Analysis of MET-amplified solid tumors using situ hybridization (CISH)

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Introduction - MET amplification has been implicated in signaling pathways that promote cell proliferation, invasion, and survival. It has been identified as an oncogenic driver in various malignancies and is currently being investigated as a potential therapeutic target. To date, MET-driven cancers, such as NSCLC, have been observed in various solid malignancies. The purpose of this study is to report our experience with MET amplification across various primary tumors using CISH.

Methods - A retrospective analysis was done on 26,619 specimens analyzed for MET amplification by CISH at a CLIA-certified lab (Caris Life Sciences). The validated CISH assay, previously validated against a FISH assay, was used to assess amplification. Concordance and correlative studies were done in MET-amplified, non-small cell lung cancer (NSCLC) specimens analyzed using a MET FISH (Dako, 2+ or 3+ staining intensity in at least 50% of tumor cell membrane) analyzing protein expression. Correlative studies involving co-existing alterations, including PD-L1 IHC, were done in the MET-amplified NSCLC cohort.

Results - MET amplification utilizing CISH was 0.7% (188/26,619) overall. MET-amplified tumors included carcinomas such as NSCLC (3.1%, 87/2767), gastric adenocarcinoma (3.1%, 1/33), esophageal and esophageophtic junctional adenocarcinoma (3.1%, 1/33), and sarcomas such as synovial sarcoma (3.1%, 1), and rare tumors such as placental-epithelial ovarian carcinoma (100%, 1/1). A sub-analysis of MET-amplified, NSCLC specimens demonstrated co-occurring protein overexpression in 10.2% (724/7125) of cases. Some MET-amplified, NSCLC specimens were found to have EGFR pathogenic/presumed pathogenic aberrations in NSCLC. FISH and co-amplification was evaluated in 26 NSCLC specimens and found in each of these tumor types shown in Figure 2, Table 2 and Figure 4. MET amplification was evaluated by FISH in 76 NSCLC specimens with a MET copy number >25. Table 2 is comparable to what has been reported in the medical literature for NSCLC in the general population.

Conclusions

• MET-CISH may be a viable alternative to FISH in detecting patients with MET-driven cancers. As this technology requires only light microscopy and a pathologist, it is easy to incorporate in a laboratory setting.

• MET amplification was found in various solid tumors, whether epithelial or mesenchymal in origin.

• In NSCLC, MET amplification may co-occur with other molecular aberrations, necessitating further studies to look into their significance.

• MET amplification, along with MET-CISH was 24% overall, may identify patients who derive benefit from MET-targeted agents currently in clinical trials. A need exists to identify patients and specific tumors who derive the most benefit.

Methodologies


References