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The clinical significance of soluble PD-1 and PD-L1 in lung cancer

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ABSTRACT

Soluble PD-1 and PD-L1 are detected in the serum and plasma of lung cancer patients. The significance of these soluble proteins as prognostic or predictive markers in lung cancer is uncertain. The testing methods used to detect soluble PD1/PD-L1 are variable with no agreement on a common definition of a positive test. The advantages of validating soluble PD1/PD-L1 relevance in lung cancer include easiness of obtaining blood samples for testing, serial measurements to assess response to treatments such as immunotherapy, and potentially early identification of cancer relapse in cases treated with curative intent. In this review, we present the available data published on soluble PD1 and PD-L1 in lung cancer.

1. Introduction

Immune checkpoint inhibitors act by blocking the binding of PD-1 on immune cells and PD-L1 on malignant cells or immune cells infiltrating the tumor. PD-1 is mainly expressed on immune cells. PD-L1 is expressed on hematopoietic and non-hematopoietic cells in addition to malignant tumors (Salmaninejad et al., 2019). The PD1/PD-L1 signaling is one of the key pathways used by tumors to abrogate the immune response. Drugs blocking PD-1/PD-L1 immune checkpoints have revolutionized cancer care by their promising efficacy in several tumor types and stages.

Both PD-1 and PD-L1 exist in two forms: membrane bound and soluble forms (Zhu and Lang, 2017). In normal serum, soluble PD-L1 (sPD-L1) is detected with the lowest levels in children age 3–10 and highest in adults age 51–70 (Chen et al., 2011). Soluble PD-L1 has a ubiquitous nature as it can be found in the plasma as well as in other liquids such as the pleural effusion of lung cancer patients (Gong et al., 2019). The soluble forms are primarily generated by proteolytic cleavage of the membrane bound form. There are 2 types of PD-1 which circulate in the soluble form: 1) One that is completely homologous with the membrane bound PD-1 (mPD-1). 2) The others have different parts of the membrane bound form spliced out (Zhu and Lang, 2017). Soluble PD-L1 is found in the supernatant of mPD-L1 positive, not negative, malignant cell lines further suggesting sPD-L1 is mostly a product of mPD-L1 cleavage (Chen et al., 2011). Matrix metalloproteinases are needed to generate sPD-L1 from mPD-L1 as using matrix metalloproteinase inhibitors decrease the level of sPD-L1 (Chen et al., 2011). Changes in the sequence of *PD-L1* exons was also found to enhance the production of truncated forms of PD-L1 that are more likely to be secreted rather than becoming membrane bound giving a genetic basis for the mechanism of producing sPD-L1 (Hassounah et al., 2019). Although many sPD-L1 variants have been identified, their exact effect on suppressing the immune system is not fully understood. For example, secPD-L1, a specific splice variant of sPD-L1, can covalently homodimerize, and mediate immunosuppression more effectively than other forms of monomeric sPD-L1 (Mahoney et al., 2019).

Soluble PD-1 and sPD-L1 were studied in malignant and non-malignant diseases (Zhu and Lang, 2017). In rheumatoid arthritis, elevated sPD-1 level was associated with disease activity and progression (Greisen et al., 2014). In autoimmune hepatitis, sPD-1 level was associated with active disease and incomplete response to therapy (Aarslev et al., 2017). In idiopathic pulmonary fibrosis (IPF), a chronic non-malignant lung disease, sPD-L1 was also found to be elevated (Jovanovic et al., 2018). Whether changes in sPD-L1 level in chronic lung diseases signal a transition from a non-malignant process to lung cancer is unknown. A study noted that higher sPD-1 level in HBV infected patients might be associated with hepatocellular carcinoma (Cheng et al., 2014). In another study (Cheng et al., 2015), sPD-L1 level was higher in NSCLC compared to normal controls. It was also concluded in the same study that *PD-L1* 8923 A/C polymorphism could be associated with increased susceptibility to NSCLC although *PD-L1* polymorphisms were not significantly associated with sPD-L1 level

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Table 1
Summary of sPD-1 and sPD-L1 studies in lung cancer.

Reference	Pathology	Number of Patients	sPD1 vs sPD-L1	ELISA	Serum vs Plasma	Driver mutation identified	Immunotherapy Used	Major Findings
Bonomi et al. (2019)	NSCLC	20	sPD-L1	MyBioSource, San Diego, CA, USA	Plasma	No	Pembrolizumab	High baseline sPD-L1 was associated with disease progression, however, this was not statistically significant
Vecchiarelli et al. (2018)	NSCLC	72	sPD-L1	CUSABIO, MD, USA	Plasma	Yes	Nivolumab	1) Elevated baseline sPD-L1 is associated with high tumor burden 2)sPD-L1 increased in patients who received chemotherapy, not TKIs or immunotherapy.
Okuma et al. (2018)	NSCLC	39	sPD-L1	PDCD1LG1; Cloud-Clone Corp, Katy, TX	Plasma	Yes	Nivolumab	High baseline sPD-L1 was associated with poor response to Nivolumab
Jin et al. (2018)	SCLC	500	sPD-L1	Quantikine R&D Systems, Minneapolis, MN, USA	Serum	No	No	High baseline sPD-L1 in SCLC was associated with no response to chemotherapy.
Zhao et al. (2017)	NSCLC	126	sPD-L1	PDCD1LG1ELISAkit,USCNLife Science, Wuhan, China	Plasma	No	No	1) sPD-L1 dropped after radiation to the lung with or without chemotherapy 2) High baseline sPD-L1 was associated with worse survival in the patients who received only radiation (not concurrent chemotherapy and radiation)
Okuma et al. (2017)	NSCLC + SCLC	96	sPD-L1	Cloud-Clone Corp. Houston, TX, USA	Plasma	Yes	No	High baseline sPD-L1 level is associated with poor survival.
Sorensen et al. (2016)	NSCLC	38	sPD-1	DuoSet human PD-1, R&D systems, Minneapolis, MN, USA, catalog no. DY1086	Serum	Yes	No	In EGFR mutated NSCLC patients receiving erlotinib, rising sPD-1 was associated with longer survival
Zhang et al. (2015)	NSCLC	174	sPD-L1	Beijing Keyingmei Science and Technology Ltd., Beijing, China; PD-L1 antibody Article Number: ab156361	Serum	Yes	No	High baseline sPD-L1 was associated with worse survival
Costantini et al. (2018)	NSCLC	43	sPD-L1	Ab214565 Human PD-L1 [28–8] ELISA Kit, Abcam	Plasma	Yes	Nivolumab	After Nivolumab, high sPD-L1 at 2 months, and rising sPD-L1 were associated with worse progression free survival
Dronca et al. (2017)	Melanoma and NSCLC	60	sPD-L1	Unspecified	Not reported	Not reported	PD-1 antibody	1) High baseline sPD-L1 was associated with no response to anti-PD-1. 2)sPD-L1 increased from baseline upon the first radiographic evaluation while on anti-PD-1

(Cheng et al., 2015). Regarding cancer outcomes, increased sPD-L1 level was associated with worse prognosis in diffuse large B cell lymphoma, natural killer/T-cell lymphoma, multiple myeloma, oral squamous cell carcinoma, melanoma and hepatocellular carcinoma (Gu et al., 2018).

There are questions to be answered about the significance of circulating sPD-1 and sPD-L1: 1) When measuring sPD-1 and sPD-L1, are these tumor or immune cell products or both? 2) Is it optimum to measure levels in plasma or serum? 3) Are elevated levels of sPD-1/sPD-L1 associated with response to immunotherapy? In this article, we review the lung cancer studies that explored sPD-1 and sPD-L1 (Table 1). We focus on the testing methods used, correlation of sPD-1 and sPD-L1 with clinical and pathological features, use of the soluble markers as prognostic and predictive tools in lung cancer especially in association with the use of immunotherapy.

2. Testing of soluble PD-1 and PD-L1

Enzyme linked immunosorbent assay (ELISA) has been the test of choice to measure sPD-1 and sPD-L1 in lung cancer. This has been done using plasma or serum. Various ELISA products with different measurement units and cutoff values of positivity were used. Positive results were mostly determined based on ROC curves specific to the study and the ELISA test used. Positive sPD-L1 tests were 0.0965 ng/ml (Zhao et al., 2017) and 7.32 ng/ml (Okuma et al., 2017) in two different lung cancer studies showing the wide range of what is considered a positive test.

New data suggests the need for a new sPD-1 and sPD-L1 ELISA testing method in the future focusing on the binding capacity of sPD-L1. Conventional ELISA systems detect sPD-L1 or sPD-1 using capture antibodies irrespective of their functional significance. Takeuchi et al. (2018) showed that a new ELISA system using PD-1-ig fusion protein for the detection and quantification of sPD-L1 with binding capacity. This assay may provide a better understanding of the functional capacity of sPD-L1 as a binder to PD-1 rather than relying on a quantitative sPD-L1 test using conventional ELISA (Takeuchi et al., 2018). It is hypothesized that measuring baseline sPD-L1 binding capacity will be more informative than a quantitative sPD-L1 ELISA in predicting lung cancer response to immunotherapy prior to starting treatment. However, as tumor burden decreases, serial quantitative sPD-L1 testing might be more reliable in assessing continued cancer response versus evolving resistance to cancer treatments such as immunotherapy.

The mPD-L1 splice product could be another variable that needs consideration when testing for sPD-L1. As sPD-L1 results from splicing of mPD-L1, it is unclear if an increase in a specific mPD-L1 splice product, the variability of the splice products, or the total quantity of sPD-L1 will be significantly associated with treatment outcomes. The increase in mPD-L1 splice variants in melanoma was associated with tumor response to cancer treatments including immunotherapy (Zhou et al., 2017). New tests that can detect the various sPD-L1 splice variants and their association with lung cancer treatment outcomes might be needed.

3. Soluble PD-1 and PD-L1 correlation with lung cancer clinical and pathological characteristics

Lung cancer studies that evaluated the association between mPD-L1 expression and clinical characteristics showed mixed results (Bassanelli et al., 2018). Features studied include age, smoking status, ethnicity, cancer histology and stage, driver mutations and tumor burden. Zhang et al. (2015) in their study of sPD-L1 in advanced stage lung cancer concluded that high baseline sPD-L1 was not significantly associated with gender, age, tumor histology, smoking history or number of metastatic organs. However, there was an association with abdominal organ metastasis (P = 0.004). In another study by Cheng et al. (2015) the sPD-L1 plasma level was studied in 288 individuals with NSCLC. The sPD-L1 level was significantly higher for those with adenocarcinoma vs squamous cell carcinoma, and in patients with stages 3 and 4 versus stages 1 and 2. Vecchiarelli et al. (2018) showed there might be a correlation between high lung cancer tumor burden and elevated sPD-L1 level in patients with advanced stage NSCLC. Okuma et al. (2017) in a lung cancer trial showed that sPD-L1 level did not correlate with any of the studied features including age, gender, performance score, histology, stage, driver genetic abnormalities or smoking history.

4. Soluble PD-1 and PD-L1 association with non-immunotherapy treatments of lung cancer

Lung cancer studies evaluated the use of sPD-1 and sPD-L1 as a prognostic tool or biomarker of response to non-immunotherapy treatments. These included NSCLC and SCLC histologies with most of them focusing on sPD-L1, not sPD-1, in advanced cancer stages. The studies were heterogenous in terms of the patients included, testing methods and reported results. In tumors other than lung cancer, studies showed that sPD-1 and sPD-L1 might have prognostic and predictive value in relation to treatment with chemotherapy and radiation. In a colorectal study (Tominaga and Akiyoshi, 2019), sPD-L1 increase after completion of concurrent chemotherapy and radiation therapy was associated with a shorter disease free survival.

In lung cancer, consistent with other cancers, the studies showed poor prognosis and worse treatment outcomes in patients with elevated sPD-L1. A meta-analysis by Wei et al. (2018) studied the effect of sPD-L1 on prognosis in solid tumors. The meta-analysis included 3 lung cancer studies (Zhao et al., 2017; Okuma et al., 2017; Zhang et al., 2015). The analysis showed that high sPD-L1 level was associated with worse overall survival in solid tumors (HR of 2.26; 95% CI 1.83–2.80, Z = 7.51, P < .001). Zhang et al. (2015) showed that elevated sPD-L1 was associated with worse survival in advanced stage NSCLC. Those with high sPD-L1 had a median survival of 18.7 months compared to 26.8 months for low sPD-L1 ($P < 0.001$) (Zhang et al., 2015). The survival difference in favor of low sPD-L1 level was also noticed in the EGFR mutated 24 out of 73 patients (32.9%) although it was not statistically significant (17.3 vs 25.4 months, $P = 0.058$). Okuma et al. (2017) assessed sPD-L1 level in 96 patients with advanced lung cancer that included NSCLC and SCLC histologies. Those with sPD-L1 level > 7.32 had significantly shorter survival than those with baseline sPD-L1 level < 7.32. Another study by Vecchiarelli et al. (2018) in advanced NSCLC showed an increase in sPD-L1 from baseline in patients who received chemotherapy, but not in patients who received other treatments such as TKIs or immunotherapy. Elevated baseline circulating sPD-L1 in patients who received chemotherapy was associated with worse time to progression and overall survival; however, this was not statistically significant (Vecchiarelli et al., 2018). In addition to Okuma et al. (2017), only one more study included small cell lung cancer. In that study, Jin et al. (2018) showed that higher sPD-L1 level before starting chemotherapy was associated with no response to chemotherapy (HR: 1.40, 95% CI: 1.05–1.87) and higher cancer related death (HR: 1.43, 95% CI: 1.08–1.87).

Regarding lung cancer and radiation to the lung, high sPD-L1 was also associated with poor outcomes. In a study from China, (Zhao et al., 2017) 126 patients with NSCLC who received radiation or concurrent chemotherapy and radiation therapy to the lung had their sPD-L1 level checked. At baseline, the median level was 107.2 pg/ml. At weeks 2 and 4 of starting treatment, sPD-L1 dropped by almost 50%. However, post radiation sPD-L1 increased to 111.1 pg/ml. In patients receiving radiation only, higher baseline sPD-L1 level was associated with worse survival (P = 0.005). In the group receiving chemotherapy and radiation therapy, survival was not significantly different between those with high vs low baseline sPD-L1. The subgroup that received higher dose radiation (68–74 Gy) and had low sPD-L1 at baseline had the longest survival. Of note, the increase in sPD-L1 after completing chemoradiation could partially explain the survival benefit seen in the PACIFIC

trial (Antonia et al., 2018) when durvalumab, an anti-PD-L1, was administered to stage III NSCLC patients after completing chemotherapy and radiation therapy.

5. Soluble PD-1 and PD-L1 association with immunotherapy in lung cancer

High mPD-L1 expression in lung cancer is predictive of better response to PD-1 inhibitors (Paz-Ares et al., 2018). However, the relationship between sPD-L1 and response to immunotherapy is unknown. It is likely that serial sPD-L1 levels will vary at different time points before and after receiving immunotherapy and should be interpreted within that context. Zhou et al. (2017) showed that higher sPD-L1 level at 5 months after starting CTLA-4 or PD-1 inhibitors in melanoma was associated with partial response to treatment, but sPD-L1 level early after completing treatment was not predictive of tumor response. It is possible that late sPD-L1 is mostly a product of the immune cells indicating continued response to treatment; however, this is hypothetical.

The combination of chemotherapy and PD-1 inhibitors has been successfully integrated into the treatment of lung cancer even in patients with low mPD-L1 expression at baseline. (Paz-Ares et al., 2018; Gandhi et al., 2018) Whether sPD-L1 plays a role in response to chemo-immunotherapy is unknown. Vecchiarelli et al. (2018) showed an increase in circulating sPD-L1 in NSCLC after chemotherapy which could partly explain the benefit seen from combining chemotherapy and immunotherapy. Other chemo-immunotherapy combination studies showed that sPD-L1 might have a prognostic and predictive value. In an advanced stage NSCLC trial, 20 patients were randomized to receive pembrolizumab as a single agent or a combination of pembrolizumab with carboplatin and paclitaxel. Measurement of sPD-L1 was done before treatment, then at 4 and 7 weeks after treatment. It was noted that high baseline sPD-L1 was associated with disease progression, although this was not significant (Bonomi et al., 2019). Another lung cancer trial included 39 NSCLC patients treated with nivolumab showed that increased baseline sPD-L1 level was associated with poor tumor response to the PD-1 inhibitor (Okuma et al., 2018). It was found that 59% of those with low sPD-L1 level at baseline had a complete or partial response vs 25% response rate in the subjects with high sPD-L1 level. The time to failure and overall survival were significantly better in those with low sPD-L1 level (Okuma et al., 2018). Costantini et al. (2018) also showed similar findings of correlation between outcomes of nivolumab treatment in NSCLC and sPD-L1 level. In 43 advanced NSCLC cases treated with Nivolumab, high sPD-L1 level at 2 months after starting Nivolumab and an increase in sPD-L1 from baseline were associated with poor response to Nivolumab and significantly decreased progression free survival (Costantini et al., 2018). In that study, low sPD-L2 in addition to other soluble markers were found to be associated with less grade 3–4 toxicities (Costantini et al., 2018). Concordant with these findings, Dronca et al. (2017) reported an abstract on 60 patients with melanoma and lung cancer who were treated with anti-PD-1. High baseline sPD-L1 (2.8 ng/mL vs. 0.7 ng/mL, $p = 0.07$) was associated with no response to anti-PD-1, with an increase in sPD-L1 level upon the first radiographic evaluation after anti-PD-1 treatment.

Both PD-1 and PD-L1 inhibitors showed survival benefit and are FDA approved for the treatment of NSCLC (Antonia et al., 2018; Paz-Ares et al., 2018). It is unknown from clinical trials whether increased sPD-L1 is associated with preferential resistance to PD-L1 inhibitors and better response to PD-1 inhibitors. Gong et al. (2019) showed that two variants of secreted PD-L1 isolated from NSCLC patients resistant to anti-PD-L1 were associated with similar resistance to anti-PD-L1 when studied in a coculture system of CD8 T cells and cancer cells. In a xenograft, only a small fraction of cells that produce PD-L1v242 was enough to confer resistance to anti-PD-L1. Alternatively, anti-PD-1 was still effective in these cases likely indicating the resistance to anti-PD-L1 was mediated by the neutralizing effect of the secreted PD-L1. Whether this translates into clinical practice choosing anti-PD-1 over anti-PD-L1 in NSCLC patients with high sPD-L1 is unknown.

6. Soluble PD1 and PD-L1 association with genetic abnormalities in lung cancer

Expression of mPD-L1 was increased in NSCLC with EGFR, ALK and other genetic abnormalities common to lung cancer (Bassanelli et al., 2018). This increase in mPD-L1 expression was associated with worse prognosis in EGFR mutated NSCLC likely through providing a mechanism for evading the immune system (Bassanelli et al., 2018). However, it is unknown if sPD-L1 is increased in oncogenic addicted NSCLC or if it is related to treatment outcomes in these patients.

Vecchiarelli et al. (2018) showed that circulating sPD-L1 is increased in NSCLC after receiving chemotherapy; however, this trend was not seen for EGFR mutated patients who received EGFR TKI. Sorensen et al. (2016) showed in 38 NSCLC patients with EGFR mutation that upon cancer progression while receiving erlotinib, those with higher sPD-1 (not sPD-L1) had longer subsequent progression free survival (HR 0.32, $p = 0.013$) and overall survival (HR 0.33, $p = 0.006$). In that study, the sPD-1 level was not related to the emergence of T790 M mutation, the most common resistance mutation in EGFR NSCLC treated with TKI. However, it is unknown if the rising sPD-1 was indicative of other “favorable” resistance mechanisms. In a study by Okuma et al, high baseline sPD-L1 in lung cancer was associated with worse survival (Okuma et al., 2017). In that study, 19/96 patients (26%) had EGFR mutation and 3/96 patients (3%) had ALK rearrangement. In a paper from China, Zhang et al. (2016) conducted a case control study on wild-type (wt) and mutated EGFR NSCLC patients. They reported in an abstract that sPD-L1 level decreased after EGFR TKI compared to the control group. It was also noticed that sPD-L1 was significantly higher in the EGFR patients who had disease progression compared to stable disease.

From the published data, both sPD-1 and sPD-L1 might have a role in the treatment strategies of oncogene driven NSCLC especially those with EGFR mutation. In wt NSCLC, the cumulative evidence is more towards the use of sPD-L1, not sPD-1, as a prognostic and predictive tool. In the oncogene addicted NSCLC, serial testing of sPD-1 at baseline and during treatment might be useful in identifying early signs of resistance to TKIs and to consider switching to a new line of treatment based on rising sPD-1 level instead of awaiting radiographic progression. This will need to be further tested in prospective trials.

7. Conclusion

There is growing data suggesting that high baseline sPD-L1 has a negative impact on lung cancer outcomes. Repeat assays of mPD-L1 are not readily feasible in the clinical setting. Once treatment is initiated, sPD-1/sPD-L1 which can be serially assayed may be valuable in assessing response to therapy and in the early recognition of emerging resistance in oncogene driven and wild type NSCLC. Furthermore, the decision on choosing a specific checkpoint inhibitor such as anti-PD1 or anti-PD-L1 for treatment of NSCLC might also be influenced by the presence of sPD-L1. While more expression of mPD-L1 makes response to anti-PD1 therapy more likely, mPD-L1 does not always correlate with response to immunotherapy. Assessment of sPD-1/sPD-L1 shows promise as a new or additional prognostic tool and biomarker in the management of NSCLC.

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Taher Abu Hejleh: Conceptualization, Methodology, Visualization.

Muhammad Furqan: Conceptualization, Methodology, Visualization. **Zuhair Ballas:** Conceptualization, Methodology, Visualization. **Gerald Clamon:** Conceptualization, Methodology, Visualization.

Declaration of Competing Interest

The authors have no competing interests to disclose.

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