Background

- The programmed cell death 1 (PD-1) and programmed death ligand 1 (PD-L1) signaling plays a critical role in tumor immune evasion. PD-1 blockade can be achieved through the use of anti-PD-1 agents, notably pembrolizumab and nivolumab.
- For both agents, higher levels of PD-L1 expression can be associated with increased response to therapy, although patients with lower PD-L1 expression levels can derive clinical benefit.
- pembrolizumab and nivolumab are antibodies that target PD-1 and showed success in treating some types of cancers. Pembrolizumab combined pembrolizumab are approved in the US and EU for the treatment of specific stages and specific conditions of certain tumors including melanoma, NSCLC, advanced renal cell carcinoma, Hodgkin lymphomas, recurrent/metastatic SCCHN (in the US only), and locally advanced/metastatic unresectable carcinoma (in the US only).
- PD-L1 assessment by IHC is frequently used for predicting resistance to immunotherapy with anti-PD-L1. However, the correlation between PD-L1 expression and response to immunotherapy remains poor and the search for better predictors of response continues, especially for combination therapy.
- EGFR mutations are common in NSCLC, but the majority of patients with NSCLC and EGFR mutations develop resistance to EGFR kinase inhibitors. Acquiring mutations in T790 and exon 20 has been reported as a cause for resistance, but the most common cause involves activation of additional signaling pathways, including MET amplification, HER2 amplification, KRAS mutation, and BRAF mutation. MET gene activation by amplification has been reported to be associated with resistance to EGFR inhibitors.

Objective

Evaluate the relative correlation between the levels of PD-L1 expression with MET gene amplification and TP53 mutation.

Methods

- Tissue samples collected from 397 non-small-cell lung cancers were studied for MET gene amplification by fluorescent in-situ hybridization (FISH) using MET (17p11.2) probe and centromere 7 probe as a control. Signals were quantified and cases were calculated.
- PD-L1 expression on the same samples was evaluated using clone SP142 and standard immunohistochemistry (IHC) procedures. Birefringence were biopsied and scored by trained/qualified pathologists at NeoGenomics laboratories.
- Samples were also sequenced using next generation sequencing (NGS) for mutations in TP53, KRAS, and EGFR.
- Statistical analysis was evaluated between variables including: Fisher’s exact, Chi-square, Wilcoxon rank sum test/Mann-Whitney U test, Spearman correlation, permutation, and the Kruskal-Wallis test.

Fisher’s exact, Chi-square, Wilcoxon’s rank sum test/Mann-Whitney U test, Spearman

in TP53, KRAS, and EGFR.

Samples were also sequenced using next generation sequencing (NGS) for mutations

in TP53, KRAS, and EGFR.

Conclusions

- MET gene amplification is correlated with higher expression of PD-L1.
- EGFR mutant lung cancers have significantly lower expression of PD-L1 when clone SP142 and NGS for detecting EGFR mutations are used, but tumors without EGFR mutation have higher levels of PD-L1, TP53 mutation, and MET activation.
- Patients with TP53 mutation had strikingly high expression of PD-L1 using the SP142 clone and higher copy numbers of the MET gene.
- These data suggest that in lung cancer, both MET and TP53 genes play a direct role in up-regulating PD-L1 expression.
- Combination therapy targeting MET and/or TP53 along with immunotherapy should be considered in treating NSCLC that is EGFR-negative, especially when TP53 is mutated or MET is amplified.

#5618