



Programmed death-ligand 1 expression discrepancy between primary tumor and metastatic lymph nodes in non-small cell lung cancer

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Immune-checkpoint inhibitors (ICI) have recently revolutionized cancer treatment of non-small cell lung cancer (NSCLC). Currently, programmed death-ligand 1 (PD-L1) represents the standard response predictor biomarker for PD-1 or PD-L1 inhibitors. PD-L1 immunohistochemistry staining scoring can be affected by different factors such as the type of antibody, the substrate (tumor cells *vs.* immune cells), type of tissue (FFPE archive *vs.* fresh biopsy) and others. Saito *et al.* reported the PD-L1 staining heterogeneity between primary *vs.* metastases sites in NSCLC (1).

PD-1 inhibitor, pembrolizumab, as monotherapy is an accepted regiment for patients with PD-L1 >50% as demonstrated in KEYNOTE-24 (2). Furthermore, the current standard-of-care in first-line therapy for advanced NSCLC regardless of PD-L1 status is pembrolizumab in combination with platinum doublet chemotherapy based on the subsequent confirmatory trials; KEYNOTE-189 (non-squamous) and KEYNOTE-407 (squamous) (3,4). Importantly, the PD-L1 $\geq 50\%$ subgroup has the best response rate to this first-line combination therapy (5).

In order to determine PD-L1 tumor proportion score (TPS) status, 22C3 antibody clone is typically used as a companion diagnostic antibody for pembrolizumab. Meanwhile, 28-8 clone was approved as the complementary

diagnostic antibody for nivolumab and atezolizumab. This is also the case for the SP263 assay (6,7). It has become apparent that these tests are now interchangeable; therefore, clinicians are welcome to use any of these tests in the future.

Nonetheless, a complication in establishing accurate TPS status arises when addressing inter- and intra- patient and tumor heterogeneity. So far, the issue of heterogeneity has seldom been discussed in PD-L1 expression in lung cancer. Saito *et al.* recently produced a report on the discrepancies in tumor PD-L1 status heterogeneity between the primary site and secondary lymph nodes by using two diagnostic assays (22C3, 28-8) (1).

A total of 35 patients with primary tumors and paired lymph node involvement were enrolled in their study, divided into no expression (TPS: <1%), low expression (TPS: 1–49%), or high expression (TPS: $\geq 50\%$). Low concordance rate was reported for both 22C3 (28.6%) and 28-8 (31.4%) assays comparing primary tumors with their respective lymph node counterparts. Summarizing, in approximately 70% of the cases, no correlation was found between the TPS status in the primary tumor and metastatic lymph node. Moreover, the study confirms that there is no significant difference between the two assay models (Pearson's chi-square test: $P < 0.001$).

These findings raise the question of the role of TPS

Table 1 The discrepancy rate between primary and metastatic lesions

Cancer type	Biomarker type	Discrepancy rate, %	Concordance rate, %	Reference
Melanoma	BRAF	13.40	86.60	(8)
Breast	ER	17.80	82.20	(9)
	PR	45.40	54.60	
	HER2	13.30	86.70	
Colon	KRAS	8	92	(10)
	BRAF	8	92	
	PIK3CA	7	93	
Kidney	PD-1	27	73	(11)
	PD-L1	22	78	
Lung cancer	PD-L1	70	30	(1)

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; PD-L1, programmed death-ligand 1; PD-1, programmed death 1.

status in guiding ICI treatment decision making in correlation to the biopsy site. The discrepancy is more prominent in the high expressing primary tumors (>50%) for which in comparison with their metastatic lymph nodes presented no or low PD-L1 expression. Indicating that careful assessing should be performed when biopsying only metastatic lymph nodes which may not represent the PD-L1 expression status of the primary tumor. Revealing the importance of a deeper understanding of the lung tumor heterogeneity in order to provide the best treatment strategy.

Previous studies have also emphasized the importance of tumor heterogeneity and the discrepancy between primary and metastatic lesions in different driver mutations and type of cancer, such as in metastatic melanoma carrying BRAF mutation, Valachis *et al.* reported a discrepancy rate of 13.4% between primary and metastatic lesions in BRAF, while a 7.3% discrepancy was found between two metastatic lesions (8). In breast cancer, the reported receptor status discordance between primary and metastatic lesions in estrogen receptor, progesterone receptor, and HER2 were found to be 17.8, 45.4, and 13.3% respectively (9). In colon cancer the median biomarker concordance rate between primary and metastatic colorectal cancer was 81% (10). In renal cell carcinoma, both PD-1 and PD-L1 expression were higher in primary versus metastatic tumors (11). None of these examples of heterogeneity fall in the discrepancy range found in work conducted by Saito *et al.* summarized in *Table 1*.

The current study, as well as previous ones, indicate that biopsy site should be noted in future clinical trials.

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Footnote

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