoya, JAPAN

Purpose: Epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) is effective in patients with EGFR mutations. This survey aimed to determine progression disease (PD) and median time to progression in such patients is generally up to 12 months. Usually, treatment with EGRF-TKI is terminated when disease progression (PD) is confirmed, while acute exacerbation after the withdrawal of EGF-TKI has been reported. To investigate current clinic management beyond PD with gefitinib, multicenter survey was conducted in Japan.

Objective: All patients with EGFR mutation-positive non-small cell lung cancer confirmed PD in the treatment of gefitinib in 2010, were included in this survey to evaluate patients characteristics, progression free survival and overall survival with gefitinib, selection of regimen beyond PD, and response rate.

Result: From the six participating institute, 64 cases (median age 69 years old, exon19 in 34 cases, exon21 in 20 cases, another type in 4 cases respectively) had been enrolled. Gefitinib has been used as first line in 35 cases, as second line in 25 cases, as 3rd line or more in 6 cases. Progression free survival was 13 months, and overall survival was 33 months. In PFS and OS, there is no difference between first line and second line use with gefitinib. Response rate shows good efficacy in patients with good performance status. Beyond PD, gefitinib administration was continued in 9 cases (including additional combined therapy in 4 cases), and erlotinib was switched in 15 cases when platinum doublet in 2 cases, another monotherapy in 19 cases respectively. Response rate was shown 32% in gefitinib, 26.7% in erlotinib for each PD.

Conclusion: In the patients with active EGFR mutation, it is confirmed that antitumor effectiveness is recognized in patients who continues to be treated under EGF-TKI after progression of gefitinib.

Disclosure: All authors have declared no conflicts of interest.

IS CHANGE TO ANOTHER TREATMENT IMMEDIATELY AFTER FAILURE OF GEFTINIB RECOMMENDED IN PATIENTS HARBORING ACTIVATING EPIDERMAL GROWTH FACTOR RECEPTOR MUTATIONS?

K. Asami, T. Okuma, T. Hirashima, M. Kawahara, T. Kawaguchi, K. Okishio, N. Otomo, T. Takuchi

1Clinical Oncology, Kinki-choz Chest Medical Center, Sakai, JAPAN, 2Radiology, Kitai-choz Chest Medical Center, Sakai, JAPAN, 3Department of Thoracic Malignancy, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Osaka, JAPAN, 4Clinical Oncology, Federalization of National Public Service Personnel, Jpn Med Aid Associations, Osaka, JAPAN, 5Internal Medicine, Kinki-choz Chest Medical Center, Sakai-City, JAPAN, 6Internal Medicine, National Hospital Organization Kinki-choz Chest Medical Center, Sakai, JAPAN

Background: Gefitinib is an effective agent for use in treating patients suffering from non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations. However, no optimal strategies have been established for treating these patients after gefitinib fails. Here, we conducted a retrospective study to assess the survival benefit of continued gefitinib treatment in these cases.

Patients and methods: We analyzed gefitinib responders with activating EGFR mutations who developed progressive disease (PD) during the course of therapy. Prognostic variables were analyzed using a Cox proportional-hazards model.

Results: Among the 146 patients retrospectively reviewed, exon 19 deletion mutations and L858R point mutations were detected in 78 and 68 patients, respectively. Median survival time after PD confirmation was 14.9 months (95% confidence interval [CI]: 7.9-21.9), and the median duration of continued gefitinib therapy (n = 3.4 months). Patients who continued gefitinib therapy showed a significant improvement in overall survival (p = 0.01). However, median survival time after PD was 14.9 months (95% confidence interval [CI]: 7.9-21.9), and the median duration of continued gefitinib therapy was 3.4 months. Patients who continued gefitinib therapy showed a significant improvement in overall survival (p = 0.01).

Conclusion: Continuation of gefitinib beyond PD is an effective optional treatment in EGFR-mutated patients.

Disclosure: All authors have declared no conflicts of interest.

POST-PROGRESSION SURVIVAL AFTER ERLOTINIB TREATMENT IN PATIENTS WITH ADVANCED NSCLC

M.P. Trojaník1, A.C. Paiazó1, S. Iríbevaro2, P. Resgino2, D. Pastorelli2, A. Jirillo2

1Pharmacy Department, Istituto Oncologico Veneto, IRCCS, Padova, ITALY, 2Evaluation and Introduction of New Drugs in Cancer Therapy Unit, Istituto Oncologico Veneto IRCCS, Padova, ITALY, 3Medical Oncology II, Istituto Oncologico Veneto ICR-IRCCS, Padova, ITALY

Erlotinib is a potent inhibitor of epidermal growth factor receptor tyrosin-kinase activity and its efficacy has been demonstrated for the treatment of advanced NSCLC in large randomized trials. A prospective observational study was run, using institutional data collected through web-based National Oncology registry, from December 2006 to May 2011. The patients with non-small cell lung cancer, unselected for EGFR mutation/amplification and after at least one line chemotherapy, were treated with erlotinib (150 mg/day orally) until disease progression. Every patient was checked prospectively for toxicity, clinical outcomes, previous line treatments, length of treatment and for treatments following erlotinib using hospital databases. In overall study population (130 patients), the median Time to Progression (TTP) and Overall Survival (OS) were 2.4 and 4.4 months, respectively and 1-year survival rate was 25%. 4 patients achieved partial response and 23 patients achieved stable disease, making the disease control rate 21%. Grade 1-2 rash and diarrhoea were the most frequent adverse events. The subgroup analysis showed significantly improved OS for patients with chemotherapy post-erlotinib (pemetrexed, docetaxel) compared to those with no chemotherapy.

Disclosure: All authors have declared no conflicts of interest.

ERLOTINIB ROLE IN PRETREATED EGFR WILD TYPE CAUSIAN PATIENTS: A RETROSPECTIVE OBSERVATIONAL STUDY


1st Oncological Pulmonary Unit, San Cambio High Specialization Hospital, Rome, ITALY

Introduction: Erlotinib in UE was approved in unselected A-NSCLC patients (pts) (2nd/3rd line and switch maintenance) and in EGFR mutated pts.

Methods: We conducted a retrospective mono-institutional observational study (Jan 2007- May 2012) of Caucasian pts with A-NSCLC, all EGFR wild-type (WT), who received erlotinib in 2nd, 3rd, 4th, 5th line of therapy.191 pts with pretreated A-NSCLC were evaluated, including 108 (57%) treated with erlotinib as 2nd line.

Results: Of 108 pts who received erlotinib in 2nd line the median PFS was 8,4 weeks (wks) with an Overall Survival(OS) of 16,8 wks, of which 59 pts (55%) with ECOG PS 2-3 who had 4,2 wks of mPFS and 8,4 wks of mOS. Selecting pts according to PS 1 had mPFS of 12,6 wks and mOS of 21 wks, compared with 49 pts (45%) with ECOG PS 2-3 who had mPFS of 6,4 wks and mOS of 15,8 wks. Selecting pts according to PS 1 vs PS 2-3 who had mPFS of 12,6 wks and mOS of 21 wks, compared with 49 pts (45%) with ECOG PS 2-3 who had mPFS of 6,4 wks and mOS of 15,8 wks.
represented by 19 pts (32%) female, adenocarcinoma, PS1, never/former smokers with a mPFS of 25.2 wks and mOS of 37.8 wks against the worst one defined by 7 pts (12%) male, squamous, current smokers with mPFS of 8.4 wks and mOS of 16.8 wks. In subsequent lines of therapy where the mPFS of 8.9 wks and with a mOS of 21.0 wks, the PS played a decisive role: PS 1 63 pts (76%) showed respectively 12.6 wks and 25.2 wks of mPFS and mOS respect of 4.2 wks and 8.4 wks of 20 pts (24%) with PS 2/3.

Conclusions: 90% of the Caucasian patients do not express the EGFR mutation, estimated to date in no more than 50-60% of patients diagnosed with A NSCLC. Erlotinib is a standard treatment in 2nd / 3rd line, without adequate studies comparing with chemotherapy in wild-type population. This retrospective analysis, original for the assessment of EGFR mutational status and for the large number of cases, confirms the predictive/prognostic role of the PS 1 for the WT EGFR pts treated with erlotinib across all the lines (p = 0.001), limiting the advantage in the PS 2/3. Moreover, the results of the 2nd line shows that it is possible to identify a group of WT pts with positive characteristics (PS 1, ADC, never / former smokers, female) to receive a greater benefit in survival (p = 0.03) with the use of erlotinib.

Disclosure: All authors have declared no conflicts of interest.

1347

EGFR-TYROSINE KINASE INHIBITOR TREATMENT BEYOND PROGRESSION IN LONG-TERM RESPONDENTS TO ERLOTINIB IN ADVANCED NON-SMALL CELL LUNG CANCER: RELEVANCE OF EGFR MUTATION STATUS

M. Faehling1, R. Eckert1, T. Kampj,1 J. Strtèr1, G. Ott,2 W. Spengler6
1 Klinik für Kardiologie und Pneumologie, Klinikum Esslingen, Esslingen, GERMANY, 2 Oncology Group Practice, Wendlingen, GERMANY, 3 Oncology, Oncology Group Practice, Wendlingen, GERMANY, 4 Pathology, Institut für Pathologie, Esslingen, GERMANY, 5 Pathology, Robert Bosch Krankenhaus, Stuttgart, GERMANY, 6 Medizinische Klinik II, Universitätsklinik Tübingen, Tübingen, GERMANY

Introduction: Some patients with advanced NSCLC show prolonged disease stabilization on treatment with an EGFR-tyrosine kinase inhibitor (TKI) such as erlotinib. It is not clear how to treat patients who progress after prolonged response to erlotinib. We hypothesized that TKI therapy beyond progression with added chemotherapy, radiotherapy or best supportive care may improve survival.

Patients and methods: We retrospectively analyzed all NSCLC patients treated with erlotinib at our institutions since 2004 who progressed after at least stable disease on erlotinib for at least six months. The first 16 patients did not receive further TKI treatment after progression (controls). The following 25 patients were treated with TKI beyond progression (TKI patients). Overall survival (OS) was analyzed for the whole population, a case-control analysis of pairs matched for gender, smoking status, histology, best response to first TKI therapy, and therapy line. Furthermore, OS of patients with known EGFR mutation status (n = 24) and those treated with pemetrexed (n = 21) is reported.

Results: Treatment with TKI and chemotherapy was well tolerated. TKI patients had a significantly longer OS from progression on TKI (case control: median 14.5 vs. 2.0 months, HR 0.154) and longer OS from diagnosis of lung cancer (case control: median 26.8 vs. 12.6 months, 0.420). In NSCLC, proliferative signaling through the Ras/Raf/MEK/ERK pathway is often activated from K-ras mutations. Their efficacy as monotherapy for treating advanced NSCLC has been demonstrated in several trials. In them, only the use of platinum-based therapy has been associated with improved survival.

Conclusion: DC with TKI identify a good prognostic group of pts. Good and prolonged response (> 6 mos) to the first line cht and a PS ≤ 1 are useful predictive factors to select pts who could benefit from receiving a cytotoxic treatment after target agents failure. Aggressive cht strategies do not seem to produce a real advantage in this setting.

Disclosure: All authors have declared no conflicts of interest.

1348

EFFICACY OF CHEMOTHERAPY (CHT) BEYOND TYROSINE KINASE INHIBITORS (TKI) IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS (PTS) UNSELECTED FOR EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATION

P. Tranta1, R. Iacovelli1, A. Palazzo1, D. Pelegrino1, C. Mosillo2, F. Rubini2, A. Preri1, V. Magri1, A. De Benedetto1, E. Cortesi1
1 Department of Radiology, Oncology and Human Pathology, Sapienza University of Rome, Rome, ITALY, 2 Department of Radiology, Oncology and Human Pathology, Policlinico Umberto I, Rome, ITALY

Background: After failure of a second or third line therapy with TKI, many clinicians offer to their advanced NSCLC pts a new line of cht, even if there are no prospective trials that support this choice. We report our experience about cytotoxic treatment administered after a target therapy with Erlotinib or Gefitinib in pts with unknown EGFR mutational status or EGFR wild type.

Patients and methods: Since January 2003 to December 2011, 84 pts received TKI in second or third line and after progression 34 of them were treated with at least one subsequent line of cht. We collected response data, analyzed overall survival (OS) and progression free survival (PFS) of cht beyond TKI with Kaplan-Meier method and correlated them with Disease Control (DC) and PFS of first line cht and TKI using log-rank test.

Results: 29 out of 34 pts received cht as third and 5 pts as forth line treatment. 67.6% of pts received a monotherapy, while 32.4% a combination treatment, platinum based in 7 cases. A response rate (RR) of 20.5% and a DC rate of 52.9% were registered. Median OS post-TKI and PFS were 13 (95% CI, 6.3-19.6) and 3 months (mos) (95% CI 0.5-6.5) respectively. OS of pts who obtained DC during TKI was 18.2 mos compared to 5.7 mos of pts not responder to target treatment (p = 0.019). At univariate analysis good PS ≤ 1 after TKI (p = 0.022), DC (p = 0.025) and PFS > 6 mos with first line cht (p = 0.002) were found to be the only predictive factors of a better PFS with post-TKI cht. At multivariate analysis only the PFS > 6 mos with first line cht was confirmed as an independent predictive factor of better PFS in post-TKI setting (p = 0.05). Age more or less than 65 years (p = 0.7) use of combination (p = 0.84) and platinum-based therapy (p = 0.75) seems not to improve survival outcome and DC of cht beyond TKI.

Conclusions: DC with TKI identify a good prognostic group of pts. Good and prolonged response (> 6 mos) to the first line cht and a PS ≤ 1 are useful predictive factors to select pts who could benefit from receiving a cytotoxic treatment after target agents failure. Aggressive cht strategies do not seem to produce a real advantage in this setting.

Disclosure: All authors have declared no conflicts of interest.

1349

SORafenib in Advanced Non-Small-Cell Lung Cancer: A Retrospective Analysis of Patients in Progression After Two or More Lines of Therapy

S. Vazquez-Estevez1, S. Varela1, B. Campos2, R. Garcia-Campeol3, E. Alvarez4, G. Quinto1, L. Anton-Aparicio5, J.R. Mel6
1 Oncology, Hospital Universitario Lucus Augusti, Lugo, SPAIN, 2 Oncology, Hospital Universitario Lucus Augusti de Lugo, Lugo, SPAIN, 3 Oncology, Complejo Hospitalario Universitario A Coruña, A Coruña, SPAIN, 4 Medical Oncology, Complejo Hospitalario A Coruña, A Coruña, SPAIN

Background: Soraferin (SOR) is a potent inhibitor of c-Raf, b-Raf VEGFR-1/2/3 and PDGFR-b. In NSCLC, proliferative signaling through the Ras/Raf/MEK/ERK pathway is often activated from K-ras mutations. Their efficacy as monotherapy for treating advanced NSCLC has been demonstrated in several trials. In them, SOR improved the rate of disease stabilization in patients who had previously been treated with chemotherapy. Our objective is to confirm the clinical and safety results in daily clinical activity.

Methods: Between October 2008 and December 2011, 16 Caucasian patients with metastatic NSCLC and measurable disease were treated after having received two or more prior lines of therapy for metastatic disease.SOR was administered at a starting dose of 400 mg bid continuously in 28-day cycles. The primary end-point was Progression Free Survival (PFS). The secondary end-points were Overall Survival (OS) and Response Rate (RR).

Results: Median age was 59 years (40-86). 100% patients were PS 0(ECOG) 0/1 (51/11, 31/69%). Most were males (n = 10, 62%). The predominant histologic type was adenocarcinoma (n = 10, 62%). Eighteen (81%) patients were in stage IV at diagnosis. The predominant metastatic sites were lung (n = 9, 56%), lymph nodes, (n = 6, 38%), pleura (n = 4, 25%) and bone (n = 3, 18%). All the pts received an activating EGFR mutation. However, both in patients with and without an activating EGFR mutation, patients treated with erlotinib beyond progression had a longer survival.

Conclusions: In our case-control analysis in long-term erlotinib responders, treatment with TKI beyond progression in addition to chemotherapy or radiotherapy was feasible and produced overall survival. A prolonged survival with erlotinib beyond progression was observed in both EGFR-mutation positive and negative long-term responders to erlotinib.

Disclosure: All authors have declared no conflicts of interest.

1350

METASTATIC NSCLC OUTCOMES AT A SINGLE CANADIAN INSTITUTION OVER A DECADE

S. Otsuka, W. Boland, D. Hao, D. Morris, D.G. Bebb
Oncology, Tom Baker Cancer Centre/University of Calgary, Calgary, AB, CANADA

Background: In the past 10 years, the standard of care in non small cell lung cancer has seen the adoption of several less toxic and better tolerated therapies, allowing a greater proportion of metastatic patients the opportunity to receive 2nd and even 3rd line treatment. We investigated whether this improvement in the number of available therapies for metastatic NSCLC has had any bearing on overall patient survival, by retrospectively analyzing patients diagnosed in 1999, 2004 and 2009 at our centre.

Methods: Demographic details, clinical variables and outcome data were gathered retrospectively via chart review, on NSCLC patients diagnosed at the Tom Baker

Downloaded from https://academic.oup.com/annonc/article-abstract/23/suppl_9/ix400/218620 by guest on 20 August 2018
Tokyo, JAPAN, 2Department of Radiology, Tokyo Medical and Dental University, Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, 1999 to 14.7 months (95% CI: 9.6-14.4) in 2009 (p = 0.2).

systemically treated patients over 1999-2009, from 10.8 months (95% CI: 8.4-13.3) in addition, there was a trend towards increasing median overall survival (MOS) of treatment almost doubled (6.9% in 1999, 9.0% in 2004 and 12.7% in 2009). In 2009). During this time, the proportion of patients who received 2 or more lines of treatment was 6.9% in 1999, 9.0% in 2004 and 12.7% in 2009. This study also suggests a trend toward an increased MOS of patients who received palliative systemic therapy (18.9% in 1999, 23.0% in 2004 and 23.1% in 2009).

Conclusions: Our analysis suggests that there is an increasing proportion of metastatic NSCLC patients being treated systemically at our centre, specifically, the proportion of patients being treated with two or more lines of systemic therapy has increased over the decade from 1999-2009. This study also suggests a trend toward an increased MOS of patients who received palliative systemic therapy (18.9% in 1999, 23.0% in 2004 and 23.1% in 2009). In 2009). During this time, the proportion of patients who received 2 or more lines of treatment was 6.9% in 1999, 9.0% in 2004 and 12.7% in 2009. This study also suggests a trend toward an increased MOS of patients who received palliative systemic therapy (18.9% in 1999, 23.0% in 2004 and 23.1% in 2009).

All authors have declared no conflicts of interest.

Background: Eligibility is often narrowed in clinical trials of targeted drugs because of specific adverse effects. Modified eligibility criteria can affect endpoints such as overall survival independently of the actual effect of an investigational drug.

Methods: Patients with stage IIIIB/IV, non-squamous non-small cell lung cancer (NSCLC) who started chemotherapy from 2005 to 2009 were reviewed. Bevacizumab (BV) was first used to treat lung cancer at our institution in 2010. We divided patients into BV-eligible (A) and ineligible (B) groups. To estimate survival, Kaplan-Meier curves were calculated and compared between the groups using the log-rank test. We also examined the prognostic impact of age, gender, M factor, performance status (PS), use of platinum in first-line chemotherapy, history of hemoptysis, major blood vessel invasion (MVI) by the tumor and clinically significant cardiovascular disease upon overall survival using the Cox proportional hazards model. A radiologist who was blinded to the clinical outcomes evaluated MVI. All tests were two sided with a significance level of 0.05.

Results: Among 576 patients with lung cancer who underwent chemotherapy at our department, 283 of them had stage IIIIB/IV non-squamous NSCLC. After excluding 15 patients with indications for combined chemoradiotherapy and 22 patients with PS 3/4, the remaining 147 patients were classified into cohort A. Overall survival was significantly better in cohort A (median, 14.9 months) than in cohort B (median, 8.6 months; hazard ratio, 0.55; 95% CI, 0.42-0.74; P <.0001). Multivariate analysis indicated that gender, PS, a history of hemoptysis and MVI are significant prognostic factors.

Conclusion: Eligibility for BV itself is a powerful prognostic factor for patients with non-squamous NSCLC.

Disclosure: All authors have declared no conflicts of interest.

Background: In combination with platinum doublets prolongs survival and delays PD in chemo-naïve pts with advanced non-SCLC and its safety profile has been widely described in clinical trials. In this study we aim to evaluate the behavior, clinical profile and patterns of PD of real-life nSCLC pts treated with B in 44 Spanish institutions.

Methods: AVVA is a multicenter, epidemiological study to define the clinical profile (gender, age, PS, histology, stage, comorbidities, tumor load, Tx, response and tolerability) and describe the patterns of PD. Pts diagnosed with advanced nSCLC and evidence of PD after treatment (Tx) with standard chemotherapy (CT) plus B up to 6 cycles followed by maintenance B were included.

Results: Data of 158 pts are presented. Clinical profile was: median age 58 years (range 34-79); male 65%; stage IV 91%; adenocarcinoma 77%; ECOG PS 0/1/2 (35/56/9); never/current/former smokers (%) 24/30/46. 64% of pts presented relevant concomitant disease at baseline (27% cardiovascular disease, 24% pulmonary disease). Tx received: B plus carboplatin-doublet/cisplatin-doublet/other (%) 70/25/5. Median no. of cycles for CT/B: 6/9. Patterns of PD: 44% presented high tumor load (tumor diameter 25 mm and ≥ 5 lesions); 97% of pts presented intra-thoracic disease; 53% presented extra-thoracic disease and 13% only pulmonary disease. High tumor load was associated with extra-thoracic disease (p = 0.05). ORR was 53% (95% CI: 45-61) and disease control rate was 85%. Best response was achieved after a median of 4 cycles (range 1-16). ECOG 0/1 at PD (%): 15/50. Median PFS was 7.7 months (95% CI: 7.3-8.1). No differences were found in ORR or PFS according to tumor load and intra/extra-thoracic disease. Grade 3/4 toxicities were: venous thrombosis (3.2%), diarrhea (0.6%), hemoptysis (0.6%), pulmonary embolism (0.06%) and mucositis (0.6%).

Conclusions: B was effective in this real-life patients’ population, irrespective of tumor load and location of the disease. These results confirm the well-established safety profile and the efficacy of B as frontline Tx in nSCLC.

Disclosure: All authors have declared no conflicts of interest.

Background: The additional effects of bevacizumab (B) as a first line chemotherapy for non-squamous (Nsq) non-small cell lung cancer (NSCLC) have been established. However, its efficacy as a second line or higher chemotherapeutic agent is not sufficiently investigated. Docetaxel (D) is a standard second line therapy for NSCLC, and the synergistic effects of a combination of D and B (D + B) have been demonstrated in preclinical models. Therefore, this phase II study evaluated the efficacy and safety of D + B in patients with previously treated Nsq NSCLC.

Methods: Patients with histologically or cytologically confirmed Nsq NSCLC (20-74 years) with an Eastern Cooperative Oncology Group performance status (PS) of 0-2
Conclusions: A combination of D and B was highly active in patients with previously treated NsQ NSCLC, further study is warranted.

Disclosure: All authors have declared no conflicts of interest.

---

**PHASE II TRIAL OF SINGLE-AGENT PEMETREXED IN CHEMOINAIVE ELDERLY PATIENTS WITH ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC) AND ITS ACCRUAL RATE IN A COMMUNITY-BASED CLINICAL TRIAL GROUP: LCEN1001**

N. Sakai1, T. Yokoyama2, K. Kishi3, T. Takao4, I. Tsujino5, N. Takahashi5, S. Pilotto7, R. Camisa1, A. Ardizzoni1

1Division of Medical Oncology, Department of Internal Medicine, Tokai University School of Medicine, Tokyo, JAPAN, 2Department of Respiratory Medicine, Kyorin University Hospital, Tokyo, JAPAN, 3Dept. of Respiratory Medicine, Toranomon Hospital, Tokyo, JAPAN, 4Division of Respiratory Medicine, Itabashi Chuo Medical Center, Itabashi, JAPAN, 5Respiratory Medicine, Nihon University School of Medicine, Tokyo, JAPAN, 6Biosatistics and Epidemiology, Yokohama City University Medical Center, Yokohama, JAPAN

Background: Optimal treatment for elderly patients with advanced NSCLC has been under investigation. This study evaluated the safety and efficacy of single-agent pemetrexed for elderly patients with advanced NSCLC. Moreover, the reasons that prevented accrual and the preferential regimen for such patients in a community-based group were investigated.

Patients and methods: Chemonaive elderly (≥70 years) patients with stage IIIIB/IV non-squamous NSCLC received 500 mg/m² of pemetrexed (day 1, every 3 weeks) for 4-6 cycles. As a QOL assessment, FACT-L lung cancer symptom subscale and Comprehensive Geriatric Assessment were also evaluated. Moreover, clinical trial enrollment decisions were noted.

Results: From May 2010 to October 2011, 119 consecutive patients were diagnosed as chemonaive elderly (≥70 years) patients with stage IIIIB/IV non-squamous NSCLC. Among 25 patients, they were enrolled in phase II trial. Characteristics were m/f, 19/6; median age, 78 years (range 70-89); PS 0/1/2, 6/18/1; stage IIIIB/IV, 6/19. After a median of 4 cycles of pemetrexed, the ORR and DCR were 16.0% and 68.0%, respectively. Furthermore, the median PFS was 12.6 months and the median OS was not reached. Grade 3/4 hematoxicity consisted of leucopenia (20%), neutropenia (24%), thrombocytopenia (4%), and anemia (12%), whereas grade 3/4 non-hematologic toxicity consisted of nausea (4%), anorexia (12%), fatigue (8%), pneumonitis (3%), febrile neutropenia (0%), and treatment-related death (0%). Among 168 patients who were not enrolled in the trial, 83 and 85 patients were eligible and ineligible, respectively. Therefore, the accrual rate was 25 (23.1%) of 108 eligible patients and 25 (13.0%) of total 193 patients, whereas ineligible rate was 85 (44.0%) of total 193 patients. The most common reason for not participating in the trial despite appropriate eligibility was the preference of platinum doublet chemotherapy (57.8%), whereas the most common treatment choice for ineligible patients was best supportive care (67.1%).

Conclusions: Single-agent pemetrexed has shown moderate activity and is well tolerated as first-line treatment for advanced NSCLC in elderly patients. However, in our community-based clinical trial group, platinum doublet chemotherapy was the preferential regimen for such patients.

Disclosure: All authors have declared no conflicts of interest.

---

**ERYTHROCYTE MEAN CORPUSCULAR VOLUME CHANGE DURING PEMETREXED TREATMENT IN ADVANCED NON SMALL CELL LUNG CANCER PATIENTS**

S. Buri1, P. Bordi1, M. Tiseo2, S. Paniri3, S. Novello4, E. Briai5, S.G. Rapiti6, S. Pini6, R. Camisa1, A. Ardizzoni1

1Oncologia Medica, Azienda Ospedaliera-Universitaria di Perma, Parma, ITALY, 2Oncologia Medica, Azienda Ospedaliera di Parma, Parma, ITALY, 3Oncologis, Azienda Istituti Ospitalieri di Cremona, Cremona, ITALY, 4Department of Clinical and Biological Sciences - Thoracic Oncology Unit, Azienda Ospedaliero-Universitaria ASOU San Luigi Gonzaga, Orbassano (TO), ITALY, 5Medical Oncology, Azienda Ospedaliera Universitaria Integrata Verona - "Borgo Roma", Verona, ITALY, 6Department of Clinical and Biological Sciences - Thoracic Oncology Unit, Azienda Ospedaliero-Universitaria ASOU San Luigi Gonzaga, Orbassano, ITALY

Introduction: Pemetrexed (Pem) has been approved for the treatment of advanced non small cell lung cancer (NSCLC) non-squamous histology, both as 1st and 2nd line treatment with or without platinum compounds, respectively. Pem is an antimetabolite drug, that inhibits enzymes involved in nucleotides bio-synthesis arresting cancer cells cycle. Literature data show the effect of antimitabolites on increment of erythrocyte mean corpuscular volume (MCV) in cancer patients (pts) treated with capetitabine and, recently, a positive correlation between increased MCV and response to capetitabine-based therapy has emerged [Arlan et al, Tamori 2011; Dellapasqua et al, Breast 2012]. The aim of this study was the evaluation of the impact of Pem on MCV change and its possible correlation with disease control rate (overall response + stable disease rate) (DCR), progression free survival (PFS) and overall survival (OS) in NSCLC pts.

Methods: A retrospective collection of clinical and laboratory data (including basal MCV and maximum MCV occurred during Pem therapy) in 165 advanced NSCLC pts treated with Pem from 4 Italian centres was performed.

Results: Pts characteristics: 59% men, median age 64 years (range 36-83), 58% ECOG PS 0, 90% stage IV and 10% stage IIIB (according 6th TNM), 87% adenocarcinoma histotype, 74% current or ex-smokers, 59% as 1st line, 41% ≥ 2 line, 68% in combination with a platinum compound, median cycle 4 (range 1-29). All pts received vitamin B12 and folic acid supplementation. Mean MCV significantly increased from basal (89.4 fl) to “during treatment” (94.8 fl), with mean ΔMCV = 5.2 fl (t test for paired data, p < 0.0001). The median time from therapy start to maximum MCV was 2.3 months (mos). DCR was 84% and 62% [χ² test, p = 0.002], median PFS was 6 [95% CI 5.7-8.1] and 3.6 [95% CI 1.9-5.3] mos [p = 0.0019], and median OS was 16.0 [95% CI 7.9-24.1] and 10.8 [95% CI 9.0-12.6] mos [p = 0.0346], in ΔMCV > 5 fl (n = 68) and in ΔMCV ≤ 5 fl (n = 97) pts, respectively.

Conclusion: Pem induces significant increase of erythrocyte MCV. ΔMCV > 5 fl on Pem therapy appears to be correlated with better DCR, PFS and OS. These data should be related to a decreased metabolism of Pem and subsequent increased drug exposure in pts who develop higher ΔMCV during treatment. A larger prospective evaluation could be useful to better clarify these findings.

Disclosure: All authors have declared no conflicts of interest.

---

**PHASE II STUDY OF PEMETREXED IN ELDERLY (≥75) NON-SQUAMOUS NON-SMALL-CELL LUNG CANCER: KYOTO THORACIC ONCOLOGY RESEARCH GROUP TRIAL 0901**


1Respiratory Medicine, Kyoto University-Graduate school of medicine, Kyoto, JAPAN, 2Respiratory Medicine, Hyogo Prefectural Amagasaki Hospital, Amagasaki, JAPAN, 3Thoracic Surgery, Shimane Prefectural Central Hospital, Izumo, JAPAN

Background: Single-agent chemotherapy with non-platinum agents, such as vinorelbine, gemcitabine, and docetaxel (DOC), is considered to be a standard therapeutic option for elderly non-squamous cell lung cancer (NSCLC). Previous randomized trials have reproducibly demonstrated that pemetrexed (PEM) is more effective for non-squamous NSCLC, in contrast to be less effective for squamous cell lung cancer. In addition, although in second-line setting, subgroup analysis of the...
≤70) in terms of both efficacy and toxicity.

Methods: Eligible patients had a performance status 0 to 2, failure of second-line or third-line chemotherapy, and adequate organ function. Patients received AMR 35 mg/m2 intravenously on days 1-3 every 3 weeks. The primary endpoint was disease control rate (DCR: CR + PR + SD). Secondary endpoints were overall survival (OS), progression-free survival (PFS), response rate (CR + PR), and toxicity profile. Elderly patients were defined as those at least 70 years of age at the time of enrollment. The efficacy and safety data for AMR therapy was compared between the elderly and younger patients (< 70 years).

Results: There were 14 elderly and 27 younger patients in this study. Elderly patients accounted for 34% of the study cohort. Clinical characteristics such as PS or histologic subtypes were similar between the groups. The median number of treatment cycles was 3 in elderly and 2 in younger patients. The overall response rate and DCR were 14.3% and 71.4% in elderly patients and 7.4% and 55.5% in younger patients, respectively (p = 0.42 and 0.26). Median PFS was 3.6 and 2.4 months (p = 0.70), whereas median survival time was 11.3 and 13.9 months (p = 0.67) in elderly and younger patients. The most common grade 3/4 toxicity was neutropenia (64.3 vs. 70.4%); overall, there was no major difference in the incidence of hematological and nonhematological toxicities between the groups. No treatment-related death was observed in this study.

Conclusion: Third-line or fourth-line AMR yielded the similar efficacy and toxicity profiles between elderly and younger NSCLC patients. Data from this post-hoc analysis encourage prospective evaluation of potential benefit of AMR in elderly NSCLC patients.

Disclosure: All authors have declared no conflicts of interest.

Impact: This study confirms the efficacy and safety of AMR in elderly patients, which is important for improving outcomes for elderly patients with advanced-stage NSCLC.

Objective: To study the current status of the NSCLC bone metastasis (BM) in China, including the diagnosis, NTX parameters, and the efficacy and safety of bisphosphonates (BP) treatment.
Methods: NSCLC patients with radiographic verification of BM were treated with at least one kind of BP in this prospective observational study. NTX, SRE incidence and adverse event (AE) data were collected at baseline and every 3 months after treatment. Treatment continued at least until death. NTX levels were characterized as normal (N; <50 nmol/mmol) or elevated (E; ≥ 50 nmol/mmol).

Results: By the time of this analysis, 580 patients were enrolled into this study with the median follow-up of 6.1 months. There were 566 patients with baseline NTX results. Most patients (86.7%) had BM diagnosed using CT containing method. The E baseline NTX patients were 374 (66.6%). Patients with multiple BM (459 pts, 81.2%) had significantly higher NTX baseline level than those with single BM (108.9 vs 67.3 nmol/mmol, p = 0.003). The OS was 23.2 months. The overall SRE was 22.2%, and the annual SRE was 3.4 times/person/year. Patients with E baseline NTX had trend of earlier onset of SRE (the median time to first SRE: 1.2 vs 1.6 months, p = 0.179) and shorter OS (20.6 vs not reached, months), especially after 15 months. The frequency of adverse events was 17.1%, study drug related AE was 7.1%, and serious AE was 2.6%. There were no significant changes in serum creatinine levels before and after bisphosphate therapy. No cases of osteonecrosis of the jaw (ONJ) were observed. Zoledronic Acid-related AE was observed in 37 cases (7.7%), and SAE was observed in 14 cases (2.9%).

Conclusion: NSCLC bone metastasis is a relatively common and serious clinical problem in Chinese patients, which were most frequently identified by CT. Baseline NTX level has significant negative impact on SRE. Prolonged bisphosphate therapy could help reduce SRE with acceptable safety profiles.

Disclosure: All authors have declared no conflicts of interest.

1360 RETROSPECTIVE STUDY OF RADIOLOGICAL FINDINGS OF PULMONARY EMBOLISMS (PE) IN PATIENTS (PTS) WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)
1Department of Medical and Biological Sciences - Thoracic Oncology Unit, Azienda Ospedaliero-Universitaria ASOU San Luigi Gonzaga, Orbassano, ITALY, 2Department of Respiratory and Critical Medicine- ASUO San Luigi Gonzaga, Orbassano, ITALY, 3Department of Medical Oncology, University Hospital Santa Maria della Misericordia, Udine, ITALY

Introduction: Venous thromboembolism (VTE) is one of the leading cause of death for cancer pts, with an incidence of 1 event per 110-120 patients, mainly within the first year from diagnosis. Cancer pts with VTE show a 2.2-fold increase in mortality and lung cancer is the second tumor type with the highest incidence of VTE. Considering that chemotherapy is associated with a 6 times increased risk of VTE and that biological agents, especially antiangiogenetic compounds, cause an additional risk, the aim of the study is to evaluate, with a radiological retrospective evaluation, the real incidence of PE in selected cohorts of advanced NSCLC patients and the impact of PE on survival.

Materials and methods: This retrospective monocentric study enrolled 141 advanced NSCLC pts, diagnosed between June 2007 and June 2008 (cohort 1), and between January 2010 and December 2010 (cohort 2). Pts were mostly men, with a median age of 63 years, performance status 0 and a prevalence of comorbidities predisposing to VTE of 42.0% and 70.0% in first and second cohort, respectively. 74.1% and 43.3% of pts received biological agents in first and second cohort; 39.5% and 81.2% had significantly higher NTX baseline level than those with single BM (108.9 vs 67.3 nmol/mmol, p = 0.003). The OS was 23.2 months. The overall SRE was 22.2%, and the annual SRE was 3.4 times/person/year. Patients with E baseline NTX had trend of earlier onset of SRE (the median time to first SRE: 1.2 vs 1.6 months, p = 0.179) and shorter OS (20.6 vs not reached, months), especially after 15 months. The frequency of adverse events was 17.1%, study drug related AE was 7.1%, and serious AE was 2.6%. There were no significant changes in serum creatinine levels before and after bisphosphate therapy. No cases of osteonecrosis of the jaw (ONJ) were observed. Zoledronic Acid-related AE was observed in 37 cases (7.7%), and SAE was observed in 14 cases (2.9%).

Conclusion: NSCLC bone metastasis is a relatively common and serious clinical problem in Chinese patients, which were most frequently identified by CT. Baseline NTX level has significant negative impact on SRE. Prolonged bisphosphate therapy could help reduce SRE with acceptable safety profiles.

Disclosure: All authors have declared no conflicts of interest.

1362I P PHASE II STUDY OF SORAFENIB MONOTHERAPY IN THE PATIENTS WITH ADVANCED OR RECURRENT NON-SMALL-CELL LUNG CANCER AFTER FAILURE OF EGFR-TKI (CTONG0605)
Q. Zhou1, C. Zhou2, G. Chen3, Y. Cheng2, C. Huang2, L. Zhang2, Y-L. Wu1
1Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, CHINA, 2Lung Cancer Institute, Shanghai Pulmonary Hospital, Shanghai, CHINA, 3Haifeng Medical University Affiliated Tumor Hospital, Haifeng, CHINA, 4Jilin Province Tumor Hospital, Jilin, CHINA, 5Fujian Province Tumor Hospital, Fujian, CHINA, 6Sun Yat-Sen University Cancer Center, Guangzhou, CHINA

Background: Sorafenib is a multikinase inhibitor with antitumor and anti-angiogenic activity. This study was designed to evaluate the efficacy and tolerability of sorafenib monotherapy for patients with advanced lung adenocarcinoma previously treated with EGFR tyrosine-kinase inhibitors.

Methods: A phase II, single arm clinical trial (NCT00922584) was conducted in 6 centers in China. Patients with stage IIIIB or IV adenocarcinoma, ECOG score of 0-2, no more than 1 previous chemotherapy regimen with 1 prior EGFR-TKI treatment failure, or, with K-ras mutation were enrolled. Patients received oral sorafenib 400mg bid continuously until disease progression or intolerable toxicity.

Results: Between Dec 2008 and Jun 2010, 65 patients were enrolled and 64 could be analyzed. The median time of sorafenib administrated was 3.7 months (range, 0.23 - 14months). The median follow-up time was 5.5 months (range, 0.3 – 30.6months). The primary endpoint disease control rate (DCR) was 32.8%, including 2 (3.2%) partial responses and 19 (29.7%) patients with stable disease (lasting more than 3 months), which did not meet the predefined statistical hypothesis of 38.4%. However, the secondary endpoint including median PFS and OS were improved compared with previous chemotherapy regimen. The OS was significantly longer compared with previous chemotherapy regimen (2.5 vs 1 months, p=0.03).

Conclusion: The higher incidence of PE in the second cohort, despite a lower exposure to biological and antiangiogenetic agents, could be related to a greater thrombogenic action of these drugs, but also a higher prevalence of comorbidities predisposing to VTE. Descriptive analysis was confirmed by survival data, underlining the need of further studies to clarify the role of predisposing factors for PE.

Disclosure: All authors have declared no conflicts of interest.
reaction (HFSR) (71.9%), and the incidence at 2weeks, 8weeks, 12weeks was 64.1%, 45.3% and 37.5% respectively, showing a decline of HFSR incidence along with the time of therapy. 21.9% of patients occurred ≥grade 2 other dermatologic reactions other than HFSR, followed by diarrhea (26.2%), hypertension (15.4%). Dose interruptions due to toxicity happened in 19 patients (29.2%).

**Conclusion:** Sorafenib monotherapy has encouraging efficacy improving PFS and OS with tolerable toxicity as second or third line treatment in patients with advanced lung adenocarcinoma who failed prior chemotherapy and EGFR-TKI treatment. Further randomized studies are needed to confirm the clinical benefit of sorafenib in such patients.

**Disclosure:** All authors have declared no conflicts of interest.

### A RANDOMIZED, PHASE II, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ONARTUZUMAB (METMAb) WITH EITHER BEVACIZUMAB + PLATINUM + PACLITAXEL OR PEMETREXED + PLATINUM AS FIRST-LINE TREATMENT FOR PATIENTS (PTS) WITH STAGE IIIIB OR IV NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (NSCLC)

**H. Wakelee**1, W. Yu1, K. Rittgerweg2, V.E. Paton2

1Thoracic Oncology, Stanford University Cancer Center, Stanford, CA, UNITED STATES OF AMERICA, 2Oncology, Genentech Inc, South San Francisco, CA, UNITED STATES OF AMERICA

**Background:** Dysregulation of the HGF/Met pathway has been associated with tumorigenesis in many malignancies, including NSCLC. Onartuzumab (MetMAb) is a recombinant, humanized, monovalent monoclonal antibody directed against Met. In a phase I/II study, onartuzumab (+/- bevacizumab) was well tolerated in pts with advanced solid tumors (Moss et al. Ann Oncol 2010;21(Suppl. 8):Abstr. 504P). In a phase II study of pts with previously treated NSCLC, onartuzumab + erlotinib was associated with a significant benefit in PFS (HR 0.53; p = 0.04) and OS (HR 0.57; p = 0.02) compared to erlotinib alone in pts with Met IHC diagnostic-positive (Met-positive) tumors (Spigel et al. J Clin Oncol 2011;29(Suppl.):Abstr. 7505). Pts with Met-negative tumors who received onartuzumab + erlotinib reported worse outcomes compared with erlotinib alone (PFS HR 1.82; p = 0.05; OS HR 1.78; p = 0.16). The most commonly reported adverse events associated with onartuzumab are peripheral edema and fatigue.

**Methods:** In this phase II study, pts with squamous NSCLC are randomized (1:1) to receive 4 cycles of paxlitaxel, carboplatin (or carboptin) and either placebo or onartuzumab. Pts without disease progression may continue to receive placebo or onartuzumab as maintenance therapy until disease progression, unacceptable toxicity, or death. The primary study endpoint is PFS in all pts. Pts by Met IHC diagnostic status (Met positive vs Met negative) will also be analyzed. Secondary endpoints include OS, ORR, safety, and PK. A minimum of 110 pts will be randomized to achieve 55 pts with Met-positive squamous NSCLC. A maximum of 55 pts with Met-negative squamous NSCLC will be enrolled. This study is open for accrual; further details can be found on ClinicalTrials.gov (NCT01519804).

**Disclosure:** F.R. Hirsch: Advisory relationship: Genentech-Roche, Boehringer-Ingelheim, Pfizer, Merck-Serono, Bristol-Myers Squibb. Research funding (through University of Colorado): Imclone-Lilly, Celgene, Morphoetek. Board of Directors: IASLC. D. Gandara: Dr Gandara reports a consultant/advisory relationship with Genentech, Inc. He also receives research funding (through University of Colorado): Imclone-Lilly, Celgene, Morphoetek. W. Yu: Dr Yu is a full-time employee of Genentech, Inc. and minimal stockholder of Hoffmann-La Roche, Inc.

### MUTATION: CENTRAL JAPAN LUNG STUDY GROUP - TREATED NON-SMALL CELL LUNG CANCER PATIENTS WITHOUT EPIDEMICAL GROWTH FACTOR RECEPTOR MUTATION: CENTRAL JAPAN LUNG STUDY GROUP (CJLSQ) 0903 TRIAL

**M. Morita1, H. Taniguchi2, H. Saka3, J. Shinb0, R. Suzuki5, E. Kojima4, T. Harada1, M. Kondo1, H. Saito5, H. Hasegawa5, Y. Hasegawa1, M. Taniguchi1**

1Respiratory Medicine, Nagoya University Graduate School of Medicine, Nagoya, JAPAN, 2Department of Respiratory Medicine and Allergy, Tosei General Hospital, Seto, JAPAN, 3Medical Oncology & Respiratory Medicine, National Hospital Organization Nagoya Medical Center, Nagoya, JAPAN, 4Respiratory Medicine, Ogasawara Municipal Hospital, Ogasawara, JAPAN, 5Respiratory Medicine, Toyohashi Municipal Hospital, Toyohashi, JAPAN

**Background:** Erlotinib has been shown moderate activity for previously treated non-small cell lung cancer (NSCLC) patients with wild-type epithelial growth factor receptor (EGFR). However, the sensitivity of methods for detection of EGFR mutations can influence the efficacy of erlotinib. Moreover, it is controversial about association between K-ras mutations and erlotinib resistance in EGFR wild-type NSCLC. Here, we conducted a phase II study of erlotinib for previously treated NSCLC patients without EGFR mutation screened by PNA-LNA PCR clamp methods, which is known to be highly sensitive method for the detection of EGFR mutations. Furthermore, we have planned exploratory analysis of EGFR mutation status and screening of K-ras mutation status by the Scorpion ARMS method, which is also highly sensitive method among patients whose samples are available for analysis.

**Patients and methods:** Major eligibility criteria were advanced NSCLC with no prior chemotherapy and EGFR wild-type NSCLC. In this study, we have conducted a phase II study of erlotinib for previously treated NSCLC patients without EGFR mutation screened by PNA-LNA PCR clamp methods, which is known to be highly sensitive method for the detection of EGFR mutations. Furthermore, we have planned exploratory analysis of EGFR mutation status and screening of K-ras mutation status by the Scorpion ARMS method which is also highly sensitive method among patients whose samples are available for analysis.

**Disclosure:** All authors have declared no conflicts of interest.
LONG-TERM ERLOTINIB THERAPY IN PATIENTS WITH ADVANCED NON-SMALL CELLO Lung CANCER (NSCLC): INTERIM ANALYSIS OF BASELINE CHARACTERISTICS

C. Chouaid¹, R. Gervais², C. Locher³, D. Moro-Sibilot⁴, B. Commenges⁵, S. Chenoufi⁶

¹APHP, Pneumologie, APHP, Paris, FRANCE, ²Oncologie, CAC, Caen, FRANCE, ³Pneumologie, Meaux, Meaux, FRANCE, ⁴Pneumologie, CHU Grenoble, Grenoble, FRANCE, ⁵France, Roche, Neuilly, FRANCE

Background: Erlotinib has been shown to improve outcomes in patients with recurrent or progressive NSCLC after platinum based chemotherapy. In this clinical setting, some patients derived long-term benefits from erlotinib treatment with at least 9 months of Progress Free Survival (PFS). The aim of this non-interventional prospective study was to analyze the clinical characteristics of these patients. A secondary objective was to evaluate erlotinib long-term safety.

Patients and methods: Patients with advanced NSCLC with recurrent or progressive NSCLC after platinum based chemotherapy treated for at least 9 months by erlotinib followed and followed for at least 24 months have been included prospectively. Patients’ demographics, clinical and histological characteristics, treatments received before erlotinib initiation, data related to erlotinib therapy (line of treatment, dosage, duration of treatment, tolerability), median PFS, objective response rate, overall survival, safety and quality of life data were recorded.

Results: Between June 2010 and June 2011, 205 patients have been included in 76 French institutions. Patients’ characteristics were: mean age, 67.4 ± 10.1 years; Caucasian, 96.5%; ECOG performance status (PS) 0/1/2, 39.3/54.6/14.1 (%); male, 42.9%; current/former/never smokers, 5.9/45.6/38.5 (%), adenocarcinoma, 82.2%; stage IV/IIIIB, 83.3/16.7 (%). Among 42 patients tested, 50% presented activating epidermal growth factor receptor (EGFR) mutation. Erlotinib was administered as first/second/third line treatment in 20.5/50.7/22.4 (%) of patients. Since treatment initiation, most frequent reported grade 3/4 toxicities were folliculitis (8.8%) and diarrhea (4.4%).

Conclusion: These are, to our knowledge, the first data reported prospectively of long-responders with advanced NSCLC treated with erlotinib. The long-term benefit of erlotinib according to the results of this interim analysis seems to be more marked in patients with adenocarcinoma, good PS and never or former smokers. Otherwise the benefit seems to be independent of gender. Erlotinib was well tolerated without life-threatening toxicities.

Disclosure: Chennoufi S is employed by Roche France.