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

Sonam Puri¹, Joseph Markowitz²

¹Department of Hematology and Oncology, H. Lee Moffitt Cancer Center, Tampa, Florida, USA

²Department of Cutaneous Malignancy, H. Lee Moffitt Cancer Center, Tampa, Florida, USA

Abstract

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.

Correspondence to: Joseph Markowitz, MD, PhD. Assistant Member, H. Lee Moffitt Cancer Center and Research Institute; Assistant Professor, Department of Oncologic Sciences, USF Morsani School of Medicine, 10920 N. McKinley Drive, MKC-4CUTA, Tampa, FL 33612, USA. joseph.markowitz@moffitt.org.

Footnote

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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.

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References

1. Weide B, Martens A, Hassel JC, et al. Baseline biomarkers for outcome of melanoma patients treated with pembrolizumab. Clin Cancer Res 2016;22:5487–96. [PubMed: 27185375]

2. Chuk MK, Chang JT, Theoret MR, et al. FDA Approval Summary: Accelerated Approval of Pembrolizumab for Second-Line Treatment of Metastatic Melanoma. *Clin Cancer Res* 2017. [Epub ahead of print].
3. Beaver JA, Theoret MR, Mushti S, et al. FDA Approval of Nivolumab for the First-Line Treatment of Patients with BRAFV600 Wild-Type Unresectable or Metastatic Melanoma. *Clin Cancer Res* 2017. [Epub ahead of print].
4. Weber JS, D'angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol* 2015;16:375–84. [PubMed: 25795410]
5. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. *N Engl J Med* 2015;372:2521–32. [PubMed: 25891173]
6. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med* 2015;373:23–34. [PubMed: 26027431]
7. Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *Lancet Oncol* 2015;16:908–18. [PubMed: 26115796]
8. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 2015;372:320–30. [PubMed: 25399552]
9. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N Engl J Med* 2015;372:2006–17. [PubMed: 25891304]
10. Topalian SL, Hodi FS, Brahmer JR et al. Safety, activity, and immune correlates of Anti-PD-1 antibody in cancer. *N Engl J Med* 2012;366:2443–54. [PubMed: 22658127]
11. Patel SP, Kurzrock R. PD-L1 expression as a predictive biomarker in cancer immunotherapy. *Mol Cancer Ther* 2015;14:847–56. [PubMed: 25695955]
12. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47. [PubMed: 19097774]
13. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;15:361–87. [PubMed: 8668867]
14. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol* 2009;27:6199–206. [PubMed: 19917835]
15. Weide B, Elsässer M, Büttner P, et al. Serum markers lactate dehydrogenase and S100B predict independently disease outcome in melanoma patients with distant metastasis. *Br J Cancer* 2012;107:422–8. [PubMed: 22782342]
16. Diem S, Kasenda B, Spain L, et al. Serum lactate dehydrogenase as an early marker for outcome in patients treated with anti-PD-1 therapy in metastatic melanoma. *Br J Cancer* 2016;114:256–61. [PubMed: 26794281]
17. Martens A, Wistuba-Hamprecht K, Geukes Foppen M, et al. Baseline peripheral blood biomarkers associated with clinical outcome of advanced melanoma patients treated with ipilimumab. *Clin Cancer Res* 2016;22:2908–18. [PubMed: 26787752]
18. Delyon J, Mateus C, Lefeuvre D, et al. Experience in daily practice with ipilimumab for the treatment of patients with metastatic melanoma: an early increase in lymphocyte and eosinophil counts is associated with improved survival. *Ann Oncol* 2013;24:1697–703. [PubMed: 23439861]
19. Kelderman S, Heemskerk B, Van Tinteren H, et al. Lactate dehydrogenase as a selection criterion for ipilimumab treatment in metastatic melanoma. *Cancer Immunol Immunother* 2014;63:449–58. [PubMed: 24609989]
20. Ku GY, Yuan J, Page DB, et al. Single-institution experience with ipilimumab in advanced melanoma patients in the compassionate use setting: lymphocyte count after 2 doses correlates with survival. *Cancer* 2010;116:1767–75. [PubMed: 20143434]
21. Peggs KS, Quezada SA, Chambers CA, et al. Blockade of CTLA-4 on both effector and regulatory T cell compartments contributes to the antitumor activity of anti-CTLA-4 antibodies. *J Exp Med* 2009;206:1717–25. [PubMed: 19581407]

22. Woo SR, Turnis ME, Goldberg MV, et al. Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. *Cancer Res* 2012;72:917–27. [PubMed: 22186141]
23. Wang C, Thudium KB, Han M, et al. In vitro characterization of the anti-PD-1 antibody nivolumab, BMS-936558, and in vivo toxicology in non-human primates. *Cancer Immunol Res* 2014;2:846–56. [PubMed: 24872026]