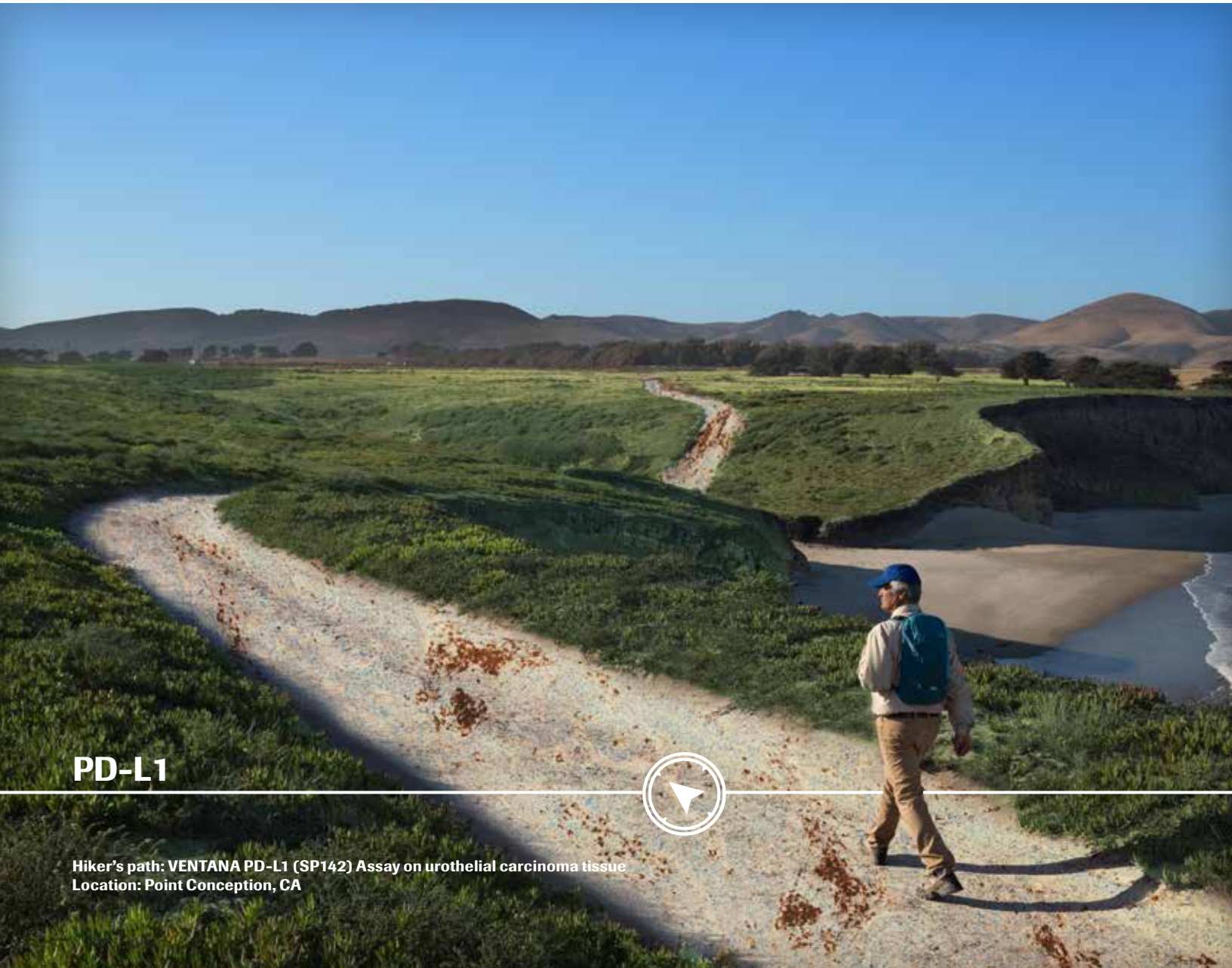
VENTANA PD-L1 (SP142) Assay

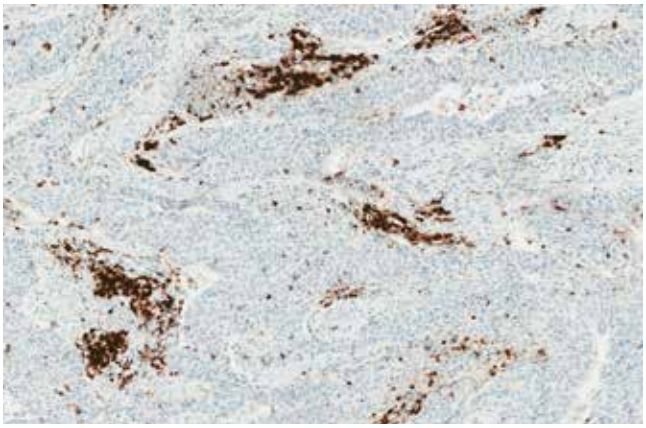
Guiding immunotherapy



Hiker's path: VENTANA PD-L1 (SP142) Assay on urothelial carcinoma tissue
Location: Point Conception, CA

VENTANA PD-L1 (SP142) Assay

Assess UC patient benefit from TECENTRIQ®



Positive UC tissue stained with PD-L1 (SP142) assay, 10x

Intended use statement

VENTANA PD-L1 (SP142) Assay is a qualitative immunohistochemical assay using rabbit monoclonal anti-PD-L1 clone SP142 intended for use in the assessment of the PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) urothelial carcinoma tissue stained with OptiView DAB IHC Detection Kit and OptiView Amplification Kit on a VENTANA BenchMark ULTRA instrument. PD-L1 status is determined by the proportion of tumor area occupied by PD-L1 expressing tumor-infiltrating immune cells (% IC) of any intensity.

PD-L1 expression in ≥ 5 % IC determined by VENTANA PD-L1 (SP142) Assay in urothelial carcinoma tissue is associated with increased objective response rate (ORR) in a non-randomized study of TECENTRIQ® (atezolizumab).

This product is intended for *in vitro* diagnostic (IVD) use.

PD-L1 diagnostic confidence

Using the right test to determine PD-L1 status for immunotherapy options is important, and the VENTANA PD-L1 (SP142) Assay is the only Health Canada approved test for TECENTRIQ® in urothelial carcinoma (UC) patients. This novel assay is also the first to evaluate patient PD-L1 expression using immune cell staining and scoring within the tumor microenvironment, providing you with information that can guide immunotherapy decisions.
Determining a patient's PD-L1 expression level can give insight to the objective response rate (ORR) that may be achieved from TECENTRIQ®*.

The VENTANA PD-L1 (SP142) Assay:

- Health Canada approved to assess UC patient treatment benefit from TECENTRIQ®
- Informative for the clinician of a patient's potential objective response rate (ORR)
- Designed to enhance visual contrast of immune cell staining within the tumor microenvironment
- Stains PD-L1 in both tumor cells (TC) and tumor-infiltrating immune cells (IC)

The PD-L1 (SP142) Assay gives you the confidence to guide immunotherapy decisions in UC.

**All patients in the study observed benefit from TECENTRIQ® regardless of PD-L1 status*

Rabbit
Monoclonal
IHC antibody developed by Spring Bioscience

Fully
Automated
With specific and robust signal

Highly
Reproducible
Accurate scoring and educational resources

About PD-L1

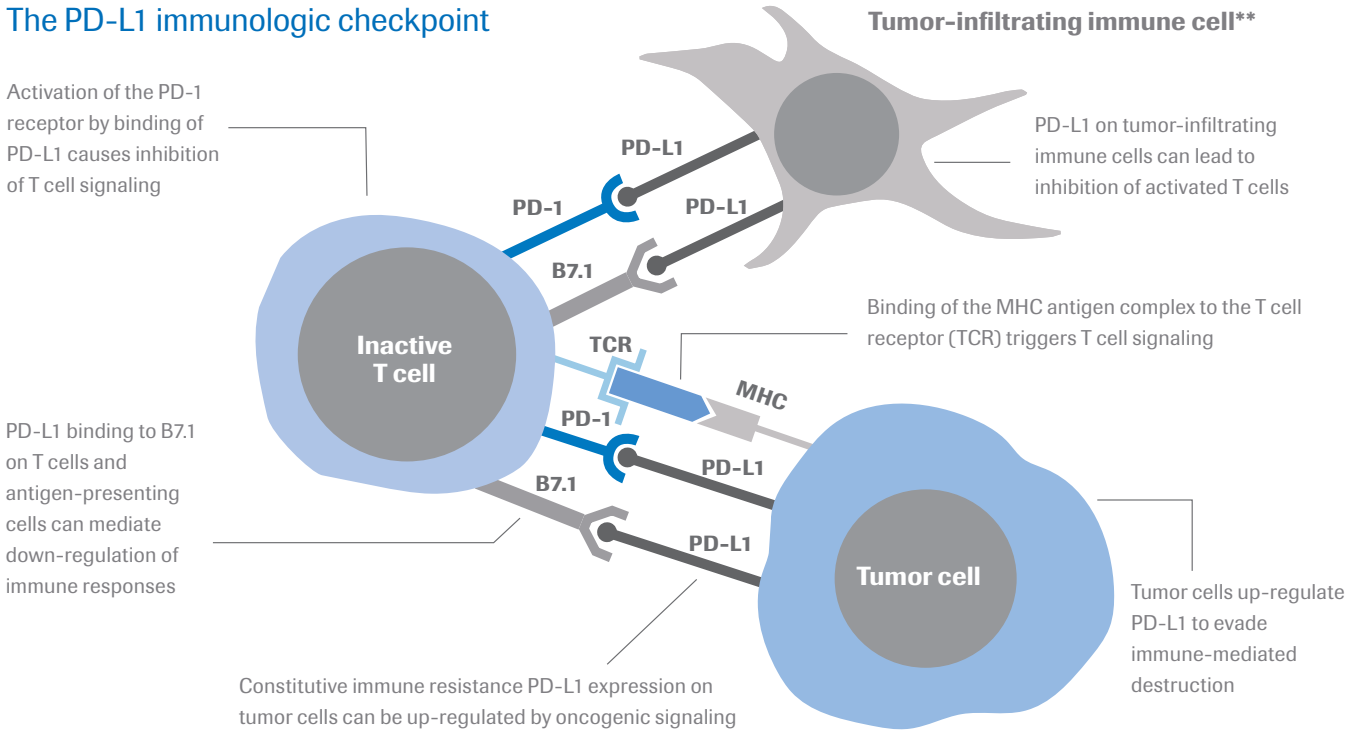
PD-L1 is a transmembrane protein that down-regulates immune responses through binding to its two inhibitory receptors, programmed death-1 (PD-1) and B7.1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, which is sustained in states of chronic stimulation such as in chronic infection or cancer[1]. Ligation of PD-L1 with PD-1 inhibits T cell proliferation, cytokine production and cytolytic activity, leading to the functional inactivation or exhaustion of T cells. B7.1 is a molecule expressed on antigen presenting cells and activated T cells. PD-L1 binding to B7.1 on T cells and antigen presenting cells can mediate down-regulation of immune responses, including inhibition of T-cell activation and cytokine production[2]. PD-L1 expression has been observed in immune cells and tumor cells[3,4]. Aberrant expression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion[1]. Therefore, interruption of the PD-L1 / PD-1 pathway represents an attractive strategy to reinvigorate tumor-specific T cell immunity suppressed by the expression of PD-L1 in the tumor microenvironment.

PD-L1 in urothelial carcinoma

Urothelial carcinoma (also known as urothelial cell carcinoma, transitional cell carcinoma of the urinary tract, or urothelial bladder cancer) is the most common cancer of the urinary system worldwide. The majority of urothelial tumors arise in the bladder with the remainder originating in the renal pelvis, urethra or ureter. Transitional cell carcinoma (TCC) is the most common histologic subtype associated with bladder cancer and accounts for greater than 90 % of all urothelial carcinoma cases in the industrialized world. Non-urothelial subtypes (e.g. squamous cell, adenocarcinoma, small cell carcinoma) are more frequent in other areas of the world[5].

Elevated PD-L1 expression on tumor cells has been associated with a poor prognosis in patients with urothelial carcinoma[6]. PD-L1 is widely expressed in tumor cells and tumor-infiltrating mononuclear cells (TIMCs) and PD-L1 expression in TIMCs appears to be associated with longer survival in patients who developed metastases[7]. The association between PD-L1 expression in tumor cells or tumor-infiltrating immune cells and clinical benefit with PD-L1 / PD-1 pathway inhibitors has been reported in clinical trials[8,4,9,11]. Furthermore, targeting the PD-L1 pathway, based on IC expression, has demonstrated activity in patients with advanced urothelial carcinoma who have failed or refused standard-of-care therapies[10].

The PD-L1 immunologic checkpoint

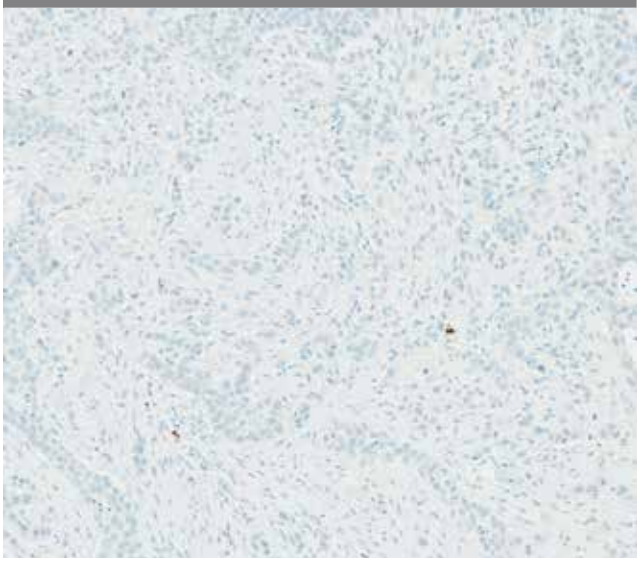


VENTANA PD-L1 (SP142) Assay staining in immune cells

The PD-L1 (SP142) Assay has been designed to stain and visualize PD-L1 protein on tumor-infiltrating immune cells. The assay is robust and specific across a range of PD-L1 expression levels and provides a strong staining signal through amplification.

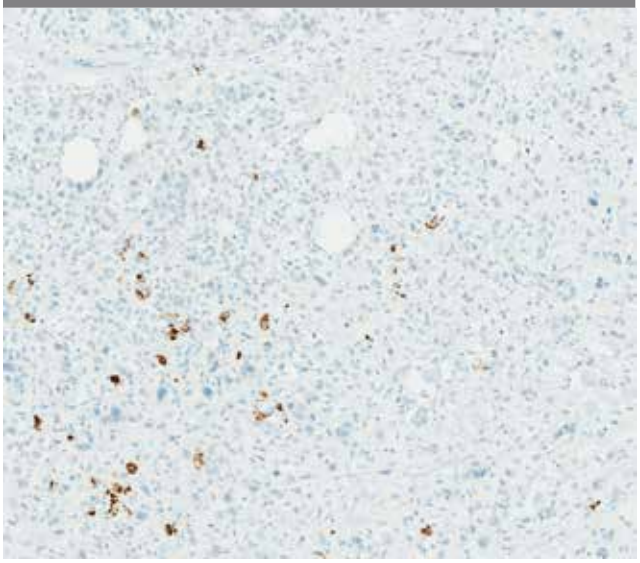
Examples of PD-L1 IC staining and score

% IC Staining is < 1 %



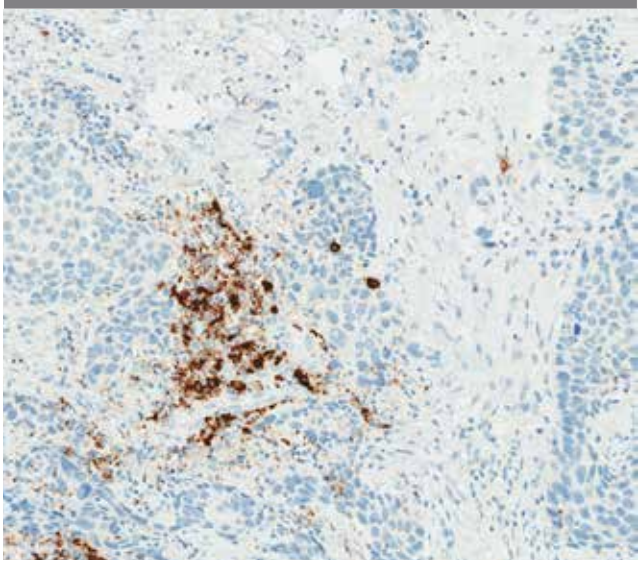
Low expression in urothelial carcinoma tissue, 10x

% IC Staining is ≥ 1 % and < 5 %



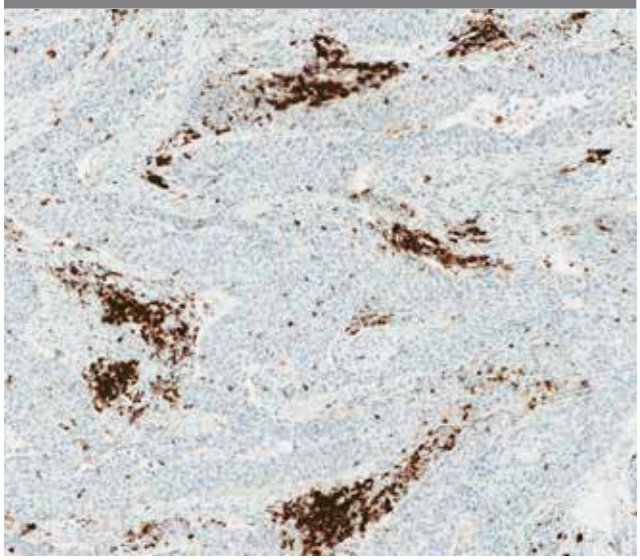
Low expression in urothelial carcinoma tissue, 10x

% IC Staining is ≥ 5 % and < 10 %



High expression in urothelial carcinoma tissue, 10x

% IC Staining is ≥ 10 %



High expression in urothelial carcinoma tissue, 10x

PD-L1 scoring algorithm for urothelial carcinoma

Tumor-infiltrating immune cell staining assessment	PD-L1 expression
Absence of any discernible PD-L1 staining -or- Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering < 5% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peritumoral stroma	< 5%
Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering ≥ 5% of tumor area occupied by tumor cells, associated intratumoral and contiguous peritumoral stroma	≥ 5%

PD-L1 clinical relevance in urothelial carcinoma

Response rates

PD-L1 expression	ORR*
< 5%	9.5%
≥ 5%	26.0%

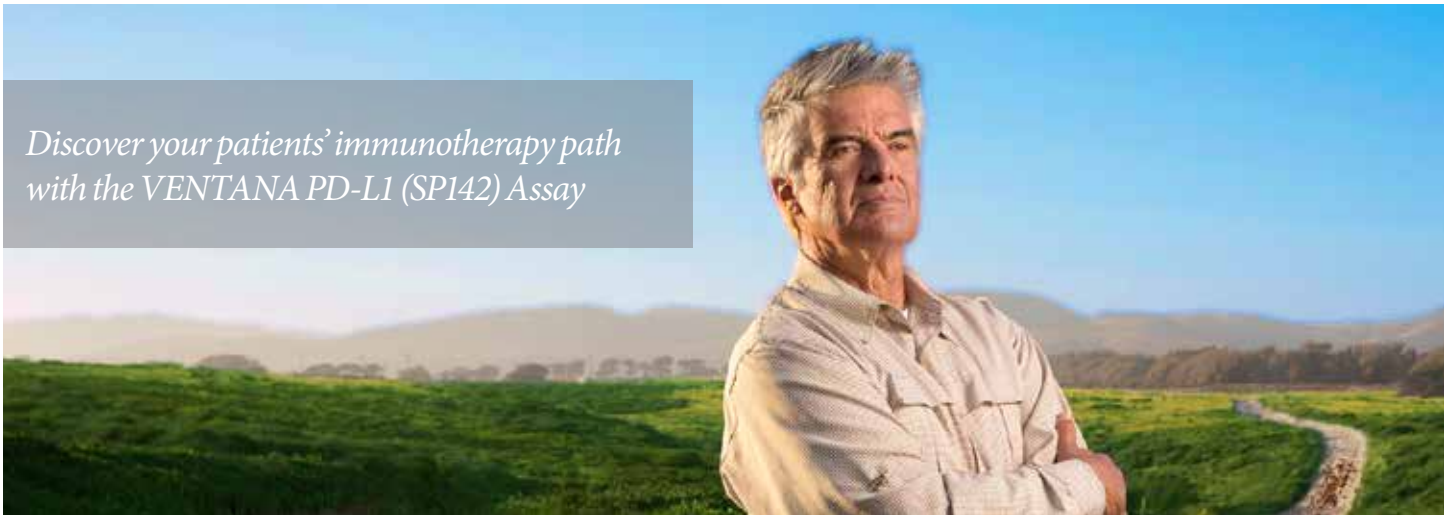
Prevalence

PD-L1 expression	Population
< 5%	68%
≥ 5%	32%

Outcomes and prevalence data based on IMvigor 210 (n = 311)

- PD-L1 expression was determined using the VENTANA PD-L1 (SP142) Assay
- PD-L1 expression in ≥ 5% of IC was associated with higher response rates, however levels of PD-L1 expression in < 5% of IC did not preclude response
- Trial was an open-label, multicenter, single-arm phase II study that evaluated the safety and efficacy of TECENTRIQ® in people with locally advanced or mUC, regardless of PD-L1 expression
- ClinicalTrials.gov number NCT02108652

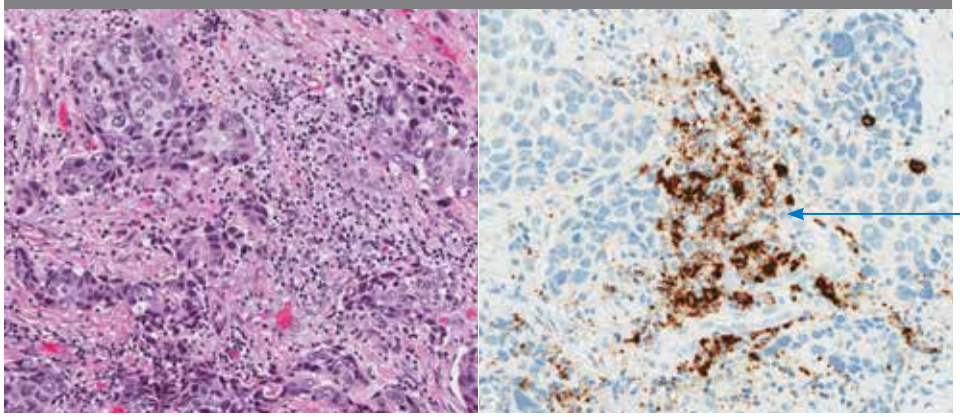
** ORR - Objective response rate defined as a proportion of patients with reduction in tumor burden of a pre-defined amount*



PD-L1 expression in the tumor microenvironment

The PD-L1 (SP142) Assay stain highlights a heterogeneous population of immune cells. The majority of these cells are morphologically consistent with lymphocytes, macrophages, dendritic cells and granulocytes. Immune cell staining can be observed as aggregates in intratumoral or contiguous peritumoral stroma as single cell spread among tumor cells, or in association with tumor cell staining.

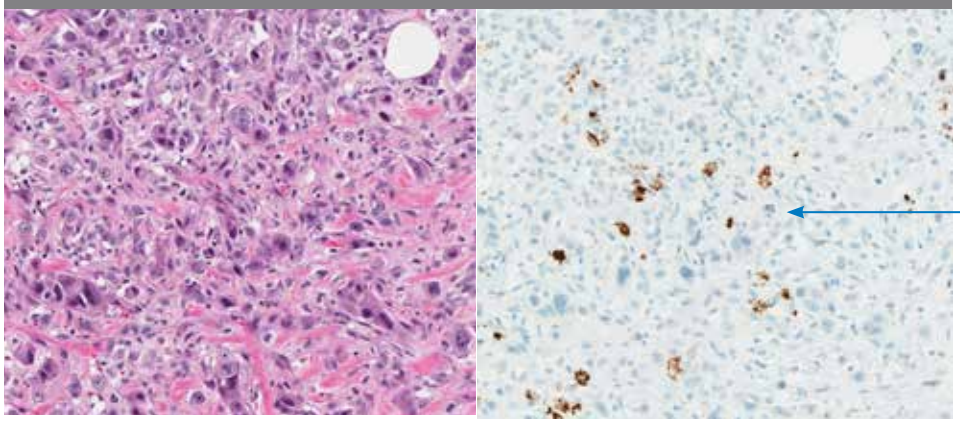
Often observed as aggregates in the intra- or peritumoral stroma



Punctate IC staining in the intratumoral stroma

Urothelial carcinoma tissue, 10x

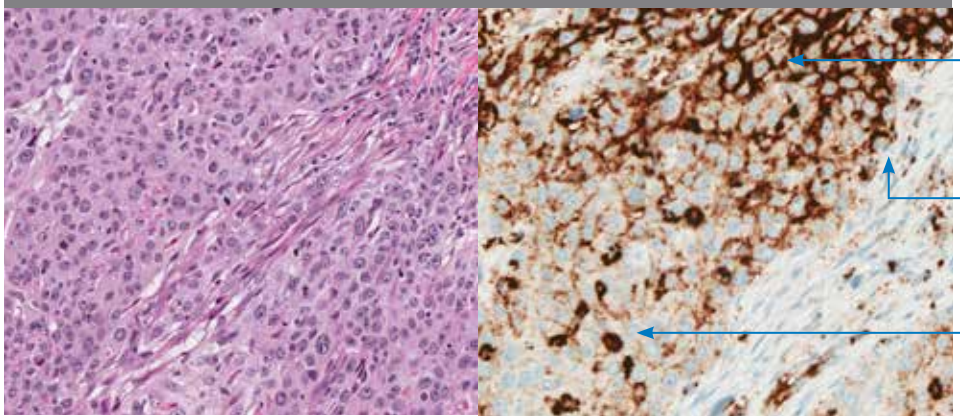
Occasionally observed as single-cell spread (diffuse) among tumor cells with or without aggregates



IC single-cell spread

Urothelial carcinoma tissue, 10x

Staining occasionally observed in TC and IC simultaneously



*Strong TC staining**

IC aggregate in the stroma

IC single-cell spread

Urothelial carcinoma tissue, 10x

**TC staining not used to assess the status of this assay in UC*

PD-L1 assay performance

Inter-laboratory reproducibility	Positive agreement % (95% CI)*	Negative agreement % (95% CI)	Overall agreement % (95% CI)
Overall average agreement (across sites, days and readers)	98.3% (96.6-99.2%)	87.4% (83.8-90.2%)	92.8% (90.9-94.4%)
Between-reader agreement (average of all sites, two readers / site)	89.3% (78.1-96.0%)	86.6% (75.1-94.6%)	88.1% (84.6-90.8%)

Reader precision	Positive agreement % (95% CI)	Negative agreement % (95% CI)	Overall agreement % (95% CI)
Inter-reader precision (average of all three readers' comparisons)	92.6% (84.7-96.6%)	87.4% (83.8-90.2%)	92.8% (90.9-94.4%)
Intra-reader precision (average of all three readers' agreement rates between first and second reads)	89.3% (77.6-95.3%)	86.6% (75.1-94.6%)	88.1% (84.6-90.8%)

** CI- confidence interval*

VENTANA PD-L1 (SP142) Assay			OptiView DAB IHC Detection Kit		OptiView Amplification Kit	
Catalog number	**740-4859**	07709374001	**760-700**	06396500001	**860-099**	06718663001
Quantity	50 tests		250 tests		250 tests	
Positive control	Tonsil					
Species	Rabbit					
Localization	Membranous and / or Cytoplasmic					

References

1. Blank, C and Mackensen, A, Contribution of the PD-L1 / PD-1 pathway to T-cell exhaustion: an update on implications for chronic infections and tumor evasion. Cancer Immunol Immunother, 2007. 56(5): p. 739-745.
2. Butte MJ, Keir ME, Phamduy TB, et al. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity. 2007;27(1):111-122.
3. Dong H, Zhu G, Tamada K, Chen L. B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion. Nat Med. 1999;5(12):1365-1369.
4. Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. 2014;515(7528):563-567.
5. Chalasani V, Chin JL, Izawa JI. Histologic variants of urothelial bladder cancer and nonurothelial histology in bladder cancer. Can Urol Assoc J. 2009;3(6 Suppl 4):S193-198.
6. Nakanishi J, Wada Y, Matsumoto K, et al. Overexpression of B7-H1 (PD-L1) significantly associates with tumor grade and postoperative prognosis in human urothelial cancers. Cancer Immunol Immunother. 2007;56(8):1173-1182.
7. Bellmunt, J, Mullane, SA, Werner, L, et al., Association of PD-L1 expression on tumor-infiltrating mononuclear cells and overall survival in patients with urothelial carcinoma. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO, 2015. 26(4): p. 812-817.
1. Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol. 2010;28(19):3167-3175.
2. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366(26):2443-2454.
3. Powles T, Eder JP, Fine GD, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature. 2014;515(7528):558-562.
4. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. The Lancet. 2016. Web.

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