OXFORD

JNCI J Natl Cancer Inst (2021) 113(8): djab005

doi: 10.1093/jnci/djab005
First published online February 1, 2021
Editorial

EDITORIAL

PD-L1 in Breast Cancer: The Road to the Perfect Biomarker Is Fraught With Uncertainty

Bora Lim, MD*

Breast Oncology, Baylor College of Medicine, Houston, TX, USA

*Correspondence to: Bora Lim, MD, Baylor College of Medicine, Dan L Duncan Comprehensive Cancer Center (Clinic), 7200 Cambridge St., 7th Floor, Houston, TX 77030, USA (e-mail: Bora.Lim@bcm.edu).

Breast cancer was once considered an "immune-cold" tumor, based on earlier trials testing single-agent anti-PD1 or anti-PD-L1 agents in breast cancer that showed disappointing efficacy (1-3). Thankfully, this did not reduce the research community's enthusiasm to develop immune checkpoint inhibitors (ICI) as meaningful therapeutics for patients with breast malignancies. IMpassion130, the first landmark randomized controlled study to hit a home run, demonstrated the efficacy in the first-line metastatic triple-negative breast cancer (TNBC) of the anti-PD-L1 agent atezolizumab in combination with the chemotherapeutic agent nab-paclitaxel, which improved progression-free survival and overall survival (OS) (4). Patients who benefited in this study had immune cell PD-L1 expression of at least 1%. KEYNOTE-355, another landmark randomized controlled study, investigated the combination of the anti-PD1 agent pembrolizumab and either nab-paclitaxel, paclitaxel, or carboplatin and gemcitabinein first-line metastatic TNBC and also found improved progression-free survival and OS (5). These 2 trials resulted in the approval of atezolizumab and pembrolizumab as first-line therapies for surgically unresectable locally advanced or metastatic TNBC. Furthermore, the combination of chemotherapy with either atezolizumab (IMpassion031 and NeoTRIPaPDL1 trials) (6,7) or pembrolizumab (KEYNOTE-522 trial) showed evidence of efficacy in the neoadjuvant setting (8).

A major question within the breast cancer community after the approval of 2 ICI drugs was which patients will benefit from adding ICI to chemotherapy. Measurement of PD-L1 levels became a critical component in determining patient benefit and even reimbursement by insurance companies. However, the essays used to measure PD-L1 vary between different ICI drugs. The IMpassion trials used the sp142 PD-L1 immunohistochemistry assay (Ventana, Tucson, AZ), measuring PD-L1 staining in both tumor cells and immune cells (9). The KEYNOTE studies used the 22C3 PD-L1 immunohistochemistry assay (Agilent, Carpinteria, CA) to calculate a combined positive score estimated as the ratio of PD-L1-positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells × 100 (10). The heterogeneity in assays used to evaluate PD-L1 levels has been a major challenge for breast cancer researchers, physicians, and patients. The same dilemmas faced by our lung cancer and urothelial cancer colleagues several years ago, including the efforts to address inconsistencies between different PD-L1 assays and scoring criteria to determine ICI benefit, have now arrived at the doorstep of the breast cancer community (11).

Hence, the article by Emens and colleagues (12) in this issue of the Journal reporting a detailed evaluation of PD-L1 and other potential biomarkers of clinical efficacy from the IMpassion130 trial is timely and relevant. The authors confirmed the specific benefit of combining atezolizumab with nab-paclitaxel in patients with positive immune cells for PD-L1. In the total intention-to-treat population, the median OS was 21 vs 18.7 months (stratified hazard ratio [HR] = 0.86, 95% confidence interval [CI] = 0.72 to 1.02), weakly favoring the addition of atezolizumab to chemotherapy. However, in the exploratory OS analysis in patients with positive immune cells for PD-L1, the median OS was 25 vs 18 months (stratified HR = 0.71, 95% CI = 0.54 to 0.94), more strongly favoring the atezolizumab group. The location of the obtained tissue and timing of the tissue collection for the PD-L1 measurement did not seem to influence the benefit from the combination therapy. Although the study was not designed to investigate tissue-tropism of PD-L1 expression, Emens and colleagues (12) found statistically significantly lower PD-L1 expression levels in the liver compared with the lymph nodes. Recent reports by Rozenblit and colleagues (13) also suggested such a tissue tropism, with the highest PD-L1 expression levels noted in the lymph nodes and lower levels found in the liver and bone—both in immune cells (IC) and tumor cells. Given the organ-dependent composition of ICs, one can hypothesize that the tissue tropism of ICs and PD-L1 expression influences ICI efficacy, although the study by Emens and colleagues (12) was not powered to answer this question. They did however find that although PD-L1 expression was lower in metastatic lesions compared with matched primary tumors, the documented PD-L1 expression levels from the primary tumors still correlated with ICI clinical benefit. It should

Received: December 21, 2020; **Accepted:** January 12, 2021

be noted that at least one-third (37 patients) of all tested primary tumor tissues was acquired before the patients developed macrometastatic disease. These patients will often receive perioperative cytotoxic chemotherapy known to cause T-cell exhaustion (14). On the contrary, matched primary and metastatic lesions obtained simultaneously shared similar immune cell PD-L1 expression levels (63 patients), suggesting the organ site of PD-L1 measurement might be interchangeable in some cases. It remains to be determined whether focusing more on the expression levels of PD-L1 and other biomarkers in metastatic lesions will be more informative. To answer this, we will need a prospective evaluation of chronological and matched samples in a larger number of patients.

Emens and colleagues (12) also investigated associations between therapeutic efficacy and tumor-infiltrating lymphocytes (TILs), CD8+ T cells, and the presence of the *BRCA* mutation as a surrogate marker of the DNA-damaging repair pathway. In this study, immune cell PD-L1 positivity was associated with clinical benefit regardless of high or low expression levels of either TIL or CD8. Thus, it remains unclear whether TIL or CD8+ T cells add predictive value to PD-L1 levels. Furthermore, *BRCA* mutation (either germline or somatic) was not associated with PD-L1 expression levels in immune cells, and the benefit of atezolizumab was noted in patients with PD-L1–positive immune cells regardless of *BRCA* mutation status. Samstein and colleagues (15) recently reported the selective contribution of *BRCA1* mutation to tumor microenvironment changes. Homologous recombination repair deficiency score has shown preliminary promising results in discerning breast cancer immunogenicity (16). These reports support the need for a comprehensive preplanned analysis to investigate the correlation of DNA-damaging repair pathways and ICIs efficacy. Most importantly, such analysis can further guide us to make better treatment decisions.

Improving patient outcomes is the goal of biomarker research. In this context, the toxicities of ICIs should not be overlooked, particularly when ICI is incorporated in curable patients such as those receiving neoadjuvant therapies. When patients walk in the clinic with documented PD-L1 expression levels measured by commercially available multiomics profiling, we should consider the complexities of PD-L1 positivity measurement and other associated biomarkers that can influence our treatment decisions. We in the breast cancer community had to wait for more than a decade to see the first approved ICI drug, and there is a long road ahead of us. It is now time to join forces to select the optimal population who will benefit from the combination of anti-PD1 or anti-PD-L1 ICI with chemotherapeutics.

Funding

Not applicable.

Notes

Role of the funder: Not applicable.

Disclosures: The author has no conflicts of interest to disclose.

Author contributions: The author conceptualized, drafted, and revised the manuscript for publication.

Data Availability

Not applicable.

References

1. Emens L, Cruz C, Eder J, et al. Long-term clinical outcomes and biomarker analyses of atezolizumab therapy for patients with metastatic triple-negative breast cancer: a phase 1 study. *JAMA Oncol*. 2019;5(1):74.
2. Adams S, Schmid P, Rugo H, et al. Phase 2 study of pembrolizumab (pembro) monotherapy for previously treated metastatic triple-negative breast cancer (mTNBC): KEYNOTE-086 Cohort A. *J Clin Oncol*. 2017:35(suppl 15):1008.
3. Nanda R, Chow LQ, Dees EC, et al. Pembrolizumab in patients with advanced triple-negative breast cancer: phase Ib KEYNOTE-012 study. *J Clin Oncol*. 2016; 34(21):2460–2467.
4. Schmid P, Rugo H, Adams S, et al. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2020; 21(1):44–59.
5. Cortes J, Cescon DW, Rugo HS, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. *Lancet Oncol*. 2020;396(10265):1817–1828.
6. Gianni L, Huang C-S, Egle D, et al. Abstract GS3-04: Pathologic complete response (pCR) to neoadjuvant treatment with or without atezolizumab in triple negative, early high-risk and locally advanced breast cancer. NeoTRIPaPDL1 Michelangelo randomized study. *Cancer Res*. 2020;80(suppl 4). 10.1158/1538-7445.SABCS19-GS3-04.
7. Mittendorf E, Zhang H, Barrios C, et al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2020;396(10257):1090–1100.
8. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for early triple-negative breast cancer. *N Engl J Med*. 2020;382(9):810–821.
9. Herbst R, Soria J, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature*. 2014;515(7528): 563–567.
10. Kulangara K, Zhang N, Corigliano E, et al. Clinical utility of the combined positive score for programmed death ligand-1 expression and the approval of pembrolizumab for treatment of gastric cancer. *Arch Path Lab Med*. 2019; 143(3):330–337.
11. Martinez-Morilla S, McGuire J, Gaule P, et al. Quantitative assessment of PD-L1 as an analyte in immunohistochemistry diagnostic assays using a standardized cell line tissue microarray. *Lab Invest*. 2020;100(1):4–15.
12. Emens LA, Molinero L, Loi S, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer: biomarker evaluation of the IMpassion130 study. *J Natl Cancer Inst*. 2020.
13. Rozenblit M, Huang R, Danziger N, et al. Comparison of PD-L1 protein expression between primary tumors and metastatic lesions in triple negative breast cancers. *J Immune Ther Cancer*. 2020;8(2):e001558.
14. Gustafson C, Jadhav R, Cao W, et al. Immune cell repertoires in breast cancer patients after adjuvant chemotherapy. *J Clin Ivest Insight*. 2020; 5(4):e134569.
15. Samstein RM, Krishna C, Ma X, et al. Mutations in BRCA1 and BRCA2 differentially affect the tumor microenvironment and response to checkpoint blockade immunotherapy. *Nat Cancer*. 2020;1(12):1188–1203.
16. Kraya AA, Maxwell KN, Wubbenhorst B, et al. Genomic signatures predict the immunogenicity of BRCA-deficient breast cancer. *Clin Cancer Res*. 2019;25(14): 4363–4374.