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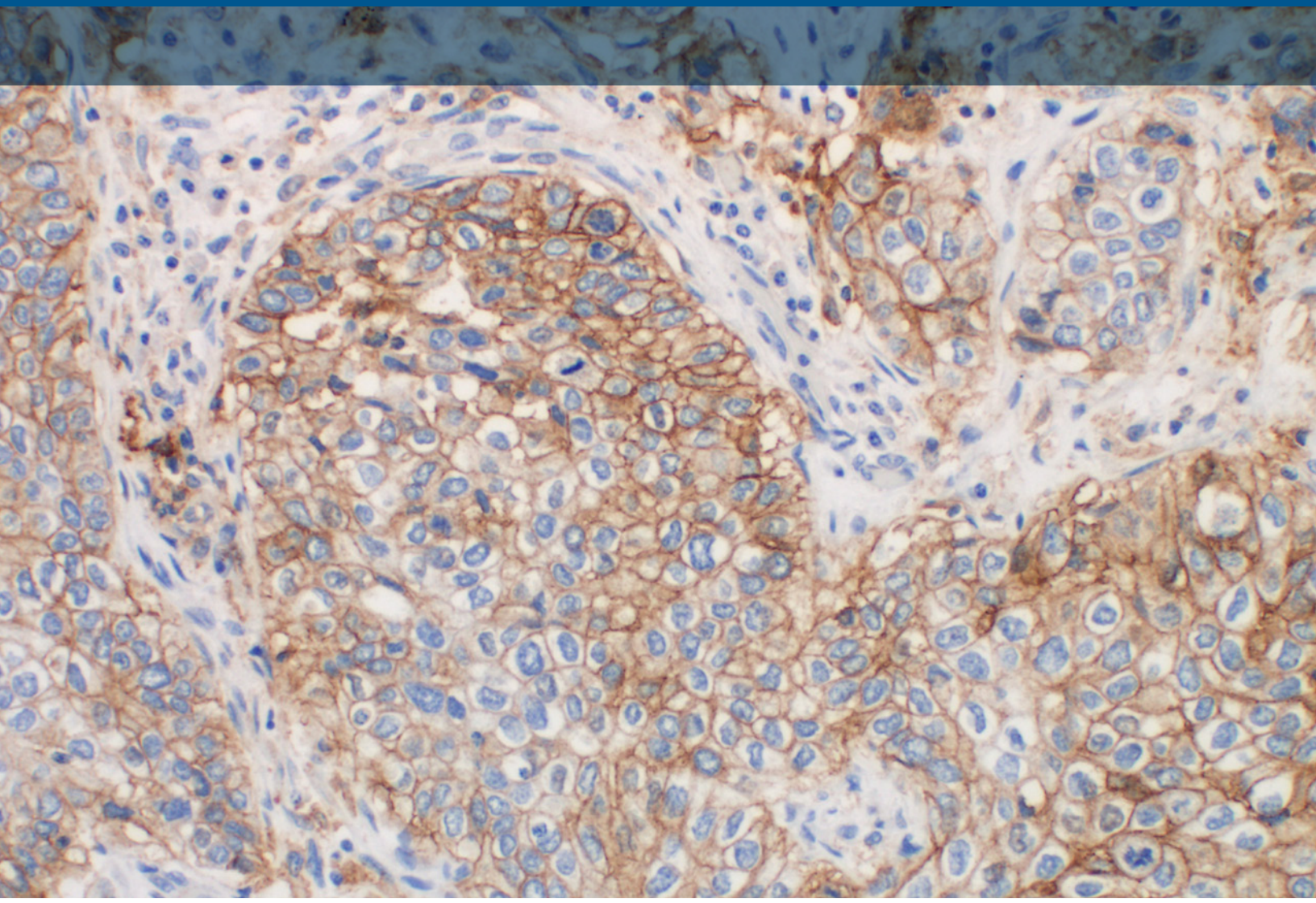
Dako

PD-L1 IHC 28-8 pharmDx Interpretation Manual - NSCLC

FDA-approved for in vitro diagnostic use



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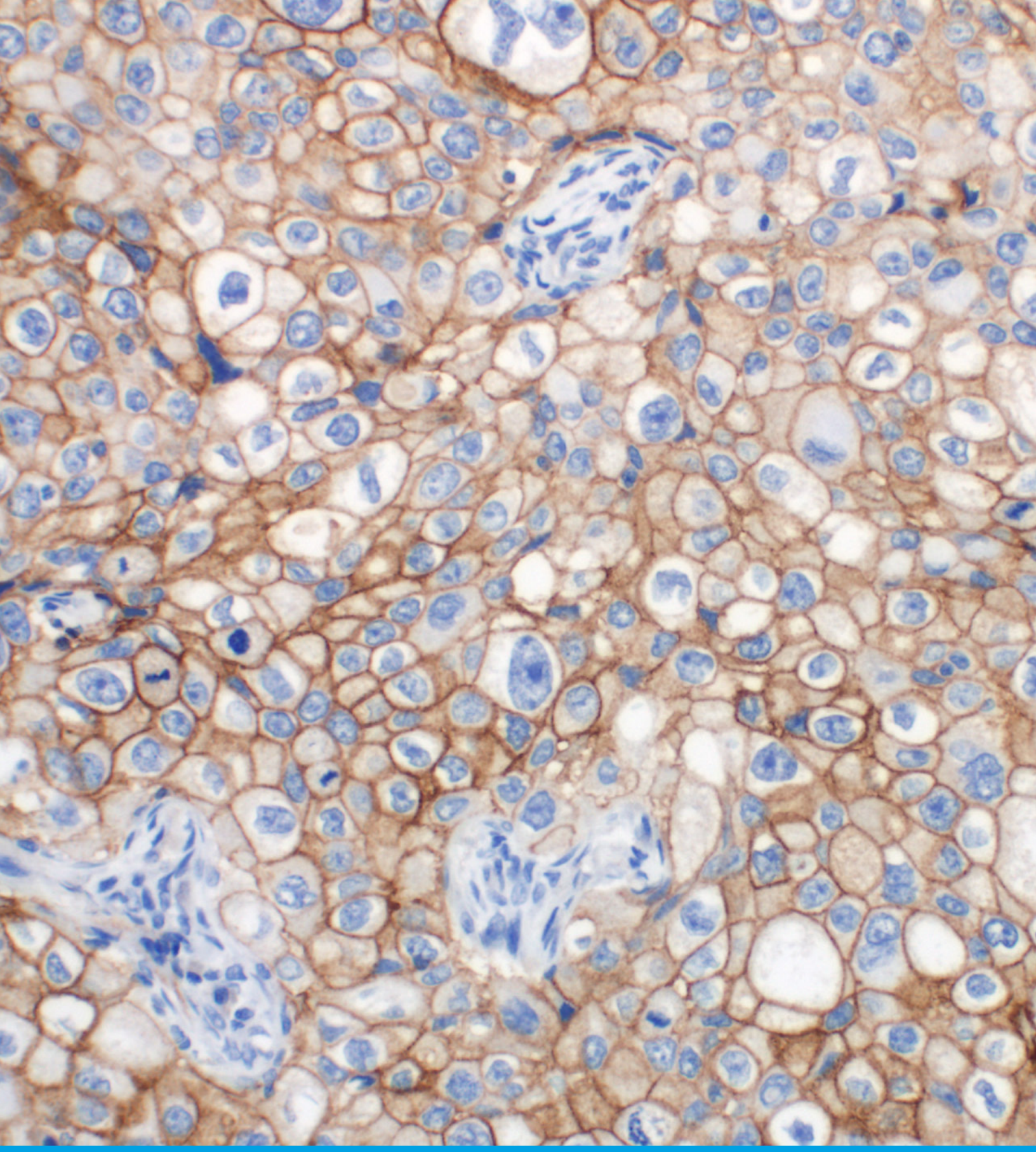


PD-L1 IHC 28-8 pharmDx
Interpretation Manual - NSCLC

Introduction

PD-L1 IHC 28-8 pharmDx Intended Use

For In Vitro Diagnostic Use

PD-L1 IHC 28-8 pharmDx is a qualitative immunohistochemical assay using Monoclonal Rabbit Anti-PD-L1, Clone 28-8 intended for use in the detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC), squamous cell carcinoma of the head and neck (SCCHN), and urothelial carcinoma (UC) tissues using EnVision FLEX visualization system on Autostainer Link 48.

PD-L1 protein expression is defined as the percentage of evaluable tumor cells exhibiting partial or complete membrane staining at any intensity.

Companion Diagnostic Indication

Tumor Indication	PD-L1 Expression Clinical Cut-off	Intended Use
NSCLC	≥ 1% tumor cell expression	PD-L1 IHC 28-8 pharmDx is indicated as an aid in identifying NSCLC patients for treatment with OPDIVO® (nivolumab) in combination with YERVOY® (ipilimumab).

PD-L1 expression (≥ 1% or ≥ 5% or ≥ 10% tumor cell expression), as detected by PD-L1 IHC 28-8 pharmDx in non-squamous NSCLC may be associated with enhanced survival from OPDIVO®.

PD-L1 expression (≥ 1% tumor cell expression), as detected by PD-L1 IHC 28-8 pharmDx in SCCHN may be associated with enhanced survival from OPDIVO®.

PD-L1 expression (≥ 1% tumor cell expression), as detected by PD-L1 IHC 28-8 pharmDx in UC may be associated with enhanced response rate from OPDIVO®.

See the OPDIVO® and YERVOY® product labels for specific clinical circumstances guiding PD-L1 testing.

PD-L1 expression as detected by PD-L1 IHC 28-8 pharmDx in NSCLC is associated with an overall survival benefit from OPDIVO® (nivolumab) in combination with YERVOY® (ipilimumab)*

PD-L1 IHC 28-8 pharmDx Interpretation Manual - Overview

This NSCLC PD-L1 IHC 28-8 pharmDx Interpretation Manual is provided as a tool to help guide pathologists and laboratory technicians to achieve correct and reproducible results. The goal of this manual is to familiarize you with the requirements for scoring NSCLC specimens stained with PD-L1 IHC 28-8 pharmDx. For the evaluation of non-squamous NSCLC specimens at the PD-L1 ≥ 1%, ≥ 5%, ≥ 10% clinical cut-offs, refer to the nsNSCLC Interpretation Manual.
The PD-L1 IHC 28-8 pharmDx package insert contains guidelines and technical tips for ensuring high-quality staining in your laboratory.

A review of this NSCLC PD-L1 IHC 28-8 pharmDx Interpretation Manual will provide a solid foundation for evaluating NSCLC slides stained with PD-L1 IHC 28-8 pharmDx. For more details, please refer to the current version of the package insert provided with PD-L1 IHC 28-8 pharmDx or visit www.agilent.com.

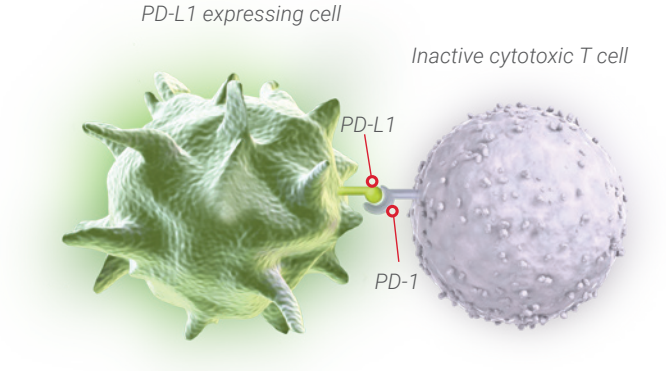
The included photomicrographs are NSCLC unless otherwise noted.

M.D. Hellmann, et al. Nivolumab plus Ipilimumab in Advanced Non–Small-Cell Lung Cancer, The New England Journal of Medicine, 2019.

The Role of the PD-1/PD-L1 Pathway in Cancer

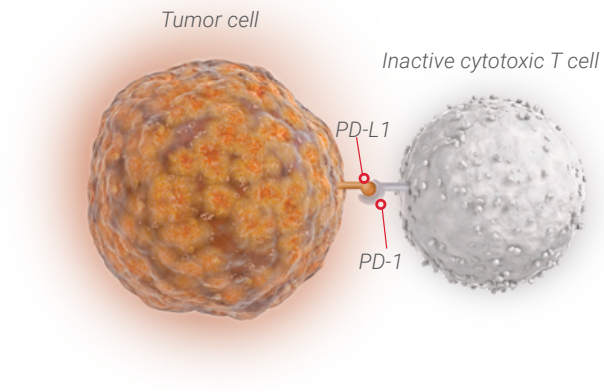
Limiting damage to healthy tissue

Inactivation of T cells limits damage to healthy tissue.



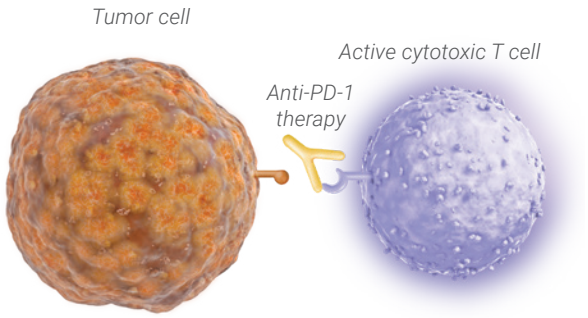
The tumor escapes detection

Inactivation of T cells reduces tumor cell killing.



Immuno-oncology therapies harness the immune response to fight tumors

Blocking PD-L1 enables cytotoxic T cells to actively remove tumor cells.



Study Data for PD-L1 IHC 28-8 pharmDx in NSCLC

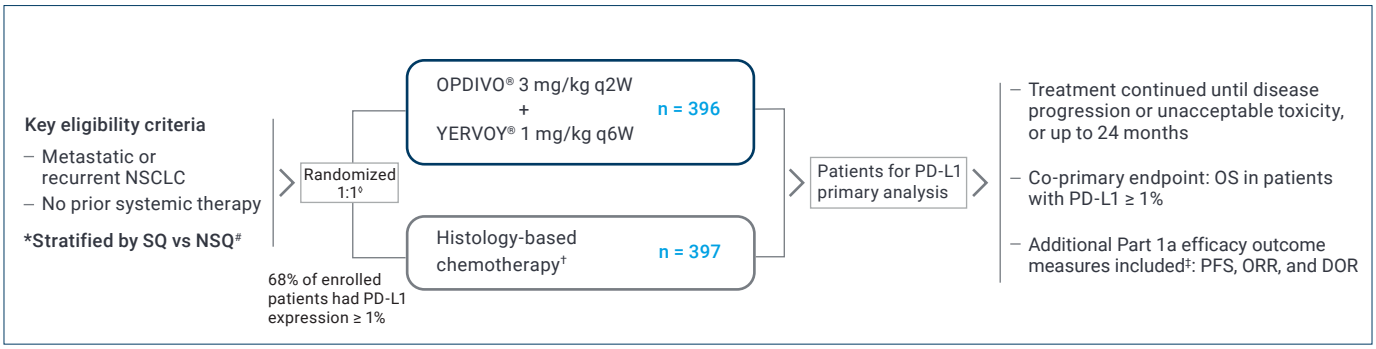
In CHECKMATE 227 detection of PD-L1 expressing tumor cells in NSCLC patient specimens was associated with an overall survival benefit from OPDIVO® (nivolumab) + YERVOY® (ipilimumab) treatment for the patient.^

- CHECKMATE-227 investigated the validity of PD-L1 IHC 28-8 pharmDx for the assessment of PD-L1 status in NSCLC patients treated with OPDIVO® (nivolumab) in combination with YERVOY® (ipilimumab)
- The study was a Phase III, randomized, multi-center, multi-cohort, open-label study in patients with mNSCLC, who were previously untreated for advanced disease

For patients with mNSCLC

In landmark phase-3 study OPDIVO® (nivolumab) + YERVOY® (ipilimumab) was assesed in patients regardless of histology.*

CHECKMATE 227 Part 1a: PD-L1 expression ≥ 1% (n=793) study design#



◊ Patients were randomized to additional study arms: Part 1a (PD-L1 ≥ 1%) included an arm for OPDIVO® (nivolumab) monotherapy 240 mg q2w (n=396).
In CHECKMATE 227, patients in the comparator arm received up to 4 cycles of platinum-doublet chemo q3w; NSQ: pemetrexed + cisplatin or carboplatin, with optional pemetrexed maintenance following chemo; SQ: gemcitabine + cisplatin or carboplatin.
‡ In CHECKMATE 227 Part 1a, the primary efficacy outcome measures were OS. Additional descriptive efficacy outcome measures included PFS, ORR, and DOR.
DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ORR = overall response rate; PFS = progression-free survival; q2w = every 2 weeks; q6w = every 6 weeks.

^*M.D. Hellmann, et al. Nivolumab plus Ipilimumab in Advanced Non–Small-Cell Lung Cancer, The New England Journal of Medicine, 2019.*

The Clinical Value of PD-L1 IHC 28-8 pharmDx Expression in NSCLC

– As per CHECKMATE 227 study results, in patients with a PD-L1 expression ≥ 1%, the **Median Duration of Overall Survival** was **17.1 months** with OPDIVO® (nivolumab) + YERVOY® (ipilimumab) and **14.9 months** with Chemotherapy group.

Efficacy outcomes in patients with tumor PD-L1 expression ≥ 1%:
Overall survival with OPDIVO® (nivolumab) + YERVOY® (ipilimumab), and Histology-based Chemotherapy.

Table 1. Efficacy Results (PD-L1 ≥ 1%) - CHECKMATE-227.

	OPDIVO® (nivolumab) + YERVOY® (ipilimumab) (n = 396)	Chemotherapy (n = 397)
Overall Survival		
Events (%)	258 (65.2)	298 (75.1)
Median (months) (95% CI)	**17.1 (15, 20.1)**	**14.9 (12.7, 16.7)**
Hazard ratio (97.72% CI)[a]	0.79 (0.65, 0.96)	–
Stratified log-rank p-value	0.0066	–
Progression-free Survival		
Hazard ratio (95% CI)[a]	0.82 (0.69, 0.97)	–
Median (months)[b] (95% CI)	5.1 (4.07, 6.31)	5.6 (4.63, 5.82)

[a] Based on a stratified Cox proportional hazard model.
[b] Kaplan-Meier estimate.

- As per CHECKMATE 227 results, the **Median Duration of Response (mDOR)**, the two years data for PD-L1 ≥ 1% group is **23.2 months** with OPDIVO® (nivolumab) + YERVOY® (ipilimumab) vs **6.2 months** for Chemotherapy group.
- **Overall Response Rate** was **35.9%** with OPDIVO® (nivolumab) + YERVOY® (ipilimumab) and **30%** with Chemotherapy.

Efficacy outcomes in patients with tumor PD-L1 expression ≥ 1%:
Median Duration of Response with OPDIVO® (nivolumab) + YERVOY® (ipilimumab), and Histology-based Chemotherapy.

Table 2. Efficacy Results of Overall Response Rate and Duration of Response in patients with Tumor PD-L1 Expression ≥ 1%.

	PD-L1 Expression ≥ 1%	
Variable	**OPDIVO® (nivolumab) + YERVOY® (ipilimumab)***	**Chemotherapy**
	(N = 396)	**(N = 397)**
Overall Response Rate-no. (%)	142 (35.9)	119 (30.0)
95% CI	31–41	26–35
Duration of Response (months)		
Median	**23.2**	**6.2**

Response was assessed according to the Response Evaluation Criteria in Solid Tumors, version 1.1, 5 by blinded independent central review.
* nivolumab (3 mg/kg every 2 weeks) + ipilimumab (1 mg/kg every 6 weeks).

PD-L1 IHC 28-8 pharmDx Overview

Code SK005

PD-L1 IHC 28-8 pharmDx contains optimized reagents and protocol required to complete an IHC staining procedure of FFPE specimens using Autostainer Link 48 and PT Link Pre-treatment module.

Following incubation with the primary monoclonal antibody to PD-L1 or the Negative Control Reagent (NCR), specimens are incubated with a linker antibody specific to the host species of the primary antibody and then are incubated with a ready-to-use visualization reagent consisting of secondary antibody, molecules and horseradish peroxidase molecules coupled to a dextran polymer backbone. The enzymatic conversion of the subsequently added chromogen results in precipitation of a visible reaction product at the site of the antigen. The color of the chromogenic reaction is modified by a chromogen enhancement reagent. The specimen may then be counterstained and coverslipped. Results are interpreted using a light microscope. Control Slides containing two formalin-fixed, paraffin-embedded human cell lines are provided to validate staining runs.

PD-L1 IHC 28-8 pharmDx staining procedure.

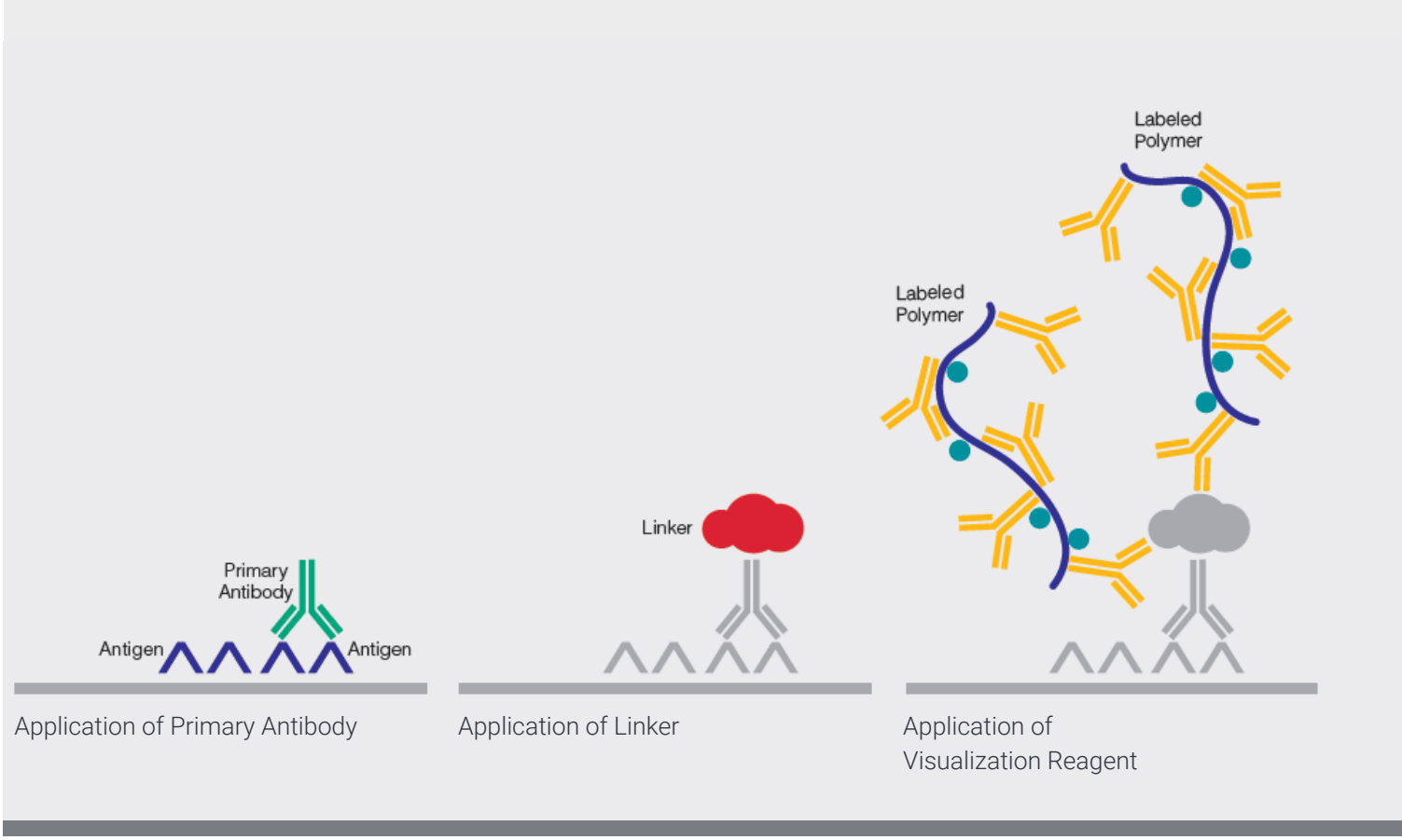


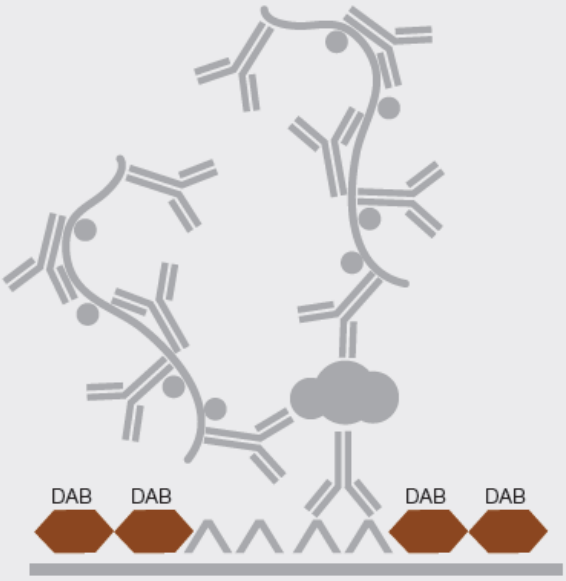
Figure 1. PD-L1 IHC 28-8 pharmDx staining component.

All PD-L1 IHC 28-8 pharmDx reagents are to be performed on Autostainer Link 48. All reagents must be used as indicated in the IFU in order for the test to perform as specified.

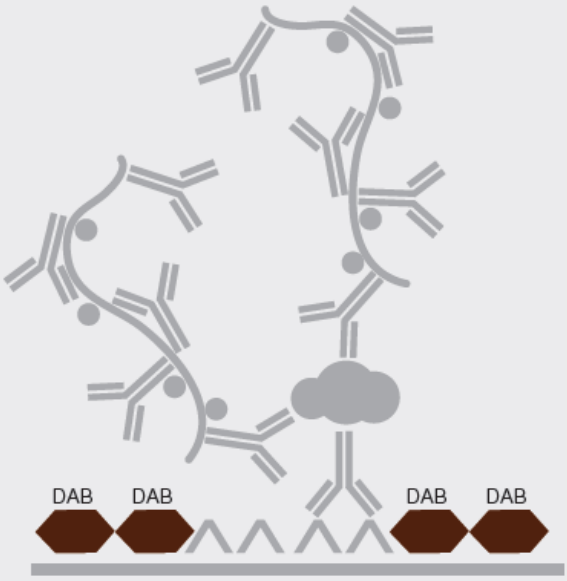
PD-L1 IHC 28-8 pharmDx contains reagents to perform 50 tests in up to 15 individual run, see Figure 1.

- EnVision FLEX Target Retrieval Solution, Low pH, 50x
- Peroxidase-Blocking Reagent
- Primary Antibody: Monoclonal Rabbit Anti-PD-L1, Clone 28-8
- Negative Control Reagent
- PD-L1 IHC 28-8 pharmDx Anti-Rabbit LINKER
- Visualization Reagent-HRP
- DAB+ Substrate Buffer
- DAB+ Chromogen
- DAB Enhancer
- PD-L1 IHC 28-8 pharmDx Control Slides

EnVision FLEX Wash Buffer (20x) (Code K8007), EnVision FLEX Hematoxylin (Code K8008), are required but not included in the kit. Refer to IFU for a required materials and equipment.



Application of DAB+ Substrate Chromogen Solution



Application of DAB Enhancer

Technical Considerations for Optimal Performance of PD-L1 IHC 28-8 pharmDx

Optimal staining performance is achieved by adhering to the PD-L1 IHC 28-8 pharmDx protocol. Technical problems relating to the performance of PD-L1 IHC 28-8 pharmDx may arise in two areas; those involving specimen collection and specimen preparation prior to performing the test, as well as problems involving the actual performance of the test itself. Technical problems related to the performance of the test generally are related to procedural deviations and can be controlled and minimized through training and thorough understanding of the product instructions by the user.

Specimen Collection and Preparation

Specimens must be handled in a way that preserves the tissue for immunohistochemical staining. Tissue should be stained and interpreted as close to the time of biopsy as possible. Use the recommended methods of tissue processing for all specimens.

Tissue Processing

Formalin-fixed, paraffin-embedded tissues are suitable for use. Specimens should be blocked into a thickness of 3 mm or 4 mm, fixed in 10% Neutral Buffered Formalin (NBF) and dehydrate and clear in a series of alcohols and xylene, followed by infiltration with melted paraffin. An ischemia time from excision to formalin fixation start time of less than 30 minutes, followed by immersion in neutral buffered formalin for 24–48 hours is recommended. The paraffin temperature should not exceed 60 °C. The use of PD-L1 IHC 28-8 pharmDx on decalcified tissues has not been validated and is not recommended.

Cut tissue specimens into sections of 4–5 µm. After sectioning, mount tissues on FLEX IHC microscope slides, Code K8020, or Fisherbrand Superfrost Plus charged slides and then placed in a 58 ± 2 °C oven for 1 hour. To preserve antigenicity, NSCLC tissue sections, once mounted on slides, should be stored in the dark at 2–8 °C, or room temperature up to 25 °C, and stained within 4 months of sectioning **except** for squamous NSCLC. Squamous NSCLC tissue sections that are stored at room temperature should be stained within 2 months of sectioning. Slide storage and handling conditions should not exceed 25 °C at any point post mounting to ensure tissue integrity and antigenicity.

Positive and Negative Control Tissues (Lab-Supplied)

Differences in processing and embedding in the user's laboratory may produce significant variability in results. Include positive and negative control tissue in each staining run, in addition to the PD-L1 IHC 28-8 pharmDx Control Slides.

Select positive and negative control tissue from NSCLC specimens. Fix, process, and embed the control tissue in the same manner as patient specimens. Control tissue processed differently from the patient specimen validates reagent performance only and does not verify tissue preparation. The ideal positive control tissue gives weak to moderate positive staining. The variety of different cell types present in most tissue sections offers internal negative control sites; this should be verified by the user.

PD-L1 IHC 28-8 pharmDx Staining Procedure

The PD-L1 IHC 28-8 pharmDx reagents and instructions have been designed for optimal performance. Further dilution of the reagents, alteration of incubation times, temperatures, or instruments may give erroneous results.

Reagent Storage

Store all components of PD-L1 IHC 28-8 pharmDx, including Control Slides, in the dark at 2–8 °C when not in use on Autostainer Link 48. Do not use after the expiration date printed on the outside package.

Reagent Preparation

Equilibrate all components to room temperature (20–25 °C) prior to immunostaining.

EnVision FLEX Target Retrieval Solution, Low pH (50x)

Prepare a sufficient quantity of 1x Target Retrieval Solution, Low pH by diluting Target Retrieval Solution, Low pH (50x) 1:50 using reagent-quality water; the pH of 1x Target Retrieval Solution should be 6.1 ± 0.2. One 30 mL bottle of Target Retrieval Solution, Low pH (50x), diluted 1:50 will provide 1.5 L of 1x reagent, sufficient to fill one PT Link tank, which will treat up to 24 slides per use. Discard 1x Target Retrieval Solution after three uses and no longer than 5 days after dilution. Note the FLEX Target Retrieval Solution, low pH (50x) is a red-colored solution.

Additional EnVision FLEX Target Retrieval Solution, Low pH (50x), if required, is available as Code K8005.

EnVision FLEX Wash Buffer (20x)

Prepare a sufficient quantity of Wash Buffer by diluting Wash Buffer (20x) 1:20 using reagent-quality water for the wash steps. Store unused 1x solution at 2-8 °C for no more than one month. Discard buffer if cloudy in appearance. Refer to the User Guide for your Autostainer Link 48 for further information. EnVision FLEX Wash Buffer (20x) is available as Code K8007.

DAB+ Substrate-Chromogen Solution

Add 1 drop of DAB+ Chromogen per mL of DAB+ Substrate Buffer and mix. Prepared DAB+ Substrate-Chromogen is stable for 5 days if stored in the dark at 2–8 °C. Mix the DAB+ Substrate-Chromogen Solution thoroughly prior to use. Any precipitate developing in the solution does not affect staining quality.

- If using an entire bottle of DAB+ Substrate Buffer, add 9 drops of DAB+ Chromogen. Although the DAB+ Substrate Buffer label states 7.2 mL, this is the usable volume and does not account for the "dead volume" of DAB+ Substrate Buffer in the bottle.
- The color of the DAB+ Chromogen may vary from clear to lavender brown. This will not affect the performance of the product. Dilute as per the guidelines above. Adding excess DAB+ Chromogen to the DAB+ Substrate Buffer results in deterioration of the positive signal.

Control Slides

Each slide contains sections of two pelleted, formalin-fixed, paraffin-embedded cell lines: NCI-H226** with positive PD-L1 protein expression (originating from human lung squamous cell carcinoma with positive PD-L1 protein expression) and MCF-7 with negative PD-L1 protein expression (originating from human breast adenocarcinoma with negative PD-L1 protein expression).

Staining Protocol

Program slides by selecting PD-L1 IHC 28-8 pharmDx staining protocol from the options in the DakoLink drop-down menu. All of the required steps and incubation times for staining are preprogrammed in the DakoLink software. Print and attach slide labels to each slide.

Deparaffinization, Rehydration and Target Retrieval

Use PT Link, Code PT100/PT101/PT200, to perform the Deparaffinization, Rehydration and Target retrieval 3-in-1 procedure.

- Set Pre-heat and Cool to 65 °C, and set Heat to 97 °C for 20 minutes.
- Fill PT Link tanks with 1.5 L per tank of EnVision FLEX Target Retrieval Solution, Low pH, working solution to cover the tissue sections.
- Pre-heat the Target Retrieval Solution, Low pH to 65 °C.
- Immerse Autostainer racks containing mounted, FFPE tissue sections into the pre-heated Target Retrieval Solution, Low pH in PT Link tank. Incubate for 20 minutes at 97 °C.
- When targeting retrieval incubation has been completed, and the temperature has cooled to 65 °C, remove each Autostainer slide rack with slides from the PT Link tank and immediately place the slides into a tank (e.g., PT Link Rinse Station, Code PT109) containing room temperature EnVision FLEX Wash Buffer working solution.
- Leave Autostainer rack with slides in room temperature EnVision FLEX Wash Buffer for 5 minutes.

*** Dr. AF Gazdar and Dr. JD Minna at NIH are acknowledged for their contribution in developing NCI-H226 (ATCC Number: CRL-5826™).*

Staining and Counterstaining

- Place the Autostainer rack with slides on the Autostainer Link 48. Ensure slides remain wet with buffer while loading and prior to initiating the run. Dried tissue sections may display increased non-specific staining.
- Select the PD-L1 IHC 28-8 pharmDx protocol. The instrument performs the staining and counterstaining procedures by applying the appropriate reagent, monitoring the incubation time, and rinsing slides between reagents. Counterstaining using EnVision FLEX Hematoxylin, Code K8008, for 7 minutes, is included in the staining protocol. Do not allow slides to dry prior to mounting.

Mounting

Use nonaqueous permanent mounting media. To minimize fading, store slides in the dark at room temperature (20–25 °C).

PD-L1 IHC 28-8 pharmDx Technical Checklist

Customer Name / Institution: _____

Name and Title: _____

Autostainer Link 48 Serial Number: _____ Software Version: _____

		Yes	No
1.	Regular preventive maintenance is performed on the Autostainer Link 48 and PT Link?	☐	☐
2.	PD-L1 IHC 28-8 pharmDx is used before the expiration date printed on the outside of the box?	☐	☐
3.	All PD-L1 IHC 28-8 pharmDx components, including Control Slides, are stored in the dark at 2–8 °C?	☐	☐
4.	All PD-L1 IHC 28-8 pharmDx components, including Control Slides, are equilibrated to room temperature (20–25 °C) prior to immunostaining?	☐	☐
5.	Appropriate NSCLC positive and negative control tissues are identified?	☐	☐
6.	Tissues are fixed in neutral buffered formalin?	☐	☐
7.	Tissues are infiltrated with melted paraffin, at or below 60 °C?	☐	☐
8.	Tissue sections of 4–5 µm are mounted on FLEX IHC Microscope Slides, or Fisherbrand Superfrost Plus charged slides?	☐	☐
9.	Non-squamous NSCLC specimens are stained within 4 months of sectioning when stored in the dark at 2–8 °C or at room temperature up to 25 °C?	☐	☐
10.	Squamous NSCLC specimens are stained within 4 months of sectioning when stored in the dark at 2–8 °C or within 2 months of sectioning when stored in dark at room temperature up to 25 °C?	☐	☐
11.	EnVision FLEX Target Retrieval Solution, Low pH is prepared properly?	☐	☐
12.	EnVision FLEX Wash Buffer is prepared properly?	☐	☐
13.	DAB+ Substrate-Chromogen Solution is prepared properly?	☐	☐
14.	The Deparaffinization, Rehydration and Target Retrieval 3-in-1 procedure is followed, using PT Link?	☐	☐
15.	Slides remain wet with buffer while loading and prior to initiating run on Autostainer Link 48?	☐	☐
16.	The PD-L1 IHC 28-8 pharmDx protocol is selected on Autostainer Link 48?	☐	☐
17.	Slides are counterstained with EnVision FLEX Hematoxylin?	☐	☐
18.	Do you have all the necessary equipment to perform the PD-L1 IHC 28-8 pharmDx according to the protocol? If not, specify what is missing in the comments below.	☐	☐

If you answered "No" to any of the above, consult with your local Dako Technical Support Representative for assistance.

Additional Observations or Comments:

_____

_____

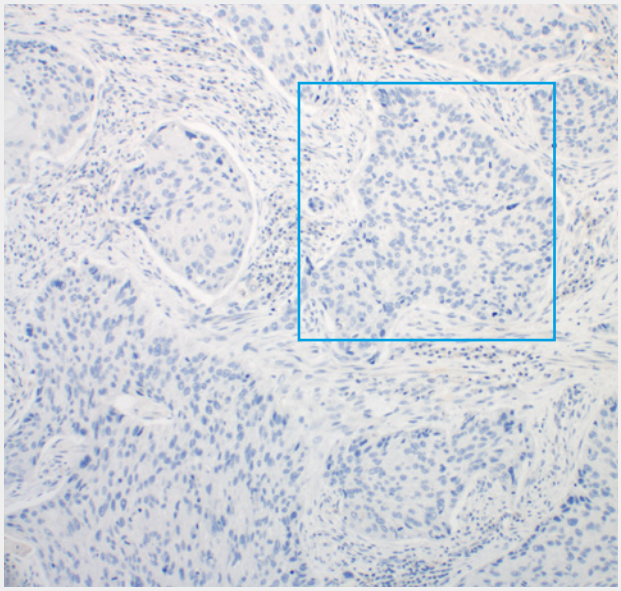
_____

Guidelines for Scoring PD-L1 IHC 28-8 pharmDx

Agilent emphasizes that scoring of PD-L1 IHC 28-8 pharmDx must be performed in accordance with the guidelines established in the IFU, within the context of best practices and the pathologist's experience.

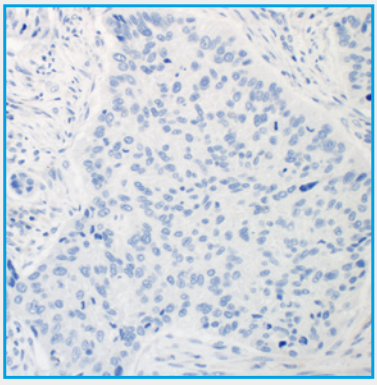
The percentage of viable tumor cells exhibiting circumferential or partial linear plasma membrane PD-L1 staining at any intensity determines PD-L1 IHC 28-8 pharmDx result. Scoring guidelines and reporting recommendations are presented in Figure 2. See page 25, for an example of a pathology report form for PD-L1 IHC 28-8 pharmDx.

< 1% of the viable tumor cells exhibit complete circumferential or partial linear plasma membrane staining at any intensity.

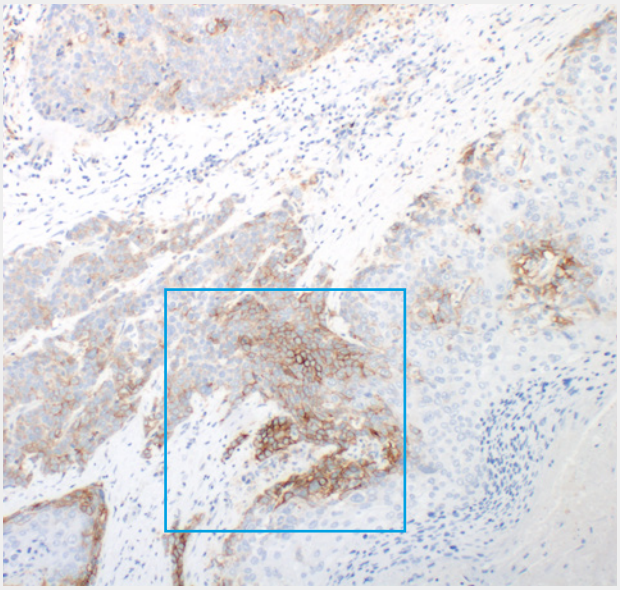


PD-L1 expression

< 1%



≥ 1% of the viable tumor cells exhibit complete circumferential or partial linear plasma membrane staining at any intensity.



PD-L1 expression

≥ 1%

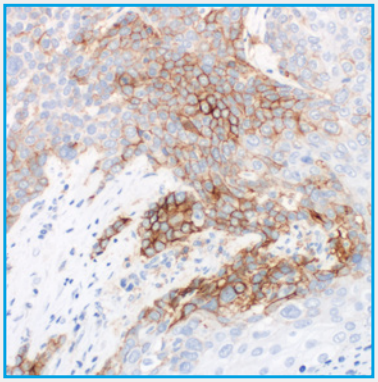


Figure 2. Guidelines for scoring and reporting PD-L1 IHC pharmDx results.

Photomicrograph Acknowledgment
Data and biospecimens used in this project were provided by Center Hospitalier Universitaire de Nice, Nice, France, and US Biolab Corporation, Inc., Gaithersburg, MD with appropriate ethics approval and through Trans-Hit Biomarkers Inc.

The data and images of a NSCLC tissue sample used in this project were provided by TransHit Bulgaria, SofiaBio, with appropriate ethics approval and through Trans-Hit Biomarkers Inc.

Tissue samples were supplied by Asterand Bioscience.

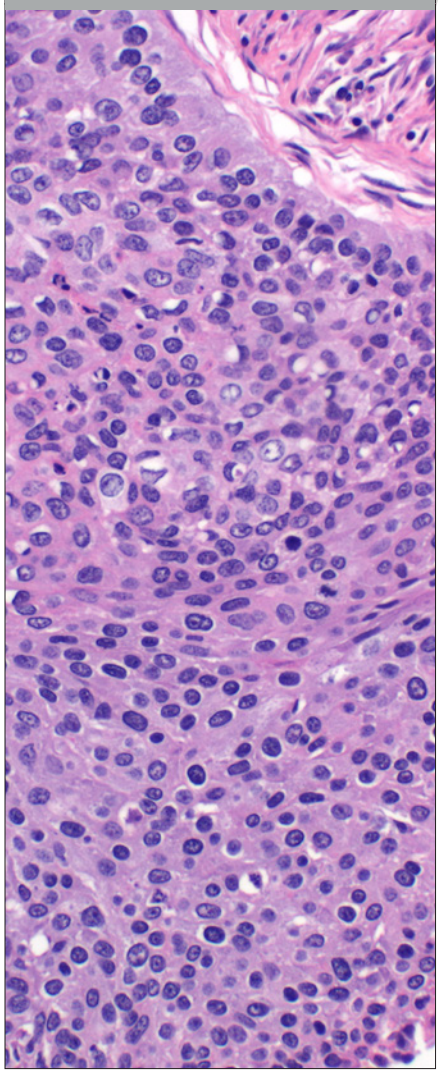
Recommended Slide Order for Interpretation of PD-L1 IHC 28-8 pharmDx

The following flow of slide review is recommended when conducting interpretation of PD-L1 IHC 28-8 pharmDx.
Refer to detailed description on pages 20–22.

1

Patient Specimen stained with H&E
Histology and Preservation Quality

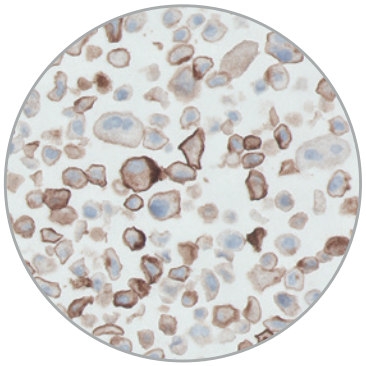
Acceptable



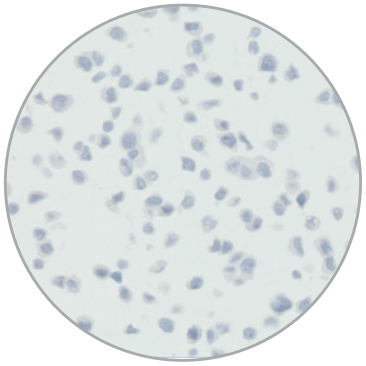
2

PD-L1 IHC 28-8 pharmDx Control Slide
Stained with PD-L1 Primary Antibody

Acceptable



PD-L1 Positive Control

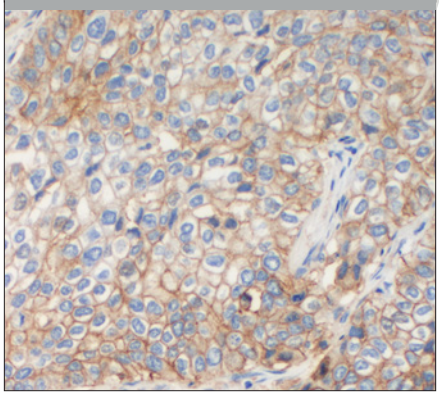


PD-L1 Negative Control

3A

Positive Control Tissue
Stained with PD-L1 Primary Antibody

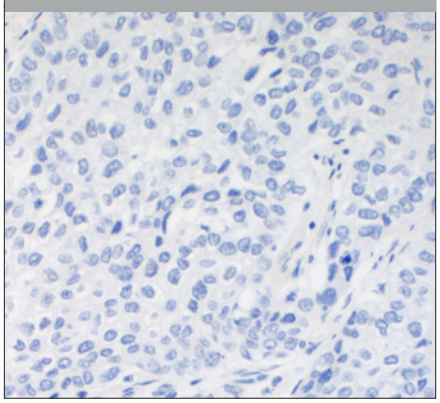
Acceptable



3B

Positive Control Tissue
Stained with Negative Control Reagent

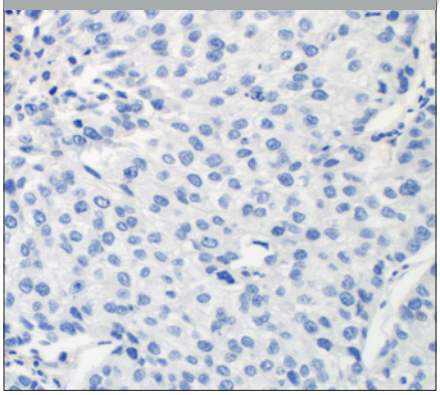
Acceptable



4A

Negative Control Tissue
Stained with PD-L1 Primary Antibody

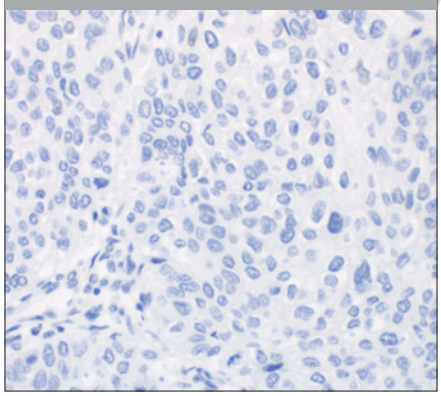
Acceptable



5

Patient Specimen
Stained with Negative Control Reagent

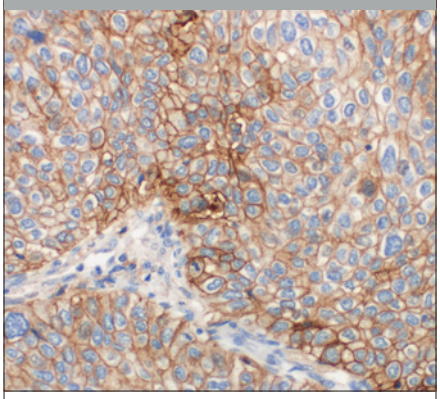
Acceptable



6

Patient Specimen
Stained with PD-L1 Primary Antibody

Acceptable



≥ 100 viable tumor cells should be present for scoring.

Include when scoring:

- Score viable tumor cells exhibiting complete circumferential or partial linear plasma membrane staining at any intensity.
- Determine the percentage of stained viable tumor cells in the entire specimen.

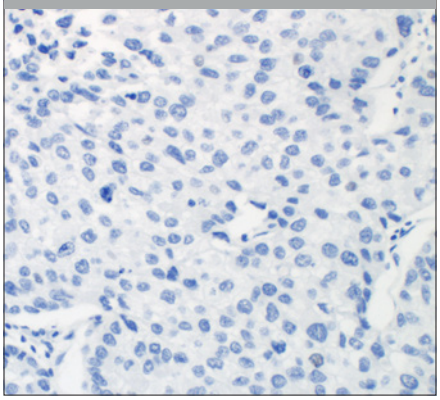
Exclude from scoring:

- Cytoplasmic staining
- Immune cells
- Normal cells
- Necrotic cells
- Cellular debris

4B

Negative Control Tissue
Stained with Negative Control Reagent

Acceptable



Recommendations for Interpretation of PD-L1 IHC 28-8 pharmDx in NSCLC

PD-L1 IHC 28-8 pharmDx evaluation must be performed by a pathologist using a bright field microscope. Before examining the patient specimen for PD-L1 staining, it is important to examine the hematoxylin and eosin (H&E) and controls first to assess staining quality. Examine a serial section of the patient specimen stained with H&E for histology and preservation quality. Then, examine the PD-L1 IHC 28-8 pharmDx Control Slide, the positive and negative control tissue slides, and the patient specimen slide stained with the Negative Control Reagent. Lastly, examine the patient specimen stained with Primary Antibody to assess the staining of viable tumor cells.

PD-L1 staining is defined as complete circumferential or partial linear plasma membrane staining at any intensity. Cytoplasmic staining, if present, is not considered positive for scoring purposes. Non-malignant cells and immune cells (e.g., such as infiltrating lymphocytes or macrophages) may also stain with PD-L1; however, these should not be included in the scoring for the determination of PD-L1 positivity.

Positive control tissue slides and negative control tissue slides should be supplied by the laboratory. Only the Control Slide is provided in the PD-L1 IHC 28-8 pharmDx.

Patient Specimen Stained with H&E

A hematoxylin and eosin (H&E) stained section is required for the evaluation of histology and preservation quality. PD-L1 IHC 28-8 pharmDx and the H&E staining should be performed on serial sections from the same paraffin block of the specimen.

PD-L1 IHC 28-8 pharmDx Control Slide

Examine the PD-L1 IHC 28-8 pharmDx Control Slide to ascertain that reagents are functioning properly. Each slide contains sections of cell pellets with positive and negative PD-L1 expression, see Figure 3. If any staining of the Control Slide is not satisfactory all results with the patient specimens should be considered invalid. Do not use the Control Slide as an aid in the interpretation of patient results.

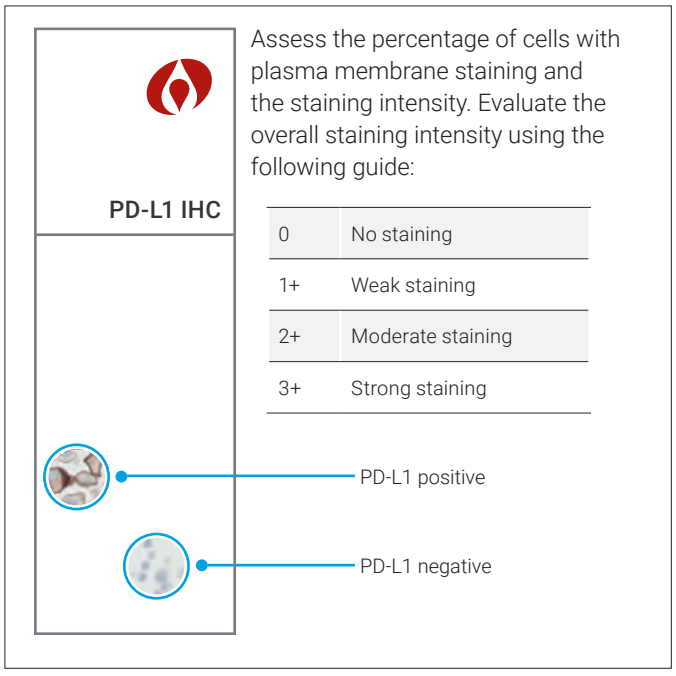


Figure 3. Each Control Slide contains sections of cell pellets with positive and negative PD-L1 expression.

For the PD-L1 positive cell pellet, the following staining is acceptable, see Figure 4.

- Plasma membrane staining of ≥ 80% of cells
- ≥ 2+ average staining intensity
- Non-specific staining < 1+ intensity

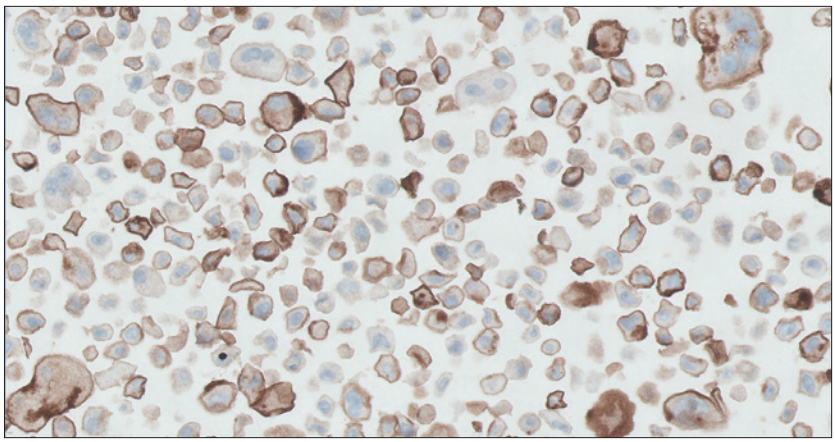


Figure 4. Acceptable Positive PD-L1 Control.

For the PD-L1 negative cell pellet, the following staining is acceptable, see Figure 5.

- No plasma membrane staining
- Any background staining is of less than 1+ staining intensity

Staining of a few cells in the negative pellet may occasionally be observed. The presence of 10 or less cells with distinct plasma membrane staining, or cytoplasmic staining with ≥ 1+ intensity within the boundaries of the cell pellet are acceptable.

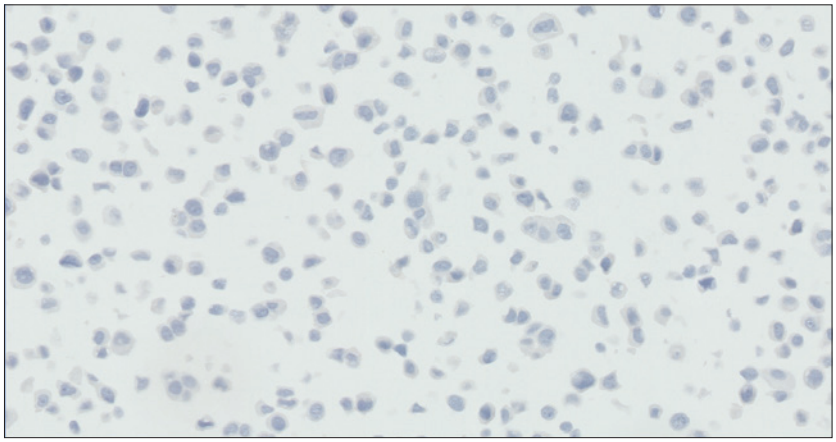


Figure 5. Acceptable Negative PD-L1 Control.

Positive Control Tissue Slides

Examine the positive NSCLC control tissue slides (Primary Antibody, NCR) to ascertain if tissues are correctly prepared, and reagents are functioning properly. Any background staining should be of less than 1+ staining intensity. Exclude necrotic or nonviable tumor cells from the evaluation. If the staining of positive control tissues is not satisfactory, all results with the patient specimens should be considered invalid. Do not use control tissue as an aid in the interpretation of patient results.

Negative Control Tissue Slides

Examine the negative NSCLC control tissue slides (Primary Antibody, NCR) to confirm that there is no unintended staining. Any background staining should be less than 1+ staining intensity. If the plasma membrane staining of malignant cells occurs in the negative control tissue, all results with the patient specimens should be considered invalid. Do not use control tissue as an aid in the interpretation of patient results.

Patient Specimen Stained with Negative Control Reagent

Examine the patient specimen stained with Negative Control Reagent to ascertain that reagents are functioning properly. Absence of plasma membrane staining of viable tumor cells is satisfactory. Staining by the Negative Control Reagent must not show positive membrane staining and non-specific background should be less than or equal to 1+ staining intensity. If any staining is not satisfactory, results with the patient specimen should be considered invalid.

The Negative Control Reagent indicates non-specific background staining and allows better interpretation of patient specimen stained with the Primary Antibody.

Patient Specimen Stained with Primary Antibody

Staining should be assessed within the context of any non-specific background staining of the patient specimen stained with Negative Control Reagent. A minimum of 100 viable tumor cells should be present in the PD-L1 stained patient slide to evaluate the patient slide.

1. At 4x objective magnification, carefully examine the tumor areas of the entire specimen. All areas with viable tumor cells on the specimen should be evaluated. Exclude non-malignant cells, necrotic cells, and cellular debris. Non-specific cytoplasmic staining, if present, should be disregarded.
2. Use the 10–20x objective magnifications to determine the percentage of viable tumor cells expressing PD-L1 membranous staining. The 40x objective can be used for confirmation if needed. Tumor cells are considered to be PD-L1 positive if they exhibit either partial linear or complete circumferential staining of the plasma membrane at any intensity. Non-malignant cells and immune cells (e.g., infiltrating lymphocytes or macrophages) may also stain with PD-L1 but must be excluded.
3. Record if the specimen has tumor PD-L1 expression < 1% or ≥ 1%. When determining the percentage of stained tumor cells in the entire specimen, the numerator is the number of stained viable tumor cells and the denominator is the total number of viable tumor cells in the specimen.

$$\%\ \text{PD-L1 expression} = \frac{\#\ \text{PD-L1 staining tumor cells}}{\text{Total \# viable tumor cells}} \times 100$$

Tips and Special Considerations

- Include the entire specimen for evaluation of PD-L1 expression
- Use higher magnifications to confirm cell types and areas absent of staining
- Be careful not to overlook weak 1+ staining, which can be missed at 4x and 10x
- Disregard non-specific cytoplasmic staining
- Necrotic tissue may stain but should be excluded
- Exclude any non-malignant cells and immune cells
- Granular staining must demonstrate a perceptible and convincing membrane pattern

Indeterminate Specimen

The tumor cell membrane has been hampered for reasons attributed to the biology of the tumor tissue sample rather than improper sample preparation. For example, high cytoplasmic staining of the tumor cells can hamper scoring of the membrane staining. An additional cut section or section from another block of the same patient may be required for PD-L1 IHC 28-8 pharmDx evaluation.

PD-L1 IHC 28-8 pharmDx Suggested Scoring Methods for Calculating Tumor PD-L1 Expression

Agilent offers two different examples of scoring techniques that may be used when assessing stained specimens exhibiting different staining patterns.

Example 1: Calculating % PD-L1 expression in a specimen with a small PD-L1 staining tumor area

At a lower objective magnification, assess the entire specimen for presence of PD-L1 staining in viable tumor cells at any intensity. Any non-malignant and immune cells staining PD-L1 positive must be excluded.

- In this example, assume the number of tumor cells is equally distributed in the tumor and that there are a total of 1,000 viable tumor cells in the entire specimen.
- 10% of the tumor area has staining, 90% of the tumor area has no staining.

At a higher objective magnification, carefully examine PD-L1 staining tumor area (blue circle in Figure 6). PD-L1 positive staining is defined as complete circumferential and/or partial linear plasma membrane staining of tumor cells at any intensity.

- 50 out of 100 viable tumor cells are staining PD-L1 positive in the single region of the tumor area (Method 1) which may also be described as: 50% PD-L1 positive in a single region representing 10% of the tumor area (Method 2).

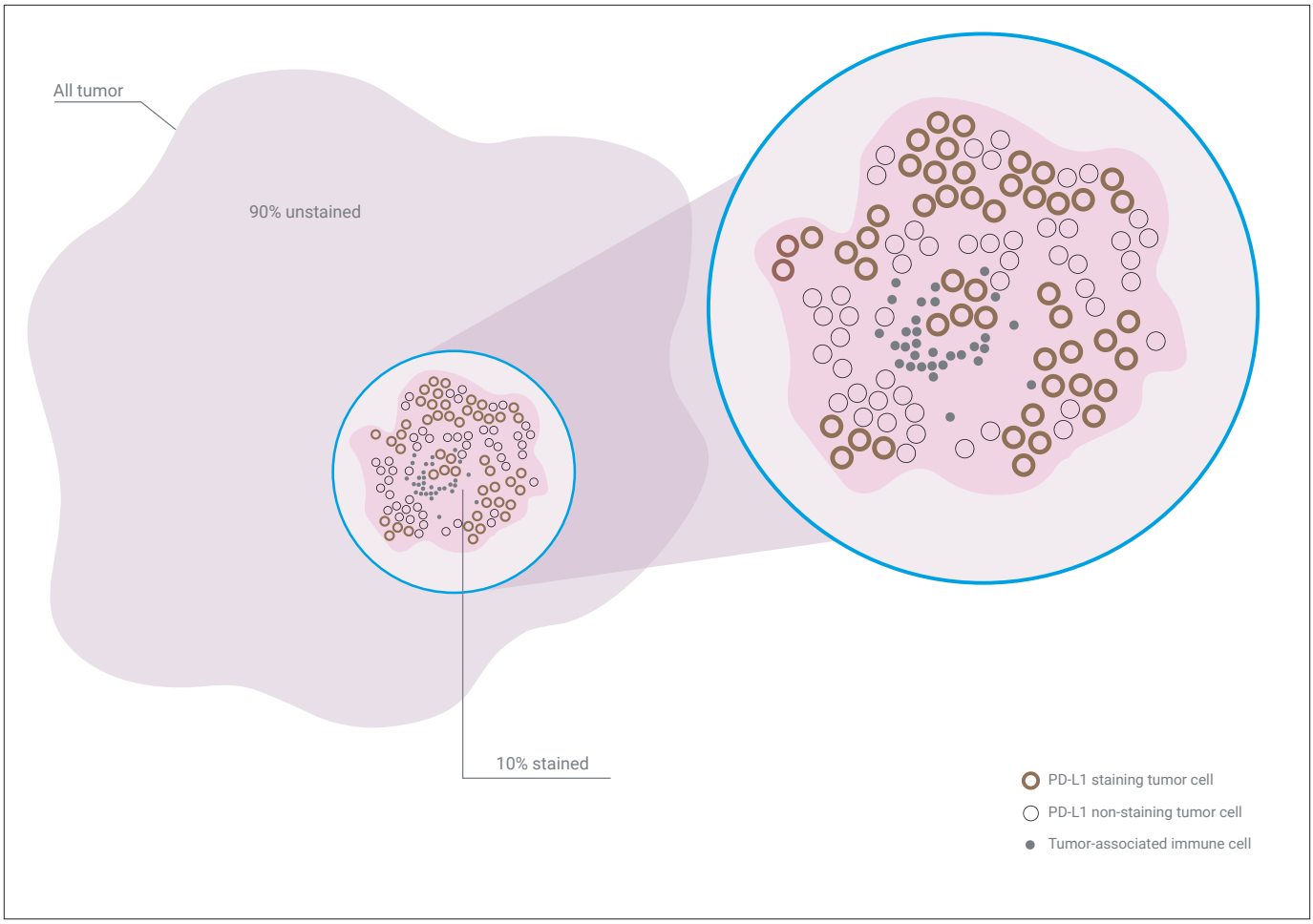


Figure 6. Example of tumor with small PD-L1 staining area.

Determine the overall percentage of PD-L1 staining tumor cells for the entire specimen as shown:

Method 1

$$\frac{\text{50 tumor cells staining PD-L1 positive}}{\text{1,000 viable tumor cells}} \times 100 = \text{5\% PD-L1 expression}$$

Method 2

$$\frac{\text{50\% x 10\%}}{\text{100}} = \text{5\% PD-L1 expression}$$

Example 2: Calculating % PD-L1 expression in a specimen with heterogeneous staining

At a lower objective magnification, assess the entire specimen for presence of PD-L1 staining in viable tumor cells at any intensity. Visually divide the tumor area into regions. Any non-malignant and immune cells staining PD-L1 positive must be excluded.

- The tumor area is divided into four equivalent quadrants in Figure 7.

At a higher objective magnification, assess and calculate the percentage of PD-L1 staining tumor cells in each quadrant. PD-L1 positive staining is defined as complete circumferential and/or partial linear plasma membrane staining of tumor cells at any intensity.

- The percentage of PD-L1 staining tumor cells for each of the four respective quadrants are: 80%, 30%, 50% and 100%.

Figure 7. Example with heterogenous PD-L1 staining area.

Determine the overall percentage of PD-L1 staining tumor cells for the entire specimen:

$$\frac{(80\% + 30\% + 50\% + 100\%)}{4 \text{ quadrants}} = 65\% \text{ PD-L1 expression}$$

PD-L1 IHC 28-8 pharmDX Reporting Results: NSCLC

Suggested information to include when reporting results with PD-L1 IHC 28-8 pharmDx in NSCLC

PD-L1 IHC 28-8 pharmDx, Code SK005

Summary of Sample Tested:

Date of Run: _____ PD-L1 IHC 28-8 pharmDx Lot: _____

Staining Run Log ID: _____ Specimen ID: _____

Patient Identifier: _____

Type of Service: IHC Stain with Manual Interpretation

Other: _____

Type of Tissue: _____

Additional Tests Performed with PD-L1 IHC 28-8 pharmDx: _____

PD-L1 IHC 28-8 pharmDx Controls Results:

PD-L1 IHC 28-8 Control Cell Slide:	Pass ☐	Fail ☐
Positive Control Tissue Slides:	Pass ☐	Fail ☐
Negative Control Tissue Slides:	Pass ☐	Fail ☐
Patient Specimen, Negative Control Reagent:	Pass ☐	Fail ☐

PD-L1 Results: PD-L1 IHC 28-8 pharmDx is indicated as an aid in identifying NSCLC patients for treatment with OPDIVO® (nivolumab) in combination with YERVOY® (ipilimumab).

Viable Tumor Cells Present: ☐ ≥ 100 cells ☐ Not evaluable

☐ PD-L1 expression is ≥ 1% ☐ PD-L1 expression is <1%

OPDIVO® in combination with YERVOY® is indicated as an aid in identifying NSCLC patients whose tumors have PD-L1 expression ≥ 1% in tumor cells.

Note that OPDIVO® may be associated with enhanced survival in nsNSCLC patients whose tumors have PD-L1 expressions (> 1%, > 5% and > 10% in tumor cells). Refer to the PD-L1 IHC 28-8 pharmDx assay Instructions for Use (IFU) and OPDIVO® product label for specific clinical circumstances.

OPDIVO® and YERVOY® are registered trademarks of Bristol-Myers Squibb Company.

PD-L1 IHC 28-8 pharmDx Immunostaining Examples in NSCLC

Positive Control Specimen

An example of non-small cell lung cancer stained with PD-L1 IHC 28-8 pharmDx. The staining shows a range of PD-L1 expression and staining intensity. This specimen would be appropriate to use as a positive control specimen for the detection of subtle changes in assay sensitivity. Note the partial linear (**red arrows**) and complete circumferential (**black arrows**) plasma membrane staining.

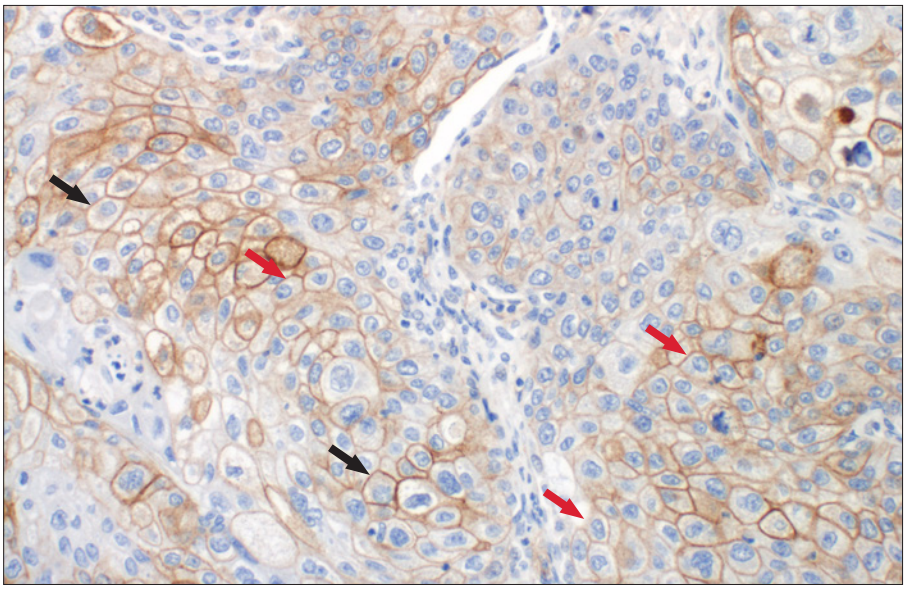


Figure 8. 20x magnification.

Distinguishing Tumor Cells from Immune Cells

NSCLC specimen showing strong staining of intratumoral associated immune cells (**red arrows**), while the tumor cells are negative (**black arrows**) for PD-L1 positivity.

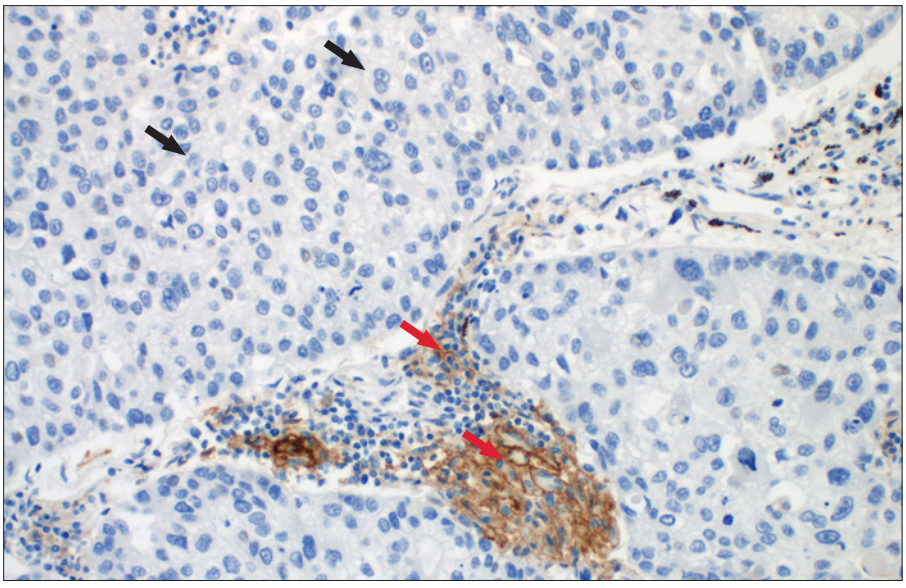


Figure 9. 20x magnification.

Distinguishing Tumor Cells from Immune Cells

Anthracotic pigment is an accumulation of carbon from inhaled smoke or coal dust. This example shows anthracotic pigment, small granular black spots, located within the immune cells (**red arrows**) which are helpful to distinguish from tumor cells. Anthracotic pigment is not found within tumor cells, which are PD-L1 negative (**black arrow**).

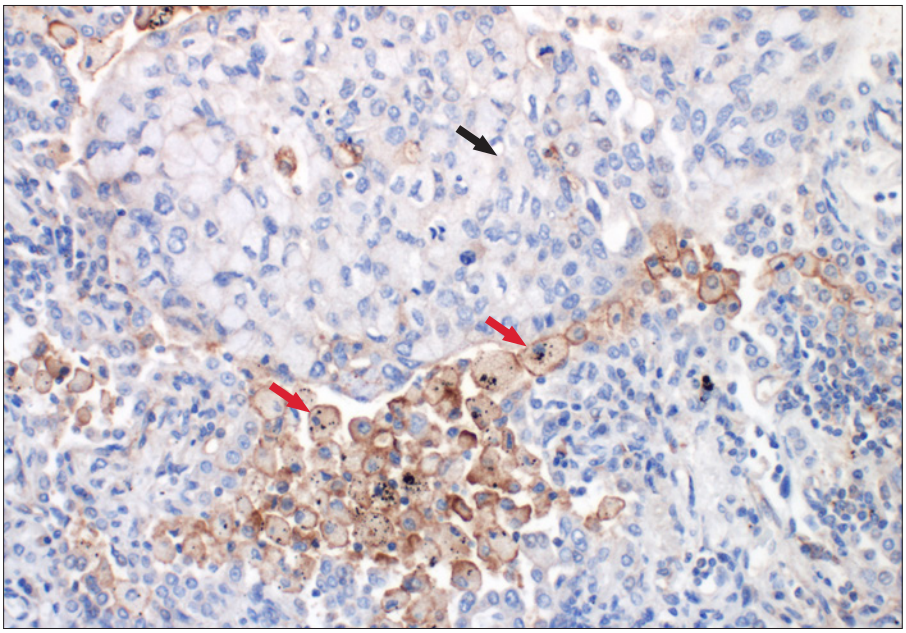


Figure 10. 20x magnification.

Distinguishing Tumor Cells from Immune Cells

Non-small cell lung cancer showing PD-L1 positive staining of macrophage (**red arrows**) and lymphocyte (**blue arrow**) immune cells and tumor cells (**black arrows**). Note the staining of immune cells are not included in determining the percent PD-L1 expression.

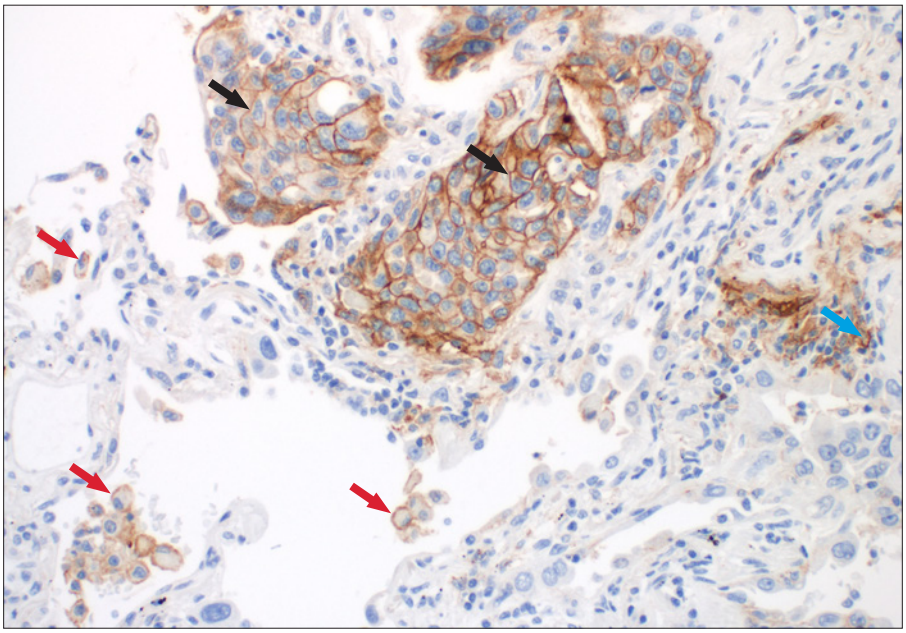


Figure 11. 20x magnification.

Cytoplasmic Staining

Positive linear membrane (**black arrows**) staining of the tumor is observed and is distinguishable from the cytoplasmic staining.

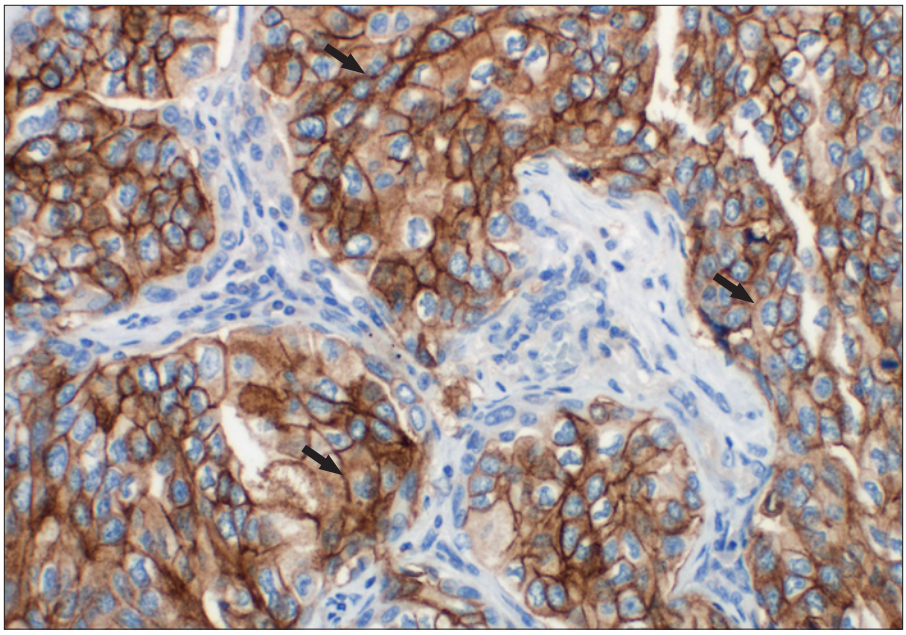


Figure 12. 20x magnification.

Granular Staining

Granular staining (**red arrow**) is present in the cytoplasm of tumor cells. Positive linear membrane staining of the tumor is observed (**black arrows**).

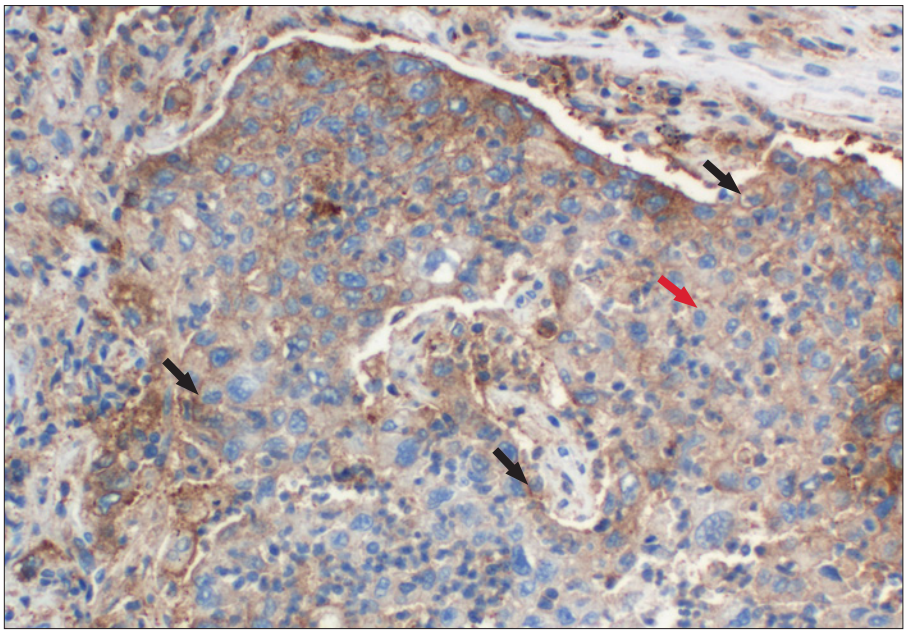


Figure 13. 20x magnification.

PD-L1 IHC 28-8 pharmDx NSCLC Case Examples

Case 1: PD-L1 expression < 1%

No tumor cells are exhibiting PD-L1 staining in this case example. The PD-L1 expression is 0%.

Figure 14a. 10x magnification.

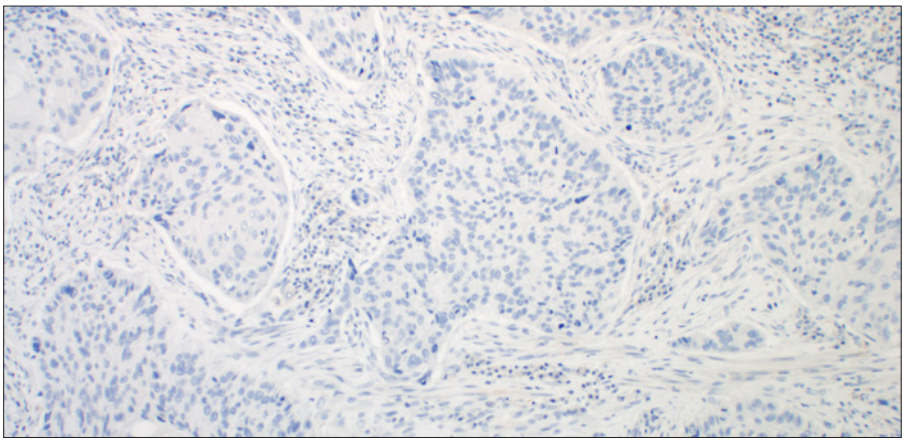


Figure 14b. 20x magnification.

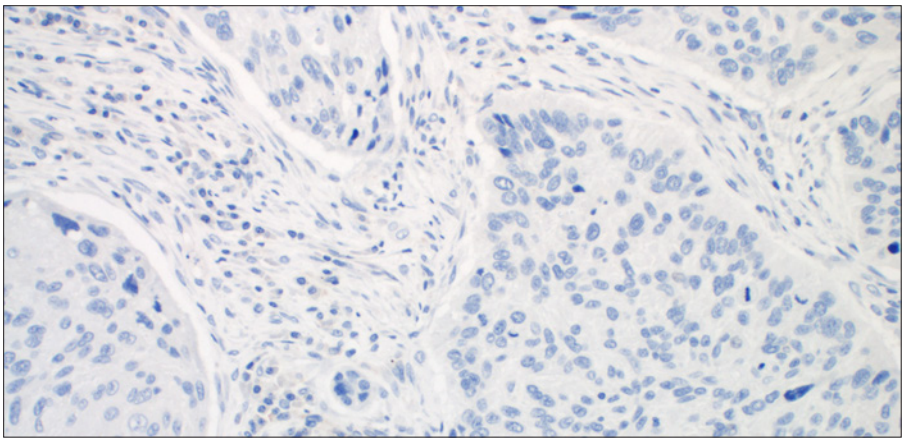
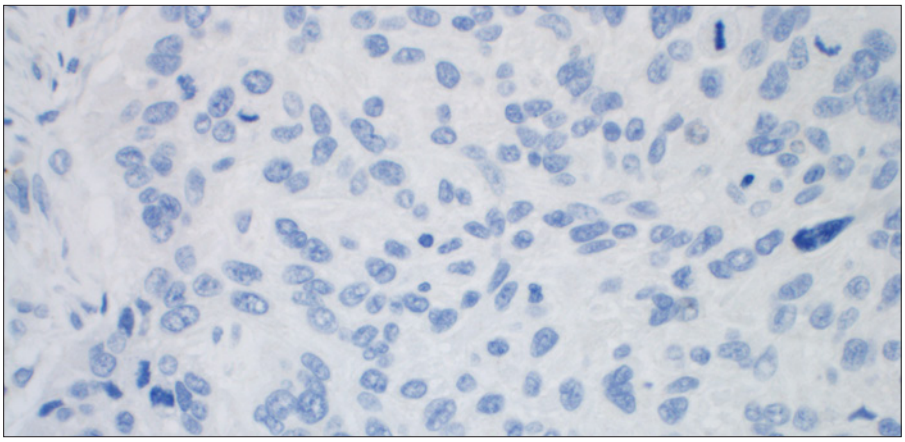


Figure 14c. 40x magnification.



Case 2: PD-L1 expression < 1%

There is presence of staining in this case example. Most of the staining appears to be non-specific, with the exception of a few tumor cells exhibiting partial linear membrane staining. The PD-L1 expression is < 1%.

Figure 15a. 10x magnification.

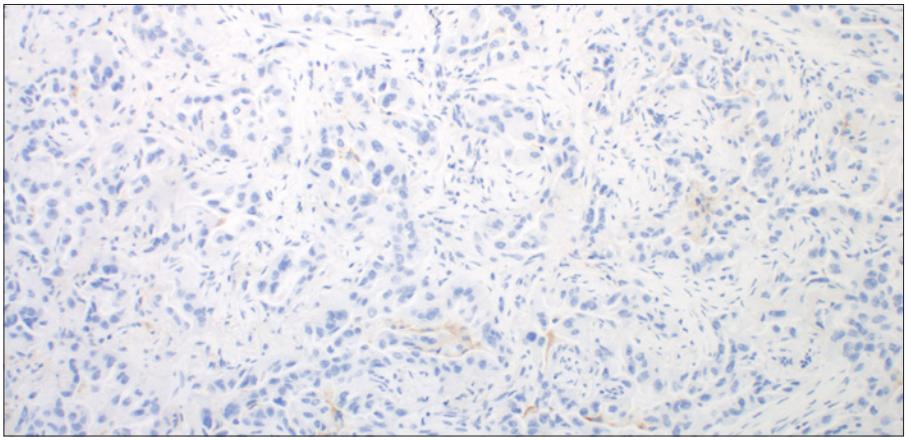


Figure 15b. 20x magnification.

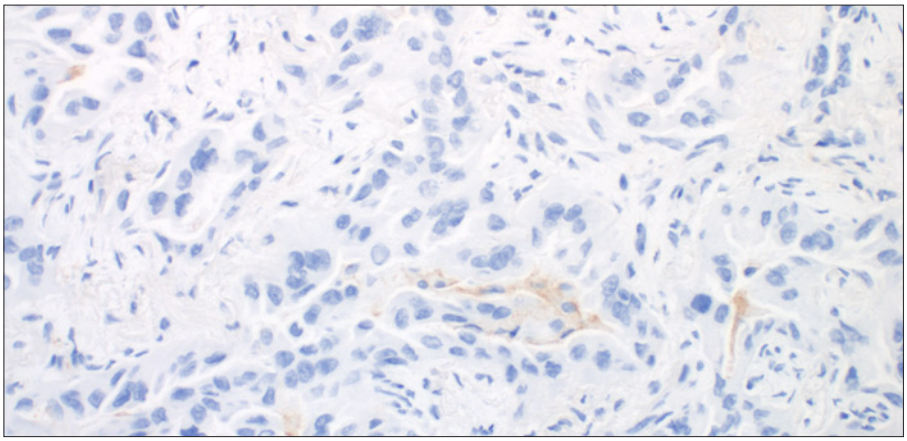
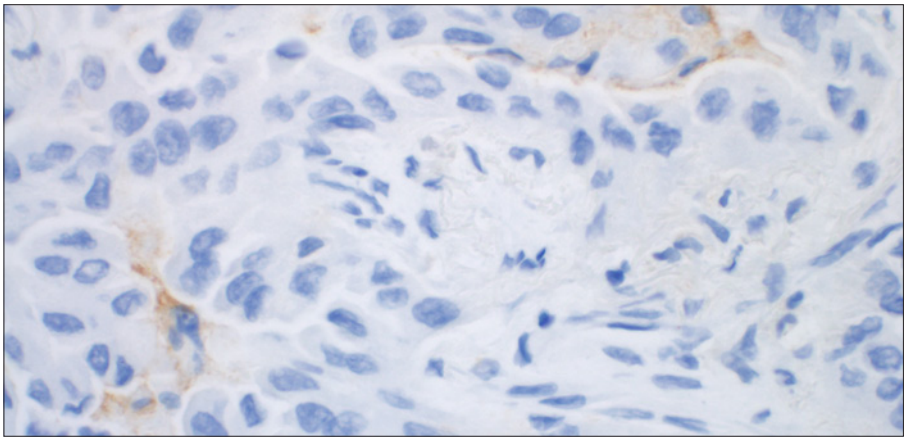


Figure 15c. 40x magnification.



Case 3: PD-L1 expression < 1%

There is presence of staining in this case example. Most of the PD-L1 staining is exhibited in the immune cells. A few tumors cells exhibit PD-L1 expression. The PD-L1 expression is < 1%.

Figure 16a. 10x magnification.

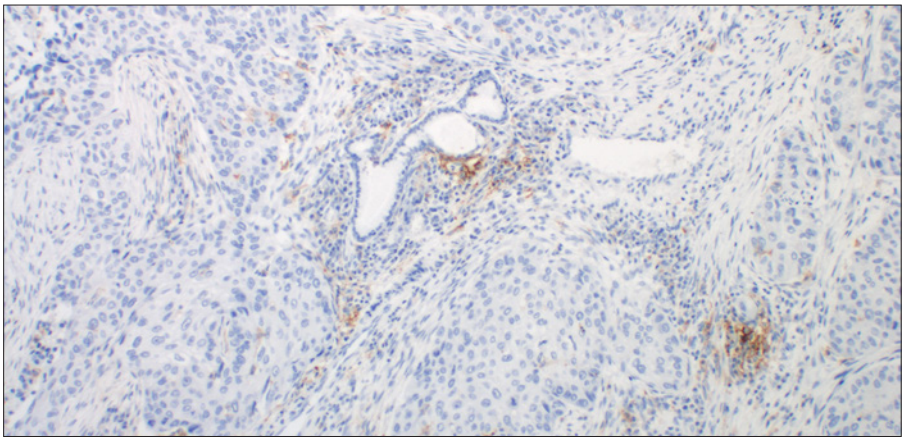


Figure 16b. 20x magnification.

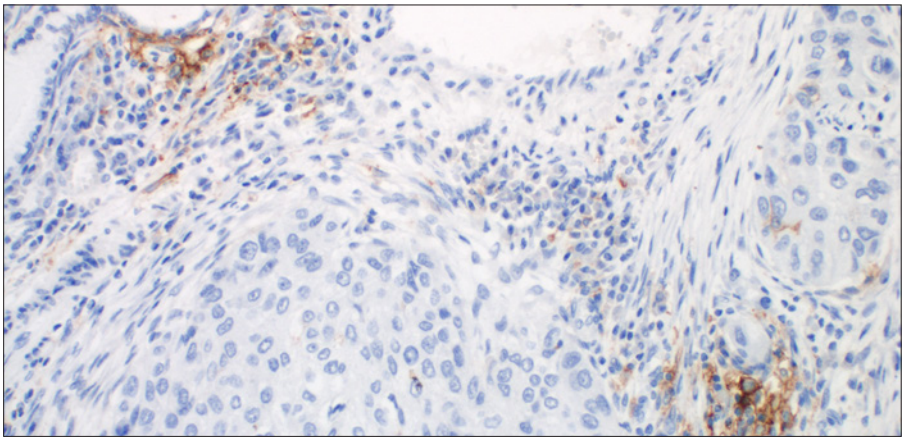
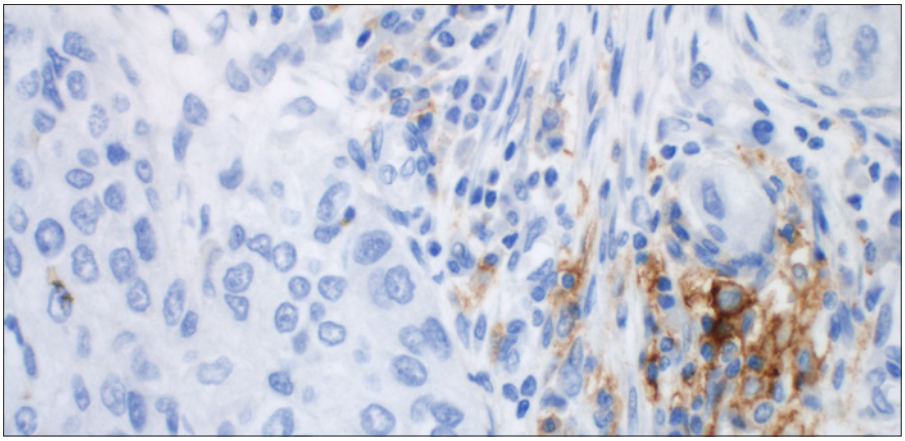


Figure 16c. 40x magnification.



Case 4: PD-L1 expression ≥ 1%

This case example demonstrates partial and complete membrane staining in the tumor cells. The PD-L1 expression is near and above the 1% clinical cut-off (PD-L1 expression 1–3%).

Figure 17a. 10x magnification.

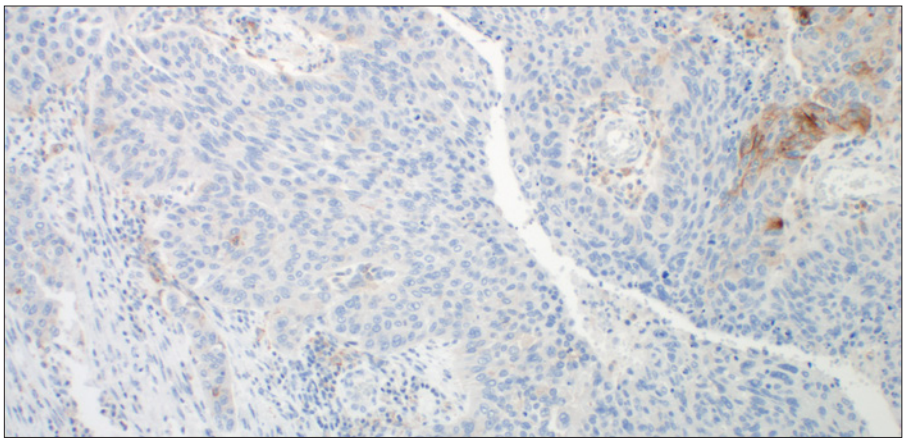


Figure 17b. 20x magnification.

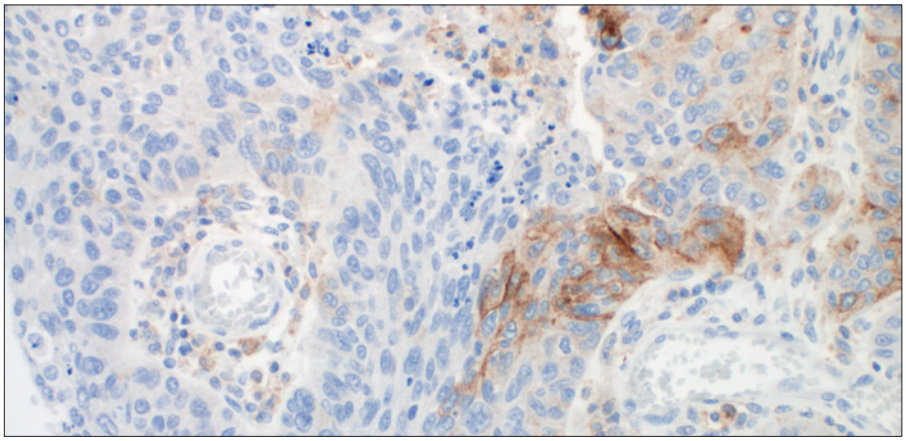
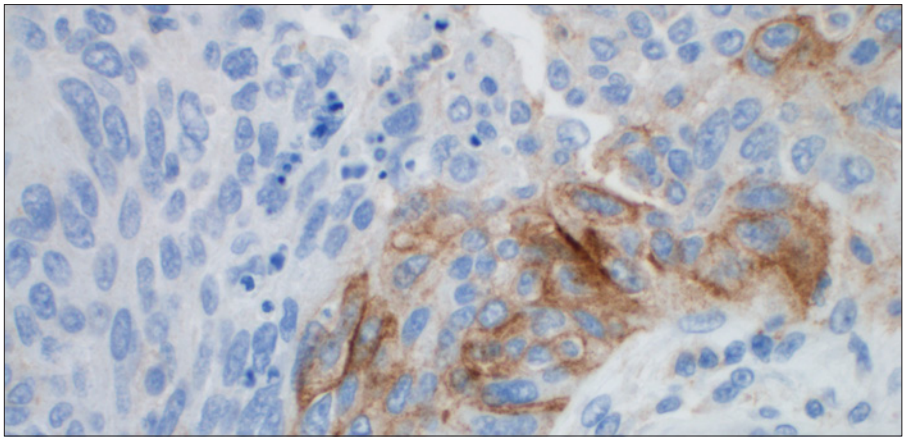


Figure 17c. 40x magnification.



Case 5: PD-L1 expression ≥ 1%

This case example demonstrates partial and complete membrane staining in the tumor cells. The PD-L1 expression is near and above the 1% clinical cut-off (PD-L1 expression 5–10%).

Figure 18a. 10x magnification.

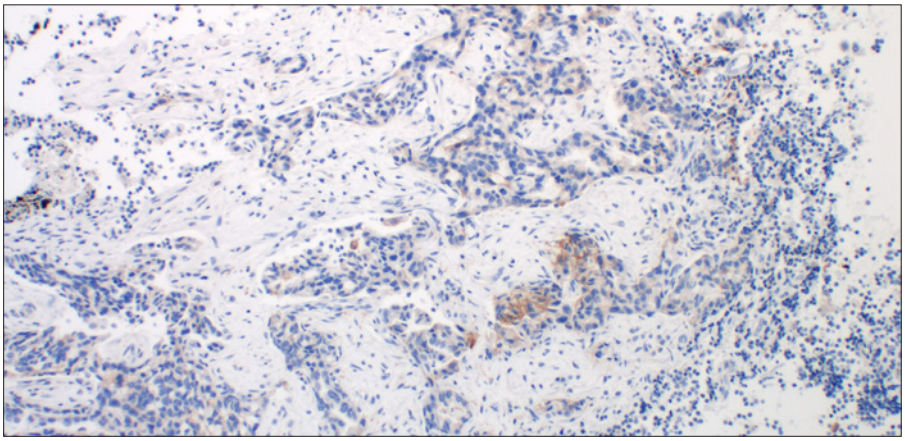


Figure 18b. 20x magnification.

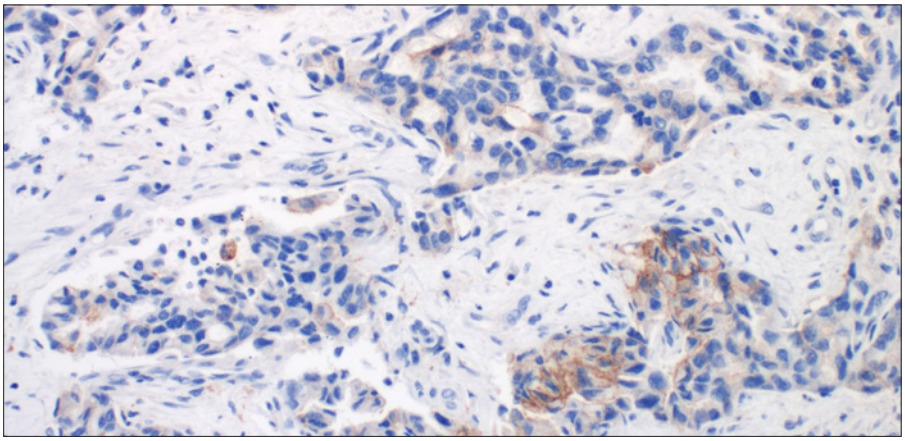
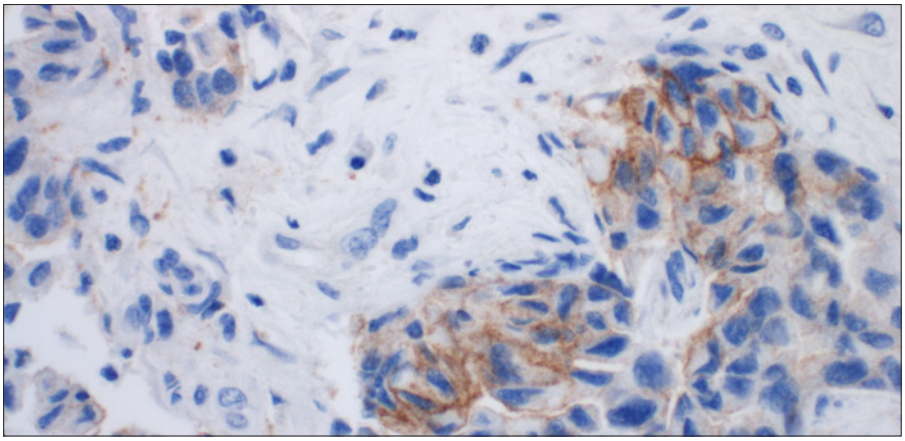


Figure 18c. 40x magnification.



Case 6: PD-L1 expression ≥ 1%

This case example demonstrates partial and complete membrane staining in the tumor cells. This case represents moderate PD-L1 expression of 20–30%.

Figure 19a. 10x magnification.

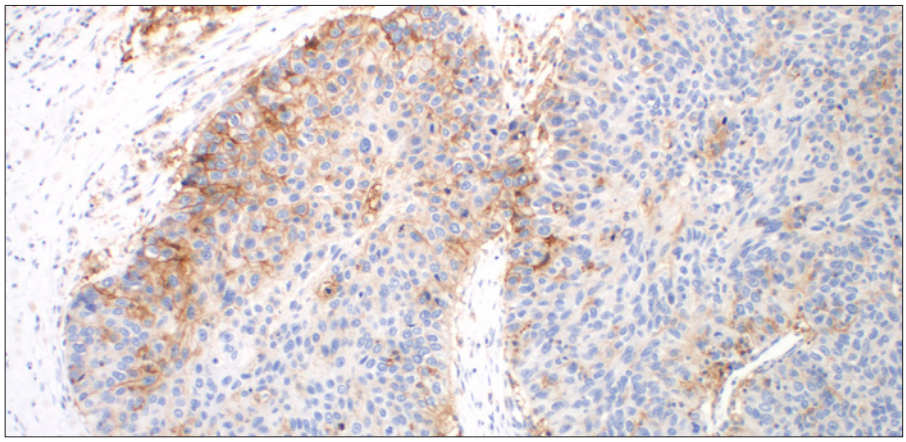


Figure 19b. 20x magnification.

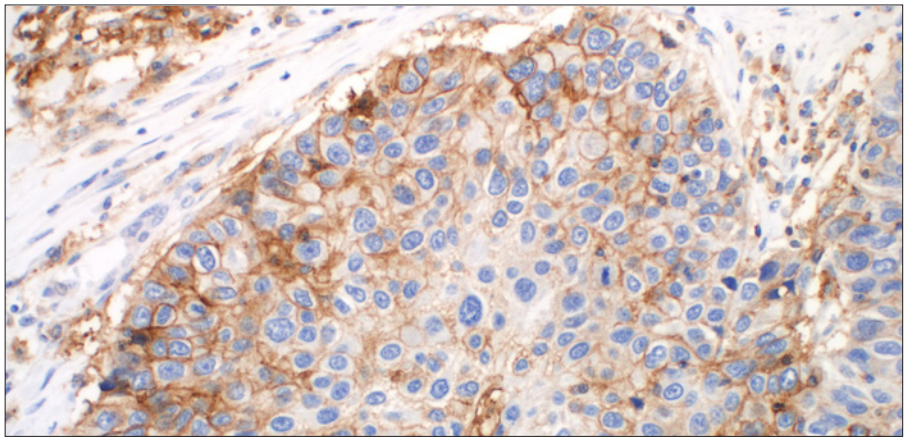
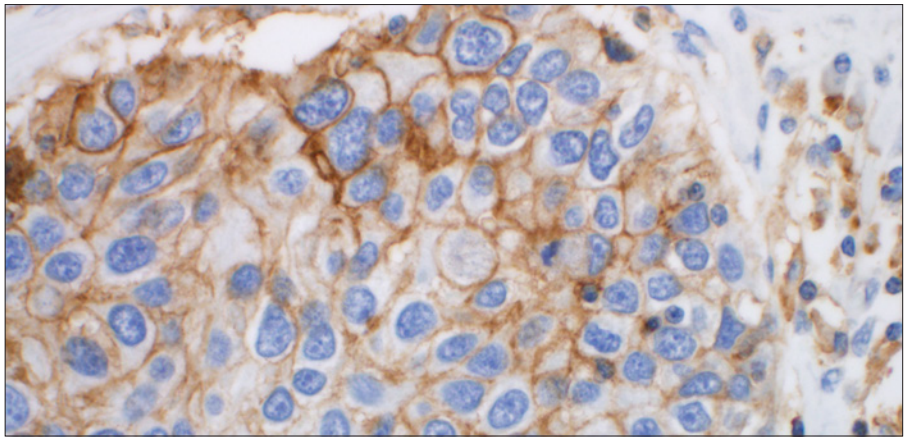


Figure 19c. 40x magnification.



Case 7: PD-L1 expression ≥ 1%

This case example demonstrates partial and complete membrane staining in the tumor cells. This case represents moderate to high PD-L1 expression of 50–60%.

Figure 20a. 10x magnification.

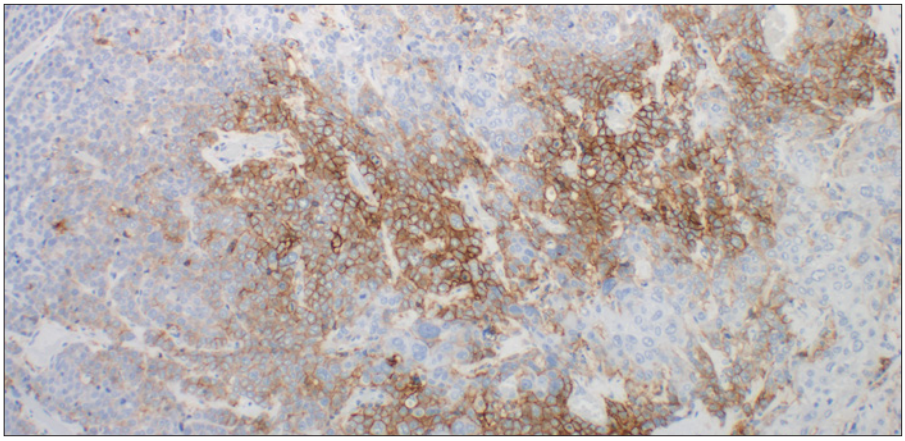


Figure 20b. 20x magnification.

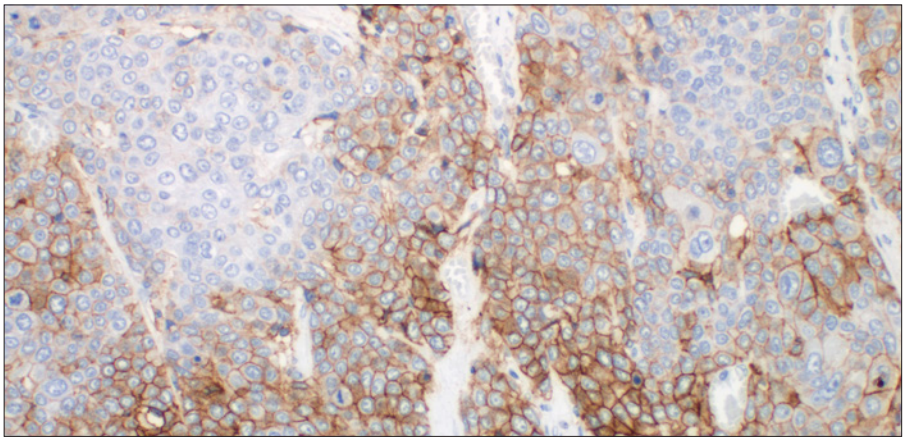
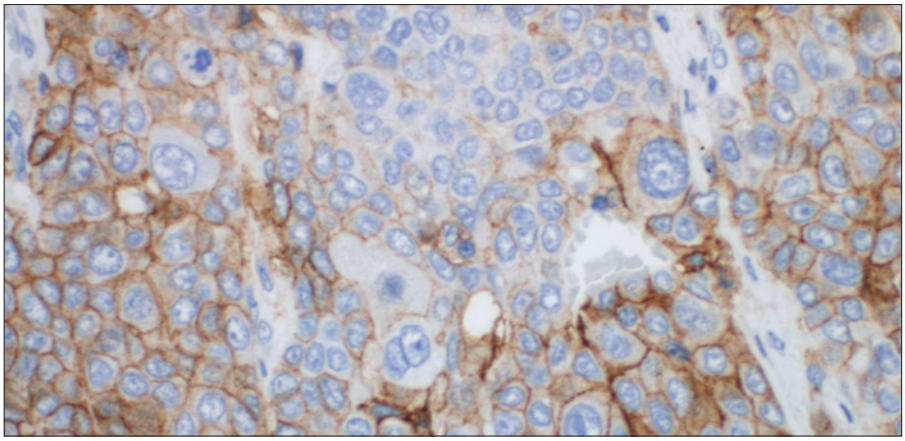


Figure 20c. 40x magnification.



Case 8: PD-L1 expression ≥ 1%

This case example demonstrates partial and complete membrane staining in the tumor cells. This case represents high PD-L1 expression of 95–100%.

Figure 21a. 10x magnification.

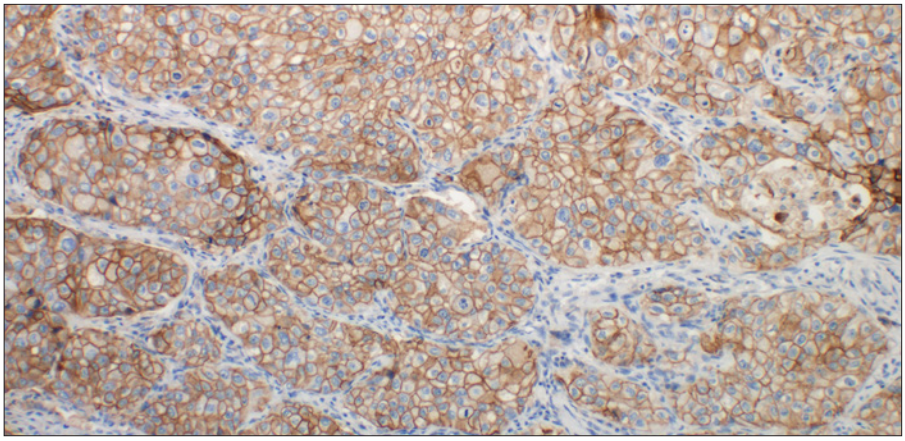


Figure 21b. 20x magnification.

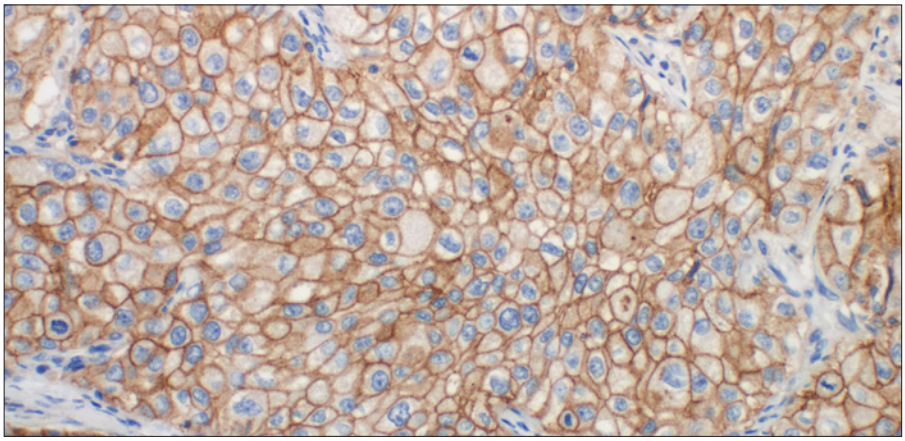
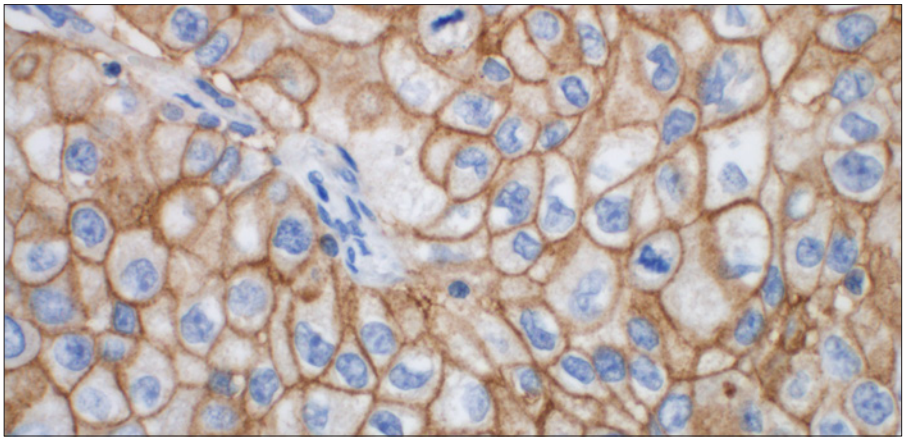


Figure 21c. 40x magnification.



Challenging Cases for NSCLC PD-L1 IHC 28-8 pharmDx

Case 1: PD-L1 expression < 1%

This example shows a high number of PD-L1 positive immune cells staining which is not included in determining the % PD-L1 expression.

Figure 22a. 10x magnification.

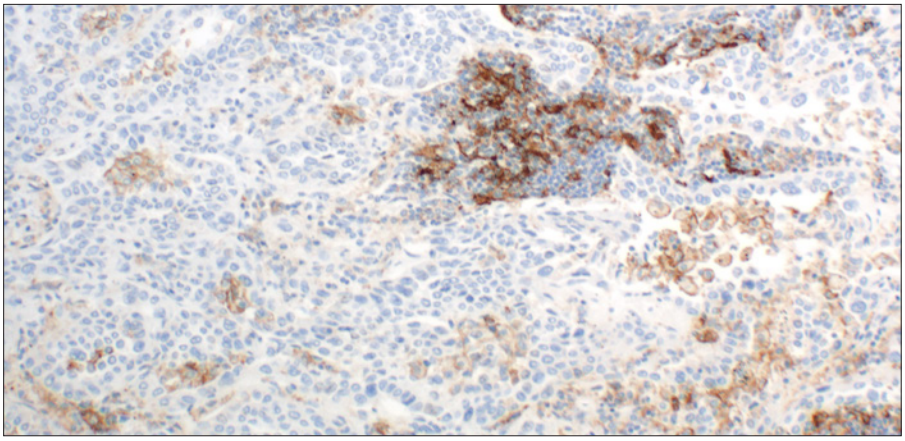


Figure 22b. 20x magnification.

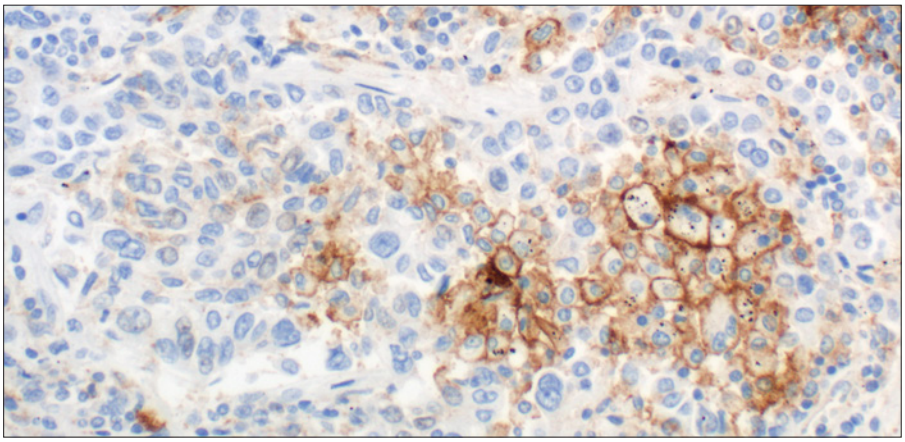
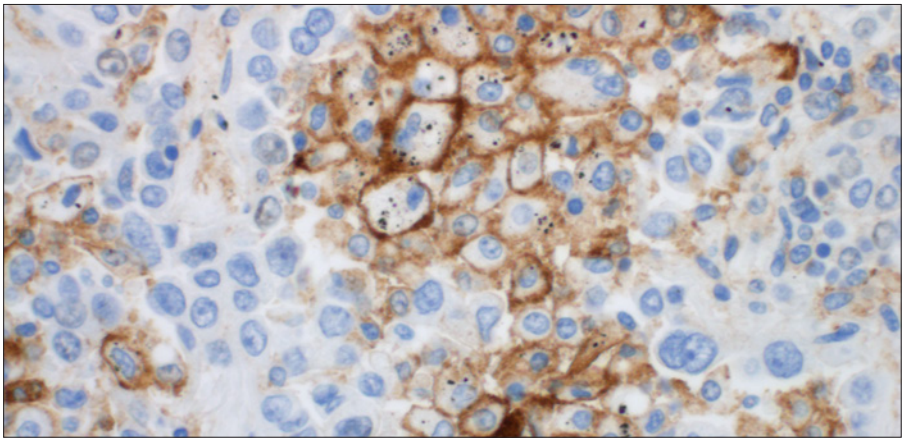


Figure 22c. 40x magnification.



Case 2: PD-L1 expression < 1%

This example shows a few PD-L1 positive tumor cells, which are confirmed at a higher objective (20x, 40x). However, the number of tumor cells staining PD-L1 positive are less than 1% when divided by the total number of viable tumor cells in the entire specimen.

Figure 23a. 10x magnification.

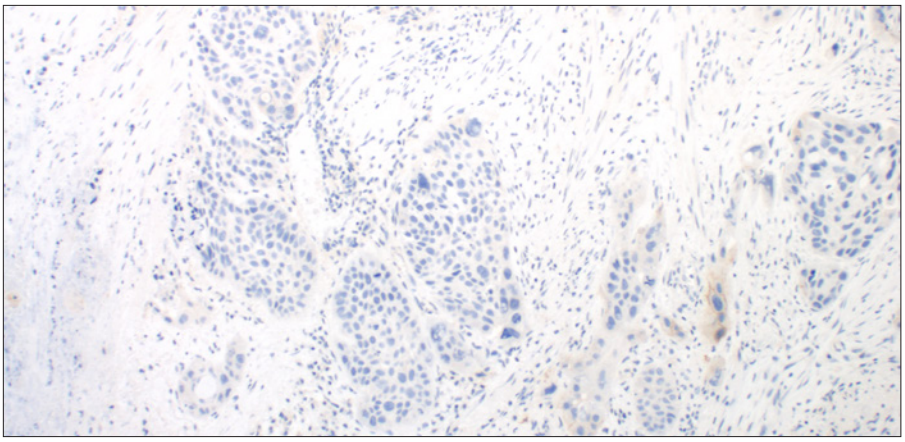


Figure 23b. 20x magnification.

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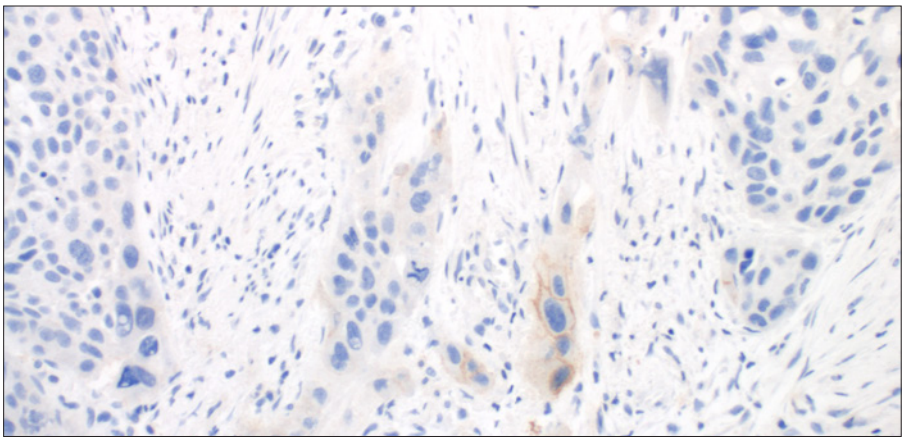
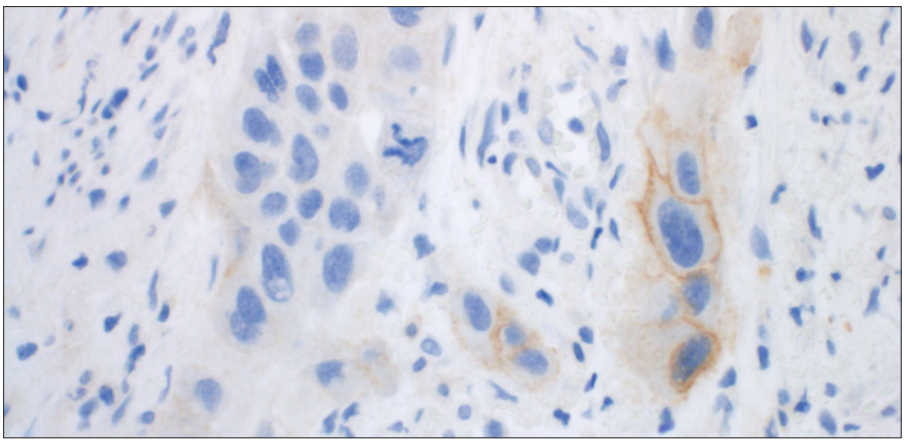


Figure 23c. 40x magnification.



Case 3: PD-L1 expression ≥ 1%

This example shows weak PD-L1 positive tumor cells, which may be missed at a lower objective (4x, 10x) but is confirmed at a higher objective (20x, 40x).

Figure 24a. 10x magnification.

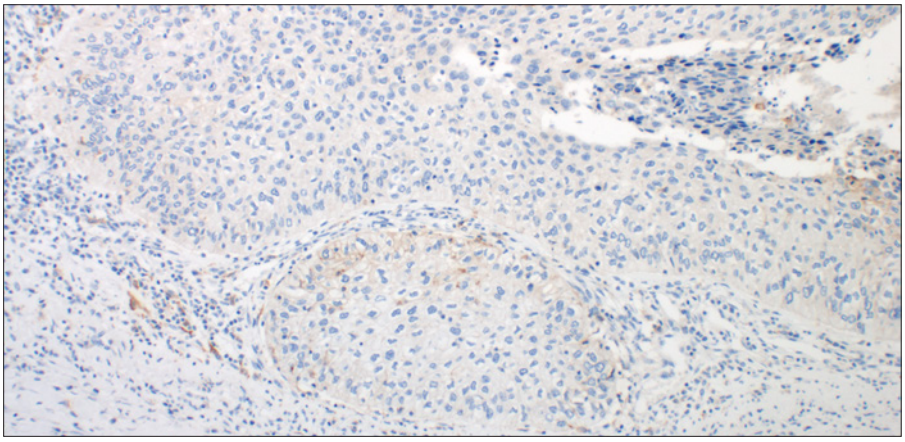


Figure 24b. 20x magnification.

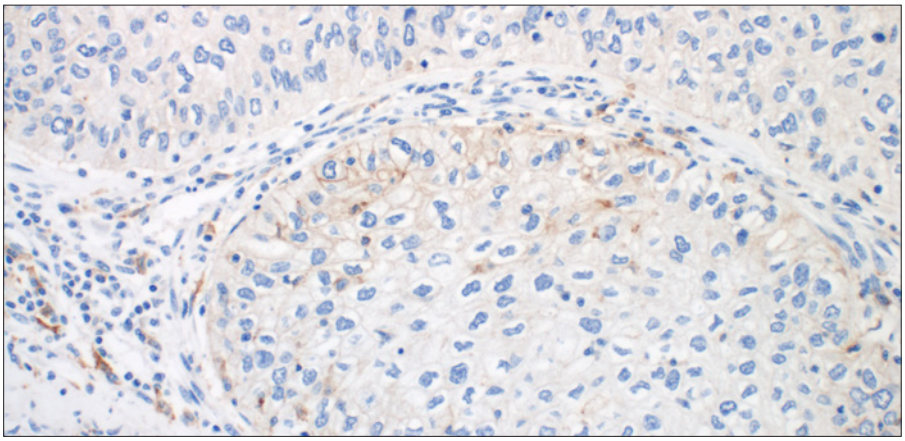
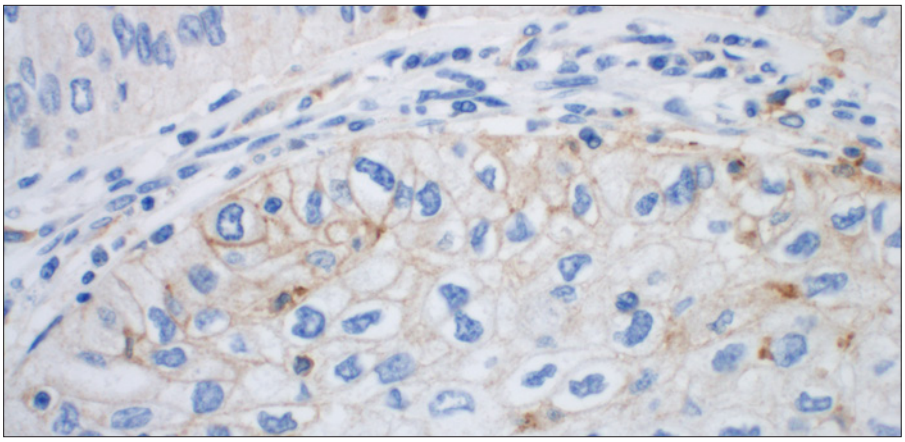


Figure 24c. 40x magnification.



Case 4: PD-L1 expression ≥ 1%

This example shows positive PD-L1 staining in the tumor cells in the presence of non-malignant cells. Reactive fibroblasts must not be mistaken as tumor cells or included in the denominator when determining the % PD-L1 expression. Reference to the H&E may provide assistance when differentiating between reactive fibroblasts and tumor cells as shown on page 43. Note that cytoplasmic staining is also present.

Figure 25a. 10x magnification.

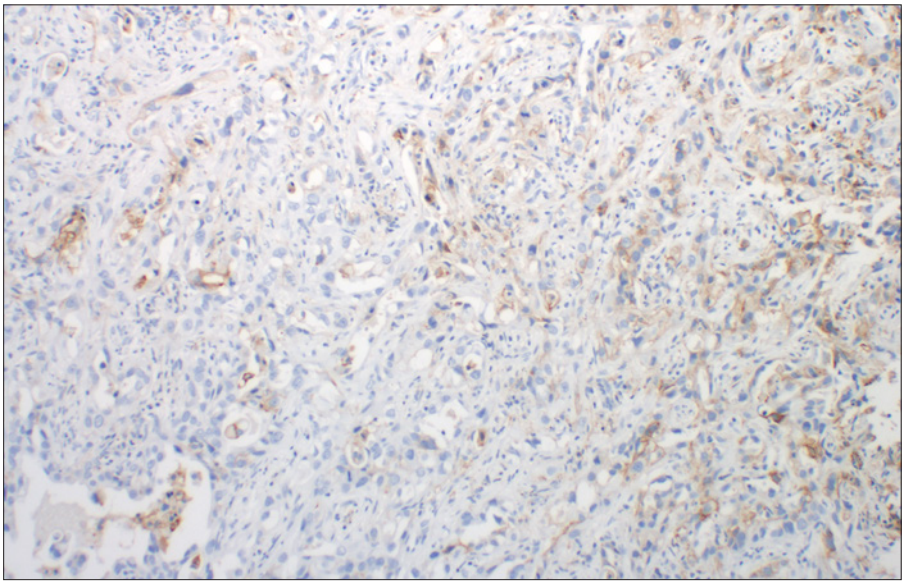
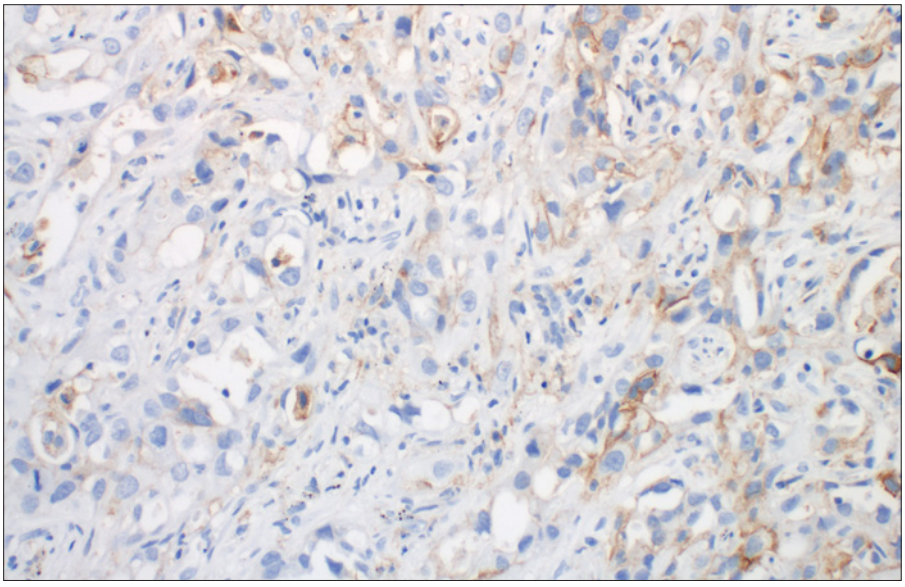


Figure 25b. 20x magnification.



Reactive fibroblasts (**red arrow**) may be mistaken as tumor cells (**black arrow**). Confirmation of cells types must be confirmed in the context of the H&E slide as shown. Reactive fibroblasts can express non-specific staining but must be excluded from scoring. PD-L1 positive and negative staining tumor cells are observed and considered when determining the percent of PD-L1 expression in the tumor cells.

Figure 25c. 40x magnification.

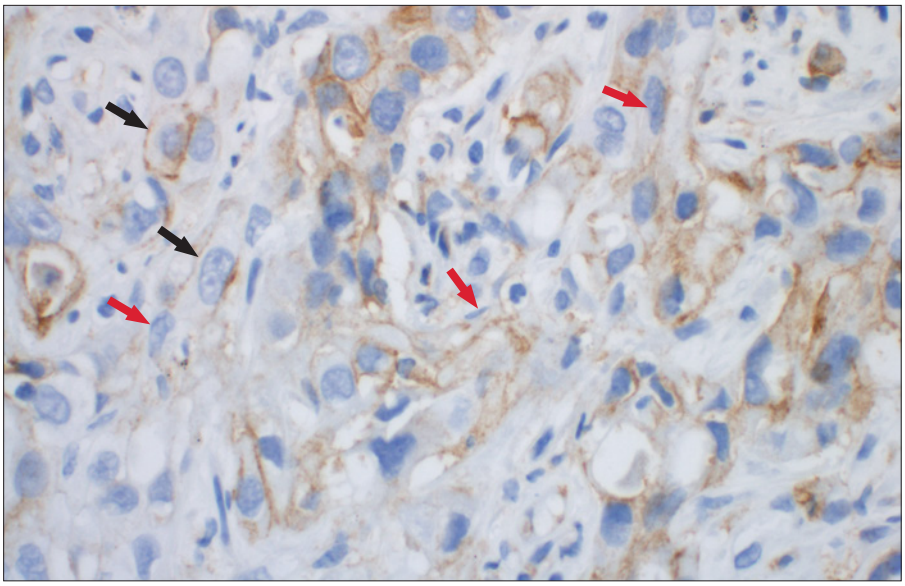
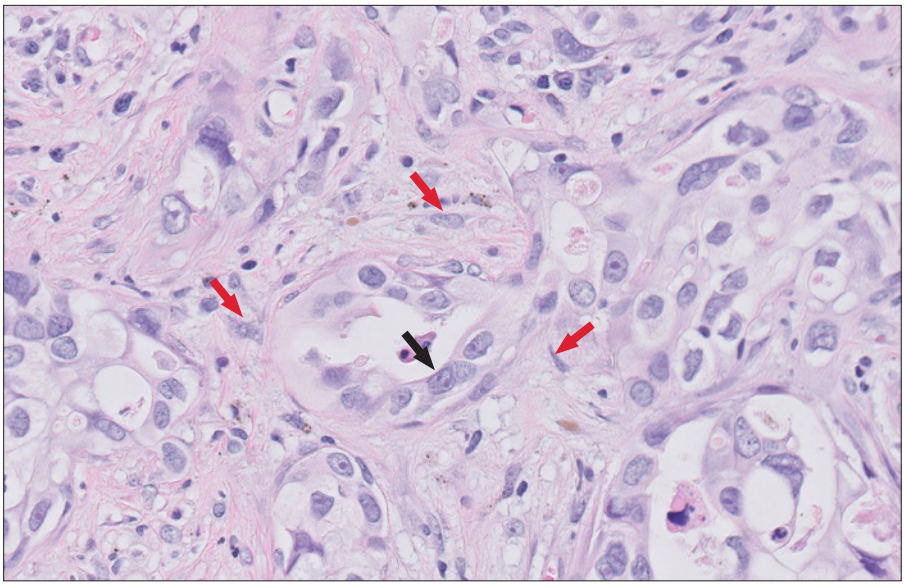


Figure 25d. 40x magnification.



Artifacts

Non-specific Background Staining

Background staining is defined as diffuse, non-specific staining of a specimen. It is caused by several factors. These factors include, but are not limited to, pre-analytic fixation and processing of the specimen, incomplete removal of paraffin from sections, and incomplete rinsing of slides.

The use of fixatives other than 10% neutral buffered formalin may be a source of background staining.

Possible Cause of Background

- Improper drying of slides; ensure slides remain wet with buffer while loading onto Autostainer Link 48 and prior to initiating run
- Improper deparaffinization procedure
- Incomplete rinsing of reagents from slides

The non-specific background staining present on the negative control tissue specimen (NCR) is useful in determining the level of background staining in the same patient tissue specimen stained with PD-L1. All specimens must have ≤ 1+ non-specific background staining.

This NSCLC example may be considered an indeterminate case if the excess cytoplasmic staining hampers scoring. Positive linear membrane staining of the tumor is observed (**black arrow**), however cytoplasmic staining is excessive in much of the specimen (**red arrow**).

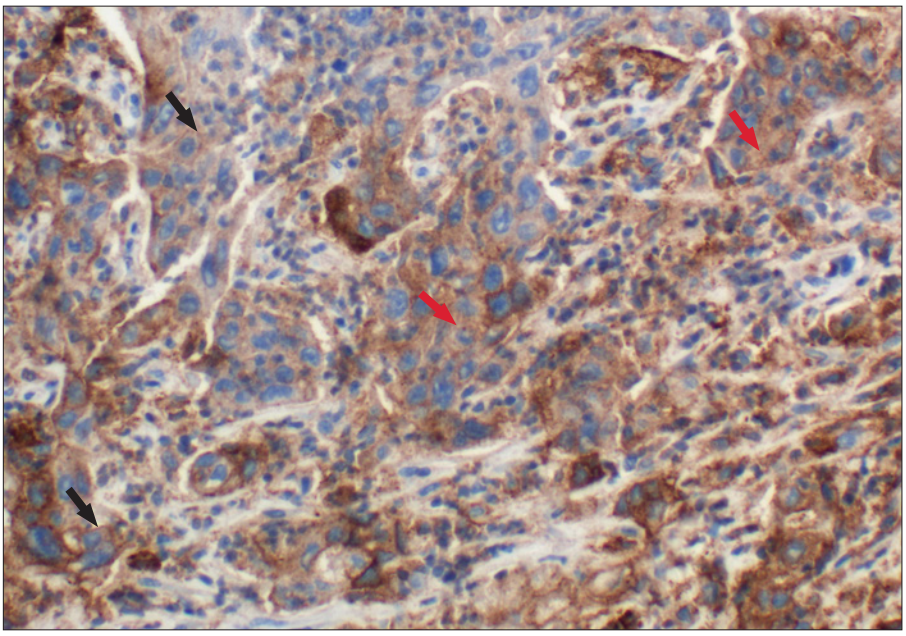


Figure 26. 20x magnification.

Necrosis

Necrotic tissue may show non-specific staining and should not be included in the scoring.
Note: If the specimen is excessively necrotic and contains < 100 viable tumor cells, the specimen is considered not evaluable.

Necrotic tissue may show non-specific staining and should not be included in scoring percent positivity of the tumor. Care should be taken to the only include viable tumor cells for scoring and not necrotic regions.

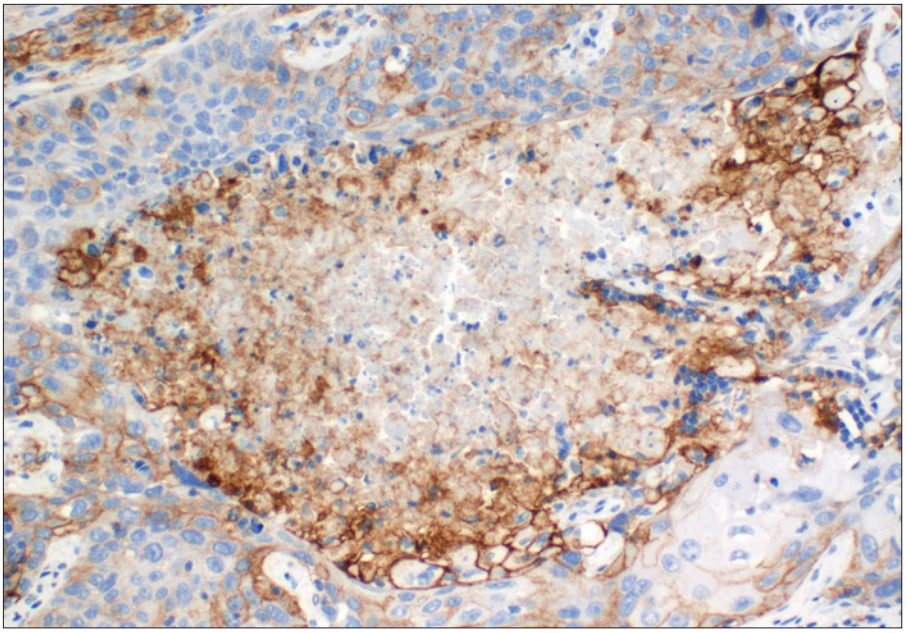


Figure 27. 20x magnification.

Troubleshooting Guide for PD-L1 IHC 28-8 pharmDx

Problem	Probable Cause	Suggested Action
1. No staining of control or specimen slides.	1a. Programming error.	1a. Verify that the SK005 PD-L1 IHC 28-8 pharmDx program was selected for programming of slides.
	1b. Lack of reaction with DAB+ Substrate - Chromogen Solution. (DAB).	1b. Verify that DAB+ Substrate-Chromogen Solution was prepared properly.
	1c. Sodium azide in wash buffer.	1c. Use only Dako Wash Buffer, Code K8007.
	1d. Degradation of Control Slide.	1d. Check kit expiration date and kit storage conditions on outside of package.
2. Weak staining of specimen slides.	2a. Inappropriate fixation method used.	2a. Ensure that only neutral buffered formalin fixative and approved fixation methods are used.
	2b. Insufficient reagent volume applied.	2b. Check size of tissue section and reagent volume applied.
	2c. Inappropriate wash buffer used.	2c. Use only Dako Wash Buffer, Code K8007.
3. Weak staining of specimen slides or the positive cell line on the Dako-supplied Control Slide.	3a. Inadequate target retrieval.	3a. Verify that the 3-in-1 pre-treatment procedure was correctly performed.
	3b. Inappropriate wash buffer used.	3b. Use only Dako Wash Buffer, Code K8007.
4. Excessive background staining of slides.	4a. Paraffin incompletely removed.	4a. Verify that the 3-in-1 pre-treatment procedure was correctly performed.
	4b. Slides dried while loading onto the Autostainer Link 48.	4b. Ensure slides remain wet with buffer while loading and prior to initiating run.
	4c. Non-specific binding of reagents to tissue section.	4c. Check for proper fixation of the specimen and/or the presence of necrosis.
	4d. Inappropriate fixation method used.	4d. Ensure that only neutral buffered formalin fixative and approved fixation methods are used.
5. Tissue detached from slides.	5a. Use of incorrect microscope slides.	5a. Use Dako FLEX IHC Microscope Slides, (Code K8020), or Fisherbrand Superfrost Plus slides.
	5b. Inadequate preparation of specimens.	5b. Cut sections should be placed in a 58 ± 2 °C oven for 1 hour prior to staining.
6. Excessively strong specific staining.	6a. Inappropriate fixation method used.	6a. Ensure that only approved fixatives and fixation methods are used.
	6b. Inappropriate fixation method used.	6b. Use only Dako Wash Buffer, Code K8007.
7. Excessively strong specific staining.	7. When heated the Target Retrieval Solution turns cloudy in appearance.	7. This is normal and does not influence staining.

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