ASCO 2026 Guideline: Rethinking PD-L1 Testing

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Few biomarkers have travelled a more turbulent path than programmed death-ligand 1 (PD-L1). Introduced as a companion diagnostic for immune checkpoint inhibition in non-small cell lung cancer (NSCLC), PD-L1 immunohistochemistry (IHC) rapidly became one of the most consequential stains in the histopathology laboratory. Its tumour proportion score (TPS) is a continuous variable translated into clinical thresholds of 1% and 50%, on which major treatment decisions may depend.[1]

The American Society of Clinical Oncology (ASCO) living guideline for stage IV NSCLC without driver alterations, published in 2026 as version 2026.3.0 and subsequently updated as 2026.3.1, redefines the place of PD-L1 in the diagnostic pathway.2,3 PD-L1 IHC remains a strong recommendation supported by high-quality evidence. For patients with TPS of 50% or higher, single-agent pembrolizumab, cemiplimab or atezolizumab remains strongly recommended; lower expression levels generally favour immunotherapy–chemotherapy combinations.[2] The crucial message, however, is that a validated PD-L1 assay should accompany a validated tissue and/or blood-based broad multigene panel. PD-L1 IHC alone is insufficient to guide treatment.[2]

This is more than a therapeutic update; it is a diagnostic reframing. PD-L1 is no longer a solitary gatekeeper but one element of an integrated biomarker assessment. Comprehensive next-generation sequencing, preferably incorporating RNA analysis for fusion detection, is emphasized, while combined tissue and plasma testing may improve the detection of actionable alterations.[2] A tumour with high PD-L1 expression may still harbour a targetable driver alteration that changes first-line treatment. Selecting therapy from the PD-L1 result before molecular findings are available could therefore lead to inappropriate management.

For pathologists, the guideline places tissue stewardship at the centre of practice. Many patients with advanced NSCLC are diagnosed using a small biopsy or cytology cell block. The specimen must support histological classification, PD-L1 staining and increasingly broad molecular analysis. Unnecessary immunostains, repeated sectioning and poorly coordinated send-out testing can exhaust tissue before the most clinically important investigations are completed. Reflex pathways agreed by pathologists, oncologists and molecular laboratories are therefore essential.

The requirement for a validated assay also highlights persistent concerns about PD-L1 standardisation. The Blueprint phase 2 project demonstrated broadly comparable tumour-cell staining with the 22C3, 28-8 and SP263 assays, whereas SP142 showed lower sensitivity. Interobserver reliability was strong for tumour-cell scoring but poor for immune-cell scoring.4

Interpretation remains another vulnerable step. In a multicentre study, interobserver agreement was good but imperfect at both the 1% and 50% thresholds, and brief training produced little improvement.[5] Cases close to a cut-off are particularly difficult because weak membranous staining, necrosis, crush artefact, macrophages and scant viable tumour may alter classification. Combined positive score assessment in other tumour types introduces

further variability because inflammatory cells must also be identified and counted.[6] Laboratories should incorporate appropriate controls, competency assessment, external quality assurance and a mechanism for second review of borderline cases.

The 2026.3.1 update, which added retifanlimab plus platinum-based chemotherapy as an option for selected patients irrespective of PD-L1 level, further illustrates why PD-L1 cannot function as the sole treatment discriminator.[3,8] As therapeutic options expand, the clinical meaning of a PD-L1 category will continue to evolve. The living-guideline model is therefore appropriate, but laboratories must establish a method for rapidly translating updates into test algorithms and report comments.

For resource-constrained settings, including Bangladesh, simultaneous broad molecular testing and PD-L1 IHC may be limited by cost, access and turnaround time. ASCO 2026 does not diminish the importance of PD-L1; it places the stain in its proper context. The pathologist is now the steward of tissue and the integrator of morphology, protein expression and genomic information.

References

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