HETEROGENEITY OF MET ASSESSED BY IMMUNOHISTOCHEMISTRY (IHC) AND FLUORESCENCE-IN-SITU HYBRIDIZATION (FISH) IN NONSQUAMOUS NON-SMALL CELL LUNG CANCER (NSNSCLC)

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Aim: Disappointing results have been observed in advanced NSCLC patients receiving MET inhibitors based on histological or immunohistochemical criteria. The aim of this study was to assess the impact of MET intratumor heterogeneity on MET evaluation and potentially on adequate selection of nNSCLC patients for clinical trials.

Methods: Samples were obtained from a cohort of 120 patients. Of these, 47 were incorporated in a tissue microarray (TMA), selecting 4 histologically distinct areas of the tumor for heterogeneity studies. Assessment of Met expression was performed by IHC (SP44 Ventana) using H-score and MetMab criteria. FISH was used to assess gene copy number (GCN) (MET and CEP7 probes from Vysis). Using different scoring methods, correlation with clinico-pathologic and molecular features (KRAS, EGFR) and between Met expression and GCN was investigated. Heterogeneity of Met status between different tumor cores was examined.

Results: Seventy percent of the patients were male and 55% were current smokers. Median age was 66 years and 36% were stage IV nNSCLC. Of 127 samples, 90% were adenocarcinomas. Nineteen percent and 11% harbored KRAS and EGFR mutations, respectively. Forty-eight percent were MET-High according to MetMab criteria, and median H-score was 140 (range 0-400). Increased Met expression was associated with advanced stage (p = 0.001) and with former or no smoking history (p = 0.038). Mean MET GCN was 2.8 and 9 cases were considered FISH-positive (GCN >=5). Increased MET GCN was associated with solid histological pattern. Met H-score was directly associated with GCN (p = 0.036). Intra-class correlation coefficient between 4 tissue cores was 0.57, both for Met H-score and GCN. In three patients considered FISH-positive, 4 out of 12 cores were FISH-negative.

Conclusions: Classification of Met-driven tumors is challenging due to lack of robustness of methods and criteria for defining Met positivity. MET heterogeneity may hinder adequate patient selection for clinical trials with MET inhibitors.

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