Table 1 Summary of 'The Oxford Levels of Evidence 2' (adapted from Oxford Centre for Evidence-Based Medicine Levels of Evidence Working Group)

Level 1	Level 2	Level 3	Level 4	Level 5
Systematic review or meta-analysis	Randomized trial or observational study with dramatic effect	Non-randomized, controlled cohort, or follow-up study	Case series, case–control, or historically controlled study	Mechanism-based reasoning

process in order to obtain the highest possible agreement among the experts, however, the minimum threshold was defined as 75% approval among the voting members. Evidence supporting panel recommendations was graded according to the Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence Working Group 'The Oxford Levels of Evidence 2' (2016 version). A summary of the OCEBM grading scale may be found in table 1. The level of evidence (LE) for a given consensus recommendation is expressed in parentheses following the recommendation (eg, LE:1). Recommendations without an associated LE were based on expert consensus.

DIAGNOSTIC TESTS AND BIOMARKERS

Biomarker testing may identify patients who are more likely to derive benefit from regimens incorporating targeted therapies or immunotherapies as opposed to cytotoxic chemotherapy alone, and thus has become an essential component in determining the optimal treatment of patients with NSCLC. Although biomarkers for patient selection for other thoracic malignancies are an ongoing area of research, PD-L1 expression in SCLC or mesothelioma is not known to be predictive of benefit withimmunotherapy at this time. While ICIs have improved clinical outcomes for some patients, only a subset of patients experience deep, durable responses as a result of ICI therapy.[36]

For immunotherapy specifically, research is ongoing to identify biomarkers with predictive value for response to ICIs for patients with lung cancer. Across solid tumors, several tumor biomarkers have been validated thus far to predict improved outcomes after ICI treatment: PD-L1 expression, microsatellite instability (MSI)/mismatch repair deficiency (dMMR), and tumor mutational burden (TMB). FDA-approved indications for some ICIs, including in lung cancer, are dependent on PD-L1 expression above a specific cut-off by an approved companion diagnostic (discussed in the **PD-L1 expression** section below). Additionally, pembrolizumab is approved for tissue-agnostic use in tumors that are MSI-high (MSI-H) and/or dMMR as well as in tumors with high TMB (TMB-H),[30] and dostarlimab (anti-PD-1 ICI) is approved for tissue-agnostic use in dMMR tumors.[37]

PD-L1 expression

At the time of manuscript writing, all FDA-approved ICI regimens for lung cancer and mesothelioma include one agent that targets the PD-(L)1 axis. As such, several clinical trials have attempted to stratify patients by the level of PD-L1 expression in tumor cells (TCs) and/or infiltrating immune cells (ICs) in an effort to identify patients most likely to benefit from ICI therapy. Currently, eligibility for four of the ICIs indicated for the treatment of advanced NSCLC is conditional based on PD-L1 expression above a specific cut-off (currently, no FDA approvals for SCLC or mesothelioma are dependent on PD-L1 expression). Additionally, eligibility for some ICI indications in the adjuvant setting requires confirmed tumor PD-L1 expression by an FDA-approved test (data supporting the approval, as well as outcomes across PD-L1 expression subgroups, are described in the ***Resectable NSCLC*** section). For all of the agents with indications for PD-L1-positive NSCLC, the FDA has approved corresponding companion diagnostics that assess PD-L1 expression using immunohistochemistry (IHC). It is important to note that these assays are not all equivalent or interchangeable, as will be discussed below in the **Concordance in PD-L1 testing** section. Additionally, different thresholds for PD-L1 expression define eligibility across indications. The most commonly used cut-off values are PD-L1 expression ≤1%, 1%–49%, and ≥50%. In real-world analyses, roughly 44% of tumors have PD-L1 expression <1%, 25% of tumors have PD-L1 expression 1%–49%, and around 31% of tumors have PD-L1 expression ≥50%.[38] A comprehensive review of PD-L1 as a predictive biomarker was published in 2021.[39]

The VENTANA PD-L1 SP142 assay is the FDA-approved companion diagnostic for atezolizumab, an anti-PD-L1 ICI, which may be used in the treatment of PD-L1-high NSCLC as a first-line monotherapy in patients with no *EGFR/ALK* alterations.[40] The SP142 assay defines high PD-L1 expression in lung cancer as ≥50% of TCs staining positive for PD-L1 (TC ≥50%), or as PD-L1-expressing ICs covering ≥10% of the tumor (IC ≥10%).[40] The FDA approval of atezolizumab for this indication was based on data from IMpower110 (NCT02409342), in which the subgroup of patients with high PD-L1 expression exhibited a significant overall survival (OS) advantage with ICI treatment compared with platinum-based chemotherapy, a benefit that was not seen for patients with tumors in other PD-L1 expression categories (TC ≥5% or IC ≥5%; TC ≥1% or IC ≥1%).[41]

The anti-PD-1 ICI nivolumab is approved in combination with ipilimumab for the first-line treatment of metastatic NSCLC, if no *EGFR/ALK* alterations are present and tumors are PD-L1 ≥1% (≥1% of TCs in the sample staining positive for PD-L1).[3 29] The PD-L1 IHC 28–8 pharmDx assay was used to evaluate PD-L1 expression during the CheckMate 227 trial (NCT02477826), and