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LETTER TO THE EDITOR

The evolving role of pathology in early triple-negative breast cancer in the era of immunotherapy

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Dear Editor,

The management of early triple-negative breast cancer (TNBC) has undergone a fundamental transformation with the introduction of immune checkpoint inhibitors, creating new opportunities and new responsibilities for practising pathologists. This therapeutic shift has fundamentally expanded the role of pathology from tumour classification towards integrated assessment of the tumour immune microenvironment. The phase III KEYNOTE-522 trial established peri-operative pembrolizumab in combination with neoadjuvant chemotherapy as the standard treatment for patients with high-risk stage II–III TNBC, demonstrating significant improvements in pathological complete response (64.8% vs. 51.2%) and, more recently, overall survival.[1,2] Consequently, the 2024 European Society for Medical Oncology (ESMO) Clinical Practice Guideline recommends pembrolizumab-containing regimens for eligible patients with early TNBC.[3] As treatment strategies continue to evolve, pathologists are increasingly expected not only to establish the diagnosis but also to provide clinically meaningful assessment of the tumour immune microenvironment to support precision immuno-oncology.

The efficacy of immunotherapy in early TNBC is closely related to its highly immunogenic tumour microenvironment, characterised by increased neoantigen formation, stromal tumour-infiltrating lymphocytes (TILs) and adaptive programmed death-ligand 1 (PD-L1) expression, making it particularly amenable to immune checkpoint blockade.[4] Among the immune biomarkers, stromal TILs have consistently demonstrated strong prognostic value, with higher TIL levels associated with increased pathological complete response rates and improved long-term survival following neoadjuvant therapy.[5,6] However, their role in treatment selection continues to evolve. The 2024 ESMO Clinical Practice Guideline recognises that TILs provide additional prognostic and predictive information, particularly in TNBC, but concludes that there are currently no validated TIL thresholds for treatment decisions.[3] Likewise, although PD-L1 is an established predictive biomarker in metastatic TNBC, PD-L1 expression should not be used to guide treatment decisions in early breast cancer, as the benefit of peri-operative pembrolizumab is observed irrespective of PD-L1 status.[3] These recommendations emphasise that biological relevance does not necessarily equate to current clinical utility, while reinforcing the need for continued validation and standardisation of immune biomarkers in early TNBC.

The expanding use of immunotherapy has redefined the contribution of pathology to the management of early TNBC. The contemporary breast pathology report is evolving beyond tumour diagnosis and receptor classification to include clinically meaningful assessment of the tumour immune microenvironment. Among the available biomarkers, stromal TILs have emerged as one of the most promising pathology-derived biomarkers because they can be assessed on routine haematoxylin and eosin-stained sections using standardised methodology without additional ancillary testing.[5] Higher TIL levels are associated with improved pathological response and favourable long-term outcomes following neoadjuvant therapy.[5,6] Recent evidence also suggests that TILs may refine treatment stratification in selected patients with lower-risk disease. A 2026 systematic review and meta-analysis reported that patients with T1aN0 TNBC have an excellent prognosis irrespective of TIL levels, whereas those with T1bN0 tumours and stromal TILs ≥50% achieved excellent long-term survival, supporting

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further evaluation of TIL-guided treatment individualisation.[7] Similarly, the 2026 ASCO Educational Book highlighted the biological heterogeneity of stage I TNBC and identified stromal TILs, tumour proliferation and circulating tumour DNA as promising biomarkers for future personalised treatment strategies.[8] These observations are consistent with emerging Malaysian data which demonstrated in a cohort of 130 patients with TNBC, PD-L1 expression was significantly associated with increased $CD4^+$ and $CD8^+$ TIL densities.[9] Although preliminary, these findings support the complementary role of PD-L1 and TIL assessment in characterising the tumour immune microenvironment. These developments reinforce the increasingly important role of pathologists not only in diagnosis, but also in refining prognostic assessment, supporting multidisciplinary treatment decisions and facilitating future biomarker-driven precision immuno-oncology.

As immunotherapy becomes embedded in the standard management of early TNBC, the role of the pathologist must evolve in parallel. While accurate tumour classification remains fundamental, the contemporary breast pathology report is increasingly expected to characterise the tumour immune microenvironment and provide clinically meaningful information that complements conventional histopathological assessment. Although biomarkers such as stromal TILs have not yet reached the threshold for routine treatment selection, accumulating evidence suggests that they will play an increasingly important role in risk stratification and treatment individualisation. Continued prospective validation and generation of local evidence will be essential before these biomarkers can be fully integrated into routine clinical practice. Ultimately, the future breast pathology report may no longer simply define tumour subtype but increasingly characterise the tumour immune landscape that informs treatment selection, prognostication and precision immuno-oncology.

Keywords: Triple-negative breast cancer; immunotherapy; tumour-infiltrating lymphocytes; tumour immune microenvironment; PD-L1

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