

# Imaging PD-L1 Expression in Melanoma Brain Metastases

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See the associated article on page 899.

**B**rain metastases, often originating from melanoma, lung cancer, or breast cancer, are the most common tumor in the brain and are associated with a dismal prognosis (1). Nearly 12% of patients with melanoma develop brain metastases, leading to a reduction in median survival to less than 9 mo. Brain metastases pose a significant challenge for treatment, as the disease state is highly refractory and central nervous system penetration of drugs across an intact blood–brain barrier is poor (1). Therapeutics targeting immune checkpoint proteins have shown intracranial activity in melanoma brain metastases, indicating an immune-active microenvironment (1). However, a deeper insight into the genetic and immunologic underpinnings of brain metastases and their response to immune system–targeted therapies is needed to overcome potential resistance mechanisms. Programmed death ligand 1 (PD-L1) is an immune checkpoint protein that is abundantly expressed by tumors (2). In this issue of *The Journal of Nuclear Medicine*, Nienhuis et al. characterize the changes in PD-L1 expression in brain and extracranial metastases in melanoma patients receiving immune checkpoint therapy (3).

Unlike conventional treatment methods, immune checkpoint therapeutics target the immune system. Efficacy can then be independent of tumor histology and genetic alterations, thus providing durable benefits in a variety of cancer types (2). Among the targets, the immune checkpoint proteins cytotoxic T-lymphocyte–associated antigen 4, programmed death 1, and its ligand PD-L1 are the best characterized, with several inhibitors receiving approvals from the Food and Drug Administration (2). Long-term treatment benefits are observed in a small percentage of patients when these inhibitors are given as single-agent therapy (4). Durable benefits have been observed in a higher percentage of patients when different checkpoint inhibitor combinations are used or when checkpoint inhibitors are combined with chemotherapy, targeted therapy, or radiotherapy (2,5).

Enrichment of patients to further improve the outcomes of cancer immunotherapy is based on high tumor PD-L1 expression, tumor mutation burden, and DNA mismatch repair deficiency (6).

To date, PD-L1 detection by immunohistochemistry received several Food and Drug Administration approvals as a complementary or companion diagnostic. However, the current landscape of PD-L1 immunohistochemistry as a predictive biomarker is complex (7). Although issues pertaining to the use of multiple antibody clones and staining platforms have been addressed by the Blueprint project, immunohistochemistry assays do not fully capture the heterogeneity in PD-L1 expression within and across patients (7). Moreover, immune responses are atypical, are unpredictable, and differ on the basis of tumor type, thus needing real-time noninvasive imaging analysis of changes in the tumor microenvironment.

Radiolabeled analogs of several anti-PD-L1 antibodies have been investigated to noninvasively quantify PD-L1 levels in pre-clinical tumor models and in cancer patients (7). Results from early clinical studies show that PD-L1 radiotracer uptake can readily be detected by PET and is highly heterogeneous within and across patients (7). The PET tracer used by Nienhuis et al., <sup>18</sup>F-BMS-986192, possesses the advantage of being labeled with <sup>18</sup>F, a radionuclide with a favorable energy profile and half-life, and exhibits faster pharmacokinetics facilitating image acquisition at 60 min for rapid PD-L1 quantification. <sup>18</sup>F-BMS-986192 is an engineered small adnectin protein with a dissociation constant of less than 35 pM for PD-L1 (8). It exhibited PD-L1–specific uptake in human tumor xenografts in vivo and concordance with PD-L1 immunohistochemistry staining in non–small cell lung cancer (NSCLC) tissues ex vivo (8). Heterogeneous <sup>18</sup>F-BMS-986192 uptake was observed within and between melanoma patients in this study, similarly to previous studies on NSCLC (9). Although <sup>18</sup>F-BMS-986192 uptake was significantly higher in NSCLC tumors for lesions with at least 50% tumor PD-L1 expression measured by immunohistochemistry, as compared with lesions with less than 50% expression (9), the sensitivity of the radiotracer in quantifying PD-L1 level as a continuous variable remains to be established for sustained use in melanoma. Nearly 35% of melanoma tumors exhibit PD-L1 tumor proportion scores of less than 50% (6), and PD-L1 expression on tumor cells is lower in melanoma than in other cancers, including NSCLC and renal cell carcinoma (6). Establishing the sensitivity of PD-L1 imaging agents is needed to further guide clinical decisions, as most melanoma trials have used a cut point of 5% PD-L1 positivity whereas NSCLC trials used 50%.

Although some homogeneity is observed in spatially and temporally separated brain metastasis in their genetic and immunologic profile, they are highly divergent from extracranial metastases (10). No significant differences in PD-L1 expression between melanoma brain and extracranial metastases were observed in that study, however (10). Although no significant differences were observed in

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baseline  $^{18}\text{F}$ -BMS-986192 uptake between brain and extracranial metastases (mostly lung), a trend toward lower radiotracer uptake in brain metastases could be observed, perhaps because of the poor blood–brain barrier permeability of the radiotracer. In contrast, on treatment,  $^{18}\text{F}$ -BMS-986192 scans showed significantly lower uptake of the radiotracer in brain metastases than in extracranial metastases.  $^{18}\text{F}$ -BMS-986192 uptake was also observed to be heterogeneous within brain metastases, as could be explained by the fact that some brain metastases can disrupt the blood–brain barrier. The absence of correlative immunohistochemistry data or prior validation of the tracer to detect variable PD-L1 levels makes it difficult to interpret these observations. Combining imaging studies with tissue biomarker analyses, when feasible, would provide a deeper understanding of the organ-specific immune contexture and its relationship to imaging measurements and move us toward developing composite biomarkers.

In this report, the authors observed that lesions with high baseline  $^{18}\text{F}$ -BMS-986192 uptake, when corrected for blood-pool activity, respond well to nivolumab or ipilimumab-plus-nivolumab therapy. This observation is in line with prior clinical studies establishing that PD-L1 expression in the melanoma tumor microenvironment is a predictor of response to immune checkpoint therapeutics (11). Timing the imaging studies during treatment to capture the transient kinetics of immunologic effects is challenging, however. Early on-treatment biopsies collected at 1.4 mo in melanoma patients showed a highly statistically significant increase in PD-L1 levels in responders, compared with nonresponders (12). In this study, authors observed that radiotracer uptake in metastases at 6 wk after treatment positively correlates with tumor size at follow-up at 12 wk. Because of the nature of the study and lack of cross validation, it is difficult to discern the underlying factors contributing to increased radiotracer uptake, which include tumor progression, pseudo progression due to an influx of immune cells, and the resulting PD-L1 induction. The challenge here again will be to ensure optimal imaging times and cross correlation of imaging measures with immunohistochemistry.

Despite the dramatic improvements in advanced melanoma treatments and outcomes, brain metastases remain a significant challenge. Brain metastases are diagnosed in nearly 60% of patients with advanced melanoma and often show isolated progression, although disease is controlled in extracranial metastases. Noninvasively quantifying PD-L1 and other relevant biomarkers in the tumor microenvironment and establishing a relationship to response, as shown here,

will play an important role in improving the efficacy of immunotherapy for this patient group.

## DISCLOSURE

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