In an elegant study by Weide et al., baseline biomarkers to predict responses to anti-programmed death-1 (PD-1) (pembrolizumab) therapy in melanoma patients were investigated (1).

The PD-1 receptor is responsible for suppressing T cell responses to melanoma. Pembrolizumab and nivolumab are currently the two FDA approved anti PD-1 antibodies for the treatment of metastatic melanoma (2, 3). The overall response rate (ORR) with anti PD-1 agents is approximately 30% and patients experience clinical benefit for a longer period of time than traditional chemotherapy (4-8). Recent studies show that the response to anti-PD-1 agents can be significantly improved by combining anti PD-1 and anti CTLA-4 therapy, but this benefit is outweighed by the higher risk of severe immune related adverse events (6,9).

Currently, there is lack of well-defined biomarkers for predicting the response and tolerability of anti PD-1 therapy. The programmed death receptor ligand-1 (PDL-1) on tumor cells binds to PD-1 on T cells. Many studies have utilized the measurement of PDL-1 expression on tumor cells by immunohistochemistry as a marker of response. For example, in the phase 1 study utilizing the nivolumab antibody, objective responses to therapy were only observed in patients with PDL-1 expression in tumors (defined as >5% PDL-1 expression) (10). Even though most studies reported an association between higher PDL-1 expression and clinical responses to nivolumab monotherapy, responses were observed in patients whose tumors did not express PDL-1 (6). Consequently, both nivolumab and pembrolizumab are approved for treatment of malignant melanoma irrespective of PDL-1 expression status on tumor cells. This variability in response based on PDL-1 expression may be partly explained by differences in antibodies utilized for immunohistochemistry studies and the lack of uniformity in thresholds for PDL-1 positivity across studies (11). With increasing utilization of immunotherapy in clinical practice, there is an urgent need for development of novel biomarkers for prognostication and risk stratification of patients undergoing anti PD-1/ PDL-1 therapy.

Weide et al. studied patients with advanced melanoma treated with at least one dose of pembrolizumab and analyzed them in three separate cohorts defined as the discovery cohort (177 patients), the confirmation cohort (182 patients) and the validation cohort (257 patients) (1). The majority of patients had received at least one line of therapy prior to pembrolizumab (97.9%) and all patients were followed from the date of the first dose of pembrolizumab to the date of last contact with a medical provider or death (median follow up of 5.5 months). Differences in overall survival were assessed by 15 pretreatment variables (including age, gender, patterns of distant metastases and laboratory assessment including LDH and blood counts obtained from the electronic medical record).
Best overall response was defined as the time period between the start of pembrolizumab therapy until this therapy was changed or the patient experienced progression of melanoma as defined by RECIST version 1.1 criteria (12). Based on the analysis of data from all three cohorts, Weide et al. concluded that 4 biomarkers including lower LDH levels associated with any distant disease have the worst metastasis to a non-pulmonary visceral site or high LDH in the AJCC staging system (14,15). Patients with an advanced metastatic melanoma that have been incorporated ranging from 0.779–0.782. Concordance or discriminatory index for survival models and noted a predictability of patient prognosis with a discriminatory ability of the survival models in the study of patient outcome from the survival model (13). The prediction and a value of 1 indicating perfect prediction values range from 0.5–1 with a value of 0.5 indicating poor is a measure of the predictability of a survival model. Its differential blood count is a widely available, feasible, and non-invasive source of potential predictive and prognostic biomarkers for patients on pembrolizumab therapy. The authors noted that a higher relative lymphocyte count and eosinophil count was predictors of favorable prognosis in advanced melanoma. Similar findings were observed in studies performed with melanoma patients on anti-cytotoxic T lymphocyte receptor antigen-4 (CTLA-4) agent ipilimumab. In those cases higher lymphocyte and eosinophil count at baseline and during treatment were associated with improved overall survival and progression free survival (17,18,20). Both anti PD-1 and anti CTLA-4 agents work by inhibiting receptors on the surface of T cells, preventing receptor ligand interactions and leading to inhibition of T cell inactivation resulting in sustained anti tumor responses (21-23). The similarity in the predictive role of the number of circulating leukocytes in treatment response observed for both these agents points to a possible association between circulating leukocyte count and T cell reactivity. Therefore, as the authors mention, there is a need for larger prospective studies looking at checkpoint inhibitor naive patients receiving pembrolizumab as their first treatment. Fortunately, all of these assessments are performed as standard of care in melanoma and can be measured in a prospective fashion.

In conclusion, the present study investigates the role of predictive biomarkers for assessing the prognosis of melanoma patients undergoing pembrolizumab therapy. The strengths of the study includes its large sample size, its multicenter design, the reproducibility of results across three different cohorts, and the evaluation of potential predictive markers with feasible testing that can be easily incorporated into clinical practice. As the authors correctly point out, even though the data is encouraging, it has certain inherent limitations related to its retrospective design. The current prognostic model needs to be validated in larger prospective studies or randomized control trials before it can be used to directly guide clinical decisions and plan treatment strategies for patients on anti-PD1 therapy. It is encouraging that a model that includes routine
blood assessments and radiographic evaluation of sites of melanoma metastases may be useful to predict which patients will respond to pembrolizumab and potentially other checkpoint antibodies.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References


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