IASLC

2021 Targeted Therapies of Lung Cancer Meeting

FEBRUARY 17-20, 2021 | WORLDWIDE VIRTUAL EVENT
MARCH 3-4, 2021 | HIGHLIGHTS FOR EUROPE & ASIA

ABSTRACTS

#TTLC21

CONQUERING THORACIC CANCERS WORLDWIDE

IASLC TTLC 2021 Abstracts

Table of Contents

Best Fellows Oral Talks	3
Posters	10
Author Index	33

Best Fellows Oral Talks

BEST FELLOWS ORAL TALK
FEBRUARY 20, 2021, 10:10–11:10 EST

S12.02: Neratinib Efficacy in Patients with EGFR Exon 18-Mutant Non-Small Cell Lung Cancer (NSCLC): Findings from the SUMMIT Basket Trial

Amy L. Cummings[1], Valentina Boni[2], Christophe Dooms[3], Barbara Haley[4], Satiago Viteri[5], Amit Mahipal[6], J. Marie Suga[7], Lisa D. Eli[8], Alshad S. Lalani[8], Richard Bryce[8], Feng Xu[8], Naisargee Shah[8], Fairooz Kabbinavar[8], Jonathan W. Goldman[9]

[1]University of California at Los Angeles, Hematology & Oncology, Santa Monica, United States of America, [2]START Madrid-CIOCC, Hospital Universitario, Madrid Sanchinarro, Madrid, Spain, [3]University Hospitals Leuven, Leuven, Belgium, [4]UT Southwestern Medical Center, Dallas, United States of America, [5]Instituto Oncologico Dr Rosell. Hospital Universitario Dexeus. Grupo QuironSalud, Barcelona, Spain, [6]Mayo Clinic, Rochester, United States of America, [7]Kaiser Permanente Cancer Research Center, Vallejo, United States of America, [8]Puma Biotechnology Inc., Los Angeles, United States of America, [9]University of California at Los Angeles, Los Angeles, United States of America

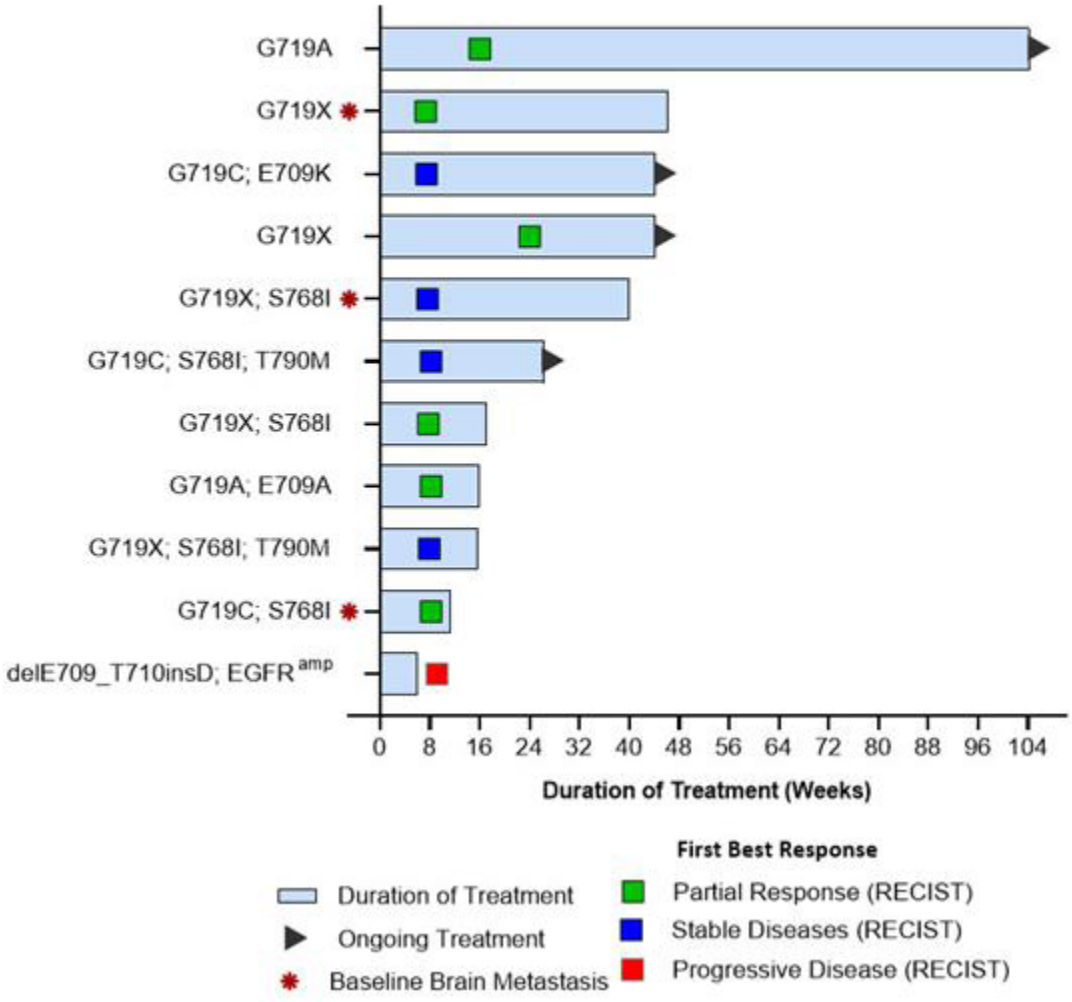
Background: EGFR exon 18 mutations comprise 3–5% of all EGFR mutations in NSCLC and have inferior response to first-generation EGFR TKIs compared to classical EGFR mutations [cBioPortal 2020; Sharma et al. 2007]. A prior phase 2 neratinib trial of pretreated EGFR-mutated NSCLC patients showed 3 PRs, 1 SD and mPFS of 52.7 weeks in four exon 18 (G719X)-mutation patients [Sequist et al. 2010]. Initial data from the neratinib-treated EGFR exon 18-mutant NSCLC cohort in the phase 2 SUMMIT basket trial (NCT01953926) are presented.

Methods: Patients with EGFR exon 18-mutant NSCLC and ECOG PS 0–2 were treated with neratinib (240 mg po daily). Prior EGFR TKIs, chemotherapy, and checkpoint inhibitors (IO) were allowed. Loperamide prophylaxis (first 8 weeks) was mandatory. Study endpoints: objective response rate (ORR) at week 8 (±1 week); ORR (RECIST 1.1 confirmed); duration of response (DOR); clinical benefit rate (CBR); PFS; safety (NCI CTCAE, v4.0); biomarkers.

Results: Eleven patients with EGFR exon 18-mutant NSCLC were evaluable for efficacy/safety. Baseline characteristics: median age 67 (range 56–83) years; male (55%), white (91%); ECOG PS 0/1 (45%/55%). Prior lines of therapies: 2 (range 1–3): first- and/or second-generation EGFR TKIs (91%); chemotherapy (55%); IO (27%). One patient's tumor had delE709_T710insD mutation and EGFR co-amplification. Three patients had a single G719X mutation. Seven patients had complex G719X plus ≥1 additional EGFR mutation (E709X, S768I, T790M). Responses were noted irrespective of single or complex G719X mutations (Figure 1). No grade 3 diarrhea was reported. Efficacy results are summarized in Table 1.

Conclusion: Meaningful neratinib activity, regardless of single or complex G719X mutation, was seen in TKI-pretreated NSCLC patients with EGFR exon 18 mutations. ORR and mPFS appear better than previously reported for other EGFR TKIs in TKI-refractory patients. The neratinib SUMMIT trial continues to enroll EGFR exon 18-mutant NSCLC patients.

Figure 1. Treatment duration and first best response: *EGFR* exon 18-mutant NSCLC cohort receiving neratinib monotherapy



Neratinib
EGFR exon 18-mutant
Non-small cell lung cancer
Basket trial

BEST FELLOWS ORAL TALK
FEBRUARY 20, 2021, 10:10–11:10 EST

S12.03: Concurrent Mutations in STK11 and KEAP1 Promote Ferroptosis Protection and SCD1 Dependence in Lung Cancer

Triparna Sen[1]

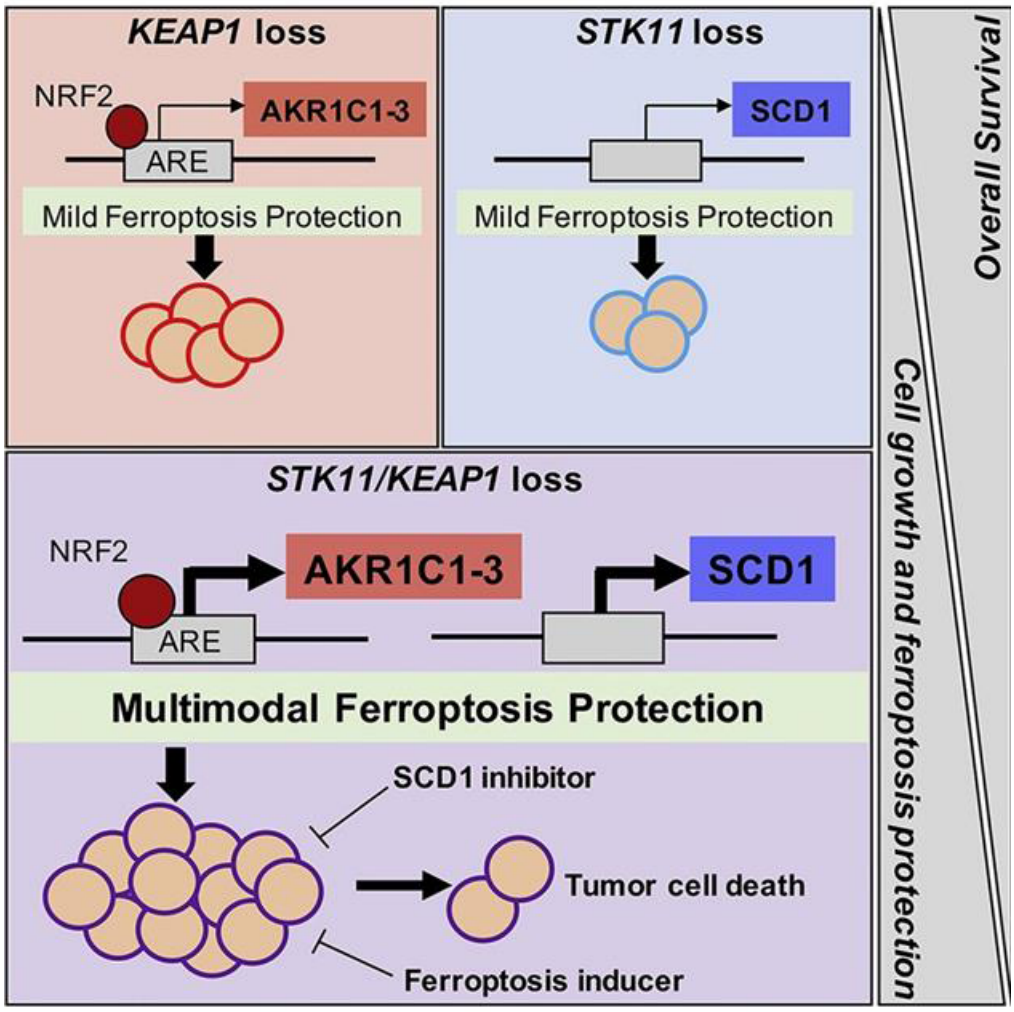
[1]*Memorial Sloan Kettering Cancer Center, New York, United States*

Background: About 15% of lung adenocarcinoma (LUAD) have deletions or inactivating mutations of STK11, and a similar percentage have inactivation of KEAP1. STK11 and KEAP1 loss are strongly co-associated ($p<0.001$), and our team has found that among all possible gene pairs in the 468-gene MSK-IMPACT genomic panel, co-occurrence of these two mutations is the strongest driver of poor outcome in LUADs, conferring resistance to both standard chemotherapy and immunotherapy, resulting in an average overall survival of less than 8 months from diagnosis. Little is known about the cooperativity of these two mutations. An in-depth understanding of the biological and functional consequences of STK11 and KEAP1 co-mutation is an urgent clinical need that is essential to identify effective therapeutic targets.

Methods: We sequentially profiled 1,235 patients with metastatic LUAD by next generation sequencing (MSK-IMPACT). We used CRISPR/Cas9 gene editing to create stable knockouts of STK11, KEAP1, or both genes, in three LUAD lines; H358, H292, H1993. We then performed cell proliferation, bulk RNA sequencing, proteomic and metabolomic analyses of these models. Furthermore, to identify genetic vulnerabilities selective for LKB1/KEAP1 co-mutant tumors, we performed CRISPR/Cas9 screens in isogenic in vitro models using a curated "druggable genome" sgRNA library that targets 1,463 genes encoding proteins that are direct targets of currently available therapies or are immediately downstream of a directly targetable protein.

Results: MSK-IMPACT demonstrated that STK11/KEAP1 co-mutation predicts short overall survival in patients with LUAD independent of KRAS status. As expected, STK11/KEAP1 co-mutation promotes tumor cell proliferation and migration in vitro and significantly enhanced tumor growth in vivo. Bulk RNA sequencing demonstrated that STK11/KEAP1 co-mutant cells have higher expression of genes involved in ferroptosis protection and are resistant to ferroptosis inducing agents. CRISPR/Cas9 screen identified ferroptosis regulator SCD as an essential gene required for proliferation and survival of STK11/KEAP1 co-mutant cells. Genetic and pharmacological inhibition of SCD1 prevented the growth of STK11/KEAP1 co-mutant cells and sensitized these cells to ferroptosis induction. Finally, in vivo inhibition of SCD1 significantly delayed tumor growth in STK11/KEAP1 co-mutant LUAD.

Conclusion: This study describes, for the first time, ferroptosis evasion as a survival mechanism for STK11/KEAP1 mutant tumors. We further identify SCD as an essential gene in STK11/KEAP1 co-mutant LUAD. Further studies to design and test targeted SCD1 inhibitors, either alone or in conjunction with agents targeting ferroptosis, represents a promising strategy to improve outcomes in this cohort of patients with limited therapeutic options and poor prognosis.


KEAP1 loss
NRF2
AKR1C1-3
ARE
Mild Ferroptosis Protection
STK11 loss
SCD1
Mild Ferroptosis Protection
STK11/KEAP1 loss
NRF2
AKR1C1-3
SCD1
ARE
Multimodal Ferroptosis Protection
SCD1 inhibitor
Tumor cell death
Ferroptosis inducer
Overall Survival
Cell growth and ferroptosis protection

BEST FELLOWS ORAL TALK
FEBRUARY 20, 2021, 10:10–11:10 EST

S12.04: Beyond Steroids Immunosuppressants in Steroid-refractory Immune Related Adverse Events

Jia Luo[1], Jason Beattie[1], Paige Fuentes[1], Hira Rizvi[1], Jacklynn Egger[1], Mark Kris[1], Mario Lacouture[1], Maya Gambarin[1], Bianca Santomasso[1], David Faleck[1], Matthew Hellmann[1]

[1]*Memorial Sloan Kettering Cancer Center, New York, United States*

Background: The optimal management for severe immune related adverse events (irAEs) from immune checkpoint blockade is unclear, especially in patients who do not respond or become intolerant to steroids. Consensus guidelines suggest alternative immunosuppressants based on the limited literature and expert opinion.

Methods: We examined patients with lung cancers at MSK treated with immune checkpoint blockade (ICB) from 2013-2020. Pharmacy records were queried to identify patients who received systemic steroids as well as an additional immunosuppressant, such as a TNFα inhibitor or mycophenolate mofetil. Patient records were manually reviewed to examine baseline characteristics, management, and outcomes.

Results: Among 2,750 patients with lung cancers treated with ICB, 51 (2%) (NSCLC n=44, SCLC n=7) received both steroids and an additional immunosuppressant for a severe irAE (TNFα inhibitor (73%), mycophenolate mofetil (20%)) (Figure 1). The most common events were colitis (53%), pneumonitis (20%), hepatitis (12%), and neuromuscular (10%) (Figure 2). Nearly all (88%) were grade 3 severity or higher. Indications for an additional immunosuppressant were initial non-response to steroids (steroid-refractory, 65%), later intolerance to/dependence on steroids (steroid-resistant, 29%), or upfront use (6%). At 90 days after start of an additional immunosuppressant, 57% (29/51) were improved from their irAE, 18% (9/51) were unchanged, and 25% (13/51) were deceased. Improvement was more common in hepatitis (5/6) and colitis (18/27) but less common in neuromuscular (1/5) and pneumonitis (3/10). Of patients who died, 8/13 were attributable directly to the irAE and 4/13 related to toxicity from immunosuppression (3, infection-related deaths; 1, drug-induced liver injury leading to acute liver failure).

Conclusion: Response to additional immunosuppressants in steroid-refractory/resistant immune related adverse events is heterogenous. While these treatments help some patients, many remain refractory, can die and/or experience other unintended toxicities from immunosuppression. A more precise understanding of the underlying pathophysiology of specific irAEs is needed to guide biologically-informed treatments for severe irAEs.

Figure 1

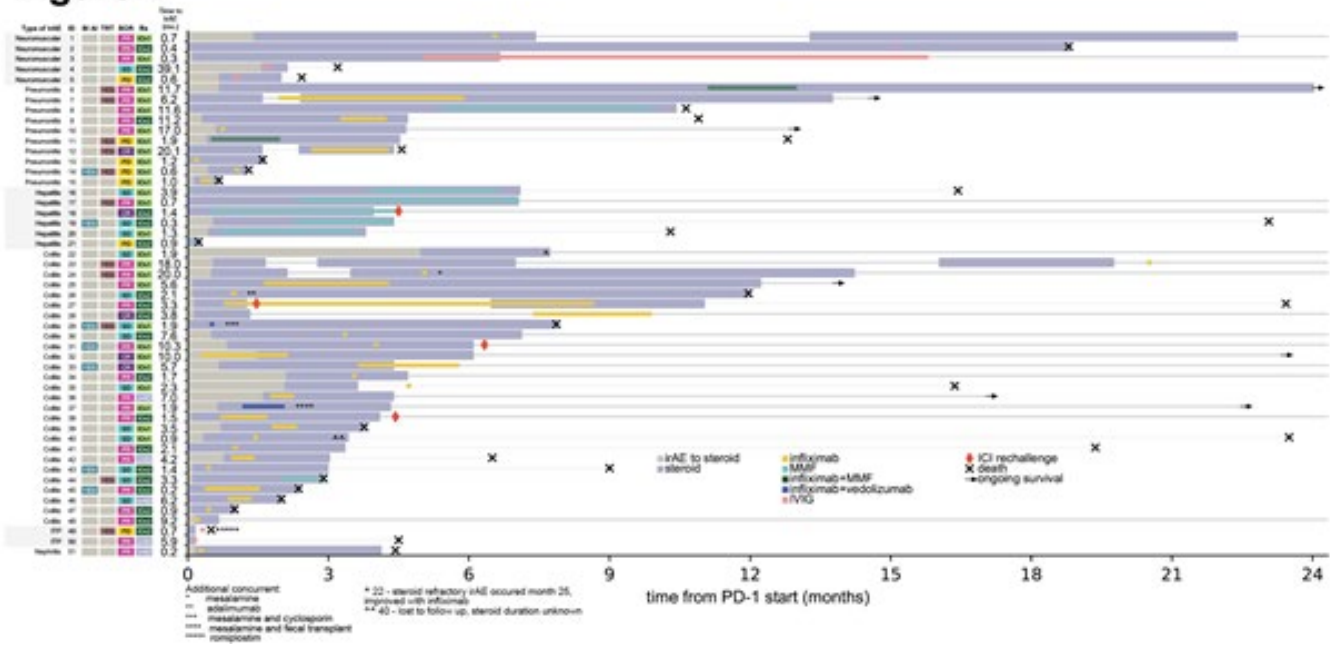
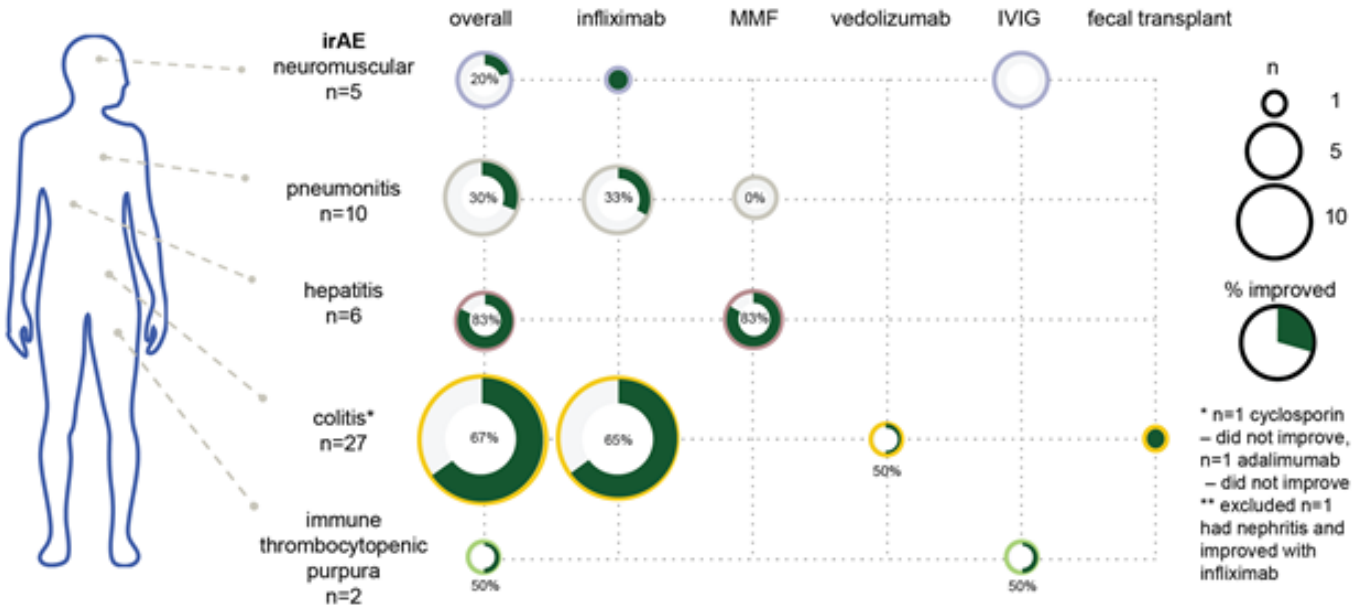


Figure 2



BEST FELLOWS ORAL TALK
FEBRUARY 20, 2021, 10:10–11:10 EST

S12.05: Identifying B7-H6 as a Prospective Immunotherapy Target in Small Cell Lung Cancer

Portia Thomas[1,2], Sarah Groves[3], Yun-Kai Zhang[4], Jia Li[5], Paula Gonzalez-Ericsson[6], Shamilene Sivagnanam[7], Courtney Betts[7], Cindy Lowe[8], Hua Chang Chen[5], Qi Liu[5], Heidi Chen[5], Kelli Boyd[8], Vito Quaranta[3], Prasad Kopparapu[4], Yingjun Yan[4], Lisa Coussens[7], Darren Tyson[3], Wade Iams[4], Christine Lovly[4,9]

[1]Department of Microbiology, Immunology, and Physiology, School of Medicine, Meharry Medical College , Nashville , United States, [2]School of Graduate Studies and Research, Meharry Medical College , Nashville, United States, [3]Department of Biochemistry, Vanderbilt University , Nashville, United States, [4]Division of Hematology-Oncology, Department of Medicine, Vanderbilt University Medical Center , Nashville, United States, [5]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, United States, [6]Breast Cancer Research Program, Vanderbilt Ingram Cancer Center, Vanderbilt University , Nashville, United States, [7]Department of Cell, Developmental and Cancer Biology, Knight Cancer Institute, Oregon Health & Science University , Portland, United States, [8]Department of Pathology, Immunology, and Microbiology, Vanderbilt University Medical Center , Nashville, United States, [9]Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, United States

Background: Small cell lung cancer (SCLC) is an aggressive, neuroendocrine malignancy with limited treatment options and median survival of approximately 1 year after diagnosis, even with treatment. Patients with SCLC typically respond to platinum-based cytotoxic chemotherapy, but drug resistance and resultant disease progression rapidly develop, driving the 5-year patient survival rate to < 5%. The emergence of immunotherapy offers promising therapeutics for this disease; PD-L1 immune checkpoint inhibitors, atezolizumab and durvalumab, have received regulatory approval for the first-line treatment of patients with extensive-stage SCLC. However, when used in combination with platinum-based chemotherapy, these PD-L1 inhibitors only improve overall survival by 2–3 months. This may be due to the observation that <20% of SCLC tumors express PD-L1 at >1%. Evaluating the composition and abundance of checkpoint molecules in SCLC may identify molecules beyond PD-L1, that are amenable to therapeutic targeting.

Methods: We analyzed RNA-Seq data from SCLC cell lines (n=108) and primary tumor (n=81) specimens for expression of 39 functionally validated, inhibitory checkpoint ligands. Further, we generated tissue-microarrays containing SCLC cell lines and SCLC patient specimens to confirm expression of these ligands by immunohistochemistry. We annotated patient outcomes data, including treatment response and overall survival.

Results: The checkpoint ligand B7-H6 (NCR3LG1) exhibited increased protein expression relative to PD-L1 in cell lines and tumors ($p < 0.05$). Higher B7-H6 protein expression correlated with longer progression-free survival ($p=0.0368$) in patients and increased total immune infiltrates (CD45+). Furthermore, increased B7-H6 gene expression in SCLC tumors correlated with a decreased activated NK cell gene signature, suggesting a complex interplay between B7-H6 expression and immune signature in SCLC.

Conclusions: We interrogated 39 inhibitory checkpoint molecules in SCLC and found that B7-H6, a tumor-specific antigen, is highly expressed and associated with progression-free survival. In addition, 26/39 immune checkpoint proteins in SCLC tumors were more abundantly expressed than PD-L1, indicating an urgent need to investigate additional checkpoint targets for therapy, in addition to PD-L1.

Posters

P01.01: Female Lung Cancer: An Emerging Issue in Bangladesh

Muhammad Rafiqul Islam[1], ATM Kamrul Hasan[1], Hasan Shahrear Ahmed[2], Ishrat Nur Ridi[1], Farida Arjuman[1], Noor Ishrat Eshita[1]
[1]National Institute Of Cancer Research & Hospital, Dhaka, Bangladesh, [2]Bangabondhu Sheikh Mujib Medical university, Dhaka, Bangladesh

Background: Lung cancer is the second most prevalent cancer in women in Bangladesh and is the leading cause of death. Studies have shown that the prevalence of smoking in women in Bangladesh is decreasing, however the incidence of lung cancer is increasing. However, to this day patient characteristics of lung cancer in women has not been completely delineated. This utter lack of information makes it challenging to identify women at risk and provide optimal education and tailor screening programs. We examined the socioeconomic status and characteristics of women with new diagnosis of lung cancer at a tertiary care Center in Dhaka, Bangladesh.

Method: This was a descriptive observational study using out database of women with cancer who were treated at the medical oncology department of National Institute of Cancer Research and Hospital (NICRH) from January 2018 to December 2019. Data collected included demographics, exposure to tobacco products, and clinicopathological details. Confidentiality was assured and anonymity maintained. Data collection was performed in adherence to institutional guidelines.

Result & discussion: Amongst the 4423 women registered in the cancer database, 515 had lung cancer (11.73%). It was the 4th prevalent cancer after breast (40.24%), gastrointestinal tract (24.32%) and gynaecological cancers (13.39%). 82.07% were non-small cell lung cancer (NSCLC), 6.43% were small cell carcinoma, and 11.50% were other histologies including some mixed types. Of the NSCLC patients, 55.56% were adenocarcinoma and 26.51% were squamous cell carcinoma. The average age of the patients was 54.28 years and of those, 16.27% of patients were ≤ 40 years old. 34.17% of the patients denied tobacco use; 23.50% were cigarette smokers; 59.81% used betel nut and chewed tobacco, and 32.15% used more than one form of tobacco. Majority (80.4%) of the patients belonged to very low socio-economic status with mean monthly familial income of less than $120.

Conclusion: Unlike in other countries, only 55% of the NSCLC patients had pure adenocarcinoma histology. While less than a quarter of the female population were smokers, 59.81% endorsed using betel nut and smokeless tobacco. Other factors, which were not evaluated in this study such as using firewood, straw or dung as heat sources for cooking and second-hand smoking could contribute to high incidence of lung cancer in Bangaldeshi women and these factors should be evaluated in a prospective setting. Understanding risk factors will help prioritize prevention and early screening efforts.

P02.01: Increase in Tumour PD-L1 Expression in Non-small Cell Lung Cancer Following Thermal Vapour Ablation is Not Related to Systemic Inflammatory Response

Kanishka Rangamuwa[1,2], Tracy Leong[3], Marie-Liesse Asselin-Labat[4], Steve Bozinovski[5], Michael Christie[8], Phillip Antipa[6], Tom John[7], Louis Irving[1], Daniel Steinfort[1,2]

[1]Department of Respiratory Medicine, Royal Melbourne Hospital, Melbourne, Australia, [2]Department of Medicine (RMH), University of Melbourne, Melbourne, Australia, [3]Department of Respiratory Medicine, Austin Hospital, Melbourne, Australia, [4]Personalised Oncology Division, Walter Eliza Hall institute, Melbourne, Australia, [5]School of Health and Biomedical Sciences, RMIT University, Bundoora, Australia, [6]Department of Thoracic Surgery, Royal Melbourne Hospital, Melbourne, Australia, [7]Peter MacCallum Cancer Centre, Melbourne, Australia, [8]Department of Pathology, Royal Melbourne Hospital, Melbourne, Australia

Background: Limited evidence suggests thermal ablation with modalities such as cryoablation or radiofrequency ablation can induce and anti-cancer immune response that could enhance the efficacy of immunotherapy with anti PD-1/PD-L1 immune checkpoint inhibitor therapy. This study reports pilot data demonstrating changes in PD-L1 expression on tumour cells after bronchoscopic thermal vapour ablation.

Methods: This was a prospective treat and resect study. Bronchoscopic thermal vapour ablation (vapour ablation) is a novel bronchoscopic technique that is currently being developed for the treatment of non-small cell lung cancer (NSCLC). As part of this prospective treat-and-resect study, patients underwent vapour ablation five days prior to surgical lobectomy. Tissue and blood pre- and post- ablation were analysed.

Tissue from biopsy samples were used for pre-ablation analysis, and was compared to post ablation lobectomy samples. Two areas, defined as areas of injured tumour and areas of viable tumour, were assessed. PD-L1 expression on tumour cells was assessed by immunohistochemistry on all tissue samples.

Peripheral blood was assessed for white cell count (WCC), neutrophil count, lymphocyte count and C-reactive protein (CRP) levels to determine inflammatory response.

Results: Five patients with a mean age of 66.2(±5.59) years underwent vapour ablation. All tumours were adenocarcinoma and located in the right upper lobe.

PD-L1 expression was zero in all patients prior to vapour ablation. Post ablation three (60%) patients demonstrated an increase in tumour PD-L1 expression in areas of injured tumour. In these patients PD-L1 positive tumour cells varied between 20-50% of tumour area. One patient had an increase in PD-L1 expression to 5% in areas of viable tumour (figure 1A).

There was an increase in mean WCC from 7.3(±2.24) 10^9/L to 8.52(±3.47) 10^9/L . This was characterized by a mean increase in neutrophils from 4.56(±1.91) 10^9/L to 5.94(±3.15) 10^9/L and a reduction in mean lymphocytes from 1.92(±0.46) 10^9/L to 1.58(±0.22) 10^9/L. CRP level increased from a mean of 3.4(±2.72) mg/L to 35.22(±45.22) mg/L. The degree of increase in CRP did not appear to correlate with change in PD-L1 expression (figure 1B).

Conclusion: Significant increase in tumour expression of PD-L1 was observed in 3 of 5 patients who underwent bronchoscopic thermal vapour ablation of tumours. This finding warrants further investigation of peripheral blood and tumour microenvironment to determine the degree and quality of an adaptive immune response, and the potential for augmentation of clinical response to Immune check point inhibitor therapy in NSCLC.

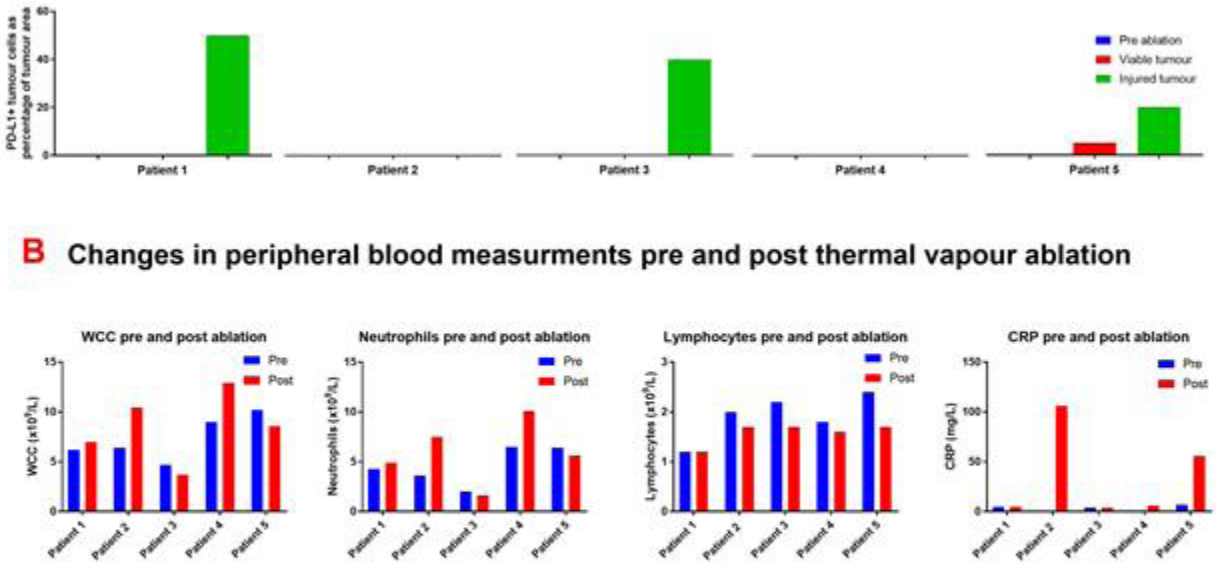


Figure 1:

(A) PD-L1 expression on tumour cells appears to increase in three patients post thermal vapour ablation.

(B) An increase in WCC, Neutrophils, CRP and decrease in lymphocytes is seen in patients post vapour ablation. The degree of change in inflammatory marker does not correlate with changes in PD-L1 expression.

P03.01: Comparison of Tumor Mutational Burden in Paired Primary Versus Lung Cancer Brain Metastasis

Matthew Strickland[1], Philipp Hähnel[1], Joanna Mora[1], Naema Nayyar[1], Sam Markson[1], Albert Kim[1], Edwin Nieblas-Bedolla[2], Scott Carter[1], Justin Gainor[1], Priscilla Brastianos[1]

[1]Massachusetts General Hospital, Boston, United States, [2]University of Washington School of Medicine, Seattle, United States

Background: Central nervous system (CNS) metastases are a devastating complication of non-small cell lung cancer (NSCLC) characterized by high rates of morbidity and mortality. Immune checkpoint inhibitors (ICIs) are now standard therapies for metastatic NSCLC and have demonstrated intracranial activity in a subset of patients. Nonetheless, as only a minority (20-30%) of NSCLC patients achieve intracranial responses with ICIs, there is an urgent need for effective biomarkers. Tumor mutational burden (TMB) is a putative biomarker in NSCLC for predicting efficacy of ICI, but the relationship between TMB and tissue sampling site in NSCLC (primary versus brain metastasis) remains underexplored.

Methods: We analyzed a cohort of 66 patients with metastatic lung adenocarcinoma who had paired primary and brain metastasis samples obtained between 1996 and 2014. Whole exome sequencing was used to estimate TMB of each sample. TMB was defined as non-synonymous mutations per coding region and reported as mut/Mb.

Results: Among 66 patients with NSCLC and paired primary tumor-brain metastasis specimens identified, 21 (32%) were male and 45 (68%) were female. Smoking status was known for 65 patients; the majority were smokers/former smokers (N=59; 91%). Imaging data was available for 62 patients. Twenty-six (42%) patients had synchronous primary-brain metastases (+/- 3 months based upon imaging assessment). The remaining 36 (58%) primary-brain metastasis pairs were metachronous. In total, 39 (53%) primary specimens and 37 (50%) brain metastasis specimens had a TMB of 10 mut/Mb or greater (p=0.8988). Median TMB for primary tumors was 10.73 mut/Mb (0.03-50.58) versus 10.64 mut/Mb (1.09-55.71) in brain metastases (p=0.0012). Among synchronous primary-brain tumor specimens, there was no significant difference in median TMB estimates between primary and brain metastases specimens (16.41 vs. 12.00; p=0.2330). However, we observed a statistically significant difference in median TMB between primary and brain metastases among metachronous specimens (8.67 vs. 12.50; p=0.0007).

Conclusion: Lung adenocarcinoma brain metastases frequently contain high TMB (≥10 mut/Mb). Analysis of paired primary-brain metastasis specimens showed no clinically meaningful differences in TMB estimates between sites. However, TMB was observed to be significantly higher in brain metastasis specimens diagnosed in the metachronous setting versus synchronous. Therefore, a diagnosis of metachronous brain metastasis may be associated with CNS disease harboring a higher TMB compared to primary disease. Additionally, clinicians should consider resected synchronous brain metastasis samples as reliable surrogates for TMB estimation. Further work in larger cohorts is needed to validate these findings.

P04.01: Non-small Cell Lung Cancer (NSCLC) Comprehensive Genomic Profiling: Integrating Expanded Genomic Sequencing into the Canadian Publicly Funded Health Care Model

Kirstin Perdrizet[1,2], Tracy Stockley[3,4], Jennifer H. Law[1], Muqdas Shabir[1], Roxanne Fernandes[1], Tong Zhang[4], Lisa Le[5], Ming-Sound Tsao[3,4], Suzanne Kamel-Reid[3,4], Prodipto Pal[3,4], Michael Cabanero[3,4], Joerg Schwock[3,4], Hyang Mi Ko[3,4], Geoff Liu[1,3], Penelopy Bradbury[1,3], Adrian Sacher[1,3], Frances Shepherd[1,3], Natasha Leighl[1,3]

[1]Department of Medical Oncology, Princess Margaret Cancer Centre, University Health Network, Toronto, Canada, [2]William Osler Health System, Brampton, Canada, [3]University of Toronto, Toronto, Canada, [4]Department of Laboratory Medicine and Pathology, University Health Network, Toronto, Canada, [5]Department of Biostatistics, Princess Margaret Cancer Centre, University Health Network, Toronto, Canada

Background: Standard of care (SOC) molecular diagnostics for stage IV NSCLC (non-small cell lung cancer) patients in Ontario, Canada includes publicly reimbursed EGFR/ALK/ROS1, and selected BRAF testing. Other genomic alterations are not tested routinely; however, enhanced molecular testing may broaden targeted treatment options for patients. This study evaluated costs, identified actionable targets, and determined clinical trial eligibility as a result of using CGP (comprehensive genomic profiling) in stage IV NSCLC patients.

Methods: This was a prospective study of stage IV NSCLC out-patients at Princess Margaret Cancer Centre (Toronto, Canada) without EGFR/ALK/KRAS/BRAF alteration (unless failure of prior targeted therapy) from February 2018- August 2020. Consenting patients had diagnostic tumor specimens tested using CGP with the Oncomine Comprehensive Assay version 3 (ThermoFisher Scientific; 161 genes: hotspots, fusions, and copy number variations). Primary endpoints were incremental actionable targets identified and clinical trial opportunities as a result of CGP. Secondary endpoints included treatment outcomes and cost from the Canadian public healthcare perspective.

Results: Of 182 enrolled patients, 134 (74%) completed CGP, and 48 (26%) screen failed. Mean age of the completed cohort was 61 years, female 60% (N=80), never/light smokers 64% (N=86), Asian 32% (N=43), previously treated with targeted therapy 22% (N=29). Actionable targets beyond SOC testing (or SOC actionable target but previously unknown) were identified in 28% (N=38): ERBB2 (N=11), BRAFV600 (N=3), BRAF fusion (N=2), RET fusion (N=2), NRG fusion (N=3), MET exon 14 (N=4), KRASG12C (N=9), EGFR (N=2), ROS-1 fusion (N=2). New clinical trial options were identified in 75% (N=100). To date, 16% (N=21) of patients have had a change to their anti-cancer therapy. This change included targeted therapy in all (N=21) of these patients. Failure of CGP was primarily a result of insufficient tissue [77% (N=37) of screen failures], usually due to tissue exhaustion from prior SOC molecular testing. Incremental cost (beyond single gene EGFR/ALK/BRAF/ROS-1) of CGP per case were estimated at $270-710 CAD depending on whether costs are based on a research or clinical laboratory setting.

Conclusion: CGP consolidates genomic testing, identifies additional actionable targets, increases clinical trial eligibility, and has a direct impact on anti-cancer treatment for patients. A key barrier to implementation is lack of funding for CGP in the Canadian publicly funded health system. The incremental cost of CGP is expected to decrease over time as further Health Canada approved treatments targeting novel biomarkers become available.

P05.01: Detection of DNA Replication Blocker SLFN11 in Tumor Tissue and Circulating Tumor Cells to Predict Platinum Response in Small Cell Lung Cancer

Bingnan Zhang[1], Allison Stewart[1], Carl Gay[1], Qi Wang[1], Robert Cardnell[1], Junya Fujimoto[1], Luisa Fernandez[2], Adam Jendrisak[2], Cole Gilbertson[2], Joseph Schonhoft[2], Joshua Jones[2], Amanda Anderson[2], Ignacio Wistuba[2], Jing Wang[1], Rick Wenstrup[2], Lauren Byers[1]

[1]MD Anderson Cancer Center, Houston, United States, [2]Epic Sciences, San Diego, United States

Background: Small cell lung cancer (SCLC) is an aggressive form of neuroendocrine carcinoma, notable for early metastases and rapid relapse despite initial response to frontline platinum-based chemotherapy. To date, there are no validated predictive biomarkers in SCLC, hence all patients are treated the same way. Preclinical studies identified SLFN11, a putative DNA/RNA helicase that blocks replication at stressed replication fork, as a predictive biomarker to a wide range of agents targeting DNA damage such as platinum, topoisomerase I/II inhibitors and PARP inhibitors. Based on these observations, pre-specified biomarker analyses in a clinical trial demonstrated SLFN11 predicts better clinical outcomes in SCLC patients when treated with PARP inhibitor combinations such as temozolomide and veliparib.

Methods: To better characterize the prevalence, heterogeneity and predictive value of SLFN11 in SCLC, we developed and validated a SLFN11 immunohistochemistry (IHC) assay meeting Clinical Laboratory Improvements Amendments (CLIA) standards, and a novel circulating tumor cell (CTC) assay (Epic Sciences®) to detect the expression level of SLFN11 in SCLC tumors or CTCs and correlated with clinical outcomes.

Results: We found that SLFN11 was expressed by IHC in roughly 50% of the SCLC clinical tumor samples, from three separate clinical trial cohorts (total of 207 extensive-stage SCLC patient samples). There was a wide range of H-scores by IHC which suggests heterogeneity in SLFN11 expression (H-score range 1.5-235). Similarly, analyses of patient CTCs from blood samples confirmed that SLFN11 is expressed in about 50% of treatment-naïve patients, however SLFN11 expression decreased significantly in patients on platinum treatment and at the time of relapse. Most patients had CTCs with pathologic features consistent with SCLC (i.e., were small, round, had high nuclear-to-cytoplasm ratios, and had salt-and-pepper like chromatin textures), although inter- and intra- patient heterogeneity was observed and SLFN11 expression was observed independent of morphologic subtype. Interestingly, SLFN11 expression was also found in white blood cells in the blood samples and was highest in platinum-naïve patients and lowest in patients while on platinum.

Conclusion: Together, these data highlight the potential of SLFN11 as a predictive biomarker in SCLC. Based on our group and others' previous work, SLFN11 positivity by IHC is being used for selection of patients in an ongoing clinical trial (NCT04334941). In addition, given the substantial challenge of obtaining adequate tumor tissue in SCLC either at initial diagnosis or with re-biopsies, blood-based CTC analyses are an important tool to detect SLFN11 expression. Because of the dynamic nature of SLFN11 expression, CTC analyses can be especially valuable for longitudinal monitoring and may have real-time implications for treatment choice and response.

P06.01: The ASCENT Trial: A Phase II Study of Neoadjuvant/Adjuvant Afatinib, Chemoradiation +/- Surgery for Stage III EGFR-Mutant NSCLC

Andrew Piper-Vallillo[1], Raymond Mak[2], Michael Lanuti[1], Alona Muzikansky[1], Julia Rotow[2], Pasi Janne[2], Mari Mino-Kenudson[1], Scott Swanson[2], Cameron Wright[1], David Kozono[2], J. Paul Marcoux[2], Zofia Piotrowska[1], Henning Willers[1], Lecia Sequist[1]

[1]Massachusetts General Hospital, Boston, United States, [2]Dana-Farber Cancer Center, Boston, United States

Background: The ADAURA trial showed benefit to adjuvant osimertinib in stage III EGFR-mutant (EGFRm) NSCLC, but the role of TKI induction is unknown. In 2011, we began ASCENT, a phase II trial of neoadjuvant and adjuvant afatinib in addition to standard of care (SOC) curative-intent therapy for EGFRm stage III NSCLC (NCT01553942). The study closed early for slow accrual. This is the final analysis.

Methods: ASCENT enrolled patients with EGFRm, stage IIIA/B (AJCC 7th ed.) NSCLC amenable to curative-intent chemoradiation therapy (CRT) ± surgery. Resectability was determined by the treating multidisciplinary team at diagnosis. Patients received neoadjuvant afatinib 40mg QD x 2 months, then concurrent CRT (≤ 4 cycles of cisplatin/pemetrexed and 3D conformal RT or Intensity-modulated RT personalized to tumor size, site, operability) +/- surgery and an optional 2 years of adjuvant afatinib. The primary outcome was objective response rate (ORR) to neoadjuvant afatinib. Major pathologic response (MPR) was defined as < 10% residual tumor at resection, complete pathologic response (CPR) as no residual tumor.

Results: 19 patients (14F/5M), median age 56 (range 34-75) were enrolled. 12 had EGFR del19, 7 L858R. 10 were classified as potentially resectable stage IIIA at diagnosis, 9 as unresectable IIIA/B. All completed two months of neoadjuvant afatinib; 5 (26%) required afatinib dose reduction. The ORR after neoadjuvant afatinib was 11/19 (58%; 95% CI, 33-80%). 1 patient initially deemed inoperable became a surgical candidate based on response to neoadjuvant afatinib; 2 patients progressed on neoadjuvant afatinib or exhibited findings that clarified their presenting stage as IV; both discontinued the protocol. The remaining 17 patients proceeded to CRT with pre-op median radiotherapy dose of 54 Gy (range 45-66; n=10), definitive median dose of 67 Gy (range 63-72; n=7). Among 10 patients who underwent resection (all via lobectomy), the MPR rate was 70% (6 MPR, 1 CPR). 13 (68%) patients started adjuvant afatinib after surgery (7) or definitive CRT (6); 4 completed 2 years, 3 discontinued early (median 1.5 months), 2 recurred during adjuvant afatinib and 4 remain on adjuvant therapy. Key grade 3/4 toxicities included rash (n=6), diarrhea (5), esophagitis (3), nausea (3), pneumonitis (2) and febrile neutropenia (1); there were no treatment-related deaths. With median follow-up of 30.6 months (range 3.1-96.3), 9 (47%) patients have recurred, with 5/9 having CNS-only recurrence. Recurrences occurred in 3/10 surgical patients and 5/7 definitive CRT patients. Median PFS was 34.6 months (95% CI 16.9-66.1) and median OS was 69.1 months (95% CI 29.4-NR). 2-year OS is 88% (95% CI 59-97%).

Conclusion: In stage III EGFRm NSCLC, 2 months of neoadjuvant afatinib is associated with an ORR comparable to that seen in advanced disease and does not impair receipt of SOC chemoradiotherapy ± surgery. PFS and OS are favorable in this single-arm study. The high rate of CNS-only recurrence highlights the potential for improved outcomes with more CNS-penetrant EGFR TKIs. Along with the interim results of ADAURA, these results support genotype-directed therapies in stage III EGFRm NSCLC, though the optimal sequence of TKI therapy will need to be defined.

P07.01: Sequencing of TKI With or Without Brain Radiotherapy (RT) in EGFR Mutated or ALK Rearranged Non-small Cell Lung Cancer (NSCLC) with Brain Metastases

Nicholas Giustini[1], Nicolas Villanueva[1], Anna Menzl[1], Klarissa Son[1], Daniel Simpson[1], Jona Hattangadi-Gluth[1], Hatim Husain[1], Sandip P. Patel[1], William Mitchell[1], James Urbanic[1], Kathryn Gold[1], Parag Sanghvi[1], Sonia Jain[1], Lyudmila Bazhenova[1]

[1]UCSD, San Diego, United States

Background: Within NSCLC, patients with the most common actionable mutations, epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK), are at high risk for developing brain metastases (BMs) with BMs present in close to 25% of patients at diagnosis of advanced disease. In EGFR mutated NSCLC, a multi-institutional retrospective analysis demonstrated upfront RT followed by EGFR tyrosine kinase inhibitors (TKIs) was associated with improved survival compared to those treated with early generation TKI followed by RT upon intracranial progression. However, while early generation TKIs demonstrate poor CNS penetration, newer generation TKIs exhibit excellent intracranial efficacy and challenge the paradigm that surgery or RT must be used upfront in all cases.

Methods: A single-institution retrospective study of patients diagnosed with metastatic NSCLC and BMs with either activating EGFR mutations or ALK rearrangements was performed. The analysis aimed to evaluate outcomes in patients who received TKI alone versus stereotactic radiosurgery (SRS) followed by TKI versus whole brain radiotherapy (WBRT) followed by TKI. TKI therapy was separated by early (erlotinib, gefitinib, afatinib, crizotinib, or experimental) versus newer (osimertinib, alectinib, brigatinib, ensartinib, or lorlatinib) generation. Intracranial overall response rate (icORR), intracranial disease control rate (icDCR), intracranial progression free survival (icPFS), and overall survival (OS) were evaluated.

Results: Eighty-five patients were evaluated, 27% receiving TKI alone, 47% receiving upfront SRS followed by TKI, and 26% receiving upfront WBRT followed by TKI. Of the total cohort, 81% had an EGFR mutation and 19% had an ALK rearrangement. Patients receiving TKI alone were more likely to have asymptomatic BMs and smaller BMs. The icORR for upfront TKI, SRS, and WBRT cohorts was 73.9%, 67.5%, and 81.8%, respectively (pearson chi-square, p = 0.682). The icDCR for upfront TKI, SRS, and WBRT cohorts was 82.6%, 92.5%, and 81.8%, respectively (pearson chi-square, p = 0.363). The median icPFS for upfront TKI, SRS, and WBRT cohorts was 12.7 months (95% CI, 4.1-21.4), 18.1 months (95% CI, 9.1-27.0), and 20.7 months (95% CI, 13.7-27.6), respectively (log-rank, p = 0.683). The median OS for upfront TKI, SRS, and WBRT cohorts was 35.0 months (95% CI, 14.5-55.4), 33.4 months (95% CI, 22.0-44.7), and 25.5 months (95% CI, 15.0-36.0), respectively (log-rank, p = 0.264). On multivariable analysis, patients <64 years old, ECOG PS 0-1, and BM that were resected, without leptomeningeal carcinomatosis, <10mm in size, or ≤10 in number, all had prolonged survival. In the EGFR mutated cohort, the use of newer generation TKIs and the presence of EGFR exon 19 deletion were associated with prolonged survival.

Conclusion: Delaying upfront RT in favor of initial treatment with EGFR or ALK TKI alone for brain metastases was not associated with an inferior survival in the era of newer generation TKIs. The use of osimertinib compared to older generation EGFR TKIs was associated with improved survival. This analysis was limited by the retrospective nature of the study, small numbers within groups analyzed, and heterogeneity between groups.

P07.02: Management of Advanced Non-small Cell Lung Cancer Patients Harbouring ROS1 Rearrangement- Experience From a Tertiary Cancer Centre in Eastern India

Saheli Saha[1], Ritesh JM Santosham[1], Moses Arunsingh S[1], Tapesh Bhattacharyya[1], Bivas Biswas[1], Deepak Dabkara[1]
[1]*Tata Medical Center, Kolkata, India*

Background: ROS 1 gene rearrangement is present in about 1-2% of advanced non-small-cell lung cancer patients (NSCLC). Several tyrosine kinase inhibitors (TKI) like Crizotinib, Entrectinib have been approved for use in these patients. However, availability and financial constraints for the use of ROS1 TKIs serve as factors influencing decisions regarding therapy. The present study was undertaken with the aim to audit our institutional practice and evaluate the outcomes of advanced NSCLC patients harbouring ROS1 gene rearrangement in our institution.

Method: Patients with advanced NSCLC patients harbouring ROS1 rearrangement mutation and who received treatment at our center were extracted retrospectively from the electronic medical records of our hospital. A waiver of consent was granted for this audit by the Institutional Review Board. The data on baseline clinico-demographic characteristics, the agents used in first and subsequent lines of therapy, follow up duration and time to progression were collected. The statistical analysis was carried out with the SPSS version 25 using non-parametric methods.

Results: From 2017 to 2020, 1019 patients with advanced NSCLC were screened for ROS1 mutation by Fluorescent In situ Hybridization (FISH), of which 29 patients tested positive (2.8%). Of these, two patients were treated with a radical intent and one progressed later and went on to receive palliative therapy. In total, 28 patients with ROS1 mutation were treated with palliative intent of whom 20 received systemic therapy with the remaining eight patients presenting in a poor performance status (PS) that precluded any form of anticancer therapy. Thirteen were female patients and the median age was 54 years (IQR: 44-61). 18 patients were ECOG performance status 0 or 1 with the remaining 5 patients PS 3 or 4. Two patients had brain metastasis at presentation. Twelve patients received first line treatment with TKI, with 10 patients receiving Crizotinib and 2 Ceritinib while the rest 8 patients were treated with platinum based doublet chemotherapy. The median progression free survival with first line treatment for those on chemotherapy was 13 months (95% CI - 0 - 27.8) compared with 10 months for those on TKIs (95% CI: 2.8 - 17.2), p = 0.06. The overall survival was also not statistically different between those receiving first line chemotherapy (13.9 months, 95% CI: 10.6 - 65.4) vs TKI (5.3 months, 95% CI 2.5 - 23.5), p=0.13. Three patients on first line chemotherapy went on to receive second line TKI therapy.

Conclusion: Even as lung cancer treatment is becoming personalised, access to treatment remains limited in developing countries. Seven patients in our series received first line chemotherapy owing to financial constraints with three of them receiving treatment with TKI on progression. Encouragingly however, the outcomes were not inferior with first line chemotherapy compared to TKI showing chemotherapy to be a feasible option for these patients.

P08.01: Precision Targeted Therapy for RET-driven NSCLC and Emerging Evidence of Acquired Resistance to RET-Specific Tyrosine Kinase Inhibitors

Johnathan Ebben[1], Chelsie Sievers[1], Nan Sethakorn[1], Ticiana Leal[1]

[1]*University Of Wisconsin, Madison, United States*

Background: Precision medicine approaches targeting the molecular drivers of tumor growth have revolutionized the treatment of non-small cell lung cancer (NSCLC). To date, multiple tyrosine kinase inhibitors (TKIs) targeting mutant EGFR, ALK-rearranged, and ROS1-rearranged NSCLCs are approved in the first line setting. RET-fusion driven NSCLCs are the most recent addition to this growing list of targetable drivers with the recent FDA of two novel small molecule RET kinase inhibitors, pralsetinib (BLU-667) and selpercatinib (LOXO-292). The use of TKIs in EGFR-mutant NSCLC has foreshadowed the unfortunate reality that a majority of patients ultimately develop resistance to TKIs. Here we present the case of a patient who developed TKI resistance via MET amplification following treatment with cabozantinib and selpercatinib for RET-fusion NSCLC to highlight the role of serial mutational analysis in the management of evolving TKI resistance and to review what is known about overcoming MET-dependent resistance.

Methods: We present here a case of TKI resistance in a patient with KIF5B-RET fusion advanced NSCLC. Following progression on cabozantinib, he was started on selpercatinib. After disease progression at multiple sites, he underwent repeat tissue biopsy followed by next generation sequencing. We review the changes in tumor mutational profile over his clinical course, as well as existing literature regarding MET-dependent resistance mechanisms.

Results: At the time of initial diagnosis molecular profiling revealed a KIF5B-RET fusion. The patient underwent radiotherapy followed by 6 cycles of carboplatin/ pemetrexed/ bevacizumab with a partial response. Upon osseous progression, he initiated cabozantinib, remained on therapy for 4 months with subsequent progression at multiple sites. He was treated with selpercatinib for 23 months before oligometastatic progression. Molecular analysis via cell-free DNA again revealed KIF5B-RET fusion without any alterations known to cause TKI resistance. He was continued on selpercatinib for an additional 6 months before progression at multiple sites. Repeat molecular profiling from tissue biopsy now revealed a new MET amplification (copy number 34). Given the relatively short history of RET-specific TKIs, mechanisms of resistance are not well understood. In the literature MET amplifications at baseline may contribute to a shortened duration of benefit from selpercatinib in a case series of 4 patients. In this series the authors piloted the combination of selpercatinib plus crizotinib with one patient experiencing a clinical and radiographic response for 10 months while on the combination.

Conclusion: Precision medicine approaches have revolutionized the treatment of NSCLC. While multikinase TKIs have largely failed RET-fusion driven cancers, the recent approval of the RET-specific TKIs pralsetinib and selpercatinib have improved treatment responses for this subset of patients with NSCLC. This case highlights an ongoing need for a better understanding of the mechanisms of resistance to RET-specific TKIs, the utility of serial mutational analysis, and the need for more evidence on dual RET and MET inhibition.

P09.01: Response to Standard Therapies and Comprehensive Genomic Analysis for Patients with Lung Adenocarcinoma with EGFR Exon 20 Insertions

Noura Choudhury[1], Adam Schoenfeld[1], Jessica Flynn[1], Christina Falcon[1], Hira Rivzi[1], Charles Rudin[1], Mark Kris[1], Maria Arcila[1], Glenn Heller[1], Helena Yu[1], Marc Ladanyi[1], Gregory Riely[1]

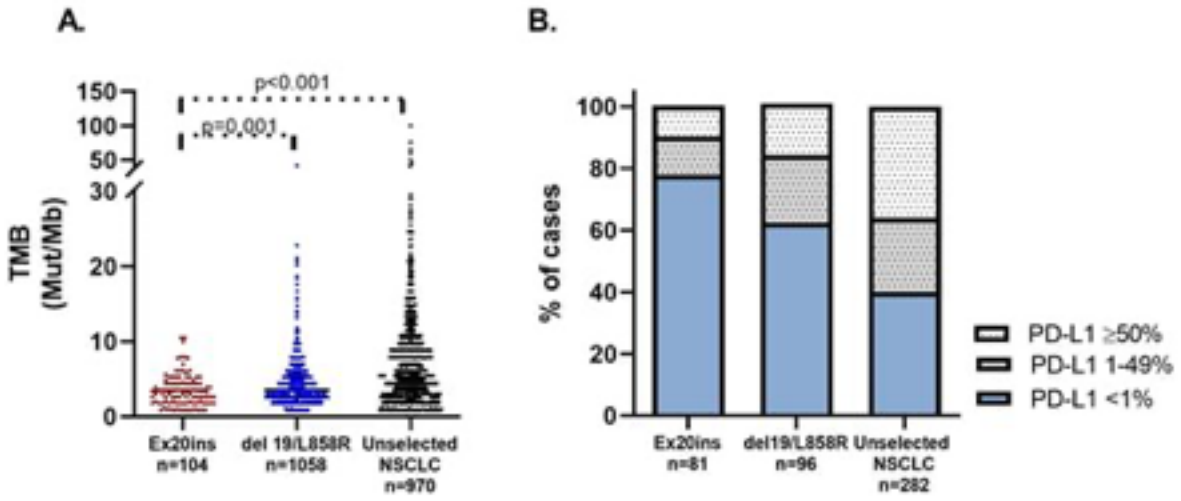
[1]*Memorial Sloan Kettering Cancer Center, New York, United States*

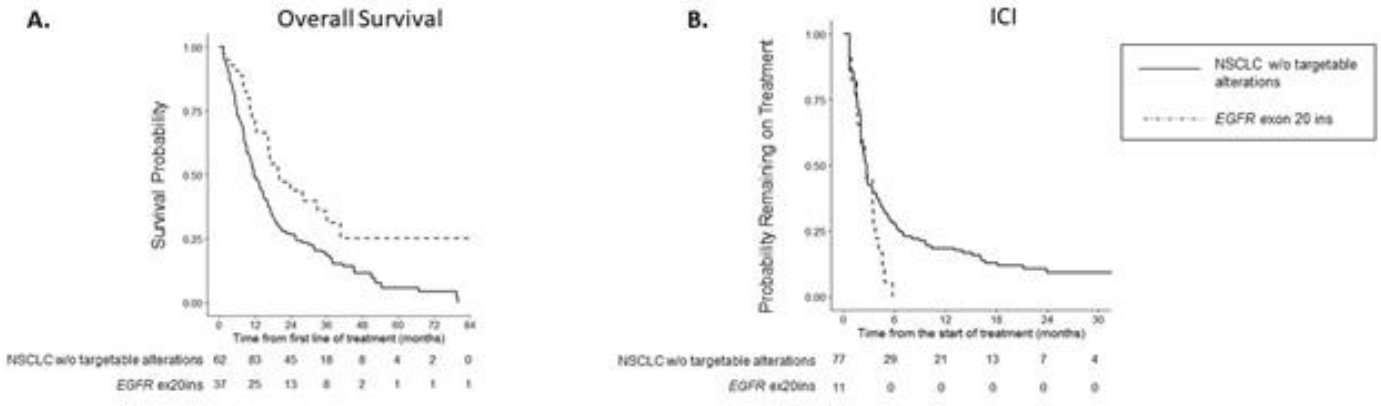
Background: EGFR exon 20 insertions (ex20ins) are an uncommon genotype in non-small cell lung cancer (NSCLC) for which targeted therapies are currently being developed. We sought to describe treatment outcomes as well as genomic and immunophenotypic characteristics of these tumors.

Methods: In this single-institution retrospective study, we identified sequential patients with NSCLC with EGFR ex20ins and compared their clinical outcomes and pathologic features with other NSCLC patients.

Results: Among 6,291 patients with NSCLC, 106 (2%) had EGFR ex20ins. Patients with EGFR ex20ins cohort were more likely to be Black, Asian or have light or no smoking history (p<0.01 for each). Median tumor mutational burden (TMB) (3.4 vs. 5.5, p<0.001) and proportion of tumors with PD-L1 expression ≥1% (22 vs. 60%, p<0.001) were lower in EGFR ex20ins compared to unselected NSCLC and EGFR del 19/L858R (median TMB 3.5, p=0.001; 39% PD-L1≥1%, p=0.02) (Figure 1). Compared to a control cohort of patients with metastatic NSCLC without targetable alterations (n=192), EGFR ex20ins patients had longer overall survival (median 20 vs. 12 mo, HR 0.56, p=0.007) and longer time to treatment discontinuation (TTD) for platinum chemotherapy (median 7 vs. 4 mo, HR 0.6, p=0.02), and no significant improvement in TTD for immune checkpoint inhibitors (ICI) (HR 1.75, p=0.05) (Figure 2).

Conclusion: With better outcomes on platinum chemotherapy, patients with EGFR ex20ins NSCLC have improved prognosis, lower PD-L1 expression, lower TMB, and derive less benefit from ICI compared to patients with NSCLC without a targetable oncogene. Improving molecularly targeted therapies could provide greater benefit for patients with EGFR ex20ins.




A.
Overall Survival
Survival Probability
1.00
0.75
0.50
0.25
0.00
0
12
24
36
48
60
72
84
Time from first line of treatment (months)
NSCLC w/o targetable alterations 62 83 45 18 8 4 2 0
EGFR ex20ins 37 25 13 8 2 1 1 1
B.
ICI
Probability Remaining on Treatment
1.00
0.75
0.50
0.25
0.00
0
6
12
18
24
30
Time from the start of treatment (months)
NSCLC w/o targetable alterations 77 29 21 13 7 4
EGFR ex20ins 11 0 0 0 0 0
NSCLC w/o targetable alterations
EGFR exon 20 ins

P09.02: Mutated EGFR Pulmonary Adenocarcinoma Experience of the Medical Oncology Department of the Hassan II Hospital University in Fez

Yassine El Ouai[1], Zineb Benbrahim, Karima Oualla, Lamiae Amaadour, Samia Arifi, Nawfel Mellas

[1]*University Hospital Hassan Ii, Fez, Morocco*

Introduction: The discovery of the activating mutation of EGFR and their link with the response to TKI has made it possible to highlight a specific group of patients who can be effectively treated by these targeted therapies.

The aim of this work is to describe the main epidemiological, clinical and evolutionary aspects of this pathology.

Materials and Methods: This is a prospective study about 140 cases of pulmonary adenocarcinoma collected in the medical oncology department of the Hassan II hospital university in Fez during a period of thirty months from October 2017 to April 2020. All patients were included having histologically confirmed pulmonary adenocarcinoma.

Results: The mean age at diagnosis was 60.18 years, with a sex ratio of 2 in favor of the male. Smoking was the main risk factor (58%). The clinical symptoms were dominated by chest pain (29%), cough (26.3%) and dyspnea (23%).

The elective site was the right upper lobe (27%).

52% of patients were metastatic at the time of diagnosis. The elective site of metastases was in descending order: pulmonary and bone (13.6%), hepatic (10.9%), cerebral (11%) and adrenal (5.45%).

22% of patients were EGFR mutated, 52% female and 48% male. 48% of the patients were smoking and 52% non-smoking.

The most frequent mutations were found in exons 19 (35%), 20 (19%), 21 (6%) and 18 (3%).

109 EGFR WT patients (77.85%) received chemotherapy.

Progression-free survival was around 9.6%.

Fourteen patients (45.16%) received anti-EGFR TKI as a first line of therapy.

Five patients (16%) had grade II skin toxicity.

Progression-free survival was around 15.7 months.

Seventeen patients (54.8%) received platinum and taxane chemotherapy, with PFS on the order of 12.3 months.

Conclusion: TKI has revolutionized the prognosis of EGFR mutated adenocarcinoma, hence the interest in the generalization of treatment for all candidates.

P09.03: Mechanism of Growth-Inhibitory Effect of Pemetrexed Disodium Heptahydrate on Human PC9 (EGFR Exon 19 Deletion) Cells

Md Mohiuddin[1], Hideharu Kimura[1], Takashi Sone[1], Satoshi Watanabe[1], Hiroki Matsuoka[1], Keigo Saeki[1], Nanao Terada[1], Miki Abo[1], Kazuo Kasahara[1]

[1]*Department Of Respiratory Medicine, Kanazawa University, Kanazawa, Japan*

Background: Pemetrexed disodium heptahydrate (pemetrexed) in combination with another drug, is recommended for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). However, the specific participants and precise mechanisms are still not well understood. Here, we examine the in vitro effects of pemetrexed and further elucidate its potential molecular mechanism.

Methods: PC9 cells were treated with pemetrexed and then evaluated with cell viability assay, Giemsa staining, DAPI staining, flow cytometry (FCM), SA-β-Gal staining, and western blotting.

Results: We found that pemetrexed reduced the proliferation of PC9 cells. The cells treated with pemetrexed showed morphological signs of apoptosis. The apoptotic effect of pemetrexed was related to the generation of ROS and the loss of mitochondrial membrane potential. Cell cycle analysis showed that pemetrexed arrested PC9 cells in the G1 phase. Cellular senescence was associated with pRb hyperphosphorylation and CDK overexpression. Regarding the molecular mechanism of its apoptosis, pemetrexed can induce phosphorylation of p53 at ser 15 and ser 46. Moreover, the expression of extrinsic pathway proteins, such as Fas/FasL, DR4/TRAIL, and FADD, was elevated following pemetrexed treatment.

Conclusion: Collectively, in addition to apoptosis, pemetrexed can also cause specific adverse reactions, thus providing a new target for reducing lung toxicity.

P09.05: EGFR-TKIs Associated Cardiotoxicity in Lung Cancer Patients: An Analysis of FAERS Database

Dongchen Sun[1,2,3,4], Jiaqing Liu[1,2,3,4], Huaqiang Zhou[1,2,3], Ting Zhou[1,2,3], Yaxiong Zhang[1,2,3], Wenfeng Fang[1,2,3], Yunpeng Yang[1,2,3], Yan Huang[1,2,3], Li Zhang[1,2,3]

[1]Department of Medical Oncology, Sun Yat-sen University Cancer Cente, Guangzhou, China, [2]State Key Laboratory of Oncology in South China, Guangzhou, China, [3]Collaborative Innovation Center for Cancer Medicine, Guangzhou, China, [4]Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, China

Background: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), such as gefitinib, erlotinib, afatinib and osimertinib, have greatly improved the survival of lung cancer patients with EGFR mutation. Although multiple life-threatening cardiac adverse events associated with EGFR-TKIs have been observed, there are limited large-scale studies characterizing their cardiotoxicities.

Methods: Utilizing the US Food and Drug Administration (FDA) Adverse Reporting System (FAERS) database, we identified all lung cancer patients with adverse events (AEs) that were considered to be associated only with EGFR-TKIs from 2016 to 2020 (N=17,261). We excluded reports with missing age and sex and cases not used for primary lung cancer. Cardiac AEs were classified into cardiac failure (CF), atrial fibrillation (AF), QT prolongation, myocardial infarction (MI), pericardial effusion (PE) and others. Logistic regression and Chi-square test were performed using R software.

Results: Overall, there were 9,577 AEs associated with TKIs, of which 495 (5.2%) were cardiac disorder. Patients' baseline characteristics were shown in Table 1. There was a positive association between the incidence of cardiac AEs and advanced age (OR=2.05, 95% CI:1.65-2.57), treatment with osimertinib (OR=4.32, 95% CI:2.97-6.50) and treatment with combined types of TKIs (OR=3.87, 95% CI:2.32-6.48). However, no association was observed between the incidence of cardiac AEs and histology of lung cancer (Table 2). Furthermore, compared to other TKIs, increased risk of CF ($p<0.001$) and QT prolongation ($p<0.001$) were observed in patients who received osimertinib, while there was no significant differences in the risk of MI, AF and PE.

Conclusion: In conclusion, patients who are older and those who recieved osimertinib and combination of TKIs tended to have increased risk of cardiac AEs, especially increased risk of CF and QT prolongation. Physicians need to realize the cardiotoxicity of EGFR-TKIs, fulfill early identification and intervention of cardiac AEs and consult cardiologists to deal with these problems when necessary.

	Patients with Cardiac Disorders	Patients without Cardiac Disorders
Total Number of Reported AEs (%)	495(5.17)	9082(94.8)
Reporting Year (%)		
2016	90(18.2)	3039(33.5)
2017	104(21.0)	1585(17.5)
2018	109(22.0)	1616(17.8)
2019	118(23.8)	1438 (15.8)
2020	74(14.9)	1404(15.5)
EGFR-TKI (%)		
Gefitinib	30(6.1)	1179(13.0)
Erlotinib	104(21.0)	3528(38.8)
Afatinib	74(14.9)	1636(18.0)
Osimertinib	253(51.1)	2423(26.7)
Combination	34(6.9)	316(3.5)
Sex (%)		
Female	323(65.3)	5786(63.7)
Male	172(34.7)	3296(36.3)
Age, yrs (%)		
>=65	386(78.0)	5731(63.1)
<65	109(22.0)	3351(36.9)
Histology (%)		
Small cell lung cancer	2(0.4)	35(0.4)
Non-small cell lung cancer (NOS)	301(60.8)	3761(41.4)
Lung adenocarcinoma	78(15.8)	1081(11.9)
Lung squamous carcinoma	3(0.6)	27(0.3)
Lung adenosquamous carcinoma	1(0.2)	6(0.1)
Lung cancer (NOS)	110(22.2)	4172(45.9)

Variable		N	Odds ratio	p
age	<65	3460	Reference	
	≥65	6117	2.05 (1.65, 2.57)	<0.001
EGFR_TKI	Gefitinib	1209	Reference	
	Erlotinib	3632	1.74 (1.15, 2.71)	0.01
	Afatinib	1710	1.63 (1.07, 2.56)	0.03
	Osimertinib	2676	4.32 (2.97, 6.50)	<0.001
	Combination	350	3.87 (2.32, 6.48)	<0.001
histology	Small cell lung cancer	37	Reference	
	Non−Small cell lung cancer (NOS)	4062	1.32 (0.39, 8.25)	0.70
	Lung adenocarcinmoa	1159	1.69 (0.49, 10.67)	0.48
	Lung squomous carcinoma	30	2.85 (0.43, 23.25)	0.28
	Lung adenosquamous carcinoma	7	2.89 (0.12, 36.98)	0.42
	Lung cancer (NOS)	4282	0.53 (0.16, 3.35)	0.40

P09.06: Restoring Therapeutic Efficacy of Osimertinib in EGFR-driven NSCLC by Targeting the BMP/Endoglin Signaling Axis

Manish Thiruvalluvan[1], Sandrine Billet[1], Karen Reckamp[1], Neil Bhowmick[1,2]

[1]Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, United States, [2]VA Greater Los Angeles Healthcare System, Los Angeles, United States

Background: Approximately 15-20% of non-small cell lung cancer (NSCLC) patients develop mutations in the epidermal growth factor receptor (EGFR) that can be targeted by tyrosine kinase inhibitors (TKIs). Osimertinib, a third generation TKI, has emerged as the standard of care for patients diagnosed with EGFR driven NSCLC. Despite its dramatic efficacy in advanced NSCLC, resistance is found to develop within two years of treatment for most patients and is difficult to combat due to its heterogeneous nature. This problem beckons an approach to improve efficacy of osimertinib that will allow for greater drug sensitization to curtail rapidly growing malignancies.

Methods: We established an osimertinib-resistant cell line (H1975R) from parental H1975 NSCLC cells (H1975P), which harbors both L858R and T790M EGFR mutations. Through gradual dose escalation over a period of four to six months, we achieved an osimertinib IC50 three-log greater than the parental line. Human lung fibroblast line MRC5 was co-cultured with multiple NSCLC cell lines to assess the impact of the microenvironment on osimertinib efficacy and resistance. We used 10x single cell RNA sequencing and RT-PCR to characterize EGFR signaling, changes in EGFR bypass mechanisms, and acquisition of small cell features. H1975R cell line was tested alone and in combination with MRC5 cells in culture and in xenografted mice, by subjecting them to combination therapy of osimertinib and carotuximab, a monoclonal antibody that targets endoglin (CD105) and blocks BMP signaling.

Results: NSCLC cells (A549 and H1975) exhibited elevated CD105 expression on their cell surface in response to EGFR inhibition by gefitinib and osimertinib treatment. The single agent treatment with carotuximab or the combination osimertinib and carotuximab treatment of A549, H1975P, HCC827 cells agent had little effect compared to osimertinib treatment alone. Culturing NSCLC cells alongside lung fibroblasts, MRC5, significantly reduced the efficacy of osimertinib. However, carotuximab demonstrated significantly improved osimertinib H1975P response when co-cultured with lung fibroblasts. Interestingly, proliferation of H1975R cells was greatly inhibited by carotuximab, which was further suppressed in combination with osimertinib. Through single cell sequencing, we identified that H1975R cells exhibited greater expression of bypass signaling factors such as MEK, ERK and PIK3CA, including a dramatic increase in expression of small cell markers that was validated by RT-PCR. There was a significant downregulation of the bypass signaling and small cell markers by carotuximab treatment. Xenografts of H1975R cells presented with reduced tumor expansion when subjected to combination therapy of carotuximab and osimertinib, compared to either drug alone or the control.

Conclusion: Experiments with lung fibroblasts suggest that the tumor microenvironment in NSCLC tumors plays a key role in determining cellular outcomes to osimertinib. We successfully constructed an osimertinib-resistant cell line, H1975R, that exhibited increased expression of EGFR bypass signaling and small cell markers. The heterogeneous osimertinib-resistant cells were found to have restored sensitivity to EGFR inhibition in the context of CD105 signaling inhibition by carotuximab. CD105 inhibition was able effectively reduce the size of osimertinib-resistant tumors. Taken together, these results suggest a novel treatment strategy for NSCLC patients that develop resistance to Osimertinib.

P10.01: The Frequency of KRAS Mutations in Brazilian Lung Cancer Patients

Rodrigo De Oliveira Cavagna[1], Flávia Escremim de Paula[2], Iara Santana[2,3], Vinicius Duval da Silva[3], Eduardo Caetano A. da Silva[3], Carlos Eduardo Bacchi[4], José Elias Miziara[5], Josiane Mourão Dias[6], Pedro De Marchi[1,7], Leticia Ferro Leal[1,8], Rui Manuel Reis[1,2,9,10]

[1]Molecular Oncology Research Center, Barretos Cancer Hospital, Barretos, Brazil, [2]Molecular Diagnostic Laboratory, Barretos Cancer Hospital, Barretos, Brazil, [3]Department of Pathology of Barretos Cancer Hospital, Barretos, Brazil, [4]Bacchi Laboratory, Botucatu, Brazil, [5]Department Thoracic Surgery, Barretos Cancer Hospital, Barretos, Brazil, [6]Department of Medical Oncology, Barretos Cancer Hospital, Barretos, Brazil, [7]Oncoclinicas, Rio de Janeiro, Brazil, [8]Barretos School of Health Sciences Dr. Paulo Prata – FACISB, Barretos, Brazil, [9]Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal, [10]ICVS/3B's – PT Government Associate Laboratory, Braga/Guimaraes, Portugal

Background: Lung cancer is the deadliest cancer worldwide. Targeted therapies have revolutionized clinical management of non-small cell lung cancer (NSCLC) patients; however, only a subset of patients harbors the targeted mutations that benefit of tailored therapies. The KRAS mutations are present in a quarter of NSCLC cases, and, until lately, no targeted therapy was available for these cases. Recently, a new agent, Sotorasib (AMG-510), has shown promising results in NSCLC tumors harboring the KRAS mutation p.Gly12Cys. In Brazil, the knowledge of the KRAS mutations frequency and its variants are scarce. We aimed to address the frequency of the KRAS mutations, specifically the p.Gly12Cys mutation, in Brazilian NSCLC.

Methods: A series of Brazilian NSCLC patients (n=863) were molecularly analyzed for the KRAS mutational status. The KRAS mutational data previously reported on the Brazilian NSCLC series was also collected. The KRAS mutations were found in 26% of patients (n=220/863), and the most frequent was the p.Gly12Cys, corresponding to 35.5% of KRAS-mutated cases and 9% of all NSCLC cases (n=78/863). Additional KRAS variants were p.Gly12Val (23.6% of KRAS-mutated cases; n=52) and p.Gly12Asp (16.4% of KRAS-mutated cases; n=36) cases. Overall, 25% (n=695) of all reported Brazilian NSCLC cases (n=2752) harbor KRAS mutations, and the most frequent variant was p.Gly12Cys, corresponding to 9% of all Brazilian NSCLC cases (n=256/2752). In conclusion, almost 10% of Brazilian NSCLC patients harbor the KRAS p.Gly12Cys mutation, and they can potentially be benefited by the newly agent Sotorasib.

P10.02: Inhibitory Effect of Pemetrexed Disodium Heptahydrate on the Growth of KRAS-Dependent A549 Lung Cancer Cells

Md Mohiuddin[1], Hideharu Kimura[1], Takashi Sone[1], Satoshi Watanabe[1], Hiroki Matsuoka[1], Keigo Saeki[1], Nanao Terada[1], Miki Abo[1], Kazuo Kasahara[1]

[1]*Department Of Respiratory Medicine, Kanazawa University, Kanazawa, Japan*

Background: Pemetrexed disodium heptahydrate (pemetrexed) is currently available for the treatment of patients with advanced non-small cell lung cancer (NSCLC). Meanwhile, KRAS mutations occur in over 30% of all lung cancer cases; in this study, we examined the anticancer ability of pemetrexed in KRAS-dependent A549 lung cancer cells.

Methods: A549 cells were treated with pemetrexed for 72 h and then evaluated with flow cytometry (FCM) and western blotting.

Results: The apoptotic effects of pemetrexed were observed through increased levels of cleaved caspase-9 (Asp 315), cleaved caspase-3 (Asp 175) and cleaved PARP. Furthermore, pemetrexed enhanced ROS-mediated DNA damage and increased pro-apoptotic Bax protein expression to induce loss of mitochondrial membrane potential (MMP). The elevated protein expression of β-galactosidase was associated with cellular senescence induction. Importantly, pemetrexed induced cytotoxicity without inhibiting the RAS/RAF/MEK/ERK signaling pathway, while it induced autophagy via the AMPK/mTOR signaling pathway.

Conclusion: Collectively, these results suggest that, in addition to apoptosis, pemetrexed induced autophagy and cellular senescence, providing a promising direction for KRAS-targeted therapy development.

P11.01: Correlation Between Histological Subtypes and Prognosis in Patients with Early Stage Lung Adenocarcinoma: An Observational Retrospective Cohort Study

Stylianos Gaitanakis[1], Foteini Chatzivasiloglou[2], Levon Toufektzian[3], Georgios Nakos[4], Dimitra Grapsa[5], Timothy Sakellaridis[1], Konstantinos Syrigos[5]

[1]417 NIMTS, Athens, Greece, [2]Nikaia General Hospital, Piraeus, Greece, [3]Athens Medical Group, Athens, Greece, [4]University of Cyprus, Nicossia, Cyprus, [5]Sotiria General Hospital of Chest Diseases, Athens, Greece

Background: 2018 WHO classification for lung cancer has prevailed as a more clinically accurate one since the most common diagnosis of mixed adenocarcinoma should be further divided into five invasive subtypes (lepidic, acinar, papillary, solid, and micropapillary). The objective of the present study is to identify whether, in early-stage adenocarcinoma, subtypes correlate with patients' future prognosis.

Methods: We retrospectively evaluated a series of resected stage I and II lung adenocarcinomas (102 patients) that were treated with R0 anatomic resection at the Thoracic Surgery Department of Sotiria General Hospital of Thoracic Diseases. The predominant histological subtype was identified by a non-institutional pathologist.

Three overall prognostic groups were identified: low grade: adenocarcinoma in situ, minimally invasive adenocarcinoma and lepidic predominant; intermediate grade: papillary predominant and acinar predominant and high grade: solid predominant and micropapillary predominant.

Disease-free survival (DFS) and overall survival (OS) were correlated with clinical, histological, and classification parameters for the participants.

Results: Concerning OS, the patients with high-grade subtype had significantly poorer survival than the patients with low and intermediate grade adenocarcinoma (p<0,001). With solid and micropapillary subtype being independent prognostic factors for worse survival. Of equal importance were the results for the DFS, where patients of intermediate grade had less frequent recurrence than the patients with high-grade adenocarcinoma (p<0,001).

Moreover, multivariate analysis showed that male gender and no adjuvant chemotherapy for the high-grade group were significant poor prognostic factors concerning OS and recurrence.

Conclusion: Predominantly micropapillary and solid tumors constitute aggressive subtypes which are correlated with earlier and more frequent recurrences after successful surgical treatment. The recent 2015 IASLC/ATS/ERS classification may determine the personalized prospective therapeutic approach of the different histologic subtypes of lung adenocarcinoma.

Considering the high probability for recurrence of micropapillary or solid tumors even for stage I, adjuvant therapies should be considered for this subgroup of patients.

P11.02: Expressions of Biomarkers of Malignant Pleural Mesothelioma at Pham Ngoc Thach Hospital, Vietnam in 5 Years From 2015-2019

Nguyen Son Lam[1]

[1]*Pham Ngoc Thach Hospital, Ho Chi Minh City, Viet Nam*

Introduction: The survey of the biomarkers of MPM partly aims to build a standard in diagnosis and anticipate upcoming treatment trends for this malignant tumors. In Vietnam, currently there are no extensive studies on the biomarkers of MPM in large quantities. We carry out research on MPM biomarkers for the following objectives:

1. Investigation of diagnostic epidemiological markers and diagnostic immunochemistry biomarkers in diagnostic MPM.

2. Investigation of gene mutation expressions and PD-L1 expressions in MPM.

3. Application in diagnostic evaluation and future treatment trends for MPM.

Methods: Retrospective, descriptive statistics with cross-section. Investigation of manifestations: epidemiology, diagnostic immunohistochemistry, gene driver expressions, and immune check point PD-L1 expressions in MPM.

Results: a. There is evidence of presentative asbestos bodies (16.93%) and SV-40 (7.26%).

b. Calretinin, Glut-1, XiAP and WT-1 immunohistochemistry markers [Positive ratios: 105 cases (84.68%), 102 cases (82.26%), 103 cases (83,06%) and 116 cases (93.54%)] have been the highest expressions in the cases of MPM and has the best value in diagnosing MPM.

c. The most important gene expression have been recognized: p16 Deletion and BAP1 [Positive rates: 8 cases (6.45%) and 15 cases (12.09%)]. There is possibility of application in targeted treatment.

d. There is a positive PD-L1 ratio with two markers 22C3 and SP263 [Positive rate: 17 cases (13.71%) and 25 cases (20.16%)]. This also leads to applicability for immunotherapy for MPM.

Conclusion: Through a survey of biomarkers in 124 cases MPM at Pham Ngoc Thach Hospital from 2015-2019 we have brought the following statements:

For diagnosis: There is evidence of presence of asbestos body and SV-40 and the IHC markers of Calretinin, Glut-1 and WT-1 have been the highest expressions in the cases of MPM and have been the best values in epidemiological diagnosis and positive diagnosis of MPM.

For treatment: The most important gene expressions have been p16 Deletion and BAP1 and a positive PD-L1 ratio with two markers: 22C3 and SP263. This also leads to the possibility of targeted application and immunotherapy for MPM.

Keywords: Malignant Pleural Mesothelioma, Epitheliod MPM, Sarcomatoid MPM, Biphasic MPM, Well-differentiated Papillary MPM, Adenomatoid MPM, Anaplastic MPM, Deletion p16: p16 deletion, BAP1: BRCA1 associated protein-1 (ubiquitin carboxy-terminal hydrolase)

	Epithelioid MPM (Cases)	Sarcomatoid MPM (Cases)	Biphasic MPM (Cases)	Well-diff. Papil. MPM (Cases)	The Other MPM (Cases)	Total (Cases & %)
EGFR	1	0	0	1	0	2 (1,61%)
VEGF	1	0	2	0	0	3 (2,42%)
PDGF	3	0	0	0	1	4 (3,23%)
HGF/c-Met	0	1	3	0	0	4 (3,23%)
mTOR	0	0	1	0	0	1 (0,81%)
hTNF-α	2	1	0	0	1	4 (3,23%)
Deletion p16	3	0	4	1	2	8 (6,45%)
BAP1	6	1	5	0	3	15(12,09%)

Table 1: Distribution of Gene Expressions of MPM

	Epithelioid MPM (Cases)	Sarcomatoid MPM (Cases)	Biphasic MPM (Cases)	Well.diff.Papil. MPM (Cases)	The Other MPM (Cases)	Total (Cases & %)
22C3 Dako [TC(+) = 50%]	11	1	3	1	1	17 (13,71%)
SP263 Ventana [TC(+) = 25%]	14	1	7	1	2	25 (20,16%)

Table 2: Expressions of immune check points PD-L1 of MPM

Author Index

A

A. da Silva, Eduardo Caetano	P10.01
Abo, Miki	P09.03, P10.02
Ahmed, Hasan Shahrear	P01.01
Amaadour, Lamiae	P09.02
Anderson, Amanda	P05.01
Antipa, Phillip	P02.01
Arcila, Maria	P09.01
Arifi, Samia	P09.02
Arjuman, Farida	P01.01
Arunsingh S, Moses	P07.02
Asselin-Labat, Marie-Liesse	P02.01

B

Bacchi, Carlos Eduardo	P10.01
Bazhenova, Lyudmila	P07.01
Beattie, Jason	S12.04
Benbrahim, Zineb	P09.02
Betts, Courtney	S12.05
Bhattacharyya, Tapesh	P07.02
Bhowmick, Neil	P09.06
Billet, Sandrine	P09.06
Biswas, Bivas	P07.02
Bozinovski, Steve	P02.01
Boni, Valentina	S12.02
Boyd, Kelli	S12.05
Bradbury, Penelopy	P04.01
Brastianos, Priscilla	P03.01
Bryce, Richard	S12.02
Byers, Lauren	P05.01

C

Cabanero, Michael	P04.01
Cardnell, Robert	P05.01
Carter, Scott	P03.01
Cummings, Amy L.	S12.02
Chatzivasiloglou, Foteini	P11.01
Chen, Heidi	S12.05
Chen, Hua Chang	S12.05
Choudhury, Noura	P09.01
Christie, Michael	P02.01
Coussens, Lisa	S12.05

D

Dabkara, Deepak	P07.02
De Marchi, Pedro	P10.01
Dooms, Christophe	S12.02
De Oliveira Cavagna, Rodrigo	P10.01
Duval da Silva, Vinicius	P10.01

E

Ebben, Johnathan	P08.01
Egger, Jacklynn	S12.04
El Ouai, Yassine	P09.02
Eli, Lisa D.	S12.02
Escremim de Paula, Flávia	P10.01
Eshita, Noor Ishrat	P01.01

F

Falcon, Christina	P09.01
Faleck, David	S12.04
Fang, Wenfeng	P09.05
Fernandes, Roxanne	P04.01
Fernandez, Luisa	P05.01
Ferro Leal, Leticia	P10.01
Flynn, Jessica	P09.01
Fuentes, Paige	S12.04
Fujimoto, Junya	P05.01

G

Gainor, Justin	P03.01
Gaitanakis, Stylianos	P11.01
Gambarin, Maya	S12.04
Gay, Carl	P05.01
Gilbertson, Cole	P05.01
Giustini, Nicholas	P07.01
Gold, Kathryn	P07.01
Goldman, Jonathan W.	S12.02
Gonzalez-Ericsson, Paula	S12.05
Grapsa, Dimitra	P11.01
Groves, Sarah	S12.05

H

Hähnel, Philipp	P03.01
Haley, Barbara	S12.02
Hasan, ATM Kamrul	P01.01
Hattangadi-Gluth, Jona	P07.01
Heller, Glenn	P09.01
Hellmann, Matthew	S12.04
Huang, Yan	P09.05
Husain, Hatim	P07.01

I

Iams, Wade	S12.05
Irving, Louis	P02.01
Islam, Muhammad Rafiqul	P01.01

J

Jain, Sonia	P07.01
Janne, Pasi	P06.01
Jendrisak, Adam	P05.01
John, Tom	P02.01
Jones, Joshua	P05.01

K

Kabbinavar, Fairooz	S12.02
Kamel-Reid, Suzanne	P04.01
Kasahara, Kazuo	P09.03, P10.02
Kim, Albert	P03.01
Kimura, Hideharu	P09.03
Kimura, Hideharu	P10.02
Ko, Hyang Mi	P04.01
Kopparapu, Prasad	S12.05
Kozono, David	P06.01
Kris, Mark	P09.01, S12.04

L

Lacouture, Mario	S12.04
Ladanyi, Marc	P09.01
Lalani, Alshad S.	S12.02
Lam, Nguyen Son	P11.02
Lanuti, Michael	P06.01
Law, Jennifer H.	P04.01
Le, Lisa	P04.01
Leal, Ticiana	P08.01
Leighl, Natasha	P04.01
Leong, Tracy	P02.01
Li, Jia	S12.05
Liu, Geoff	P04.01
Liu, Jiaqing	P09.05
Liu, Qi	S12.05
Lovly, Christine	S12.05
Lowe, Cindy	S12.05
Luo, Jia	S12.04

M

Mahipal, Amit	S12.02
Mak, Raymond	P06.01
Marcoux, J. Paul	P06.01
Markson, Sam	P03.01
Matsuoka, Hiroki	P09.03, P10.02
Mellas, Nawfel	P09.02
Menzl, Anna	P07.01
Mino-Kenudson, Mari	P06.01
Mitchell, William	P07.01
Miziara, José Elias	P10.01
Mohiuddin, Md	P09.03, P10.02
Mora, Joanna	P03.01
Mourão Dias, Josiane	P10.01
Muzikansky, Alona	P06.01

N

Nakos, Georgios	P11.01
Nayyar, Naema	P03.01
Nieblas-Bedolla, Edwin	P03.01

O

Oualla, Karima	P09.02

P

Pal, Prodipto	P04.01
Patel, Sandip P.	P07.01
Perdrizet, Kirstin	P04.01
Piotrowska, Zofia	P06.01
Piper-Vallillo, Andrew	P06.01

Q

Quaranta, Vito	S12.05

R

Rangamuwa, Kanishka	P02.01
Reckamp, Karen	P09.06
Reis, Rui Manuel	P10.01
Ridi, Ishrat Nur	P01.01
Riely, Gregory	P09.01
Rivzi, Hira	P09.01, S12.04
Rotow, Julia	P06.01
Rudin, Charles	P09.01

S

Sacher, Adrian	P04.01
Saeki, Keigo	P09.03, P10.02
Saha, Saheli	P07.02
Sakellaridis, Timothy	P11.01
Sanghvi, Parag	P07.01
Santana, Iara	P10.01
Santomasso, Bianca	S12.04
Santosham, Ritesh JM	P07.02
Schoenfeld, Adam	P09.01
Schonhoft, Joseph	P05.01
Schwock, Joerg	P04.01
Sen, Triparna	S12.03
Sequist, Lecia	P06.01
Sethakorn, Nan	P08.01
Shabir, Muqdas	P04.01
Shah, Naisargee	S12.02
Shepherd, Frances	P04.01
Sievers, Chelsie	P08.01
Simpson, Daniel	P07.01
Sivagnanam, Shamilene	S12.05
Son, Klarissa	P07.01
Sone, Takashi	P09.03, P10.02
Steinfort, Daniel	P02.01
Stewart, Allison	P05.01
Stockley, Tracy	P04.01
Strickland, Matthew	P03.01
Suga, J. Marie	S12.02
Sun, Dongchen	P09.05
Swanson, Scott	P06.01
Syrigos, Konstantinos	P11.01

T

Terada, Nanao	P09.03, P10.02
Thiruvalluvan, Manish	P09.06
Thomas, Portia	S12.05
Toufektzian, Levon	P11.01
Tsao, Ming-Sound	P04.01
Tyson, Darren	S12.05

U

Urbanic, James	P07.01

V

Villanueva, Nicolas	P07.01
Viteri, Satigo	S12.02

W

Wang, Jing	P05.01
Wang, Qi	P05.01
Watanabe, Satoshi	P09.03, P10.02
Wenstrup, Rick	P05.01
Willers, Henning	P06.01
Wistuba, Ignacio	P05.01
Wright, Cameron	P06.01

X

Xu, Feng	S12.02

Y

Yan, Yingjun	S12.05
Yang, Yunpeng	P09.05
Yu, Helena	P09.01

Z

Zhang, Bingnan	P05.01
Zhang, Li	P09.05
Zhang, Tong	P04.01
Zhang, Yaxiong	P09.05
Zhang, Yun-Kai	S12.05
Zhou, Huaqiang	P09.05
Zhou, Ting	P09.05