The use of baseline biomarkers to predict outcome in melanoma patients treated with pembrolizumab

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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 ratio (≤2.5 *vs.* >2.5, defined as actual LDH value divided by upper limit of normal for each institution), the patterns of distant metastases (unresectable stage III, distant lymph nodes, soft tissue or lung only metastasis *vs.* other visceral organ involvement), higher relative lymphocyte count (≥17.5% *vs.* <17.5%) and higher relative eosinophil count (≥1.5% or <1.5%) in the pretreatment setting were independently associated with overall survival and best overall response in patients with advanced melanoma treated with pembrolizumab.

The patterns observed in these four variables divided patients into distinct prognostic categories. Patients with all four favorable factors had a very good prognosis with a 1-year survival of 83.9% (n=70). The 1-year survival in patients with 3 or 2 favorable prognostic factors was 68.1% (n=160) and 49.9% (141), respectively. In contrast, patients with 1 or no favorable factors had a poor prognosis with a 1-year survival of 14.3% (n=109) and 14.7% (n=32), respectively. Similarly, a strong correlation was observed between the number of favorable factors and best overall response with an objective response in 58.3%, 38.4%, 24.3% patients with 4, 3, or 2 favorable prognostic factors and a 7.7% or 3.7% objective response rate in patients with 1 or 0 factors. Additionally, the relative lymphocyte and eosinophil count remained significant with exclusion of the other prognostic markers for melanoma (LDH level and pattern of distant metastases). Concordance index is a measure of the predictability of a survival model. Its values range from 0.5–1 with a value of 0.5 indicating poor prediction and a value of 1 indicating perfect prediction of patient outcome from the survival model (13). The authors calculated the concordance indices (c index) or discriminatory ability of the survival models in the study and noted a predictability of patient prognosis with a concordance or discriminatory index for survival models ranging from 0.779–0.782.

Baseline serum the LDH and pattern of visceral metastases are well-established prognostic factors for advanced metastatic melanoma that have been incorporated in the AJCC staging system (14,15). Patients with a metastasis to a non-pulmonary visceral site or high LDH levels associated with any distant disease have the worst prognosis with a 1-year survival of 33% followed by patients with lung only metastasis or a metastasis to a distant site on the skin or lymph node with normal LDH levels (1-year survival of 52% and 63%, respectively) (14). LDH levels tend to correlate with increasing tumor burden with higher pretreatment levels associated with worse overall survival in melanoma patients on pembrolizumab or ipilimumab (16-19).

The 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.

Footnote

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

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