Correlation Between MET Gene Amplification and TP53 Mutation in Upregulating PD-L1 Expression in EGFR-Wild-Type Lung Cancer

#5618

Maher Albitar, MD • Sucha Sudarsanam, MS • Wanlong Ma, MS • Shiping Jiang, MD • Wayne Chen, MD • Vincent Funari, PhD • Steven Brodie, PhD • Sally Agersborg, MD, PhD

NeoGenomics Laboratories, Aliso Viejo, CA, USA

Background

- The programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) signaling axis plays a critical role in tumor immune evasion.
- PD-1 blockade can be achieved through the use of anti-PD-1 agents, notably nivolumab and pembrolizumab.
- 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.
- Nivolumab and pembrolizumab are antibodies that target PD-1 and showed success in treating some types of cancers. Nivolumab or/and 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 lymphoma, recurrent/metastatic SCCHN (in the US only), and locally advanced/ metastatic urothelial carcinoma (in the US only).
- PD-L1 assessment by IHC is frequently used for predicting response to immunotherapy with anti-PD-L1. However, the correlation beatween 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.
- Our prior studies showed a correlation between TP53 mutation and PD-L1 expression in NSCLC.

Objective

Evaluate the relative correlation between the levels of PD-L1 expression with MET gene amplification and EGFR, KRAS, or TP53 mutations in non-small-cell lung cancers.

Methods

- Tissue samples collected from 397 core biopsies or resections from lung cancers were studied for MET gene amplification by fluorescent in-situ hybridization (FISH) using MET (7q31) probe and centromere 7 probe as a control. Signals were quantified and ratios were calculated.
- PD-L1 expression on the same samples was evaluated using clone SP142 and standard immunohistochemistry (IHC) procedures. Biopsies were reviewed and scored by trained/certified pathologists at NeoGenomics Laboratories.
- Samples were also sequenced using next generation sequencing (NGS) for mutations in TP53, KRAS, and EGFR.
- Standard statistical tests evaluated correlations between variables including: Fisher's exact, Chi-square, Wilcoxon's rank sum test/Mann-Whitney U test, Spearman correlation, Pearson correlation, and the Kruskal-Wallis test.

Result

Figure 1. PD-L1 Expression in NSCLC Using IHC Clone SP142
166 of 397 (42%) lung cancers expressed various levels of PD-L1.

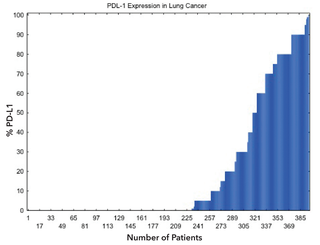


Table 1. PD-L1 Expression Levels

<5%	7%
<20%	15%
<50%	23%
>=50%	19%

PD-L1 Expression

- Of the 397 patients, various levels of PD-L1 were expressed in 166 patients (42%, Figure 1).
- 27 patients (7%) had expression in between 1% and 5% of tumor cells, 61 (15%) between 1% and 20%, 92 (23%) between 1% and 50%, and 74 (19%) had PD-L1 expression in >50% of tumor cells (Table 1).

Figure 2: Establishing Cut-off Point for MET Amplification by FISH
MET: Centromere Ratio of 1.5 was determined as the cut-off. MET amplification was observed in 4% of patients.

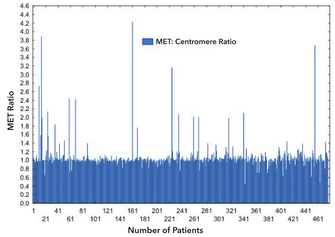
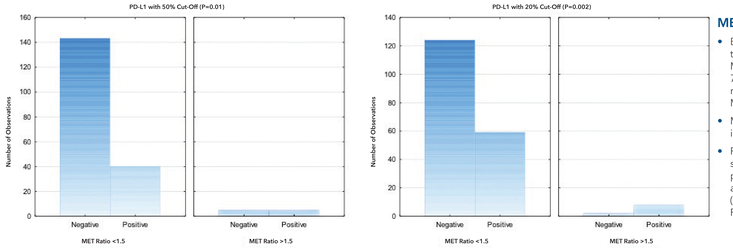


Figure 3. Higher Levels of PD-L1 Expression in Patients with MET Amplification



MET Amplification

- Based on testing 471 patients of various tumors (including 397 NSCLC) by FISH for MET copies as compared to chromosome 7 centromere, we established that a cut-off ratio of 1.5 is appropriate for determining MET amplification (Figure 2).
- MET signal:centromere signal ratio was >1.5 in 16 (4%) of the 397 patients.
- Patients with MET:centromere ratio >1.5 had significantly higher percentage of PD-L1 positivity as a continuous variable (P=0.004), as they did with PD-L1 cut-offs of 5% (P=0.01), 20% (P=0.002), and 50% (P=0.01, Figure 3).

Figure 4. Reverse Correlation Between EGFR Mutation and PD-L1 Expression as Continuous Variable

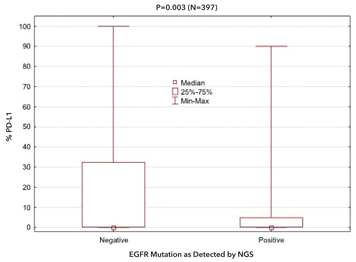
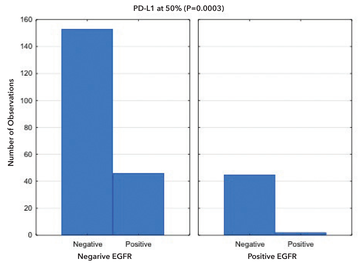


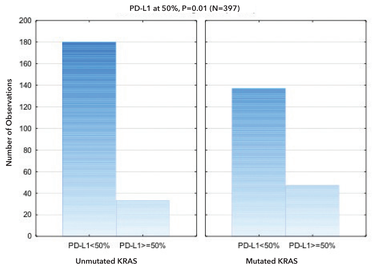
Figure 5. Reverse Correlation Between EGFR Mutation and PD-L1 Expression Using 50% Cut-Off



EGFR Mutation

- 69 of the 379 NSCLC patients (17%) had an EGFR mutation using NGS (Figure 4).
- Patients with EGFR mutation had significantly lower levels of PD-L1 expression (P=0.003) when PD-L1 was considered as a continuous variable.
- When a cut-off point of 50% was used for PD-L1 expression, the EGFR-mutant cases had significantly fewer positive cases (P=0.0003, Figure 5).
- There was no correlation between high MET:centromere ratio and EGFR mutation in this untreated patient group.

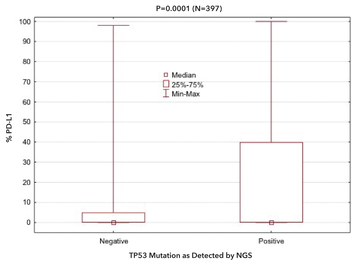
Figure 6. Higher PD-L1 Expression (>50%) In Lung Cancer with KRAS Mutation



KRAS Mutation

- 184 of 397 NSCLC patients (46%) had KRAS mutation using NGS.
- There was no correlation between KRAS mutation and overall PD-L1 expression (P=0.4) when PD-L1 was considered as a continuous variable.
- Low level positive correlation (P=0.01) between KRAS mutation and PD-L1 expression was observed when a PD-L1 cut-off of 50% was used.
- There was no correlation between MET:centromere ratio and KRAS mutation.
- Except for two patients, all samples with KRAS mutation also had wild-type EGFR.

Figure 7. Higher PD-L1 Expression in Lung Cancer with TP53 Mutation



TP53 Mutation

- 225 of 397 NSCLC patients (57%) had a TP53 mutation using NGS.
- Patients with TP53 mutation had significantly higher MET amplification (MET: centromere ratio ≥1.5, P=0.01).
- TP53 mutation was significantly more common in EGFR wild-type cases (P=0.0002).
- There was significant correlation between TP53 mutation and overall PD-L1 expression (P=0.0001) when PD-L1 was used as a continuous variable (Figure7).
- Positive correlation between TP53 mutation and PD-L1 expression was also detected when PD-L1 cut-off points of 50% or 5% were used (P=0.0004 and P=0.007, respectively).

Conclusions

- MET gene activation 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.