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Circulating Tumor Cells (CTCs) as Biomarker for PD-1/PD-L1 Blockade Immunotherapy

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Description

The PD-1/PD-L1 (programmed death-1, programmed death-1 ligand-1) checkpoint is involved in dampening autoimmunity of peripheral tissues to help control local inflammatory responses. It is reported that this pathway activation results in peripheral immunologic tolerance in T cells [1]. As an identified ligand of PD-1, PD-L1 expressed in tumor cells facilitates tumor escape by inducing a net immunosuppressive effect after binding to PD-1 present on the surface of activated T cells and B cells [2]. The enhanced understanding of the complex interplay between the tumor and the immune system has promoted the development of anti-PD therapy for the treatment of human cancers. Antibodies blocking PD-1/PD-L1 have demonstrated durable responses in a number of different advanced malignancies [3,4]. However, while increasing a baseline T-cell-specific immune response, immune checkpoint inhibitors might result in autoimmune-like/inflammatory side-effects, which cause collateral damage to normal organ systems and tissues, such as skin, lung and liver [5]. Therefore, detection of potential biomarkers that may predict benefit is pivotal in order to optimize clinical efficacy and safety of checkpoint blockade immunotherapy.

Emerging data suggest that patients with PD-L1-positive tumors are more likely to benefit from PD-1/PD-L1 blockade immunotherapy than those with PD-L1-negative tumors [6-9]. Tumor-associated PD-L1 immunohistochemistry (IHC) is the solely plausible biomarker to predict responses to PD-1/PD-L1 blockade and FDA has approved 4 different PD-L1 IHC assays for companion diagnostics (Table 1). However, there are multiple unresolved issues for IHC evaluation considering different IHC antibodies, primary versus metastatic biopsies, and heterogeneity of tumors. Wide variability is observed in the positive percentage in different tumor samples. Melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC) and bladder cancer are tumors classically associated with clinical responses to PD-1 checkpoint inhibition therapy, and the relevant PD-L1 IHC expression ranges widely from 14% to 100% [10-12]. It implies the possibility for PD-L1 IHC as a predictive biomarker for PD-1/PD-L1 blockade immunotherapy. In comparison, PD-L1 expression in colorectal cancer and sarcoma ranges from 12% to 53%, but the relevant responses to immune checkpoint inhibition are much weaker, indicating that tumor PD-L1 IHC expression is not the sole predictive determinant for drug response [13]. Moreover, between the matched primary tumor and distant metastasis, only a weak correlation in PD-L1 IHC detection was observed, suggesting that the primary tumor is not an adequate surrogate for PD-L1 expression detection in metastatic sites [14]. Therefore, PD-L1 detection for dynamic changes at different sites and time points will certainly be a challenge.

The analysis of blood samples for circulating tumor cells (CTCs) detection and characterization is an alternative non-invasive approach to predict response and monitor real-time response to treatment. To explore the monitor potential of CTCs during chemotherapy of metastatic breast cancer, Hartkopf et al. analyzed the correlation between changes of CTC levels and chemotherapy response assessed using radiographic Response Evaluation Criteria in Solid Tumors (RECIST) criteria and CA 15-3 concentrations. They observed that changes in CTC counts during the course of chemotherapy significantly correlated with response to chemotherapy and is useful in monitoring therapy efficacy [15,16]. In another study, synchronously decreases in CTC count and FLT-PET signal were found in patients undergone docetaxel therapy [17]. These proofs indicate the possibility of circulating tumor cells changes as a predicator in monitoring chemotherapy response.

Following the flourish of checkpoint blockade immunotherapy, more and more researchers are focusing on the characterization of PD-L1 on CTCs and the possibility of CTCs/PD-L1 as a biomarker for PD-1/PD-L1 blockade immunotherapy. Mazel et al. first reported the feasibility of PD-L1 evaluation in CTCs from breast cancer patients [18]. At the meeting of ASCO 2016, Boffa et al. demonstrated that patients with higher burden of PD-L1+ CTCs had a poor prognosis in lung cancer compared to those patients with low/negative PD-L1+ CTCs. In metastatic bladder cancer, patients with high PD-L1+/CD45−CTC burden and low burden of apoptotic CTCs had lower overall survival [19]. These findings suggest the possibility using PD-L1 positive CTCs to evaluate prognosis in metastatic cancers. A lately study evaluated the dynamic changes of PD-L1 positive CTCs in NSCLC patients treated with PD-1 inhibitor Nivolumab. The authors correlated the status of PD-L1 positive CTCs with outcome. They found patients without PD-L1+ CTCs at 6 months of treatment all obtained a clinical benefit, while patients with PD-L1+ CTCs all experienced a disease progression. This observation indicates that PD-L1 expression on CTCs might have predictive significance in late course of anti PD-1 checkpoint immunotherapy [20]. Another latest case report has proposed that the PD-L1 assessment of CTCs might help identifying suitable patients for anti-PDL1 therapy [21]. Moreover, there are studies suggesting that PD-L1 may be induced by multiple therapies, such as cytotoxic chemotherapy, targeted agents, or radiation therapy, which may act as an immunologic escape response in tumors [22]. Therefore, assessment of PD-L1 expression on CTCs might allow serial assessment of the status of PD-L1 expression during therapy, especially

PD-L1 detection antibody	Company	Companion therapeutic agents	Histologies
PD-L1 IHC 28-8 pharmDx	Dako	OPDIVO (nivolumab), YERVOY (ipilimumab)	NSCLC, melanoma
Ventana SP263	Roche	Imfinzi(durvalumab)	UC
PD-L1 IHC 22C3 pharmDx	Dako	Keytruda (pembrolizumab)	NSCLC
Ventana SP142	Roche	Tecentriq (Atezolizumab)	UC, NSCLC

Table 1: FDA approved PD-L1 IHC assays.

when repeat biopsies are impractical during the therapeutic course. Unlike traditional treatment directly targeting tumors, PD-1/PD-L1 blockade immunotherapy works via restoring immune system. The unique mechanism and the corresponding dynamic changes in PD-L1 status highlight the feasibility of PD-L1 positive CTCs as a predicator of immunotherapeutic response and a monitor biomarker for PD-1/PD-L1 blockade therapy.

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