Your Guide for Accurate Scoring in Cervical Cancer Using PD-L1 IHC 22C3 pharmDx

Agilent Dako

Use this quick scoring guide as a reference when evaluating cervical cancer specimens for PD-L1 expression using PD-L1 IHC 22C3 pharmDx.

For more information on Combined Positive Score (CPS) assessment, review the Cervical Cancer Interpretation Manual or eLearning Program at www.agilent.com.

Steps for scoring

Determine specimen adequacy
Verify that the specimen has ≥ 100 viable tumor cells

Evaluate controls
Ensure that in-house controls and Control Cell Line Slide demonstrate acceptable staining

Evaluate PD-L1 staining
Estimate the number of PD-L1 staining cells (CPS numerator) and the total number of viable tumor cells (CPS denominator)

Calculate CPS and determine PD-L1 expression level
Report results: CPS < 1, No PD-L1 Expression; or CPS ≥ 1, PD-L1 Expression

Definition of CPS and PD-L1 staining cells

CPS represents the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.

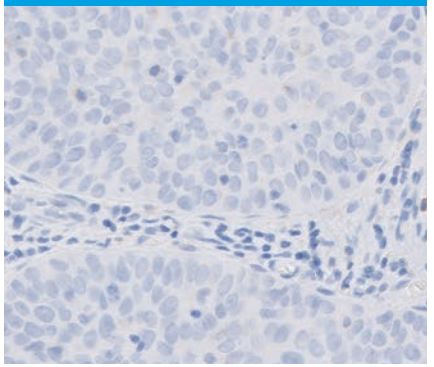
$$\text{CPS} = \frac{\text{\# PD-L1 staining cells (tumor cells, lymphocytes, macrophages)}}{\text{Total \# viable tumor cells}} \times 100$$

Note: *CPS is reported as a whole number. Although the result of the calculation can exceed 100, the maximum score is defined as CPS 100.*

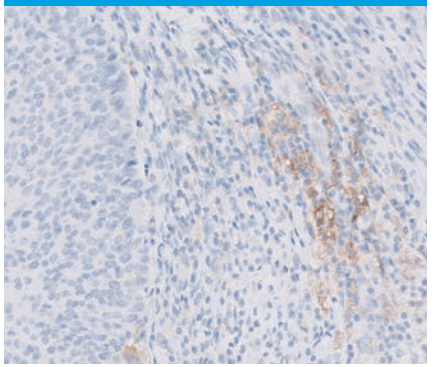
By definition, **PD-L1 staining cells** in cervical cancer are:

- **Tumor cells** with convincing partial or complete linear membrane staining (at any intensity) that is perceived distinct from cytoplasmic staining
- **Lymphocytes and macrophages** (mononuclear inflammatory cells, MICs) within the tumor nests and/or adjacent supporting stroma with membrane and/or cytoplasmic staining (at any intensity). MICs must be directly associated with the response against the tumor

CPS < 1



CPS ≥ 1



Intended Use
For in vitro diagnostic use.

PD-L1 IHC 22C3 pharmDx is a qualitative immunohistochemical assay using Monoclonal Mouse Anti-PD-L1, Clone 22C3 intended for use in the detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC), gastric or gastroesophageal junction (GEJ) adenocarcinoma, and cervical cancer tissues using EnVision FLEX visualization system on Autostainer Link 48.

Non-Small Cell Lung Cancer (NSCLC)
PD-L1 protein expression in NSCLC is determined by using Tumor Proportion Score (TPS), which is the percentage of viable tumor cells showing partial or complete membrane staining at any intensity. The specimen should be considered to have PD-L1 expression if TPS ≥ 1% and high PD-L1 expression if TPS ≥ 50%.

PD-L1 IHC 22C3 pharmDx is indicated as an aid in identifying NSCLC patients for treatment with KEYTRUDA® (pembrolizumab). See the KEYTRUDA® product label for expression cutoff values guiding therapy in specific clinical circumstances.

Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma
PD-L1 protein expression in gastric or GEJ adenocarcinoma is determined by using Combined Positive Score (CPS), which is the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. The specimen should be considered to have PD-L1 expression if CPS ≥ 1.

PD-L1 IHC 22C3 pharmDx is indicated as an aid in identifying gastric or GEJ adenocarcinoma patients for treatment with KEYTRUDA® (pembrolizumab).

Cervical Cancer
PD-L1 protein expression in cervical cancer is determined by using Combined Positive Score (CPS), which is the number of PD-L1 staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. The specimen should be considered to have PD-L1 expression if CPS ≥ 1.

PD-L1 IHC 22C3 pharmDx is indicated as an aid in identifying cervical cancer patients for treatment with KEYTRUDA® (pembrolizumab).

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Cervical cancer CPS numerator

Tissue Elements	Included	Excluded
Tumor Cells	Convincing partial or complete linear membrane staining (at any intensity) of viable invasive cervical tumor cells	– Non-staining tumor cells – Tumor cells with only cytoplasmic staining
Immune Cells	Membrane and/or cytoplasmic* staining (at any intensity) of mononuclear inflammatory cells (MICs) within tumor nests and adjacent supporting stroma†: – Lymphocytes (including lymphocyte aggregates) – Macrophages‡ Only MICs directly associated with the response to the tumor are scored	– Non-staining MICs – MICs associated with cervical intraepithelial neoplasia (CIN I-III) – MICs associated with benign cells including squamous or glandular mucosa, cervical polyps, and microglandular hyperplasia – MICs (including lymphoid aggregates) associated with ulcers and other processes not associated with the tumor, such as cervicitis – Neutrophils, eosinophils, and plasma cells
Other Cells	Not included	– CIN I-III – Benign cells including squamous or glandular mucosa, cervical polyps, and microglandular hyperplasia – Stromal cells (including fibroblasts) – Necrotic cells and/or cellular debris

Cervical cancer CPS denominator

Included	Excluded
All viable tumor cells	Any necrotic or non-viable tumor cells
Not included	All immune cells of any type
Not included	– CIN I-III – Benign cells including squamous or glandular mucosa, cervical polyps, and microglandular hyperplasia – Stromal cells (including fibroblasts) – Necrotic cells and/or cellular debris

** In MICs, membrane and cytoplasmic staining are often indistinguishable due to high nuclear to cytoplasmic ratio. Therefore, membrane and/or cytoplasmic staining of MICs is included in the CPS numerator; † Adjacent MICs are defined as being within the same 20× field as the tumor. However, MICs that are NOT directly associated with the response to the tumor should be excluded; ‡ Macrophages and histiocytes are considered the same cells*

Partial and complete linear membrane staining

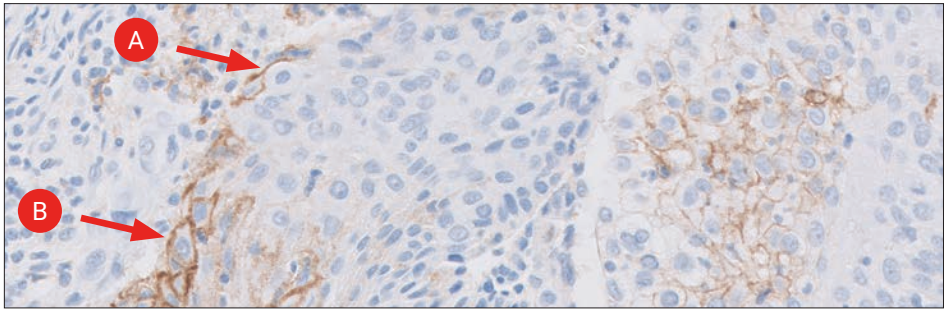


Figure 1: PD-L1 staining of partial (A) and complete (B) linear membrane staining of tumor cells (20× magnification).

Tumor-associated immune cells

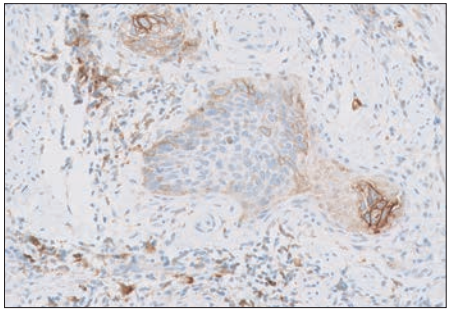
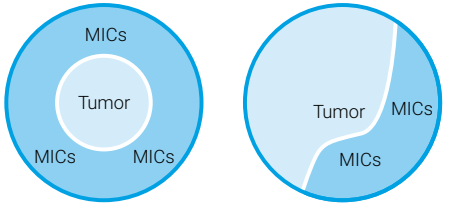


Figure 2: When positioning the tumor cells in the approximate center of a 20× field, PD-L1 staining mononuclear inflammatory cells that are present within the same field should be included in the numerator (20× magnification).



Simulation of a 20× microscope field showing tumor surrounded by tumor-associated MICs.

For more information about PD-L1 IHC 22C3 pharmDx and its use in cervical cancer, please visit www.agilent.com/chem/PDL122C3

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