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Letter to the Editors

Comment on the manuscript "Histological subtype is associated with PD-L1 expression and CD8+ T-cell infiltrates in triple-negative breast carcinoma" by Salisbury et al. (Ann Diagn Pathol 2022; 57: 151901, https://doi.org/10.1016/j.anndiagpath.2022.151901)

To the editor:

I read with great interest a recent paper written by Salisbury et al. published in the April 2022 issue of the *Annals of Diagnostic Pathology* [1]. In their study, the authors explored a small cohort of triple-negative breast carcinomas (TNBC) for biomarkers of response to immune checkpoint inhibitors. They also analyzed the tumor-infiltrating lymphocytes, the percentage and ratio between the CD4+ and CD8+ T-cells. The topic is highly relevant given the recent "booming" and advances in the field followed by the Food and Drug Administration (FDA) approvals of immune checkpoint inhibitors for the treatment of TNBC: Atezolizumab, which was initially approved and then withdrawn voluntarily by Genentech in August 2021, and pembrolizumab, which was approved in July 2021. For the PD-L1 assessment, the authors employed two corresponding and approved companion diagnostic (CDx) tests, namely SP142 (Ventana) and 22C3 (Agilent) antibodies, revealing some essential discrepancies that had been previously reported. Notably, they also used two different scoring systems for the two antibodies of which combined positive score (CPS) also takes into account the PD-L1 expression in the tumors cells (CPS = "Number of PD-L1–positive cells/Tumor cells, lymphocytes, and macrophages/divided by the total number of viable tumor cells in the assessed area, multiplied by 100"). However, they did not report the PD-L1 expression in the tumor cells, which would be helpful to know. In addition, some images highlighting the observed discrepancies would be very welcome for pathology journals like Annals of Diagnostic Pathology. In my experience, some cancers like metaplastic (spindle cell variant) carcinoma frequently exhibit PD-L1 expression on the tumor cells [2]. Although they had a small metaplastic carcinoma cohort (n = 5), they did not provide the morphologic subtypes of metaplastic carcinomas. On the other hand, apocrine carcinomas tend to be PD-L1 negative, as confirmed in this study. In addition, apocrine carcinomas exhibit a low tumor mutational burden (TMB) and are microsatellite stable (MSS), as reported in several recent studies [3-5]. The molecular features make apocrine carcinoma patients less likely to benefit from immune checkpoint inhibitors.

Based on gene expression profiling data, the "luminal androgen receptor" (LAR) subtype may constitute 20–40% of TNBCs [6,7]. The current TNBC cohort also had a substantial number of apocrine carcinomas (18/72, 25%) based on morphologic assessment alone. I wonder if apocrine morphology was supplemented by androgen receptor (AR) confirmation (by immunohistochemistry), as suggested in the most recent WHO breast cancer classification [8]. This might affect the total number of "pure apocrine carcinomas" in your cohort.

Taken together, this is another valuable study that further contributes to better molecular characterization of a large and heterogeneous group of TNBC.

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Semir Vranic
College of Medicine, QU Health, Qatar University, 2713 Doha, Qatar

E-mail address: svranic@qu.edu.qa.

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