

than TKI alone. We observed that VEGFR-2 was expressed at relatively high levels in HCC827-GR than other cell line without METamp, and VEGF pathway inhibition by bevacizumab resulted in decreased phospho-c-Met in HCC827-GR cell lines. This result provided *in vitro* evidence that bevacizumab can reduce MET pathway activation. **Conclusion:** This study provided basic knowledge and evidence for patients harboring concomitant EGFR and *de novo* MET amplification who may obtain favorable response to combinatorial treatment of TKI and bevacizumab. Encouraging antitumor activity of TKI+bevacizumab support further development of this combination for patients with advanced NSCLC and other solid tumors. **Keywords:** EGFR, *de novo* MET, bevacizumab

P3.13-13

Afatinib in Lung Adenocarcinoma Harboring *de novo* EGFR Exon 20 Insertions.

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Background: NSCLC, particularly adenocarcinoma, has been successfully treated with upfront targeted therapies according to respective oncogenic mutations in a tailor-made model. EGFR-TK inhibitors (TKI) have exhibited major responses, improving PFS, RR and even mOS (a subset treated with afatinib). This drug has emerged as the best option for those with uncommon mutations, but until now is broadly unknown its action in exon 20 mutations, which accounts for nearly 3% of all and, classically, is associated to worse response to 1st-generation TKI. **Method:** Here, in this retrospective analysis, is reported the past medical history and clinical outcomes of two patients who presented with *de novo* EGFR exon 20 insertions: D770_N771insSVD and Ser768_Asp770dup. The patient were treated in two different Cancer Centers in Brazil and the mutations were identified with Next Generation Sequencing (NGS) by Illumina HiSeqs of Foundation Medicine (FM) and the other by a local certified laboratory using Ion Torrent-PGM Thermo Fischer v5.0. Analysis were performed in tissue samples extracted from FFPE. The follow-up was obtained from electronic charts. **Result:** Patient 1: never-smoker 66 y/o lady, without comorbidities, presented 12 mo ago with dry cough, thoracic pain and -10% of weight. CT scan revealed extensive ground-glass infiltration area and multiple bilateral pulmonary nodules. Lung biopsy pointed out a mod. differentiated adenocarcinoma of predominantly lepidic pattern (IHC: AE1/2+, CK20-, CK7+, Napsin A+, TTF1+). With this, rtPCR (Cobas Mu test v.2) detected an exon 20 insertion, thus ineligible to upfront EGFR-TKI. However, was chosen to re-analyze it using NGS (FM). After a TAT of only 2 weeks, we retrieved the result which showed a poorly described mutation: EGFR exon 20 insertion D770_N771insSVD. Afatinib 30mg/day was started and, only three days after the initiation, the patient decreased the dry cough and fatigue. CT scans showed stable disease after 45 days of continuous use. Patient 2 had a more extensive past medical history: 1L chemo, followed by nivolumab and docetaxel. Lastly, NGS revealed an uncommon EGFR exon 20 insertion (Ser768_Asp770dup). Rapid clinical improvement was observed (less fatigue and dyspnea), but occurred liver progression in the first control, 4w after initiation. **Conclusion:** This study confirms that rare mutations have been increasingly seen due to the employment of improved sensitivity genetic techniques, like NGS. Furthermore, reveals two rare examples of rapid clinical response to afatinib in patients harboring EGFR exon 20 insertions.

Finally, despite it could be an option for management of this broadly unknown situation, it suggests caution because of the short-lasting benefit in some. **Keywords:** exon 20 insertions, EGFR, Afatinib

P3.13-14

Identification of Novel Mutations by High-Throughput Sequencing in T790M Wildtype/*cMET* Unamplified NSCLC with Acquired Resistance to EGFR TKIs

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Background: Lung cancer remains the leading cause of cancer-related death worldwide. Though most patients with EGFR activating mutations are sensitive to EGFR tyrosine kinase inhibitors (TKIs), tumors will inevitably acquire resistance to first generation EGFR TKIs. *EGFR* T790M mutation and *cMET* amplification are common mechanisms. Further study is needed to explore unknown genomic alterations contributing to drug resistance. **Method:** In the screening period of ASTRIS (D5160C00022) study of single center, tumor and blood samples from 69 stage IIIB-IV NSCLC patients defined as acquired resistance to first generation EGFR TKIs (Gefitinib, Elortinib or Ecotinib) were collected. The cobas® and Droplet digital PCR (ddPCR) were used to detect T790M mutations in tumor samples and plasma ctDNA. *cMET* amplification were evaluated by Fluorescence *in situ* Hybridization (FISH). Exome sequencing were performed in four T790M wildtype/*cMET* unamplified samples. **Result:** The T790M mutation rate of FFPE tissue cobas, plasma cobas and plasma ddPCR testing were 54.5%, 21.3% and 30.4% respectively. Taking all testing methods into account, the T790M positive rate was 52.2%. In 21 samples which tumor re-biopsy was performed, 14 were T790M positive (66.7%). *cMET* amplification were identified in 3 out of 7 T790M negative samples. Exome sequencing in 4 T790M wildtype/*cMET* unamplified samples and paired white blood cells identified a cohort of candidate key mutated genes including *BRAF*, *FGFR1*, *PAK1*, *PCNT*, *PEBP4* and *SOX3*. **Conclusion:** EGFR T790M mutation and *cMET* amplification are main mechanisms leading to EGFR TKI resistant in lung adenocarcinoma. These key mutated genes identified in the present study would need further functional study validation. **Keywords:** exome sequencing, *cMET*, T790M

P3.13-15

First-Line Afatinib Dose Initiation and Adjustment in Patients with EGFR Mutant Advanced Non-Small Cell Lung Cancer

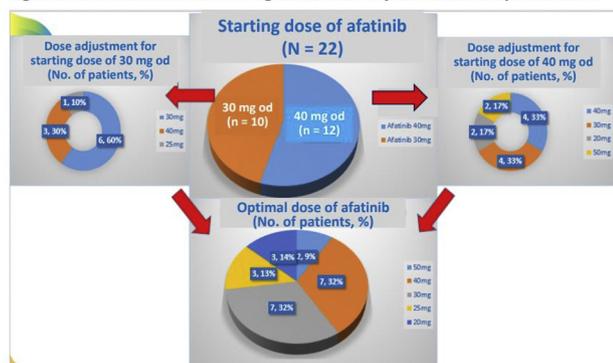


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Background: The recommended starting dose of afatinib is 40mg od with 20mg, 30mg and 50mg tablets available for dose adjustment. **Method:** This is a retrospective observational study of starting dose, dose adjustment and optimal dose of first-line afatinib in patients with

EGFR mutant advanced non-small cell lung cancer in University Malaya Medical Center from 1st December 2014 to 30th April 2018. **Result:** Of 22 patients on first-line afatinib, the starting dose was 40 mg od in 12 patients and 30 mg od in 10 patients (Figure 1). Among the 12 patients started on afatinib 40mg od, 4 (33.3%) did not require dose adjustment, 4 (33.3%) needed dose reduction to 30mg od, 2 (16.7%) needed dose reduction to 20mg od, and 2 (16.7%) had dose escalation to 50mg od. Among 10 patients started on afatinib 30mg od, 6 (60%) did not require dose adjustment, 1 (10%) needed dose reduction to 25mg od and 3 (30%) had dose escalation to 40mg od. Dose reduction was to reduce the cost of treatment in 1 patient and to reduce drug-related side-effects in the rest. Dose escalation was exclusively to improve disease control. The overall response rate and disease control rate was 80% (8/10) and 90% (9/10) in patients who did not require dose adjustment; while the respective rates were 85.7% (6/7) and 100% (7/7) in patients who had dose reduction. The optimal dose of afatinib defined by good disease control and tolerable side-effects was 50mg od in 9.1% (2/22), 40mg od in 31.8% (7/22), 30mg od in 31.8% (7/22), 25mg od in 13.6% (3/22) and 20mg od in 13.6% (3/22) of patients. **Conclusion:** We suggest starting afatinib at 30mg od and adjust the dose accordingly because dose adjustment is not required in most cases on this starting dose and it is the commonest optimal dose. **Keywords:** afatinib, dose adjustment, Optimal dose

Figure 1 First-line afatinib starting dose, dose adjustment and optimal dose



gene rearrangement. The coexistence of EGFR mutations and EML4-ALK rearrangements have been described as extremely rare. Perhaps this is due to its low prevalence and the sensitivity of available diagnostic modalities. All India Institute of Medical Sciences, Bhubaneswar, is an upcoming institute of national importance situated in eastern India. No report on EGFR mutation and EML4-ALK rearrangement has been published so far from this region of India. **Method:** We retrospectively analysed the available data of patients from June 2014 to April 2018. Genetic testing was done from tissue block specimens immediately after establishing the histology. EGFR mutation analysis were done using commercially available Real Time PCR and ALK-positivity was assessed with immunohistochemistry (IHC) by VENTANA ALK (D5F3) CDx Assay. We investigated the course of disease with the efficacy of targeted therapy in EGFR/ALK co-altered NSCLCs. **Result:** Out of 251 NSCLC cases, 198 had adenocarcinoma and only four patients (1.6%) had concomitant EGFR/ALK co-alterations. Of the EGFR mutations, two were positive for Exon 19 and other two were positive for Exon 21. Mean age for Exon 19 and Exon 21 positive patients were 40 and 63 respectively. All four patients were male and had advanced stages of lung cancer. Mutation in all the four patients were detected from initial tissue biopsy and they were negative for ROS1. Three patients had received platinum based doublet regimen followed by EGFR-TKI and one patient received Erlotinib. None had received Crizotinib yet. **Conclusion:** The coexistence of EGFR mutations and EML4-ALK rearrangements is low but higher than other geographical areas. Since the two alterations may coexist from the beginning of diagnosis, future perspective in management could be finding potential efficacy of a double inhibition of both ALK and EGFR mutations. **Keywords:** EGFR, ALK, NSCLC

P3.13-17

A Retrospective Study: Central Nervous System Response to Osimertinib in Patients with Advanced NSCLC



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Background: Central nervous system (CNS) metastases are common in patients with non-small-cell lung cancer (NSCLC). More than 30% of patients who progress during or after treatment with epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) have CNS metastases. Osimertinib, a third-generation EGFR-TKI, has been demonstrated promising intracranial efficacy in patients with advanced NSCLC from several large scale randomized control trials. We aimed to explore clinical impact of osimertinib for patients with CNS metastases, advanced NSCLC in real world setting. **Method:** Patients with advanced NSCLC who received osimertinib after progression of prior EGFR-TKIs and CNS metastases on baseline brain scan were retrospectively collected from Cancer Hospital Chinese Academy of Medical Sciences. Primary outcome was objective response rate (ORR) and secondary objectives were disease control rate (DCR), progression-free survival (PFS), time to tumor response, median best percentage change from baseline in CNS target lesion (TL) size and safety. **Result:** Between Apr 1, 2017, and Dec 30, 2017, 22 patients met selection criteria, 15 with ≥ 1 measurable CNS lesion (RECIST 1.1) were

P3.13-16

Concomitant EML4-ALK Rearrangement and EGFR Mutation in Non-Small Cell Lung Cancer Patients: Data from Eastern Indian Hospital.



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Background: Clinical guidelines recommend routine testing for genetic mutations in all adenocarcinoma of lung, including ALK EML4