Prevalence of programmed death ligand-1 in patients diagnosed with non-small cell lung cancer in Lebanon

Ghina Fakhri, Reem Akel, Ibrahim Khalifeh, Hassan Chami, Adel Hajj Ali, Majd Al Assaad, Haneen Atwi, Humam Kadara and Arafat Tfayli

Abstract

Introduction: Programmed death ligand-1 expression has been shown to be a good predictor of response to cancer therapy with checkpoint inhibitors. Its expression varies among different tumor types and among non-small cell lung cancer patients with different clinical and demographic characteristics. The prevalence and determinants of programmed death ligand-1 expression have been previously reported from various regions of the world, but data from Lebanon are lacking. This study examines the prevalence and the clinical, demographic and pathological predictors of programmed death ligand-1 expression in patients diagnosed with non-small cell lung cancer in Lebanon.

Methods: Medical records of 180 patients diagnosed with primary non-small cell lung cancer at our institution and tested for programmed death ligand-1 expression were reviewed. Clinical, demographic and pathological information were collected and correlated with programmed death ligand-1 expression using the chi-square test and logistic regression.

Results: One hundred eleven of the 180 non-small cell lung cancer tumor samples tested positive for programmed death ligand-1 expression (61.7%). 27.2% of those tumor samples expressed programmed death ligand-1 in 1%–49% of tumor cells, while 34.4% of tumor samples expressed programmed death ligand-1 in 50% or more of their cells. Squamous histology and advanced stage were significant predictors of programmed death ligand-1 expression (odds ratio = 2.79, 95% confidence interval [1.13–6.90], \( p = 0.012 \) and odds ratio = 2.48, 95% confidence interval [1.23–4.99], \( p = 0.044 \), respectively).

Conclusion: Similar to reports from other populations, our results suggest that programmed death ligand-1 expression in non-small cell lung cancer is highly prevalent in the Lebanese population, especially in patients with advanced stage at diagnosis or squamous cell carcinoma histology. Because of the small sample size, while more that 60% of the patients are Lebanese, the results of this article cannot be extrapolated to the Middle Eastern and the Levantine population.

Keywords

Programmed death ligand-1, non-small cell lung cancer, immunotherapy, immune markers, histology

Date received: 1 February 2021; accepted: 15 August 2021

Introduction

As a consequence of the ongoing tobacco epidemic, lung cancer is projected to continue being the leading cause of cancer death in both men and women.\(^1\) The majority of lung cancer patients are diagnosed at a later stage with an associated 5-year survival currently at 18%.\(^2,3\) Non-small cell lung cancer (NSCLC) represents around 85% of all lung cancer cases and, up until recently, platinum-based chemotherapy had been the standard of care for treating patients with advanced NSCLC.\(^4–7\) Recent advances in immunotherapy using checkpoint inhibitors have drastically changed the treatment strategies for this disease, which will hopefully lead to better patient outcomes.\(^8–10\)

Corresponding author:
Arafat Tfayli, Naef K. Basile Cancer Institute, American University of Beirut Medical Center, P.O. Box: 11-0236, Riad El Solh 1107 2020, Beirut 1107, Lebanon.

Email: at35@aub.edu.lb
Recent studies have shown that the tumor microenvironment may be modulated through programmed death ligand-1 (PD-L1) and its receptor programmed death-1 (PD-1). PD-1 is a member of the CD28 family and is a key checkpoint receptor for escaping the immune response expressed mainly on activated effector T lymphocytes, such as those that infiltrate tumors. The ligand of PD-1 (PD-L1) is overly expressed in many tumors such as lung and colorectal cancers. Once bound to its receptor, PD-L1 induces cellular apoptosis of effector T lymphocytes, thus reducing the effectiveness of the immune response.

Antibodies targeting PD-1 and PD-L1 such as Pembrolizumab, Nivolumab and Atezolizumab have been developed and extensively studied. These PD-1 inhibitors were granted Food and Drug Administration (FDA) approval for the treatment of NSCLC after showing better outcomes in clinical trials.

PD-L1 expression varies in different tumors and in different tumor microenvironments. It also varies according to clinical, demographic and pathological characteristics. Data regarding the prevalence of PD-L1 are emerging worldwide but are lacking in the Middle East generally and Lebanon specifically. The relation of PD-L1 expression to clinical and demographic characteristics remains controversial in some studies owing to the discrepancies in testing for PD-L1 and the different standards in assessing the cut-off for positivity. This study examines the prevalence of PD-L1 expression in patients diagnosed with NSCLC at a tertiary care medical center in Lebanon and determines the clinical, demographic and pathological predictors of PD-L1 expression.

**Materials and methods**

**Subjects and samples**

Medical records of patients diagnosed with primary NSCLC and tested for PD-L1 expression between January 2016 and February 2018 were analyzed retrospectively at our institution. This study was approved by the Institutional Review Board and is in accordance with the Helsinki Declaration of 1975. NSCLC patients with pathology reports clearly delineating the PD-L1 status were selected. Of 200 cases identified, 20 were excluded for incomplete clinical and demographic information. A pathologist reviewed all cases to confirm the histology and select a representative area of tumor cells for PD-L1 assessment. Information was collected at the time of diagnosis and included age, sex, nationality, smoking status, family history of lung cancer, tumor stage, histology and grade, as well as the presence and extent of PD-L1 expression, and the presence of epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangement. All patients were treated following standard-of-care and did not previously receive anti-PD-1 or anti-PD-L1 therapy. Staging was performed according to the American Joint Committee on Cancer eighth edition manual.

**EGFR and ALK status determination**

EGFR mutation analysis was performed on paraffin-embedded tissue using ARMS and Scorpions technologies to detect 29 somatic mutations in the EGFR oncogene in real-time polymerase chain reaction (PCR) on the Rotor-Gene platform. Results classified mutations into four locations: Exon 18, 19, 20 and 21. The immunohistochemical status of ALK translocation was assessed through Ventana D5F3 using a multimer detection system.

**PD-L1 status**

PD-L1 expression was assessed on formalin-fixed paraffin-embedded (FFPE) tumor tissues using a qualitative immunohistochemistry (IHC) assay (PharmDx kit; Merck & Co Inc, Rahway, NJ, USA). This assay uses the primary antibody 22C3 clone anti-PD-L1 mouse monoclonal antibody to detect and visualize the PD-L1 protein in NSCLC among other cancers using the EnVision FLEX visualization system on Autostainer Link 48. Our assessment was performed using the Ventana automated immunostainer on 4 µm-cut positively charged slides. Positive and negative controls were run along each assessment. IHC was assessed by the pathologist and PD-L1 was considered positive when membranous staining was present in 1% or more of tumor cells. Staining intensity of PD-L1 was also assessed and scored as one, two or three.

**Statistical analysis**

The main outcome of this study was to determine the prevalence of PD-L1 expression in NSCLC patients at a large tertiary care medical center in the Levant area. Descriptive statistics summarizing the clinical and demographic characteristics of the patients and the pathological characteristics of their tumor samples are presented. The main dependent variable was the PD-L1 status categorized as positive (more than 1% of tumor cells) or negative. The independent (exposure) variables were the various clinical and demographic characteristics of the patients and the pathological characteristics of the tumor samples. Patient’s clinical and demographic characteristics and the pathological characteristics of their tumor samples were compared between PD-L1 expression categories using Pearson’s chi-square tests or Fisher’s exact tests. Logistic regression was used to evaluate potential predictors of PD-L1 expression including age (≥ or <65 years), sex, smoking status (current/former smoking and never-smoking), histology (squamous and adenocarcinoma) and stage (advanced (stage IV) and early stage (stage I–III)). Regression models were adjusted for age, sex and smoking. Analysis was performed using the statistical package IBM SPSS software version 24.0 (SPSS Inc., Chicago, IL, USA). p-value < 0.05 was considered statistically significant.
## Results

### Demographic data

The demographic characteristics of our sample are presented in Table 1. The mean age was 65.0 ± 10.5 years and the majority were Lebanese (81.1%), males (67.8%), and current or previous cigarette smokers (78.9%).

### Clinical characteristics

The majority of patients had stage IV disease at diagnosis (58.9%) while 11.7% and 8.9% had stage I or stage II disease, respectively. The most common histological type was adenocarcinoma (73.3%), while 23.9% of the patients had squamous cell carcinoma. The majority of the tumor samples showed moderate (35.6%) or poor differentiation (35.6%). Of the patients with adenocarcinoma with adequate sample for EGFR testing (n = 99), 18 had mutated EGFR while 2% of adenocarcinoma adequate for ALK testing (n = 101), had ALK rearrangement (Table 1).

### Pathological characteristics

One hundred eleven of the 180 NSCLC samples tested positive for PD-L1 expression (61.7%). In particular, 27.2% of the tumor samples expressed PD-L1 positivity in 1%–49% of tumor cells, while 34.5% of those samples expressed PD-L1 in 50% or more of the cells. A representative figure of the different IHC profiles is presented in Figure 1.

### Association of PD-L1 expression with patient and tumor characteristics

The histologic type of NSCLC was significantly associated with PD-L1 expression, with 76.7% of tumors with squamous histology had PD-L1 expression versus 58.3% of tumors with adenocarcinoma histology (p = 0.012). Tumor stage was also significantly associated with PD-L1 expression where 67.9% of tumors diagnosed at an advanced stage (IV) expressed PD-L1 compared with 52.9% of tumors diagnosed at a loco-regional stage (I, II and III, p = 0.044). Other demographic, clinical or pathological characteristics that were assessed were not significantly associated with PD-L1 expression. Males were as likely to have PD-L1 expressing tumors as females (62.3% vs 60.3%, p = 0.870). Despite having a numerically higher percentage of tumor that tested positive for PD-L1 in patients older than 65 as compared to younger patients (67.4 vs 55.7%), this did not reach statistical significance (p = 0.106). The majority of patients in this study were either Lebanese or Iraqi without a difference in PD-L1 positivity among these two nationalities, 61.6% and 63.6%, respectively. PD-L1 was expressed in 61.3% of respective samples from current smokers and former smokers compared to a similar 62.1% in never-smokers (Table 2). The odds ratios and 95% confidence intervals for age, gender, smoking status, stage and tumor histologic type were reported as 1.61 [0.81–3.17], 0.84 [0.40–1.77], 1.06 [0.42–2.62], 2.48 [1.23–4.99] and 2.79 [1.13–6.90], respectively. Adjustment for age, sex and smoking did not impact the association of PD-L1 expression with stage and tumor histologic type (odds ratio (OR) = 2.48, 95% confidence interval (CI) [1.23–4.99], p = 0.044 and OR = 2.79, 95% CI [1.13–6.90], p = 0.012, respectively). The association between PD-L1 expression and presence of EGFR mutation or ALK rearrangement could not be assessed due to the small number of patients who tested positive (Table 1).

### Table 1. Demographic, clinical and pathological characteristics of the study population.

| Characteristics          | N (%) |
|--------------------------|-------|
| Age (years) (mean ± SD)  | 65.0 ± 10.5 |
| Sex                      |       |
| Male                     | 122 (67.8) |
| Female                   | 58 (32.2) |
| Nationality              |       |
| Lebanese                 | 146 (81.1) |
| Iraqi                    | 22 (12.2) |
| Others                   | 12 (6.7) |
| Smoking status           |       |
| Never                    | 29 (16.1) |
| Current                  | 63 (35.0) |
| Ex-smoker                | 79 (43.9) |
| Unknown                  | 9 (5.0) |
| Cancer stage at diagnosis|       |
| I                        | 21 (11.7) |
| II                       | 16 (8.9) |
| III                      | 33 (18.3) |
| IV                       | 106 (58.3) |
| Tumor histology          |       |
| Adenocarcinoma           | 132 (73.3) |
| Squamous                 | 43 (23.9) |
| Other                    | 5 (2.8) |
| Tumor grade              |       |
| Well-differentiated      | 6 (3.3) |
| Moderately differentiated | 64 (35.6) |
| Poorly differentiated     | 64 (35.6) |
| Unknown                  | 46 (25.5) |
| PD-L1 expression         |       |
| Negative                 | 69 (38.3) |
| 1%–49%                   | 49 (27.2) |
| 50% or more              | 62 (34.5) |
| EGFR mutation (N = 99)   |       |
| Wild type                | 81 (81.9) |
| Mutant                   | 18 (18.1) |
| ALK translocation (N = 101)|     |
| Negative                 | 99 (98.0) |
| Positive                 | 2 (2.0) |

SD: standard deviation; PD-L1: programmed death ligand-1; EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase.

---

Fakhri et al.
This study shows that the majority of NSCLC tumors sampled at a tertiary care oncology center in Lebanon expressed PD-L1 and that squamous cell carcinoma and advanced stage tumors were significant predictors of PD-L1 expression, both twice as likely to express PD-L1.

This study represents the first attempt to examine the prevalence of PD-L1 expression in adults diagnosed with NSCLC in the Lebanese population and attempt to correlate...
it with demographic, clinical and pathological characteristics. According to the most recent cancer registry in Lebanon, a total of 1212 cases of lung cancer are diagnosed every year with the majority of them having NSCLC. The association of sustained clinical benefits and improved progression-free survival after treatment with PD-1 blockers has been established in several clinical trials. Yet, studies in Lebanon and the Middle East, generally, are lacking regarding expression of the PD-L1.

Therefore, the finding of high prevalence of PD-L1 expression in our sample is important as it highlights the need to test for PD-L1 and for considering immunotherapy in the therapeutic strategies in our NSCLC patient population. However, in Lebanon, data on the prevalence of PD-L1 expression in patients diagnosed with NSCLC are non-existent. This study is the first to report this prevalence in 180 patients with histologically confirmed NSCLC and who have not received prior systematic treatment for their disease.

While there are no prior reports regarding PD-L1 expression in the Middle Eastern countries to compare our findings to, several studies have assessed PD-L1 prevalence worldwide. The mean age of our cohort was 65 years with the majority being Lebanese males who are either current or prior smokers. Most of the cases had adenocarcinoma and were diagnosed at a late-stage, very similar to those reported in the Lebanese National Cancer Registry.

Our reported prevalence of PD-L1 expression (61.7%) is comparable to other reports from other parts of the world, which ranged between 50% and 70%. The prevalence of PD-L1 expression was 68% in the Keynote-001, 010 and 024 clinical trials participants in whom PD-L1 expression was assessed using methods similar to this study (22C3 PharmDx). Other studies have reported a prevalence of PD-L1 expression ranging from 7.4% to 82%, and this variability can be explained by the use of different PD-L1 expression cut-offs (1 vs 10% of tumor cells) and different antibodies to detect PD-L1 expression (28-8 vs SP142). Similar to prior reports, we also found that advanced stage IV and squamous cell carcinoma histology are significantly predictors of PD-L1 expression. It is noteworthy to mention that this study’s participants had not received systemic treatment prior to PD-L1 testing, an important consideration since PD-L1 expression is a dynamic marker that might change in response to therapy.

Limitations

One obvious limitation of this article is its retrospective nature in a single center which could lead to selection bias. The number of patients from neighboring countries is not sufficient enough to warrant a representative sample from countries of the Middle East. In addition to that, follow-up data for these patients are not available and as such no survival analysis could be performed. For the same reason, the data about the treatment given to the patient could not be collected and the treatment response could not be determined. Also, for the purpose of this study, the power analysis was not done. Despite the fact that this is the first paper to study PD-L1 expression from the population in Lebanon, a larger sample size is warranted.

Conclusion

The prevalence of PD-L1 expression in NSCLC samples from patients assessed in a tertiary care center in Lebanon is similar to other populations around the world such as the Western or the Asian. This article sheds the light on the importance of evaluating immune markers expression in patients with NSCLC in view of the high prevalence of PD-L1 in our sample cohort and their established link to optimal targeted therapy. Our knowledge about the microenvironment of lung tumors is changing and more studies regarding PD-L1 expression as well as other immune markers are needed to improve the choice of therapy and prognosis of NSCLC.

Author contributions

Substantial contributions to the conception or design of the work, data acquisition and/or interpretation. Drafting and/or critical revision of the final manuscript. Approval of the final version to be submitted. This manuscript has been read and approved by all the authors, the requirements for authorship as stated above have been met, and each author believes that the manuscript represents honest work.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical approval

Ethical approval for this study was obtained from the American University of Beirut Institutional Review Board (approval no. BIO-2018-0048).

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

Informed consent

It is not applicable. Obtaining a written consent was waived by the institutional review board.

ORCID iD

Arafat Tfayli https://orcid.org/0000-0002-0633-2538

Data availability

The raw data used to support the findings of this study are available from the corresponding author upon request.
References

1. WHO. World Health Organization cancer fact sheet. Geneva: WHO, 2018.
2. Siegel RL, Miller KD and Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016; 66(6): 7–30.
3. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 2016; 66(4): 271–289.
4. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical, and radiologic advances since the 2004 classification. J Thorac Oncol 2015; 10(9): 1243–1260.
5. Osmani L, Askin F, Gabrielson E, et al. Current WHO guidelines and the critical role of immunohistochemical markers in the subclassification of non-small cell lung carcinoma (NSCLC): moving from targeted therapy to immunotherapy. Semin Cancer Biol 2018; 52(Pt. 1): 103–109.
6. Scagliotti GV, De Marinis F, Rinaldi M, et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. J Clin Oncol 2002; 20: 4285–4291.
7. Ettinger DS, Wood DE, Aisner DL, et al. Non-small cell lung cancer, version 5.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2017; 15(4): 504–535.
8. Kelly RJ, Gulley JL and Giaccone G. Targeting the immune system in non-small-cell lung cancer: bridging the gap between promising concept and therapeutic reality. Clin Lung Cancer 2010; 11: 228–237.
9. Oxnard GR, Binder A and Janne PA. New targetable oncogenes in non-small-cell lung cancer. J Clin Oncol 2013; 31: 1097–1104.
10. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012; 12: 252–264.
11. Karachaliou N, Cao MG, Teixido C, et al. Understanding the function and dysfunction of the immune system in lung cancer: the role of immune checkpoints. Cancer Biol Med 2015; 12(2): 79–86.
12. Hou W, Wolkhod BD and Chen L. PD-L1 (B7-H1) and PD-1 pathway blockade for cancer therapy: mechanisms, response biomarkers, and combinations. Sci Transl Med 2016; 8: 328rv324.
13. Ametungta M, Asadi K, Lin X, et al. PD-L1 and tumor infiltrating lymphocytes as prognostic markers in resected NSCLC. PLoS ONE 2016; 11(4): e0153954.
14. Baron EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015; 372: 2018–2028.
15. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-negative, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016; 387: 1540–1550.
16. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 2016; 375: 1823–1833.
17. Teng MW, Ngiov SF, Ribas A, et al. Classifying cancers based on T-cell infiltration and PD-L1. Cancer Res 2015; 75: 2139–2145.
18. Shimoji M, Shimizu S, Sato K, et al. Clinical and pathologic features of lung cancer expressing programmed cell death ligand 1 (PD-L1). Lung Cancer 2016; 98: 69–75.
19. Huynh TG, Morales-Oyarvide V, Campo MJ, et al. Programmed cell death ligand 1 expression in resected lung adenocarcinomas: association with immune microenvironment. J Thorac Oncol 2016; 11(11): 1869–1878.
20. Dix Junqueira Pinto G, de Souza Viana L, Scapulatempo Neto C, et al. Evaluation of PD-L1 expression in tumor tissue of patients with lung carcinoma and correlation with clinical and demographic data. J Immunol Res 2016; 2016: 9839685.
21. Velcheti V, Schalper KA, Carvajal DE, et al. Programmed death-ligand 1 expression in non-small cell lung cancer. Lab Invest 2014; 94: 107–116.
22. Yang CY, Lin MW, Chang YL, et al. Programmed cell death-ligand 1 expression in surgically resected stage I pulmonary adenocarcinoma and its correlation with driver mutations and clinical outcomes. Eur J Cancer 2014; 50(7): 1361–1369.
23. Cancer AJCo. American Joint Committee on Cancer staging manual. Chicago, IL: Cancer AJCo, 2018.
24. Health MoP. Lebanese National Cancer registry. 2015. National Cancer Registry (moph.gov.lb)
25. Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 2018; 378: 2078–2092.
26. Tflya I, Rafei H, Mina A, et al. Prevalence of EGFR and ALK mutations in lung adenocarcinomas in the levant area: a prospective analysis. Asian Pac J Cancer Prev 2017; 18: 107–114.
27. Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. JAMA 2014; 311: 1998–2006.
28. Naderi S, Ghorra C, Haddad F, et al. EGFR mutation status in Middle Eastern patients with non-squamous non-small cell lung carcinoma: a single institution experience. Cancer Epidemiol 2015; 39(6): 1099–1102.
29. Jazieh AR, Jaafar H, Jaloudi M, et al. Patterns of epidermal growth factor receptor mutation in non-small-cell lung cancers in the Gulf region. Mol Clin Oncol 2015; 3(6): 1371–1374.
30. Chen YB, Mu CY and Huang JA. Clinical significance of programmed death-ligand 1 expression in patients with non-small cell lung cancer: a 5-year-follow-up study. Tumori 2012; 98(6): 751–755.
31. Zhang M, Li G, Wang Y, et al. PD-L1 expression in lung cancer and its correlation with driver mutations: a meta-analysis. Sci Rep 2017; 7: 10255.
32. Lin G, Fan X, Zhu W, et al. Prognostic significance of PD-L1 expression and tumor infiltrating lymphocyte in surgically resectable non-small cell lung cancer. Oncotarget 2017; 8: 83986–83994.
33. Sorensen SF, Zhou W, Djeled-Filhart M, et al. PD-L1 expression and survival among patients with advanced non-small cell lung cancer treated with chemotherapy. Transl Oncol 2016; 9(1): 64–69.
34. Pan Y, Zheng D, Li Y, et al. Unique distribution of programmed death ligand 1 (PD-L1) expression in East Asian non-small cell lung cancer. J Thorac Dis 2017; 9(8): 2579–2586.
35. Kim MY, Koh J, Kim S, et al. Clinicopathological analysis of PD-L1 and PD-L2 expression in pulmonary squamous cell carcinoma: comparison with tumor-infiltrating T cells and the status of oncogenic drivers. Lung Cancer 2015; 88(1): 24–33.
36. Kerr KM, Tsao MS, Nicholson AG, et al. Programmed death-ligand 1 immunohistochemistry in lung cancer: in what state is this art. *J Thorac Oncol* 2015; 10(7): 985–989.

37. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015; 373: 123–135.

38. Joseph Grosso CEH, Inzunza D, Cardona DM, et al. Association of tumor PD-L1 expression and immune biomarkers with clinical activity in patients (pts) with advanced solid tumors treated with nivolumab (anti-PD-1; BMS-936558; ONO-4538). *J Clin Oncol* 2017; 31(15): 3016.

39. Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature* 2014; 515: 563–567.

40. Tretiakova M, Fulton R, Kocherginsky M, et al. Concordance study of PD-L1 expression in primary and metastatic bladder carcinomas: comparison of four commonly used antibodies and RNA expression. *Mod Pathol* 2018; 31(4): 623–632.

41. Konishi J, Yamazaki K, Azuma M, et al. B7-H1 expression on non-small cell lung cancer cells and its relationship with tumor-infiltrating lymphocytes and their PD-1 expression. *Clin Cancer Res* 2004; 10: 5094–5100.

42. Sun J-M, Choi Y-L, Choi S-J, et al. PD-L1 expression and survival in patients with non-small cell lung cancer (NSCLC) in Korea. *J Clin Oncol* 2017; 35: 8066.

43. Buttner R, Gosney JR, Skov BG, et al. Programmed death-ligand 1 immunohistochemistry testing: a review of analytical assays and clinical implementation in non-small-cell lung cancer. *J Clin Oncol* 2017; 35: 3867–3876.

44. Chan AWH, Tong JHM, Kwan JSH, et al. Assessment of programmed cell death ligand-1 expression by 4 diagnostic assays and its clinicopathological correlation in a large cohort of surgical resected non-small cell lung carcinoma. *Mod Pathol* 2018; 31(9): 1381–1390.

45. Dang TO, Ogunniyi A, Barbee MS, et al. Pembrolizumab for the treatment of PD-L1 positive advanced or metastatic non-small cell lung cancer. *Expert Rev Anticancer Ther* 2016; 16: 13–20.