Distribution of PD-L1 expression in diverse cancer types: experience with over 10,000 cases

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Abstract

Background: Blocking the programmed death-1 (PD-1) pathway has clinical benefit in metastatic cancer and has led to the approval of the mAbs to treat several cancer types. Expression of PD-L1 ligand (PD-L1) on the cell surface of tumor cells is generally associated with a higher likelihood of response to PD-1 blockade in multiple studies. We analyzed distribution of PD-L1 in a wide variety of tumor types, studied underlying mechanisms of expression and compared methods of detection.

Methods: 10,187 tumor samples were tested for the expression of PD-L1 (SP142 antibody, Spring Biosciences). Expression (IHC) of PD-L1 in a selected number of cases was compared to 3 additional monoclonal antibodies (SP263, Ventana; 22c3 and 28-8 DAKO). Cases were considered positive if ≥5% of the tumor cells exhibited membranous positivity with 2+/3+ intensity (5, 6). In selected cases, PD-L1 gene amplification was explored using the next generation sequencing (NGS) data and in situ hybridization assays (FISH and CISH). A 58kb probe was designed to cover the JAK2/PD-L1/PD-L2 gene region at 9p24.1 (chr9:4985240-5571285). A second probe was designed to cover the peri-centromeric region of chromosome 9 (chr9:3879360-38446085) as a chromosome copy number control. Both probes were designed to be free of repetitive sequences and synthesized using Agilent’s oligo-based SureFISH technology. The 9p24.1 and peri-centromeric probes were labeled with Texas Red and fluorescein fluorochromes, respectively.

Results

>14,000 tumor samples were tested for the expression of PD-L1 (clone SP142, Spring Biosciences). Expression (IHC) of PD-L1 in a selected number of cases was compared to 3 additional monoclonal antibodies (SP263, Ventana; 22c3 and 28-8 DAKO). PD-L1 gene amplification was calculated using the next generation sequencing (NGS) data.

Results: Using the ≥2+ intensity and ≥5% IHC threshold, PD-L1 was detected with the highest frequency in thymic carcinoma (63%), followed by lymphomas (42%), head and neck squamous carcinoma (35%), anal carcinoma (31%), non-small cell lung cancer (30%), thyroid carcinoma (29%), bladder carcinoma (22%), cervical carcinoma (20%), melanoma (19%), and esophageal and esophagogastric junction carcinoma (15%). Significant differences between genonomically defined cancer subtypes were observed (e.g. 4-fold more frequent PD-L1 expression in MSH-H colorectal and endometrial carcinomas vs. MSS counterparts). Analytical comparison of 4 different, yet well-established, IHC antibodies’ clones in malignant lymphomas: (A): Case of marginal zone lymphoma: Negative by all 4 clones; (B): Peripheral T-cell lymphoma: Positive by all 4 clones; (C): Diffuse Large B-cell lymphoma (variable positivity): copy number variation analysis by NGS did not detect underlying PD-L2/PD-L1/JAK2 alterations at 9p24.

Conclusions: Targetable PD-L1 protein expression is identified in numerous cancer types, including some rare but highly overexpressing types not previously validated. Threshold determination for predictive purposes remains challenging, but concordance between 4 antibodies was superb. High PD-L1 gene amplification (alone or co-amplification with JAK2 gene) is detected in a minority of carcinomas, and additional methods of detection (e.g. in-situ hybridization) may be needed. Additional studies are needed to determine if gene amplification is predictive of response.

References


Materials and Methods

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Results Continued (updated)

Table 1. Concordance between SP142 and other three anti-PD-L1 antibodies’ clones of cases including NSCLC, melanoma, breast, colorectal and renal cell carcinomas.

![Figure 1. PD-L1 expression (SP-142 clone) across different tumor types (>14,000 cases).](image1)

* Since abstract submission, >4,000 additional cases were tested and were added to the presentation.

Figure 2. Concordance in IHC expression (2+ ≥5% positive tumor cells) of 4 different anti-PD-L1 clones in malignant lymphomas: (A) Case of marginal zone lymphoma: Negative by all 4 clones; (B): Peripheral T-cell lymphoma: Positive by all 4 clones; (C): Diffuse Large B-cell lymphoma (variable positivity): copy number variation analysis by NGS did not detect underlying PD-L2/PD-L1/JAK2 alterations at 9p24.

Figure 3. In situ hybridization assays (FISH, A, CISH, B) showing 9p24 amplification (PD-L1/PD-L2/JAK2) in a case of diffuse large B-cell lymphoma with PD-L1 overexpression by IHC (not shown). PD-L1 gene amplification was also observed in a small subset of tested tumors (4% breast, 2% NSCLC, 1% ovarian cancer).

![Figure 4. Results Continued (updated).](image2)

Results Continued (updated)

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![Figure 5. Table 1. Concordance between SP142 and other three anti-PD-L1 antibodies’ clones of cases including NSCLC, melanoma, breast, colorectal and renal cell carcinomas.](image3)