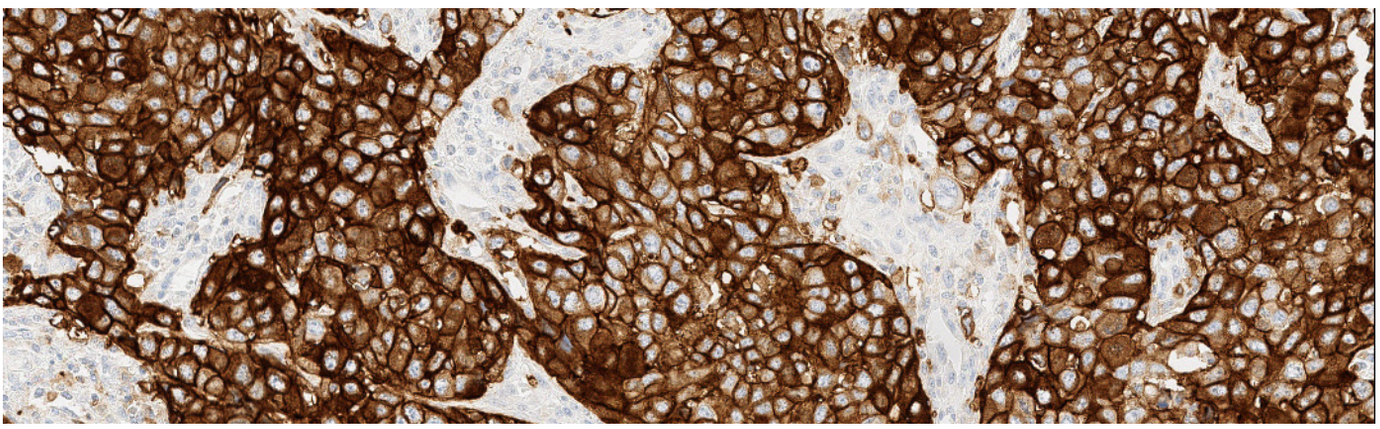
VENTANA PD-L1 (SP263) Assay

Guiding immunotherapy for urothelial carcinoma

Hiker's path: VENTANA PD-L1 (SP263) Assay on urothelial carcinoma tissue
Location: Rancho San Fernando Rey, CA

VENTANA PD-L1 (SP263) Assay

The only FDA approved test to predict a urothelial carcinoma patient's response to IMFINZI™ (durvalumab)



VENTANA PD-L1 (SP263) Assay staining in urothelial carcinoma (UC) with membranous and cytoplasmic staining of the tumor cells, and immune cell staining within the stroma

Intended use statement

VENTANA PD-L1 (SP263) Assay is a qualitative immunohistochemical assay using rabbit monoclonal anti-PD-L1 clone SP263 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 on a VENTANA BenchMark ULTRA instrument.

PD-L1 status is determined by the percentage of tumor cells with any membrane staining above background or by the percentage of tumor-associated immune cells with staining (IC+) at any intensity above background. The percent of tumor area occupied by any tumor-associated immune cells (Immune Cells Present, ICP) is used to determine IC+, which is the percent area of ICP exhibiting PD-L1 positive immune cell staining. PD-L1 status is considered High if any of the following are met:

- ≥ 25% of tumor cells exhibit membrane staining; or,
- ICP > 1% and IC+ ≥ 25%; or,
- ICP = 1% and IC+ = 100%

PD-L1 High status as determined by VENTANA PD-L1 (SP263) Assay was associated with increased objective response rate (ORR) in a single arm study of IMFINZI (durvalumab).

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

Empowering pathologists to answer PD-L1 questions

Using an approved assay to determine PD-L1 status for immunotherapy options is important. VENTANA PD-L1 (SP263) Assay equips pathologists by

- Identifying urothelial carcinoma patients most likely to benefit from IMFINZI (durvalumab)
- Providing robust PD-L1 staining in both tumor cells (TC) and tumor-infiltrating immune cells (IC)

Full automation

Reproducible staining

Standardization

In-house testing

Efficient workflow

Rapid results

Training

Precision scoring

Confidence

About PD-L1

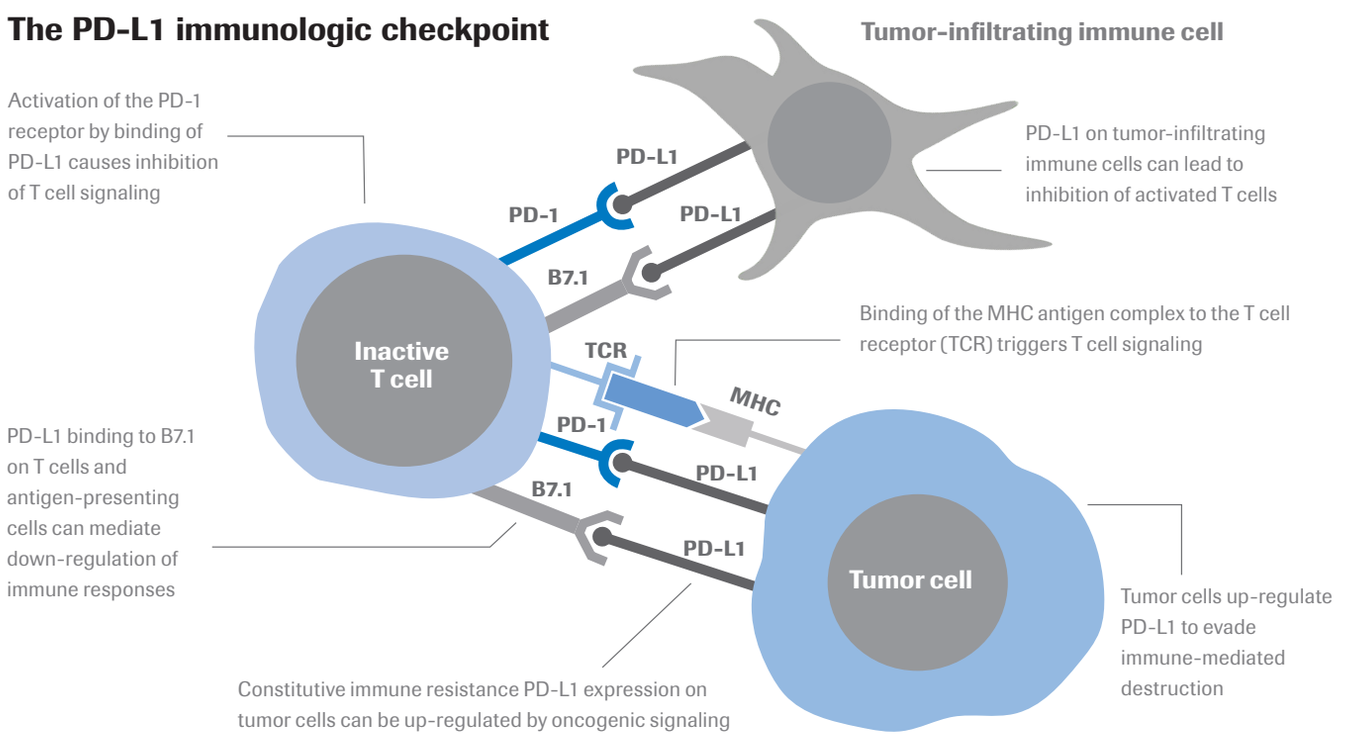
PD-L1 is a transmembrane protein that down-regulates immune responses through binding to its two receptors, programmed death-1 (PD-1) and B7.1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, which is sustained in states of chronic stimulation such as in chronic infection or cancer.[1] Binding 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 and tumor-associated immune cells has been reported to impede anti-tumor immunity, resulting in immune evasion.[1,4] 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.

About urothelial carcinoma

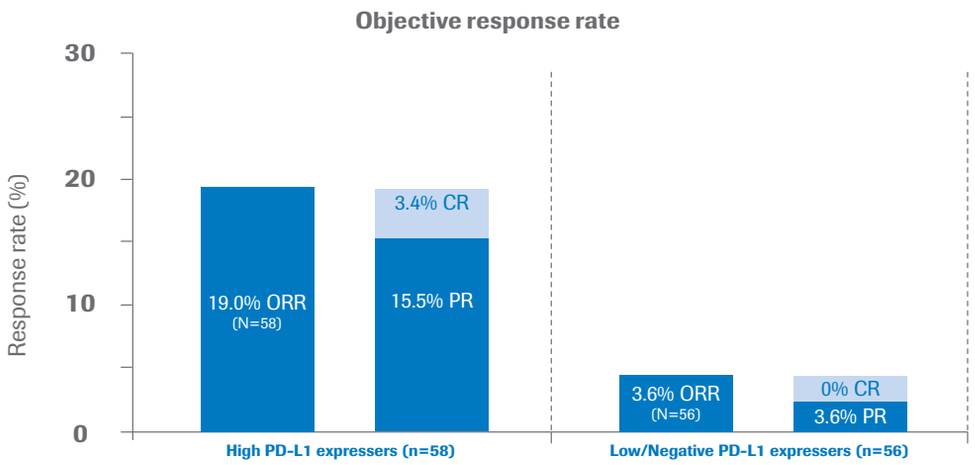
Urothelial carcinoma (also known as urothelial cell carcinoma, transitional cell carcinoma of the urinary tract or urothelial bladder cancer) is the most common cancer of the urinary system worldwide. The majority of urothelial tumors arise in the bladder with the remainder originating in the renal pelvis, 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 (eg, squamous cell, adenocarcinoma, small cell carcinoma) are more frequent in other areas of the world.[5]

The PD-L1 immunologic checkpoint



PD-L1 clinical outcome study

The efficacy of IMFINZI (durvalumab) was evaluated in a multicenter, multi-cohort, open-label clinical trial, Study 1. Tumor specimens were evaluated for PD-L1 expression on tumor cells (TC) and immune cells (IC) using the VENTANA PD-L1 (SP263) Assay.



ORR = objective response rate CR =complete response PR = partial response

ORR determined binded independent central review (BICR) of target lesion diameter according to RECIST criteria.

45% of patients were high expressers of PD-L1

- Of the 128 patients, 58 were classified as PD-L1 high (TC ≥ 25% or IC+ ≥ 25%), 56 as PD-L1 low/negative (TC < 25% and IC+ < 25%) and samples for 14 patients were inadequate for evaluation.
- PD-L1 high expression in patients with urothelial carcinoma was associated with numerically increased ORR.

VENTANA PD-L1 (SP263) Assay staining

The cellular staining pattern for VENTANA PD-L1 (SP263) Assay is membranous and/or cytoplasmic staining of tumor cells. Immune cells demonstrate linear membrane, diffuse cytoplasmic and/or punctate staining. With exceptional sensitivity and specificity, the assay is able to detect PD-L1 protein and provide excellent visualization.

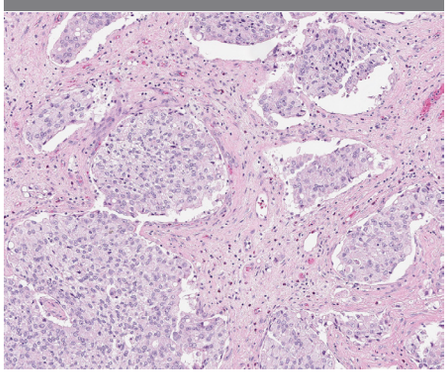
PD-L1 staining patterns and intensities

Urothelial carcinoma cases stained with the VENTANA PD-L1 (SP263) Assay are assessed for both the percentage of tumor cells with membrane staining and the percentage of tumor-associated immune cells with membrane, cytoplasm or punctate staining.

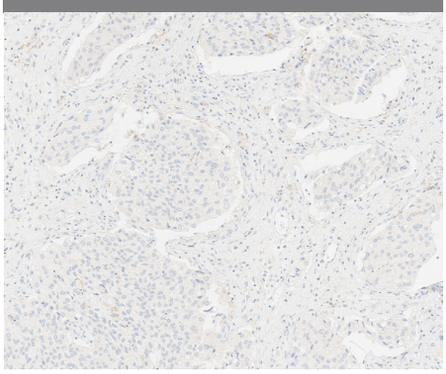
H&E, PD-L1 tumor cell (TC) and immune cell (IC) staining

PD-L1 Low/Negative

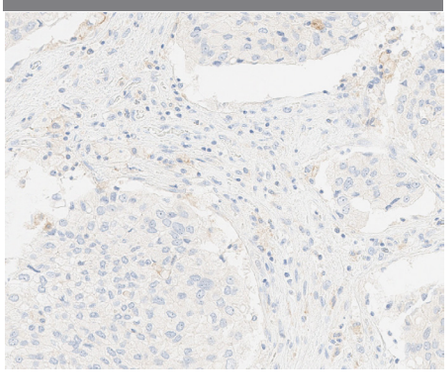
Case A H&E stain 10x



TC- 0% IC- 0% Status < 25% 10x

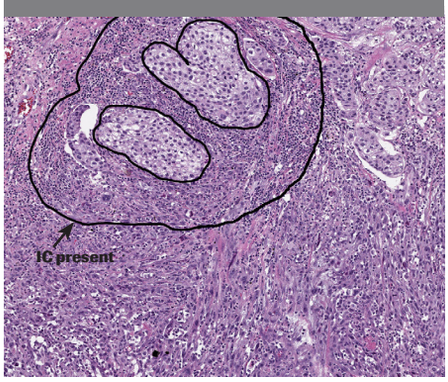


TC- 0% IC- 0% Status < 25% 20x

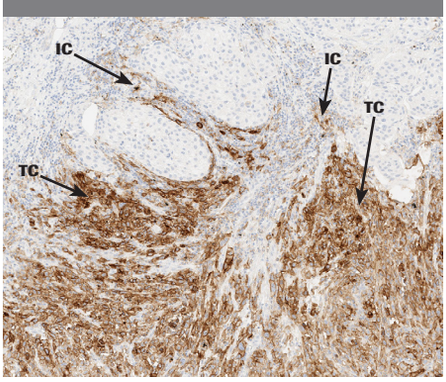


PD-L1 High

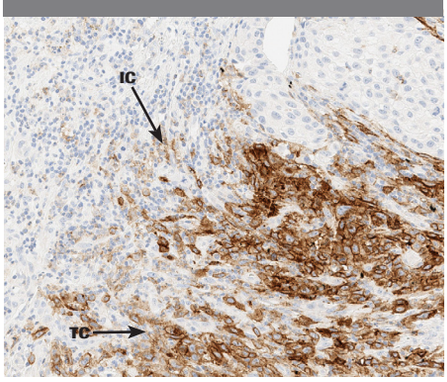
Case B H&E stain 10x



TC+ 100% IC+ 25% Status ≥ 25% 10x

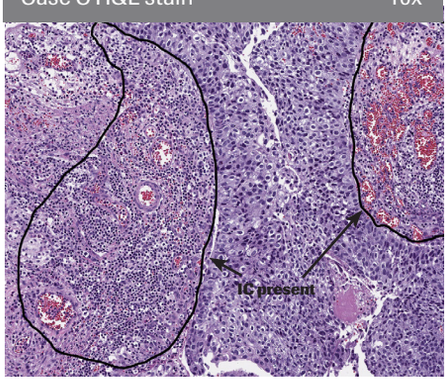


TC+ 100% IC+ 25% Status ≥ 25% 20x

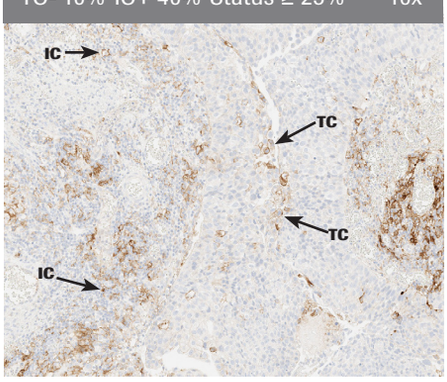


PD-L1 High

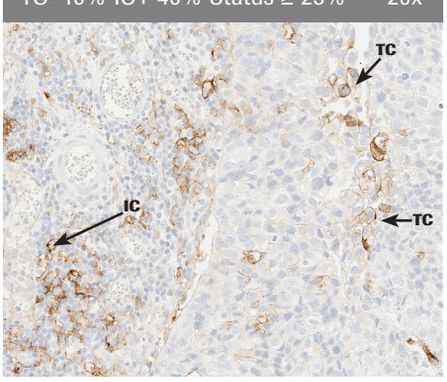
Case C H&E stain 10x



TC- 10% IC+ 40% Status ≥ 25% 10x

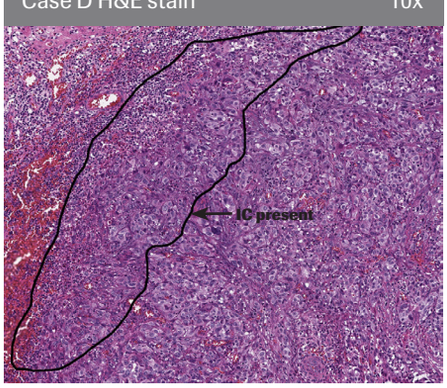


TC- 10% IC+ 40% Status ≥ 25% 20x

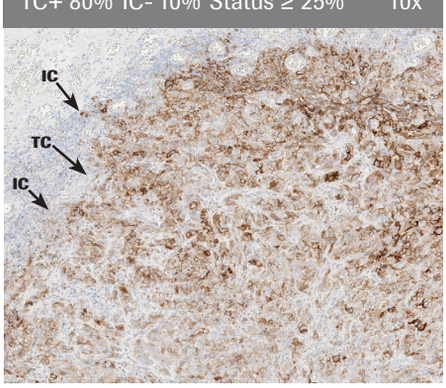


PD-L1 High

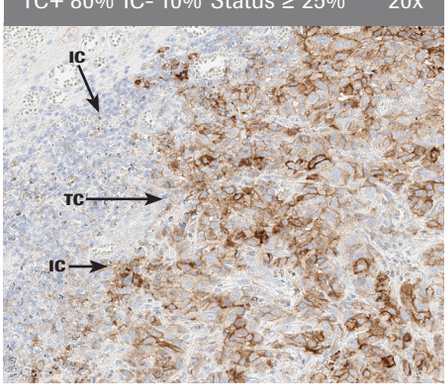
Case D H&E stain 10x



TC+ 80% IC- 10% Status ≥ 25% 10x



TC+ 80% IC- 10% Status ≥ 25% 20x



PD-L1 expression in the tumor microenvironment

Immune cell staining in this assay exhibits a range of staining intensity: negative; weak, diffuse cytoplasmic and/or weak to strong membranous signal. PD-L1 expression has been observed in lymphocytes, macrophages, histiocytes, plasma cells and neutrophils. A punctate pattern of staining may be seen in association with lymphocytes.

For details, please refer to VENTANA PD-L1 (SP263) Assay Staining of Urothelial Carcinoma Interpretation Guide (1014738EN Rev A).

Confident diagnosis

High inter-/intra-reader precision and inter-laboratory reproducibility demonstrate reproducibility and robustness of VENTANA PD-L1 (SP263) Assay. Reader precision and laboratory reproducibility of VENTANA PD-L1 (SP263) Assay staining of urothelial carcinoma specimens per combined tumor cell and tumor-associated immune cells scoring algorithm[6]

Reader precision	Overall percent agreement (95% CI)*
Inter-reader precision (average of all three reader pairwise comparisons for the first read) n =143	93.0%
Intra-reader precision (average of all three readers' agreement rates between first and second reads) n =145	92.4%

* CI- confidence interval

Inter-laboratory reproducibility	Overall percent agreement (95% CI)
Overall agreement (across sites, days and readers) n =778	92.3%
Inter-site agreement (average of site-to-site pairwise comparisons) n =7760	87.5%
Inter-reader agreement (average of reader-to-reader pairwise comparisons within each site) n =389	86.1%

Ordering information

	VENTANA PD-L1 (SP263) Assay	OptiView DAB IHC Detection Kit	Rabbit Monoclonal Negative Control Ig
Catalog number	**740-4907**	**760-700**	**790-4795**
Ordering code	7208162001	06396500001	06683380001
Quantity	50 tests	250 tests	250 tests
Positive control	Placenta		
Species	Rabbit		
Localization	Membranous and/or Cytoplasmic		

Automation: optimized for use on VENTANA BenchMark ULTRA Series Instruments

References

1. Blank C, 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):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. Massard C, Gordon MS, Sharma S, et al. Safety and efficacy of durvalumab (MEDI4736), an anti-programmed cell death ligand-1 immune checkpoint inhibitor, in patients with advanced urothelial bladder cancer. J Clin Oncol. 2016; 34(26):3119-25.
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. Ventana Medical Systems Inc. VENTANA PD-L1 (SP263) Assay Package Insert.

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