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## 7th Latin American Conference on Lung Cancer (LALCA 2016)

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Background: Patients with epidermal growth factor receptor (EGFR)-mutant lung carcinoma eventually developed acquired resistance to EGFR tyrosine kinase inhibitors (TKI). In 50% of these cases, a secondary EGFR mutation, T790M, underlies the acquired resistance. Other alterations include amplification of MET, PIK3CA, mutations, changes in MAPK1, HER2, AXL and even transformation to small cell lung carcinoma (SCLC). We assessed historical, clinical characteristics and survival outcomes in Hispanic patients with EGFR mutation after disease progression.

Method: 34 EGFR-mutant lung cancer patients with acquired resistance to EGFR TKIs were identified as part of a prospective registry (active between January 2011 and January 2015) in which post-progression tumor specimens were collected for molecular analysis using SNPShot tumor genotyping assay to detect mutations in EGFR, KRAS, BRAF, PIK3CA, TP53, MET and Her2, and FISH for MET, ALK and EGFR. Samples also underwent immunohistochemistry analysis for E-cadherin, synaptophysin, CD56 and PDL1. Post-progression interventions, response and survival were assessed and compared to those with and without T790M.

Results: Mean age was 59.4±13.9 years; 62% were female, 65% were never-smokers and 53% had a performance status ≥280%; main metastatic sites were lung (66/47%), bone (20/58%), brain (18/52%) and liver (15/58%). All patients received erlotinib as first-line treatment and documented mutations were: 60% Del13 (Del1746–750) and 40% L858R. Overall response rate (ORR) with first-line TKI was 61.8% and progression free survival (PFS) was 16.8 months (range, 13.7–19.9 m). After progressing to TKI, all patients were re-biopsied, of whom 16 had the T790M mutation (47.1%); 5 had PIK3CA mutations (14.7%), 5 had EGFR amplification (14.7%), 2 had a KRAS mutation (5.9%), 3 had MET amplification (8.2%), 2 had Her2 alterations (5.8%, deletions/insertions in ezo), and one had SCLC transformation (2.9%). 79.4% received treatment after progression. ORR for post-TKI treatments was 47.1% (CR 2/PR 14) and median PFS was 8.3 months (95%CI 2.2–36.6). There were no differences in PFS according to gender (p=0.10) or type of acquired alteration (p=0.63). Median survival was 32.9 months (95%CI 30.4–35.3), and only the use of post-progression therapy affected OS in multivariate analysis (p=0.05).

Conclusion: Hispanic patients with acquired resistance to EGFR TKIs continued to be sensitive to other treatments after progression.

O.02: PLASMA NEXT GENERATION SEQUENCING OF OVER 5,000 ADVANCED NON–SMALL CELL LUNG CANCER PATIENTS WITH CLINICAL CORRELATIONS

Philip C. Mack1, Kimberly C. Banks1, Oliver A. Zill2, Stefanie A. Mortimer1, Darya I. Chudova1, Justin Odegaard1, Christine E. Lee1, Rebecca J. Nagy1, Helmy Eltoukhy1, Amirali Talasaz1, Richard Lanman1, David R. Gandara1

1University of California Davis Cancer Center, Sacramento/CA/UNITED STATES OF AMERICA, 2Guardant Health, Inc., Redwood City/CA/UNITED STATES OF AMERICA, 3Dept. of Medicine, University of California Davis Cancer Center, Sacramento/CA/UNITED STATES OF AMERICA

Background: NSCLC is genomically complex with several guideline-recommended genotypic targets. Next-generation sequencing (NGS) of circulating tumor DNA (ctDNA) enables non-invasive detection of these targets but liquid biopsy studies to date are modestly sized.

Method: A highly accurate, deep-coverage (16,000x) ctDNA plasma NGS test targeting 54-70 genes (Guardant360) was used to genotype 5,206 advanced-stage NSCLC patients (6/2014 – 4/2016); 85% of samples were ordered at clinical progression and 15% at baseline when tissue was of insufficient quantity (QNS) for recommended genotyping. Frequencies of somatic ctDNA alterations per gene were compared to those previously described in tissue sequencing compendia (e.g., TCGA). Accuracy of ctDNA sequencing (PPV) was assessed by comparing available tissue testing to ctDNA results in 229 consecutive patients. Clinical utility (identifying treatment-impacting alterations) was examined in 362 consecutive NSCLC patients (6/2014–6/2015) with tissue testing data available and in the 85% of ctDNA samples ordered at clinical progression.

Results: Somatic ctDNA alterations were detected in 86% of cases; EGFR mutations in 25%, KRAS mutations in 17% and other uncommon-to-rare alterations at lesser frequencies. Alteration patterns among driver oncogenes were highly consistent with those from TCGA (Pearson r=0.92, 0.99, and 0.99 for EGFR, KRAS, and fusion breakpoint location). PPV of ctDNA-detected variants in 229 samples with matched tissue testing reports was 100% forEGFR/TP53 tumors and 98% forEGFR/ROS1, 96% for ALK, RET, or ROS1 fusions, and 100% for KRASG12/13D12 mutations. As expected, PPV was lower (27%) for EGFR/ROS1fusions in ctDNA, indicating later acquisition of this resistance mutation, not present at initial tissue biopsy. In 63% (229/362) of consecutive NSCLC cases, tissue was QNS or under-genotyped (UG). In these QNS/UG cases, alterations not previously identified (EGFR, ALK, RET, BRAF, MET, KRAS) were found via ctDNA in 24% (51/229). Among 1,116 EGFR-mutant NSCLC cases, resistance mutations were identified at progression at frequencies consistent with published literature: EGFRmutant 47%, METamp 5%, ERBB2 amp 5%, FGF3 fusions 0.4%, ALK/other fusions 1%, BRAF mutations 1.8%, PTEN inactivation 2.5%, NFI inactivation 3%, RB1 inactivation 3%, KRAS mutations 1.9%.

Conclusion: This series represents the largest NSCLC ctDNA study to date. Genotypic patterns of driver mutations in this large clinical ctDNA cohort were consistent with TCGA. However, TCGA is earlier stage and thus lacks secondary resistance mutations such as EGFRmutant prevalent in ctDNA. CtDNA NGS identified new targetable alterations at progression and also when tissue biopsy was QNS/UG. Studies employing ctDNA in serial testing for evolution of resistance alterations are ongoing.

O.01: ACQUIRED RESISTANCE TO EGFR-TKIS IN EGFR-MUTANT LUNG ADENOCARCINOMA AMONG HISPANICANS (RBIOP–CLICAP)

Andrés F. Cardona1, Oscar Arrieta4, Martín I. Zapata1, Leonardo Rojas1, Beatriz Wills1, Hernán Carranza1, Noemi Reguart1, Carlos Vargas1, Jorge Otero1, Luis Corrales-Rodríguez2, Claudio Martín1, Pilar Archila3, Mauricio Cuello10, Carlos Ortiz1, Rafael Rosell1

1Clinical And Translational Oncology Group, Clínica del Country, Bogotá/COLOMBIA, 2Thoracic Oncology Unit, Instituto Nacional de Cancerología, Mexico DF/MEXICO, 3Internal Medicine Department, Fundación Santa Fe de Bogotá, BOGOTA/COLOMBIA, 4Oncology Department, Hospital Universitario San Ignacio, Bogotá/COLOMBIA, 5Internal Medicine Department, Johns Hopkins Hospital, Baltimore/UNITED STATES OF AMERICA, 6Medical Oncology, Hospital Clinic, Barcelona/SPAIN, 7Medical Oncology, CIMCA / Hospital San Juan de Dios, San José/COSTA RICA, 8Thoracic Oncologic Unit, Instituto Alexander Fleming, CIUDAD DE BUENOS AIRES/ARGENTINA, 9Foundation for Clinical and Applied Cancer Research, Bogotá/COLOMBIA, 10Hospital De Clinicas, Universidad de la República (UdelAR), Montevideo/URUGUAY, 11Cancer Biology & Precision Medicine Program, Catalan Institute of Oncology, Barcelona/SPAIN

Background: Advanced non–small cell lung cancer (NSCLC) is earlier stage and thus lacks secondary resistance mutations such as EGFR tyrosine kinase inhibitors (TKI). In 50% of these cases, the secondary EGFR mutation, T790M, underlies the acquired resistance. Other alterations include amplification of MET, PIK3CA, deletions/insertions in e20, and one had SCLC. KRAS mutation (5.9%), 3 had MET amplification (8.8%), 2 had Her2 fusions 0.4%, 1.8% 5% and 3% forALK, RET, or ROS1 fusions, and 100% for KRASG12/13D12 mutations. As expected, PPV was lower (27%) for EGFR/ROS1fusions in ctDNA, indicating later acquisition of this resistance mutation, not present at initial tissue biopsy. In 63% (229/362) of consecutive NSCLC cases, tissue was QNS or under-genotyped (UG). In these QNS/UG cases, alterations not previously identified (EGFR, ALK, RET, BRAF, MET, KRAS) were found via ctDNA in 24% (51/229). Among 1,116 EGFR-mutant NSCLC cases, resistance mutations were identified at progression at frequencies consistent with published literature: EGFRmutant 47%, METamp 5%, ERBB2 amp 5%, FGF3 fusions 0.4%, ALK/other fusions 1%, BRAF mutations 1.8%, PTEN inactivation 2.5%, NFI inactivation 3%, RB1 inactivation 3%, KRAS mutations 1.9%.

Conclusion: This series represents the largest NSCLC ctDNA study to date. Genotypic patterns of driver mutations in this large clinical ctDNA cohort were consistent with TCGA. However, TCGA is earlier stage and thus lacks secondary resistance mutations such as EGFRmutant prevalent in ctDNA. CtDNA NGS identified new targetable alterations at progression and also when tissue biopsy was QNS/UG. Studies employing ctDNA in serial testing for evolution of resistance alterations are ongoing.
Keywords: liquid biopsy, circulating tumor DNA, Non–small Cell Lung Cancer, matched therapy

O.03: COST EFFECTIVENESS OF IMMUNE CHECKPOINT INHIBITORS IN NON–SMALL CELL LUNG CANCER RELATIVE TO PD–L1 EXPRESSION

Pedro Aguiar Jr1, Ramon De Mello2, Hakaru Tadokoro3, Ilka Santoro3, Hani Babiker4, Kiran Avancha4, Barbara Gutierrez5, Carmelia Barreto3, Gilberto Lopes6

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Background: Recent clinical trials have shown that immune checkpoint inhibitors are active against several neoplasms, including lung cancer. Tumor PD–L1 receptor expression is being studied as a predictive biomarker. The objective of our study is to assess the cost–effectiveness and economic impact of nivolumab and pembrolizumab with and without the use of PD–L1 as a biomarker.

Method: We developed a decision–analytic model to determine the cost–effectiveness of PD–L1 assessment and second–line treatment with NIVO or PEMBRO versus docetaxel. The model used outcomes data from randomized clinical trials and drug acquisition costs from the United States. We also included the costs of adverse events and post–progression therapies. Published utility values were used. Health effects were expressed as quality-adjusted life–years (QALY) and incremental cost-effectiveness ratios (ICER) were calculated.

Results: We included three RCTs (two with NIVO and one with PEMBERO). Among all patients with squamous histology, the incremental QALY of NIVO was 0.23. The ICER was US$ 128,000. PD–L1 expression improved incremental QALY only for patients with PD–L1 > 5% and > 10% (by 15% and 18% respectively). Among all patients with non–squamous histology, the incremental QALY of NIVO was 0.12. The ICER was US$ 121,000. PD–L1 expression improved incremental QALY for patients with PD–L1 > 1%, > 5% and > 10% (by 67%, 15% and 13%, respectively). This lead to an ICER drop (US$ 72,000, 47,000 and 51,000, respectively). KeyNote–010 included 36% of patients at the third–line of treatment, all patients treated with PEMBERO had at least 1% of PD–L1 expression; the incremental QALY was 0.13. The ICER was US$ 116,000. PD–L1 expression above 50% improved QALY by 18% and the ICER was US$ 98,000.

Conclusion: Use of PDLI expression as a biomarker may increase the cost–effectiveness of treatment with immune checkpoint inhibitors and further validation is warranted.

Keywords: biomarker, immunotherapy, cost–effectiveness, access

O.04: PROFILING OF MET–AMPLIFIED NON–SMALL CELL LUNG CANCER (NSCLC), CORRELATION TO CMET PROTEIN EXPRESSION/ MET EXON 14 SKIPPING

David Arquello1, Andreas Voss1, Zoran Gatalica2, Ryan Bender3

1Medical Affairs, Caris Life Sciences, Phoenix/AZ/UNITED STATES OF AMERICA, 2Medical Affairs, Caris Life Sciences, Basel/SWITZERLAND

Background: Recent genomic studies of molecular subtypes of NSCLC revealed a plethora of data surrounding its underlying biology. Knowledge of EGFR–driven NSCLC has changed the way one molecular subtype is being managed. While MET–driven NSCLC has been documented, a lot remains unknown about this molecular subtype of NSCLC, in contrast to EGFR– and KRAS–mutated molecular subtypes. The purpose of this study is to investigate the genomics of MET–amplified NSCLC to further understand its tumor biology, and to indicate potential for clinical trials.

Method: In total, 3,540 NSCLC specimens underwent multiplexed testing at a CAP/ISO/CLIA–certified laboratory (Caris Life Sciences). Analysis included protein expression by immunohistochemistry (IHC), gene amplification by in situ hybridization (ISH), fusions by ArcherDx FusionPlex assay, and copy number variance (CNV)/mutation by next generation sequencing (NGS). The laboratory validated CISH assay, utilizing a gene copy number > 5 to assess gene amplification.

Results: In this cohort, 3.1% (109/3,540) patients were MET–amplified. In MET–amplified tumors (n=109), protein expression by IHC showed no ALK expression (0/36), positive EGFR at 47.5% (38/80), and positive PD–L1 at 56.0% (36/64, using 5% cut off value with SP142 antibody), with a sub–group showing a PD–L1 positive rate (50% cut off) of 68.8% (n=16) using the recently FDA approved companion diagnostics kit (22C3 antibody). For gene translocation by FISH, ALK was 2.5% (2/79) and ROS1 was 0.0% (0/97). For mutational analysis, BRAF mutations were 6.5% (6/92), EGFR was 23.1% (21/91), ERBB2 was 1.1% (1/92), and KRAS was 13.0% (12/92). ForMET–amplified NSCLC specimens, CMET protein expression was detected in 92.5% (74/80), MET amplification by CNV was 66.7% (4/6), MET mutation rates were 5.4% (5/92), and MET fusion was found in 20.0% (1/5). Evaluation of the 3,540 specimens revealed 17 MET exon 14 skipping mutations with only two showing amplification (1.8%, 2/17).

Conclusion: Our analysis reveals potentially targetable aberrations in MET–driven NSCLC. High PD–L1 rates in this group indicate potential for targeting with PD–Iblockade therapy and potential for combined immune blockade/MET inhibition therapy. Differences in CMET alterations indicate the need to analyze patient specimens for MET using different technologies and to find the optimal threshold for MET. Further studies of this molecular subtype of NSCLC are urgently needed to elucidate the optimal therapy for these patients.

Keywords: tumor profiling, MET
Background: Nivolumab (nivo) is the first anti–programmed death-1 agent to demonstrate a survival benefit vs docetaxel (doc) in patients (pts) with previously treated advanced (adv) non–squamous (NSQ) and SQ NSCLC. Here we report the impact of nivo vs doc on disease–related symptoms in pts with adv NSQ NSCLC from the CheckMate 057 study.

Method: Lung Cancer Symptom Scale (LCSS) was assessed every other cycle (Q4W) for nivo and every cycle (Q3W) for doc for the first 6 mo on treatment (tx), then every 6 wks and at 2 post–tx follow-up visits. LCSS includes the average symptom burden index (ASBI; based on 6 symptoms: anorexia, fatigue, cough, dyspnea, hemoptysis, and pain) and the 3–item global index (3-IGI; symptom distress, interference with activities, and health–related quality of life [HRQoL]). LCSS changes from baseline (BL) and time to first deterioration (TTD) in symptoms were estimated.

Results: Analyses of mean changes from BL in the LCSS ASBI and 3-IGI indicated numerical differences favoring nivo vs doc emerging at the first common assessment (wk 12) and persisting throughout the entire assessment period. At common assessments with >10 pts in each arm (to wk 48), the differences were significant (CIs excluding no difference) for the ASBI at wks 12, 24, 30, and 42, and for the 3-IGI at wks 24 and 30. Five of 6 symptoms (including pain and fatigue) and 2 of 3 items of the 3-IGI (HRQoL and symptom distress) had significant differences favoring nivo at ≥2 common assessments. TTD (based on the minimally important difference [MID]) was longer with nivo vs doc for the ASBI (HR=0.65; 95% CI: 0.49, 0.85) and 3-IGI (HR=0.63; 95% CI: 0.48, 0.82), with Kaplan–Meier curves between tx arms separating at ~2 months. TTD for individual symptoms within the ASBI and individual items of the 3-IGI showed a similar pattern. The proportion of pts with improvement in the LCSS ASBI greater than the MID by wk 12 was similar for nivo (17.8%; 95% CI: 13.6, 22.7) and doc (19.7%; 95% CI: 15.2, 24.7).

Conclusion: These results from this large, phase III study indicate that pts with previously treated adv NSQ NSCLC had significantly better symptom burden outcomes and HRQoL while on tx with nivo vs doc. TTD was significantly longer in nivo– vs doc–treated pts.

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Conclusion: PD-L1 overexpression can be considered as a predictive biomarker for immune checkpoint inhibitors for NSCLC, independent of previous treatments or tumor histology. Response rate may be up to three times higher in PD-L1 positive patients than in patients with tumors that do not express it. Further biomarker evaluation is warranted.

Keywords: immunotherapy, biomarker, PD-L1, Personalized Medicine

PD1.03 (also presented as P1.12): EGFR MUTATION TESTING PATTERNS AND RESULTS IN BRAZIL AND THE NEED FOR GREATER PUBLIC HEALTH AWARENESS OF MOLECULAR TESTING

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Background: Epidermal growth factor receptor (EGFR) mutation testing allows for optimal selection of therapy with tyrosine kinase inhibitors in patients with non-small-cell lung cancer (NSCLC). Previous studies have shown a variation in EGFR genotype according to ethnic background, with scarce data about EGFR mutation status and testing patterns among Brazilian patients with NSCLC.

Method: Between 2011 and 2013, as part of a program sponsored by a pharmaceutical company in Brazil, tumor samples of patients with stage IIIb/IV NSCLC were submitted, at the discretion of the attending physicians, for EGFR mutation testing. All analyses were performed at 02 reference laboratories, as follows: after microdissection, DNA was isolated from serial sections of formalin-fixed, paraffin-embedded tumor tissue to obtain at least 70% tumor cells. Exons 18, 19, 20 and 21 of the EGFR gene were analysed using Sanger sequencing. EGFR mutation rate was calculated and its frequency compared between clinical subgroups using chi-square test. Data about smoking status was incomplete and thus not included in this analysis. Furthermore, a commercial database with 3,296 patients treated in Brazil in 2014 was evaluated for mutation testing patterns.

Results: 3,364 tests out of 3,771 samples analyzed (1,799 male; 1,942 female) yielded informative results. EGFR mutation was present in 25.5% (857/3364) of informative samples. Deletions in exon 19 were the most frequent alteration detected (54%), followed by point mutations in exon 21 (28%) and exon 20 (9.7%). The most important predictors for the presence of EGFR mutations were adenocarcinoma histology (p<0.001), 89% of positive tests occurred in this histology; and female gender (p<0.001), for which 30.2% of the patients tested were positive. No differences in EGFR mutation frequency were found between age groups or regions within the country. In the commercial database of patients with NSCLC treated in the country in 2014, 1,792 patients had adenocarcinomas, 930 had squamous cancer, 71 had large cell cancer and 99 had other histologies. Overall, 34% of patients were tested for mutations (47% in the private sector and 20% in public centers); the corresponding number was 50% for patients with adenocarcinoma (62% of cases in the private and 33% in the public settings, respectively) and 10% for patients with squamous cancer. Of note fewer than 5% of patients overall were tested for ALK alterations.

Conclusion: To the best of our knowledge, this is the largest study to assess EGFR mutation status in Latin America and in Brazil. Our findings suggest that the frequency of EGFR mutation in this cohort was lower than that found in Asia, but higher than in Caucasian populations, confirming findings seen in other Latin American countries. Despite this high prevalence, a significant number of patients, especially in the public sector, are not currently tested for mutations in the country, and further advocacy efforts are necessary to improve this situation.

Keywords: EGFR, non small cell lung cancer, prevalence
PD1.04 (also presented as P2.19): INFREQUENT STAINING PATTERNS IN ALK IMMUNOHISTOCHEMISTRY: CORRELATION WITH FISH ANALYSIS
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Background: ALK gene rearrangements are infrequent alterations in lung cancer and are present in 3-5% of non small cell lung carcinomas (NSCLC). ALK status is an important predictive factor in NSCLC. As ALK rearranged tumors have shown sensitivity to Crizotinib treatment. Immunohistochemistry (IHC) has become a valuable tool in assessing ALK status, however unusual staining patterns, such as heterogeneous diffuse moderate and focal intense stains, may occur and can make evaluation difficult.

Method: We correlated immunohistochemistry unusual staining patterns with ALK status by fluorescence in situ hybridization (FISH). Of 851 cases tested, we found 14 (1.6%) cases with inconclusive staining patterns that can be summarized in: a) diffuse granular cytoplasmatic moderate stain, with or without background mucin stain (10 cases) b) focal intense granular cytoplasmatic stain in overall negative or weakly positive tumors (4 cases). Both studies were performed on unstained 4 um formalin-fixed paraffin embedded tumor tissue sections. IHC was performed on an automatized Benchmark staining module (Ventana, Tucson, AZ) using monoclonal Ventana ALK (D5F3) CDx assay with Optiview amplification kit (Ventana Medical System). FISH was performed using ALK break-apart probe set (Vysis LSI ALK Dual Color, Abbott Molecular) after 2xSSC/Proteinase K pretreatment. Sections were analyzed under a fluorescence microscope, using appropriate filters (Olympus BX51, Tokyo,Japan). Cases were considered ALK-FISH positive if ≥15% tumor cells showed split red and green signals (separation of 2 diameters or more) and/or single red signals.

Results: Of 10 moderate granular cytoplasmatic stain cases, 4 had also abundant mucin background stain 6 where markedly heterogeneous with areas of weak and moderate cytoplasmatic granular stain. Nine were FISH negative, one yielded no signals (uninformative result) and one specimen corresponded to an acid decalcified specimen and was not evaluated by FISH. Focal intense stain was observed in 5 samples, 3 corresponded to surgical specimens and the rest to small needle biopsies, one of the surgical specimens was FISH positive and the rest, negative.

Conclusion: Since the approval of Ventana ALK (D5F3) IHC CDx Assay by FDA, IHC has become a widely used tool for assessing ALK status. Guidelines suggest that weak to moderate granular stain should be interpreted as negative and focal intense granular stain in any number of cells, as positive. Even though our sample is small, moderate granular stain was consistently negative by FISH analysis, however, focal intense stain shows more discordant results between tests. No suggestions are made on what should be the minimum amount of tumor in a sample to report an IHC assay. Interestingly we didn’t find rearrangements on small samples with focal intense IHC positivity and the only FISH positive case was a surgical specimen with focal intense stain. Even though some of these patients with IHC positive/FISH negative results have been reported as responders to Crizotinib, further studies are needed. Lastly, one specimen with moderate cytoplasmatic IHC stain was uninformative due to lack of signals and one case was a decalcified tissue. This raises the issue of the need to standardize preanalytical variables, which can be difficult in some areas of Latin America.

Keywords: non small cell lung carcinoma, fish, ALK, immunohistochemistry

PD1.05 (also presented as P1.49): THE GENOMICS OF YOUNG EMERGING LUNG CANCER
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Background: Lung cancer is increasingly understood as a disease made up of genomically defined subtypes requiring distinct treatment strategies. We hypothesize that young age at diagnosis (<40 years) is a clinical characteristic associated with an increased chance for a targetable genomic alteration (GA). Our study will prospectively characterize the somatic and germline genomics of young lung cancer.

Method: Accrual opened in July 2014. Patients (pts) are eligible if diagnosed with bronchogenic lung cancer < age 40. The study website, allows for virtual consenting and remote participation from anywhere in the world. We defined 7 GA of interest based on the Lung Cancer Mutation Consortium (LCMC) (EGFR, KRAS, HER2, BRAF, ALK, ROS1, RET). We aim to show the prevalence of targetable GA in our stage 4 adenocarcinoma (AC) pts will be greater in our population compared to the LCMC, with an increase from 35% to 50%; and an improvement in use of targeted therapy from 22% to 40%. Study subjects without a known genotype undergo genomic profiling with the FoundationOne test.

Results: Preliminary results of 71 pts with stage 4 AC show that 82% have either an ALK re-arrangement n=32 (45%), an EGFR activating mutation n=17 (24%), a ROS1 fusion n=5 (7%), a RET fusion n=2 (3%) or a HER2 mutation n=2 (3%). Other GA of interest in those with AC includes TP53, ATM and BRCA2 mutations. 49% of our accrual has come from web based consenting. The majority of subjects have come from North America and Europe; and we would like representation from Latin America.

Conclusion: Thus far in our prospective series our results have far exceeded our statistical expectations, with 82% of our stage 4 AC pts having an actionable mutation. We have defined a genomically enriched subtype of lung cancer and laid the groundwork for further studies of germline and environmental lung cancer risk factors. We are planning a large-scale Case Control study of the Epidemiology of YLC. Web based consenting is a feasible method of bringing research to the patient.

Keywords: Genomics, Young Emergent Lung Cancer, Remote Consenting
PD1.06 (also presented as P2.41): PEMBROLIZUMAB VS DOCETAXEL FOR PREVIOUSLY TREATED NSCLC (KEYNOTE–010): ARCHIVAL VS NEW TUMOR SAMPLES FOR PD–L1 ASSESSMENT

Roy S. Herbst1, Paul Baas2, Jose L. Perez–Gracia1, Enriqueta Felip4, Dong–Wan Kim1, Ji–Youn Han1, Julian Molina3, Joo–Hang Kim4, Catherine Dubos Arvis4, Myung–Ju Ahn5, Margarita Majem7, Mary Jo Fidler2, Veerle Surmont8, Gilberto De Castro Jr1, Marcelo Garrido8, Yue Shentu10, Marisa Dooled–Filhart16, Ellie Im16, Edward B. Garon17

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Background: In KEYNOTE–010, pembrolizumab demonstrated superior OS over docetaxel in patients with PD–L1–expressing advanced NSCLC that progressed after ≥2 cycles of platinum–doublet chemotherapy (HR 0.54, P = 0.0002 for 2 mg/kg and HR 0.50, P < 0.0001 for 10 mg/kg in the PD–L1 tumor proportion score [TPS] ≥ 50% population; HR 0.71, P = 0.0008 and HR 0.61, P < 0.0001 in the TPS ≥ 1% population). We assessed outcomes in patients who enrolled in KEYNOTE–010 based on whether PD–L1 expression was measured in archival or new tumor samples.

Method: KEYNOTE–010 (NCT01090565) was an international, open–label, phase 3 clinical trial. PD–L1 expression was assessed at a central laboratory by immunohistochemistry using the 22C3 antibody. Archival tumor samples were initially allowed, but with a protocol amendment, only new (ie, no intervening therapy between collection and start of study drug) tumor samples were permitted. Eligible patients were randomized 1:1:1 to pembrolizumab 2 or 10 mg/kg Q3W or docetaxel 75 mg/m2 Q3W for 24 months or until disease progression, intolerable toxicity, or other reason. Response was assessed per RECIST v1.1 by independent central review every 9 weeks. Survival was assessed every 2 months. Primary end points were OS and PFS in the PD–L1 TPS ≥ 50% and ≥ 1% populations. Pembrolizumab doses were pooled for this protocol–specified analysis.

Results: Of the 1034 patients enrolled, PD–L1 expression was assessed in archival tumor samples in 456 (44%) patients and new tumor samples in 578 (56%). Median time between sample collection and PD–L1 assessment was 250 days (range, 3–2510) for archival samples and 11 days (range, 1–371) for new samples. PD–L1 TPS was ≥ 50% for 40% of archival and 45% of new samples. Archival samples were used in 48% of the 222 patients with squamous histology and 43% of the 724 patients with nonsquamous histology. Pembrolizumab significantly improved OS in both the TPS ≥ 50% and ≥ 1% populations, regardless of whether enrollment was based on archival or new tumor samples (Table). The PFS benefit of pembrolizumab over docetaxel was similar in patients enrolled based on archival and new samples (Table).

Conclusion: Pembrolizumab demonstrated superior OS over docetaxel regardless of whether new or archival samples were used to assess PD–L1 expression. The incidence of PD–L1 TPS ≥ 50% was similar in archival and new samples. These data suggest a new biopsy may not be required for this predictive PD–L1 assay, thus sparing patients from risks associated with sample collection and avoiding resource utilization.

Keywords: biopsy, immunohistochemistry, PD–L1, pembrolizumab
PD2.01 (also presented as P1.13): LUNG CANCER CHROMOSOMAL ABERRATIONS AND GENE EXPRESSION PROFILES OF HISPANICS LIVING IN THE US OR LATIN AMERICA ARE SIMILAR

Luis E. Raez1, Edgardo S. Santos2, Jennifer Mourafetis1, Alice Y. Kim4, Brian Hunis1, Candice Sarel1, Libbith Castillero5, Evelio Velis6
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Background: The incidence of epidermal growth factor receptor mutations (EGFR) in lung cancer tumors in Latin America (LATAM) are higher than the US counterparts. Our hypothesis is that the frequency of EGFR and other genomic alterations in Hispanic (H) patients (pts) living in the US is higher than non-Hispanic Whites (NHW).

Method: Next generation sequencing (NGS) and FISH were done in tumors of pts with NSCLC to identify genomic aberrations such as ALK, RET, ROS-1, KRAS, c-Met and BRAF at Memorial Cancer Institute and Lynn Cancer Center in Florida. Gene expression profile (GEP) was not available for all pts. Chi-square and Fisher’s exact tests were used to assess associations between GEP and ethnicity. All summary statistics on time-to-event variables were calculated according to the Kaplan–Meier method and were compared by means of the log-rank test. Adjusted hazard ratios and 95% confidence intervals were reported based on the results of a multivariate Cox regression model for overall survival.

Results: GEP were ordered in 492 pts and tumor samples were sufficient in 436 pts (88%). 25% were H, 61% women, 34% non-smokers and 93% had adenocarcinomas. EGFR mutations were seen in 22% of the tumors (76% in exons 19&21, and 13% in exons 18&20). There was an increase in EGFR exon 19 in H vs. NHW (82 vs. 45%) (p<0.05). Other results of GEP: ALK 5%, RET 4%, ROS-1 8%, c-MET 31%, KRAS 30%, and BRAF 5%. There was no significant association in GEP between H vs. NHW. There were no differences in survival between H and NHW in any of these groups.

Conclusion: Frequency of EGFR mutations in H pts living in the US is similar to the ones reported in LATAM and higher than NHW in US and Europe. However GEP between H and NHW is similar in South Florida, except for EGFR exon 19 mutation which is more common in H than NHW. More studies need to be done to validate these findings.

Keywords: Hispanics, EGFR mutations, ALK, KRAS

PD2.02 (also presented as P1.44): PHASE I/II TRIAL OF X-396, A NOVEL ALK INHIBITOR, IN PATIENTS WITH ALK+ NSCLC

Ticiana Leal1, Heather Wakelee2, Jeffrey Infante3, George Blumenschein4, Karen Reckamp5, Corey Carter6, Saima Waqa7, Jon Gockerman8, Christine Lovly9, Gary Dukart10, Kimberly Harrow11, Chris Liang12, James Gibbons13, Leora Horn14
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Background: X-396 is a novel, potent anaplastic kinase lymphoma (ALK) small tyrosine kinase inhibitor (TKI) with additional activity against MET, ABL, Axl, EphA2, LTK, ROS1, SLK. It has demonstrated significant anti-tumor activity in both ALK TKI–naive and crizotinib-resistant models of ALK fusion–positive NSCLC.

Method: In this multicenter phase I/II study, patient (pts) with advanced solid tumors enrolled in the phase I dose escalation portion of the study and given X-396 on a continuous 28-day schedule (NCT01625234). Doses from 25 up to 250 mg once daily were evaluated and 225 mg was selected for further evaluation in the phase II expansion. Patients in this phase were required to have ALK + NSCLC and measurable disease. Cohorts included pts who were 1) ALK-TKI naive, 2) Pts who progressed on prior crizotinib and had not received a second generation ALK TKI, 3) Pts who progressed on a second generation ALK TKI (may also have received crizotinib), 4) Pts with central nervous system (CNS) metastases, 5) Pts with leptomeningeal disease. All pts were assessed for adverse events (AEs) using CTCAE version 4.03, response to therapy was assessed using RECIST 1.1.

Results: As of December 09, 2015 data cutoff, 57 pts (31 men, 26 women) have been enrolled. Median age is 56 (20–79) years, the majority of pts had ECOG performance status 1 (67%). The most common drug–related AEs included rash (49%), nausea (28%), vomiting (25%), and fatigue (23%). Most AEs were grade (G) 1–2. The G3 treatment–related AEs were rash (7 pts), fatigue (1 pt), decreased appetite (1 pt), dehydration (1 pt), pruritus (1 pt), and face edema (1 pt). In particular, no G3 treatment–related gastrointestinal toxicity or liver enzyme elevation has been reported. To date 27 ALK+ NSCLC pts treated at doses 200 mg or greater are evaluable for response; partial response (PR) was achieved in 19 pts (70%) and stable disease (SD) in 2 pts (7%). In the crizotinib–naïve pts (n=8), responses were observed in 7 pts (88%). In the 12 pts with prior crizotinib, but no other ALK TKIs, 10 pts (83%) achieved PR and 1 (8%) SD. CNS responses have been observed in both crizotinib–naïve and crizotinib resistant pts. The median duration of treatment in the 27 evaluable ALK+ pts is 16+ weeks, with the longest being 128+ weeks.

Conclusion: X-396 is well tolerated and induces responses in both
crizotinib-naive and crizotinib-resistant ALK+ NSCLC pts, as well as patients with CNS lesions. Enrollment is ongoing in the expansion cohorts.

**Keywords:** X-396, ALK+ NSCLC

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**PD2.04 (also presented as Pt.42): PEM/CBP/BEV FOLLOWED BY MAINTENANCE PEM/BEV IN HISPANIC PATIENTS WITH NSCLC: OUTCOMES ACCORDING TO TS, ERCC1 and VEGF**

Leonardo Rojas, Andrés F. Cardona, Oscar Arrieta, Beatriz Wills, Luis Corrales-Rodriguez, Hernán Carranza, Carlos Vargas, Jorge Otero, Claudio Martín, Mauricio Cuello, Carlos Ortiz, Rafael Rosell

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**Background:** To evaluate the efficacy and safety of pemetrexed, carboplatin and bevacizumab (PCB) followed by maintenance pemetrexed and bevacizumab (PB) in chemotherapy-naive patients with stage IV non-squamous non–small cell lung cancer (NSCLC) through the influence of thymidylate synthase (TS), ERCC1 and VEGF mRNA expression on several outcomes. The primary endpoints were the overall response rate (ORR), progression–free survival (PFS) and overall survival (OS).

**Method:** Patients were administered pemetrexed (500 mg/m 2), carboplatin (AUC, 5.0 mg/ml/min) and bevacizumab (7.5 mg/kg) intravenously every three weeks for up to four cycles. Maintenance pemetrexed and bevacizumab was administered until disease progression or unacceptable toxicity.

**Results:** One hundred forty-four Hispanic patients with a median follow–up of 13.8 months and a median number of maintenance cycles of 6 (range, 1–32) were assessed. The ORR among the patients was 66% (95% CI, 47% to 79%). The median progression–free and overall survival (OS) rates were 7.9 months (95% CI, 5.9–10.0 months) and 21.4 months (95% CI, 18.3 to 24.4 months), respectively. Median TS, ERCC1 and VEGF mRNA levels were 1.45 (range, 0.17–2.52), 0.58 (range, 0.44–1.20), and 2.72 (range, 1.84–3.21), respectively. OS was significantly higher in patients with the lowest TS mRNA levels [29.6 months (95%CI 26.3–32.9)] compared with those with higher levels 9.3 months (95%CI 6.6-12.0); p=0.0001]. ERCC1 mRNA levels also influenced the OS [median for ERCC1 mRNA<0.58 28.7 months (95%CI 26.2–31.2) vs. ERCC1 mRNA>0.58 11.1 months (95%CI 9.6–12.7); p=0.0001] as well as VEGF mRNA levels [median OS for VEGF mRNA<2.72 26.4 months (95% CI 22.8–30.0) vs. VEGF mRNA>2.72 18.2 months (95%CI 8.4–27.9); p=0.009]. TS mRNA did not influence treatment response, however the ORR was significantly higher in patients with low levels of ERCC1 (p = 0.003) and elevated VEGF (p = 0.005). Multivariate analysis found that TS mRNA levels (p=0.0001), VEGF mRNA levels (p=0.007) and PS (p=0.014) were independent prognostic factors.

**Conclusion:** Overall, PCB followed by maintenance pemetrexed and bevacizumab was in Hispanic patients with non–squamous NSCLC. This regimen was associated with prolonged OS, particularly in patients with low TS, ERCC1 and VEGF mRNA expression. These biomarkers alone or in combination may be useful to assess the prognosis of patients with NSCLC treated with CBP/Pem/Bev.

**Keyword:** mRNA expression levels, ERCC1, TS, VEGF, response, outcome

PD2.05 (also presented as Pt.43): RADIOSURGERY, A NEW PARADIGM IN METASTATIC NON–SMALL CELL LUNG CANCER (NSCLC) TO THE BRAIN: AN UPDATE

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**Background:** The purpose of the study is to report our updated results using Gamma Knife Radiosurgery (GKS) for the management of brain metastases from NSCLC in an unselected group of patients

**Method:** This is a retrospective review of 616 patients (336 males and 280 females) who were treated with GKS independently of primary status from October 1993 to April 2016. The rationale of treatment was to improve survival and quality of life. Ages ranged from 19 to 91 years, with a median age of 64 years. A total of 1085 procedures were performed. Doses ranged from 12 to 24 Gy, mean minimum dose delivered was 15.5 Gy. Seventy five patients of 615 had tumors retreated.

**Results:** The median overall survival for the entire group was 6.6 months, with 14.2 months for 25% of the patients and 56.5 months for 5% of them by Kaplan Meier Survival Analysis. Survival at 1, and 5 years are 28%, 4.2% respectively. The median follow–up was from 2 months to 276 months. Overall local control by lesion was 95%. Thirty four out of 486 evaluable documented deaths were due to progression of brain metastases. The other 411 documented deaths were due to progression of disease unrelated to brain metastases. Our longest surviving patient is currently alive 21 years after treatment with GKS to 15 tumors in 3 procedures with local control up–to this date. There was no radiation–induced dementia. Only 3% developed radiation necrosis diagnosed both pathological and by imaging studies.

**Conclusion:** Our results continue to show excellent local control associated with prolonged survival and a low risk of neurological death in spite of advanced stage disease. Number of lesions should not be a contraindication for Radiosurgery in NSCLC. Our report confirms the fact that for patients with NSCLC whole brain radiations should be reserved for late and extensive stage brain disease and or after failure from SRS. GKS provides high local control regardless of the number of lesions or presence of extra cranial disease. We also demonstrated in our retrospective analysis that re–treatment is feasible and safe.

**Keywords:** brain metastases, NSCLC, GKS, Radiosurgery

PD2.06 (also presented as Pt.41): BAYESIAN NETWORK META–COMPARISON OF MAINTENANCE TREATMENTS FOR ADVANCED NON–SMALL–CELL LUNG CANCER (NSCLC) PATIENTS

Gilberto Lopes

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**Background:** Recent trials suggested that maintenance treatments improve outcomes for patients not progressing after first–line therapy for advanced NSCLC. However, physicians have little guidance on selecting which patients benefit the most and what drug or regimen is optimal. Here, we report a systematic review and network meta–analysis (NMA) of current evidence assessing relative efficacies of maintenance options in unselected populations, as well as in subgroups determined by EGFR mutation, histology, and response to induction.

**Method:** PubMed and conference proceedings were reviewed and
individual study relative efficacy measures were meta-analyzed in a Bayesian hierarchical model. The primary and secondary outcomes, Overall Survival (OS) and Progression Free Survival (PFS), respectively, were evaluated in terms of (i) posterior surface under cumulative ranking curve (SUCRA), (ii) probability of being best treatment, (iii) probability of outperforming no maintenance, and (iv) posterior median hazard ratios with 95% credible intervals, in an unselected population, as well as by EGFR mutation status, histology, and response to induction. Secondary outcomes were overall survival (OS) and adverse events.

**Results:** Twelve trials evaluating eight maintenance treatments in 3,850 patients were included in NMA. Selected maintenance treatments showed substantial PFS and OS benefits with probabilities ≥99% and ≥92% respectively of outperforming no maintenance. Results suggest the following strategy for optimal OS and PFS: (i) switch to or continue pemetrexed or switch to anti-EGFR TKI for nonsquamous patients, (ii) continue gemcitabine for squamous patients, (iii) switch to docetaxel or continue gemcitabine for responders to previous induction, and (iv) switch to or continue pemetrexed or switch to anti-EGFR TKI for patients with stable disease post-induction.

**Conclusion:** Maintenance treatments improve PFS and OS in good performance status patients with stage IIIb/IV NSCLC not progressing after first-line chemotherapy. Benefits are optimized by targeting specific maintenance treatments to selected patient groups guided by histology and response to previous induction.

**Keywords:** lung cancer, chemotherapy, maintenance

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**POSTER SESSION 1**
**FRIDAY, AUGUST 26, 2016**

**P1.01: HERBAL MEDICINE TODAY: CLINICAL AND RESEARCH ISSUES**

**Track: Prevention, Early Detection, Epidemiology and Tobacco Control**

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**Background:** Efficacy and Effectiveness of a Traditional Herbal Remedy To evaluate the efficacy, effectiveness and safety of a traditional herbal remedy requires answers to some basic questions: European medicinal plants from traditional uses to scientific knowledge. It is very important to keep in mind the differences between explanatory and pragmatic studies, and the concepts of efficacy and effectiveness. Efficacy is the benefit a treatment produces under ideal conditions, often using carefully defined subjects, while effectiveness defines the benefit the treatment produces in routine clinical practice. Explanatory trials evaluate the efficacy of a treatment under controlled conditions that optimize isolation of the treatment effect through design features, such as a control or placebo, randomization, standardized protocols, homogeneous samples, blindness; these type of studies often represent the treatment of a particular patient, that is not the usual patient that enters a medical office. Pragmatic studies do not provide conclusive information on the specificity of the treatment effect but they have some interesting characteristics.

**Results:** Pragmatic trials (PT) are designed to find out about how effective a treatment actually is in everyday practice; while explanatory trials are designed to find out whether a treatment has any efficacy, almost always compared with placebo under ideal conditions. PT answers questions about the overall effectiveness of an intervention, and cannot study the contributions of its different components. The participant to these studies will need to be representative of the wider population because results need to be generalized; so wide criteria of inclusion are needed, so that patients having more medical diseases or taking different medications are included. It would be more satisfactory and sensible to choose conditions where conventional treatment is often unsatisfactory like irritable bowel syndrome or panic crises. In PT it is not usually mandatory to use a placebo, while it is needed with both arms of the trial on normal practice, since the aim is to produce an evidence to facilitate a real practical choice.

**Conclusion:** Herbal–derived remedies need a powerful and deep assessment of their pharmacological qualities and safety issues due to the large and growing use of natural–derived substances all over the world, which cannot rely only on the tradition or supposed millenarian beliefs; explanatory and pragmatic studies are useful and complementary in the acquisition of reliable data both for health caregiver and patients. Evidence–based medicine (EBM) was first conceived by Archibald Cochrane as a cultural and methodological approach to clinical practice to make decisions; based on clinical expertise and the most intimate knowledge of the individual patient’s clinical situations, it de-emphasizes unsystematic clinical experience as ground for medical decision–making, and stresses the rigorous analysis of evidence from clinical research. An important problematic of EBM is the difficulty to be easily applied in everyday practice, in a ABC system, especially in the field of complementary...
Keywords: evidence based medicine, explanatory trials, herbal medicine, mainstream medicine, physiotherapy, pr, makp

P1.02: LUNG CANCER – A PREVIOUSLY YEARS SURVIVAL STUDY. FIRST STATISTICAL EVIDENCE AT NATIONAL INSTITUTE OF ONCOLOGY IN PARAGUAY

Track: Prevention, Early Detection, Epidemiology and Tobacco Control

Silvia J. Ayala Leon¹, Miguel Agüero Pino¹, Cinthia Gauna Colás¹, Maria Rita Pereira¹, Miguel Ayala Leon¹
¹Central. Instituto Nacional del Cancer. Prof. Dr. Manuel Riveros,., Capiata/ PARAGUAY, ²Instituto Nacional de Cardiologia Ignacio Chavez, Mexico DF/MEXICO

Background: We actually are developing a data recollection to compare actual survival data with the past data at our patients, but we found that we have not survival studies in lung cancer population at our institution. So previously to compare we need past evidence.

Method: Between January 2004 and December 2007, all patients diagnosed with SCLC and NSCLC treated at National Institute of Oncology at Asuncion – Paraguay. Database and medical records of patients were reviewed. The data were captured in a database previously designed in the SPSS v20.0 program for statistical processing The survival analysis was made with the Kaplan–Meier method to estimate the graft survive. We use Log Rank (Mantel-Cox), Breslow (Generalized Wilcoxon), Tarone–Ware with p <0.05 as significative.

Results: Survival at lung cancer patients show that 65% of patient were alive at 1.5 years and only 45% were alive at 3 years. 45% of patients consulting from rural places were alive at 3 years and 55% of patients consulting from urban places (P>0.05). At 1 year smoker patients 70% were alive and 65% nonsmoker were alive and at 3 years found that 0% of nonsmoker patient were alive and 35% of smokers were alive. (P<0.05). Patient who consumed alcohol regularly had 35% of survive at 3 year and non-alcohol consumers 70% survive. (P<0.05). Patients who had exposure to toxic environmental agents at 3 year 45% were alive versus 75% patients with no exposure to toxic environmental agents. (p <0.05). Survival percentage at 3 years of patient that first motive for consultation was cough 75% were alive, 20% of dyspnea, 35% of chest pain, 45% of hemoptysis and 25% of tumor mass. (p<0.05) At NSCLC stages show survival percentage at 3 year of: IB 100%, IIB 60%, IIIA 15%, IIIB 55%, IV 15%. (P<0.05). 3 year survival related to type treatment was 90% of chemotherapy and radiotherapy were alive. Patients under chemotherapy 75% were alive and those under palliative care 0% were alive. (P<0.05). At NSCLC surviving chemotherapy schemes at 3 years show that 100% patients receiving CBBCA + VT6 were alive. 95% patients with VP16+ CDDP. 75% CBBCA + PTX. (P<0.05).

Conclusion: In our study we found that patients had 2.23 year of media survival. Chemotherapy and radiotherapy showed high survival percentages. We found no statistical relation with survival and gender, living place, professional occupation. Atypical chemotherapy schemes to threat NSCLC were documented this could be related that at previously years our institution only had economical access to the mentioned types of drugs because our patients come from low incomes and weren’t able to get other types of drugs.

Keywords: Survival Analysis, Lung Neoplasms, Latin America

P1.03: UTILITY OF A COMBINED PANEL OF SIX SERUM TUMOR MARKERS FOR LUNG CANCER

Track: Prevention, Early Detection, Epidemiology and Tobacco Control

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Background: We have previously identified six serum tumor markers (TM) [CEA, CA15.3, SCC, CYFRA 21-1, NSE and ProGRP] related to the presence of lung cancer (LC). Objectives: To (1) validate their individual performance in an independent cohort; and, (2) explore if their combined assessment (≥1 abnormal TM value) is a more accurate marker for LC presence.

Method: We determined these six TM in 4,092 consecutive individuals referred to our institution by their primary care physician because of the clinical suspicion of LC.

Results: LC was excluded in 1,667 individuals and confirmed in 2,425 patients (2,045 with non–small cell LC (NSCLC) and 380 with small–cell LC (SCLC)). Results: (1) validated the previously reported performance of each individual TM; (2) showed that their combined assessment (≥1 abnormal TM) had a better sensitivity, specificity, NPV and PPV (88%, 86%, 83.7% and 87.3%, respectively) that each TM considered individually; and, (3) increased the diagnostic performance (AUC) of a clinical model that included tumor size, age and smoking status; (3) in patients with radiographic nodules <3cm, the NPV of the TM panel was 72.8%, hence providing some support for a more conservative diagnostic approach; and, (4) identified two TM (NSE and ProGRP) that differentiate the risk of NSCLC from that of SCLC.
Conclusion: The combined assessment of a panel of six serum TM is a more accurate marker for LC presence that these same TM considered individually. The potential of these TM in the diagnostic and screening settings deserves further research Molina R, Marrades RM, Augé JM, Escudero JM, Viñolas N, Reguera N, Ramirez J, Fillella X, Molins L, Agustí A. Am J Respir Crit Care Med. 2016 Feb 15;193(4):427-37.

Keywords: tumor markers, lung cancer diagnosis, histological diagnosis, progpr

Pt.04: DEFINING THE GENETIC ARCHITECTURE OF LUNG CANCER ETIOLOGY

Track: Prevention, Early Detection, Epidemiology and Tobacco Control

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Background: Lung cancer is considered an archetypical environmentally induced disease because of the high risk from exposure to tobacco smoke. However, family studies clearly identified familial aggregation, beyond effects from familial correlations in smoking behavior. Family studies and genome wide association studies have identified selected variants influencing lung cancer risk but have been underpowered to provide a more comprehensive assessment of genetic architecture.

Method: We conducted a genome-wide association analysis using the Oncoarray, a genotyping platform that comprises over 530,000 genetic markers and designed to query variation influencing cancer risk. Here, we present the largest genome-wide scan of lung cancer risk but have been underpowered to provide a more comprehensive assessment of genetic architecture.

Results: Results identified 24 loci influencing lung cancer risk for loci with minor allele frequencies of 0.5% or higher, of which 14 had not previously reached genome-wide significance levels. Odds ratio effect sizes ranged from 0.37 for the functional variants rs17879961 in CHEK2 to 2.12 for rs1571835 in BRCA2. [JF] indicating the role of selected uncommon variants in strongly influencing lung cancer risk. Among the novel variants identified, 6 influenced overall lung cancer risk, 6 were specific to adenocarcinoma and 1 each [JF2] influenced never and ever smokers respectively. Aside from previously described variants in the CHRNA5 and CYP2A6 regions that influence cigarette consumption, all other loci showed significant heterogeneity among histologies. Array based heritability analysis also indicates no significant shared heritability between adenocarcinoma and squamous carcinoma, again pointing to striking etiological heterogeneity, other than that due to known smoking behavior related loci between these forms of lung cancer. Evaluation of eQTL results derived from normal lung tissue identified consistent cis-acting effects of the variant rs77468143 influencing expression of a little know gene SECISBP2L, rs6920364 influencing the extracellular ribonuclease RNASET2, and rs146729428 in the EPHX2, involved in inflammation. Several loci that influenced adenocarcinoma alone influenced telomere maintenance or cell cycle, while several of the squamous cancer-specific loci are involved in recombination repair.

Conclusion: These results indicate striking variation among histological subtypes of lung cancer. Further studies are ongoing to identify the impact that smoking has on lung cancer risk for these loci. These analyses provide a comprehensive assessment of genetic effects on lung cancer risk and will elucidate how these interact with smoking behavior. We would like to extend this study to include participants from Latin American countries because these were not yet well represented by our analyses.

Keywords: Epidemiology, Histologic Variation in Risk, Genetic Epidemiology, Genetic Risk Factors

Pt.05: AN INTERNATIONAL EPIDEMIOLOGICAL ANALYSIS OF YOUNG PATIENTS DIAGNOSED WITH NSCLC (ADUJOV-CLICAP)

Track: Prevention, Early Detection, Epidemiology and Tobacco Control

Luis Corrales-Rodríguez1, Oscar Arrieta2, Luis Masi, Omar O. Castillo-Fernandez4, Normand Blais3, Claudio Martin4, Ludwig Bacon2, Allan Ramos-Esquível8, Mauricio Cuello6, Leonardo Rojas11, Melissa Juárez11, Andrés F. Cardona11
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Background: Even though lung cancer remains a disease of the older population with a median age of 70 years, still a proportion of patients are diagnosed at 40 years or younger. In several studies, patients diagnosed with primary lung cancer under the age of 40 tend to be never-smokers, are stage IV adenocarcinoma, and tend to have somatic genomic alterations such as an epidermal growth factor receptor (EGFR) activating mutation or a EML4-ALK translocation. Therefore, it is crucial to determine the epidemiological characteristics of lung cancer patients under diagnosis under the age of 40. Few studies have documented and analyzed this characteristics. Our study groups the largest population of patients less than 40 years old diagnosed with NSCLC.

Method: In this epidemiological retrospective study, a total of 247 patients (Argentina=61, Canada=12, Colombia= 59, Costa Rica=13, Mexico=89, Panama=19, and Peru=76) with a histological confirmed non–small cell lung cancer aged 40 years or less at diagnosis were included for analysis. Data collected included age, gender, histology, stage, EGFR and ALK mutation analysis, and date of death or last follow-up. Progression free survival (PFS) and overall survival (OS) were also recorded.

Results: NSCLC patients aged 40 years or less accounted around a 4% of the total NSCLC population. The median age was 34.5 years (range 14–40), 11 (45%) were men, 136 (53%) were women, and 190 patients (76.9%) were non-smokers. Adenocarcinoma was the most frequent histological subtype with 201 patients (81.4%), 24...
patients (9.7%) were squamous and 22 patients (8.9%) had another histologic subtype. 213 patients (86.2%) were stage IV at diagnosis while 22 patients (8.9%) were stage III. The site(s) of metastasis was obtained in 202 of 213 stage IV patients where 39.6% (n=80) had lung metastasis, 35.6% (n=72) had SNC metastasis, and 31.7% (n=64) had bone metastasis. EGFR mutation (EGFRm) analysis was determined in 102 patients with 39 patients (38.2%) having an EGFRm. EML4-alk analysis was determined in 164 patients with 11 patients having a positive translocation (6.7%). The OS for the total population was 14.4 months (95%CI=11.2–17.6) and the PFS was 5.7 months (95%CI=4.9–6.5), and there was no statistical significant difference according to histological subtype. According to EGFR, OS for EGFRm(+) was 42 months (95%CI=30.8–54.0) and for EGFRm (−) was 19.4 months (95%CI=14.8–24.0) (p=0.002); PFS for EGFRm(+) was 11.9 months (95%CI=6.3–17.5) and for EGFRm (−) was 7.1 months (95%CI=5.3–8.9) (p=0.005). Regarding EML4-alk translocation, OS for alk(+) was 28.0 months (95%CI=15.4–40.6) and for alk(−) was 10.6 months (95%CI=6.9–14.3) (p=0.065).

**Conclusion:** NSCLC patients aged 40 years or younger constitute a small but important proportion of patients with this diagnosis. Other risk factors may be involved in the pathogenesis of the disease in this population due to a low smoking history of these patients. SNC metastasis at diagnosis seems to be more frequent in this population. EGFR mutation and EML4-alk translocation frequency is higher than the frequency reported in the general population.

**Keywords:** NSCLC, young, EGFR, ALK

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**Pt.06: LUNG NODULE VOLUMETRY: ANALYSIS OF THE MEASUREMENT VARIATION**

**Track:** Prevention, Early Detection, Epidemiology and Tobacco Control

Diana Penha, Wilson Ezequiel Neto, Klaus Irion, Colin Monaghan, Bruno Hochhegger, Enrique Guedes Pinto, Edson Marchiori

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**Background:** The purpose of the study was to determine the intra-scan variability of volumetric measurements of solid pulmonary nodules.

**Method:** In this retrospective study, 827 consecutive patients that underwent cardiac multi-phase CT scan were evaluated. All the CT exams were performed on a 256-row CT scanner (SIEMENS Somatom Definition Flash) using 0.6mm slice thickness and soft kernel. The image reconstructions were done using 10 phases in 10% of each RR interval. The images were evaluated in the axial plane to identify the lung nodule and after the automatic tool for lung lesions – volumetry was applied. The volume of the nodule was determined two times according with two different phases of the scan for each patient.

**Results:** 66 pulmonary nodules with medium volume of 8mm were included. The mean nodule volumetry difference was 531mm3 or 21.6%. Confidence interval of difference observed on measurements taken on different cardiac phases: Percentile 5 = 15mm3 or 0.00%; Percentile 50 = 62mm3 or 14%, and Percentile 95 = 1696mm2 or 58%. The volume measurements showed significant variability for any one given nodule during a single multi-phase scan (p<0.05). There was no correlation between the volume measurement of the nodule

and the difference between the volume measurements.

**Conclusion:** There is significant cardiac phase variability in lung nodule volume measurement.

**Keywords:** variation, Lung, volumetry, nodule

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**Pt.07: UNIVERSITY STUDENTS’ PERCEPTIONS ABOUT EFFECTIVENESS OF MPOWER POLICIES ON TOBACCO CONTROL**

**Track:** Prevention, Early Detection, Epidemiology and Tobacco Control

Omar O. Castillo-Fernandez, Maria Lim, Lilian Montano, Doris Bellido, Roberto Lopez

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**Background:** Tobacco use is a leading preventable cause of disease, disability and death worldwide. To expand the fight against the tobacco epidemic, WHO has introduced the MPOWER package of six proven policies: 1.- Monitor tobacco use and prevention policies, 2.- Protect people from tobacco smoke, 3.- Offer help to quit tobacco use 4.- Warn about the dangers of tobacco 5.- Enforce bans on tobacco advertising, promotion and sponsorship, and 5.- Raise taxes on tobacco. The aim of this study was to evaluate the student’s perception about the effectiveness of each intervention.

**Method:** Students surveyed had to evaluate each policy in a binary answer (less effective or very effective). Chi squared test was used to compare answers between smokers and never smokers.

**Results:** 212 students answer the questionnaire. 113 females (53.3%) and 99 males (46.7%). Median age 21 years. 49 smokers (23.2%) and 162 never smokers (76.8%). Median age of start smoking 16 years, median of cigarettes per week was 7 (1–48). There were not discrepancies in effectiveness between two groups in monitor tobacco use policies (p=0.27). 52% of never smokers and 26% of smokers consider that protect people from tobacco smoke is very effective (p=0.001). Offer help to quit tobacco is consider very effective in 32% of smokers versus 57% of never smoker (p=0.003). To require effective package warning labels is very effective in 25% of smoker and 50% of never smoker (p=0.002). Implement counter-tobacco advertising is equally effective for half of both groups (p=0.20). To obtain free media coverage of anti-tobacco activities is very effective in 53% of never smokers and 36% of smokers (p=0.04). To enforce bans on tobacco advertising promotion and sponsorship is very effective in 56% of never smokers and in 40% of smokers (p=0.053). Increase tax rates for tobacco products and ensure that they are adjusted periodically to keep pace with inflation and rise faster than consumer purchasing power is very effective for 41% of smoker and 56% of never smoker (p=0.062). Strengthen tax administration to reduce the illicit trade in tobacco products did not show difference in effectiveness in both group (p=0.13).

**Conclusion:** MPOWER policies are useful to prevent smoking. The perception of the effectiveness of each intervention varies according tobacco use

**Keywords:** policies, smoking, students, MPOWER
P1.08: UPDATED ANALYSIS OF GLOBAL EPIDEMIOLOGY OF EGFR MUTATION IN ADVANCED NON-SMALL CELL LUNG CANCER

Track: Prevention, Early Detection, Epidemiology and Tobacco Control

Gustavo Werutsky1, Marcio Debiasi2, Fernanda H. Sampaio2, Paulo R. Nunes Filho1, Clarissa Matias1, Mauro Zukin1, Facundo Zaffaroni1, Gilberto Lopes2

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Background: Epidermal growth factor receptor (EGFR) mutations represent an important predictive factor for response to EGFR inhibitors. This study aims to describe the worldwide epidemiology of EGFR mutations in lung cancer patients.

Method: MEDLINE was searched to identify original studies describing prevalences of EGFR mutations in countries around the world. Key search terms included “lung cancer”, “NSCLC” and “non–small cell lung cancer” in combination with the following terms: “EGFR”, “EGFR mutation” and “epidermal growth factor receptor”. The search was limited to studies in humans and published in English, Portuguese or Spanish. No date limits were used. All studies describing the prevalence of EGFR mutations were included, provided they used any of the validated testing methods (direct sequencing, amplification refractory mutation system, length analysis, or denaturing high–performance liquid chromatography). We excluded the following types of studies: (i) animal models, (ii) abstracts, letters and posters for which the full study was not published and (iii) histologies other than NSCLC.

Results: Our search retrieved 2,369 articles dated from 2004 to 2015, of which 199 were selected based on the criteria described above. 117 of these studies (58.9%) were published between 2011 and 2015, only 22 (11.1%) were clinical trials and 177 (88.9%) were cohort studies, case series or epidemiological series. We found articles from 35 different countries worldwide, accounting for 66,664 patients. The median global prevalence of EGFR mutation was 33.07% (IQR 19.90–47.52%). Table 1 shows the results of EGFR mutation prevalence per country and region. The most common mutations reported were 54.55% (IQR 45.45–67.50%) in exon 19 and 36.36% (IQR 28.57–47.06%) in exon 21. We found significantly higher median prevalences of EGFR mutation in part of Asian population (India, China, Japan and Taiwan) (42.7%; p<0.001), women (47.7%; p<0.001), non-smokers (33.6%; p<0.001) and adenocarcinoma (39.7%; p<0.001). There was no difference in EGFR mutation prevalence by test methodology.

Conclusion: We found 33.1% median overall prevalence of EGFR mutations, which is slightly higher than previous reports of 15–20% in NSCLC. This finding might be bias by selected population tested. Higher prevalences were identified in southeastern Asian populations, females, non-smokers and adenocarcinoma. The differences observed between countries and regions might have an important impact in public health policies and the design of future randomized clinical trials.

Keyword: NSCLC; EGFR; World; epidemiology

P1.09: DELAYS IN THE DIAGNOSIS AND TREATMENT OF LUNG CANCER

Track: Prevention, Early Detection, Epidemiology and Tobacco Control

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IONC – Universidad Católica de Córdoba, Córdoba/ARGENTINA

Background: In 2010 in our center we analyzed delays in diagnosis and treatment of lung cancer. The results were a delay of 8.4 weeks from the first symptom to diagnosis and 19.3 weeks from diagnosis to the start of treatment. The objective of this study is to compare the current delays with the delays achieved in 2010 with and without the literature.

Method: We analyzed the last 31 medical records of patients with diagnosis of lung cancer who were referred to our center. The time between the beginning of the symptoms, diagnosis and treatment was measured in weeks.

Results: The 31 patients had a median delay between first symptoms to the diagnostic of 6.5 weeks and a delay from the diagnostic to the start of treatment of 13.6 week. The median symptom–to–treatment delay was 15.6 weeks.

Conclusion: In this study we observed a delay of 15.6 weeks from the first symptom to start treatment. We have decreased delay in diagnosis of 8.4 to 6.5 weeks and also decreased the time from starting treatment of 19.3 to 13.6 weeks. The delay between onset of symptoms and the initiation of treatment in our population is similar to the data reported by CHEST study, published in 2005 by the Finns Group.

Keyword: Delays, diagnosis, lung, symptom

P1.10: FOLLOW-UP ON RESULTS OF A MULTIDISCIPLINARY TEAM IN THE MANAGEMENT OF NON-SMALL CELL LUNG CANCER IN A DEVELOPING COUNTRY

Track: Prevention, Early Detection, Epidemiology and Tobacco Control


Hospital San Juan de Dios–CCSS, San José/COSTA RICA

Background: In 2010 in our center we analyzed delays in diagnosis and treatment of lung cancer. The results were a delay of 8.4 weeks from the first symptom to diagnosis and 19.3 weeks from diagnosis to the start of treatment. The objective of this study is to compare the current delays with the delays achieved in 2010 with and without the literature.

Method: We analyzed the last 31 medical records of patients with diagnosis of lung cancer who were referred to our center. The time between the beginning of the symptoms, diagnosis and treatment was measured in weeks.

Results: The 31 patients had a median delay between first symptoms to the diagnostic of 6.5 weeks and a delay from the diagnostic to the start of treatment of 13.6 week. The median symptom–to–treatment delay was 15.6 weeks.

Conclusion: In this study we observed a delay of 15.6 weeks from the first symptom to start treatment. We have decreased delay in diagnosis of 8.4 to 6.5 weeks and also decreased the time from starting treatment of 19.3 to 13.6 weeks. The delay between onset of symptoms and the initiation of treatment in our population is similar to the data reported by CHEST study, published in 2005 by the Finns Group.

Keyword: Delays, diagnosis, lung, symptom
Method: A MDT including Medical Oncology, Pneumology, Pathology, Thoracic Surgery, Radiology and Radiation Oncology met in a weekly basis starting November 2011. All patients with a possible lung cancer evaluated at the hospital were discussed by the team and recommendations were given. Data of patients with NSCLC seen by the multidisciplinary team after November 2011 and until April 2016 was compared to a historic data of NSCLC patients diagnosed in the same hospital between 2003 and 2008 when there was no multidisciplinary team involved in patient care. Exclusion criteria included insufficient clinical information. Epidemiologic data was analyzed and survival curves were obtained. OS was calculated from time of histologically confirmed diagnosis to time of death.

Results: Patients diagnosed during both periods were included for survival analysis. The first period of 2003–2008 included 87 NSCLC pts while the second period of 2011–2016 included 231 NSCLC pts. Between 2003–2008, the distribution according to the stage was as follows: stage I=10.9% (n=10), stage II=2.2% (n=2), stage III=45.7% (n=42), and stage IV=41.3% (n=38). Between 2011–2016 the distribution according to the stage was: stage I=4.1% (n=5), stage II=5.0% (n=6), stage III=25.9% (n=31), stage IV=65% (n=78). The median OS for the entire population of the first period (2003–2008) was 6.13 months (95%CI=4.75–7.51), while in the second period (2011–2016) was 7.1 months (95%CI=6.61–9.60). This difference was statistically significant with a p=0.038 (95%CI=0.59–0.98) (Figure1). When stage IV only patients were analyzed, in the period 2003–2008 the median OS was 4.5 months (95%CI: 2.0 – 8.7) and for the period 2011–2016 the median OS was 7.6 months (95% CI: 5.1 – 10.1). This difference was not statistically significant (p=0.12).

Conclusion: The inclusion of a MDT in the management of NSCLC has lead to an improvement in overall survival. The differences seen in the distribution of the stages probably accounts to subdiagnosis of metastatic disease in the first period. This distribution in the second period is comparable to that published in the literature. Eventhought the percentage of metastatic disease was higher in the second period, survival including all stages was higher in this period of time, and this can be a result of a more integral management in the MDT setting. The MDT approach could be considered an option to improve the management and outcomes of NSCLC patients in a developing country.

Keywords: NSCLC, Multidisciplinary team, Integral management

Pt.11: SURVEILLANCE SYSTEM OF TABAQUISM IN CUBA 1995–2014 AND EARLY DETECTION IN HEAVY SMOKERS

Track: Prevention, Early Detection, Epidemiology and Tobacco Control

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Background: The Surveillance of tabaquism is essential for the prevention and control of principal causes of morbidity, discapacity and mortality in the Cuban population. It was started in 1995 and its objectives were to identify the distribution and tendency in some segments in the population and to contribute to implement and to evaluate the effectiveness of the stocks from the local to the national level.

Method: It has been representative of population of 15 years and over, over nine Cuban’s millions, provinces and municipalities, of urban and rural areas. The information was obtained through homes interviews. In 2010 its progressive decentralization stood out when it took effect at the country’s 16 cities. The tendencies were determined, the attributable mortality and also were identified the heavy smokers at community level.

Results: It was observed a tendency toward the decrease of principal variables correlated to the smoke behavior, even the 2011: sex, age of start, educational level, color of the skin, principal labor activity, global initiation in the consumption, exposition to the second hand smoke and increment of prevalence of smokers in teens and young people at the urban areas. The mortality attributable represented the 13 % of the general mortality of the country and the heavy smokers the 10 %, without distinction for sex. Cuba has an useful surveillance system of tabaquism based in the population, with the national–province technical capacity increased, a solid base for the scientific research, the decision making in health, another sectors and social organizations and contributing formulate national health’s projections. It has become implemented at each province of manner decentralized.

Conclusion: The surveillance system has contributed new knowledge on the magnitude and distribution of tabaquism in Cuban population with emphasis in early detection in heavy smokers, to evidence differences in subgroups of the population, to evaluate the effectiveness of interventions, and making the projections of the Public Health Cuban in order to reduce the burden from the non communicable diseases.

Keywords: Surveillance, Tobacco control, Epidemiology, mortality attributable

Pt.12 (also presented as PD.03): EGFR MUTATION TESTING PATTERNS AND RESULTS IN BRAZIL AND THE NEED FOR GREATER PUBLIC HEALTH AWARENESS OF MOLECULAR TESTING

Track: Prevention, Early Detection, Epidemiology and Tobacco Control

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Background: Epidermal growth factor receptor (EGFR) mutation testing allows for optimal selection of therapy with tyrosine kinase inhibitors in patients with non–small–cell lung cancer (NSCLC). Previous studies have shown a variation in EGFR genotype according to ethnic background, with scarce data about EGFR mutation status and testing patterns among Brazilian patients with NSCLC.

Method: Between 2011 and 2013, as part of a program sponsored by a pharmaceutical company in Brazil, tumor samples of patients with stage IIIb/IV NSCLC were submitted, at the discretion of the attending physicians, for EGFR mutation testing. All analyses were performed at 02 reference laboratories, as follows: after microdissection, DNA was isolated from serial sections of formalin-fixed, paraffin-embedded tumor tissue to obtain at least 70% tumor cells. Exons 18, 19, 20 and 21 of the EGFR gene were analysed using Sanger sequencing. EGFR mutation rate was calculated and its frequency compared between clinical subgroups using chi-square test. Data about smoking status was incomplete and thus not included in this analysis. Furthermore, a commercial database with 3,296 patients treated in Brazil in 2014 was evaluated for mutation testing patterns.

Results: 3,364 tests out of 3,771 samples analyzed (1,799 male; 1,942 female) yielded informative results. EGFR mutation was present in 25.5% (857/3364) of informative samples. Deletions in exon 19 were the most frequent alteration detected (54%), followed by
point mutations in exon 21 (28%) and exon 20 (9.7%). The most important predictors for the presence of EGFR mutations were adenocarcinoma histology (p<0.001), 89% of positive tests occurred in this histology; and female gender (p<0.001), for which 30.2% of the patients tested were positive. No differences in EGFR mutation frequency were found between age groups or regions within the country. In the commercial database of patients with NSCLC treated in the country in 2014, 1,792 patients had adenocarcinomas, 930 had squamous cancer, 71 had large cell cancer and 99 had other histologies. Overall, 34% of patients were tested for mutations (47% in the private sector and 20% in public centers); the corresponding number was 50% for patients with adenocarcinoma (62% of cases in the private and 33% in the public settings, respectively) and 10% for patients with squamous cancer. Of note fewer than 5% of patients overall were tested for ALK alterations.

**Conclusion:** To the best of our knowledge, this is the largest study to assess EGFR mutation status in Latin America and in Brazil. Our findings suggest that the frequency of EGFR mutation in this cohort was lower than that found in Asia, but higher than in Caucasian populations, confirming findings seen in other Latin American countries. Despite this high prevalence, a significant number of patients, especially in the public sector, are not currently tested for mutations in the country, and further advocacy efforts are necessary to improve this situation.

**Keywords:** EGFR, non small cell lung cancer, prevalence

### P1.13 (also presented as PD2.01): LUNG CANCER CHROMOSOMAL ABERRATIONS AND GENE EXPRESSION PROFILES OF HISPANICS LIVING IN THE US OR LATIN AMERICA ARE SIMILAR

**Track:** Prevention, Early Detection, Epidemiology and Tobacco Control

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**Background:** The incidence of epidermal growth factor receptor mutations (EGFR) in lung cancer tumors in Latin America (LATAM) are higher than the US counterparts. Our hypothesis is that the frequency of EGFR and other genomic alterations in Hispanic (H) patients (pts) living in the US is higher than non-Hispanic Whites (NHW).

**Method:** Next generation sequencing (NGS) and FISH were done in tumors of pts with NSCLC to identify genomic aberrations such as ALK, RET, ROS-1, KRAS, c-Met and BRAF at Memorial Cancer Institute and Lynn Cancer Center in Florida. Gene expression profile (GEP) was not available for all pts. Chi-square and Fisher’s exact tests were used to assess associations between GEP and ethnicity. All summary statistics on time-to-event variables were calculated according to the Kaplan–Meier method and were compared by means of the log–rank test. Adjusted hazard ratios and 95% confidence intervals were reported based on the results of a multivariate Cox regression model for overall survival.

**Results:** GEP were ordered in 492 pts and tumor samples were sufficient in 436 pts (88%). 25% were H, 61% women, 34% non-smokers and 93% had adenocarcinomas. EGFR mutations were seen in 22% of the tumors [76% in exons 19&21, and 13% in exons 18&20]. There was an increase in EGFR exon 19 in H vs. NHW (82% vs. 45%) (p<0.05). Other results of GEP: ALK 5%, RET 4%, ROS-1 8%, c-MET 31%, KRAS 30%, and BRAF 5%. There was no significant association in GEP between H vs. NHW. There were no differences in survival between H and NHW in any of these groups.

**Conclusion:** Frequency of EGFR mutations in H pts living in the US is similar to the ones reported in LATAM and higher than NHW in US and Europe. However GEP between H and NHW is similar in South Florida, except for EGFR exon 19 mutation which is more common in H than NHW. More studies need to be done to validate these findings.

**Keywords:** Hispanics, EGFR mutations, ALK, KRAS

### P1.14: ENERGY–BASED INSTRUMENTS FOR PULMONARY ARTERY LIGATION IN THORACOSCOPIC MAJOR LUNG RESECTION

**Track:** Early Stage NSCLC (Stage I – III)

**Yoshio Tsunezuka

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**Background:** During thoracoscopic major lung resection, especially lobectomy (TS–Lob), in patients with lung cancer, intraoperative bleeding by suture ligation’s failure of pulmonary arteries (PA) and the recover can be more challenging than during standard thoracotomy. We consider energy–based instruments (EBIs) are useful clinical tools for dividing pulmonary arteries in TS–Lob, investigated whether several EBIs were experimentally and clinically safe and effective for ligation of PA.

**Method:** Experimental study: The burst pressures (BP) of PA in resected pulmonary lobe in patients with lung cancer with each EBIs was attached to a digital pressure monitor to record maximal intraluminal pressure (mmHg). Samples were stained with HE and EVG for histological analysis. Clinical study: A total of 601 PA were analyzed. We performed TS–Lob with 3–ports for lung cancer patients. Thick segmental pulmonary arteries (diameter>7mm) were divided with staplers, pulmonary arteries with 5mm and larger in diameter were ligated with 1–0 suture material at the central site and the peripheral site was ligated and incised with the EBIs. As EBIs, we used LigaSure™(LS-V), LigaSure™Blunt-tip(LS-B), LigaSure™Blunt-tip37(LS-B–New), LigaSure™Maryland (LS-M),EnSeal™(ES)and Harmonic Scarpel™ (HS).

**Results:** Experimental study: There was no significant differences in the BP among four VSS (458/452/468/455 mmHg) but higher with...
VSS compared to HS(211mmHg) and ES(358mmHg). Histological burst point was the base of sealing site. All EBs maintained enough BP above venous blood pressure. Sorter sealing time with ES was insufficient for sealing arteries, their BP is lower (322mmHg) than LS and ES with standard sealing time(8s). Histopathologically, the cut end of artery was completely sealed and degenerated by the VSS and ES, the length of the sealing site was longer than HS. However the sealing tissues was destroyed and rough in ES, the cause was suspected to be that the cutter system, I-Blade, was not sharp but dull. While the cutter system of LS are sharp. In LS group, almost intima and media layer invaginated into the vessel lumen, but in ES all layers were completely fused. Clinically, Intraoperative bleeding highly occurred in ES group (76.9%;9 bleeding cases in 13 arteries) or HS group(22.9%;4/18) .There was single case of delayed bleeding in LS–V group (1.5%;1/68), and no bleeding case in LS–B group(0/151) . LS–B–New(0/168) and LS–M group(0/142).In almost all cases, the timing of bleeding of PA treated with ES or HS was not just after the cutting, occurred during intraoperative moving of lung specimens. 

**Conclusion:** These studies demonstrated the clinical safety and efficacy of the all LS devices to seal of PA in TS-Lob, LS is high performance tool for lung cancer surgery.

**Keywords:** vessel sealing system, pulmonary artery, thoracoscopic surgery, lung cancer

**P1.15: COMPARISON OF PULMONARY FUNCTION AFTER ROBOTIC-ASSISTED VIDEO-THORACOSCOPIC LOBECTOMIES VS SEGMENTECTOMIES**

**Track: Early Stage NSCLC (Stage I – III)**

Maria F. Echavarria1, Anna Cheng1, Frank Velez2, Emily Ng3, Eric Toloza3, Jacques–Pierre Fontaine1, Carla Moodie1, Joseph Garrett1

1University of South Florida, Tampa/FL/UNITED STATES OF AMERICA, 2University of South Florida, Tampa/UNITED STATES OF AMERICA, 3Moffitt Cancer Center, Tampa/FL/UNITED STATES OF AMERICA

**Background:** Lobectomy is the standard surgical procedure for early stage lung cancer, but sub–lobar resection is being debated. We aimed to compare pulmonary function outcomes after robotic–assisted video–assisted Thoracoscopic (R–VATS) segmentectomy versus lobectomy. We compared preoperative pulmonary function tests (FEV1, DLCO) for patients undergoing R-VATS pulmonary lobectomy vs segmentectomy. We then predicted amounts of change from preoperative values and predicted postoperative values for each pulmonary function after surgery.

**Method:** We retrospectively analyzed prospectively collected data from 251 consecutive patients who underwent lobectomy (N=208) and segmentectomy (N=43) via R-VATS by one surgeon. Unpaired Student’s t-test and Chi–square tests were used to determine statistical significance (p≤0.05) in outcomes after R-VATS segmentectomy vs lobectomy. Majority of patients had no prior lung surgery. We used the formula, “Predicted(PFT)=Preop(PFT) x (I–(Segments x 0.0556))”, where 0.0556=seg/18seg. For patients with prior resections, the number of segments previously resected was taken into account (iseg/(18–Prior resection)).

**Results:**

**Table 3: Pulmonary Function Tests**

<table>
<thead>
<tr>
<th></th>
<th>Segmentectomy (n = 43)</th>
<th>Lobectomy (n = 208)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-op FEV1 (L)</td>
<td>2.08±0.1 (0.87–4.42)</td>
<td>2.52±0.05 (0.34–4.45)</td>
<td>0.081</td>
</tr>
<tr>
<td>Pre-op FEV1 (%)</td>
<td>76.4±2.5 (76–125)</td>
<td>85±2.1±5 (28–133)</td>
<td>0.024</td>
</tr>
<tr>
<td>Pre-op DLCO (ml/min/mmHg)</td>
<td>15.3±0.7 (7.35–31.8)</td>
<td>17.3±0.4 (7.34–32.5)</td>
<td>0.062</td>
</tr>
<tr>
<td>Pre-op DLCO (%)</td>
<td>65.3±5.9 (35.0–120)</td>
<td>74±6.1 (14.9–131)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

**Mean ± SEM; (range)**

**Table 4: Predicted Post-Operative Lung Function and Change from Pre-Operative Lung Function.**

<table>
<thead>
<tr>
<th></th>
<th>Segmentectomy (n = 43)</th>
<th>Lobectomy (n = 208)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted Post-op FEV1 (L)</td>
<td>1.94±0.1 (0.81–4.17)</td>
<td>1.83±0.04 (0.47–3.61)</td>
<td>0.61</td>
</tr>
<tr>
<td>Predicted Change from Preop FEV1 (L)</td>
<td>0.13±0.02 (0.06–0.57)</td>
<td>0.089±0.02 (0.02–1.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Predicted Post-op FEV1 (%)</td>
<td>69.8±3.3 (31.3–188.1)</td>
<td>67.4±2.2 (24.4–115.0)</td>
<td>0.58</td>
</tr>
<tr>
<td>Predicted Change from Preop FEV1 (%)</td>
<td>6.8±4.7 (5.6–22.2)</td>
<td>20.6±4.0 (11.1–40.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Predicted Post-op DLCO (ml/min/mmHg)</td>
<td>14.4±0.9 (7.7–11.9)</td>
<td>13±6.0 (4.4–28.6)</td>
<td>0.69</td>
</tr>
<tr>
<td>Predicted Change from Preop DLCO (ml/min/mmHg)</td>
<td>1.3±1.0 (0.44–3.15)</td>
<td>3.6±0.1 (0.65–8.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Predicted Post-op DLCO (%)</td>
<td>59±2.9 (27.2–113.9)</td>
<td>58.9±1.1 (20.9–103.49)</td>
<td>0.87</td>
</tr>
<tr>
<td>Predicted Change from Preop DLCO (%)</td>
<td>8.9±4.7 (5.5–22.2)</td>
<td>20.8±4.0 (11.1–40.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Mean ± SEM; (range)**

Preoperative FEV1 (%) and DLCO (%) were statistically significant between the two groups. In addition, FEV1 and DLCO trended to be lower in segmentectomy patients. As expected, predicted changes between preoperative and postoperative FEV1 and DLCO values were statistically significant. Less of a change noted on segmentectomy patients. Predicted post–operative FEV1 and DLCO did not show any significant difference between the two groups, and did not show any trend toward significance between the two groups.

**Conclusion:** While pre-operative PFTs were significantly lower in segmentectomy patients compared to lobectomy patients, predicted post-operative PFTs do not differ significantly between the two groups. In addition, predicted changes for FEV1 and DLCO are significantly less in patients undergoing R-VATS segmentectomy. These findings negate the difference in pre-operative PFTs between these groups of patients. Thus, R-VATS segmentectomy preserves FEV1 and DLCO relative to R-VATS lobectomy. We conclude that R-VATS segmentectomy may be considered as a viable alternative in order to conserve lung volume.

**Keyword:** Robotic lung surgery PFTs
P1.16: COMPARISON OF PERI-OPERATIVE OUTCOMES AFTER ROBOTIC-ASSISTED VIDEO-THORACOSCOPIC LOBECTOMIES VERSUS SEGMENTECTOMIES

Track: Early Stage NSCLC (Stage I – III)

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Background: Lobectomy is the standard procedure for early stage lung cancer. The role of sub-lobar resection is currently under investigation for selected patients. Published comparisons between conventional VATS, R-VATS, and open lobectomy and segmentectomy have been reported. Benefits of R-VATS surgery include decreased post-operative pain, shorter length of stay (LOS), and a quicker return to daily activities. The goal of our study was to compare peri- operative outcomes after R-VATS lobectomy vs segmentectomy. Comparison between these two procedures using robotic instruments has not been published.

Method: We retrospectively analyzed prospectively collected data from 253 consecutive patients who underwent lobectomy (N=208) and segmentectomy (N=45) via R-VATS performed by one surgeon. Unpaired Student’s t-test and Chi-square test were used to determine statistical significance (p ≤ 0.05) of intra- and post- operative outcomes between these 2 groups.

Results:

Table 1: Gender, Age, and Smoking Status of Patients

<table>
<thead>
<tr>
<th></th>
<th>Segmentectomy (n=208)</th>
<th>Lobectomy (n=45)</th>
<th>p-value</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>121 (49%)</td>
<td>20 (44%)</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>87 (51%)</td>
<td>25 (56%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>64.2±12.0 (22-79)</td>
<td>61.7±13.6 (24-76)</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>27.2±5.0 (17.43-46)</td>
<td>27.4±4.0 (14.59)</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>Smoking history (packs per day)</td>
<td>0.06±0.03 (0-5.55)</td>
<td>1.12±0.06 (0-5)</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>45 (88%)</td>
<td>21 (88%)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>22 (12%)</td>
<td>6 (12%)</td>
<td>0.88</td>
<td>0.86</td>
</tr>
</tbody>
</table>

There was no significant difference of intra-operative blood loss between lobectomy and segmentectomy patients (87.5 vs 200 ml; p=0.91). Furthermore, intra-operative complications between these 2 groups were also not statistical difference (8/208 vs. 4/45; p=0.70). However, the mean duration of R-VATS segmentectomy was longer than R-VATS lobectomy (28.6min vs. 20.75min; p=0.01). Total post-operative complications in the segmentectomy group were not significantly different than in the lobectomy group (24.4% vs. 8.4%; p=0.071). Cardiovascular complications did not differ between the two groups. Notably, there was no significant difference in terms of post-operative respiratory failure, pneumonia, hemothorax, prolonged air leak, length of stay, and in-hospital mortality. Individual complications that were significant were the rates of pneumothorax after chest tube removal (p=0.032) and effusion/empyema (p=0.011) requiring intervention.

Conclusion: R-VATS segmentectomy may be considered as an alternative procedure to R-VATS lobectomy in order to conserve lung function.

Keyword: robotic lung surgery outcomes
P1.17: IMPROVED SURVIVAL FOR STAGE-2 (N1) PULMONARY ADENOCARCINOMA AND SQUAMOUS CELL CARCINOMA AFTER PULMONARY LOBECTOMY

Track: Early Stage NSCLC (Stage I – III)

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2Thoracic Oncology, Moffitt Cancer Center, Tampa/FL/UNITED STATES OF AMERICA

Background: Non-small cell lung cancer (NSCLC) is comprised of various histologies, including adenocarcinoma (AD), squamous cell (SQ), neuroendocrine (NE), and adenosquamous (AS). We evaluated postoperative survival of stage-2 (N1) NSCLC patients (pts), who underwent lobectomy from 1988 to 2013, and compared survival between 1988–2003 and 2004–2013.

Method: Using the Surveillance, Epidemiology, and End Results (SEER) database, we identified stage-II (T1N1Mo or T2N1Mo) NSCLC pts who underwent lobectomy during 1988–2013, but excluded those who had radiation therapy or multiple primary NSCLC tumors. We grouped the pts by histology and performed Kaplan–Meier survival analyses, with log–rank test used to compare 5-yr cancer-specific survival of each major histologic subtype between 1988–2003 versus 2004–2013.

Results: Of 2,937 pts, there were 1790 (60.9%) AD pts, 978 (33.3%) SQ pts, 113 (3.8%) NE pts, and 113 (3.8%) AS pts. From 1988–2003, 5-yr survival did not differ between AD (41.6%), SQ (45.9%), NE (55.2%), and AS (46.4%) (p = 0.63). For AD pts, 5-yr survival improved significantly from 35.6% to 45.4% (p < 0.0001) between 1988–2003 versus 2004–2013, respectively, while median survival time (MST) improved from 37.0±3.8 mon in 1988–2003 to 60 mon in 2004–2013 (p < 0.0001). For SQ pts, 5-yr survival also improved significantly from 39.5% to 51.0% (p = 0.004) between eras, while MST improved from 37.0±3.8 mon in 1988–2003 to 60 mon in 2004–2013 (p = 0.005). Neither 5-yr survival for AS pts nor for NE pts changed significantly between 1988–2003 and 2004–2013 (35.5% vs. 38.2%, p = 0.21, for AS; 50.6% vs. 50.8%, p = 0.55, for NE). The T1N1:T2N1 ratio in AD pts was higher than in SQ pts in both eras as well as over the entire study period (all p < 0.01), while that for NE pts was higher than in SQ pts only in 2004–2013 and over 1988–2013 (both p < 0.01).

Conclusion: Using SEER data, we found significantly improved postoperative 5-yr cancer-specific survival for stage-2 (N1) AD and SQ, but not for AS pts or for NE pts, between 1988–2003 and 2004–2013. A higher proportion of T2N1 did not worsen survival for SQ pts. These results likely reflect more minimally invasive surgery and improved perioperative care and/or adjuvant chemotherapy for stage-2 (N1) NSCLC pts.

Keywords: Stage-2 (N1) NSCLC, Lobectomy, Adenocarcinoma, Squamous Cell Carcinoma

P1.18: LONG-TERM CLINICAL OUTCOMES AND SAFETY PROFILE FOR CENTRAL LUNG SBRT FOR NSCLC

Track: Early Stage NSCLC (Stage I – III)

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1Radiation Oncology, Mayo Clinic, Rochester/MN/UNITED STATES OF AMERICA
2Radiation Oncology, Veterans Affairs Ann Arbor Health System, Ann Arbor/MI/UNITED STATES OF AMERICA

Background: Previous studies suggest central lung SBRT is associated with an increased risk of severe toxicity relative to peripherally located tumors when using high SBRT dose levels. Initial results from RTOG 0813 suggest a safe toxicity profile for central lung SBRT with moderate SBRT dosing. We reviewed our institutional data to further evaluate the safety and efficacy of central lung SBRT.

Method: We reviewed our prospectively collected SBRT database for patients with centrally located NSCLC who received SBRT between April 2008 and November 2014. A central tumor was defined as within or touching the proximal bronchial tree zone or mediastinal structures. The most frequent dose and fractionation was 50 Gy in 5 fractions (59%) and 48 Gy in 4 fractions (31%). Local, regional, and distant control (LC, RC, DC) and overall survival (OS) were calculated using Kaplan–Meier estimates. Radiation Therapy Oncology Group Common Toxicity Criteria was used for toxicity grading. Univariate and multivariate (MVA) were performed using Cox proportional hazards regression models.

Results: A total of 99 central lung tumors in 93 patients were included for analysis. The median age of the group was 73.8 (range, 40–95). The median follow-up time of living patients was 50 months. The mean tumor size was 20 mm (range, 5–70). The most common histology was squamous cell carcinoma (43.8%). A total of 33% of patients had prior lung surgery and 7% had prior radiotherapy. The 5-year rates of LC, RC, and DC were 86%, 77%, and 82%, respectively. The median and 5-year OS were 3.5 years and 34.5%, respectively. We did not identify any univariates that predicted for tumor control or other clinical outcomes. Two
patients (1.8%) experienced acute cardiopulmonary toxicity ≥ grade 3 including a grade 3 and 5 radiation pneumonitis. The rate of late toxicity ≥ grade 3 was 16% (grade 3=14%, grade 4=1%, grade 5=1%). This included radiation pneumonitis (10%), upper airway necrosis and distal lung collapse (3%), myocardial dysfunction (2%), and worsening pulmonary function (1%). One patient experienced a late grade 5 toxicity after upper airway necrosis resulting in atelectasis and pulmonary compromise. 

**Conclusion:** SBRT for central NSCLC using moderate SBRT dose and fractionation provides high rates of LC. We observed acceptably low rates of grade 4 or 5 toxicity potentially attributable to SBRT. Our data contributes to the growing body of data supporting efficacy SBRT for central lung NSCLC.

**Keywords:** NSCLC, SBRT, Central Lung Cancer, Early Stage NSCLC

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**Pt19: BARRIERS TO DELIVER PERSONALIZED MEDICINE TO YOUNG PATIENTS WITH NON-SMALL CELL LUNG CANCER IN LATIN AMERICA**

**Track:** Early Stage NSCLC (Stage I – III)

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Biomedical Research Group In Thorax, Fundación Valle del Lili, Universidad Icesi, Cali/COLOMBIA

**Background:** Young patients with NSCLC are a particular subset of patients. Within this group, the disease is strongly related with driver mutations rather than smoking history, therefore, these patients would benefit from targeted therapy (TT) which has evidenced to be superior over standard chemotherapy. We aimed to estimate the prevalence of EGFR mutations and EML4-ALK fusions and describe treatment patterns and clinical outcomes in young patients with NSCLC of a reference hospital from Cali–Colombia.

**Method:** Our clinic data base queried for NSCLC cases from June–2013 to February–2016. Young patients were defined as those aged 50 years or less. Eleven patients were included. Patient’s demographics, clinicopathological characteristics and presence of EGFR or EML4-ALK mutations were analyzed. The primary outcomes were overall follow up and survival.

**Results:** This series included n patients aged 50y or less. Ten patients were women (90.9%), nine of them were never-smokers (90%). 81.8% had lung adenocarcinoma (n=9), 9.1% large-cell carcinoma (n=1) and 9.1% giant-cell carcinoma (n=1). Nine patients were diagnosed at stage-IV and two patients at stages IA and IIB. Six patients (54.5%) were positive for either EGFR mutations (n=3) or EML4-ALK fusions (n=3) and two of them received TT with a tyrosine kinase inhibitor. Interestingly, all patients under 40y were mutated. Regarding to follow-up, 63.6% were not able to be followed, 27.3% died. Only one patient, who received TT with erlotinib, was followed-up at our institution (Table 1).

**Conclusion:** Our findings go along with previous reports on NSCLC behavior in young patients. Those diagnosed with primary NSCLC tend to be never-smokers, women and stage-IV adenocarcinoma, with a high rate of mutations. In our series, all patients under the age of 40 had genomic alterations, with ALK fusions being more prevalent. Unfortunately, due to procedural circumstances within Colombia’s healthcare system, the follow–up of these patients was not performed as international guidelines recommend. In this regard, our nation, ruled by the Constitution of 1991, states the Principle of Integrality which along with law No.17 of 2015 state that services and health technologies should be provided in a comprehensive manner. Furthermore, the responsibility of providing them cannot be fragmented at the expense of the patient’s health. Despite our institution has suitable medical staff and technology to ensure an optimal attention, according to the best evidence available, nation’s healthcare system issues may interfere. We provide evidence to make a wake-up call to health services managers in order to claim the Principle of Integrality to every patient from the country.

**Keywords:** Non–small Cell Lung Cancer, young patients, Personalized Medicine

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<th>N° patient</th>
<th>Diagnosis date</th>
<th>Gender</th>
<th>Age (y)</th>
<th>Smoking</th>
<th>Histology</th>
<th>Stage</th>
<th>Molecular tests</th>
<th>Positive mutation</th>
<th>Treatment</th>
<th>Follow up</th>
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<td>Adenocarcinoma</td>
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<td>Adenocarcinoma</td>
<td>IV</td>
<td>EGFR</td>
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<td>EGFR and EML4-ALK</td>
<td>EGFR</td>
<td>Palliative</td>
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<td>09/12/2014</td>
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<td>IA</td>
<td>EML4-ALK</td>
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<td>No data</td>
<td>Chemotherapy and TKI</td>
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</table>
Lung cancer is the leading cause of cancer related death worldwide when considering both genders. The optimal treatment is complete surgical resection. The objective of this study was to analyze morbidity and mortality of anatomic lung resections in Brazil.

**Method:** The Brazilian Society of Thoracic Surgery (BSTS) uses a customized version of the ESTS platform as its national database (BSTS Database). From August to December 2015, 1367 patients were registered. In the current analysis, we included only patients who underwent anatomic lung resections; wedge resections and unspecified cases were excluded. The main outcome was postoperative hospital mortality and the secondary outcome was complication rate and profile.

**Results:** Out of the 1367 cases registered, 902 were anatomic lung resections. Patient’s mean age was 59.6 years (+-15.2) and 52.5% were women. The baseline diagnosis (n=597) was lung cancer in 450 (75.3%), bronchiectasis or lung malformations in 70 (11.7%), tuberculosis-associated lung destruction in 57 (9.5%), and it varied significantly across different procedures performed, complication profile was also different between lobectomy and pneumonectomy (Table I). Overall mortality rate was 2.6% (23/843) and it varied significantly across different procedures performed, lobectomy 1/641 (1.7%), pneumonectomy 11/62 (18.8%), bilobectomy 3/28.7%, and 4 in 5.4%. The resections performed were lobectomy in 681 cases (75.5%, 45% of which were VATS), pneumonectomy in 71 (7.9%, 13% VATS), bilobectomy 39 (4.3%, 13% VATS), and segmentectomy 3/104 (2.8%). Most relevant complications in patients with fatal outcome were pneumonia (n1), myocardial infarct (n2), bleeding requiring reoperation (n3), and impossibility to wean from mechanical ventilation (n4).

<table>
<thead>
<tr>
<th>Complication</th>
<th>All patients</th>
<th>Lobectomy</th>
<th>Pneumonectomy</th>
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<tbody>
<tr>
<td>Major Cardiovascular Complications</td>
<td>546 (14.8%)</td>
<td>113 (20%)</td>
<td>13 (20.7%)</td>
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<tr>
<td>Pneumonia</td>
<td>32 (10.9%)</td>
<td>64 (11.4%)</td>
<td>5 (7.9%)</td>
</tr>
<tr>
<td>All-cause Deaths</td>
<td>11 (1.4%)</td>
<td>46 (8.2%)</td>
<td>3 (4.6%)</td>
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<tr>
<td>Atelectasis</td>
<td>41 (1.4%)</td>
<td>36 (6.4%)</td>
<td></td>
</tr>
<tr>
<td>Arrial Arrhythmia</td>
<td>29 (1.9%)</td>
<td>20 (3.6%)</td>
<td>3 (4.8%)</td>
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<tr>
<td>Delirium</td>
<td>10 (1.5%)</td>
<td>14 (2.5%)</td>
<td>2 (1.2%)</td>
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<tr>
<td>Empyema</td>
<td>14 (1.9%)</td>
<td>4 (0.7%)</td>
<td>6 (9.3%)</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>12 (1.6%)</td>
<td>10 (1.9%)</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Myocardial Infarct</td>
<td>13 (1.8%)</td>
<td>8 (1.4%)</td>
<td>2 (1.2%)</td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td>10 (1.3%)</td>
<td>9 (1.6%)</td>
<td>1 (1.6%)</td>
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<tr>
<td>Respiratory Failure</td>
<td>8 (1.1%)</td>
<td>5 (0.9%)</td>
<td>3 (4.6%)</td>
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<tr>
<td>Reintubation</td>
<td>8 (1.1%)</td>
<td>5 (0.9%)</td>
<td>3 (4.6%)</td>
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<tr>
<td>Bronchopulmonary Fistula</td>
<td>5 (0.7%)</td>
<td>3 (0.5%)</td>
<td>2 (3.1%)</td>
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<tr>
<td>Tracheoesophageal Fistula</td>
<td>4 (0.5%)</td>
<td>3 (0.5%)</td>
<td>1 (1.6%)</td>
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<tr>
<td>ARDS</td>
<td>3 (0.4%)</td>
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<td></td>
</tr>
<tr>
<td>Initial ventilation &gt;48 hours</td>
<td>3 (0.4%)</td>
<td>2 (0.4%)</td>
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<tr>
<td>Cerebral-Vascular Complications</td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td></td>
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<tr>
<td>Pulmonary Edema</td>
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<tr>
<td>Other</td>
<td>93 (12.3%)</td>
<td>63 (12%)</td>
<td>17 (27%)</td>
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<tr>
<td>Any complication</td>
<td>277 (36.7%)</td>
<td>207 (36.8%)</td>
<td>60 (44.6%)</td>
</tr>
</tbody>
</table>

**Conclusion:** Mortality and major morbidity rates of anatomic lung resections in Brazil are similar to other international series. Nevertheless, the high incidence of infectious complications as pneumonia and empyema is an issue to be further studied.

**Keywords:** Lung Resection, Anatomical Resection, Lobectomy, lung cancer

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**P1.21: NOVEL PET PARAMETERS AS PREDICTORS OF PATHOLOGIC RESPONSE IN PATIENTS WITH STAGE IIIA(N2) NSCLC RECEIVING TRIMODALITY THERAPY**

**Track:** Early Stage NSCLC (Stage I – III)

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**Background:** Positron emission tomography (PET) scan is commonly utilized to evaluate treatment response in patients with NSCLC cancer. Complete pathologic response (pCR) following neoadjuvant chemoradiation has been associated with improved overall survival (OS). However, studies have reported conflicting results regarding the predictive value of PET response and pathologic response in this population. The aim of this study was to evaluate the correlation between post-neoadjuvant therapy PET response and pCR utilizing novel FDG-PET parameters.

**Method:** This retrospective study included 32 patients with stage IIIA(N2) NSCLC cancer treated with neoadjuvant chemoradiation (CRT) followed by resection from 2004 to 2014. All patients underwent PET prior to and after neoadjuvant CRT. Chi-square analysis was utilized to assess correlations between PET response, pCR, near-complete pathologic response (defined as <10% viable tumor), and nodal response. Maximal standard uptake value (SUV), standard uptake ratio (SUR) [normalized independently to liver (SUR-L) and blood pool (SUR-BP)], metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were measured pre- and post-chemoradiation.

**Results:** A total of 32 patients (14 females, 18 males) were included. Median age was 64.5 years (range, 43–77) and median follow-up was 2.6 years. Histologic subtypes included adenocarcinoma (71.8%) and squamous cell carcinoma (21.9%). The majority of patients had T2 disease (65.6%). The rate of pCR and near-complete pathologic response within the primary lesion was 34.3% and 56.2%, respectively. The rate of nodal pCR was 43.8%. Median survival was 4.88 years, and 5 yr OS 44.0% [95% CI: 33.1 – 54.9%], 5 yr OS for patients who achieved pCR or near-complete response was 68.1% [95% CI: 52.8–83.4%] or 52% [95% CI: 38–66%, p=0.32] versus 32.8% [95% CI: 19.6–46%] and 32.7% [95% CI: 16.0–49.4%, p=0.32] for those who did not, respectively. The majority of patients exhibited at least a partial response to treatment on FDG-PET, which manifested as a reduction in SUV (mean 49.1%, range -21.8-86.4%), and total lesion glycolysis (TLG) were measured pre- and post-chemoradiation.

**Conclusions:** Positron emission tomography (PET) scan is commonly utilized to evaluate treatment response in patients with NSCLC cancer. Complete pathologic response (pCR) following neoadjuvant chemoradiation has been associated with improved overall survival (OS). However, studies have reported conflicting results regarding the predictive value of PET response and pathologic response in this population. The aim of this study was to evaluate the correlation between post-neoadjuvant therapy PET response and pCR utilizing novel FDG-PET parameters.

**Keywords:** Positron emission tomography, Neoadjuvant therapy, Chemoradiation, Pathologic response, Lung cancer.
P1.22: TEMPORAL SURVIVAL IMPROVEMENT FOR STAGE-II (T3N0M0) LUNG ADENOCARCINOMA AFTER PULMONARY LOBECTOMY

Track: Early Stage NSCLC (Stage I – III)

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1University of South Florida, Morsani College of Medicine, Tampa/FL/UNITED STATES OF AMERICA, 2Thoracic Oncology, Moffitt Cancer Center, Tampa/FL/UNITED STATES OF AMERICA

Background: Stage-II non–small cell lung cancer (NSCLC) includes T3N0M0 tumors, which include tumors with lung metastases within the same lobe or involving the chest wall, diaphragm, or mediastinal pleura, while NSCLC is comprised of various histologies, including adenocarcinoma (AD), squamous cell carcinoma (SQ), and adenosquamous (AS) and neuroendocrine (NE) carcinomas. We sought to determine temporal changes in survival of stage-II (T3N0M0) NSCLC patients (pts) between 1988–2013 based on histology.

Method: We searched the Surveillance, Epidemiology, and End Results (SEER) database for T3N0M0 NSCLC pts who underwent lobectomy during 1988–2013. We excluded pts who had radiation therapy or multiple primary NSCLC tumors and, by including only lobectomy pts, effectively excluded those with tumors within 2 cm of the carina. We grouped pts by histology and performed Kaplan–Meier survival analyses, with log–rank test to compare postoperative 5-yr cancer-specific survival between histology groups and for 1988–2003 versus 2004–2013.

Results: Of 1,201 pts, there were 605 (50.3%) AD pts, 523 (44.3%) SQ pts, 42 (3.5%) AS pts, and 31 (2.6%) NE pts. From 1988–2013, 5-yr survivals differed significantly between NE (87.3%), AD (46.3%), SQ (41.6%), and AS (34.8%) (p<0.05), with median survival times (MST) also differing between NE (“not reached”), AD (50mon), SQ (34±4.1mon), and AS (17±4.4mon) (p<0.05) (Figure 1). There were no significant differences in 5-yr survival between histologies for 1988–2003 (p>0.167), but 5-yr survivals did significantly differ between histologies for 2004–2013 (p<0.05). For AD pts, 5-yr survival improved from 29.3% for 1988–2003 to 49.8% for 2004–2013 (p<0.05), while MST improved from 32±5.0mon for 1988–2003 to 58.0mon for 2004–2013 (p<0.05) (Figure 2). For SQ pts, 5-yr survival did not change significantly (37.2% vs. 43.9%; p=0.111), while MST improved from 29.0±6.3mon to 36.0±5.1mon (p=0.046), for 1988–2003 versus 2004–2013. The apparent 5-yr survival improvement for AS pts (20.5% vs. 45.7%) was not statistically significant (p=0.41).

Conclusion: Using SEER data for stage-II (T3N0Mo) cases, postoperative 5-yr cancer-specific survival and MST improved for AD pts, while only MST improved for SQ pts between 1988–2003 and 2004–2013. These results likely reflect development of adjuvant targeted therapy for AD pts.

Keywords: Stage-2 NSCLC, Adenocarcinoma, T3MoM0, Lobectomy

P1.23: CHEMOTHERAPY IN LUNG CANCER AT NATIONAL INSTITUTE OF ONCOLOGY AT PARAGUAY: A RETROSPECTIVE STUDY, 8 YEARS OF EXPERIENCE

Track: Advanced NSCLC

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1Central, Instituto Nacional del Cancer. Prof. Dr. Manuel Riveros., Capiata/ PARAGUAY, 2Instituto Nacional de Cardiologia Ignacio Chavez, Mexico DF/MEXICO

Background: Lung cancer is the third most common cancer and the leading cause of cancer deaths in the Americas, with 324,000 new cases and 262,000 deaths each year. There are only few official data of Lung Cancer in Paraguay.

Method: Between January 2004 and December 2011, all patients diagnosed with SCLC and NSCLC treated with chemotherapy at National Institute of Oncology at Asuncion– Paraguay were analyzed retrospectively. Demographic information, treatment modalities, tumor response, were recorded. SPSS 19 was used to analyze the data with p <0.05 as significance.

Results: We studied 370 subjects, 28% received chemotherapy, 14.8% chemotherapy plus radiotherapy, 11% surgery plus chemotherapy. At IIIA stage NSCLC 18.2% was treated with PTX.
and CBDCA 1 cycle and 18.2% with PTX+CBDCA 4 cycles (p < 0.05).

IIIB stage NSCLC: 17.6% patients received PTX+CBDCA 4 cycles and 22.1% PTX+CBDCA 6 cycles (p < 0.05). At IIIA stage NSCLC received PTX + CBDCA 4 cycles. (p < 0.05). SCLC has no statistical significance relation between stage and type of chemotherapy. The tumor response to first-line chemotherapy shows 45.4% has no response. 32.1% has response (p < 0.05), 17.6% abandoned treatment (p < 0.05).

Patients who received PTX+CBDCA show a high percentage of abandoned treatment as 20% and patients receiving CDDP + VP-16 had a high abandoned treatment of 80% (p < 0.05). 59.8% patients treated with chemotherapy were from countryside places and 40.2% from urban places (p > 0.05), 25.6% of patients receiving chemotherapy and 29.6% were receiving chemotherapy and radiotherapy were farmers (p < 0.05). 80.4% patients receiving chemotherapy were smokers (p < 0.05). 45.1% patients consumed alcohol regularly (p < 0.05). Only 12.7% patients had family lung cancer genetic precedence (p < 0.05). 53.5% patient receiving chemotherapy had a stage 2 of ECOG Performance Status (p < 0.05). Tumor response to chemotherapy at NSCLC show: 100% patients who received dFdC+CDDP 4 cycles; 65.5% with PTX+CBDCA 4 cycles; 42.9% CDDP+VP-16 4 cycles; 65% PTX + CBDCA 6 cycles; 100% of CDDP+ VP16 6 cycles; 100% of dFdC 6 cycles (p < 0.05). SCLC has no statistical significance at this analysis. At Second line chemotherapy to NSCLC 23.8% received dFdC + CDDP 1 cycle and 14.3% PTX+CBDCA 1 cycle. Only 3 patients received third line chemotherapy with PTX+CBDCA 1 cycle, Pemetrexed 1 cycle, CDDP+dFdC 1 cycle. No patients with SCLC received second or third line chemotherapy. Conclusion: We found patient’s living residence differences but has no statistical significance. 25.6% work as farmers. Majority of patients were smokers, 25% had exposure to toxic environmental agents. First line chemotherapy regimes with PTX+CBDCA at different NSCLC stages were predominant. After first line chemotherapy only 17.6% of patients abandoned treatment. Patients receiving CDDP+VP-16 abandoned chemotherapy more frequently. Almost half of patients were at ECOG stage 2. At different schemes of first line chemotherapy we found that majority of high percentages of tumor response to chemotherapy with PTX+CBDCA was involved.

Keywords: Lung Neoplasms, Drug therapy, Latin America

P1.24: 1ST LINE TREATMENT WITH ERLOTINIB IN ADVANCED NON-SQUAMOUS NSCLC: OUR EXPERIENCE. CCSS, SAN JOSE COSTA RICA

Track: Advanced NSCLC

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Hemato-oncología, CCSS, San Jose, COSTA RICA

Background: Lung cancer is one of the most important topics in oncology nowadays. The advent of new therapies, for example TKIs (Erlotinib), has changed the way we approach this disease. Social security in Costa Rica has allowed oncologist and patients the opportunity to treat and be treated respectively with new therapies besides chemotherapy. Five years ago, we decided to organize a multidisciplinary approach to lung cancer patients with our thoracic oncology clinic and obtain statistics related with the treatment we use.

Method: We reviewed all the patients who were treated with erlotinib since 2013 (complete data available) and reviewed the evolution of the patients, therapy side effects and progression free survival. (Retrospective study). From January 2013 to May 2016, a total of 149 patients were tested. 45 were positive for some EGFR mutation and 29 received Erlotinib as first line treatment. Results: From January 2013 to May 2016, 149 patients were tested for some EGFR mutation. 45 were positive for some EGFR mutations (frequency of mutation around 30% in our general) and 29 received Erlotinib as first line therapy. The group of 16 patients who did not receive a TKI, were early lung cancer stage or absence of the patient to the medical appointment. From de treated patients, 79.3% (23) were female, and 20.7% male. The average age to start treatment was 62.1±12.7 years. 24.3% used to smoke at the moment of diagnosis. The frequency of EGFR exon mutation was: 6.9% exon 18, 55.2% exon 19, 13.8% exon 20 and 37.9 exon 21. The most common site of metastasis were 44.8% in pleura, 41.4% contralateral lung, 20.7% in bones, 13.8% adrenal gland, 10.3% liver and 6.9% in central nervous system. The median of follow up was 13.5 months (2-14 months), and the majority of patients received just first line of treatment (poor performance status or patient decision). 34.5% had stable disease, 31% partial response and 3.4% complete response. (68.9% of patients had treatment response) Side effects: 75.8% had some grade of rash (58.6% grade II), 3.4% diarrhea and 6.9% fatigue. The PFS was 10.0 months and the OS 15 months. (12.8-17.2 months)

Conclusion: The use of target therapy is definitely, a new horizon in the management of lung cancer. Nevertheless, the cost of such drugs can be high for developing countries and hard to maintain in social security. However, the opportunity to review our experience with our own patients, has enable us to understand that TKIs as first line should be a real option, with similar results to worldwide studies. Today, thanks to works like this, we can count on drugs such erlotinib at disposal in our institution, without additional paperwork.

Keywords: PFS, erlotinib, EGFR, exon

P1.25: EXPERIENCE WITH ERLOTINIB AND GEFITINIB IN PATIENTS WITH EGFR MUTATION POSITIVE ADVANCED LUNG CANCER

Track: Advanced NSCLC

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Background: Tyrosin kinase inhibitors (TKIs) are the standard treatment options in patients with advanced lung cancer that harbours activating EGFR mutations. Erlotinib, Afatinib and Gefitinib have shown better efficacy compared to chemotherapy in terms of PFS, response rates and quality of life in the first line treatment; however there are limited trials comparing directly this 3 drugs to establish which the best is.

Method: We retrospectively reviewed the medical records of patients with lung cancer EGFR mutation positive exposed to gefitinib or erlotinib from 2011 to 2015. The primary objective was to compare the PFS (progresión free survival) in those patients treated with TKIs as the first line treatment and the secondary objective was to analyze the factors associated with OS (overall survival) in the entire population. PFS and OS were evaluated by Kaplan-Meier and long rank test and multivariate analysis was made with Cox regression.
Results:

A total of 333 patients have been evaluated for EGFR status, 94 were positive (28.2%). 80 patients with EGFR mutation received treatment for metastatic disease; 34 with TKI only (42.5%), 45 with TKI and chemotherapy (56.3%) and 1 patient chemotherapy only. The group receiving TKI, 30 patients were treated with erlotinib and 24 with gefitinib as the first line treatment. The PFS in the first line with Erlotinib was 10.1 months (95% CI 7.3–12.9) and Gefitinib 7.8 months (95% CI 4.1–11.4); (HR =0.589 CI 95 % 0.297–1.167) p=0.125. Median OS was 23.6 and 2.62 months for patients with ECOG 0–2 vs 3–4 (p = 0.001), 26.2 vs 9.8 months for patients exposed to TKI and chemotherapy vs TKI only (p = 0.008) and 23.65 vs 11.7 months for patients with exon 19 vs exon 21 mutation (p = 0.07); respectively. Cox regression analysis revealed that patients exposed to TKI and QT was the only independent prognostic factor (p = 0.024).

Conclusion: In this retrospective analysis, there was no significant difference in PFS between erlotinib and Gefitinib in the first line. It is important to expose patients with EGFR mutation to TKI and also chemotherapy to achieve an acceptable overall survival.

Keywords: EGFR mutation, PFS, erlotinib, gefitinib

P1.26: A CASE OF NON SMALL CELL LUNG CANCER EGFR MUTATION EXON 18 POSITIVE WITH POOR RESPONSE TO TARGETED THERAPY

Track: Advanced NSCLC

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¹Pulmonology, Hospital Beatriç Ângelo, Loures/PORTUGAL, ¹Medical Oncology, Hospital Beatriç Ângelo, Loures/PORTUGAL

Background: Besides the common exons 19 and 21 EGFR–activating mutations in non small cell lung cancer, exon 18 mutations are rare, with prevalences ranging from 1% to 4% and are associated with sensitivity to EGFR-TKI therapy. However, reports in literature show conflicting results.

Method: Review and report a case of a male patient with lung adenocarcinoma EGFR exon 18 positive with poor response to erlotinib.

Results: Case report of a 63 year old male patient, former smoker, who presented with a 15-day history of left thoracic pain. A thoracoabdominal CT scan was performed and showed a mass with 56 mm in the left lower lobe, ipsilateral pleural effusion, micronodules in the left upper lobe and right lower lobe, mediastinal and left internal mammary lymphadenopathy and lytic lesions in both iliac bones. A bone scan confirmed the iliac metastases. A bronchofibroscopy was performed with generalized inflammation of the bronchial tree; the histopathological exam showed lung adenocarcinoma (CK7+, TTF1+, CK20+, p63–). EGFR mutation p.G719X in exon 18 positive. The diagnostic of lung adenocarcinoma stage IV (EGFR exon 18 positive) was assumed and the patient started treatment with erlotinib 150 mg/day. After 3 months thoracic progression was observed. The patient started first line of chemotherapy with platinum and pemetrexed, with partial response after 6 cycles. Maintenance therapy with pemetrexed was started, the patient completed 2 cycles to date.

Conclusion: Despite single point G719X mutations are associated with sensitivity to targeted therapy we present a case with poor response to erlotinib. The studies and case reports in literature have shown discordant results. Some authors argue that single EGFR exon 18 mutations may be an indicator of poor prognosis compared with classic activating mutations or complex exon 18 mutations; however these are based on a small number of patients and need to be validated in larger series. To date, the behavior of these neoplasm with rare mutations are not completely understood. Further investigations are required to address these differences. Perhaps the role of T790M EGFR mutations in TKI–naïve patients has to be considered.

Keywords: tyrosine kinase inhibitors, exon 18, lung cancer

P1.27: A CLINICOPATHOLOGICAL STUDY OF RESECTED PULMONARY PLEOMORPHIC CARCINOMA

Track: Advanced NSCLC

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Background: Pleomorphic carcinoma of the lung is a rare disease, classified as a subtype of sarcomatoid carcinoma of the lung. It has been recognized that distant metastases occur more frequently, many cases carry a poor prognosis, even when early-stage disease is diagnosed.

Method: In this study, 49 consecutive patients who had undergone surgical resection for pulmonary pleomorphic carcinoma were retrospectively examined. There were 43 men and 6 women, and their mean age was 67 years old (range: 44–84). Forty patients were smokers.

Results: Thirty patients were preoperatively diagnosed with non–small cell lung cancer but only one was preoperatively diagnosed with preemorphic carcinoma. Concerning the operative procedures, a lobectomy was performed in 39 patients (bronchoplasty in 1, chest wall resection in 7, left atrium resection in 1), bileobectomy in 2, pneumonectomy in 2 (left atrium resection in 1), segmentectomy in 1 and partial resection in 5. Nodal status was classified as pN0 disease in 16 (32.7%) patients, pN1 disease in 16 (32.7%) and pN2 or pN3 disease in 16 (32.7%). 1 patients was stage IV disease, had a solitary brain metastasis and a tumor in right lower lobe invasion to left atrium. Pathologically Sarcomatous elements were as follows: 27 spindle cell types (55.1%), 9 giant cell types (18.3%),
and 8 combined spindle and giant cell types (16.3%). Epithelial components were adenocarcinoma in 27 (55.1%) patients, squamous cell carcinoma in 9 (18.3%) patients, and large cell carcinoma in 8 (16.3%) patients. Both lymphatic and blood vessel invasion detected in 32 patients. Distal recurrence sites after curative resection were lung (10/22patients:45.5%), bone (6.27%), mediastinal lymph nodes(6), brain(6), pararenal(5:23%) chest wall or pleura(4:18%) and femoral muscle(2:9%). Five-year overall survival and disease-free survival were 43.5% (N0:71%, N1+N2 35%), disease-free survival was 50.2%. Adjuvant chemotherapy was performed in 21 patients. Among the 21 patients who received adjuvant chemotherapy, four cycles of carboplatin with paclitaxel or gemcitabine chemotherapy were performed in 20 (95%) patients. Among the 21 patients who underwent adjuvant chemotherapy, there was no mortality related to chemotherapy.

**Conclusion:** It was difficult to have preoperative exact diagnosis with pleomorphic carcinoma. Many long survival patients had No–histological component of sarcoma or adenocarcinoma tumor with platinum–doublet adjuvant chemotherapy. It is necessary to select appropriate treatment strategies to prevent postoperative recurrence even for early staged patients.

**Keywords:** pleomorphic carcinoma, surgery, prognosis

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**P1.28: OVERALL SURVIVAL IN PATIENTS WITH METASTATIC LUNG ADENOCARCINOMA TREATED AT INSTITUTO ONCOLOGICO NACIONAL, PANAMA**

**Track:** Advanced NSCLC

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**Background:** Lung cancer usually has a poor prognosis because most of the patients (pts) present with advanced or metastatic disease at the time of diagnosis. The aim of this study was to evaluate factors that affect overall survival in our population.

**Method:** From January 2012 to December 2014, a retrospective analysis of epidemiological characteristics of pts with metastatic lung adenocarcinoma who received treatment in the Instituto Oncologico Nacional was performed. Survival was estimated using Kaplan–Meier method and log rank test. Multivariable analysis was performed using Cox regression.

**Results:** 148 patients were analyzed. Median age 65 years. 75 (51.2%) females and male 73 (48.3%). non-smokers 86 (58.1%), Initial Stage II 2 pts (1.4%) III 15 pts (10.1%) and IV 131 (88.5%). Mutations on EGFR 53 pts (35.88%), non-mutated 91 patients (61.5%), non-assessable in 4 (2.7%). 113 pts (76.3%) received chemotherapy as first line treatment and 33 (23.6%) TKI (Erlotinib or Gefitinib). Median overall survival was 12.05 months 95% CI (10.9–13.1). Overall survival predictors were: mutation on EGFR HR 0.37 95% CI (0.23–0.57), ECOG 2–3 HR 2.4 95% CI (1.5–3.7) and loss of weight HR 1.6 95% CI (1.07–2.50).

**Conclusion:** The prognostic factors found in our population are similar with what has been reported in the literature.

**Keyword:** overall survival, adenocarcinoma

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**P1.29: “REAL WORLD” USE OF LIQUID BIOPSY IN PATIENTS WITH LUNG ADENOCARCINOMA AND CORRELATION WITH TUMOR TISSUE GENETIC PROFILE**

**Track:** Advanced NSCLC

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**Background:** Several genomic abnormalities have been discovered in adenocarcinoma of the lung (adenoca) in the last year; however, adequate quantity of tumor tissue for molecular analysis is a major handicap to offer most of the patients (pts) a personalized medicine. Reasons such as difficulty to perform tumor biopsy (TBx) either because of tumor location or patient’s co-morbid conditions are among the common factors for lack of molecular profiling results (MPR). Hence, liquid biopsy (LBx) has emerged as a potential alternative to detect these genomic alterations.

**Method:** We analyzed 81 consecutive pts to whom a LBx using Guardant 360 test was ordered in our thoracic oncology clinics at Lynn Cancer Institute. Boca Raton, Florida and Memorial Cancer Institute, Hollywood, Florida. Results from tissue molecular profiling from each subject was obtained or recovered for comparison. MPRs from this cohort was developed by different CLIA laboratories (e.g. Response Genetics, Caris, Foundation Medicine, BioTheranostics, and Genoptix). For LBx analysis, only Guardant 360 test was considered. The Guardant 360 test assays a panel of 70 genes (see Fig. 1) to identify genomic alterations in cancer-associated somatic variants with high sensitivity. Cell-free DNA (cfDNA) is extracted from plasma and genomic alterations are analyzed by massively parallel sequencing of amplified target genes.

**Results:** The distribution by gender was 56 female patients and 25 males; Median age 69 (range, 27-99). 65/81 pts (80%) had at least 1 genomic alteration by LBx (range, 1-10). Most common abnormalities found in LBx were: TP53 (32 pts), EGFR (27 pts), NFI (16 pts), KRAS (9 pts), MET (10 pts). From this 65 pts with + LBx results, 49 pts (75%) had tumor MPRs for comparison. Major reasons for lack of tumor tissue MPRs: insufficient tumor (18/81; 22%). For comparison between the 2 modalities, we considered all pts with available results in both tests; hence, 63 pts were used to compare TBx with LBx. 33 pts out of 63 (52%) had at least 1 similar genomic abnormality or MPRs found in both TBx and LBx. Most of the concordance was in EGFR alterations (17/22; 77%). LBx caught 10 additional EGFR genomic aberrations not being identified by TBx (a total of 27 EGFR genomic aberrations were identified in LBx), 14 EGFR found in LBx were actionable; 3/10 of mutant EGFR found only in LBx were actionable.

**Conclusion:** LBx using Guardant 360 evaluation offers an alternative to identify genomic alterations including actionable mutations; still, insufficient tumor is the major reason for lacking of tumor MPRs and more advances to obtain TBx are needed. Our cohort had 48% concordance between LBx and TBx.

**Keywords:** liquid biopsy, lung cancer, biomarkers, cell free DNA
Pt 30: CLINICAL EFFICACY AND TOLERABILITY OF BEVACIZUMAB IN ELDERLY PATIENTS WITH ADVANCED NON–SQUAMOUS NSCLC

Track: Advanced NSCLC

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Background: The effect of bevacizumab (Bev) in patients (pts) with metastatic non squamous non–small cell lung cancer (NSq–NSCLC) stratified by age have been analyzed in two retrospective studies. First analysis was from ECOG 4599 (pts < or ≥ 70 years old) and second analysis was a pooled analysis between ECOG 4599 and PointBreak clinical trials. In the later, pts were grouped by age: < 65, 65-74, 75-74, ≥ 75 years. Carboplatin/Paclitaxel (C/P) + Bev was associated with significant increases in overall survival (OS) relative to C/P alone in all groups but > 75 years old. There were no adverse events (AEs) in pts < or ≥ 75 years old in the C/P/Bev group vs C/P alone.

Method: Using our electronic database, we used three variables: lung cancer, ≥ 75 years old, and Bev. In the last 67 months (August 2010–March 2016), we found 27 pts with these characteristics. All patients had NSq–NSCLC and all patients were treated with the attempt to initiate maintenance therapy (MTX) with Bev alone or doublet MTX therapy with pemetrexed (Pem) and Bev or any combination with Bev. We analyzed safety and tolerability as well as number of Bev cycles given to this cohort of pts.

Results: Twenty pts were females and 7 were males; all pts had adenocarcinoma histology. The initial systemic therapy was distributed as follow: 14 pts received C/Pem/Bev and 13 pts received C/P/Bev. Maintenance (MTX) was either Bev alone or Pem/Bev. Median age was 77 years old (range, 75-86). Most common AEs were: fatigue (n=7), vomiting (n=2), and diarrhea (n=2). Serious AEs (SAEs) requiring stop Bev were: hypertensive crisis (n=1), gastrointestinal perforation (secondary to duodenal ulcer; n=1) and grade 3 epistaxis (n=1). No embolic events, nphrothelial, fistula perforation, RPLS, and pulmonary hemorrhage were reported in this cohort. A total of 17 pts (65%) received MTX; 6 pts did not move into MTX phase and there are 4 pts who are still on initial chemotherapy (CTX) phase. Median cycles of MTX therapy using Bev or Pem/Bev was 7 (range, 4-42); median total of Bev cycles including initial therapy was 9 (range, 2-48). Median progression–free survival (PFS) was 8.3 months.

Conclusion: In our 27 pts older than 75 years old, we found 3 SAEs. Our pts had good ECOG PS (0–1); 12 pts (44%) had 1 comorbid condition. Median PFS was 8.3 months in this cohort; PFS reported in ECOG 4599 was 6.2 months and in Pointbreak study was 6.0 months for C/Pem/Bev and 5.6 C/P/Bev groups. With careful clinical evaluation, our experience indicates that Bev can be offered to elderly pts. Bev was well tolerated in this cohort of patients older than 75 years.

Keywords: Angiogenesis, elderly patient, bevacizumab, lung cancer

Pt 31: PLEURAL EMPYEMA AND BRONCHO PLEURAL FISTULA AFTER LUNG RESECTIO: ANALYSES OF 29 PATIENTS TREATED IN OUR CLINIC

Track: Advanced NSCLC

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Background: Bronchopleural fistula (BPF) and pleural empyema are serious complications after anatomical and non anatomical lung resection although is rare. But with high mortality rate particularly after radical pneumonectomy, a BPF may arise either from denhiscence or disruption of a bronchial closure after anatomical lung resection (segmentectomy, lobectomy; bilobectomy, pneumonectomy)or bronchoplastic sleeve resection and nonanatomical lung resection (wedge resection). Postoperative bronchopleural fistula is classified based in time of onset after surgery; as early (within first week); intermediate (between 7 and 30 days);and late after (30 days). Malnutrition, immunosuppressive steroids therapies, prior thoracic radiation therapy, poorly controlled lung and pleural infection, active smokers, and the use of induction of chemotherapy are a number of predisposing factors that may developing bronchial fistula and subsequent pleural empyema. Also others factors related with technical side are , long bronchial stump, large diameter bronchial stump, positive resection margin of bronchial stump, devascularisation of bronchial stump from cauter or unappropriate sutures during bronchial closure. Also risk factors for bronchopleural fistula are right pneumonectomy, Diabetes, Completion Pneumonectomy, Active TB, Extrapleural Pneumonectomy, COPD, positive pressure ventilation ,large postoperative fluid requirement, benign diagnosis prolonged chest tube utiliz. Empyema and BPF are extremely uncommon after lobectomy in contemporary series, particularly after thoracoscopic lobectomy. Empyema is seen in less than 2% of cases, and BPF in less than 1%. Post–pneumonectomy BPF and empyema are associated with mortality rates that vary from 5% up to nearly 50%.

Method: We are analysing our patients treated with pleural empyema and bronchopleural fistula, treated previously with lung resection,anatomical und non anatomical for malignant und benignen lung disease. Its retrospective study for period of time 2005–2015. The number of patients treated during 2005-2016 with pulmonary reexion is 560. Mean age of patients 58±5.6 years (ranging from 13–87 years old). Male 420 patients and female 140 patients. Realized of kind Interventi are 47 patients pneumonectomy, 448 patients anatomical lobectomy, 12 patients segmentectomy, 18 patients bilobectomy, 35 patients non anatomical resection (wedge lung resection).

Results: Bronchial fistula as a major complication occurred in 29 patients after lobectomy in 16 patients, after pneumonectomy in 8 patients, in 5 patients after right pneumonectomy and 3 after left pneumonectomy, in 3 patients after segmentectomy, in 2 patients after wedge lung resection. Fistul bronchial pulmonary without pleural empyema 3 patients. Treated only pleural drainage for a long time 11 patients. In 2 patients are treated by using of fibrin glue bronchoscopically in bronchial fistulae under 5 mm and without infection. By open window are treated 18 patients according Elosser and Clagett –Virculla. Mean time hospital stay of patients treated with bronchial fistula et pleural empyema is 25 ± 5 days
P1.32: PRIMARY LUNG CANCER PRESENTING AS PNEUMOTHORAX

Track: Advanced NSCLC

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Background: Spontaneous pneumothorax is divided into primary and secondary. Primary SP most commonly affects the young and healthy. The secondary type can develop with obstruction, infection, infarction, neoplasm and diffuse lung disease. SP as a complication of primary lung carcinoma (LC) is rare. It is estimated that only 2% of all SP is coexistent with malignant lung diseases, either primary or secondary. This tumor complication must be especially considered in older patients. Objectives: Analysis of our patients with primary lung cancer presenting as pneumothorax

Method: Between 2010–2015 we treated in our clinic among 340 adults (260 men and 80 women) presenting with spontaneous pneumothorax, there were 11 men and four women with lung cancer. Ten squamous cell carcinoma, three adenocarcinoma and one oat cell carcinoma. Pneumothorax led to the diagnosis in 11 cases and the remaining occurred as a complication of known neoplastic disease. The average age was 60 years from (32–72 years old). In all such patients, the pneumothorax occurred in the same side as the carcinoma only in one patient pneumothorax occurred contralateral side. The main cause of SP was the rupture of a necrotic tumor nodule or necrosis of subpleural metastases. It also became the communication cause between the bronchus and pleural cavity, producing a bronchopleural fistula that resulted in pneumothorax. We demonstrate that these case reports of lung cancer with pneumothorax are a rare complication of primary lung carcinoma.

Results: We analyze these 15 cases treated in our hospital. In patients with normal chest x-ray film findings after lung expansion, further investigation for neoplastic disease is not justified. But we need to perform and chest CT and other investigation in patients with heavy smoking, chronic bronchitis, bullous emphysema and incomplete lung expansion after chest drainage also patients with age over 50 years old. All patients was first treated by pleural drainage and then in 10 patients multimodal treatment according lung cancer staging and 5 patients pleural drainage and palliative treatment, receiving chemotherapy and/or radiotherapy for lung cancer.

Conclusion: Spontaneous pneumothorax in association with lung cancer is rarely seen. Pneumothorax can be the first sign of lung cancer. The most common possibility for SP complicating lung cancer is the tumour necrosis mechanism or, in separate cases, rupture of the emphysematous bullae. Lung cancer should always be considered as a possible cause of SP in elderly patients or in heavy smokers. The occurrence of a pneumothorax in patients with lung cancer, worsening prognosis. Five-year survival is poor, suggesting that lung cancers present as pneumothorax at an advanced stage of disease.

Keywords: Bronchopleural fistula, open window, malignant disease

P1.33: AFATINIB VERSUS CHEMOTHERAPY FOR EGFR MUTATION-POSITIVE NSCLC PATIENTS AGED ≥65 YEARS: SUBGROUP ANALYSIS OF LUX-LUNG 3/6

Track: Advanced NSCLC

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Background: Afatinib, an irreversible Erbb family blocker, significantly improved progression–free survival (PFS) versus platinum–doublet chemotherapy as first–line treatment in patients with EGFR mutation–positive (EGFRm+) non–small cell lung cancer (NSCLC) in the LUX–Lung 3 (LL3; 11.1 vs 6.9 months, HR=0.58, p<0.001) and LUX–Lung 6 (LL6; 11.0 vs 5.6 months, HR=0.58, p<0.001) trials. Afatinib also significantly improved overall survival (OS) versus chemotherapy in patients with Del19–positive (LL3; 33.3 vs 21.1 months, HR=0.54, p=0.0015; LL6; 31.4 vs 18.4 months, HR=0.54, p=0.023). Here we report the efficacy and safety of afatinib versus chemotherapy patients aged ≥65 years in the LL3 and LL6 trials.

Method: Patients with EGFRm+ stage IIB/IV NSCLC (LL3: n=345; LL6: n=364) were randomized 2:1 to afatinib (40 mg/day) or up to 6 cycles of chemotherapy (LL3: cisplatin/pemetrexed; LL6: cisplatin/gemcitabine). Patients were stratified by EGFR mutation type (Del19/ L858R/other) in both LL3 and LL6, and also by race (Asian/non–Asian) in LL3. Pre–specified analyses by age (<65/≥65 years) and post–hoc analyses by age within mutation subgroups were performed.

Results: A total of 220 patients aged ≥65 years were randomized; 134 in LL3 and 86 in LL6. Afatinib significantly improved PFS versus chemotherapy in these patients (LL3: 13.6 vs 8.2 months, HR=0.60 [95% CI: 0.37–0.96], p=0.03; LL6: 13.1 vs 4.1 months, HR=0.17 [95% CI: 0.07–0.41], p<0.0001). OS was similar with afatinib versus chemotherapy in all patients aged ≥65 years, with a trend towards improved OS with afatinib versus chemotherapy in those with
NSCLC harboring common EGFR mutations (LL3: 31.6 vs 24.9 months, HR=0.73 [95% CI: 0.43–1.21], p=0.22; LL6: 23.2 vs 19.0 months, HR=0.60 [95% CI: 0.33–1.16], p=0.10). In Del19–positive patients aged ≥65 years, afatinib significantly improved OS versus chemotherapy in LL3 (41.5 vs 14.3 months, HR=0.39 [95% CI: 0.19–0.80], p=0.0073) and demonstrated a trend towards improved OS in LL6 (34.1 vs 21.1 months, HR=0.57 [95% CI: 0.24–1.36], p=0.20). In both studies, the most common treatment-related grade 3/4 adverse events (AEs) in afatinib–treated patients aged ≥65 years were diarrhea (LL3: 21%; LL6: 8%), rash/ acne (LL3: 19%; LL6: 9%), nail effects (6% LL3 only) and stomatitis (LL3: 10%; LL6: 3%).

**Conclusion:** Consistent with the overall population, afatinib conferred significant improvements in PFS versus chemotherapy in EGFRm+ NSCLC patients aged ≥65 years, with improved OS in those with Del19–positive disease. The AE profile in patients aged ≥65 years across both trials was similar to that observed in the overall population.

**Keywords:** afatinib, EGFR, Non–small Cell Lung Cancer, age

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**P1.34: FIRST-LINE AFATINIB VS GEFITINIB FOR PATIENTS WITH EGFR MUTATION-POSITIVE NON–SMALL-CELL LUNG CANCER: THE LUX-LUNG 7 TRIAL**

**Track:** Advanced NSCLC

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**Background:** The irreversible ErbB family blocker afatinib and the reversible EGFR TKI gefitinib are approved for first–line treatment of advanced EGFRm+ NSCLC. This phase IIb trial prospectively compared afatinib versus gefitinib in this setting.

**Method:** Patients with stage IIB/IV EGFRm+ adenocarcinoma received afatinib (40 mg/day) or gefitinib (250 mg/day) until disease progression or beyond if deemed beneficial. Co–primary endpoints were: progression–free survival (PFS), time to treatment failure (TTF), and overall survival (OS). Other endpoints included objective response rate (ORR), adverse events (AEs) and patient–reported outcomes (PROs; EQ–5D utility and EQ–VAS scores). In case of grade ≥3 selected grade 2 drug–related AEs the dose of afatinib could be reduced to 30 mg or 20 mg (minimum).

**Results:** 319 patients were randomized (afatinib: 160; gefitinib: 159). Baseline characteristics were generally balanced (afatinib versus gefitinib): female: 56% vs 66.7%; Asian: 58% vs 55.3%; Del19 mutation: 58.1 vs 58.5%; PFS [HR [95% CI]] 0.73 [0.57–0.95]; p=0.007) and TTF (0.73 [0.58–0.92]; p=0.007) were significantly improved with afatinib versus gefitinib, with consistent effects by mutation type and race (Asian/non–Asian) subgroups. Afatinib significantly improved ORR versus gefitinib (70.0 vs 56.0%; p=0.008); median duration of response was 10.1 versus 8.4 months. OS is not yet mature. The most common grade ≥3 drug–related AEs were diarrhea (12.5%) and rash/acne (9.4%) with afatinib and elevated ALT/AST (8.8%) with gefitinib. Drug–related interstitial lung disease was reported in 10.6% and 4.7% patients treated with afatinib and gefitinib, respectively. Rates of discontinuation due to treatment–related AEs were the same in each arm (6.3%). There was no significant/clinically meaningful difference in baseline to post–baseline mean EQ–5D (afatinib: 0.72 to 0.77; gefitinib: 0.73 to 0.80; p=0.142) or EQ–VAS (afatinib: 69.7 to 74.5; gefitinib: 71.2 to 76.0; p=0.203) with afatinib and gefitinib. 39% of patients in the afatinib arm had at least dose reduction from 40 mg. Dose reduction of afatinib did not negatively impact PFS (<40mg vs ≥40mg HR [95% CI]: 1.34 [0.90–2.00]; p=0.144) but the incidence and severity of treatment–related AEs was lower following dose reduction (pre– and post–dose reduction [in the 63/160 patients who had a reduction] diarrhea: 25.4 to 9.5%; rash/ acne: 20.6 to 3.2%). Dose reduction of afatinib did not diminish its effects on PROs (EQ–5D <40 mg: 0.69 to 0.74, ≥40 mg: 0.73 to 0.77; EQ–VAS <40 mg: 72.4 to 70.5, ≥40 mg: 68.6 to 75.4).

**Conclusion:** Afatinib significantly improved PFS, TTF and ORR versus gefitinib in EGFRm+ NSCLC patients. AEs were manageable and treatment–related discontinuations were low in both arms. Improvements in PROs were similar in patients treated with afatinib or gefitinib. Dose reduction of afatinib reduced the incidence and severity of treatment–related AEs without compromising efficacy or PROs.

**Keywords:** afatinib, gefitinib, EGFR, non–small–cell lung cancer

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**P1.35: THE ROLE OF SALVAGE SBRT IN RECURRENT LUNG CANCER AFTER PREVIOUS RADIOTHERAPY**

**Track:** Advanced NSCLC

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**Background:** Locoregional recurrences are a frequent challenge in patients treated with radio–chemotherapy for locally advanced NSCLC. Conventional external beam radiation therapy (EBRT) is rarely given as salvage treatment because of the risk of toxicity. There is a paucity of published studies evaluating the role of SBRT in this clinical setting. Our purpose is to construe the role of stereotactic body radiation therapy (SBRT) in the management of recurrent lung cancer from our early experience with SBRT for salvage treatment in patients previously treated with radiation therapy.

**Method:** Between 2008 and 2014 a group of 10 patients, 6 males and 4 females with biopsy proven Non–small cell lung cancer (NSCLC) underwent 14 radiosurgical procedures for salvage therapy after failing initial radiation treatment. Patients’ age ranged from 54 to 88 years with a median of 74 years. Intervals from initial radiation treatment to salvage SBRT were 3 to 33 months with a median of 13 months. SBRT treatments were delivered using Intensity Modulated Volumetric Arc Therapy (VMAT). All patients received concomitant chemotherapy.

**Results:** Overall survival after salvage radiosurgery ranged from 6 to 60 months with a median of 29. Four of the ten patients are alive with disease locally controlled. Of the remaining 6 patients, 4 had distant progression of disease with brain metastases and one had both brain and lung metastases. The other patient had a regional failure. Toxicities were found in three of the ten (30%) patients with grade I pneumonitis. The overall survival since the day of the
first radiation therapy course ranged from 54 to 88 months with a median of 74 months. Fifty percent of the patients survived more than 3 years after the salvage SBRT.

**Conclusion:** In our early experience, salvage SBRT is a promising modality for treating lung cancer patients who failed after conventional irradiation, achieving excellent results in terms of local control with acceptable toxicity. Further prospective studies are needed for confirmation and to determine optimal fractionation schemes.

**Keywords:** Lung Cancer Radiosurgery, Salvage SBRT, Recurrent lung cancer, NSCLC

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**P1.36:** NON–SMALL–CELL LUNG CANCER AND BRAIN METASTASES IN BRAZIL

**Track:** Advanced NSCLC

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**Background:** Brain metastases (BM) are common and affect near to 40% of patients with non–small–cell lung cancer (NSCLC) and the prognosis of this population is usually poor. Few data are available about this group of patients and patients from Brazil are usually underrepresented. Also, data on real life outcomes are lacking in the medical literature.

**Method:** Patients with the diagnosis of NSCLC and developed BM from January 2005 to December 2014 at a University Hospital in South of Brazil were identified by electronic database. Medical records were reviewed and demographic data, tumor and treatment characteristics were collected. OS and PFS were estimated by Kaplan–Meier curves. Multivariate analysis was performed to identify factors associated with survival. Statistical analysis was performed with SPSS 22.0.

**Results:** Seventy patients were collected for this analysis. Patient characteristics revealed a mean age of 59.83 ± 8.72 years. 55% female, 86% Caucasian, a positive smoking history in 83%, 71.5% had adenocarcinoma. At the moment of the diagnosis of brain metastases, 45% of patients had a Karnofsky performance status <70, 20% had the systemic disease under controlled, 66% had extracrural metastases and 37% had more than 3 brain lesions. Twenty patients (29%) were submitted to a curative treatment (surgery or radiosurgery), 36 (51%) whole brain radiation and 14 (20%) best support of care. The median follow–up is 14.17 months. Sixty–six patients (95%) have died with an OS of 12.62 months (95% IC, 9.96 to 15.27). The overall median survival time following diagnosis of BM was 5.06 months and according to the treatment was 13.24 months for radiosurgery, 8.34 months for resection, 5.9 months for whole brain radiotherapy and 0.46 months for best support of care. Also, patients with synchronous metastases had better outcome after the diagnosis that those with metachronous metastases, 7.16 versus 1.64 months, p=0.17.

**Conclusion:** To our knowledge, this is the first report of patients from Brazil with NSCLC and BM. Our data is similar to other reports about this subject and no prognostic factor for the development of brain metastases was identified. Risk factors to identify patients at high risk to develop brain disease should be further studied.

**Keywords:** non–small–cell, brain metastases, Brazil, outcomes

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**P1.37:** FIRST LINE TREATMENT OUTCOME FOR EGFR MUTATED METASTATIC NON–SMALL CELL LUNG CANCER—A SINGLE INSTITUTION 5 YEARS EXPERIENCE

**Track:** Advanced NSCLC

Shahid Gilani, Apurna Jegannathen, G Vanpittius, S Vengalil, S Giridharan

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**Background:** Non–Small Cell Lung Cancer (NSCLC) Classification is rapidly evolving depending upon histology and driver mutations. 10–15% of patients with advanced NSCLC have a tumour with an EGFR mutation. 20–30% of adenocarcinomas have epidermal growth factor receptor (EGFR) mutations. These mutations promote cell growth and cell survival. EGFR domain can have mutation from exon 18 to exon 21 but most common (90%) EGFR mutations are exon 19 deletions or exon 21 point mutation, especially L858R. EGFR mutated lung adenocarcinomas are uniquely susceptible to selective Tyrosine Kinase Inhibitors (TKIs). Such patients may experience dramatic tumour shrinkage and show durable response to TKIs. Recent trials have shown improvement in Overall Survival (OS) Progression Free Survival (PFS) with TKIs as compared to chemotherapy as first line treatment. We looked at safety, efficacy, OS and PFS in EGFR mutated metastatic adenocarcinoma patients treated with TKIs over 5 years at University Hospital of North Midlands UK.

**Method:** Hospital electronic notes were retrospectively studied for patients undergoing TKIs treatment either with Gefitinib, Afatinib or Erlotinib for mNSCLC over 5 years from January 2011 to December 2015. Subset analysis of treatment outcome with efficacy and safety was also performed comparing 3 TKI drugs.

**Results:** 2498 total lung cancer patients were diagnosed over 5 years. Among them 636 were adenocarcinoma, of whom 51 were metastatic. Among metastatic adenocarcinoma, 23 (45%) were positive for EGFR mutation. 13 females and 10 males with median age of 66 years. 15 (65%) had exon 19 deletion and 7 (30%) had exon 21 point mutation. All received treatment either with Gefitinib, Afatinib or Erlotinib as first line. All had ECOG performance status 0 to 2. Median OS was 12 months, median PFS was 10 months. Majority of side effects were Grade 1/2. Common side effects observed were skin rash, pruritus, dry eyes, fatigue and diarrhoea. One patient on Gefitinib developed Grade 3 pneumonitis. Dose modification and treatment interruption was done in 5 (21%) patients. No toxicity related death was seen. Currently 13 (56%) patients are still on treatment. Subset analysis has shown better OS and PFS favouring Erlotinib over Gefitinib and Afatinib.

**Conclusion:** Our results were comparable with LUX–Lung 3 trial demonstrating significant PFS, OS and tumour response when treated with first line TKI as standard therapy either with Gefitinib, Afatinib or Erlotinib. Toxicity was manageable. Current study demonstrates that median OS may extend beyond 12 months as more than half of the patients are still on treatment.

**Keywords:** Non–Small Cell Lung Cancer (NSCLC), EGFR mutations, tyrosine kinase inhibitors, response
Conclusion: NLR pre-treatment measurements can provide months (p = 0.16). Among the 77 patients with high NLR, 23 patients (out of the 88 patients with low present NLR) had TILs in their tumor samples with an OS of 11 months; the 36 patients who did not have TILs had an OS of 10 months (p = 0.15). 40 patients with present TILs (out of the 77 patients with high NLR) had an OS of 10.4 months and the remaining 37 with no present TILs, had an OS of 7 months (p = 0.16).

Conclusion: NLR pre-treatment measurements can provide important prognostic outcomes in patients with NSCLC. In this study, we found that OS and PFS were significantly associated with the value of NLR, with significantly lower outcomes in patients who showed an NLR > 3.44. But when we try to relate the NLR with the presence or absence of TILs, the results are not statistically significant. We are actively working on adding a more significant number of patients.

Keyword: NSCLC, NHL, prognostic, TILs

Pr.39: ONLY TWO RARE METASTASIS OF LUNG ADENOCARCINOMA?

Track: Advanced NSCLC

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Background: Cutaneous metastases develop in 1-12% of patients with lung cancer and in 20-60% of cases the skin lesions present before or synchronously with the diagnosis of the primary tumor. Similarly, metastatic tumors to the oral soft tissues are uncommon and account for 0.1% of all oral malignancies; the lung constitutes the origin of metastases in 3% in men and 9.4% in women.

Method: Review and report a case of a male patient with lung adenocarcinoma who presented with a scalp metastasis and progressed with a oral soft tissue metastasis.

Results: Case report of a 60 year old male patient, former smoker, who presented with a single exophytic red-colored lesion, fixed, hard and painless, with 2 cm of diameter in the scalp. A biopsy was performed, the histopathological exam showed metastases of lung adenocarcinoma (TTF1+, CK7+, p63- and p16-) EGFR and ALK negative. The thoracic study confirmed lung adenocarcinoma T4 N2 Mb. The patient started local radiotherapy and first line of chemotherapy with platinum and pemetrexed. Seven months after diagnosis onset of cognitive/behavioral changes and oral pain, difficulty in chewing and dysphagia. A cranial CT scan was performed, with cerebral metastasis. An exophytic single lesion in the floor of the mouth was observed and biopsied; the histopathological exam showed adenocarcinoma TTF1+, CK7+, p63- and p16-.. CNS radiotherapy and second line of chemotherapy with docetaxel was initiated. The patient died 11 months after diagnosis of infectious complications.

Conclusion: The authors report a case that “started” and “ended” with a patient with lung adenocarcinoma EGFR mutation negative that had a very uncommon form of presentation and progression. In these rare locations of metastases biopsy is required for the diagnosis and immunohistochemistry has to be done for most of the cases for further confirmation.

Keywords: metastasis, non small cell lung cancer, lung adenocarcinoma

Pr.40: COMPARATIVE STUDY OF CHEMOTHERAPY REGIMENS BASED ON PLATINUM AND ITS DIFFERENT TOXICITIES IN PATIENTS WITH ADVANCED NSCLC

Track: Advanced NSCLC

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IONC – Universidad Católica de Córdoba, Cordoba/ARGENTINA

Background: Chemotherapy is the standard treatment for patients with advanced non–small cell lung cancer (NSCLC) who have EGFR WT and no ALK translocation. First line treatment is based on doublets platinum in combination with other agents as Paclitaxel or Gemcitabine. In our institution we performed a phase II study, that was presented en ASCO 2001 and was adopted by many places to use in patients with PS>1 and comorbidities, comparing the scheme...
Cisplatin-Gemcitabine (CDDP/G) on day 1, 8 and 15 (weekly) versus the standard scheme with CDDP on day 1 and G on day 1 and 8. This data showed that this schedule is less toxic than those combinations of G and CDDP used in known phase III studies, and also has higher compliance by patients with PS>2, maintaining efficacy in terms of OR, PFS, OS and symptomatic control. The objective is to compare the toxicity profile and quality of life (QOL) of weekly chemotherapy regimens based on doublets platinum associated with gemcitabine and paclitaxel.

**Method:** 163 patients (p) with NSCLC stage IIIb or IV were evaluated. Prior to each chemotherapy cycle, hematological, renal and hepatic function were tested. Patients were randomized to receive CDDP 30 mg/m² and G 800 mg/m² (CDDP/G arm), or Carboplatin AUC2 and P 80 mg/m² (C/P arm) on day 1, 8 and 15 every 28 days. To evaluate toxicities CTC V3.0 was used and the assessing of symptoms was according Lung Cancer Symptom scale every 28 days.

**Results:** We included 163p with NSCLC stage IIIb (52p) and IV (111p). The median age was 60.3 years. 123p received CDDP/G and 40p received C/P. As for toxicity we observed that both regimens was well tolerated, with thrombocytopenia and neutropenia being the major toxicities; minimal non-hematologic side effects were seen (table 1). Regarding QOL, fatigue and loss of appetite were the most symptoms reported by patients in both schemes. Relative to dyspnea, hemoptysis, pain and cough there was symptomatic improvement with both schemes.

**Table 1.**

<table>
<thead>
<tr>
<th>TOXICITY</th>
<th>C/G (123p)</th>
<th>C/P (40p)</th>
</tr>
</thead>
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<tr>
<td></td>
<td>CI</td>
<td>III</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>25(20.7%)</td>
<td>20 (16.7%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>29(23.5%)</td>
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<tr>
<td>Thrombocytopenia</td>
<td>26(21.3%)</td>
<td>46(38.0%)</td>
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<tr>
<td>Fatigue</td>
<td>24(19.5%)</td>
<td>30 (24.4%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>18 (14.7%)</td>
<td>10 (8.1%)</td>
</tr>
<tr>
<td>Hepatic toxicity</td>
<td>7 (5.9%)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td>8 (6.5%)</td>
<td>3 (2.4%)</td>
</tr>
</tbody>
</table>

**Conclusion:** The patients in the CDDP/G arm showed more thrombocytopenia, nausea and kidney toxicity at all grades compared to those in C/P arm, who showed more neutropenia, anemia and fatigue. No treatment discontinuation was recorded. Both chemotherapy regimens were well tolerated and showed improvement in symptom control. The two schemes on day 1, 8 and 15 had similar toxicity profiles with absence of toxicity G4 and had less side effects compared to the standard scheme with CDDP on day 1 and G on day 1 and 8 used in the literature.

**Keyword:** NSCLC, toxicities, platinum, schemes

P1.41 (also presented as PD2.06): BAYESIAN NETWORK META-COMPARISON OF MAINTENANCE TREATMENTS FOR ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS

**Track:** Advanced NSCLC

**Gilberto Lopes**
Oncoclinicas Group, São Paulo/BRAZIL

**Background:** Recent trials suggested that maintenance treatments improve outcomes for patients not progressing after first-line therapy for advanced NSCLC. However, physicians have little guidance on selecting which patients benefit the most and what drug or regimen is optimal. Here, we report a systematic review and network meta-analysis (NMA) of current evidence assessing relative efficacies of maintenance options in unselected populations, as well as in subgroups determined by EGFR mutation, histology, and response to induction.

**Method:** PubMed and conference proceedings were reviewed and individual study relative efficacy measures were meta-analyzed in a Bayesian hierarchical model. The primary and secondary outcomes, Overall Survival (OS) and Progression Free Survival (PFS), respectively, were evaluated in terms of (i) posterior surface under cumulative ranking curve (SUCRA), (ii) probability of being best treatment, (iii) probability of outperforming no maintenance, and (iv) posterior median hazard ratios with 95% credible intervals, in an unselected population, as well as by EGFR mutation status, histology, and response to induction. Secondary outcomes were overall survival (OS) and adverse events.

**Results:** Twelve trials evaluating eight maintenance treatments in 3,850 patients were included in NMA. Selected maintenance treatments showed substantial PFS and OS benefits with probabilities ≥99% and ≥92% respectively of outperforming no maintenance. Results suggest the following strategy for optimal OS and PFS: (i) switch to or continue pemetrexed or switch to anti-EGFR TKI for nonsquamous patients, (ii) continue gemcitabine for squamous patients, (iii) switch to docetaxel or continue gemcitabine for responders to previous induction, and (iv) switch to or continue pemetrexed or switch to anti-EGFR TKI for patients with stable disease post-induction.

**Conclusion:** Maintenance treatments improve PFS and OS in good performance status patients with stage IIIb/IV NSCLC not progressing after first-line chemotherapy. Benefits are optimized by targeting specific maintenance treatments to selected patient groups guided by histology and response to previous induction.

**Keywords:** lung cancer, chemotherapy, maintenance
**Track: Advanced NSCLC**

**Leonardo Rojas**, Andrés F. Cardona, Oscar Arrieta, Beatriz Wills, Claudio Martin, Mauricio Cuello, Carlos Ortiz, Rafael Rosell

**Background:** To evaluate the efficacy and safety of pemetrexed, carboplatin and bevacizumab (PCB) followed by maintenance pemetrexed and bevacizumab (PB) in chemotherapy-naive patients with stage IV non–squamous non–small cell lung cancer (NSCLC) through the influence of thymidylate synthase (TS), ERCC1 and VEGF mRNA expression on several outcomes. The primary endpoints were the overall response rate (ORR), progression–free survival (PFS) and overall survival (OS).

**Method:** Patients were administered pemetrexed (500 mg/m²), carboplatin (AUC, 5.0 mg/ml/min) and bevacizumab (7.5 mg/kg) intravenously every three weeks for up to four cycles. Maintenance pemetrexed and bevacizumab was administered until disease progression or unacceptable toxicity.

**Results:** One hundred forty–four Hispanic patients with a median follow–up of 13.8 months and a median number of maintenance cycles of 6 (range, 1–32) were assessed. The ORR among the patients was 66% (95% CI, 47% to 79%). The median progression–free and overall survival (OS) rates were 7.9 months (95% CI, 5.9–10.0 months) and 21.4 months (95% CI, 18.3 to 24.4 months), respectively. Median TS, ERCC1 and VEGF mRNA levels were 1.45 (range, 0.17–2.52), 0.58 (range, 0.44–1.20), and 2.72 (range, 1.84–3.21), respectively. OS was significantly higher in patients with the lowest TS mRNA levels [29.6 months (95% CI 26.2–32.9] compared with those with higher levels 9.3 months (95% CI 6.6–12.0); p = 0.0001]. ERCC1 mRNA levels also influenced the OS [median for ERCC1 mRNA<0.58 28.7 months (95% CI 18.3–32.7) vs. ERCC1 mRNA>0.58 11.1 months (95%CI 9.6–12.7); p = 0.0001]. As well as VEGF mRNA levels [median OS for VEGF mRNA<2.72 26.4 months (95%CI 22.8–30.0) vs. VEGF mRNA>2.72 18.2 months (95%CI 8.4–27.9); p = 0.009]. TS mRNA did not influence treatment response, however the ORR was significantly higher in patients with low levels of ERCC1 (p = 0.003) and elevated VEGF (p = 0.005). Multivariate analysis found that TS mRNA levels (p = 0.0001), VEGF mRNA levels (p = 0.007) and PS (p = 0.014) were independent prognostic factors.

**Conclusion:** Overall, PCB followed by maintenance pemetrexed and bevacizumab was in Hispanic patients with non–squamous NSCLC. This regimen was associated with prolonged OS, particularly in patients with low TS, ERCC1 and VEGF mRNA expression. These biomarkers alone or in combination may be useful to assess the prognosis of patients with NSCLC treated with CBP/Pem/Bev.

**Keywords:** mRNA expression levels, ERCC1, TS, VEGF, response, outcome

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**Track: Advanced NSCLC**

**Beatriz Amendola**, Azik Wolf, Sammie Coy

**Background:** The purpose of the study is to report our updated results using Gamma Knife Radiosurgery (GKS) for the management of brain metastases from NSCLC in an unselected group of patients

**Method:** This is a retrospective review of 616 patients (336 males and 280 females) who were treated with GKS independently of primary status from October 1993 to April 2016. The rationale of treatment was to improve survival and quality of life. Ages ranged from 19 to 91 years, with a median age of 64 years. A total of 1085 procedures were performed. Doses ranged from 12 to 24 Gy, mean minimum dose delivered was 15.5 Gy. Seventy five patients of 615 had tumors retreated.

**Results:** The median overall survival for the entire group was 6.6 months, with 14.2 months for 25% of the patients and 56.5 months for 5% of them by Kaplan Meier Survival Analysis. Survival at 1, and 5 years are 28%, 4.2% respectively. The median follow–up was from 2 months to 276 months. Overall local control by lesion was 95%. Thirty four out of 486 evaluable documented deaths were due to progression of brain metastases. The other 411 documented deaths were due to progression of disease unrelated to brain metastases. Our longest surviving patient is currently alive 21 years after treatment with GKS to 15 tumors in 3 procedures with local control up–to this date. There was no radiation–induced dementia. Only 3% developed radiation necrosis diagnosed both pathological and by imaging studies.

**Conclusion:** Our results continue to show excellent local control associated with prolonged survival and a low risk of neurological death in spite of advanced stage disease. Number of lesions should not be a contraindication for Radiosurgery in NSCLC. Our report confirms the fact that for patients with NSCLC whole brain radiations should be reserved for late and extensive stage brain disease and or after failure from SRS. GKS provides high local control regardless of the number of lesions or presence of extra cranial disease. We also demonstrated in our retrospective analysis that re–treatment is feasible and safe.

**Keywords:** brain metastases, NSCLC, GKS, Radiosurgery
**P1.44 (also presented as PD2.02): PHASE I/II TRIAL OF X-396, A NOVEL ALK INHIBITOR, IN PATIENTS WITH ALK+ NSCLC**

**Track: Advanced NSCLC**

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**Background:** X-396 is a novel, potent anaplastic kinase lymphoma (ALK) small tyrosine kinase inhibitor (TKI) with additional activity against MET, ABL, Axl, EPHA2, LTK, ROS1, SLK. It has demonstrated significant anti-tumor activity in both ALK TKI-naive and crizotinib-resistant models of ALK fusion-positive NSCLC.

**Method:** In this multicenter phase I/II study, patient (pts) with advanced solid tumors enrolled in the phase I dose escalation portion of the study and given X-396 on a continuous 28-day schedule (NCT01625234). Doses from 25 up to 250 mg once daily were evaluated and 25 mg was selected for further evaluation in the phase II expansion. Patients in this phase were required to have ALK + NSCLC and measurable disease. Cohorts included pts who were:

1) ALK-TKI naive, 2)Pts who progressed on prior crizotinib and had not received a second generation ALK TKI, 3) Pts who progressed on a second generation ALK TKI (may also have received crizotinib), 4)Pts with central nervous system (CNS) metastases, 5) Pts with leptomeningeal disease. All pts were assessed for adverse events (AEs) using CTCAE version 4.03, response to therapy was assessed using RECIST 1.1.

**Results:** As of December 09, 2015 data cutoff, 57 pts (31 men, 26 women) have been enrolled. Median age is 56 (20-79) years, the majority of pts had ECOG performance status 1 (67%). The most common drug-related AEs included rash (49%), nausea (28%), vomiting (25%), and fatigue (23%). Most AEs were grade (G) 1-2. The G3 treatment-related AEs were rash (7 pts), fatigue (1 pt), decreased appetite (1 pt), dehydration (1 pt), pruritus (1 pt), and face edema (1 pt). In particular, no G3 treatment-related gastrointestinal toxicity or liver enzyme elevation has been reported. To date 27 ALK+ NSCLC pts treated at doses 200 mg or greater are evaluable for response; partial response (PR) was achieved in 19 pts (70%) and stable disease (SD) in 2 pts (7%). In the crizotinib-naive pts (n=8), responses were observed in 7 pts (88%). In the 12 pts with prior crizotinib, but no other ALK TKIs, 10 pts (83%) achieved PR and 1 (8%) SD. CNS responses have been observed in both crizotinib-naive and crizotinib resistant pts. The median duration of treatment in the 27 evaluable ALK+ pts is 16+ weeks, with the longest being 128+ weeks.

**Conclusion:** X-396 is well tolerated and induces responses in both crizotinib-naive and crizotinib-resistant ALK+ NSCLC pts, as well as patients with CNS lesions. Enrollment is ongoing in the expansion cohorts.

**Keywords:** X-396, ALK+ NSCLC

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**P1.45: IMPACT OF DOSE ADJUSTMENT ON AFATINIB SAFETY AND EFFICACY IN EGFR MUTATION-POSITIVE NSCLC: POST-HOC ANALYSES OF LUX-LUNG 3/6**

**Track: Advanced NSCLC**

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**Background:** Afatinib 40 mg/day is approved for first-line treatment of patients with EGFR mutation-positive non-small cell lung cancer (NSCLC). An established dose–adjustment protocol exists for afatinib, which can be implemented based on individual tolerability. Here we report the results of post-hoc analyses assessing the impact of afatinib dose adjustment on adverse events (AEs), pharmacokinetics (PK) and progression-free survival (PFS) in the LUX-Lung 3 (LL3) and LUX-Lung 6 (LL6) trials.

**Method:** All afatinib–treated patients from LL3 (n=239) and LL6 (n=239) were included in the analyses. In the case of drug–related grade 3 or selected prolonged grade 2 AEs at the standard afatinib monotherapy dose of 40 mg/day, the dose could be reduced by 10 mg decrements to a minimum of 20 mg/day. The incidence and impact of afatinib dose adjustment on adverse events (AEs), pharmacokinetics (PK) and progression–free survival (PFS) in the LUX-Lung 3 (LL3) and LUX-Lung 6 (LL6) trials.

**Results:** As of September 09, 2015 data cutoff, 57 pts (31 men, 26 women) have been enrolled. Median age is 56 (20-79) years, the majority of pts had ECOG performance status 1 (67%). The most common drug–related AEs included rash (49%), nausea (28%), vomiting (25%), and fatigue (23%). Most AEs were grade (G) 1-2. The G3 treatment–related AEs were rash (7 pts), fatigue (1 pt), decreased appetite (1 pt), dehydration (1 pt), pruritus (1 pt), and face edema (1 pt). In particular, no G3 treatment–related gastrointestinal toxicity or liver enzyme elevation has been reported. To date 27 ALK+ NSCLC pts treated at doses 200 mg or greater are evaluable for response; partial response (PR) was achieved in 19 pts (70%) and stable disease (SD) in 2 pts (7%). In the crizotinib–naive pts (n=8), responses were observed in 7 pts (88%). In the 12 pts with prior crizotinib, but no other ALK TKIs, 10 pts (83%) achieved PR and 1 (8%) SD. CNS responses have been observed in both crizotinib–naive and crizotinib resistant pts. The median duration of treatment in the 27 evaluable ALK+ pts is 16+ weeks, with the longest being 128+ weeks.

**Conclusion:** X-396 is well tolerated and induces responses in both crizotinib–naive and crizotinib–resistant ALK+ NSCLC pts, as well as patients with CNS lesions. Enrollment is ongoing in the expansion cohorts.

**Keywords:** X-396, ALK+ NSCLC
Most common drug-related AEs pre- and post-afatinib dose reduction

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<tr>
<th></th>
<th>LL3 Overall population (n=229)</th>
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<th>LL6 Overall population (n=239)</th>
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<tr>
<td></td>
<td>Pre-dose reduction (n=122)</td>
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</tbody>
</table>

**Results:** Dose reductions occurred in 53% (122/229) of patients in LL3 and 28% (67/239) of patients in LL6. The majority (LL3: 86%; LL6: 82%) of dose reductions occurred within the first 6 months of treatment. Dose reduction led to decreases in incidence and severity of EGFR-mediated drug-related AEs across LL3 and LL6 (Table). A combined PK analysis of LL3 and LL6 suggested that dose reduction was more likely in patients with higher afatinib plasma concentrations. Patients who dose reduced to 30 mg had geometric mean plasma afatinib concentrations of 45.6 ng/mL on Day 22 (n=22) and 23.3 ng/mL on Day 43 (n=59), compared with those who remained on 40 mg with concentrations of 24.3 ng/mL on Day 22 (n=282) and 22.8 ng/mL on Day 43 (n=284). Across LL3 and LL6, median PFS was similar in patients who dose reduced during the first 6 months of treatment versus those who remained on 40 mg/day (LL3: 11.3 vs 11.0 months, HR=1.25 [95% CI: 0.91–1.72]; LL6: 12.3 vs 11.0 months, HR=1.00 [95% CI: 0.69–1.46]).

**Conclusion:** In LL3 and LL6, afatinib demonstrated a trend towards improved overall survival (OS) versus chemotherapy in the overall study populations and significant OS improvements in patients with EGFR Del19-positive disease. Results from this post-hoc analysis indicate that tolerability-guided dose adjustment of afatinib reduces treatment-related AEs without adversely affecting efficacy.

**Keywords:** afatinib, EGFR, Non-small Cell Lung Cancer, dose adjustment

**Pt.46: PHASE I STUDY OF NIVOLUMAB + NAB-PACLITAXEL IN SOLID TUMORS: PRELIMINARY ANALYSIS OF THE NON-SMALL CELL LUNG CANCER COHORT**

*Track: Advanced NSCLC*

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**Background:** The combination of a taxane with an immune checkpoint inhibitor has demonstrated improved response across multiple solid tumors. nab–paclitaxel (nab–P) in combination with a checkpoint inhibitor has recently demonstrated promising activity in non–small cell lung cancer (NSCLC) and triple–negative breast cancer (Giaccone et al. ESMO 2015, abstract 247; Adams et al. ASCO 2016, abstract 1009). Here we present interim results from the NSCLC cohort of a phase I safety trial of nivolumab (nivo) + nab–P in advanced NSCLC (+ carboplatin [C]), advanced pancreatic cancer (+ gemcitabine [G]), and metastatic breast cancer.

**Method:** The primary objective of part 1 is to evaluate dose-limiting toxicities (DLTs). Patients (pts) treated with ≥2 cycles of nivo with chemotherapy (CT) and remained on study for 14 additional calendar days or who discontinued due to DLT prior to completing 2 cycles of nivo were considered DLT evaluable. Treatment arms could expanded in Part 2 to further assess safety, tolerability, and antitumor activity. The lung arms, C and D, were initiated sequentially in part 1 of the study. In Arm C, treatment-naive pts with stage IIB/IV NSCLC received 4 cycles of nab–P 100 mg/m² on days 1, 8, and 15 plus C AUC 6 on day 1 of a 21 day cycle in combination with nivolumab 5 mg/kg on day 15 starting at cycle 1. Enrollment for Arm D starts after Arm C is deemed safe to expand. The same regimen will be given in Arm D; however, nivolumab will be given starting cycle 3. In both NSCLC arms, nivo monotherapy begins at cycle 5.

**Results:** As of Apr 21, 2016, 20 pts have been treated in Arm C (Part 1 and 2 combined). No DLTs were observed at the time of DLT evaluation (Nov 9, 2015). Of the 14 nivo–treated, response evaluable
pts in Arm C, 7 had a PR, and 7 had stable disease (unconfirmed). Grade 2 pneumonitis was reported in 1 pt but resolved, and the pt continued on the study. The most common any–grade AEs in either arm were fatigue, nausea, and alopecia.

Conclusion: Based on the tolerability demonstrated in the combination of nivo with nab–P/C, the study has been expanded and pts are enrolling in Part 2 for Arm C. Efficacy data in Arm C, although preliminary, is encouraging. Updated data will be presented. NCT02309777.

Keywords: nab–Paclitaxel, nivolumab

P1.47: ABOUND.sqm QoL BY RESPONSE: INTERIM ANALYSIS OF SQUAMOUS NSCLC PTS TREATED WITH NAB–PACLITAXEL/ CARBOPLATIN INDUCTION THERAPY

Track: Advanced NSCLC

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Background: The correlation of radiological response & pt-reported outcomes (PROs) in advanced non-small cell lung cancer (NSCLC) remains underreported. This interim analysis evaluated quality of life (QoL) by response (RECIST v1.1) in squamous (SCC) NSCLC patients (pts) treated with nab–Paclitaxel/Carboplatin (nab–P/C) during the induction part of the phase III ABOUND.sqm study.

Method: In the ongoing phase III ABOUND.sqm study, pts with advanced SCC NSCLC are treated with first–line nab–P 100 mg/ m² d 1, 8, 15 & C AUC 6 mg-min/ml d 1 (21–d cycles) for 4 cycles (induction). Pts without disease progression are randomized 2:1 to maintenance nab–P 100 mg/m² d 1 & 8 of each 21–d cycle + best supportive care (BSC) or BSC alone until progression. The primary endpoint is PFS from randomization to maintenance QoL, an exploratory endpoint, was assessed with predefined PRO instruments, LCSS & EQ–5D–5L, on d 1 of each cycle. Pts with a radiological CR/PR are considered responders (Rs) in this analysis (57% of evaluable pts). As the study is ongoing, this pre–planned analysis included QoL & tumor response data that were reported up to the cutoff date.

Results: Baseline (BL) characteristics were similar for Rs (n = 73) & non-Rs (n = 55). Over 80% of pts completed BL + 21 post-BL PRO assessments. For LCSS, average total score & symptom burden index improved during induction chemotherapy; a higher percentage of Rs vs non-Rs had clinically meaningful improvements (≥10 mm [VAS]) from BL in composite LCSS cough, shortness of breath, & hemoptysis (56% vs 38%). Of pts reporting BL EQ–5D–5L dimension problem(s), a higher percentage of Rs vs non-Rs reported complete resolution of symptoms at least once during treatment (Table).

Conclusion: These results indicate that Rs & non-Rs maintained/ improved QoL during induction therapy with nab–P/C. Rs appeared to have greater improvements in LCSS & EQ–5D–5L. Radiological response translates into meaningful QoL improvement. NCT0207428

Keywords: nab–Paclitaxel, ABOUND.sqm, QOL, response

P1.48: NAB–PACLITAXEL + CARBOPLATIN IN ADVANCED NON–SMALL CELL LUNG CANCER: OUTCOMES IN ELDERLY PATIENTS WITH SQUAMOUS HISTOLOGY

Track: Advanced NSCLC

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Background: In a phase III trial, nab–Paclitaxel + carboplatin (nab–P/C) demonstrated clinical efficacy in patients (pts) with advanced non–small cell lung cancer (NSCLC) (Socinski et al. J Clin Oncol. 2012;30:2055–2062). This post hoc analysis specifically examined clinical outcomes of pts with squamous histology (SCC) from this phase III trial stratified by age, including pts ≥ 70 years.

Method: Pts with histologically or cytologically confirmed stage IIIB/IV NSCLC and no prior chemotherapy for metastatic disease received either nab–P 100 mg/m² on days 1, 8, and 15 or paclitaxel (P) 200 mg/m² on day 1 in combination with carboplatin (C) AUC 6 on day 1 every 21 days (randomized 1:1). Treatment continued until disease progression. Overall response rate (ORR; primary endpoint) and progression–free survival (PFS) were assessed by blinded, centralized review. P values for ORR were based on a χ² test, and those for overall survival (OS) were based on a stratified log–rank test (by geographic region: North America/Australia, Eastern Europe, or Asia/ Pacific).

Results: A total of 450 of 1052 pts had SCC. Most pts with SCC were male (90%), white (89%), and had an ECOG PS of 1 (79%); 65 pts with SCC were ≥70 years of age. In this patient cohort, the ORR was significantly higher for nab–P/C vs P/C (46% vs 20%; P = 0.029) and median OS was nearly doubled (16.9 vs 8.6 months; P = 0.018). PFS did not significantly differ between treatments in these pts. Similar findings were observed for pts with SCC in other age groups (Table). In the overall treated population, nab–P demonstrated higher dose intensity vs P in pts with SCC and in elderly pts.
**Conclusion:** Treatment with nab-P/C vs P/C resulted in significant improvements in ORR and OS in pts ≥ 70 years of age with SCC. This post hoc analysis is limited by the small number of pts and thus should be interpreted with caution. However, the results build upon other prior analyses supporting the efficacy of nab-P as the taxane of choice for these 2 discrete pt subgroups, the elderly and those with SCC.

**Keywords:** nab–Paclitaxel, squamous, elderly

### Table 1: Odds Ratios of ORR and OS in Patients ≥ 70 Years of Age

<table>
<thead>
<tr>
<th>Outcome by Age Group</th>
<th>70 Years (nab-P/C)</th>
<th>65 Years (nab-P/C)</th>
<th>60 Years (nab-P/C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>46</td>
<td>46</td>
<td>45</td>
</tr>
<tr>
<td>Ratio of ORR P value</td>
<td>2.286 0.029</td>
<td>1.799 0.012</td>
<td>1.845 0.001</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>16.9</td>
<td>13.9</td>
<td>11.8</td>
</tr>
<tr>
<td>Hazard ratio P value</td>
<td>0.50 0.018</td>
<td>0.62 0.019</td>
<td>0.70 0.027</td>
</tr>
</tbody>
</table>

**Conclusion:** nab-P/C vs P/C resulted in significant improvements in ORR and OS in pts ≥ 70 years of age with SCC. This post hoc analysis is limited by the small number of pts and thus should be interpreted with caution. However, the results build upon other prior analyses supporting the efficacy of nab-P as the taxane of choice for these 2 discrete pt subgroups, the elderly and those with SCC.

**Keywords:** nab–Paclitaxel, squamous, elderly

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**P1.49 (also presented as PD1.05): THE GENOMICS OF YOUNG EMERGENT LUNG CANCER**

**Track:** Advanced NSCLC

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**Background:** Lung cancer is increasingly understood as a disease made up of genetically defined subtypes requiring distinct treatment strategies. We hypothesize that young age at diagnosis (<40 years) is a clinical characteristic associated with an increased chance for a targetable genomic alteration (GA). Our study will prospectively characterize the somatic and germline genomics of young lung cancer.

**Method:** Accrual opened in July 2014. Patients (pts) are eligible if diagnosed with bronchogenic lung cancer < age 40. The study website, allows for virtual consenting and remote participation from anywhere in the world. We defined 7 GA of interest based on the Lung Cancer Mutation Consortium (LCMC) (EGFR, KRAS, HER2, BRAF, ALK, ROS1, RET). We aim to show the prevalence of targetable GA in our stage 4 adenocarcinoma (AC) pts will be greater in our population compared to the LCMC, with an increase from 35% to 50%; and an improvement in use of targeted therapy from 22% to 40%. Study subjects without a known genotype undergo genomic profiling with the FoundationOne test.

**Results:** Preliminary results of 71 pts with stage 4 AC show that 82% have either an ALK re-arrangement n=32 (45%), an EGFR activating mutation n=17 (24%), a ROS1 fusion n=5 (7%), a RET fusion n=2 (3%), or a HER2 mutation n=2 (3%). Other GA of interest in those with AC includes TP53, ATM and BRCA2 mutations. 49% of our accrual has come from web based consenting. The majority of subjects have come from North America and Europe; and we would like representation from Latin America.

**Conclusion:** Thus far in our prospective series our results have far exceeded our statistical expectations, with 82% of our stage 4 AC pts having an actionable mutation. We have defined a genomically enriched subtype of lung cancer and laid the groundwork for further studies of germline and environmental lung cancer risk factors. We are planning a large-scale Case Control study of the Epidemiology of YLC. Web based consenting is a feasible method of bringing research to the patient.

**Keywords:** Genomics, Young, Emergent Lung Cancer, Remote Consenting

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**P1.50 LONG-TERM SAFETY AND EFFICACY OF DARBEPOETIN ALFA IN SUBJECTS WITH ADVANCE STAGE NSCLC RECEIVING MULTI-CYCLE CHEMOTHERAPY**

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**Background:** Darbepoetin alfa (DA) is an erythropoiesis-stimulating agent (ESA) that has been shown to increase hemoglobin levels and reduce the rate of transfusions in patients with chemotherapy-induced anemia (CIA). Most studies have not shown an association between ESA use and poor outcomes, but some clinical trials have reported increased mortality and/or tumor progression. This trial was therefore designed to address the safety of DA for CIA in patients with non-small cell lung cancer (NSCLC).

**Method:** Study 20070782a is a randomized, double-blind, noninferiority trial to compare DA with placebo, and is enrolling patients with NSCLC with CIA. Eligible patients are ≥ 18 years old with Eastern Cooperative Oncology Group (ECOG) status ≤ 1, stage IV NSCLC, no prior adjuvant/neoadjuvant NSCLC therapy, ≥ 2 cycles first-line chemotherapy planned (≥ 6 weeks total), and screening hemoglobin ≤ 11 g/dL. Approximately 3,000 patients from up to 500 global sites will be randomized 2:1 to DA (500 mcg) or placebo every 3 weeks (Q3W) until disease progression or end of chemotherapy. At hemoglobin > 12 g/dL, study drug is withheld until hemoglobin ≤ 12 g/dL. Transfusions are allowed when necessary. Endpoints include overall survival (OS; primary) and progression-free survival (PFS; secondary), and will be analyzed when ~2,700 deaths have occurred. Additional safety endpoints include tumor response and rate of thromboembolic events. Superiority of DA to placebo in transfusion rates will be tested if noninferiority is achieved for OS and PFS.

**Results:** As of April 15, 2016, a total of 2,215 patients have enrolled.
The independent data monitoring committee has conducted 9 reviews of unblinded data (which included a planned formal interim analysis at 40% of planned total number of 2,700 deaths to test for harm), and has recommended continuation of the trial without changes.

**Conclusion:** Study 20070782 is the largest clinical trial in NSCLC to date, and will provide comprehensive data on the safety and efficacy of DA in patients with CIA.

**Keywords:** darbepoetin alfa, chemotherapy-induced anemia, Non-small Cell Lung Cancer, safety

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**P1.51 IMPACT OF REGULATORY DELAYS IN DRUG APPROVAL: MORTALITY AND MORBIDITY DUE TO WITH LACK OF ACCESS TO CRIZOTINIB IN BRAZIL**

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**Background:** Well-established and adequately functional drug approval legislation is indispensable to guarantee a country’s population health. Malfunctons and delays in such a crucial process have dire consequences that can be measured. The objective of this study is to evaluate what impact delays in the drug approval process may have in the survival, symptom control and quality of life of NSCLC patients in Brazil. As an example, we used the drug Crizotinib (Xalcori® Pfizer, NY, USA), which had its approval denied by the Brazilian Regulatory Agency, ANVISA in June 2014.

**Method:** To perform this analysis, we arbitrarily selected the 3-year period from August 2011 (FDA approval) to June 2014 (refusal by ANVISA). We estimated the number and prevalence of NSCLC cases eligible for treatment according to data from the Brazilian National Cancer Institute (INCA). The percentage of patients with ALK-positive tumors was inferred from the literature. We made the assumption that every ALK-positive NSCLC patient in Brazil would have access to the drug and we considered the benefits of Crizotinib according to the published literature.

**Results:** According to INCA, there are 24,460 new cases of NSCLC/year in Brazil. We estimated 17,269 (70.6%) of them presenting in stages IIIB/IV, of which 743 (4.3%) would be ALK positive qualifying for Crizotinib treatment. We estimated 707 prevalent cases of ALK+ NSCLC in Brazil at the start of our analysis (August 2011). During the 3-year period from August 2011 through June 2014, we projected 62 new cases per month. We considered efficacy information indicating a survival of 20.3 mo for second line Crizotinib vs. 6.0 mo for standard chemotherapy (Shaw et al. Lancet 2011). In parallel, a significant extension in time to deterioration of symptoms, 1.4 mo for chemotherapy vs. 5.6 mo for Crizotinib (p<0.001) was documented in a phase III trial (Shaw et al. NEJM 2013). Applying the premises above we calculated 1,367 years of life lost due to lack of access to Crizotinib. A total of 772 additional patients (as compared with chemotherapy treatment) would remain alive at the end of the 3-year period. Importantly, in this population of patients treated with palliative intent a total of 846 years of life free of symptom deterioration (cough, dyspnea and chest pain) are lost during the same period of time with significant impact in the quality of life.

**Conclusion:** We recognize methodological limitations in this work; nonetheless it is evident that the delay in the approval and registration of new drugs in Brazil does have a significant impact in the lives of cancer patients. Our primary objective while performing this analysis was to stress the point that faults in the drug approval process can be estimated. At the same time, we need to recognize the importance of a swift and more transparent, competent and efficient drug approval process.

**Keywords:** Crizotinib, ALK positive NSCLC, Drug Access, health disparities
P2.01: LUME-MESO: PHASE II/III STUDY OF NINTEDANIB + PEMETREXED/CISPLATIN IN PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA

**Track:** SCLC, Mesothelioma, Thymoma

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**Background:** Median overall survival (OS) is ~1 year with pemetrexed/cisplatin, the standard front-line treatment for patients with unresectable malignant pleural mesothelioma (MPM); additional improvements in therapy are needed. Nintedanib is an oral, twice-daily (bid), triple angiokinase inhibitor of vascular endothelial growth factor (VEGF) receptors 1–3, platelet–derived growth factor receptors α/β, and fibroblast growth factor receptor 1–3, as well as Src and Abl kinases, which are involved in regulating tumor angiogenesis, growth, and metastasis of MPM. Inhibition of the VEGF pathway has been validated as a treatment approach for MPM with bevacizumab (Zalcman G, et al. Lancet 2016;387:1405–14). Nintedanib (Ofev®) monotherapy is approved in the USA and EU for idiopathic pulmonary fibrosis. Nintedanib (VARGATEF®) in combination with docetaxel is approved in the European Union and other countries for locally advanced, metastatic or locally recurrent non-small cell lung cancer of adenocarcinoma histology after first-line chemotherapy and has shown clinical benefit in trials in several tumor types. LUME-Meso is an international, double-blind, randomized, multicenter, placebo–controlled Phase II/III study, evaluating the efficacy and safety of nintedanib combined with pemetrexed/cisplatin for the treatment of unresectable MPM. Following a data review by the internal Data Monitoring Committee (DMC) after all planned Phase II patients had been enrolled, the Phase II exploratory study was extended to a confirmatory Phase II/III trial. The trial is ongoing.

**Method:** Chemo-naïve patients from 27 countries (≥18 years of age, Eastern Cooperative Oncology Group Performance Status 0–1), with histologically confirmed epithelioid/biphasic MPM; 87 pts in Phase II (450 pts in Phase III) will be randomized (1:1) to receive up to 6 cycles of pemetrexed (500 mg/m²)/cisplatin (75 mg/m²) on Day 1 plus nintedanib (200 mg bid) or placebo on Days 2–21. Patients without disease progression (PD) will continue to receive maintenance treatment with nintedanib monotherapy/placebo until PD. The primary endpoint is progression–free survival (PFS); OS is the key secondary endpoint. The study will use an adaptive design strategy, with sample size reassessment by an external DMC based on interim analysis to ensure sufficient power for PFS/OS. Additional secondary endpoints include objective tumor response and disease control according to modified Response Evaluation Criteria in Solid Tumors. Other assessments include frequency/severity of adverse events, laboratory parameters, change in forced vital capacity (Phase II only), health-related quality of life and exploratory predictive biomarker analyses in tumor/blood specimens.

**Results:** Not applicable.

**Conclusion:** The study is currently enrolling patients into Phase III and will help to determine the efficacy and safety of nintedanib in patients with unresectable MPM. Clinical trial identifier: NCT01907100.

**Keywords:** Mesothelioma, Nintedanib, Angiogenesis, Clinical trial

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P2.02: THYMIC MALIGNANCIES. A SINGLE INSTITUTION SERIES FROM 2006–2016

**Track:** SCLC, Mesothelioma, Thymoma

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**Background:** Thymoma and thymic carcinoma are rare malignancies, despite being amongst the most common tumors of the anterior mediastinum. The incidence in the United States (US) is 0.13 per 100,000 habitants per year. Patients with thymoma can be asymptomatic during the diagnosis in 30% to 50% of the cases. The optimal treatment is complete resection. There are two types classification for Thymoma: Masaoka–Koga’s Classification, which assess the degree of invasion, and World Health Organization (WHO) that organize the histologic subtypes. Little information regarding thymic malignancies is available in Latin America.

**Method:** Retrospective service database review of patients with thymoma treated at Hospital São Lucas between 2006–2016. Inclusion criteria were age ≥18 or older with histologically confirmed thymoma. Thymomas were classified according to WHO criteria and Masaoka staging.

**Results:** In eligible 10 patients there were 80% males and 20% females. The mean age was 62 years and 40% were over 65 years. A complete Ro resection was achieved in all cases. No in hospital mortality or morbidity was verified. Conventional open approach was used in 90% and minimally invasive (VATS) in 10%. WHO AB type was the most common with 40% patients, followed by 30% A type, 20% B1 and 10% B2. Masaoka–Koga classification: 70% Type I, 20% IIa and 10% III. The body mass index was normal in half of patients. Myasthenia Gravis was present in 30% and all achieved at least partial response. CKAEn/γ markers were positive in 60%.

**Conclusion:** Thymoma was most frequent in middle age men. Complete resection was achieved in all cases: predominately Masaoka I stage and WHO AB and type. CKAEn/γ markers were positive in most cases. Multicenter studies in Latin America should be performed for better understanding of this rare disease.

**Keywords:** Thymoma, Mediastinal Tumor
P2.03: TREATMENT OF MALIGNANT PLEURAL MESOTHELIOMA BEYOND FIRST-LINE AMONG HISPANICS (MESO–CLICAP)

Track: SCLC, Mesothelioma, Thymoma

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Background: Platinum/Pemetrexed chemotherapy is standard of care in first-line (FL) treatment of malignant pleural mesothelioma (MPM). Different second and third lines regimens are also considered, but the optimal treatment has not yet been defined.

Method: The aim of this study was to evaluate clinical outcomes of second (SL) and third line (TL) therapies in a series of MPMs included in a retrospective multinational database (MeSO–CLICaP). Clinical records of MPM-patients who received treatment beyond FL from 2008 to 2016 were reviewed. Study endpoints were response, overall survival (OS), and progression-free survival (PFS) for SL and TL, stratified for patient characteristics, FL-outcomes, and type of regimen. Out of 124 patients, 79 received SL/TL and had sufficient clinical data.

Results: Of the 124 patients included in the MeSO–CLICaP registry, 79 (64%) received some treatment after first line. Median age was 59 years (range 33–81), 42 (53%) were men, 74% were current or former smokers and 77% had a baseline ECOG 0–1. After FL, 57 patients (76%) achieved disease control (PR 24/32% and SD or former smokers and 77% had a baseline ECOG 0-1. After FL, was 59 years (range 33-81), 42 (53%) were men, 74% were current was 59 years (range 33-81), 42 (53%) were men, 74% were current

Conclusion: SL-chemotherapy appears to be active in Hispanic MPM-patients, particularly in younger patients with good PS and prolonged disease control with FL chemotherapy. Considering the important limitations of this study, due to retrospective nature and the possible selection bias, prospective clinical trials are warranted to clarify these issues.

P2.04: CHARACTERISTICS AND LONG TERM OUTCOMES OF ADVANCED PLEURAL MESOTHELIOMA IN LATIN AMERICA (MESO–CLICAP)

Track: SCLC, Mesothelioma, Thymoma

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Background: Malignant pleural mesothelioma (MPM) is an aggressive tumor, usually associated with a poor prognosis. MPM is a heterogeneous disease often associated with different clinical courses. Palliative platinum-based chemotherapy may help to improve symptoms and prolong life.

Method: The MeSO–CLICaP registry identified 124 patients with advanced MPM from 5 Latin American countries diagnosed and treated between January 2008 and March 2016. Data collected included age, gender, asbestos exposure, presenting signs/symptoms, performance status, histology, stage, treatment modalities including chemotherapy, and date of death or last follow-up. Outcomes like progression free survival (PFS), overall survival (OS) and response rate (ORR) were recorded. Cox model was applied to determine variables associated with survival.

Results: Median age was 59.9 years (range 33–84), 72 (58%) were men, 69% were current or former smokers and 37 patients (30%) had previous exposure to asbestos. Ninety-six patients (77%) had a baseline ECOG 0–1, 102 (82%) were epithelioid tumors, 47 (38%) and 77 (62%) cases had stage III or IV MPM. Only 20% (n=25) underwent pleurectomy, 28% (n=35) received radiotherapy and 123 patients received platinum-based chemotherapy in first line (plus Pem 68/54% and Gem 55/44%). ORR to first line chemotherapy was 48% (CR 3.2%/PR 43%), PFS was 10.5 months (95%CI 8.2–12.8) and 47 patients had Pem maintenance (mean number of cycles 4.4+/–3). Median OS was 25.3 months (95%CI 22.3–28.3) and according to a univariate analysis, stage (p=0.03), histology (p=0.009), and Pem maintenance (p=0.014) were associated with better OS. Multivariate analysis found that stage (p=0.002), histology (p=0.021), smoking history (p=0.001) and Pem maintenance (p=0.002) were independent prognostic factors.

Conclusion: Our study identifies factors associated with a clinical benefit from chemotherapy among Hispanic patients with advanced MPM, and emphasizes the impact of histology and clinical benefit of chemotherapy on outcomes.

Keyword: Pleural mesothelioma, outcomes, survival, systemic treatment
P2.05: THE SYNTHETIC PEPTIDE CIGB-300 INHIBITS NF-κB TRANSLATION AFFECTING THE SURVIVAL AND CHEMoresistance OF NSCLC CELL LINES

Track: Biology and Pathogenesis

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Background: The CK2 is a Ser/Thr kinase that has been historically associated with cancer. It is involved in cell proliferation, survival and apoptosis by modulating diverse signaling pathways, including Wnt and NF-κB among the most relevant. CIGB-300 is a synthetic antitumor peptide with a novel mechanism of action, since it is capable of binding to CK2 substrates thus preventing the enzyme activity. NF-κB activation can reduce chemotherapy efficiency in lung cancer. We have determined that CIGB-300 inhibits NF-κB (p65) nuclear translocation. Based on this evidence, we hypothesize that supplementing cisplatin with CIGB-300 would improve the treatment efficiency. Also, CIGB-300 alters the ability of lung cancer cells to grow in a three-dimensional spheroid model.

Method: A cisplatin resistant cell line (A549-Rcisp) was developed in our laboratory by chronic administration during six months. Proteasome activity was assessed with Proteasome-Glo™ Assay kit (Promega). Proteasome Alphaph/C8 subunit and CIGB-300 cellular distribution of was analyzed by confocal immunofluorescence. Pearson’s and Manders coefficients were measured with JACoP plugin for ImageJ. Biotin-labeled CIGB-300 was used to evaluate, by immunohistochemistry, the time-course internalization of the peptide into NCI-H125 3D cultures.

Results: Nuclear p65 levels were highly increased after treating human NCI-H125 cells with cisplatin. When cells were treated with cisplatin plus CIGB-300, NF-κB activation was completely abolished. Therefore, the CIGB-300 effect on NF-κB signaling pathway prevails over cisplatin. This led us to evaluate the combined treatment in a chemoresistant setting. For this purpose we developed a cisplatin resistant A549 lung cancer cell line (A549-Rcisp). A549-Rcisp viability was 40% higher than parental cells, confirming the acquisition of cisplatin-resistance. Remarkably, A549-Rcisp showed a significant increase in CIGB-300 sensitivity as compared to the parental cell line (p<0.01; t-test). Moreover, A549-Rcisp showed an increased p65 nuclear level after cisplatin treatment, suggesting that both cisplatin resistance and CIGB-300 sensitization might be linked to the NF-κB transcription factor. Given that NF-κB dimer stability is regulated by the proteasome-selective proteolysis of its inhibitor, we studied the effect of CIGB-300 on this process. Surprisingly, we observed a significant increase on proteasome activity after 30 minutes of CIGB-300 treatment (p<0.01; ANOVA). Besides, a co-occurrence between the CK2 substrate Alphaph/C8, a member of the proteasome alpha ring, and CIGB-300 (Pearson’s=0.82, M=0.82, M=0.65) was observed. Thus, the proteasome complex is a newly identified target of CIGB-300 that may be relevant for its mechanism of action and deserves further exploration in order to determine the association with the NF-κB pathway perturbations that we have observed. Finally, as CIGB-300 inhibits 3D growth, we analyze whether it was able to affect spheroid compact structure that resembles in vivo avascular tumour conditions which makes drug-entry difficult. By immunohistochemistry we observed a fast and effective entrance of CIGB-300, detecting mark after 5 minutes of treatment. Complete spheroid penetration was reached at 60 minutes.

Conclusion: Our results show that treatment with CIGB-300 negatively modulates several characteristics associated to malignant progression by affecting different signaling pathways. Moreover, its improved effectiveness in a chemoresistance model, associated with NF-κB inhibition, indicates that CIGB-300 may become a new strategy for chemotherapy-refractory NSCLC patients.

Keywords: NF-κB, CK2, CIGB-300, NSCLC

P2.06: EXOSOMAL MIRNA ANALYSIS IN NON-SMALL CELL LUNG CANCER: NEW LIQUID BIOMARKER?

Track: Biology and Pathogenesis

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Background: Cancer cells produce a heterogeneous mixture of vesicular, among which exosomes, nanovesicles (30 to 100 nm) originated from endocytic pathway. Exosomal content is composed of proteins, DNA, lipids and different class of RNAs, such as miRNAs. miRNAs are short non-coding RNAs that is involved in inter-cellular communication. The primary objective of this pilot study is to investigate whether exosomes isolation from clinical samples (plasma from NSCLC patients) is feasible; moreover we have analyzed a selected panel of 7 exosomal miRNAs related to NSCLC status.

Method: After obtaining the informed consent, blood samples (10 ml) of 12 NSCLC patients and 6 healthy volunteers were collected in the UZA-tumor biobank. Clinical data were also collected from patients’ medical records. Exosomes were isolated by both Density Gradient (DG) centrifugation and Total Exosome Isolation kit (from plasma) (Invitrogen) according to manufacturers’ instructions. The Total exosome RNA and protein isolation kit (Invitrogen) was used for proteins recovery from exosomes for western blot analysis for western blot analysis for well-known exosomal markers like CD63, ALIX and TSG101. TEM (Transmission Electron Microscopy) analysis was performed in order to determine the size average of isolated exosomes.

Results: The total exosome RNA and protein isolation kit (Invitrogen) was used to extract small-RNA from exosomal samples. The analysis of 7 miRNAs (miR-30b,-30c, -103, -122, -195, -221) was performed on the LightCycler 480 (Roche) and the fold change was calculated according to the formula 2^ΔΔCq. miR-1228-3p was used has normalizer in the reaction.

Conclusion: This new liquid biopsy tool, exploiting exosomes, could represent a non-invasive test for patients’ management in NSCLC; exosome analysis and exosomal miRNA profiling is feasible in NSCLC but due to the limited sample size we cannot have statistic conclusion. Further analyses are needed in order to confirm these hypothesis.

Keywords: exosomes, biomarker, NSCLC, liquid biopsy
**P2.07: EVALUATION OF DIFFERENT EXOSOMAL RNA ISOLATION METHODS IN NSCLC LIQUID BIOPSIES**

**Track:** Biology and Pathogenesis

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**Background:** Exosomes are biological nanovesicles (30–100 nm), with endocytic pathway origin, created from the inward budding of multivesicular bodies (MVB). It has been described that they contain lipids, proteins and several nucleic acids, among which microRNAs and IncRNAs. Most of these components have been reported to be altered in cancer and maybe exploitable as new biomarkers. However, in the literature there is no consensus about a stable endogenous control for exosomal microRNAs analysis. Here we compare three exosomal RNA isolation methods and assess the normalizer features of exosomal hsa-miR-1228-3p in a liquid biopsy sample set of Non-Small Cell Lung Cancer (NSCLC) patients.

**Method:** After obtaining informed consent, plasma sample from NSCLC patients (N=21) and healthy donors (N=6) were collected in the Oncology Department of Antwerp University Hospital. Plasma samples were cleared through sequential centrifugation in order to remove cells, debris and microvesicles. After this step, exosomal RNA was extracted through two different methods: by Total Exosome Isolation kit – from plasma (Invitrogen©) and by sucrose density gradient ultracentrifugation and ExoRNEasy™ Kit (Qiagen©), according to manufacturer’s specifications. Exosomes characterization was performed through biophysical (Transmission and Scanning electron microscopy TEM–SEM) and biochemical analysis (Western blot for well-known exosomal marker as ALIX and Tsg101). Exosomal RNA quantity and quality was evaluated through spectrophotometry (Nanodrop ND–1000). Reverse transcription and qPCR of hsa-miR-1228–3p was performed through TaqMan microRNA assay (Applied Biosystem©). Fold of changes were calculated according to the formula 2−ΔΔCt using the healthy donors hsa-miR-1228–3p Ct as control. t-test analysis were performed between NSCLC samples depending on their protocol (SPSS 23 Statistics IBM©).

**Results:** TEM and SEM analysis shown that the isolated nanovesicles have a diameter around 30–100 nm and cup shape appearance, according to the literature. Western blot analysis demonstrated the presence of well-known exosomal markers ALIX and Tsg101 and absence of Calnexin (negative control). ExoRNEasy™ kit seems to provide the highest yield of RNA. Real time PCR analysis of hsa-miR-1228–3p has shown no significant differences between the different exosomal RNA extraction methods.

**Conclusion:** Among these methods, ExoRNEasy™ kit seems to provide the highest yield of RNA. No significant differences were found between sample groups of hsa-miR-1228–3p expression among all the used methods and we suggest that hsa-miR-1228–3p should be considered as a stable endogenous control for exosomal microRNA analysis.

**Keywords:** exosomes, miRNA, exosomal isolation, NSCLC biomarker

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**P2.08: GENE FUSIONS DETECTED IN NON–SMALL CELL LUNG CARCINOMA (NSCLC) AND SMALL CELL LUNG CARCINOMA (SCLC)**

**Track:** Biology and Pathogenesis

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**Background:** Gene fusions, first thought to be limited to hematologic malignancies and soft tissue sarcomas, are taking on more importance in many solid tumors. For instance, functional ESRI fusions in breast cancer are now associated with resistance to hormonal therapy. In NSCLC, ALK-, RET-, and ROS1-rearrangements are frequently targeted with available kinase inhibitors. However, much remains unknown regarding other chromosomal gene rearrangements. The purpose of this study is to report fusion assay results performed at a multi-omic tumor profiling facility to identify potentially novel or uncommon fusions in a variety of thoracic carcinoma.

**Method:** In total, 356 NSCLC and 20 SCLC were profiled using the ArcherDx FusionPlex Assay at a CAP/ISO/CLIA-certified laboratory (Caris Life Sciences) using FFPE specimens. Fifty-two genes were analyzed for potential gene fusions. Fusion-positive specimens were confirmed using in-situ hybridization and/or Sanger sequencing. Depending on available specimen, tumor samples were evaluated by immunohistochemistry (IHC), and next generation sequencing (NGS) for co-occurring biomarkers.

**Results:** Overall, 32 fusion transcripts in 31 of 356 NSCLC specimens contained a previously reported or novel fusion (8.7%). Fusion transcripts were found in adenocarcinoma (78.1%, 25/32) followed by SCC (15.6%, 5/32) and carcinoma, NOS (6.3%, 2/32). One NSCLC specimen contained two co-occurring fusions (EML4–ALK, PRKCG–PRKCB) and 40.6% (13/32) were either ALK (n=8), RET (n=2), or ROS1 (n=3) rearrangements. More than once detected fusions included MSMB (n=3), ERG (n=2), MAST2 (n=2), and PRKCA (n=2). Notable fusions included BRD4, FGFR3, MET, and NTRK3 detected in single cases. Sequencing analysis by NGS revealed no co-occurring deleterious mutations in BRAF, EGFR, ERBB2, MET, NRAS. However, KRAS G12 mutations were detected in 22.6% (7/31) fusion-positive specimens, all of which were adenocarcinomas. PD-L1 expression was detected in 30.4% (7/23) of fusion-positive specimens. Only one fusion (SYN2–PPARG) was identified in SCLC.

**Conclusion:** ArcherDx FusionPlex Assay is a laboratory validated assay for detection of fusions involving ALK, RET, and ROS1, and some additional directly targetable fusions. The presence of mutant KRAS and/or PD–Li in fusion–positive NSCLC could be used for novel drug combinations. These results could be useful to direct patients to clinical trials for relevant drugs. Further studies are warranted to explore the role of fusions in driving various cancers.

**Keywords:** NSCLC, SCLC, fusion gene, FFPE
Background: Targeted therapies have gained a lot of attention in non-small cell lung cancer, including several cMET inhibitors against non-small cell lung cancer (NSCLC). Nowadays, cMET amplification is used as a standard biomarker for patient selection; however, there is still discussion about the cut-off value. More recently, splicing variants of cMET, which show exon 14 skipping, are gaining importance since it has been shown that patients harboring this mutation can respond to cMET directed targeted therapy. In this study, we explored the occurrence of cMET aberrations and their correlation with cMET expression in a population of 155 primary EGFR-TKI naive NSCLC tumors. We also evaluated cMET expression and amplification in corresponding metastases. Finally, given the link between the EGFR and cMET pathways, the EGFR status was also studied.

Method: Therapy naïve resection samples were collected at the Antwerp University Hospital and the Onze-Lieve-Vrouwe Hospital Aalst. The expression of EGFR and cMET was determined by immunohistochemistry (Ventana, clones 3C6 and SP66 respectively), while cMET amplification was examined by in situ hybridization (Ventana, MET DNP and CEN7 DIG probes). EGFR mutations and cMET splice site mutations were detected by Sanger sequencing. Deep sequencing of cMET was performed with the custom designed TPME kit (Multiplicom) and sequenced on Illumina MiSeq. Significant correlations were tested using the Chi² and kappa test (SPSS 23).

Results: In 146/155 tumors cMET expression could be determined; 73/146 samples showed high (2+ or 3+ score) cMET expression and 43/148 samples showed amplification (ratio ≥ 2). No significant correlations could be determined between cMET expression and histological subtype of NSCLC (p=0.065), differentiation degree (p=0.468) and cMET amplification (p=0.214). However, a significant correlation was found between cMET expression, EGFR expression (p=0.015) and EGFR mutations (p=0.029). Splice site mutation regions were sequenced in 87/155 samples, all of which were wild-type. However, deep sequencing revealed 2 patients with splice site mutations. When comparing cMET amplification between the primary tumor and the corresponding metastases (n=40), only one sample showed amplification in the metastases and not in the primary tumor. Hence, cMET expression showed a significant correlation between primary tumors and their metastases (kappa=0.003).

Conclusion: The overall results of our study are in agreement with earlier data. Moreover, we showed that overall expression levels of cMET in primary tumors and metastases are very similar despite large intratumor heterogeneity. The two patients with cMET splice site mutations, both showed a high cMET expression and one patient had a ratio of cMET/CEN of 2. In conclusion, this study shows that high cMET expression in most NSCLC samples does not originate from presently known genetic cMET aberrations. High cMET expression is likely to be caused by temporary changes in transcription and translation, influenced by EGFR-signaling, miRNAs or other regulatory mechanisms.

Keywords: cMET, NSCLC, cMET amplification, cMET expression
with different biological behavior and effective directed therapy. The ALK Break Apart FISH Probe Kit (Abbott Molecular, Des Plaines, IL) and the VENTANA ALK (D5F3) CDx Assay has become an FDA-approved companion diagnostic for targeted therapy. The FISH assay is fraught with technical challenges: including FISH signal instability and scoring difficulties. Consequently, the assay is prone to false negatives and false positives. Two case reports are presented with different diagnostic results in ALK status by IHC and FISH and diverse clinical responses to directed therapy.

Method: ALK IHC testing was performed using the Ventana anti-ALK (D5F3) Rabbit monoclonal antibody (Roche, CE-IVD) used in combination with the OptiView DAB IHC Detection kit and OptiView Amplification Kit as a fully automated IHC assay on the Ventana BenchMark XT automated slide stainer. ALK FISH testing was performed using the Vysis ALK Break Apart Probe kit (2p23/ALK translocation detection, Abbott, CE-IVD).

Results: We examined 308 NSCLC cases and compared the FISH results to ALK IHC. Of 8 (3%) cases identified as positive expression, only 6 have ALK rearrangement. Case 1: 54 year old male, 30 pack/year smoker, evaluated in October 2015 presenting fever and cough. CT shows pulmonary mass infiltrating mediastinum and pulmonary artery and enlarged ganglionar groups 5, 6 and 7. Supraclavicular node biopsy informs moderately differentiated adenocarcinomas. PET demonstrates FDG positivity in retroperitoneal image in left diaphragmatic crus. Being defined as stage IV, he started chemotherapy with cisplatin and pemetrexed. After first cycle, ALK+ result by IHC is obtained changing treatment to Crizotinib. Further tests revealed no ALK gene rearrangement. After 60 days of treatment CT evaluation evidences disease progression switching to chemotherapy regimen. Case 2: 61 year old female smoker (18 pack/year) is diagnosed by thorax CT of a left inferior lobe mass and satellite nodal image. PET scan informs increased uptake in mediastinum nodes and pulmonary peripheral nodules. Detection of a moderately differentiated adenocarcinomas with parietal pleura and ganglionar groups 5-6 involvement is accomplished by percutaneous biopsy and mediastinoscopy. Pathologic assessment highlights ALK+ by IHC starting treatment with Crizotinib which continues at present. ALK FISH testing demonstrated no ALK gene rearrangement. Partial response is described in CT evaluation in May 2016.

Conclusion: Although FISH is the gold standard to detect ALK positive patients this two cases with different response in ALK IHC positive FISH negative points out the absence of guidelines in this rare scenario.

Keywords: ALK, non small cell lung cancer

P2.13: TESTING PROFILES IN NSCLC BIOPSY SAMPLES: MULTI-INSTITUTIONAL STUDY IN CORDOBA

Track: Pathology

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Background: Substantial advances have been made in the understanding of the biology of NSCLC in relation to the characterization of molecular abnormalities such as activations of oncogenes by mutations, translocations and amplifications, which are being used as molecular targets and predictive biomarkers. Molecular analysis of NSCLC, adenocarcinoma (AC) is now the standard of care for therapy selection.

Method: For a period of two years (from 2014 to 2016) we have studied 78 small biopsies and resection specimens of patients with NSCLC (AC) in 3 institutions of Cordoba. We determined the frequency of molecular alterations in EGFR and gene fusion ALK in our Caucasian and Hispanic populations to decide the adequate treatment.

Background: Lung cancer is the second most common cause of cancer, occurs frequently in older men (≥65 yo), with a higher risk for smokers. Approximately 14% of the new cancer cases are lung cancer, it is the leading cause of death for men and women, 1 out of 4 cancer deaths, are due to lung cancer. Non-Small Cell Lung Carcinoma (NSCLC) represents the 80% of all lung cancer diagnosis. Actually there is a significant increase in the global survival rate in patients with cancer, due to multidisciplinary approach and the advanced diagnostic and therapeutic tools, this has identify the emergence of new tumors throughout there lifes; in different anatomic places, with different histological characteristics, these are called Second Primary Cancer (SPC). The National Cancer Institute has determined that 1 of 6 patients with cancer will develop a new malignancy. We discuss a case report of two patients with lung cancer as SPC, the clinical presentation and histological
characteristics.

Method: Review of medical history, radiological and pathological studies.

Results: Case one: Woman, 80 years old, previous smoker, history of infiltrating squamous cell carcinoma of the tongue, treated with glossectomy and left lymphadenectomy, no chemotherapy or radiotherapy was needed, disease free during a 5 year period of oncology follow-up. Presents with dyspnea, cough, weight loss and thoracic pain, a year after her last follow-up, no cervical or supraclavicular lymphadenopathy, no palpable masses in neck or abdomen, decreased breaths sounds. Thorax CT with a 6 cm mass in left upper lobe, infiltrating the pleura. FBO identifies and endobronchial friable lesion in left upper lobe, with a diagnosis of Non–Small Cell Adenocarcinoma with a negative EGFR and negative ALK gene rearrangements, chemotherapy was started. Case two: Man, 75 years old, previous smoker, history of squamous cell cancer of larynx, treated with total laryngectomy, lymphadenectomy, radiotherapy and pharyngoplasty reconstruction with a pectoral flap. Presents with cough and increased secretions from the tracheostomy, fever, hemoptysis, received antibiotic treatment for pneumonia, now with deterioration of general morbi-mortality in the world, with a preventable etiology, it is one of the areas where we should keep working on, it represents a challenge in the era of personalized medicine. Regarding the SPC, in the literature, there is limited information, there are only a few studies and clinical trials, but with the development of new and better tools for diagnosis and innovative cancer treatments, we will probably face this challenge increasingly often.

Keywords: Second Primary Cancer, Non–Small Cell Lung Carcinoma, lung cancer

P2.15: TREATMENT OUTCOME OF METASTATIC BREAST ANGIOSARCOMA TO THE LUNG, IN A REFERENCE HOSPITAL IN LATIN AMERICA: A CASE REPORT

Track: Pathology

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Background: Breast Angiosarcomas (BAs), are very rare, they are classified Primary and Secondary, as a complication of the treatment (Mastectomy or radiotherapy) for breast cancer. Occurs frequently in younger women (20 – 50 y) with no previous cancer, family history or risk factors. Primary BAs incidence of 17 new cases per million women, and accounts for 0.04% of all breast malignancies. Angiosarcomas arise from the endothelial lining of the blood vessels, mainly in soft tissue and skin, it is rapidly progressive with a poor prognosis compared to other breast malignancies. Although there is not a standardized treatment, surgery has been used as first line treatment with chemotherapy and radiotherapy as adjuvants. Lately the use of Liposomal Doxorubicin and Bevacizumab has been increasing with very favorable responses. The BAs principal metastatic places are lung, bone, liver, and thorax. We describe a case of a patient with BAs, during her evolution presents a metastatic lesion to the lung.

Method: Review of medical history, radiological and pathological studies.

Results: Woman, 63 years old, with diagnosis of left BAs (intermediate grade), treated with left mastectomy, later with a local recurrence, affecting muscle in the left breast, lung metastasis (intermediate grade) was developed with only lesion in lower left lobe, mixed component, solid and ground glass, treated with lower left lung lobectomy, during the evolution developed cutaneous angiosarcoma, scalp, liver and meningeal carcinomatosis, in the last admission presented with intermittent heavy bleeding, from upper airway lesions. The patient is currently being treated with Liposomal Doxorubicin and Bevacizumab, with significant regression of metastatic lesions, intermediate tolerance because of the adverse effects. From the oncological point of view with this treatment the patient has a satisfactory evolution.

Conclusion: The importance of this case is that the Primary BAs is a rare disease, that can develop without prior exposure to surgical procedures or radiation. The metastatic or disseminated presentation represents a therapeutic challenge, in this case the implementation of antiangiogenic therapy (Bevacizumab) and the chemotherapeutic agent (Liposomal Doxorubicin), have achieved and adequate sustained treatment outcome, allowing and individualized treatment to metastasis, as the case of the lung injury that was successfully resected.

Keywords: Breast Angiosarcoma, Liposomal Doxorubicin, bevacizumab, Lung Metastasis

P2.16: ATYPICAL ADENOMATOUS HYPERPLASIA (AAH) IN A PATIENT WITH A PRIMARY CARCINOID LUNG TUMOR: CASE-REPORT

Track: Pathology

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Background: AAH is considered a premonitory lesion in the pathological pathway leading to adenocarcinoma (AC). However, previous studies have suggested a less common but existing association between AAH and other types of primary lung cancer, including carcinoid tumors (CT). We describe the case of a patient with an incidental diagnosis of typical CT in whom was found an AAH concomitantly.

Method: Review of medical history, imaging studies and pathology

Results: 59-year-old woman with history of diverticular disease visited the hospital in Sep/2015 with abdominal pain. Not abnormal findings on physical examination, but lung nodules were incidentally observed in abdominal CAT. Chest CAT reported three nodular lesions: right inferior lobe (4mm), medial segment (6 mm), lateral segment (9mm) spiculated with pleural tail and left adrenal gland (1mm). The patient refers weight loss (6kg) but denies respiratory symptoms. Chest surgery performs lung resection by thoracoscopy, obtaining a 12mm nodule with retraction of visceral pleura in the right inferior lobe. Pathology reports a typical CT, KI67 4%, low-grade neuroendocrine tumor, well differentiated, grade 1. A right inferior lobectomy was done by thoracoscopy with mediastinal lymphadenectomy. Pathology described the morphological pattern
and immunophenotypical profile of an AAH. No residual CT was found.

Conclusion: AAH has been described as a putative lesion preceding lung AC (OR 2.97; 95% CI 1.82–4.85). However, previous case–series of patients with resected lung for primary lung carcinoma found AAH in other primary lung tumor subtypes, including 3.3% patients with lung CT2. To our knowledge, this is the first case described of a typical CT with a concomitant finding of AAH. Further studies are required in larger samples to confirm this finding. Despite the strong association between AAH and AC, it must be considered as a histopathological finding in the context of other primary lung neoplasms, such as the typical CT.

Keywords: Atypical adenomatous hyperplasia, carcinoid lung tumor

P2.17: INCIDENTE DE NS CLÍNGEN CANCER BIFMARKERS IN PANAMA; DEMOGRPHIC, CLINIC AND HISTOPATHOLOGICAL FEATURES

Track: Pathology

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Background: Lung cancer is the leading cause of cancer deaths worldwide. Biomarker analysis of cancer driven mutations is helpful for determining an optimal treatment strategy. Our hospital receives the largest number of patients with lung cancer in the country, making it easier to assess the incidence, mainly epidermal growth factor receptor (EGFR) and echinoderm microtubule–associated protein–like 4-anaplastic lymphoma kinase (EML4–ALK).

Method: We included 201 patients diagnosed between 2014 and 2015 with non–small cell lung cancer, including adenocarcinoma, NOS and some squamous cell carcinoma. All files were evaluated to get demographic features. Histological slides including immunohistochemistry were reviewed by two pathologists. EGFR mutations were examined by quantitative PCR and the ALK rearrangement was analyzed by fluorescence in situ hybridization.

Results: The median age was 66.4 +/- 11.8 years old, 54.7% were female and 48.3% of our patients had a history of smoking. 72.7% of patients presented with metastatic disease at diagnosis. The diagnosis and biomarker studies were done with tissue obtained from biopsies (90.5%), surgical specimen (7.5%) and cell block (2%). In assessing the slides, the most frequent pattern was adenocarcinoma (87%), followed by subtype not otherwise specified (10.5%), and squamous cell carcinoma (2.5%). TTF-1 was evaluated in 94.5% of cases and positive expression was 82.6%. EGFR and ALK rearrangement could only be assessed in 78% and 84% of the cases, respectively. EGFR positive mutations incidence was 37.5% with 67.4% of the alterations in exon 19. Incidence for ALK rearrangement was 7%. The median overall survival observed was 17 months (11.8 – 22.2).

Conclusion: In our population, the EGFR positive NSCLC represented the 37.5%, with this finding being higher than reported in other series; exon 19 alterations being the most common. ALK rearrangement incidence was 7%. The most frequent pattern was adenocarcinoma. Most of the patients presented with Stage IV disease. The median overall survival was 17 months.

Keywords: NSCLC, lung cancer, EGFR, ALK

P2.18: RAPID ON–SITE EVALUATION (ROSE) TECHNIQUE: EXPERIENCE IN THE PULMONOLOGY UNIT OF A REFERENCE HOSPITAL IN LATIN AMERICA

Track: Pathology

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Background: Interventionist pathology, coupled with pulmonology’s diagnostic procedures, permits to optimize quantity and quality of the samples, decrease re–interventions and length of procedures and helps to do histopathologic diagnosis and molecular pathology studies, currently relevant to the prognosis and selection of treatment scheme (precision medicine), particularly in lung cancer.

Method: Descriptive, retrospective study, from April/2014 till December/2015. The simple included 73 patients who underwent ROSE procedures. Indication was determined by the pulmonologist and the chest surgeon. Clinical status, location and size of the lesion, suspicion of malignancy and tissue viability were considered.

Results: There were 42 (57.5%) women and 31 (42.5%) men, with a mean age of 61.2 ± 15.2 years old. 76.7% biopsies were taken via fibrobronchoscopy in the Endoscopy Unit or in the Intensive Care Unit and 23.3% using endobronchial ultrasound plus fine needle aspiration. In 98.3% cases adequate material was obtained and diagnosis with pathology was made. 70% of diagnostic procedures determined malignancy. 84% of diagnoses were done with biopsy and 16% with liquid–based cytology and cell block.

Conclusion: ROSE technique allows us to obtain viable and sufficient material for the diagnosis and complementary studies of molecular pathology. Within our Pulmonology and Lung Pathology Units, we establish the histopathological diagnosis with immunohistochemistry in a mean time between 24 and 36 hours, and with molecular pathology in one week, improving the opportunity for clinical decision–making.

In our experience, the implementation of diagnostic procedures in pulmonology with ROSE technique brings clear advantages: it improves the quality of services focused on the patient, facilitates handling and performance of the samples, provides fast provisional diagnoses and guarantees molecular pathology studies. Its disadvantage is centered in the necessity of additional training and learning curve of interpretation, as well as implementation of multidisciplinary groups with team–work ability to achieve the expected goals.

Keywords: cytopathology, ROSE

P2.19 (also presented as PD1.04): INFREQUENT STAINING PATTERNS IN ALK IMMUNOHISTOCHEMISTRY: CORRELATION WITH FISH ANALYSIS

Track: Pathology

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Background: ALK gene rearrangements are infrequent alterations in lung cancer and are present in 3–5% of non small cell lung carcinomas (NSCLC). ALK status is an important predictive factor in NSCLC, as ALK rearranged tumors have shown sensitivity to
Method: We correlated immunohistochemistry unusual staining patterns with ALK status by fluorescence in situ hybridization (FISH).

Results: Of 10 moderate granular cytoplasmic atypical cases, 4 had abundant mucin basement membrane in 6 with markedly heterogeneous and areas of weak and moderate cytoplasmic granular tumor. Nine were FISH negative, one yielded no signals (uninformative results) and one specimen corresponded to an acid decalcified specimen and was not evaluated by FISH. Focal intense stain was observed in 5 samples. 3 corresponded to surgical specimens and the rest to small needle biopsies, one of the surgical specimens was FISH positive and the rest, negative.

Conclusion: Since the approval of Ventana ALK (D5F3) IHC CDx Assay by FDA, IHC has become a widely used tool for assessing ALK status. Guidelines suggest that weak to moderate granular stain should be interpreted as negative and focal intense granular stain in any number of cells, as positive. Even though our sample is small, moderate granular stain was consistently negative by FISH analysis, however, focal intense stain shows more discordant results between tests. No suggestions are made on what should be the minimum amount of tumor in a sample to report an IHC assay. Interestingly we didn’t find rearrangements on small samples with focal intense IHC positivity and the only FISH positive case was a surgical specimen with focal intense stain. Even though some of these patients with IHC positive/FISH negative results have been reported as responders to Crizotinib, further studies are needed. Lastly, one specimen with moderate cytoplasmic IHC stain was uninformative due to lack of signals and one case was a decalcified tissue. This raises the issue of the need to standardize preanalytical variables, which can be difficult in some areas of Latin America.

Keywords: non small cell lung carcinoma, fish, ALK, immunohistochemistry
LALCA 2.21: ENDOBRONCHIAL ULTRASOUND TRANSBRONCHIAL NEEDLE ASPIRATION (EBUS-TBNA) EXPERIENCE IN A REFERENCE HOSPITAL IN LATIN AMERICA

**Track:** Bronchoscopy

**Liliana Fernandez, Luz F. Sua, Mauricio Velasquez, Aura Sanchez, Leidys Gutiérrez**

**Biomedical Research Group in Thorax, Fundación Valle del Lili, Universidad Icesi, Cali/COLOMBIA**

**Background:** EBUS-TBNA is a minimally invasive, cost-efficient and well-tolerated technique, which permits visualization of adjacent structures in the central airway via real-time ultrasound. Visualized images enable guided sampling of mediastinal and hilar structures. Indications include diagnosis, staging and re-staging of lung cancer, mediastinal assessment of metastatic lesions and study of non-malignant infectious and non-infectious lesions. It requires an initial evaluation from a multidisciplinary approach that includes patient’s general state, medical history analysis and images in order to evaluate risks and benefits of the procedure. A team-work with pathology is also necessary, undertaking an immediate evaluation in the room (ROSE) to improve the diagnostic performance.

**Method:** Descriptive, prospective study conducted between May-2012 and January-2015. EBUS-TBNA indications were: staging of lung tumors, diagnosis of lung or mediastinal masses, study of disturbances in lymph nodes detected in CT or PET/CT, re-staging of lung cancer and mediastinal evaluation of patients with limitations interfering execution of other invasive procedures. Lymph nodes bigger than 1cm were studied. 72 patients were intervened within the endoscopy room under deep sedation and anesthetic monitoring. The device implemented was Olympus® bronchoscope+US probe+22G FNA.

**Results:** Optimal quality and representation of the lesion was obtained in 70 (97.2%) samples. 60 (85.7%) cases were diagnosed as malignant: 50% adenocarcinomas and 20% squamous cell cancer. 83% of Diff-Quick smears represented the lesion. Five samples for nodal stage or tumoral lesion were taken. Immunohistochemistry and extraction of DNA from cellblocks was performing to study EGRF gene mutation and re-arrays of EML4-ALK gene. 8% of the series was taken to mediastinoscopy.

**Conclusion:** In our context, EBUS-TBNA is an efficient procedure to study mediastinal, paratracheal and peribronchial lesions and staging of lung cancer similarly to world-class medical literature reports. We presented the experience within Fundación Valle del Lili, a reference center in Latin America. The role of EBUS-TBNA in clinical practice goes beyond its usefulness, security and cost-effectiveness as a diagnostic tool. As it has the potential to detect early-stage lung tumors, it gives patients the possibility to be treated adequately earlier, opening the window for a better prognosis and life-quality despite an overwhelming diagnosis.

**Keywords:** bronchoscopy, endobronchial ultrasound

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LALCA 2.22: THERAPEUTIC BRONCHOSCOPY IN MULTIMODAL THERAPY FOR THE MANAGEMENT OF CENTRAL AIRWAY OBSTRUCTION IN LATIN AMERICA

**Track:** Bronchoscopy

**Liliana Fernandez, Luz F. Sua, Mauricio Velasquez, Leidys Gutiérrez**

**Biomedical Research Group in Thorax, Fundación Valle del Lili, Universidad Icesi, Cali/COLOMBIA**

**Background:** Central airway obstruction may be due to malignant and non-malignant causes. The most common is lung cancer. Usually, patients present with cough and dyspnea that can progress to respiratory failure. Therapy should be oriented to secure and restore the airway. Best technique choice depends on etiology, type and severity of lesion, technological availability and operator skill. Nowadays, a multimodal therapy is implemented, including different intervention methods for the management of these patients. We aimed to describe the experience with therapeutic flexible bronchoscopy in FVL.

**Method:** A descriptive retrospective study was conducted between Feb-2013 and Dec-2015. 70 procedures were performed in 62 patients.
patients. Symptoms, etiology, localization, severity, diagnosis, type of anesthesia, interventions and complications were analyzed. The device was a therapeutic flexible bronchoscope Olympus® and specific intervention instruments.

**Results:** Patients’ mean age was 53.4 (19-88) years old. 25 (35.7%) were women and 45 (64.2%) were men. Malignant lesions were found in 46 (65.7%) cases. More frequent symptoms were cough (95%), dyspnea (70%), chest pain (34.2%) and hemoptysis (31.4%). General anesthesia was used in 67 (95.7%) cases: 37 (55.2%) laryngeal mask and 30 (44.7%) endotracheal tube. 70% patients had severe airway obstruction and 30% moderate. 84.5% had an endobronchial mass and 35.7% external compression. Decreasing frequency of lesion location was: right-stem bronchi (38.5%), trachea (35.7%), left-stem bronqui (31.4%) and carina (17.1%). Most common malignant etiology was lung cancer (58.6%), followed by carcinoid tumor (13%) and sarcoma (10.8%). Benign etiology (34.8%) included granuloma (33%), stenosis (29.1%) and foreign bodies (20.8%). Procedures were debridement (82.8%), electrocautery (81.4%), argon plasma (41.4%), stent colocation (7.1%), balloon dilatation (8.6%) and since Oct-2015 cryoprobe for airway recanalization (11.4%). Obstruction resolution was complete for 58.7% cases and partial for 41.4%. Complications included mild hemoptysis in one case and scaling in the attention room in two patients. No reported deaths associated with the procedure.

**Conclusion:** Central airway obstruction is a complex situation that requires multidisciplinary approach. Currently, multimodal therapy is recommended combining different options of intervention, like flexible or rigid bronchoscopy, to achieve optimal results. We presented our experience in multimodal therapy using therapeutic flexible bronchoscopy.

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**Keywords:** Therapeutic bronchoscopy, central airway obstruction

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**P2.23:** EFFECTIVENESS OF METHYLNALTREXONE BROMIDE AS A TREATMENT FOR OPIOID-INDUCED CONSTIPATION IN NSCLC PATIENTS

**Track:** Supportive Care and Others

Ioannis A. Dimitroulis, Panagiota Stamou, Adamantia Liapikou, Michail Toumbis

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**Background:** Methylnaltrexone Bromide (MB) is a selective antagonist of opioid binding at the μ-receptor (μ or MOR receptor). Constipation is a quite common side effect in Non-Small-Cell–Lung–Cancer (NSCLC) patients receiving opioids for chronic pain, usually due to skeletal metastases. We set out to investigate if MB is effective in those patients who received opioids and complained of constipation.

**Method:** Forty six NSCLC patients with a life expectancy of at least three months were recruited for our study after providing written consent. All patients received either fentanyl as a transdermal patch, in its inhaled form or per os. Patients were randomized (1:1) to four weeks of treatment with either MB 12mg/0.6ml (n=22) administered subcutaneously (sc) or a placebo, on alternate days. We recorded the number of patients who defecated within four hours of the MB or placebo injection, and the number of patients needing a second dose of MB or placebo within six hours from the first dose. We recorded the side effects of this treatment. Patients were not allowed to use other laxatives.

**Results:** In the MB group after one injection, thirty five patients (76%) had a bowel movement within four hours compared with six placebo patients (13%), p=0.02. Ten patients in the MB group had a bowel movement after two or more doses of MB, raising the percentage of patients who responded to MB to 98%. The more severe the constipation, the higher the response with MB. The overall rate of adverse events was similar in the MB (42%) and placebo groups (41%). In the MB group, the most commonly reported adverse events were abdominal pain (17%), flatulence (16%), vomiting (10%), and nausea (13%). Most treatment related
adverse events were rated as mild or moderate by the patients. Discontinuation due to adverse events occurred in 5% and 6% of patients in the MB and placebo groups, respectively.

**Conclusion:** Methylnaltrexone Bromide has been shown to be superior to placebo in achieving defecation within a short time, in NSCLC patients with opioid–induced constipation. The more severe the constipation, the higher the response with MB. There were no serious adverse events. We conclude that Methylnaltrexone Bromide is effective and safe.

**Keywords:** Methylnaltrexone Bromide, opioids, constipation, Non-small Cell Lung Cancer

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**P2.24: PULMONARY–EPITHELIOID HEMANGIOENDOTHELIOMA: A CASE REPORT OF SPONTANEOUS REGRESSION**

**Track:** Supportive Care and Others

Raquel Rojas–Vigott, Cinthya Monge Castro, Steffi Romero Méndez

**Oncology, CCSS, San José/COSTA RICA**

**Background:** The epithelioid hemangioendothelioma is a rare endothelial tumor, that was described for the first time, in 1982 by Weiss and Ezinger. Liver, Lungs and soft tissues are the most frequent affected organs. Its clinical behavior is unpredictable. We discussed a case who presented this diagnosis, with the particularity of spontaneous regression.

**Method:** Review and follow up and tracing of a clinical case. Descriptive clinical study.

**Results:** We analyze the case of a 47 years old male. He had no co-morbid background. He was a smoker but suspended the habit 25 years ago. In January 2012, he came to medical consultation with history of dyspnea, chest pain and cough. X-ray showed a lung mass in left hemithorax. Consolidative process in superior lingular segment (8x6x8 cm) with concomitant nodules in superior segment of left inferior lobule were evident on the CT. In biopsies taken by bronchoscopy, it is shown parenchymal lung with heterogeneous lymphoid cells with multiple macrophages with antracosis (reactive lymphadenitis) and immunohistochemistry describing is immunoreactive for CD31, CD34 and factor VII, compatible with the diagnosis of epithelioid hemangioendothelioma. Initially, it is proposed to perform surgical management (likely pneumonectomy). The patient decided to take a while because he was undecided, and surprisingly, in the next consultation (4–5 months later) symptoms begin to sag and images showed remarkable improvement with the passage of time, and without any medical intervention. By improving, the patient decides to keep under observation, and nowadays, 4 years since the diagnosis, he maintains complete response and no symptoms, and he is having an excellent health.

**Conclusion:** The epithelioid hemangioendothelioma, is a rare vascular tumor that can arise from lungs, liver and soft tissue. Lung location corresponds to 19% of those affected. It’s more common in women than men (3:1) with a prevalence of 1/100000. Spontaneous regression has been described previously.

**Keywords:** Lung, Epithelioid, Hemangioendothelioma, regression

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**P2.26: REFERENCE TO PALLIATIVE CARE IN PATIENTS WITH ADVANCED LUNG CANCER TREATED WITH SYSTEMIC THERAPY. ION, PANAMA**

**Track:** Supportive Care and Others

Erik Arauz, Joel Moreno–Ríos, Jose Pinto Llerena, Taysser Sowley

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**Background:** Most of the patients with lung cancer are diagnosed with metastatic disease and high tumor burden with symptoms that impacts negatively in the quality of life of patients and the caregivers. There is evidence that early reference to palliative care improves quality of life, reduces costs and also less aggressive treatment at the end of life with longer survival.

**Method:** We performed a retrospective review of patients with advanced lung cancer treated with systemic therapy between 2014-2015. The primary objective was to determine the proportion of patients that were referred to palliative care, the average reference time from the start of treatment and the clinical characteristics that were associated with overall survival.

**Results:** 157 clinical records were reviewed. Median age was 65 years old. 54.1% men and 45.9% women. 113 (72%) had died at the time of the analysis. 91.8% lives with a relative and 9.2 % alone. ECOG 0–2 97.1 % and only 2.9 % had ECOG 3. 76.4% received chemotherapy only as systemic therapy. 113/157 (72%) were evaluated by the palliative care team. In the group of patients that already died, 19.5% was never evaluated by palliative care. All patients were referred for symptoms control; 67% for pain and 28% dyspnea. The first assessment of palliative care was 70% outpatient, 27.4% hospitalized and 2.6% in the emergency room. Median time from systemic treatment to request evaluation by palliative care team was 75.6 months (0–52.0 months). Median time from first evaluation by palliative care to dead was 3.6 months. Median OS for all patients was 15.1 months (9.1–19.1 months). Median Univariate analysis reported statistically significant worst overall survival in patients with ECOG 2–3 vs 0–1 (p=0.002) systemic therapy in the last month of life (median, 4.7 months vs 17.9 months, p < 0.001), smoking history (median, 10.1 months vs 17.9 months, p<0.05) and those that were evaluated in the emergency room (p<0.05).

**Conclusion:** Although actual evidence suggest that early referral to palliative care improves outcomes in patients, 19.5% of the patients that died, were never seen by the palliative care team. The time to the first evaluation is belated with a median of 7.5 months. Those patients who received systemic therapy in the last month of life had the worst survival.

**Keywords:** early palliative care, palliative care, Advanced lung cancer, Systemic Therapy
**P2.27: BLOOD SUPPLEMENT RESEARCH OF THE PERCUTANEOUS INOCULATED CANINE TRANSMISSIBLE VENEREAL TUMOR LUNG CANCER MODEL**

**Track: Supportive Care and Others**

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**Background:** Based on reported canine transmissible venereal tumor (CTVT) model, we developed an improved CTVT lung model and furthermore evaluated blood supplement of this tumor model.

**Method:** According to lung CT designed plan of percutaneous inoculation zone, 16G guiding needle was advanced into appropriate location. Two fresh CTVT tumor fragments (2.0mm) was transmitted into lung parenchyma directly. All six beagles were followed up by CT scan. After ten weeks, all six beagles underwent sequentially bronchial artery digital subtraction angiography (BA-DSA), bronchial arteries CT(BA-CT) and trans-pulmonary arterial Lipiodol CT which CT scanned after pulmonary artery were embolized with Lipiodol.

**Results:** The technical success rate of improved CTVT lung model achieved 100%(6/6). Maximum diameters of tumor growth in different time were recorded on Table 1. Total 25 nodules were found in all the beagle lungs. 9 nodules were in left lungs versus 16 in right. The typical case was shown on Figure 1. For 14 nodules larger than 2cm, imaging showed visible dilated bronchial artery leading to the tumor direction on the BA-DSA (Figure 2, limitation of abstract). In these beagles which pulmonary arteries were embolized with Lipiodol, two lesions (<1cm) were displayed with Lipiodol deposition, while a droplet-shaped Lipiodol deposition can be seen in one nodule over 2cm(Figure 3, limitation of abstract).

**Table 1**

<table>
<thead>
<tr>
<th>Maximum diameters of CTVT tumor growth</th>
<th>6 weeks</th>
<th>8 weeks</th>
<th>10 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Diameter (cm)</td>
<td>1.716±0.102</td>
<td>2.392±0.076</td>
<td>2.734±0.138</td>
</tr>
</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Number of different size lung tumors on BA-DSA and BA-MSCT</th>
<th>number</th>
<th>supplement on BA-DSA</th>
<th>supplement on BA-CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor diameter(cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1cm</td>
<td>6</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>1.0cm≤N&lt;2.0cm</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>≥2.0cm</td>
<td>14</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

**Conclusion:** It is found that tumor blood supplement is related to tumor size in CTVT lung tumor model. The bigger the tumor size was, the greater likelihood of bronchial artery was. The closer centrally located, the more likely supplied by bronchial artery. This improved model can also be used for evaluation of outcomes about various therapy methods and precision treatment.

**Keyword:** bronchial artery, blood supply, lung tumor, canine transmissible venereal tumor (CTVT)

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**P2.28: IMAGE-GUIDED RADIOFREQUENCY ABLATION OF LUNG METASTASES. A SINGLE CANCER CENTER EXPERIENCE IN PANAMA**

**Track: Supportive Care and Others**

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**Background:** Pulmonary metastatic lesions are present in 20–54% of all patients who die of cancer. Surgical studies have shown that local management of distant tumor metastasis as part of multimodal cancer therapy improves survival. Image-guided percutaneous radiofrequency ablation (RFA) has been proposed as an efficacious local therapy for lung metastases in nonsurgical candidates. Minimally invasive procedures are still to prove their clinical relevance.

**Method:** We performed a retrospective review of patients treated with RFA between 2013 and 2016. Demographic, clinical, therapeutic and prognostic variable were studied. Progression free survival was evaluated using Kaplan Meier method.

**Results:** We analyzed 20 patients, 10 men and 10 women. Median age 63 years old. ECOG 0 in 9 patients and ECOG 1 in 11 patients. 30% Colon Cancer, 25% rectal cancer, 15% Head and Neck Cancer were most common primary sites. 65% with less than 2 lesions. 45% chemotherapy, 40% chemo radiotherapy, 10% radiotherapy and 5%
% surgery were received as previous treatment. 85 % without extra pulmonary metastases. Median size of lesions was 20 mm. Median time from diagnosis to procedure was 29 months. 75 % overall respond to RFA and 15 % died. Response Rate was 57.6 %, 31.6% complete response, 26 % partial response, 31.6% stable disease and 10.5% progression were registered. 30 % Complication rate, 3 patients with pneumothorax, 2 pleural pain, 1 pleural effusion, 1 empyema and 1 cardiac arrest. Median PFS was 10 months.

**Conclusion:** RFA ablation is an effective treatment with an acceptable rate of complications supporting its incorporation into management of lung metastases for purpose of cure, stabilization and disease prolongation

**Keyword:** radiofrequency ablation, lung metastases, ablation therapy, lung

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**P2.29: AN APPROACH TO ENSURE ADEQUATE INTAKE OF NUTRIENTS FOR PATIENTS WITH LUNG CANCER**

**Track:** Supportive Care and Others

**Julissa Luvian-Morales, Martha De La Torre-Vallejo, Ana Gonzalez-Ling, Oscar Arrieta**

**Unidad Funcional De Oncologia Torácica, Instituto Nacional De Cancerologia, México/MÉXICO**

**Background:** Malnutrition is found in up to 80% of patients with advanced cancer. Several factors contribute to develop a catabolic state, such as those associated to the disease itself, low physical activity, energy and protein intake and systemic inflammation. Malnutrition has a negative impact on many aspects of Health-Related Quality of Life, treatment compliance and prognosis. International guidelines (ASPEN, ESPEN) give recommendations about protein and energy intake for cancer patients. However, patients with lung cancer (LC) often develop appetite loss, and treatment related gastrointestinal toxicities which affect their capability to have a proper nutrient intake. There are few studies that describe nutrient intake in patients with LC, moreover it is not fully described if meeting these recommendations have an impact on clinical outcomes. The aim of this study is to describe the nutrient intake of patients with LC.

**Method:** Patients diagnosed with advanced stage LC were evaluated. Nutrient intake was assessed by a food frequency questionnaire (SNUIT) validated for Mexican population; energy and protein intake were adjusted by patient weight.

**Results:** One hundred forty-four patients were included, 56.8% were female, 10.4% mean age was 61.7±12.6 years, 10.4% without any line of treatment, 63.2% were in second line of treatment. According to the body mass index (BMI), 8.3% were underweight, 51.4% had normal weight, and 40.3% were overweight or obese. Cachexia, defined as weight loss ≥10% in 6 months or ≥5% in a month, was found on 26.4% patients. As shown in Table 1, most Recommended Daily Allowance (RDA) were not met. Patients with more than 2 lines of treatment was associated with lower energy intake (<20kcal/kg of weight, p=0.049) and lower protein intake (<0.8g/kg of weight, p=0.19); there was not association with mean age, sex, functional status (ECOG) or nutritional status (subjective global assessment).

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>RDA</th>
<th>Lung cancer patients intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy intake (kcal/kg)</td>
<td>30−40</td>
<td>26.6 (19.7−33.2)</td>
</tr>
<tr>
<td>Protein intake (g/kg)</td>
<td>1−2.5</td>
<td>0.95 ± 0.39</td>
</tr>
<tr>
<td>Carbohydrates intake (%)</td>
<td>55</td>
<td>54.8 ± 8.7</td>
</tr>
<tr>
<td>Protein intake (%)</td>
<td>15</td>
<td>13.9 ± 2.6</td>
</tr>
<tr>
<td>Fat intake (%)</td>
<td>25</td>
<td>33.1 ± 7.4</td>
</tr>
<tr>
<td>Zinc intake (mg/day)</td>
<td>15</td>
<td>12.9± (7.73−19.39)</td>
</tr>
<tr>
<td>Iron intake (mg/day)</td>
<td>10</td>
<td>10.4 (7.52−12.11)</td>
</tr>
<tr>
<td>Vitamin B1 intake (mg/day)</td>
<td>2</td>
<td>1.53 (1.11−1.81)</td>
</tr>
<tr>
<td>Vitamin B6 intake (µg/day)</td>
<td>2</td>
<td>4.07 (2.26−6.0)</td>
</tr>
</tbody>
</table>

Mean ± SD; median (p25−p75)

**Conclusion:** Due to high symptomatic burden it is difficult for most patients with LC to comply with RDA. Therefore, it is important to timely assess patients’ dietary and nutritional status in order to address possible deficiencies along treatment. Further research about nutrient intake and the impact on clinical outcomes is needed.

**Keywords:** nutrient intake, Recommended Daily Allowance, advanced, malnutrition

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**P2.33: UNDERSTANDING FACTORS INFLUENCING SELF-REFERRAL OF PATIENTS FROM RESOURCE-LIMITED INSTITUTIONS SEEKING LUNG CANCER CARE**

**Track:** Supportive Care and Others

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**Background:** Patterns of lung cancer care have significant regional variation. Treatment rates of lung cancer are lower in resource-limited areas. In these settings, some individuals refer themselves to a different facility than the one they were initially diagnosed, seeking lung cancer care. To date, little is known about factors associated with this self-referral of patients from resource-limited institutions and its impact in lung cancer care and outcomes. To gain insight, we investigated factors associated with self-referral of patients in a rural region in Western Kentucky, USA.

**Method:** We focused on an area that does not have proximity to a major regional medical center (nearest major center > 70 miles away). The area encompasses 3 medical centers: A (180 beds); B (211 beds) and C (285 beds). All three institutions had surgical, radiation and medical oncology services. We identified 1806 patients who were diagnosed with lung cancer between January 1, 2006 and December 31, 2011 (Hospital A, 221 cases; Hospital B, 217 cases; Hospital C 1368 cases). Data on initial diagnosis site, cancer treatment information, patient self-referral, and survival information was obtained from each hospital cancer registry. Treatment receipt, migration and survival data was cross-referenced by each individual hospital registry with the central SEER–cancer registry data. Patient data included in the analysis were age, race,
sex, insurance, and stage at diagnosis. County level data included socioeconomic status (% of population below poverty line), median income, and education. Hazard ratios are constructed to assess survival stratified by source hospital. Relative risks were constructed to identify patterns of migration. SAS version 9.4 (SAS Institute, Cary, NC USA) was used for the analyses and a significance level was set at p≤0.05.

Results: Self-referral occurred from centers A and B to center C for 120 of 304 untreated patients. Lower rates of self-referral were associated with stage IV at diagnosis (RR = 0.34, 95% CI = 0.23-0.51, p = 0.001), female gender (RR = 0.52, 95% CI = 0.35-0.76, p = 0.001), and lower median income (-$10,000: RR = 0.60, 95% CI = 0.41-0.86, p = 0.006. Older age at diagnosis (p = 0.98), race (p = 0.25), insurance (p = 0.83), level of education (p = 0.97), and socioeconomic status (p = 0.28) were not associated with self-referral. Importantly, nearly every patient who self-referred to a different institution received treatment (n = 116, 97%). Survival was significantly improved among those who self-referred (HR = 0.54, 95% CI = 0.41-0.72, p = 0.001).

Conclusion: Late stage at diagnosis, female gender, and lower median income are associated with lower rates of self-referral to a different institution seeking lung cancer care. Other socioeconomic and demographic parameters do not influence willingness to travel for treatment. When self-referral to a facility with higher capabilities occurred, treatment receipt was more likely and survival was improved.

Keyword: Disparities, lung cancer, undertreatment, self-referral

P2.32: SURVIVAL ASSESSMENT OF NON–SMALL CELL LUNG NEOPLASIA PATIENTS IN ADVANCED STAGE TREATED WITH THE CIMAVAX-EGF VACCINE

Track: Immunotherapy

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Background: In 1995 began the clinical development of the therapeutic vaccine CIMAVx-EGF. That stage commenced with the carry out of the first clinical essay phase: I/II (denominated Pilot 1) in the Centro de Investigaciones Médico Quirúrgicas (CIMEQ) [La Habana, Cuba]. The results of that first clinical essay established the first published scientific evidence where was demonstrated the feasibility of inducing an immune response against the EGF autologous, in patients affected by different advanced tumors. Furthermore, in this study the P64K protein was confirmed as the optimum immunopotentiator to combine with the EGF and to conform the CIMAvax-EGF formulation.

Method: A descriptive and longitudinal study was conducted, in a first and second moment an analytic cohort study, executed in the Hospital Provincial “Saturnino Lora”, and in four polyclinic centers in Santiago De Cuba City, in a period between 2006-2013, in non-small cells lungs neoplasia patients, treated with the CIMAVx-EGF vaccine, with the purpose of estimate the afflicted demography according to interest variables and to identify the factors associated with mortality. The study sample was composed by 95 patients. The survival analysis was undertaken according to the Kaplan–Meier method, along with the Cox regression for the data analysis.

Results: The overall survival rate, over two years, was 20.7%, with a median survival of 13 months. The survival rate with the use of the vaccine and progression free survival rate was of 36.5% and 30.5%, respectively. The stage IIIIB, positive response to the first-line treatment, receiving the chemotherapy-radiotherapy-vaccine combination and being immunized up to four times, led to a significant higher survival rate. The findings demonstrated that the survival rate in advanced stages continues to be inferior than expected.

Conclusion: The histological epidermoid carcinoma subtype could not be associated with a better respond to the vaccine. The unfavorable response to the first-line treatment constituted a predictor of the increasing risk of death among the sized population.

Keyword: Lung neoplasia, CIMAvax-EGF vaccine, survival.

P2.33: SAFETY PROFILE OF NIVOLUMAB ADMINISTERED AS 30-MINUTE (MIN) INFUSION: ANALYSIS OF DATA FROM CHECKMATE 153

Track: Immunotherapy

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Background: Nivolumab, a programmed death-1 (PD-1) immune checkpoint inhibitor, is approved in the US for previously treated metastatic NSCLC and renal cell carcinoma, and for advanced melanoma, as well as classical Hodgkin lymphoma, and in the EU for previously treated squamous NSCLC and advanced melanoma. Here, we assess the impact of infusion time on nivolumab safety from an ongoing, predominantly community-based trial.

Method: Patients who progressed during or after receiving ≥2 prior therapy were enrolled. The primary outcome of this study is incidence of grade (gr) 3–4 and 5 and select treatment-related adverse events (TRAEs). Patients received nivolumab 3 mg/kg IV Q2W; infusion time was shortened from 60 min to 30 min following previously treated squamous NSCLC and advanced melanoma. Here, we assess the impact of infusion time on nivolumab safety from an ongoing, predominantly community-based trial.

Method: Patients who progressed during or after receiving ≥2 prior therapy were enrolled. The primary outcome of this study is incidence of grade (gr) 3–4 and 5 and select treatment-related adverse events (TRAEs). Patients received nivolumab 3 mg/kg IV Q2W; infusion time was shortened from 60 min to 30 min following an amendment to the study protocol. A comparison of toxicities by infusion time is reported in this analysis. Data for the overall population and elderly/poor performance status patient subgroups are presented in separate abstracts.

Results: A total of 322 and 355 patients, respectively, received nivolumab by 30-min or 60-min infusion; demographics for these patients are comparable to the overall population (median follow-up, 6 mo). Any gr (gr 3–4) TRAEs occurred in 53% (11) and 51% (12) of patients with 30-min or 60-min infusions, respectively. Gr 3–4 select AEs in ≥2% of patients given 30-min or 60-min infusions occurred in pulmonary (3% and 2%), hepatic (2% and 3%), and gastrointestinal (2% and 2%) categories. Any gr (gr 3–4) infusion reaction occurred in 3% and 2% (<1% and <1%) of patients given 30-min or 60-min infusions, respectively (Table). Additional data by infusion time for this subgroup will be presented, including safety
Conclusion: Nivolumab 3 mg/kg can be safely infused over 30 min, with a safety profile comparable to 60-min infusion and with a low incidence of infusion-related reactions. Clinical trials registration: NCT02066636 Reused with permission from the American Society of Clinical Oncology (ASCO). This abstract was accepted and previously presented at the 2016 ASCO Annual Meeting. All rights reserved.

P2.34: VAXIRA AND CIMAVAX-EGF THERAPEUTIC VACCINES COMBINATION IN THE ADVANCED NSCLC TREATMENT

Track: Immunotherapy

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Background: Combining cancer vaccines with different anticancer therapies such as chemotherapy, radiotherapy and other immunotherapeutic agents has had different levels of success. However, the combination of cancer vaccines with different mechanisms of action has not been explored in clinical trials. The main clinical and immunological results obtained with two different therapeutic vaccines used in advanced non-small-cell lung cancer patients, inducing an immune response against epidermal growth factor (CIMAvax-EGF) and NeuGcGM3 ganglioside (Vaxira) was explored.

Method: An exploratory phase I study was conducted to assess the feasibility of combining Vaxira and CIMAvax-EGF vaccines used in advanced NSCLC patients and determine the effect on humoral immune responses. Twenty patients with histological confirmed NSCLC stages IIB/IV were treated after progression to the standard first line cisplatin /doublet compound therapy according the treatment established in the Oncology Therapeutic Guidelines (NCCN v.04, 2016). The vaccination schedule consisted in the administration of 1mg of Vaxira by intradermic route. The first 5 doses every 14 days and the rest every 28 days concomitantly CIMAvax-EGF vaccine 0.6 mg by intramuscular route, the first 4 doses every 14 days and the rest every 28 days. Both vaccines were administered until unmanageable toxicity or patients worsening performance status. Humoral immune responses against Racotumomab anti–idiotype Mab, NeuGcGM3, EGF antigen, EGF serum levels and inhibition binding assay against EGF were measured by standard ELISA assays, induction of cell cytotoxicity in NeuGcGM3 positive expression cell lines by specific NeuGcGM3 antibodies (IgM and IgG) were measured by flow cytometry analyses (FACS).and cell-cytotoxicity assay.

Results: The distribution by clinical stage at inclusion was: 9 in stage IIB, 11 in stage IV all in progression disease. The vaccines combination antitumor responses were evaluated according the RECIST Criteria, and 50% of evaluable patients achieved partial response (PR) after 12 months of vaccination (long lasting anti–tumor response). The 20 patients (ITT) were included in an evaluation of survival (Kaplan Meier estimate), after a follow up of at least 12 months. Median survival was 6, 7 months. The combination was safe. Only mild adverse events, mainly characterized by injections site reactions, were reported. Higher antibody titers against EGF were obtained in comparison with previous CIMAvax-EGF clinical trials. All patients were classified as GAR (good antibody responder). Complete reduction in circulating EGF was obtained 2 months after vaccination. 80% of EGFR phosphorylation inhibition was obtained at month 5. Immunogenicity of racotumomab as well. anti-idiotype response was significantly higher compared with the maximum titers obtained in previous Vaxira lung cancer trials. The magnitude of anti–Neu GcGM3 antibody response and the capacity to kill ganglioside–positive tumor cell lines were equivalent to the data reported with this vaccine in previous studies.

Conclusion: The combination of Vaxira and CIMAvax-EGF vaccines has an acceptable safety profile. The present data suggest that the combination improve the humoral immune response induced by both vaccine and benefit the outcome of first line-refractory advanced NSCLC patients. A Phase II/III vaccine combination clinical trial in NSCLC advanced patients unsuitable to receive first line chemotherapy treatment is ongoing.

Keywords: combination therapy, therapeutic vaccines, NSCLC, target therapy

P2.35: NIVOLUMAB VS DOCETAXEL IN ADVANCED NSCLC: CHECKMATE 017/057 2-Y UPDATE AND EXPLORATORY CYTOKINE PROFILE ANALYSIS

Track: Immunotherapy

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Background: Nivolumab (nivo), a fully human IgG4 programmed death-1 immune checkpoint inhibitor, is approved in the US for patients (pts) with previously treated metastatic NSCLC and in the EU for pretreated locally advanced or metastatic squamous (SQ) NSCLC, based on results of 2 ph III trials.

Method: Pts with SQ (CheckMate 017) or non–squamous (NSQ; CheckMate 057) NSCLC received nivo 3 mg/kg Q3W or docetaxel (doc) 75 mg/m² Q3W (1:1 randomization) until progression or...
Background: CNS mets occur in 20%-40% of pts with adv NSCLC and are associated with poor overall survival (OS; median ~7 mo). We evaluated nivo in this subgroup by: 1) pooling nivo-treated pts with adv NSCLC and pretx (pretx) stable CNS mets at baseline (BL) across CheckMate 063 (phase [ph] II), 017 (ph III), and 057 (ph III); and 2) comparing OS with nivo vs docetaxel (doc) in pts with stable BL CNS mets in CheckMate 017 and 057.

Method: 1) Nivo-treated pts with adv NSCLC and pretx BL CNS mets from CheckMate 063 (n=3), 017 (n=9), and 057 (n=34) were pooled to assess BL characteristics, safety, and CNS progression. 2) OS was analyzed in pts with pretx BL CNS mets and squamous (SQ; CheckMate 017) or non-SQ (NSQ; CheckMate 057) NSCLC treated with nivo 3 mg/kg Q2W vs doc 75 mg/m² Q3W.

Results: Of 46 nivo-assigned pts with pretx CNS mets, 74% had prior CNS-site radiotherapy and 85% had ≥2 extra-CNS sites of mets. Median follow-up was 8.4 mo (range: 0.3-23.4); median treatment duration (n=45; 1 pt not treated) was 2.3 mo (range: 0.05-23.3). Any grade (gr) treatment-related (TR) adverse events (AEs) occurred in 67% of pts; gr 3-4 TRAEs occurred in 7%, with no TR deaths. CNS TRAEs occurred in 5 pts (11%) and were all gr 1-2 (paresthesia, n=2; dizziness, somnolence, and tremor, n=1 each). At median follow-up of 8.4 mo (range: 0.3, 23.4), median OS with nivo (n=34) vs doc (n=34) was 7.61 mo vs 7.33 mo (P=0.03, 23.3). Any grade (gr) treatment-related (TR) adverse events (AEs) occurred in 67% of pts; gr 3-4 TRAEs occurred in 7%, with no TR deaths. CNS TRAEs occurred in 5 pts (11%) and were all gr 1-2 (paresthesia, n=2; dizziness, somnolence, and tremor, n=1 each). At time of overall disease progression (PD) or last tumor assessment, 33% of pts had no evidence of CNS progression (stable/decreased CNS lesions) and 52% had unequivocal progression in the CNS (15% had no post-BL CNS assessment). In pts with pretx CNS mets from CheckMate 017, median OS (events; n; HR) with nivo (n=9) vs doc (n=8) was 4.99 mo vs 3.86 mo (6 vs 8; not determined); in CheckMate 057, median OS with nivo (n=34) vs doc (n=34) was 7.61 mo vs 7.33 mo (30 vs 27; 10.45; 95% CI: 0.62, 1.78).

Conclusion: Nivo was well-tolerated in pts with adv NSCLC and pretx CNS mets, with generally low-grade toxicities. One-third of pts had no evidence of CNS progression at time of PD/last assessment. In pts with SQ and NSQ NSCLC with pretx CNS mets, median OS was similar with nivo vs doc. Additional results (including OS and CNS progression rates in pts with/without pretx CNS mets and safety/efficacy of nivo in pts with untreated BL CNS mets from CheckMate 017) will be presented.
**P2.37: A CASE OF IMMUNE–MEDIATED PNEUMONITIS?**

**Track: Immunotherapy**

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**Background:** Immunotherapy is an effective strategy in the treatment of advanced non–small cell lung cancer. Its associated toxicities are diverse and different from those of chemotherapy, so patients and clinicians should be alert for early signs and symptoms.

**Method:** Review and report a case of a female patient with lung adenocarcinoma EGFR exon 20 and PD-L1 expression positive that underwent 3rd line of treatment with nivolumab, with clinical and radiological deterioration and progression to ARDS after the second administration of immunotherapy.

**Results:** CAMR, female gender, 72 years old, passive smoker. History of hypertension and osteoarticular disorder. The patient presented with a 4–month history of exertional dyspnea, dry cough, anorexia and weight loss. The thoracoabdominal CT scan showed bilateral pulmonary infiltrates with multiple confluent nodules and consolidation of the left upper lobe; bronchofibroscopy revealed generalized inflammatory signs, cytology of the bronchoalveolar lavage was positive for adenocarcinoma, CK20–, CK7 +, TTF1 +, EGFR exon 20 mutation positive. Due to osteoarticular pain a bone scan was performed and confirmed multiple bone metastasis.

First line platinum–doublet chemotherapy was initiated with partial response and the patient completed 3 maintenance cycles. Disease progression was observed and she underwent a clinical trial of chemotherapy vs. immunotherapy (PD-L1 expression was positive). The patient was randomized to the chemotherapy arm and completed 6 cycles with partial response. Disease progression occurred after 7 months of follow–up and she started 3rd line of treatment with nivolumab. Onset of chest pain, nausea/vomiting, prostration and malaise after the second administration of nivolumab. Forty–eight hours after administration onset of fever, elevated inflammatory parameters and opacity of the left lung base. CT showed bilateral multiple solid nodular and ground glass lesions. Respiratory infection/immune–mediated pneumonitis/disease progression was assumed and treatment with broad spectrum antibiotics and steroids was initiated. Progressive clinical and radiological deterioration occurred, with severe hypoxemic respiratory failure and progression to ARDS, requiring high doses of corticosteroids and invasive mechanical ventilation. The patient died 23 months after diagnosis. No autopsy was performed.

**Conclusion:** The range of immunological toxicities is very broad and can include any organ or system. The approach of these toxicities should be multidisciplinary. Pulmonary toxicity is one of the most feared, the diagnosis should be promptly and appropriate medical treatment should be started as early as possible.

**Keywords:** immune–mediated pneumonitis, immunotherapy, lung cancer

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**P2.38: NIVOLUMAB IN CLINICAL PRACTICE: REAL WORLD EXPERIENCE IN AN ARGENTINA ONCOLOGIC CENTER**

**Track: Immunotherapy**

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**Background:** Immunotherapy has demonstrated promising results in cancer patients. Immune checkpoint inhibition with the anti–PD–1 antibody nivolumab has improved survival in metastatic lung cancer patients. The FDA approved the use of this drug in metastatic non–small cell lung cancer (NSCLC) based on an improvement in overall survival (OS) in an international, multicenter, open–label, randomized trial comparing nivolumab to docetaxel in patients with progression on or after platinum–based chemotherapy. The augmented immune response enabled by this kind of agents has led to a particular group of side effects called immune–related adverse events (irAEs). However, the toxicity profile of nivolumab was acceptable in clinical trials. We describe here the experience with nivolumab in NSCLC patients from an Oncologic Center of Argentina.

**Method:** We included patients (pts) with NSCLC who received nivolumab in our Centre between Aug 2015 and May 2016. The adverse events were recorded from the patient chart and the responses were evaluated by the physician in charge and defined as: progressive disease (PD), stable disease (SD), partial response (PR) or complete response (CR) according to RECIST 1.1 criteria. With this information, adverse events profile, clinical benefit (SD+PR) and time to progression was evaluated. All patients who received at least one dose of Nivolumab were evaluated for toxicity and efficacy.

**Results:** 20 pts were included with a follow up of 713 m (0–175). 18 pts started nivolumab and 2 did not receive it due to disease progression. 66% were women, 39% current smoker, 66% were non squamous lung cancer. Median of number of chemotherapy lines before nivolumab was 2 (0–6), and 76% received RDT pre-nivolumab. 89% progressed to platinum treatment. Time to pre immunotherapy treatment failure was 2.84 m (IC95% 0.57–5.11). Sites of relapse or progression before nivolumab were: lung (14), lymph nodes (8), bone (3), liver (2) and adrenal gland (1). 44% were PS 0 and 50% PS 1. Number of nivolumab’s cycles was 7.5 (1–31). 41% presented adverse effect of any grade (g), 4 pts had hypotension (g.2), 2 pyrexia, 1 diarrhea (g.1), 1 arthralgia (g.1), 1 astenia (g.2), 1 rash (g.1), 1 pneumonitis (g.3), 1 acute kidney failure (g.2). The objective response rate was evaluated in 13 pts. 8/13 (61%) had objective response (CR/13, PR 7/13), 2/3 had SD and 3/13 PD. Time to response was 4 m (IC95% 2.36–7.46), time to progression was 6.57 m. Sites of relapse or progression were lung (7 pts), bone (3 pts), brain (1 pts), node (2 pts).

**Conclusion:** In this real world experience Nivolumab was well tolerated, with manageable adverse effects and promising clinical outcomes.

**Keywords:** non small cell lung cancer, immunotherapy
P2.39: LONG-TERM OS FOR PATIENTS WITH ADVANCED NSCLC ENROLLED IN THE KEYNOTE-001 STUDY OF PEMBROLIZUMAB

Track: Immunotherapy


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Background: The anti–PD-1 antibody pembrolizumab (MK-3475) received accelerated approval in the United States for the treatment of PD–L1–expressing NSCLC that progressed after platinum-containing chemotherapy; patients with a targetable EGFR mutation or ALK translocation must have also received an approved EGFR or ALK inhibitor. This approval was based on data from the large, phase 3 KEYNOTE–001 study (NCT02198587). We present updated, long-term OS data for treatment-naïve and previously treated patients enrolled in KEYNOTE–001.

Method: 550 patients received pembrolizumab 2 or 10 mg/kg Q3W or 10 mg/kg Q2W until intolerable toxicity, progression, or investigator decision. PD–L1 was assessed by immunohistochemistry using the 22C3 antibody, with positivity defined as PD–L1 expression on ≥1% of tumor cells (tumor proportion score [TPS] ≥1%). Response was assessed by RECIST v1.1 by independent central review every 9 weeks. Survival information was obtained every 2 months after treatment discontinuation.

Results: As of the September 18, 2015, data cutoff date, median follow-up duration was 22.2 months (range, 17.8–30.6) for treatment-naïve patients and 23.3 months (range, 14.2–40.1) for previously treated patients. Median OS was 22.1 months (95% CI, 17.1–27.2) for treatment-naïve patients and 10.6 months (95% CI, 8.6–13.3) for previously treated patients. 18–month OS rates were 58.2% for treatment-naïve patients and 37.0% for previously treated patients; 24–month OS rates were 44.5% and 31.3%, respectively. In both treatment-naïve and previously treated patients, OS increased with increasing PD–L1 TPS (Table).

<table>
<thead>
<tr>
<th>Median OS (95% CI), months</th>
<th>Treatment Naive N = 101</th>
<th>Previously Treated N = 449</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD–L1 TPS ≥1%</td>
<td>n = 79 22.1 (16.7–27.2)</td>
<td>n = 306 11.3 (8.3–14.0)</td>
</tr>
<tr>
<td>≥50%</td>
<td>n = 27 NR (22.1–NR)</td>
<td>n = 138 15.4 (10.6–18.5)</td>
</tr>
<tr>
<td>1%–49%</td>
<td>n = 52 19.5 (10.7–22.2)</td>
<td>n = 168 8.2 (6.0–12.7)</td>
</tr>
<tr>
<td>PD–L1 TPS &lt;1%</td>
<td>n = 12 14.7 (3.4–NR)</td>
<td>n = 90 8.6 (5.5–12.0)</td>
</tr>
</tbody>
</table>

Conclusion: Pembrolizumab is associated with promising OS for PD–L1–expressing treatment-naïve and previously treated NSCLC. Along with data from the randomized, phase 3 KEYNOTE–001 study of pembrolizumab vs docetaxel for previously treated, PD–L1–expressing NSCLC, these data support both PD–L1 as a predictive biomarker for pembrolizumab and the efficacy of pembrolizumab in patients with PD–L1–positive (ie, TPS ≥1%) NSCLC.

Keywords: advanced non–small cell lung cancer, PD–1 inhibition, pembrolizumab, PD–L1

P2.40: CIMAVAXEGF VACCINE FOR THE TREATMENT OF REAL-WORLD NSCLC PATIENTS

Track: Immunotherapy

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Background: CIMAvax–EGF is a therapeutic cancer vaccine composed by human recombinant Epidermal Growth Factor (EGF) conjugated to a carrier protein, P64K from Neisseria Meningitides and Montanide, as adjuvant. The vaccine induces antibodies against self EGF that deprivate its concentration and affect EGF–EGFR interaction. CIMAvaxEGF is registered in Cuba as switch maintenance therapy for NSCLC.

Method: A phase IV clinical trial was conducted in 65 Policlinic areas and 16 General hospitals in Cuba during 3 years. A total of 1081 advanced NSCLC patients were included without other treatment options due to progressive disease or comorbidities (n=984). Also a group of patients were treated as switch maintenance therapy with CIMAvaxEGF (n=97). The study was approved by Ethic Committee of each participant institutions. CIMAvaxEGF was administered by intramuscular injection in four sites of administration (4 subdoses of 0.25 ml), every 2 weeks the first 4 doses and after this induction phase monthly reimmunizations were given.

Results: A total of 927 patients (85.7 %) received at least one doses of CIMAvaxEGF at primary level of health assistance. The median overall survival (mOS) time for all vaccinated patients was 7.0 months, and in the subgroup of patient who received at least 4 doses of CIMAvaxEGF (induction phase) the mOS was 10.07 months (n=715). In the group of patients that received CIMAvaxEGF as switch maintenance therapy (n=97) the mOS was 11.9 months. A subgroup of patients included in the trial didn’t receive first–line chemotherapy (n=213). Median OS in this group (unfit patients) was 3.97 months irrespective of the treatment adherence, but in those patients who completed the induction phase of the treatment mOS was 7.36 months (n=124). Most frequently adverse events related
to CIMAvax were: injection–site reaction (14.5%), fever (7.0%), headache (5.8%), tremors (4.3%), and nausea (4.3%). Most of them were classified as grade 1–2 according to the CTCAE version 3. There were no deaths related to CIMAvaxEGF treatment.

**Conclusion:** CIMAvaxEGF cancer vaccine is a safe treatment option for advanced NSCLC patients that can be administered at primary level of health care assistance. The mOS of treated patients (unselected population) compares with the results reported for second–line treatments and switch maintenance therapies. Patients who completed the induction phase of the treatment reaches a better overall survival.

**Keywords:** NSCLC, cancer vaccine, real world cancer patients, primary health care assistance

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**P2.41: (also presented as PD1.06) PEMBROLIZUMAB VS DOCETAXEL FOR PREVIOUSLY TREATED NSCLC (KEYNOTE–010): ARCHIVAL VS NEW TUMOR SAMPLES FOR PD–L1 ASSESSMENT**

**Track:** Immunotherapy


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**Background:** In KEYNOTE–010, pembrolizumab demonstrated superior OS over docetaxel in patients with PD–L1–expressing advanced NSCLC that progressed after ≥2 cycles of platinum–doublet chemotherapy (HR 0.54, P = 0.0002 for 2 mg/kg and HR 0.50, P < 0.0001 for 10 mg/kg in the PD–L1 tumor proportion score [TPS] ≥50% population; HR 0.71, P = 0.0008 and HR 0.61, P < 0.0001 in the TPS ≥25% population). We assessed outcomes in patients who enrolled in KEYNOTE–010 based on whether PD–L1 expression was measured in archival or new tumor samples.

**Method:** KEYNOTE–010 (NCT02090567) was an international, open–label, phase 3 clinical trial. PD–L1 expression was assessed at a central laboratory by immunohistochemistry using the 22C3 antibody. Archival tumor samples were initially allowed, but with a protocol amendment, only new (ie, no intervening therapy between collection and start of study drug) tumor samples were permitted. Eligible patients were randomized 1:1:1 to pembrolizumab 2 or 10 mg/kg Q3W or docetaxel 75 mg/m2 Q3W for 24 months or until disease progression, intolerable toxicity, or other reason. Response was assessed per RECIST v1.1 by independent central review every 9 weeks. Survival was assessed every 2 months. Primary end points were OS and PFS in the PD–L1 TPS ≥50% and ≥25% populations. Pembrolizumab doses were pooled for this protocol–specific analysis.

**Results:** Of the 1034 patients enrolled, PD–L1 expression was assessed in archival tumor samples in 456 (44%) patients and new tumor samples in 578 (56%). Median time between sample collection and PD–L1 assessment was 250 days (range, 3–2510) for archival samples and 11 days (range, 1–371) for new samples. PD–L1 TPS was ≥50% for 40% of archival and 45% of new samples. Archival samples were used in 48% of the 222 patients with squamous histology and 43% of the 724 patients with nonsquamous histology. Pembrolizumab significantly improved OS in both the TPS ≥50% and ≥25% populations, regardless of whether enrollment was based on archival or new tumor samples (Table). The PFS benefit of pembrolizumab over docetaxel was similar in patients enrolled based on archival and new samples (Table).

<table>
<thead>
<tr>
<th>Pembrolizumab/Docetaxel</th>
<th>TPS ≥50%</th>
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<tr>
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<tr>
<td>n = 110/65</td>
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<tr>
<td>HR (95% CI)</td>
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<tr>
<td>0.60 (0.40–0.90)</td>
<td>0.81 (0.54–0.98)</td>
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<tr>
<td>n = 91/1158</td>
<td>0.64 (0.45–0.81)</td>
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<tr>
<td><strong>New</strong></td>
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<td>n = 13/18</td>
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<tr>
<td>HR (95% CI)</td>
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<tr>
<td>0.50 (0.19–1.00)</td>
<td>0.61 (0.39–0.85)</td>
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<tr>
<td>n = 30/1155</td>
<td>0.56 (0.36–0.80)</td>
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</table>

**Conclusion:** Pembrolizumab demonstrated superior OS over docetaxel regardless of whether new or archival samples were used to assess PD–L1 expression. The incidence of PD–L1 TPS ≥50% was similar in archival and new samples. These data suggest a new biopsy may not be required for this predictive PD–L1 assay, thus sparing patients from risks associated with sample collection and avoiding resource utilization.

**Keywords:** biopsy, immunohistochemistry, PD–L1, pembrolizumab

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**P2.42: AN IMMUNOTHERAPY APPROACH TO OVERCOMING RESISTANCE TO SECOND AND THIRD GENERATION EGFR INHIBITORS**

**Track:** Immunotherapy

Yosef Yarden

**Background:** Primary EGFR mutations predict sensitivity of lung cancer to tyrosine kinase inhibitors (TKIs), such as erlotinib and gefitinib. However, despite initial dramatic responses to TKIs, most patients eventually acquire resistance, primarily due to a second mutation (T790M).

**Method:** We used in vitro assays, as well as xenografts of PC9ER and H1975 NSCLC, which are resistant to erlotinib. Tumour growth was followed in mice for 3–4 months.

**Results:** Anti–EGFR antibodies recognize mutant EGFRs, hence might overcome resistance to kinase inhibitors. Employing T790M models we showed that an anti–EGFR mAb induces feedback loops that activate MET and increases two EGFR’s family members, namely HER2 and HER3, thereby over–activate ERK. A mixture of three mAbs that activate MET and increases two EGFR’s family members, namely HER2 and HER3, simultaneously targeting EGFR, HER2 and HER3 abolished feedback loops and, when tested in animals, completely inhibited erlotinib–resistant tumours. We will report our most recent results performed with AZD9291–resistant NSCLC. In addition, we will present evidence indicating that the mechanism of action of kinase inhibitors differs from the mechanism of action of monoclonal antibodies, hence combining antibodies and kinase inhibitors might elicit synergistic effects.

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**Keywords:** EGFR, EGFR inhibitors, MET, synergy, xenografts, NSCLC, cancer models

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Yosef Yarden

**Biological Regulation, Weizmann Institute, Rehovot/ISRAEL**
effects on tumours.

**Conclusion:** Our findings propose a previously untested pharmacological strategy to overcome recurring resistance of NSCLC to EGFR inhibitors. This includes resistance due to emergence of the C797S mutation, which prevents binding of third generation inhibitors to EGFR.

### P2.43: PEMBROLIZUMAB VS PLATINUM–BASED CHEMOTHERAPY FOR PD–L1+ NSCLC: PHASE 3, RANDOMIZED, OPEN–LABEL KEYNOTE–042 (NCT02220894)

**Track:** Immunotherapy

**Gilberto De Lima Lopes**, Yi–Long Wu, Sara Sadowski, Jin Zhang, Reshma Rangwala, Debra Kush, Tony Mok

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**Background:** The anti–PD-1 monoclonal antibody pembrolizumab showed a manageable safety profile and promising antitumor activity in patients with treatment–naïve NSCLC enrolled in the phase Ib KEYNOTE–001 study. KEYNOTE–042 is a randomized, open–label, international, phase 3 study comparing the efficacy and safety of pembrolizumab with those of platinum–doublet chemotherapy, the standard therapy for treatment–naïve NSCLC lacking ALK translocations or EGFR–sensitizing mutations, as first–line therapy for PD–L1–positive advanced NSCLC.

**Method:** Patients with advanced NSCLC without EGFR–sensitizing mutations or ALK translocations are being enrolled. Eligibility criteria are summarized in the Table. Patients will be randomized 1:1 to receive 200 mg pembrolizumab every 3 weeks (Q3W) or investigator’s choice of carboplatin area under the curve (AUC) 5 or 6 + paclitaxel 200 mg/m² Q3W or carboplatin AUC 5 or 6 + pemetrexed 500 mg/m² Q3W. Study design is summarized in the Figure; patient randomization will be stratified. Pembrolizumab will continue for 35 cycles or until progression, intolerable toxicity, or investigator decision; treatment may continue beyond initial radiographic disease progression in eligible patients. Discontinuation of pembrolizumab will be permitted for patients who have complete response confirmed ≥4 weeks after initial observation.

Chemotherapy will be given for a maximum of 6 cycles; patients with nonsquamous histology may subsequently optionally receive pemetrexed 500 mg/m² Q3W maintenance therapy. Adverse events (AEs) will be recorded throughout the study and for 30 days (90 days for serious AEs) thereafter and graded per NCI CTCAE v4.0. Response will be assessed every 9 weeks per RECIST v1.1 (central independent vendor review). Patients will be followed for survival every 2 months. Primary end point is overall survival in the PD–L1–positive (tumor proportion score [TPS] ≥50%) stratum and in all patients; secondary end points are progression–free survival in the TPS ≥50% stratum and in all patients, and safety and tolerability.

**Table. Patient Eligibility Criteria**

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<th>Key Inclusion Criteria</th>
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<tr>
<td>Age ≥18 years</td>
<td>EGFR sensitizing mutation or ALK translocation</td>
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<tr>
<td>Histologically or cytologically confirmed advanced NSCLC</td>
<td>Previous systemic treatment for advanced NSCLC</td>
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<td>Availability of formalin–fixed tumor sample with PD–L1 expression in ≥1% of tumor cells</td>
<td>Previous adjuvant therapy with carboplatin + paclitaxel (squamous histology)</td>
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<td>Life expectancy ≥3 months</td>
<td>Systemic steroid treatment ≤3 days before study start</td>
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<td>Measurable disease per RECIST v1.1</td>
<td>Either of the following before the first dose of study treatment</td>
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<td>Eastern Cooperative Oncology Group performance status 0 or 1</td>
<td>Major surgery within 3 weeks</td>
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<tr>
<td>Adequate organ function</td>
<td>&gt;30 Gy lung radiation therapy within 6 months</td>
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<tr>
<td>Provision of written informed consent</td>
<td>Active brain metastases</td>
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</table>

**Results:** Enrollment in KEYNOTE–042 is ongoing, and participating countries in Latin America include Argentina, Brazil, Chile, Columbia, Guatemala, Mexico, and Peru.

**Conclusion:** To date, KEYNOTE–042 has enrolled patients from 28 countries in Africa, Asia, Europe, North America, and South America, and enrollment will continue until ~1240 patients are allocated.

**Keywords:** pembrolizumab, non–small cell lung cancer, PD–L1, platinum–based chemotherapy
P2.44: AN UPDATE OF A POOLED ANALYSIS OF NIVOLUMAB FOR THE TREATMENT OF ADVANCED NSCLC AND THE ROLE OF PD-L1 AS A BIOMARKER

Track: Immunotherapy

Pedro Aguiar Jr1, Ramon De Mello1, Ilka Santoro1, Hakaru Tadokoro1, Carmelia Barreto2, Pedro Oliveira2, Gilberto Lopes2

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Background: Programmed cell death 1 (PD-1) is a T-cell surface receptor that inhibits immune response when bound to PD-L1 present on neoplasm cells. Recent studies have showed promising results with nivolumab, a monoclonal antibody that binds PD-1 and might improve the immune system. We have conducted a pooled analysis to verify the efficacy and safety of nivolumab and the role of tumoral PD-L1 expression as a biomarker to predict tumor response.

Method: It was performed a search of the English literature in Pubmed database between 1990 and June 22th 2016 and only clinical trials were included. Conferences papers were evaluated in order to update the studies data. The end point was to evaluate the overall response rate (ORR), the 1-year survival rate and safety of nivolumab in the first and second line settings.

Results: It was found 88 studies and 79 were excluded (78 non clinical trials and 1 evaluating other drug). A total of 2,162 patients (pts) were evaluated. In the second line setting, nivolumab has achieved an ORR of 15.9% (2 studies, 246 pts evaluated) and a 1-year survival rate of 40.4% (3 studies, 381 pts). In the first line setting, the ORR was 35% (1 study, 206 pts) and the 1-year survival rate was 79% (1 study, 206 pts). Nevertheless, there were substantial heterogeneity across the four arms of this study (each one had its specific dose and different combinations). Analyzing by histology, squamous cell NSCLC reached higher response (21%) than nonsquamous cell NSCLC (15%) (P = 0.01). As expected because of tumor biology and availability of post-progression treatment options, the 1-year survival rate was lower among patients with squamous cell NSCLC (32% versus 48%; P < 0.01). Nivolumab was safe, in the second-line, the grade 3 or 4 toxicity rate was 15.5% (2 studies, 246 pts), pneumonitis was observed in 6.9% of the patients (2.9% grade 3 or 4) and it was observed 5 deaths related to the treatment. In first line setting, grade 3 or 4 adverse events were found in 39.7% (1 study, 146 pts), pneumonitis was observed in 8.9% of the patients (4.8% grade 3 or 4) and a total of 3 deaths related to the treatment were informed. Tumor PD-L1 expression was assessed by immunohistochemistry in three studies (259 pts) and the cutoff adopted by the authors was 5%. About 42% of the patients were positive and it was not related to the histology and the presence or absence of previous treatment. PD-L1 expression was related to a non–statistical significant difference in ORR (RR 1.70; 95% CI 0.90 – 3.20).

Two randomized trials has shown the superiority of nivolumab over docetaxel for the second–line treatment for NSCLC.

Conclusion: Nivolumab has showed activity in the first and advanced lines for NSCLC treatment, with a manageable toxicity profile. Further studies are warranted in order to clarify immune checkpoint inhibitors combinations and predictive biomarkers.

Keywords: immunotherapy, biomarker, nivolumab, pooled analysis

P2.45: AN ESTIMATE OF THE ECONOMIC IMPACT OF TREATMENT OF NSCLC WITH IMMUNOTHERAPY RELATIVE TO PD-L1 EXPRESSION IN BRAZIL

Track: Immunotherapy

Pedro Aguiar Jr1, Ramon De Mello1, Hakaru Tadokoro1, Barbara Gutiérres1, Carmelia Barreto2, Hani Babiker3, Gilberto Lopes4

1Clinical Oncology, Universidade Federal de São Paulo, São Paulo/BRAZIL, 2Clinical Oncology, Universidade Federal do Amazonas, Manaus/Amazonas/BRAZIL, 3Honor Health, Scottsdale/AZ/UNITED STATES OF AMERICA, 4Oncoclinicas do Brasil, São Paulo/BRAZIL

Background: Delivering high quality cancer care at an affordable cost is one of the main challenges for health care professionals and policy makers, especially in low- and middle-income countries. Immune checkpoint inhibitors have achieved encouraging results in non–small cell lung cancer (NSCLC). Durable responses have been observed in approximately 20% of patients. Tumor PD-L1 receptor expression is being studied as a predictive biomarker. The objective of our study is to assess the economic impact of nivolumab and pembrolizumab with and without the use of PD-L1 as a biomarker in Brazil.

Method: We developed a decision–analytic model to determine the cost-effectiveness of PD-L1 assessment and the second-line treatment with NIVO or PEMBRO versus docetaxel. The model used outcomes data from randomized clinical trials and drug acquisition costs were estimated using current prices in the United States. We also included the costs of adverse events and post-progression therapies. Thereafter, we used Brazilian epidemiologic data to estimate the economic impact of the treatment with and without the use of PD–L1 as a biomarker.

Results: We included three RCTs (two with NIVO and one with PEMBRO). The estimated number of cases eligible for therapy with immune checkpoint inhibitors is 4,733. Treating all patients with NIVOLUMAB would cost US$ 198 million dollars each year, representing an increase of 24% in current Brazilian expenses for cancer drugs acquisition. Treating only patients with PD–L1 > 1% with NIVOLUMAB would cost 107 million dollars every year, leading to an increase of 12.9% in expenses for cancer drugs acquisition. However, with such selection, up to 46% of cases would not be treated and 315 years of life would be lost compared to treating all patients regardless of PD–L1 expression. The cost of each year–of–life saved was improved by PD–L1 selection (from US$ 223,000 to US$ 186,000). Table 1 summarizes our findings for five different scenarios of treatment. The results were similar with NIVOLUMAB and PEMBROLIZUMAB.

Keywords: immunotherapy, biomarker, nivolumab, pembrolizumab, oncology, lung cancer.
Conclusion: The use of PD-L1 expression as a biomarker for treatment with immune checkpoint inhibitors decreases the overall economic impact and the cost per life-year saved. Nevertheless, the number of life-years saved with this strategy would be significantly smaller than if we choose to treat all patients. Further study and societal discussion is needed in order to find the optimal strategy for patient selection.

Keywords: immunotherapy, Farmacoeconomy, biomarker, cost-effectiveness

P2.46 (also presented as PD1.01): LCSS AS A MARKER OF TREATMENT BENEFIT WITH NIVOLUMAB VS DOCETAXEL IN PTS WITH ADVANCED NON-SQUAMOUS NSCLC FROM CHECKMATE 057

Track: Immunotherapy

Richard J. Gralla1, David Spigel1, Bryan Bennett1, Fiona Taylor1, John R. Penrod1, Michael Derosea, Homa Dastania, Lucinda Orsini1, Clarissa Mathiase, Martin Reck1

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Background: Nivolumab (nivo) is the first anti–programmed death–1 agent to demonstrate a survival benefit vs docetaxel (doc) in patients (pts) with previously treated advanced (adv) non–squamous (NSQ) and SQ NSCLC. Here we report the impact of nivo vs doc on disease–related symptoms in pts with adv NSQ NSCLC from the CheckMate 057 study.

Method: Lung Cancer Symptom Scale (LCSS) was assessed every other cycle (Q4W) for nivo and every cycle (Q3W) for doc for the first 6 mo on treatment (tx), then every 6 wks and at 2 post-tx follow-up visits. LCSS includes the average symptom burden index (ASBI; based on 6 symptoms: anorexia, fatigue, cough, dyspnea, hemoptysis, and pain) and the 3-item global index (3-IGI; symptom distress, interference with activities, and health–related quality of life [HRQoL]). LCSS changes from baseline (BL) and time to first deterioration (TTD) in symptoms were estimated.

Results: Analyses of mean changes from BL in the LCSS ASBI and 3-IGI indicated numerical differences favoring nivo vs doc emerging at the first common assessment (wk 12) and persisting throughout the entire assessment period. At common assessments with >10 pts in each arm (to wk 48), the differences were significant (CIs excluding no difference) for the ASBI at wks 12, 24, 30, and 42, and for the 3-IGI at wks 24 and 30. Five of 6 symptoms (including pain and fatigue) and 2 of 3 items of the 3-IGI (HRQoL and symptom distress) had significant differences favoring nivo at ≥1 common assessments. TTD (based on the minimally important difference [MID]) was longer with nivo vs doc for the ASBI (HR=0.65; 95% CI: 0.49, 0.85) and 3-IGI (HR=0.63; 95% Cl: 0.48, 0.82), with Kaplan-Meier curves between tx arms separating at ≈2 months. TTD for individual symptoms within the ASBI and individual items of the 3-IGI showed a similar pattern. The proportion of pts with improvement in the LCSS ASBI greater than the MID by wk 12 was similar for nivo (17.8%; 95% CI: 13.6, 22.7) and doc (19.7%; 95% CI: 15.2, 24.7).

Conclusion: These results from this large, phase III study indicate that pts with previously treated adv NSQ NSCLC had significantly better symptom burden outcomes and HRQoL while on tx with nivo vs doc. TTD was significantly longer in nivo– vs doc–treated pts. Clinical Trial Registration: NCT01673867 Reused with permission from the American Society of Clinical Oncology (ASCO). This abstract was accepted and previously presented at the 2016 ASCO Annual Meeting. All rights reserved.
P2.47 (also presented as PD1.02): THE ROLE OF PD-L1 EXPRESSION AS A PREDICTIVE BIOMARKER IN ADVANCED NSCLC: AN UPDATE OF A NETWORK META-ANALYSIS

Track: Immunotherapy

Pedro Aguiar Jr¹, Gilberto Lopes¹, Ilka Santoro¹, Hakaru Tadokoro¹, Carmelia Barreto³, Ramon De Mello⁴
¹Clinical Oncology, Universidade Federal de São Paulo, São Paulo/BRAZIL, ²Oncoclinicas do Brasil, São Paulo/BRAZIL, ³Universidade Federal de São Paulo, São Paulo/BRAZIL, ⁴Universidade do Algarve, Faro/PORTUGAL

Background: Advanced lung cancer still portends a poor prognosis. Programmed cell death 1 (PD-1) is a negative costimulatory factor expressed on the surface of T-cells. It binds to one of its ligands; PD-L1 or PD-L2 expressed on the surface of neoplastic cells and inhibits cytotoxic T-cell responses. Several antibodies were developed against PD-1 or PD-L1 achieving encouraging results in non–small cell lung cancer (NSCLC). Durable response has been observed in approximately 20% of treated patients. The first anti PD-1 therapy for NSCLC was approved by FDA on March 2015. In order to rationalize patient selection it is necessary to develop a feasible biomarker that could predict outcomes with treatment. The objective of this meta–analysis is to determine if the tumor PD-L1 overexpression is a predictive factor.

Method: We searched English written papers published or presented between 1990 and June 22th, 2016. Only clinical trials were included and conference papers were assessed to update studies data. Phase I or II trials evaluating Anti PD-1 or Anti PD-L1 independent of tumor histology and previous treatment setting were included.

Results: 83 studies were found, and 70 were excluded (they were not clinical trials). 13 trials were included with a total of 1,612 patients. PD-L1 positive cutoff varied according to different studies, as did the specific monoclonal antibody used for the immunohistochemistry assay (range 5% to 50%). There were no differences in PD-L1 expression across different tumor histology and the presence or absence of prior treatment. The overall response rate for PD-L1 positive group was statistically significant higher (RR 2.06 – 95% CI 1.50 – 2.83). The ORR increased as higher as the PD-L1 expression cutoff value (Table 1). The progression–free survival was also higher for the PD-L1 positive group (6 studies and 897 patients; HR 0.69 – 95% CI 0.57 – 0.85) as well as the overall survival (7 studies and 1,101 patients; HR 0.73 – 95% CI 0.62 – 0.87).

Conclusion: PD-L1 overexpression can be considered as a predictive biomarker for immune checkpoint inhibitors for NSCLC, independent of previous treatments or tumor histology. Response rate may be up to three times higher in PD-L1 positive patients than in patients with tumors that do not express it. Further biomarker evaluation is warranted.

Keywords: immunotherapy, biomarker, PD-L1, Personalized Medicine

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