clinical outcomes. Different detection assays for METex14 using various platforms have yielded mixed results across studies. It is imperative to utilize reliable and validated molecular assays to identify pts to be treated with MET. RNA-based detection of METex14 is considered the gold standard, since this assay measures the direct result of deletion of exon 14 event regardless of underlying genomic events. DNA-based next-generation sequencing (NGS) must detect genomic alterations within MET exon 14 and adjacent intronic regions that alter a splicing site or delete the whole MET exon 14. Methods: The GEOMETRY mono-1 study evaluated the efficacy and safety of capmatinib in pts with EGFR-wt, ALK-neg, NSCLC harboring METex14. This retrospective analysis compared DNA-based NGS with RNA-based RT-PCR in detecting METex14 in the GEOMETRY mono-1 study. Eligible METex14-mutated pts confirmed by RT-PCR qualitative assay using RNA extracted from baseline formalin-fixed, paraffin-dipped (FFPE) tissue samples were assigned to cohorts 4 (C4; previously treated) or 5b (C5b; treatment-naive), independent of MET amplification status. Retrospectively, METex14 positive and prescreen failed negative baseline FFPE tissue samples were tested using a hybrid capture DNA-based NGS assay (FoundationOne®). The METex14 positive pts by DNA NGS were defined as having MET alterations that are predicted to lead to MET exon 14 skipping. Results: Of the 97 enrolled pts from the METex14-mutated cohorts C4 (n=69) and C5b (n=28) of the GEOMETRY mono-1 study, 73 pts had baseline tumor biopsy samples (C4, n=53; C5b, n=20) that met the requirements for the FoundationOne® NGS assay (minimum requirements: tissue volume ≥0.1 mm³, DNA yield ≥22 ng, percent tumor nuclei ≥10%). The FoundationOne® NGS assay identified METex14 in 72 of 73 positive pts, with a concordance of ≥99% to the qualitative RT-PCR test used previously for testing. The variants detected included 41 unique canonical alterations that are predicted to lead to METex14. 1 pt with only a noncanonical METex14 rearrangement was not included in the concordance analysis and reported stable disease. None of the RT-PCR negative patients were reported as positive by NGS. Conclusions: Detection of MET exon 14 skipping events can be achieved by sequencing DNA or RT-PCR. A very high concordance was observed between DNA-based hybrid-capture NGS and RNA-based RT-PCR in the detection of METex14 in FFPE tumor tissue from advanced NSCLC pts. NGS enables parallel detection of actionable alterations without sequential testing by single gene. Furthermore, this technique provides a comprehensive genomic profile to inform treatment plan and any potential mechanisms of resistance.

B12 FOXA2 Promotes the Growth of KRAS-Mutant Lung Tumors but Suppresses the Growth of EGFR-Mutant Lung Tumors in Vivo

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Background: Using GEMM (Genetically Engineered Mouse Models), we showed that a lung-lineage transcription factor NXX2-1 promotes the growth of EGFR-mutant lung tumors but suppresses the growth of KRAS-mutant lung tumors in vivo (Maeda et al., JCI 2012), suggesting that such transcription factors expressed in the lung act as a context-dependent tumor promoter or suppressor. Here, we report the roles of a pioneer transcription factor FOXA2 expressed in lung epithelium in KRAS-mutant or EGFR-mutant lung tumors in vivo. Methods: Using doxycycline-regulatable GEMM expressing mutant KRAS or mutant EGFR along with FOXA2 in lung epithelium (CCSP-rTA; oet-KrasG12D; oet-Foxa2 or CCSP-rTA; oet-EGFR;L858R; oet-Foxa2), we assessed whether FOXA2 influenced the growth of KRAS-mutant or EGFR-mutant lung tumors in vivo. The number and size of lung tumors were analyzed by microCT. The histology of the lung tumors was further analyzed by H&E and immunohistochemistry. Results: FOXA2 induced an increase in volume but not the number of KRAS-mutant lung tumors associated with lung adenocarcinoma while FOXA2 reduced the volume and number of EGFR-mutant lung tumors in vivo. Phosphohistone H3 was increased in KRAS-mutant lung tumors but decreased in EGFR-mutant lung tumors by FOXA2. Caspase-3 was not affected. These results indicate that FOXA2 differentially influences the initiation and progression of lung tumor growth depending on the type of driver oncogenes (mutant KRAS vs. mutant EGFR) in part through proliferation but not apoptosis. Conclusion: Transcription factors NXX2-1 and FOXA2 function as yin and yang to affect the growth of KRAS-mutant or EGFR-mutant lung tumors.