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Imaging PD-L1 expression in melanoma brain metastases

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Brain metastases, often originating from melanoma, lung or breast cancer, are the most common tumor in the brain and are associated with dismal prognosis (*1*). Nearly 12% of patients with melanoma develop brain metastases leading to a reduction of median survival to less than 9 months. Brain metastases pose a significant challenge for treatment as the disease state is highly refractory and the CNS penetration of drugs across an intact blood-brain barrier (BBB) 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) PD-L1 is an immune checkpoint protein that is abundantly expressed by tumors (*2*). In this month JNM, Nienhuis et al., characterized 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*). Amongst the targets, immune checkpoint proteins cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed death 1 (PD-1) and its ligand programmed death ligand 1 (PD-L1) are the most characterized with several inhibitors receiving approvals from Food and Drug Administration (*2*). Long-term treatment benefits are observed in a small percentage of patients when those 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 and radiotherapy (*2*) (*5*).

Enrichment of patients to further improve therapeutic outcomes to 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 (IHC) received several FDA approvals as a complementary or companion diagnostic. However, the current landscape of PD-L1 IHC 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, IHC assays do not fully capture the heterogeneity in PD-L1 expression within and across patients (*7*). Moreover, immune responses are atypical, unpredictable and differ based on tumor types, thus needing real-time noninvasive imaging analysis of changes in the tumor microenvironment (TME).

Radiolabeled analogs of several anti-PD-L1 antibodies have been investigated to non-invasively quantify PD-L1 levels in preclinical tumor models and in cancer patients (*7*). Results from early clinical studies show that PD-L1 radiotracer uptake can be readily detected by positron emission tomography (PET) and is highly heterogeneous within and across patients (*7*). The PET tracer used by Nienhuis et al., ^{18}F-BMS-986192, possesses the advantage of being labeled with fluorine-18, a radionuclide with favorable energy profile and half-life, and exhibits faster pharmacokinetics facilitating image acquisition at 60 min for rapid PD-L1 quantification. ^{18}F-BMS-986192 is an engineered small adnectin protein with a dissociation constant <35 pM for PD-L1(*8*). It exhibited PD-L1 specific uptake in human tumor xenografts *in vivo* and concordance with PD-L1 IHC staining in non-small cell lung cancer (NSCLC) tissues *ex vivo* (*8*). Heterogenous ^{18}F-BMS-986192 uptake was observed within and between melanoma patients in this study, similarly to previous studies in NSCLC (*9*). Although ^{18}F-BMS-986192 uptake was significantly higher in NSCLC tumors for lesions with ≥50% tumor PD-L1 expression measured by IHC as compared to lesions with <50% expression (*9*), sensitivity of the radiotracer to quantify PD-L1 level as a continuous variable remains to be established for a sustained use in melanoma. Nearly 35% of melanoma tumors exhibit PD-L1 tumor proportion scores less than 50% (*6*), and PD-L1 expression on tumor cells is lower in melanoma as compared to 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 baseline ^{18}F-BMS-986192 uptake between brain and extracranial metastases (mostly lung), a trend towards lower radiotracer uptake in brain metastases could be observed, perhaps due to the poor BBB permeability of the radiotracer. In contrast, on treatment ^{18}F-BMS-986192 scans showed significantly lower uptake of the radiotracer in the brain metastases compared to extracranial metastases. ^{18}F-BMS-986192 uptake was also observed to be heterogenous within brain metastases, which could be explained by the fact that some brain metastases can disrupt the BBB. The absence of correlative IHC data or the 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 deeper

understanding of the organ specific immune contexture, its relationship to imaging measurements, and move us towards developing composite biomarkers.

In this report, authors observed that lesions with high baseline ^{18}F-BMS-986192 uptake, when corrected for blood pool activity, respond well to nivolumab or ipilimumab-plus-nivolumab therapy. This is in line with prior clinical studies that established that PD-L1 expression in the melanoma TME is a predicter of response to immune checkpoint therapeutics (*11*). Timing the imaging studies during treatment to capture the transient kinetics of immunological effects is challenging however. Early on-treatment biopsies collected at 1.4 months in melanoma patients showed a highly statistically significant increase in PD-L1 levels in responders compared to non-responders (*12*). In this study, authors observed that radiotracer uptake in metastases at 6 weeks after treatment positively correlates with tumor size at follow up at 12 weeks. Due to 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 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 IHC.

In spite of 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. Non-invasive quantification of PD-L1 and other relevant biomarkers in the TME and establishing a relationship to response, as shown here, will play an important role in improving the efficacy of immunotherapy for this patient group.

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S.N. is a co-inventor on a pending U.S. patent covering PD-L1 imaging agents and as such are entitled to a portion of any licensing fees and royalties generated by the technology. This arrangement has been reviewed and approved by the Johns Hopkins University in accordance with its conflict-of-interest policies. S.N is a consultant for and receives funding from Precision Molecular Inc.,

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