VENTANA®   Roche

VENTANA PD-L1 (SP142) Assay

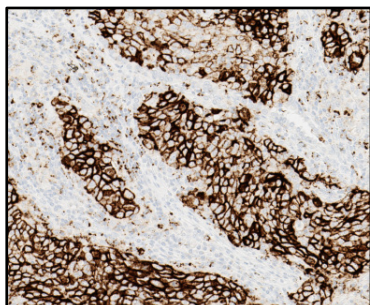REF   740-4859

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IVD   ∑/50

Figure 1. PD-L1 expression in non-small cell lung cancer.

INTENDED USE

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 programmed death-ligand 1 (PD-L1) protein in tumor cells and tumor-infiltrating immune cells in the formalin-fixed, paraffin-embedded (FFPE) tissues indicated below stained with OptiView DAB IHC Detection Kit and OptiView Amplification Kit on a BenchMark ULTRA instrument.

Determination of PD-L1 status is based on either the proportion of tumor area occupied by PD-L1 expressing tumor-infiltrating immune cells (% IC) of any intensity or the percentage of PD-L1 expressing tumor cells (% TC) of any intensity.

VENTANA PD-L1 (SP142) Assay is indicated as an aid for identifying patients for treatment with the therapy- and cutoff listed in Table 1 in accordance with the approved therapeutic product labeling.

Table 1. Companion diagnostic indications for the VENTANA PD-L1 (SP142) Assay.

Indication for use	Therapy	Cutoff
Non-Small Cell Lung Cancer (NSCLC)	TECENTRIQ	≥ 50% TC or ≥ 10% IC

Depending on therapeutic setting, PD-L1 expression in ≥ 50% TC or ≥ 10% IC determined by VENTANA PD-L1 (SP142) Assay in non-small cell lung cancer (NSCLC) patients may be associated with enhanced overall survival from TECENTRIQ (atezolizumab). Refer to the approved therapeutic product labeling for further information.

Test results of this product should be interpreted by a qualified pathologist in conjunction with histological examination, relevant clinical information, and proper controls.

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

SUMMARY AND EXPLANATION

VENTANA PD-L1 (SP142) Assay is an immunohistochemical (IHC) assay utilizing an anti-PD-L1 rabbit monoclonal primary antibody to recognize the programmed death ligand 1 (PD-L1) protein. This assay was co-developed by Roche/Ventana Medical Systems, Inc. (Ventana) and Roche/Genentech to identify patients who are most likely to respond to treatment with TECENTRIQ®.

PD-L1 is a transmembrane protein that downregulates 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] 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 downregulation of immune responses, including inhibition of T-cell activation and cytokine production.[2] PD-L1 expression has been observed in immune cells and malignant cells and aberrant expression of PD-L1 on tumor cells (TC) has been reported to impede anti-tumor immunity, resulting in immune evasion.[1,3] 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. The association between PD-L1 expression in TC or tumor-infiltrating immune cells (IC)

and clinical benefit with PD-L1/PD-1 pathway inhibitors has been reported across multiple cancers.[3-6]

Atezolizumab is an Fc-engineered, humanized, monoclonal antibody that binds to PD-L1 and blocks interactions with the PD-1 and B7.1 receptors. Atezolizumab is a non-glycosylated IgG1 kappa immunoglobulin that has a calculated molecular mass of 145 kDa.

PRINCIPLE OF THE PROCEDURE

VENTANA PD-L1 (SP142) Assay utilizes a rabbit monoclonal primary antibody that binds to PD-L1 in paraffin-embedded tissue sections. The specific antibody can be visualized using OptiView DAB IHC Detection Kit (Cat. No. 760-700 / 06396500001) followed by the OptiView Amplification Kit (Cat. No. 760-099 / 06396518001 (50 test) or 860-099 / 06718663001 (250 test)). Refer to the appropriate OptiView DAB IHC Detection Kit and OptiView Amplification Kit method sheets for further information.

MATERIAL PROVIDED

VENTANA PD-L1 (SP142) Assay contains sufficient reagent for 50 tests.

One 5 mL dispenser of VENTANA PD-L1 (SP142) Assay contains approximately 36 μg of a rabbit monoclonal antibody.

The antibody is diluted in 0.05 M Tris buffered saline, 0.01 M EDTA, 0.05% Brij-35 with 0.3% carrier protein and 0.05% sodium azide, a preservative.

Specific antibody concentration is approximately 7 μg/mL.

VENTANA PD-L1 (SP142) Assay contains a recombinant rabbit monoclonal antibody produced as purified cell culture supernatant.

Refer to the appropriate interpretation guide for detailed instructions for interpretation of VENTANA PD-L1 (SP142) Assay staining.

- VENTANA PD-L1 (SP142) Assay Interpretation Guide for NSCLC (P/N 1015703EN)

Refer to the appropriate VENTANA detection kit method sheet for detailed descriptions of: Principles of the Procedure, Materials and Methods, Specimen Collection and Preparation for Analysis, Quality Control Procedures, Troubleshooting, Interpretation of Results, and General Limitations.

MATERIALS REQUIRED BUT NOT PROVIDED

Staining reagents, such as VENTANA detection kits and ancillary components, including negative and positive tissue control slides, are not provided.

Not all products listed in the method sheet may be available in all geographies. Consult your local support representative.

The following reagents and materials may be required for staining but are not provided:

1. Benign human tonsil tissues for use as control tissue
2. Rabbit Monoclonal Negative Control Ig (Cat. No. 790-4795 / 06683380001)
3. Microscope slides, positively charged
4. Bar code labels
5. Xylene (Histological grade)
6. Ethanol or reagent alcohol (Histological grade)
    - 100% solution: Undiluted ethanol or reagent alcohol
    - 95% solution: Mix 95 parts of ethanol or reagent alcohol with 5 parts of deionized water
    - 80% solution: Mix 80 parts of ethanol or reagent alcohol with 20 parts of deionized water
7. Deionized or distilled water
8. OptiView DAB IHC Detection Kit (Cat. No. 760-700 / 06396500001)
9. OptiView Amplification Kit (Cat. No. 760-099 / 06396518001 (50 test) or 860-099 / 06718663001 (250 test))
10. EZ Prep Concentrate (10X) (Cat. No. 950-102 / 05279771001)
11. Reaction Buffer Concentrate (10X) (Cat. No. 950-300 / 05353955001)
12. ULTRA LCS (Predilute) (Cat. No. 650-210 / 05424534001)
13. ULTRA Cell Conditioning Solution (ULTRA CC1) (Cat. No. 950-224 / 05424569001)
14. Hematoxylin II counterstain (Cat. No. 790-2208 / 05277965001)
15. Bluing Reagent (Cat. No. 760-2037 / 05266769001)
16. Permanent mounting medium (Permount Fisher Cat. No. SP15-500 or equivalent)
17. Cover glass (sufficient to cover tissue, such as VWR Cat. No. 48393-060)
18. Automated coverslipper (such as the Tissue-Tek SCA Automated Coverslipper)
19. Light microscope

20. Absorbent wipes

STORAGE AND STABILITY

Upon receipt and when not in use, store at 2-8°C. Do not freeze.

To ensure proper reagent delivery and stability of the antibody, replace the dispenser cap after every use and immediately place the dispenser in the refrigerator in an upright position.

Every antibody dispenser is expiration dated. When properly stored, the reagent is stable to the date indicated on the label. Do not use reagent beyond the expiration date.

SPECIMEN PREPARATION

Routinely processed FFPE tissues are suitable for use with this primary antibody when used with VENTANA detection kits and BenchMark ULTRA instruments. Tissue fixation in 10% neutral buffered formalin (NBF) for at least 6 hours and for a maximum of 72 hours is recommended. Fixation times of less than 6 hours may result in a loss of staining for PD-L1. The amount of NBF used should be 15 to 20 times the volume of tissue. No fixative will penetrate more than 2 to 3 mm of solid tissue or 5 mm of porous tissue in a 24-hour period. Fixation can be performed at room temperature (15-25°C). [7,8]

Fixatives such as alcohol-formalin-acetic acid (AFA), PREFER fixative and other alcohol-containing fixatives have demonstrated a loss of specific staining for PD-L1 at all fixation times tested (1-72 hours); they are not recommended for use with this assay. See the interpretation guides for further discussion of the impact of specimen preparation on PD-L1 staining.

Sections should be cut approximately 4 μm thick and mounted on positively-charged glass slides. Slides should be stained promptly, as antigenicity of cut tissue sections may diminish over time and may be compromised 2 months after cutting from the paraffin block for NSCLC and tonsil specimens (see the interpretation guides and the Performance Characteristics section below).

WARNINGS AND PRECAUTIONS

1. For in vitro diagnostic (IVD) use.
2. For professional use only.
3. **CAUTION:** In the United States, Federal law restricts this device to sale by or on the order of a physician. (Rx Only)
4. Do not use beyond the specified number of tests.
5. Positively charged slides may be susceptible to environmental stresses resulting in inappropriate staining of any IHC assay (for example, lack of primary antibody or counterstain on the tissue). Ask your Roche representative for a copy of "Impacts of Environmental Stresses on IHC Positively Charged Slides" to better understand how to use these types of slides.
6. Materials of human or animal origin should be handled as biohazardous materials and disposed of with proper precautions. In the event of exposure, the health directives of the responsible authorities should be followed. [9,10]
7. Avoid contact of reagents with eyes and mucous membranes. If reagents come in contact with sensitive areas, wash with copious amounts of water.
8. Avoid microbial contamination of reagents as it may cause incorrect results.
9. For further information on the use of this device, refer to the BenchMark ULTRA instrument User Guide, and instructions for use of all necessary components located at dialog.roche.com.
10. Consult local and/or state authorities with regard to recommended method of disposal.
11. Product safety labeling primarily follows EU GHS guidance. Safety data sheet available for professional user on request.
12. To report suspected serious incidents related to this device, contact the local Roche representative and the competent authority of the Member State or Country in which the user is established.
13. For supplementary safety information, refer to the product Safety Data Sheet and the Symbol and Hazard Guide located at www.roche.com.

STAINING PROCEDURE

VENTANA PD-L1 (SP142) Assay has been developed for use on a BenchMark ULTRA instrument in combination with Rabbit Monoclonal Negative Control Ig, OptiView DAB IHC Detection Kit, OptiView Amplification Kit, and ancillary reagents. An assay-specific staining procedure must be used with VENTANA PD-L1 (SP142) Assay. Refer to Table 2 for the recommended staining protocol and required staining procedure. Any deviation from recommended test procedures may invalidate expected results. Appropriate controls must

be employed and documented. Users who deviate from recommended test procedures must accept responsibility for interpretation of patient results.

This antibody has been optimized for specific incubation times but the user must validate results obtained with this reagent.

The parameters for the automated procedures can be displayed, printed and edited according to the procedure in the instruments Operator's Manual. Refer to the appropriate VENTANA detection kit package insert for more details regarding immunohistochemistry staining procedures.

Table 2. Recommended staining protocol for VENTANA PD-L1 (SP142) Assay and Rabbit Monoclonal Negative Control Ig with OptiView DAB IHC Detection Kit and OptiView Amplification Kit on a BenchMark ULTRA instrument.

Staining Procedure: U OptiV DAB VENTANA PDL1 (SP142)	
Protocol Parameter	**Selection**
Deparaffinization	Selected
Cell Conditioning	CC1 Cell Conditioning 48 minutes
Pre-primary antibody peroxidase	Selected
Primary Antibody	VENTANA PD-L1 (SP142) Selected[a] or Negative Control Selected[a] 16 minutes, 36°C
OptiView HQ Linker	8 minutes (default)
OptiView Multimer	8 minutes (default)
Amplifier and Amplification	Selected
Amplifier and Amplification H2O2	8 minutes
Amplification Multimer	8 minutes
Counterstain	Hematoxylin II, 4 minutes[a]
Post Counterstain	Bluing Reagent, 4 minutes[a]

[a] User-selectable

QUALITY CONTROL PROCEDURES

Rabbit Monoclonal Negative Control Ig

A matched negative reagent control slide must be run for every specimen to aid in the interpretation of results. Rabbit Monoclonal Negative Control Ig, a negative reagent control antibody, is specifically matched for this assay and is used in place of the primary antibody to evaluate nonspecific staining. The staining procedure for the negative reagent control should equal the primary antibody incubation period. Use of a different negative control reagent, or failure to use the recommended negative control reagent, may cause false results.

Tonsil Tissue Control

A tissue control must be included with each staining run. Qualified benign human tonsil tissue is to be used as the control. Control tissue should be fixed as soon as possible and processed in a manner identical to patient tissues. Such tissue may monitor all steps of the analysis, from tissue preparation through staining. Tonsil tissue contains positive and negative staining elements for the PD-L1 protein and is therefore suitable for use as a tissue control. The positive and negative staining tissue components are used to confirm that the assay functioned properly.

Appropriate staining of tonsil tissue components is described in Table 3 and in the interpretation guides.

Assay Verification

Prior to initial use of an antibody or staining system in a diagnostic procedure, the specificity of the antibody should be verified by testing it on a series of tissues with known IHC performance characteristics representing PD-L1 positive and negative tissues (refer to the Quality Control Procedures previously outlined in this section of the product insert and to the Quality Control recommendations of the College of American Pathologists Laboratory Accreditation Program, Anatomic Pathology Checklist[11] or the CLSI Approved Guideline.[12] These quality control procedures should be repeated for each new antibody

lot, or whenever there is a change in assay parameters. NSCLC tissues with known PD-L1 status, and benign human tonsil samples, are suitable for assay verification.

STAINING INTERPRETATION / EXPECTED RESULTS

The VENTANA automated immunostaining procedure causes a brown colored DAB reaction product to precipitate at the antigen sites localized by the VENTANA PD-L1 (SP142) Assay antibody. The stained slide(s) are interpreted by a qualified pathologist using light microscopy. A qualified pathologist experienced in IHC procedures must evaluate tissue controls and qualify the stained product before interpreting results.

Tonsil Tissue Control Interpretation

The stained tonsil tissue control should be examined for appropriate staining. The presence of PD-L1 staining within the macrophages and lymphocytes in germinal centers and reticulated crypt epithelium of tonsil serve as positive tissue elements. Absence of staining in superficial squamous epithelium and negative immune cells in interfollicular regions of tonsil serve as negative tissue elements. Acceptability criteria are listed in Table 3. (Refer to the interpretation guides for further discussion).

If the tissue control fails to demonstrate appropriate staining, any results with the patient specimens should be considered unevaluable and repeat staining should be performed.

Table 3. Tonsil tissue control evaluation criteria.

Acceptable	Unacceptable
Positive tissue elements: Moderate to strong PD-L1 staining noted in lymphocytes and macrophages in germinal centers, with diffuse staining in reticulated crypt epithelial cells.	Excessive non-specific background staining obscuring the identification of PD-L1 positive cells.
Negative tissue elements: PD-L1 negative immune cells in the interfollicular regions with negative superficial squamous epithelium.	Weak to no PD-L1 staining noted in lymphocytes and macrophages in germinal centers, and reticulated crypt epithelial cells.

Negative Reagent Control

Non-specific staining, if present, will have a diffuse appearance and can be evaluated using the negative reagent control slide stained with Rabbit Monoclonal Negative Control Ig. Intact cells should be used for interpretation of staining results; as necrotic or degenerated cells often stain nonspecifically. If background staining is excessive, results from the test specimen should be considered invalid. Examples of background staining for this assay can be found in the interpretation guides.

Patient Tissue

Tumor cells (TC) are scored as the percentage of tumor cells with the presence of discernible PD-L1 membrane staining of any intensity. Tumor-infiltrating immune cells (IC) are scored as the proportion of tumor area, including associated intratumoral and contiguous peritumoral stroma, occupied by PD-L1 staining IC of any intensity. Patient tissue must be evaluated according to the indication-specific VENTANA PD-L1 (SP142) Assay scoring algorithm provided in the Performance Characteristics section for that indication. Refer to the indication-specific interpretation guide for additional instructions and representative images.

GENERAL LIMITATIONS

1. IHC is a multiple step diagnostic process that requires specialized training in the selection of the appropriate reagents, tissue selection, fixation, processing, preparation of the immunohistochemistry slide, and interpretation of the staining results.
2. Tissue staining is dependent on the handling and processing of the tissue prior to staining. Improper fixation, freezing, thawing, washing, drying, heating, sectioning, or contamination with other tissues or fluids may produce artifacts, antibody trapping, or false negative results. Inconsistent results may result from variations in fixation and embedding methods, or from inherent irregularities within the tissue.
3. Excessive or incomplete counterstaining may compromise proper interpretation of results.
4. The clinical interpretation of any positive staining, or its absence, must be evaluated within the context of clinical history, morphology, and other histopathological criteria. The clinical interpretation of any staining, or its absence, must be complemented by morphological studies and system-level controls as well as other diagnostic tests. It

is the responsibility of a qualified pathologist to be familiar with the antibodies, reagents, and methods used to interpret the stained preparation. Staining must be performed in a certified licensed laboratory under the supervision of a pathologist who is responsible for reviewing the stained slides and assuring the adequacy of positive and negative controls.

5. Ventana Medical Systems, Inc. provides antibodies and reagents at optimal dilution for use when the provided instructions are followed. Any deviation from recommended test procedures may invalidate expected results. Appropriate controls must be employed and documented. Users who deviate from recommended test procedures must accept responsibility for interpretation of patient results.
6. This product is not intended for use in flow cytometry, performance characteristics have not been determined.
7. Reagents may demonstrate unexpected reactions in previously untested tissues. The possibility of unexpected reactions even in tested tissue groups cannot be completely eliminated because of biological variability of antigen expression in neoplasms, or other pathological tissues. [13,14]
8. Tissues from persons infected with hepatitis B virus and containing hepatitis B surface antigen (HBsAg) may exhibit nonspecific staining with horseradish peroxidase. [15]
9. False positive results may be seen because of non-immunological binding of proteins or substrate reaction products. They may also be caused by pseudoperoxidase activity (erythrocytes), endogenous peroxidase activity (cytochrome C), or endogenous biotin (example: liver, brain, breast, kidney) depending on the type of immunostain used. [16]
10. As with any immunohistochemistry test, a negative result means that the antigen was not detected, not that the antigen was absent in the cells or tissue assayed.

SPECIFIC LIMITATIONS

1. VENTANA PD-L1 (SP142) Assay has been solely approved on the BenchMark ULTRA instrument with the OptiView DAB IHC Detection Kit and the OptiView Amplification Kit and is not approved with any other detection or instruments.
2. A patient specimen slide should be stained with Rabbit Monoclonal Negative Control Ig. Other negative control reagents are not suitable for this assay.
3. VENTANA PD-L1 (SP142) Assay antibody is stable for up to eight days at 30°C. Assay performance beyond these limits has not been established.
4. This assay has not been validated for use with cytology samples or decalcified bone specimens.
5. Patient tissue should be stained within 2 months of sectioning from the tissue block for NSCLC, and tonsil tissues. Loss of staining performance has been observed with VENTANA PD-L1 (SP142) Assay staining of tissue sections that have been stored at room temperature for longer than 2 months.
6. It is recommended that samples be fixed between 6 and 72 hours in 10% NBF. Use of fixation times or fixative types other than those recommended can lead to false negative results. Fixatives such as AFA, PREFER fixative, and other alcohol-containing fixatives have demonstrated a loss of specific PD-L1 protein staining. Refer to the interpretation guides for further discussion.
7. Artifacts such as DAB spots, Blank spots, DAB dots, and/or Speckling may require repeat staining if they interfere with the interpretation of VENTANA PD-L1 (SP142) Assay. Always compare the PD-L1-stained slide to the negative reagent control to ensure that background is acceptable. Refer to the interpretation guides for further discussion.
8. Occasional DAB dots have been observed in benign human tonsil control, cerebellum and testicular tissues and focal nuclear staining has been observed in normal pancreatic (acinar cells) and hypophyseal tissue (Table 4), however nuclear staining is not included in scoring of VENTANA PD-L1 (SP142) Assay staining.

PERFORMANCE CHARACTERISTICS

Tests for staining specificity, sensitivity, impact of tissue thickness, repeatability, and intermediate precision, as well as tests for reader precision, inter-laboratory reproducibility, and clinical outcome were conducted and the results are listed in the following section.

General Analysis Comments

Unless otherwise noted, the two-sided 95% confidence interval (CI) around estimates of agreement for all studies (excluding clinical efficacy studies) were calculated using the percentile bootstrap method from 2000 bootstrap samples. If the point estimate of Positive Percent Agreement (PPA), Negative Percent Agreement (NPA) or Overall Percent Agreement (OPA) is 0% or 100%, then Wilson score method was used to calculate 95%

CI. If the point estimate of Average Positive Agreement (APA) and Average Negative Agreement (ANA) is 0% or 100% for pairwise comparison, then transformation Wilson score method was used to calculate 95% CI.

Sensitivity and Specificity

Arrays containing a variety of normal and neoplastic tissues were stained with VENTANA PD-L1 (SP142) Assay and evaluated for the presence of immune cell staining (any immune cell staining, of any intensity) as described in Table 4 and Table 5.

In addition, an array of neoplastic tissues was evaluated for IC and TC staining with VENTANA PD-L1 (SP142) Assay as described in Table 5.

Table 4. Sensitivity/Specificity of VENTANA PD-L1 (SP142) Assay staining was determined by testing FFPE normal tissues.

Tissue	# Positive[a]/ Total Cases	Tissue	# Positive[a]/ Total Cases
Adrenal gland	1/3	Muscle, cardiac	0/3
Bladder	3/36[b]	Muscle, skeletal	0/2
Breast	1/66	Myeloid	0/2
Cerebellum	0/3[c]	Nerve, peripheral	0/3
Cerebrum	0/3	Ovary	0/3
Cervix	0/2	Pancreas	0/3[d]
Colon	2/3	Parathyroid	0/2
Endometrium	2/3	Prostate	0/3
Esophagus	0/3	Salivary gland	2/3
Hypophysis	0/3[d]	Skin	0/3
Intestine, small	1/3	Spleen	3/3
Kidney	2/3	Stomach	0/3
Lingual gland	0/1	Testis	0/3[c]
Liver	0/3	Thymus gland	3/3
Lung	1/25	Thyroid gland	1/3
Lymph node	3/3	Tonsil	3/3[c]
Mesothelium	0/3		

[a] Immune cell staining of any intensity   [b] Focal immune cell staining

[c] Focal DAB dots were observed in 1/3 cerebellum, 1/3 testis tissues and normal tonsil control

[d] Nuclear staining was observed in 1/3 pancreas and 1/3 hypophysis tissues

Table 5. Sensitivity/Specificity of VENTANA PD-L1 (SP142) Assay staining was determined by testing a variety of FFPE neoplastic tissues.

Origin	Pathology	# Positive[a]/Total Cases	
		Immune cells	Tumor cells
Abdomen	Malignant mesothelioma	1/1	0/1
Back	Neurofibroma	1/1	0/1
Bladder	Low grade malignant leiomyosarcoma	0/1	0/1
Bladder	Transitional cell carcinoma	1/1	0/1
Bone	Osteosarcoma	0/1	0/1
Breast	Invasive ductal carcinoma	1/2	0/2

Origin	Pathology	# Positive[a]/Total Cases	
		Immune cells	Tumor cells
Breast	Intraductal carcinoma with early infiltrate	1/1	0/1
Cerebrum	Glioblastoma	1/1	0/1
Cerebrum	Atypical meningioma	0/1	0/1
Cerebrum	Malignant ependymoma	0/1	0/1
Cerebrum	Oligodendroglioma	0/1	0/1
Colon	Adenocarcinoma	1/1	0/1
Colon	Interstitialoma	0/1	0/1
Esophagus	Neuroendocrine carcinoma	0/1	0/1
Esophagus	Adenocarcinoma	1/1	0/1
Intestine	Adenocarcinoma	1/1	0/1
Intestine	Stromal sarcoma	1/1	0/1
Kidney	Clear cell carcinoma	1/1	0/1
Liver	Hepatocellular carcinoma	0/1	0/1
Liver	Hepatoblastoma	1/1	0/1
Lung	Adenocarcinoma	0/1	0/1
Lung	Small cell undifferentiated carcinoma	1/1	1/1
Lung	Squamous cell carcinoma	1/1	0/1
Lymph node	Diffuse B-cell lymphoma	1/1[b]	1/1[b]
Lymph node	Hodgkin's lymphoma	1/1	1/1
Mediastinum	Diffuse B-cell lymphoma	1/1[b]	1/1[b]
Muscle, smooth	Moderate malignant leiomyosarcoma	1/1	0/1
Muscle, striated	Embryonal rhabdomyosarcoma	0/1	0/1
Ovary	Serous adenocarcinoma	1/1	0/1
Ovary	Adenocarcinoma	1/1	0/1
Pancreas	Islet cell tumor	0/1	0/1
Pancreas	Adenocarcinoma	1/1	0/1
Pelvic cavity	Anaplastic large cell lymphoma	1/1[b]	1/1[b]
Prostate	Adenocarcinoma	0/2	0/2
Rectum	Adenocarcinoma	1/1	1/1
Rectum	Moderate malignant interstitialoma	0/1	0/1
Rectum	Malignant melanoma	1/1	0/1
Retroperitoneum	Neuroblastoma	1/1	0/1
Retroperitoneum	Spindle cell rhabdomyosarcoma	0/1	0/1

| Origin | Pathology | # Positive[a]/Total Cases | |
		Immune cells	Tumor cells
Skin	Basal cell carcinoma	1/1	0/1
Skin	Squamous cell carcinoma	1/1	0/1
Spleen	Diffuse B-cell lymphoma	1/1[b]	1/1[b]
Stomach	Signet-ring cell carcinoma	1/1	0/1
Testis	Seminoma	1/1	0/1
Testis	Embryonal carcinoma	0/1	0/1
Thyroid	Medullary carcinoma	0/1	0/1
Thyroid	Papillary carcinoma	0/1	1/1
Uterine cervix	Squamous cell carcinoma	2/2	0/2
Uterus	Leiomyoma	0/1	0/1
Uterus	Adenocarcinoma	1/1	0/1
Uterus	Clear cell carcinoma of endometrium	1/1	1/1

[a] Immune cell or tumor cell staining of any intensity.

[b] Tumor cell and immune cell staining could not be differentiated.

PERFORMANCE CHARACTERISTICS

NSCLC

Scoring Algorithm – NSCLC

NSCLC tissue must be evaluated according to the VENTANA PD-L1 (SP142) Assay scoring algorithm for NSCLC provided in Table 6. High PD-L1 expression is defined as having PD-L1 expression on ≥ 50% TC or ≥ 10% IC. Refer to the interpretation guide (P/N 1015703EN) for additional instructions and representative images.

Table 6. VENTANA PD-L1 (SP142) Assay scoring algorithm for NSCLC.

STEP 1 Tumor Cell (TC) Staining Assessment		PD-L1 Expression
Presence of discernible PD-L1 membrane staining of any intensity in ≥ 50% of tumor cells		≥ 50% TC
Absence of any discernible PD-L1 staining OR Presence of discernible PD-L1 membrane staining of any intensity in < 50% of tumor cells		Proceed to Step 2
STEP 2	Tumor-Infiltrating Immune Cell (IC) Staining Assessment	PD-L1 Expression
Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering ≥ 10% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peritumoral stroma		≥ 10% IC
Absence of any discernible PD-L1 staining OR Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering < 10% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peritumoral stroma		< 50% TC and < 10% IC

Tissue Thickness – NSCLC

Tissue thickness was evaluated using NSCLC specimens. Duplicate sections at 3, 4, 5, 6, and 7 microns were stained with VENTANA PD-L1 (SP142) Assay and evaluated for PD-L1 TC and IC expression. Sample sets consisted of a minimum of 8 NSCLC specimens with a range of PD-L1 expression for each IC and TC level tested.

All tissue thicknesses demonstrated appropriate specific staining for PD-L1 and acceptable background levels for VENTANA PD-L1 (SP142) Assay staining. No sections exhibited a change in PD-L1 TC or IC level within the range of thickness tested. Ventana recommends that NSCLC specimens be cut at 4 microns for staining with VENTANA PD-L1 (SP142) Assay.

Repeatability and Intermediate Precision – NSCLC

Studies for VENTANA PD-L1 Assay staining of NSCLC specimens were completed to demonstrate:

- Intra-day Repeatability - 5 replicate slides from each NSCLC specimen were stained with VENTANA PD-L1 (SP142) Assay on a single BenchMark ULTRA instrument in a single day and evaluated for PD-L1 TC and IC expression. Sample sets consisted of 24 NSCLC specimens with a range of PD-L1 expression for each TC and IC level tested.

- Inter-day Precision - 10 slides from each NSCLC specimen were stained with VENTANA PD-L1 (SP142) Assay on a single BenchMark ULTRA instrument across 5 non-consecutive days. Sample sets consisted of 24 NSCLC specimens with a range of PD-L1 expression for each TC and IC expression level tested.

- Instrument, Antibody and Detection Lot Precision - a minimum of 9 slides from each NSCLC specimen were stained with VENTANA PD-L1 (SP142) Assay using three lots of VENTANA PD-L1 (SP142) antibody and three paired lots of OptiView DAB IHC Detection Kit and OptiView Amplification Kit, on three BenchMark ULTRA instruments. Sample sets consisted of a minimum of 18 NSCLC specimens with a range of PD-L1 expression for each TC and IC level tested.

All slides were blinded and randomized and then evaluated for PD-L1 TC or IC expression level. Repeatability and Intermediate Precision results are summarized in Table 7 and Table 8.

Table 7. Repeatability and intermediate precision of VENTANA PD-L1 (SP142) Assay staining of NSCLC specimens (PD-L1 expression ≥ 50% TC).

Repeatability/Intermediate Precision Parameter	Agreement % (95% CI)[a]
Intra-day repeatability (within a single day)	PPA: 100.0 (94.4-100.0) NPA: 100.0 (93.5-100.0) OPA: 100.0 (96.9-100.0)
Inter-day precision (5 non-consecutive days)	PPA: 100.0 (97.1-100.0) NPA: 100.0 (96.5-100.0) OPA: 100.0 (98.4-100.0)
Inter-instrument and Inter-lot precision (compared to case-level mode, across instruments and lots)	PPA: 99.7 (98.1-99.9) NPA: 95.2 (91.2-97.5) OPA: 97.9 (96.2-98.9)

[a] Two-sided Wilson score method CI

Table 8. Repeatability and intermediate precision of VENTANA PD-L1 (SP142) Assay staining of NSCLC specimens (PD-L1 expression ≥ 10% IC).

Repeatability/Intermediate Precision Parameter	Agreement % (95% CI)
Intra-day repeatability (within a single day)	PPA: 98.3 (91.1-99.7)[a] NPA: 100.0 (94.0-100.0)[a] OPA: 99.2 (95.4-99.9)[a]
Inter-day precision (5 non-consecutive days)	PPA: 96.2 (91.3-98.3)[a] NPA: 98.2 (93.6-99.5)[a] OPA: 97.1 (94.1-98.6)[a]
Inter-antibody and Inter-detection agreement (pairwise-comparison)	APA: 95.1 (91.1-98.1) ANA: 90.2 (82.3-96.2) OPA: 93.4 (88.7-97.5)
Inter-instrument and Inter-detection agreement (pairwise-comparison)	APA: 96.3 (93.2-98.8) ANA: 92.7 (86.0-97.7) OPA: 95.1 (91.2-98.4)
Inter-instrument and Inter-antibody agreement (pairwise-comparison)	APA: 96.3 (93.1-98.8) ANA: 92.6 (85.9-97.8) OPA: 95.1 (91.1-98.4)

[a] Two-sided Wilson score method CI

Reader Precision Study – NSCLC

To assess Inter- and Intra-Reader Precision, three pathologists evaluated 80 unique NSCLC cases, with a range of PD-L1 expression, that were stained with VENTANA PD-L1 (SP142) Assay. Specimens were blinded and randomized prior to evaluation for PD-L1 status using the VENTANA PD-L1 (SP142) Assay scoring algorithm for NSCLC (Table 6). Readers scored all specimens twice, with a minimum of 2 weeks between reads. The agreement rates between the readers and between each pathologist's reads are summarized in Table 9.

Table 9. Reader precision of VENTANA PD-L1 (SP142) Assay staining of NSCLC specimens.

Reader Precision	Agreement % (95% CI)
Inter-reader precision (average of reader-to-reader pairwise comparisons from first read)	APA: 88.8 (82.0-94.1) ANA: 89.0 (82.2-94.4) OPA: 88.9 (82.8-94.1)
Intra-reader precision (average of all three readers' agreement rates between first and second reads)	APA: 93.7 (89.9-96.6) ANA: 93.6 (89.8-96.7) OPA: 93.6 (90.3-96.6)

Inter-laboratory Reproducibility Study – NSCLC

An Inter-laboratory Reproducibility Study for VENTANA PD-L1 (SP142) Assay staining was conducted to demonstrate reproducibility of the assay in determining PD-L1 status in NSCLC tissue specimens. Twenty-eight unique NSCLC specimens with a range of PD-L1 expression were stained at 3 external laboratories on each of 5 non-consecutive days over a period of at least 20 days. Prior to staining, slides were blinded and randomized. At each site, the stained slides were independently evaluated by 2 pathologists (readers) using the VENTANA PD-L1 (SP142) Assay scoring algorithm for NSCLC (Table 6). Results are summarized in Table 10.

Table 10. Inter-laboratory reproducibility of VENTANA PD-L1 (SP142) Assay staining of NSCLC specimens.

Inter-laboratory Reproducibility	Agreement % (95% CI)
Overall agreement (compared to a consensus score, across sites, days and readers)	PPA: 86.6 (83.0-89.5)[a] NPA: 99.8 (98.7-100.0)[a] OPA: 93.2 (91.3-94.7)[a]
Inter-site agreement (average of site-to-site pairwise comparisons)	APA: 89.5 (80.9-95.5) ANA: 92.1 (84.4-97.1) OPA: 91.0 (90.3-91.6)[a]
Inter-reader agreement (average of reader-to-reader pairwise comparisons within each site)	APA: 93.9 (89.3-97.4) ANA: 95.4 (90.6-98.2) OPA: 94.7 (92.2-96.5)[a]

[a] Two-sided Wilson score method CI

CLINICAL PERFORMANCE
NSCLC ≥ 50% TC or ≥ 10% IC

The performance of VENTANA PD-L1 (SP142) Assay as a companion diagnostic was investigated in IMpower110 (NCT02409342), a multicenter, international, randomized, open-label trial in patients with stage IV NSCLC whose tumors express PD-L1 (TC ≥ 1% or IC ≥ 1%), who had received no prior chemotherapy for metastatic disease. The study was designed to evaluate the safety and efficacy of TECENTRIQ relative to chemotherapy consisting of a platinum agent (cisplatin or carboplatin per investigator discretion) in combination with either pemetrexed (non-squamous disease) or gemcitabine (squamous disease).

Patient specimens were stained with VENTANA PD-L1 (SP142) Assay and evaluated for staining acceptability and for PD-L1 expression. Patient specimens were FFPE NSCLC tissue from biopsies (66.0%), resections (15.7%), or of other type (18.3%); 72.4% were from primary tumors and 27.6% from metastatic tumors.

Table 11 describes the overall staining acceptability rate for VENTANA PD-L1 (SP142) Assay among all NSCLC subjects screened for the study. The rates of acceptable morphology and acceptable background for PD-L1 stained slides are also reported. Out of a total of 2909 subjects, specimens for 65 subjects failed the initial staining attempt. When staining was repeated, results for the 15 of the 65 subjects remained unacceptable (14 due to unacceptable negative reagent control and 1 due to unacceptable morphology). VENTANA PD-L1 (SP142) Assay demonstrated high initial (i.e., first-pass) and final overall staining acceptability rates: 97.8% and 99.5%, respectively. The initial and final acceptability rates for background staining and morphology were greater than 99%.

Table 11. VENTANA PD-L1 (SP142) Assay NSCLC staining performance characteristics in IMpower110.

Attribute	Acceptability rate % (n/N) (95% CI) [a]	
	Initial[b]	Final[c]
Overall staining acceptability rate	97.8 (2844/2909) (97.2-98.2)	99.5 (2894/2909) (99.2-99.7)
Morphology	99.4 (2844/2860) (99.1-99.7)	100.0 (2894/2895) (99.8-100.0)
Background	100.0 (2844/2844) (99.9-100.0)	100.0 (2894/2894) (99.9-100.0)

[a] Two-sided Wilson score method CI

[b] Initial staining attempt   [c] Final staining attempt

The evaluation of efficacy is based on the subgroup of patients with high PD-L1 expression (TC ≥ 50% or IC ≥ 10%), excluding those with EGFR or ALK genomic tumor aberrations. The trial excluded patients with a history of autoimmune disease administration of a live attenuated vaccine within 28 days prior to randomization, active or untreated CNS metastases, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization.

Randomization was stratified by sex, ECOG performance status, histology (non-squamous vs. squamous) and PD-L1 expression (TC ≥ 1% and any IC vs. TC < 1% and IC ≥ 1%). Patients were randomized (1:1) to receive one of the following treatment arms:

- Arm A: TECENTRIQ 1200 mg every 3 weeks until disease progression or unacceptable toxicity
- Arm B: Platinum-based chemotherapy

Arm B platinum-based chemotherapy regimens for non-squamous NSCLC consisted of cisplatin (75 mg/m²) and pemetrexed (500 mg/m²) OR carboplatin (AUC 6 mg/mL/min) and pemetrexed (500 mg/m²) on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles followed by pemetrexed 500 mg/m² until disease progression or unacceptable toxicity.

Arm B platinum-based chemotherapy regimens for squamous NSCLC consisted of cisplatin (75 mg/m²) on Day 1 with gemcitabine (1250 mg/m2) on Days 1 and 8 of each 21-day cycle OR carboplatin (AUC 5 mg/mL/min) on Day 1 with gemcitabine (1000 mg/m2) on Days 1 and 8 of each 21-day cycle for a maximum of 4 or 6 cycles followed by best supportive care until disease progression or unacceptable toxicity.

Administration of TECENTRIQ was permitted beyond RECIST-defined disease progression. Tumor assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory, and the results were used to define subgroups for pre-specified analyses.

The major efficacy outcome measure was overall survival (OS) sequentially tested in the following subgroups of patients, excluding those with EGFR or ALK genomic tumor aberrations: TC ≥ 50% or IC ≥ 10%; TC ≥ 5% or IC ≥ 5%; and TC ≥ 1% or IC ≥ 1%.

Among the 205 chemotherapy-naïve patients with stage IV NSCLC with high PD-L1 expression (TC ≥ 50% or IC ≥ 10%) excluding those with EGFR or ALK genomic tumor aberrations, the median age was 65.0 years (range: 33 to 87), and 70% of patients were male. The majority of patients were White (82%) and Asian (17%). Baseline ECOG performance status was 0 (36%) or 1 (64%); 88% were current or previous smokers; and 76% of patients had non-squamous disease while 24% of patients had squamous disease.

The trial demonstrated a statistically significant improvement in OS for patients with high PD-L1 expression (TC ≥ 50% or IC ≥ 10%) at the time of the OS interim analysis. There was no statistically significant difference in OS for the other two PD-L1 subgroups (TC ≥ 5% or IC ≥ 5%; and TC ≥ 1% or IC ≥ 1%) at the interim or final analyses. Efficacy results for patients with NSCLC with high PD-L1 expression are presented in Table 12 and Figure 2.

Table 12. Efficacy results from IMpower110 in patients with NSCLC with high PD-L1 expression (TC ≥ 50% or IC ≥ 10%) and without EGFR or ALK genomic tumor aberrations.

	Arm A: TECENTRIQ	Arm B: Platinum-Based Chemotherapy
Overall Survival[a]	N = 107	N = 98
Deaths (%)	44 (41%)	57 (58%)
Median, months	20.2	13.1
(95% CI)	(16.5, NE)	(7.4, 16.5)
Hazard ratio[b] (95% CI)	0.59 (0.40, 0.89)	
p-value[c]	0.0106[d]	

[a] Based on OS interim analysis. The median survival follow-up time in patients was 15.7 months.

[b] Stratified by sex and ECOG performance status

[c] Based on the stratified log-rank test compared to Arm A

[d] Compared to the allocated alpha of 0.0413 (two-sided) for this interim analysis.

CI=confidence interval; NE=not estimable

Investigator-assessed PFS showed a HR of 0.63 (95% CI: 0.45, 0.88), with median PFS of 8.1 months (95% CI: 6.8, 11.0) in the TECENTRIQ arm and 5 months (95% CI: 4.2, 5.7) in the platinum-based chemotherapy arm. The investigator-assessed confirmed ORR was 38% (95% CI: 29%, 48%) in the TECENTRIQ arm and 29% (95% CI: 20%, 39%) in the platinum-based chemotherapy arm.
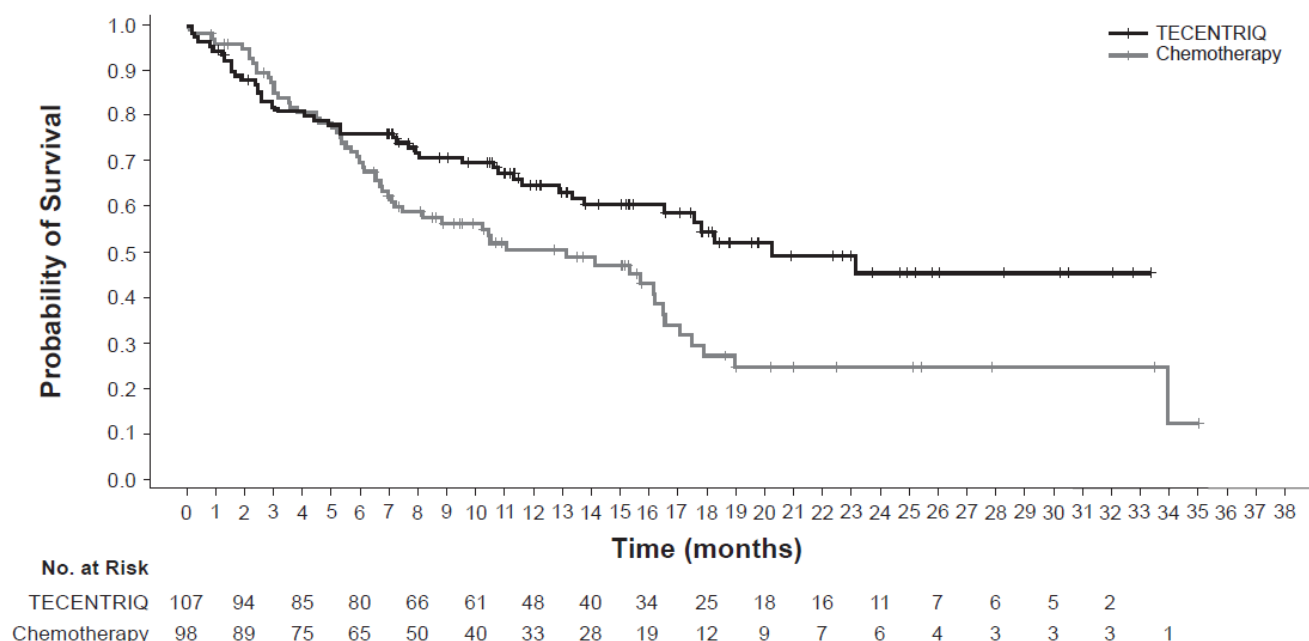
Figure 2: Kaplan-Meier plot of overall survival in IMpower110 in patients with NSCLC with high PD-L1 expression (TC ≥ 50% or IC ≥ 10%) and without EGFR or ALK genomic tumor aberrations.

The performance of VENTANA PD-L1 (SP142) Assay was investigated in OAK (NCT02008227), a Phase III multi-center, international, randomized, open-label trial designed to evaluate the efficacy and safety of TECENTRIQ treatment in patients with metastatic NSCLC who progressed during or following a platinum-containing regimen.

Patient specimens were stained with VENTANA PD-L1 (SP142) Assay and evaluated for staining acceptability and for PD-L1 expression. Patient specimens were FFPE NSCLC tissue from needle cores (34.5%), punch biopsies (16.3%), resections (28.7%), or of other type (20.5%); 66.6% were from primary tumors and 33.4% from metastatic tumors.

Table 13 describes the overall staining acceptability rate for VENTANA PD-L1 (SP142) Assay among all NSCLC specimens screened for the study. The rates of acceptable morphology and acceptable background for PD-L1 stained slides are also reported. Out of a total of 1185 specimens, 72 failed the initial staining attempt and staining was repeated. 26 of the 72 samples remained unacceptable (1 due to unacceptable tonsil control, 19 due to unacceptable negative reagent control and 6 due to unacceptable background or morphology). VENTANA PD-L1 (SP142) Assay demonstrated high initial (i.e., first-pass) and final overall staining acceptability rates: 93.9% and 97.8%, respectively. Final morphology and background acceptability rates were greater than 99%.

Table 13. VENTANA PD-L1 (SP142) Assay NSCLC staining performance characteristics in OAK.

Attribute	Acceptability rate % (n/N) (95% CI) [a]	
	Initial[b]	Final[c]
Overall staining acceptability rate	93.9 (1113/1185) (92.4-95.1)	97.8 (1159/1185) (96.8-98.5)
Morphology	98.5 (1122/1139) (97.6-99.1)	99.6 (1160/1165) (99.0-99.8)
Background	98.2 (1119/1139) (97.3-98.9)	99.7 (1161/1165) (99.1-99.9)

[a] Two-sided Wilson score method CI

[b] Initial staining attempt   [c] Final staining attempt

The OAK study enrolled 1225 patients with the primary analysis population consisting of the first 850 randomized patients; eligible patients were stratified by PD-L1 expression status in IC, by the number of prior chemotherapy regimens, and by histology. Patients were randomized (1:1) to receive either TECENTRIQ administered intravenously at 1200 mg every 3 weeks until unacceptable toxicity or either radiographic or clinical progression or docetaxel administered intravenously at 75 mg/m2 every 3 weeks until unacceptable toxicity or disease progression. Tumor specimens were evaluated prospectively for PD-L1 expression on TC and IC using VENTANA PD-L1 (SP142) Assay and the results were used to define the PD-L1 expression subgroups for pre-specified analyses described below.

In the OAK study, among patients in the primary analysis population, the median age was 64 years (range: 33 to 85), and 61% of patients were male. The majority of patients were white (70%). Approximately three-fourths of patients had non-squamous disease (74%), 10% had known EGFR mutation, 0.2% had known ALK rearrangements, and most patients were current or previous smokers (82%). Baseline ECOG performance status was 0 (37%) or 1 (63%). Seventy-five percent of patients received only one prior platinum-based therapeutic regimen.

The major efficacy outcome measure of the OAK study was overall survival (OS) in the primary analysis population (first 850 randomized patients). The results of the OAK study with a median follow up of 21 months are presented in Table 14 and Figure 3.

Tumor specimens were evaluated prospectively using VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used to define the PD-L1 expression subgroups for pre-specified analyses. Of the 850 patients, 16% were classified as having high PD-L1 expression, defined as having PD-L1 expression on ≥ 50% TC or ≥ 10% IC. In an exploratory efficacy subgroup analysis of OS based on PD-L1 expression, the hazard ratio was 0.41 (95% CI: 0.27, 0.64) in the high PD-L1 expression subgroup and 0.82 (95% CI: 0.68, 0.98) in patients who did not have high PD-L1 expression.

Table 14. Efficacy results in the primary analysis population from the OAK study.

Overall Survival	TECENTRIQ (n=425)	Docetaxel (n=425)
Deaths (%)	271 (64)	298 (70)
Median, months (95% CI)	13.8 (11.8, 15.7)	9.6 (8.6, 11.2)
Hazard ratio[a] (95% CI)	0.74 (0.63, 0.87)	
p-value[b]	0.0004	

[a] Stratified by PD-L1 expression in tumor-infiltrating immune cells, the number of prior chemotherapy regimens, and histology
[b] Based on the stratified log-rank test, CI = confidence interval
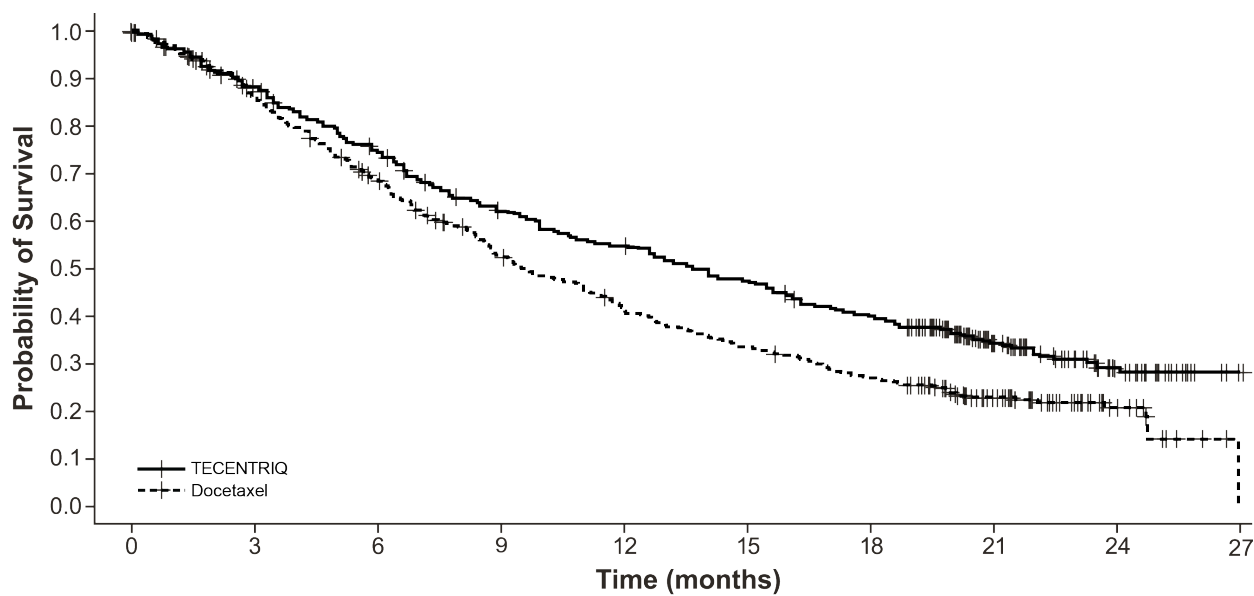
No. Patients at Risk

TECENTRIQ	425	407	382	363	342	326	305	279	260	248	234	223	218	205	198	188	175	163	157	141	116	74	54	41	28	15	4	1
Docetaxel	425	390	365	336	311	286	263	236	219	195	179	168	151	140	132	123	116	104	98	90	70	51	37	28	16	6	3

Figure 3. Kaplan-Meier plot of overall survival in the primary analysis population of OAK (NCT02008227).

TROUBLESHOOTING

Troubleshooting guidance is provided in Table 15. If a problem cannot be attributed to any of these causes, or if the suggested corrective action fails to resolve the problem, consult your local support representative.

Table 15. Troubleshooting guidance for VENTANA PD-L1 (SP142) Assay.

Problem	Probable Cause	Suggested Action
Light or no staining of slides	Incorrect staining protocol selected	Verify that U OptiV DAB VENTANA PD-L1 (SP142) procedure was used.
		Verify that VENTANA PD-L1 (SP142) was selected for Primary Antibody
	Degradation of tissue	Verify tissue was stained within the recommended time frame following sectioning.
	Dispenser malfunction	Verify nozzle cap is removed.
		Ensure dispenser is primed
		Check the priming chamber for foreign materials or particulates, such as fibers or precipitate
		Refer to inline dispenser method sheet associated with P/N 740-4859 located at www.ventana.com
	Inappropriate fixation method used	Ensure that only recommended fixatives and fixation times are used.
	Incorrect or missing bulk reagent	Ensure bulk reagents are correctly filled.
Excessive background staining of slides	Incorrect staining protocol selected	Verify that U OptiV DAB VENTANA PD-L1 (SP142) procedure was used.
	Incorrect or missing bulk reagent	Ensure bulk reagents are correctly filled.
	Inappropriate fixation method used	Ensure that only recommended fixatives and fixation times are used.
Tissue detached from slides	Use of incorrect microscope slides	Ensure positively charged microscope slides are used.

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NOTE: A point (period/stop) is always used in this document as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

Symbols

Ventana uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see dialog.roche.com for definition of symbols used):

GTIN — Global Trade Item Number

UDI — Unique Device Identification

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CONTACT INFORMATION

Ventana Medical Systems, Inc.
1910 E. Innovation Park Drive
Tucson, Arizona 85755
USA
+1 520 887 2155
+1 800 227 2155 (USA)
www.roche.com