SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	In vitro diagnostic immunohistochemistry (IHC) test for detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) human tissue sections
Device Trade Name:	VENTANA PD-L1 (SP142) Assay
Device Procode:	PLS
Applicant's Name and Address:	Ventana Medical Systems, Inc. 1910 East Innovation Park Drive Tucson, AZ 85755
Date(s) of Panel Recommendation:	None

Premarket Approval Application (PMA) Number: P160006

Date of FDA Notice of Approval: October 18, 2016

II. INDICATIONS FOR 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 PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) urothelial carcinoma and non-small cell lung cancer (NSCLC) tissue stained with OptiView DAB IHC Detection Kit and OptiView Amplification Kit on a VENTANA BenchMark ULTRA instrument. Determination of PD-L1 status is indication-specific, and evaluation 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.

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).

PD-L1 expression in ≥ 50% TC or ≥ 10% IC as detected by VENTANA PD-L1 (SP142) Assay in NSCLC may be associated with enhanced overall survival from TECENTRIQ™ (atezolizumab).

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

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the VENTANA PD-L1 (SP142) Assay labeling.

V. DEVICE DESCRIPTION

Device Kit Components

The VENTANA PD-L1 (SP142) Assay contains optimized reagents required to complete an immunohistochemical staining procedure for FFPE specimens on the BenchMark ULTRA automated staining instrument visualized using the OptiView DAB IHC Detection and the OptiView Amplification Kits. The VENTANA PD-L1 (SP142) Assay includes a recombinant rabbit monoclonal antibody produced as purified cell culture supernatant and contains sufficient reagent for 50 tests. The antibody and detection reagents are provided as ready-to-use dispensers, as listed below in Table 1.

Table 1– Overview of the VENTANA PD-L1 (SP142) Assay Components

Device Components	Packaged Form	Description
VENTANA PD-L1 (SP142) Assay	Dispenser: 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. Total protein concentration of the reagent is approximately 3 mg/mL. Specific antibody concentration is approximately 7µg/mL.
OptiView DAB IHC Detection Kit	Set of 6 dispensers packaged in a kit: 250 tests	**OptiView Peroxidase Inhibitor** contains 3.0% hydrogen peroxide solution.
		OptiView HQ Universal Linker contains a cocktail of HQ-labeled (HQ is a proprietary hapten covalently attached to the goat antibodies) antibodies (goat anti-mouse IgG, goat anti-mouse IgM, and goat anti-rabbit) (<50 µg/mL) in a buffer containing protein with ProClin 300, a preservative.
		OptiView HRP Multimer contains a mouse monoclonal anti-HQ-labeled HRP tertiary antibody (<40 µg/mL) in a buffer containing protein with ProClin 300, a preservative.
		OptiView H_2O_2 contains 0.04% hydrogen peroxide in a phosphate buffer solution.
		OptiView DAB contains 0.2% 3, 3'- diaminobenzidine tetrahydrochloride (DAB) in a proprietary stabilizer solution with a proprietary preservative.
		OptiView Copper contains copper sulfate (5.0 g/L) in an acetate buffer with a proprietary preservative.

Device Components	Packaged Form	Description
OptiView Amplification Kit	3 dispensers packaged in a kit of 50 tests or 250 tests	**OptiView Amplification** contains 0.003% HQ conjugated tyramide complex in a sodium borate solution.
		OptiView H_2O_2 contains 0.04% H_2O_2 in a sodium phosphate buffer.
		OptiView Multimer contains a mouse monoclonal anti-HQ-labeled HRP tertiary antibody (<40 µg/mL) in a buffer containing protein with ProClin 300, a preservative.
BenchMark ULTRA (IHC/ISH) automated staining instrument	Instrument installed with the VSS host system software	A PC that runs on Microsoft Windows controls and monitors the BenchMark ULTRA instrument via the host operating software.
Rabbit Monoclonal Negative Control Ig	1 dispenser packaged as 250 test kit	Intended for laboratory use as a control for nonspecific binding of rabbit immunoglobulin (Ig) in sections of FFPE tissue. One 25 mL dispenser contains approximately 250 µg of a rabbit monoclonal antibody. The antibody is diluted in 0.08 M PBS with 3% carrier protein and 0.05% ProClin 300, a preservative.

Device Instrumentation and Software

The VENTANA PD-L1 (SP142) Assay is performed on the BenchMark ULTRA automated staining instrument using the VSS software version 12.2. The VENTANA PD-L1 (SP142) Assay protocol is assay specific. The software has been designed to recognize and group the VENTANA PD-L1 (SP142) Assay, requiring that all system reagents are used together.

Specimen Preparation

Routinely processed, formalin-fixed, paraffin-embedded tissues are suitable for use with this primary antibody when used with VENTANA OptiView DAB detection kit and BenchMark ULTRA instruments. Tissue should be fixed in 10% neutral buffered formalin (NBF) for at least 6 hours and for a maximum of 72 hours at room temperature (15-25 °C). 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. Fixatives such as alcohol-formalin-acetic acid (AFA), PREFER fixative, or other alcohol-containing fixatives are not recommended for use with this assay.

Sections should be cut 4µm thick and mounted on positively-charged glass slides. Slides should be stained promptly, as antigenicity of cut tissue sections may diminish over time. Sections for NSCLC should be used within 2 months of cutting from the paraffin block.

Quality Control Procedures

Run controls are included in each staining run to establish the validity of the test results. The following controls should be run with the assay:

A. 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. The Rabbit Monoclonal Negative Control Ig is required, but is not provided in the assay kit.

B. Tonsil Tissue Control

Tonsil tissue serves as a positive and negative tissue control for the VENTANA PD-L1 (SP142) CDx Assay as it contains positive and negative staining elements for the PD-L1 protein. Control tissue should be fixed as soon as possible and processed in a manner identical to patient tissues. Such tissue may be used to monitor all steps of the analysis, from tissue preparation through staining. Cut sections of tonsil control tissue should be used within 2 months of cutting from the paraffin block.

Principles of Operation

The VENTANA PD-L1 (SP142) Assay is fully automated for use on the BenchMark ULTRA automated slide stainer from deparaffinization through counterstaining. Patient FFPE tissue specimens are cut 4μm thick and mounted on positively-charged glass slides. These slides are loaded into the Benchmark ULTRA instrument. This system first removes the paraffin wax from the tissue, and then subjects the tissue to heated antigen retrieval (cell conditioning). Antigen retrieval is the process by which the ability of antibodies to bind to the epitopes is restored to formalin-fixed tissues.

Endogenous peroxidases that could potentially react with the horseradish peroxidase conjugates (HRP) are blocked with OptiView Inhibitor (3% H_2O_2). After the endogenous peroxidase block, the VENTANA PD-L1 (SP142) Rabbit Monoclonal Primary Antibody is dispensed during the antibody incubation step and allowed to bind to its antigen for 16 minutes. The slides are then incubated with the reagents in the OptiView DAB IHC Detection Kit and OptiView Amplification Kit to achieve preferred staining of target cells. The OptiView DAB IHC Detection Kit is an indirect, biotin-free system for detecting mouse IgG, mouse IgM, and rabbit primary antibodies which produces a visible dark brown precipitate (3,3'-Diaminobenzidine) via an HRP enzymatic reaction at the antigen site. The OptiView Amplification Kit includes an HQ hapten conjugate (OptiView Amplifier), corresponding substrate (OptiView Amplification H_2O_2), and mouse anti-HQ monoclonal antibody containing HRP (OptiView Amplification Multimer). Tissues are then counterstained blue using Hematoxylin II and Bluing Reagent to create brown/blue contrast to aid the pathologist when reviewing the slides using bright field microscopy. The staining protocol is shown in Table 2 below.

Table 2 – Staining Protocol for the BenchMark ULTRA

Protocol Parameter	Selection
Deparaffinization	Selected
Cell Conditioning	CC1 Cell Conditioning, 48 minutes
Pre-primary antibody peroxidase	Selected
Antibody Incubation	16 minutes, 36°C
OptiView HQ Linker	8 minutes (default)
OptiView HRP Multimer	8 minutes (default)
OptiView Amplification	Selected
Amplifier and Amplification H_2O_2	8 minutes
Amplification Multimer	8 minutes
Hematoxylin II	4 minutes
Bluing Reagent	4 minutes

Interpretation of PD-L1 Staining

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. A qualified pathologist experienced in IHC procedures must evaluate tissue controls with a light microscope and qualify the stained product before interpreting results.

A. 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 the reticulated crypt epithelium of tonsil serves as positive tissue elements. Absence of staining in superficial squamous epithelium and negative immune cells in interfollicular regions of tonsil serves as negative tissue elements. Specimen acceptability criteria are listed in Table 3.

Table 3 – Tonsil tissue control evaluation criteria

Acceptable	Unacceptable
Positive tissue elements: Moderate to strong PD-L1 (SP142) 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 (SP142) positive cells
Negative tissue elements: PD-L1 (SP142) negative immune cells in the interfollicular regions with negative superficial squamous epithelium	Weak to no PD-L1 (SP142) staining noted in lymphocytes and macrophages in germinal centers, and reticulated crypt epithelial cells

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.

B. Negative Reagent Control Interpretation

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.

C. Patient Tissue Interpretation

Patient tissue is evaluated for staining in NSCLC tumor cells as well as immune cells per Table 4. PD-L1 staining in tumor cells demonstrates a membranous pattern occasionally accompanied by variable cytoplasmic staining. PD-L1 staining in tumor infiltrating immune cells demonstrates a punctate membranous pattern occasionally accompanied by circumferential staining. Tumor cells are scored as the proportion of viable tumor cells that show membrane staining of any intensity. Tumor-infiltrating immune cells are scored as the proportion of tumor area covered with tumor infiltrating immune cells showing PD-L1 staining of any intensity; the score is provided as a percentage. Tumor area is defined as the area occupied by the tumor cells and the associated intratumoral and contiguous peri-tumoral stroma. Tumor-infiltrating immune cells are present in the intratumoral and contiguous peritumoral stroma and include lymphocytes, macrophages, and cells with dendritic or reticular morphology.

Table 4 – 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 (TC3 or PD-L1 high expression)
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 (IC3 or PD-L1 high expression)
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

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There is currently no alternative FDA-cleared or -approved immunohistochemistry assay available for detection of PD-L1 in FFPE NSCLC tissues for assessing patients for treatment with TECENTRIQ (atezolizumab).

VII. MARKETING HISTORY

The VENTANA PD-L1 (SP142) Assay has been approved for use in the assessment of the PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) urothelial carcinoma tissue since May 18, 2016. It has not been marketed in the United States or any foreign country for the detection of PD-L1 in FFPE NSCLC tissues.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Failure of the device to perform as expected or failure to correctly interpret test results may lead to incorrect PD-L1 test results. This could result in an inaccurate estimate of a patient's benefit from atezolizumab and subsequently improper interpretation of the benefits and risks for NSCLC patients who are considering treatment with TECENTRIQ (atezolizumab).

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

Preclinical studies were performed using the VENTANA PD-L1 (SP142) Assay to establish the analytical performance of the device. These studies were conducted to characterize the assay, demonstrate the impact of pre-analytical variables on assay performance, verify precision and robustness of the assay, and establish assay stability.

1. Analytical Specificity

The antibody used in the VENTANA PD-L1 (SP142) Assay is a Rabbit Anti-Human PD-L1/CD274 Monoclonal Antibody (Clone SP142). The molecular weight of the antibody's target is 32 kDa, and the SP142 clone targets amino acids 284-290 at the cytoplasmic tail of PD-L1. The following studies were conducted with the PD-L1 (SP142) antibody to establish antibody specificity.

a. Western Blot studies

Western blot analysis was performed on whole cell lysates from four cell lines with varying expression levels of PD-L1. The four cell lines were H820 (Lung), MDA-231 (Breast), H1975 (Lung) and Calu-3 (Lung). The

cell lines were chosen based on IHC staining for PD-L1 (SP142). The relative levels of PD-L1 protein observed in these four cell lines on the Western Blot correlate with PD-L1 protein expression levels determined by IHC staining and also with mRNA expression levels for PD-L1. No unexpected staining or background was observed in any of the whole cell lysates.

b. BLAST Results for SP142 Epitope

PD-L1 is a member of the B7 family of ligands. PD-L1 (SP142) targets 7 amino acids in the cytoplasmic tail of PD-L1. NCBI BLASTp was used to search for sequence similarity using the SP142 epitope and no significant similarity was found to any other B7 family members.

c. Specificity of PD-L1 (SP142) on Cell Lines with PD-L1 or PD-L2

A series of HEK293 transfected cells lines was generated using empty vector, vector containing the PD-L1 gene, and a vector containing the PD-L2 gene. IHC staining demonstrated that PD-L1 (SP142) stains PD-L1 transfected HEK293 cells, but not PD-L2 transfected HEK293 cells.

d. Peptide inhibition studies

One lot of primary antibody was incubated with either no peptide, an unrelated non-specific peptide, or four different concentrations of the specific peptide containing the antibody binding epitope. Each of these solutions represented half the optimal concentration of the primary antibody, as the antibody was diluted 1:1 with either a peptide solution or buffer alone. In the presence of high molar concentrations of this peptide, anti-PD-L1 was completely inhibited from binding to tissue expressing PD-L1 protein as determined by the absence of IHC staining. The non-specific peptide had no effect on PD-L1 staining.

e. Immunoreactivity in Human Tissues

One lot of VENTANA PD-L1 (SP142) antibody and Rabbit Monoclonal Negative Control Ig were used to stain slides of a commercially available multi-tissue array of normal and neoplastic tissues. There were 93 normal tissues and 54 neoplastic tissues analyzed in this study. The normal tissues included 25 common types of normal human organs which represent three cases per organ type from three unique individuals. The stained tissues were evaluated by a trained pathologist for presence of positive staining, staining intensity, and background in tumor cells, tumor infiltrating immune cell, and normal cells. Results for normal tissues are shown in Table 5 and results for neoplastic tissues are shown in Table 6.

Table 5 - VENTANA PD-L1 (SP142) Assay staining on normal tissues

Tissue type	# positive*/ total cases	Tissue type	# positive*/ total cases
Adrenal gland	1/3	Muscle, cardiac	0/3
Bladder	3/36	Muscle, skeletal	0/2
Breast	1/3	Myeloid	0/2
Cerebellum	0/3**	Nerve, peripheral	0/3
Cerebrum	0/3	Ovary	0/3
Cervix	2/2	Pancreas	0/3***
Colon	2/3	Parathyroid	0/2
Endometrium	1/3	Prostate	0/3
Esophagus	0/3	Salivary gland	2/3
Hypophysis	0/3***	Skin	0/3
Intestine, small	1/3	Spleen	3/3
Kidney	2/3	Stomach	0/3
Lingual gland	0/1	Testis	0/3**
Liver	0/3	Thymus gland	3/3
Lung	1/3	Thyroid gland	1/3
Lymph node	3/3	Tonsil	3/3
Mesothelium	0/3		

*Immune cell staining;
**Focal DAB dots observed in 1/3 cerebellum and1/3 testis tissues;
***Nuclear staining observed in 1/3 pancreas and 1/3 hypophysis tissues

Table 6- VENTANA PD-L1 (SP142) Assay Staining on Neoplastic Tissues

Origin	Pathology	# positive/total cases	
		Immune cells	Tumor cells
Abdomen	Malignant mesothelioma	1/	0/1
Back	Neurofibroma	1/	0/1
Bladder	Low grade malignant leiomyosarcoma	0/ 1	0/1
Bladder	Transitional cell carcinoma	1/	0/1
Bone	Osteosarcoma	0/	0/1
Breast	Invasive ductal carcinoma	1/	0/1
Breast	Intraductal carcinoma with early infiltrate	1/ 1	0/1
Cerebrum	Glioblastoma	0/	0/1
Cerebrum	Atypical meningioma	0/	0/1
Cerebrum	Malignant ependymoma	0/	0/1
Cerebrum	Oligodendroglioma	0/	0/1
Colon	Adenocarcinoma	1/	0/1
Colon	Interstitialoma	0/	0/1
Esophagus	Squamous cell carcinoma	0/	0/1
Esophagus	Adenocarcinoma	1/	0/1
Intestine	Adenocarcinoma	1/	0/1
Intestine	Stromal sarcoma	1/	0/1
Kidney	Clear cell carcinoma	1/	0/1
Liver	Hepatocellular carcinoma	0/	0/1
Liver	Hepatoblastoma	1/	0/1
Lung	Adenocarcinoma	0/	0/1
Lung	Small cell undifferentiated carcinoma	1/ 1	0/1
Lung	Squamous cell carcinoma	1/	0/1
Lymph node	Diffuse B-cell lymphoma	1/	1/1*
Lymph node	Hodgkin's lymphoma	1/	0/1
Mediastinum	Diffuse B-cell lymphoma	1/	1/1*
Muscle, smooth	Moderate malignant leiomyosarcoma	1/ 1	0/1
Muscle, striated	Embryonal rhabdomyosarcoma	0/ 1	0/1
Ovary	Serous adenocarcinoma	1/	0/1
Ovary	Adenocarcinoma	1/	0/1
Pancreas	Islet cell tumor	0/	0/1
Pancreas	Adenocarcinoma	1/	0/1
Pelvic cavity	Anaplastic large cell lymphoma	1/	1/1*
Prostate	Adenocarcinoma	0/	0/2
Rectum	Adenocarcinoma	1/	1/1
Rectum	Moderate malignant interstitialoma	0/	0/1
Rectum	Malignant melanoma	1/	0/1
Retroperitoneum	Neuroblastoma	1/	0/1

Origin	Pathology	# positive/total cases	
		Immune cells	Tumor cells
Retroperitoneum	Spindle cell rhabdomyosarcoma	0/	0/1
Skin	Basal cell carcinoma	1/	0/1
Skin	Squamous cell carcinoma	1/	0/1
Spleen	Diffuse B-cell lymphoma	1/	1/1*
Stomach	Signet-ring cell carcinoma	1/	0/1
Testis	Seminoma	1/	0/1
Testis	Embryonal carcinoma	0/	0/1
Thyroid	Medullary carcinoma	0/	0/1
Thyroid	Papillary carcinoma	0/	1/1
Uterine cervix	Squamous cell carcinoma	2/	0/2
Uterus	Leiomyoma	0/	0/1
Uterus	Adenocarcinoma	1/	0/1
Uterus	Clear cell carcinoma of endometrium	1/	1/1

* Tumor cell and immune cell staining could not be differentiated.

2. Analytical Sensitivity

Analytical sensitivity of VENTANA PD-L1 (SP142) was assessed using 2630 NSCLC specimens, including 52 (2.0%) metastases. The prevalence and range of PD-L1 expression in NSCLC tissue specimens are shown in Table 7 below.

Table 7 - Summary of %TC and IC Distribution in Screened NSCLC Tissues

Tumor Cells (TC)			Tumor Infiltrating Immune Cells (IC)		
Cut-off	**Prevalence (TC)**	**Range of Scores**	**Cut-off**	**Prevalence (IC)**	**Range of Scores**
<1%	1947/2630 (74.0%)	0% - 100%	**<1%**	1041/2630 (39.6%)	0% - 50%
≥ 1%	683/2630 (26.0%)		**≥ 1%**	1589/2630 (60.4%)	
≥ 5%	506/2630 (19.2%)		**≥ 5%**	456/2630 (17.3%)	
≥ 50%	185/2630 (7.0%)		**≥ 10%**	166/2630 (6.3%)	

3. Repeatability

Repeatability studies for the VENTANA PD-L1 (SP142) Assay with NSCLC specimens were completed to demonstrate the following:

a. Intra-day Precision

The sample sets consisted of 18 NSCLC specimens with a range of PD-L1 expression for each TC and IC level. Tissues sections were stained with the VENTANA PD-L1 (SP142) Assay on a single BenchMark ULTRA instrument in a single day and evaluated for PD-L1 TC and IC expression.

b. Inter-day Precision

The sample sets consisted of 18 NSCLC specimens with a range of PD-L1 expression for each TC and IC level. Tissues sections were stained with the VENTANA PD-L1 (SP142) Assay using a single BenchMark ULTRA instrument on 5 non-consecutive days and evaluated for PD-L1 TC and IC expression.

c. Inter-instrument and Inter-lot Precision

The sample sets consisted of 46 NSCLC specimens with a range of PD-L1 expression for each TC and IC level. Three lots of VENTANA PD-L1 (SP142) Assay and three paired lots of the OptiView DAB IHC Detection Kit and the OptiView Amplification Kit on three BenchMark ULTRA instruments were tested.

For all studies, all slides were blinded and randomized, and then evaluated using the VENTANA PD-L1 (SP142) Assay NSCLC scoring algorithm. Results are summarized in Table 8 and 9.

Table 8 - Repeatability and Intermediate Precision of VENTANA PD-L1 (SP142) Assay staining of NSCLC specimens (PD-L1 Expression ≥ 50% TC)

Repeatability/ Intermediate Precision Parameter	Positive agreement % (95% CI)	Negative agreement % (95% CI)	Overall agreement % (95% CI)
Intra-day Repeatability (within a single day)	100.0% (88.6-100.0%)*	100.0% (83.9-100.0%)**	100.0% (92.9-100.0%)***
Inter-day Precision (5 non-consecutive days)	100.0% (94.0-100.0%)*	100.0% (90.4-100.0%)**	100.0% (96.2-100.0%)***
Inter-instrument and Inter-lot Precision (compared to case-level mode, across instruments and lots)	99.7% (98.1-99.9%)*	95.2% (91.2-97.5%)**	97.9% (96.2-98.9%)***

CI = Confidence Interval

* Positive Percent Agreement, Two-sided Wilson score method CI

** Negative Percent Agreement, Two-sided Wilson score method CI

*** Overall Percent Agreement, Two-sided Wilson score method CI

Table 9 - Repeatability and Intermediate Precision of VENTANA PD-L1 (SP142) Assay staining of NSCLC specimens (PD-L1 Expression ≥ 10% IC)

Repeatability/ Intermediate Precision Parameter	Positive agreement % (95% CI)	Negative agreement % (95% CI)	Overall agreement % (95% CI)
Intra-day Repeatability (within a single day)	100.0% (91.2-100.0%)*	100.0% (91.2-100.0%)**	100.0% (95.4-100.0%)***
Inter-day Precision (5 non-consecutive days)	100.0% (96.3-100.0%)*	100.0% (96.3-100.0%)**	100.0% (98.1-100.0%)***
Inter-antibody and Inter-detection Agreement (pairwise-comparison)	95.1% (91.1-98.1%)†	90.2% (82.3-96.2%)††	93.4% (88.7-97.5%)***
Inter-instrument and Inter-detection lots Agreement (pairwise-comparison)	96.3% (93.2-98.8%)†	92.7% (86.0-97.7%)††	95.1% (91.2-98.4%)***
Inter-instrument and Inter-antibody Agreement (pairwise-comparison)	96.3% (93.1-98.8%)†	92.6% (85.9-97.8%)††	95.1% (91.1-98.4%)***

CI = Confidence Interval

* Positive Percent Agreement, Two-sided Wilson score method CI

** Negative Percent Agreement, Two-sided Wilson score method CI

*** Overall Percent Agreement, Two-sided Wilson score method CI

† Average Negative Agreement, Bootstrapping method CI

†† Average Positive Agreement, Bootstrapping method CI

4. Reader Precision:

To assess Inter- and Intra-Reader Precision, three pathologists evaluated 80 unique NSCLC cases (45 PD-L1-positive and 35 PD-L1-negative) that were stained with the 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 (Table 4). Readers scored all specimens twice, with a minimum of two weeks between reads. The agreement rates between the readers, compared to a consensus score, across two reads, and between each

pathologist’s reads (measured as positive percent agreement (PPA), negative percent agreement (NPA), and overall percent agreement (OPA)) are summarized in Table 10.

Table 10 – Reader Precision with NSCLC specimens

Reader Precision	Agreement %*(95% CI)
Inter-reader Precision (average of all readers’ comparisons)	PPA: 89.2% (84.1-92.7%) NPA: 99.0% (96.3-99.8%) OPA: 93.5% (90.4-95.6%)
Intra-reader Precision (average of all readers’ agreement rates between first and second reads)	PPA: 90.1% (84.0-94.1%) NPA: 98.1% (92.8-99.5%) OPA: 93.6% (89.7-96.1%)

5. External Reproducibility

An inter-laboratory reproducibility study was conducted to demonstrate reproducibility of the assay in determining PD-L1 expression in NSCLC tissue specimens. Twenty-eight unique NSCLC specimens (14 PD-L1 positive and 14 PD-L1 negative) were stained at 3 external laboratories on each of 5 non-consecutive days over a period of at least 20 days. The sample set contained a total of 420 slides. Prior to reading, slides were blinded and randomized. At each site, the stained slides were independently evaluated by 2 pathologists (readers). Results are summarized in Table 11.

Table 11 - Inter laboratory Reproducibility of VENTANA PD-L1 (SP142) Assay in NSCLC

Reproducibility Parameter	Agreement % (95% CI)
Overall agreement (compared to a consensus score, across sites, days and readers)	PPA: 86.6% (83.0-89.5%) NPA: 99.8% (98.7-100.0%) OPA: 93.2% (91.3-94.7%)
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%)
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%)

*ANA = Average Negative Agreement, APA = Average Positive Agreement, NPA = Negative Percent Agreement, OPA = Overall Percent Agreement, PPA = Positive Percent agreement

6. Impact of Tissue Specimen Preparation and Treatment Studies

The objective of this study was to assess the effects of fixative type, fixation time, and delay to fixation time on PD-L1 antigenicity in formalin-fixed, paraffin-embedded tissues. This study utilized three human tumor cell line-derived murine xenograft models: CaSKi and Karpas 299, which both exhibit moderate to strong PD-L1 expression, and NCI-H820, which exhibits strong PD-L1 expression. Slides containing CaSKi, Karpas 299, and NCI- H820 xenograft tissues that were fixed under various conditions were stained in duplicate with VENTANA PD-L1

(SP142) Assay using the BenchMark ULTRA instrument.

For the fixative type and fixation time study, each case was fixed in 10% NBF, Zinc Formalin, 95% Ethanol, alcohol-formalin-acetic (AFA), Z-5, and Prefer fixatives for 1, 6, 12, 24, and 72 hours. The VENTANA anti-PD-L1 (SP142) Rabbit Monoclonal Primary Antibody demonstrated loss of stain intensity in tissues that were fixed for less than 6 hours. Prefer fixative showed diminished staining at all tested conditions. Fixatives such as AFA, PREFER fixative, or other alcohol-containing fixatives are not recommended for use with this assay.

For the delay to fixation study, each case had fixation time delayed for 0, 0.5, 1, 2, 6, and 24 hours prior to fixation in 10% NBF. All time points scored the same as immediate fixation for each of the xenografts. Thus, there was no degradation of PD-L1 antigenicity in response to delay in fixation with the VENTANA PD-L1 (SP142) Assay.

7. Impact of Tissue Thickness

The objective of this study was to verify the staining performance of VENTANA PD-L1 (SP142) Assay on NSCLC samples sectioned at various thicknesses (3, 4, 5, 6, and 7 microns) and evaluated using the scoring algorithm (Table 4). Fourteen unique cases were tested in duplicate as follows: 10 cases had PD-L1 expression at the TC3 cut-off level (5 positive, 4 negative and 1 around the cut-off), and 8 cases had PD-L1 expression at the IC3 cut-off level (4 positive, 4 negative, 2 around the cut-off). All tissue thicknesses demonstrated appropriate specific staining for PD-L1 and acceptable background levels. Sections did not exhibit a change in PD-L1 level within the range of thicknesses tested. The product labeling recommends that NSCLC specimens be cut at 4 microns for staining with VENTANA PD L1 (SP142) Assay.

8. Impact of Cut Slide Stability

The objective of this study was to determine the stability of PD-L1 antigenicity in FFPE NSCLC tissue sections stored under two different storage conditions, 4 °C and 30 °C. Cut slide stability was evaluated on NSCLC tissues from five cases at the TC3 cut-off level (2 positive, 3 negative, 1 around the cut-off) and five cases at the IC3 cut-off level (3 positive and 2 negative. Duplicate slides were tested. Slides sectioned and stained at the day 0 time point served as the baseline comparator for the remainder of the time points tested. One batch of slides was stored at a refrigerated temperature condition (4 °C) and one at an incubator temperature condition (30 °C). Slides were stained at each pre-defined designated time point (day 0, day 15,1month followed by monthly testing until 8 months) and staining results were compared to the day 0 baseline slides. PD-L1 antigen stability was determined to be one month for slides stored at 30 °C and 6 months for slides stored at 2-8 °C.

9. PD-L1 (SP142) Staining in Matched Primary vs. Metastatic NSCLC

The intent of this study was to characterize PD-L1 protein expression in tumor cells (TC) and tumor-infiltrating immune cells (IC) in matched primary and metastatic NSCLC tumors using the VENTANA anti-PD-L1 (SP142) Assay. Tissues were evaluated by one pathologist (reader) to assess PD-L1 status at the 5% TC/IC level. Eighty NSCLC cores (40 cases of primary lung cancer tissue and 40 matched lymph node metastases) were stained in duplicate with the VENTANA PD-L1 (SP142) Assay. One PD-L1 control block, containing a negative cell control pellet (Calu-3) and a positive cell control pellet (KARPAS299), was included in each run. Tonsil sections were also included as tissue controls for each run.

One metastatic lymph node case could not be evaluated for TC and IC scores due to interfering anthracotic pigment. The staining results for tumor TC and IC showed that 32 of the 39 remaining cases (82.1%) demonstrated concordant PD-L1 status for the primary and matched metastatic tumor samples. Seven of the 39 cases (17.9%) showed discordant results between the primary tumor sample and the matched metastatic tumor sample. Three of the discordant samples demonstrated positive PD-L1 status on the primary tumor and negative PD-L1 status on the matched metastatic tumor sample. Four of the discordant samples were negative for PD-L1 status on the primary tumor and positive for PD-L1 status on the matched metastatic tumor sample. The results indicate that PD-L1 protein expression may change when primary NSCLC cancers metastasize.

10. Impact of Tissue Block and Intra-Case Heterogeneity

This study evaluated existing NSCLC heterogeneity data for both block (throughout a block) and case (multiple blocks from the same case) based on the scoring criteria specified for this device. In addition, total immune cell infiltrate was analyzed. Previously stained slides were analyzed by one pathologist. For block heterogeneity studies, 24 NSCLC blocks were used. For case heterogeneity studies, 27 cases with a minimum of 2 blocks per case were used. PD-L1 expression ranged from no staining to 100% staining for both the immune cells and tumor cells. Block heterogeneity was 1/24 (4.2%) and case heterogeneity was 5/27 (18.6%). No clear patterns were identified in the total immune cell infiltrate analysis. Changes in IC scores trended with changes in total immune infiltrate which may serve as an indicator for selecting the appropriate block for testing in a NSCLC case that is negative for TC per the scoring algorithm.

11. Stability Testing

The objective of this study is to assess the stability (shelf-life and in-use) and shipping stress on three lots of the VENTANA PD-L1 (SP142) Assay. Dispensers from each of the three antibody lots were subjected to different stress conditions and then placed at intended storage (2-8 °C) for the duration of the study. Four NSCLC tissues were tested in triplicate at each time point. The

stress conditions were as follows:

a. Intended storage (2-8 °C) for the duration of the study. Testing was performed at 0, 3, 6, 9 and 12 months.
b. Product held at 30±5 °C for 192±5 hours, and then placed at 2-8 °C for the duration of the study.
c. Product held at 15±5 °C for 192±5 hours, and then placed at 2-8 °C for the duration of the study.
d. Product held at -20±5 °C for 192±5 hours, then placed at 2-8 °C for the duration of the study.

All lots passed for all conditions and support a 9 month stability claim when stored at 2 - 8°C.

B. Animal Studies

None

C. Additional Studies

None

X. SUMMARY OF PRIMARY CLINICAL STUDY

A. Study Design

The OAK study was a randomized, global, multisite, Phase III study comparing atezolizumab with docetaxel in previously treated metastatic or locally advanced NSCLC patients. The trial 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 tumor-infiltrating immune cells (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 or docetaxel administered intravenously at 75 mg/m2 every 3 weeks. Treatment with TECENTRIQ was to be continued until unacceptable toxicity or either radiographic or clinical progression, treatment with docetaxel until unacceptable toxicity, or disease progression. The OAK Study was designed with co-primary efficacy endpoints of overall survival (OS) in all randomized patients (ITT population) and in a PD-L1 selected subgroup in the primary analysis population (PP). Tumor specimens were retrospectively evaluated by a central laboratory for TC and IC status using the VENTANA PD-L1 (SP142) Assay and the results were used to define the PD-L1 expression subgroups for analyses.

1. Clinical Inclusion and Exclusion Criteria

Enrollment into the OAK trial was limited to patients who met the following inclusion criteria:

- Signed Informed Consent Form
- Ability to comply with protocol
- Aged ≥ 18 years
- Histologically or cytologically documented NSCLC that is currently locally Advanced or metastatic (i.e., Stage IIIB not eligible for definitive chemoradiotherapy, Stage IV, or recurrent) NSCLC (per the UICC/AJCC staging system, 7th edition; Detterbeck et al. 2009); pathological characterization may be from tumor specimens collected at a time when the NSCLC was at an earlier stage but must be sufficient to define patients as having either squamous or non-squamous histology.
- Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks (preferred) or at least 15 unstained slides, with an associated pathology report, for central testing and determined to be evaluable for tumor PD-L1 expression prior to study enrollment; patients with fewer than 15 unstained slides available at baseline (but no fewer than 10) may be eligible following discussion with Medical Monitor. Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellet from pleural effusion, and lavage samples are not acceptable. For core needle biopsy specimens, at least three cores should be submitted for evaluation.
- Disease progression during or following treatment with a prior platinum-containing regimen for locally advanced, unresectable/inoperable or metastatic NSCLC or disease recurrence within 6 months of treatment with a platinum-based adjuvant/neoadjuvant regimen or combined modality (e.g., chemoradiation) regimen with curative intent.
- Measurable disease, as defined by RECIST v1.1
- ECOG performance status of 0 or 1
- Life expectancy ≥ 12 weeks
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment
- For female patients of childbearing potential and male patients with partners of childbearing potential, agreement (by patient and/or partner) to use highly effective form(s) of contraception (i.e., one that results in a low failure rate [< 1% per year] when used consistently and correctly) and to continue its use for 6 months after the last dose of atezolizumab
- Patients must have recovered (i.e., improvement to Grade 1 or better) from all acute toxicities from previous therapy, excluding alopecia

Patients who did not meet any of the following criteria were excluded from study entry.

2. Follow-up Schedule

Efficacy:
Tumor assessments were conducted every 6 weeks for the first 36 weeks and

every 9 weeks thereafter. Tumor specimen slides were retrospectively evaluated by qualified pathologists for IC and TC using the VENTANA PD-L1 (SP142) Assay. The results were used to define the PD-L1 expression subgroups for the efficacy analyses.

Safety:
Patients were closely monitored for safety and tolerability throughout the study at each patient visit. Safety assessments consisted of monitoring and recording adverse events, including serious adverse events and non-serious adverse events of special interest, measurement of protocol-specified safety laboratory assessments, measurement of protocol-specified vital signs, and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

An adverse event was any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. Patients were followed for safety for 30 days following their last dose of study treatment (in both the initial treatment period and the re-treatment period) or until they received another anti-cancer therapy, whichever came first.

3. Clinical Endpoints

With regard to effectiveness, the primary efficacy endpoint of this study was overall survival (OS), defined as the time from randomization to death from any cause. Secondary efficacy outcome measures were as follows:

- Progression free survival (PFS), defined as time from randomization to the first occurrence of disease progression as determined by investigator using RECIST v1.1 or death from any cause;
- Objective response (i.e., confirmed best overall response of partial response or complete response) as determined by investigator using RECIST v1.1;
- DOR, defined as the time from first occurrence of a documented objective response to the time of disease progression as determined by the investigator using RECIST v1.1 or death from any cause, whichever comes first.

Safety was assessed for adverse events, including protocol-defined events of special interest, changes in laboratory test results, physical findings, changes in vital signs, and exposure to TECENTRIQ.

B. Accountability of PMA Cohort

An enrollment of 850 patients in the ITT population was initially planned in this study. With emerging data external to this study, the sample size of the OAK Study was increased to approximately 1100 patients (up to a maximum of 1300) in order to ensure that there are at least 220 patients with high PD-L1 expression levels, assuming a 20% prevalence of the TC3 or IC3 subgroup. The final enrollment was 1225 patients from global sites. The initial analysis of the trial is based on the

primary analysis population consisting of the first 850 randomized patients. PD-L1 expression was assessed in all enrolled patients based on the VENTANA PD-L1 (SP142) Assay. Of the 850 patients in the ITT population, 136 (16%) patients had high PD-L1 expression level (PD-L1 staining in ≥ 50% of TC or ≥ 10% of IC) and 714 (84%) did not have high PD-L1 expression level (PD-L1 staining in <50% TC and <10% IC).

C. Study Population Demographics and Baseline Parameters

The 850 ITT patients in the primary efficacy population (PP) were randomized to the atezolizumab (n = 425) and docetaxel (n = 425) arms. The secondary population comprised 1225 ITT patients, with 613 randomized to the atezolizumab arm and 612 randomized to the docetaxel arm. The demographics and baseline disease characteristics between the two treatment arms are shown in Table 12 below.

Table 12 - Demographics and Baseline Disease Characteristics

	Primary Population Docetaxel (n=425)	Primary Population Atezolizumab (n=425)	Secondary Population Docetaxel (n=612)	Secondary Population Atezolizumab (n=613)
Median age (years) Range	64.0 34−85	63.0 33−82	64.0 34−85	63.0 25−84
Age group <65 years (%)	218 (51.3)	235 (55.3)	326 (53.3)	335 (54.6)
Males (%)	259 (60.9)	261 (61.4)	379 (61.9)	378 (61.7)
Race [a]				
White (%)	296 (69.6)	302 (71.1)	432 (70.6)	438 (71.5)
Asian (%)	95 (22.4)	85 (20.0)	125 (20.4)	124 (20.2)
Tobacco use history (never smoked) (%)	72 (16.9)	84 (19.8)	96 (15.7)	112 (18.3)
Non-squamous histology per eCRF (%)	315 (74.1)	313 (73.6)	452 (73.9)	452 (73.7)
ECOG performance status score of 1 (%) [b]	265 (62.4)	270 (63.5)	378 (61.8)	392 (63.9)
One prior therapy (%) [c]	320 (75.3)	320 (75.3)	465 (76.0)	464 (75.7)

ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; ITT = intent to treat.
a Race also includes American Indian or Alaska Native, Black or African American, Native Hawaiian or other Pacific Islander, other, multiple, and unknown
b Versus ECOG performance status score of 0
c Versus two prior therapies.

D. Safety and Effectiveness Results

1. Safety Results

The VENTANA PD-L1 (SP142) Assay involves testing on FFPE NSCLC specimens. These tissues are routinely removed as part of the practice of medicine for the diagnosis of NSCLC by pathologists. Removal of these tissues, therefore, presents no additional safety hazard to the patient being tested.

The safety with respect to treatment with TECENTRIQ was addressed and summarized as part of the drug approval. Please see BLA 761041 for more information.

2. <u>Effectiveness Results</u>

The Phase III study was designed with OS as the major efficacy outcome measure. In the overall ITT population, irrespective of PD-L1 expression level, results demonstrated a statistically significant improvement in OS in patients randomized to TECENTRIQ as compared with docetaxel. Median OS in the ITT population was 13.8 months for TECENTRIQ compared to 9.6 months for docetaxel (HR=0.73, 95% CI: 0.62-0.87). These results demonstrate that there is a clinically meaningful benefit of TECENTRIQ in the ITT population. Figure 1 shows the Kaplan-Meier Plot of OS in the primary population, and Table 11 shows the efficacy results for the primary analysis population.

Figure 1 - Kaplan-Meier Plot of OS in the Primary Population (ITT)

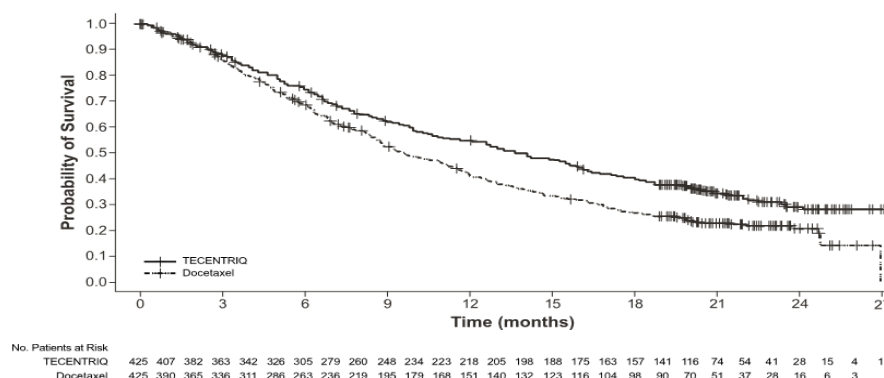

Table 13 - Efficacy Results in the Primary Analysis Population

	TECENTRIQ (n=425)	Docetaxel (n=425)
Overall Survival		
Deaths (%)	271 (64%)	298 (70%)
Median, months	13.8	9.6
(95% CI)	(11.8, 15.7)	(8.6, 11.2)
Hazard ratio[1] (95% CI)	0.74 (0.63, 0.87)	
p-value[2]	0.0004	

[1] Stratified by PD-L1 expression in tumor infiltrating immune cells, the number of prior chemotherapy regimens, and histology
[2] Based on the stratified log-rank test
CI=confidence interval

In the study, tumor specimens were evaluated retrospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory to define the PD-L1 expression subgroups for analyses. Of the 850 patients in the ITT population, 16% were classified as having high PD L1 expression. In the high PD-L1 expression subgroup, median OS was 20.5 months for TECENTRIQ and 8.9

months for docetaxel. Further, 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. These results support that there is clinical benefit of TECENTRIQ as compared to docetaxel, and further indicate that high PD-L1 expression is associated with increased OS vs that in patients who do not have high PD-L1 levels.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Hematology and Pathology Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The performance of the VENTANA PD-L1 (SP142) Assay was supported by the analytical and clinical validation studies.

The clinical performance of the VENTANA PD-L1 (SP142) Assay was demonstrated in a Phase III, global, multicenter, randomized, open label trial in patients with metastatic lung cancer who had progressed during or following a platinum-containing regimen. The Phase III study was designed with OS as the major efficacy outcome measure. In the ITT population, results demonstrated a statistically significant improvement in OS, in patients randomized to TECENTRIQ as compared with docetaxel and after a minimum follow up of 19 months. Median OS in the ITT population (regardless of PD-L1 status) was 13.8 months for TECENTRIQ compared to 9.6 months for docetaxel (HR=0.73, 95% CI: 0.62-0.87). In the high PD-L1 expression subgroup, median OS was 20.5 months for TECENTRIQ and 8.9 months for docetaxel. Thus, PD-L1 expression in $\geq$50% of TC and $\geq$10% of IC, as determined by the VENTANA PD-L1 (SP142) Assay, in NSCLC tissues may be associated with enhanced overall survival.

B. Safety Conclusions

The VENTANA PD-L1 (SP142) Assay is an *in vitro* diagnostic device, which tests tumor FFPE specimens collected from patients with NSCLC. The risks of the device are based on data collected in the clinical study. Failure of the device to perform as expected may lead to a failure to correctly interpret test results. The process of testing on FFPE tumor specimens does not present additional significant safety concerns, as these samples are routinely removed for diagnosis.

C. Benefit-Risk Conclusions

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The results from the VENTANA PD-L1 (SP142) Assay are associated with clinically meaningful OS in patients treated with TECENTRIQ (atezolizumab) and may help physicians determine the best treatment regimen and tailor therapies accordingly. The main risk of the VENTANA PD-L1 (SP142) Assay is obtaining a false result and consequently the potential to adversely affect patient management. However, this is not significant since this device is a complementary diagnostic and results from the clinical study demonstrated that patients, irrespective of PD-L1 status, may receive a benefit from TECENTRIQ. The risks associated with a false result are, therefore, relatively low.

Given the available information above, the data support that, for patients with previously treated locally advanced or metastatic NSCLC who are being considered for treatment with TECENTRIQ (atezolizumab), the probable benefits outweigh the probable risks.

Patient Perspective Information

This PMA did not include specific information on patient perspectives for this device.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The provided studies support the use of the VENTANA PD-L1 (SP142) Assay in NSCLC patients who are being considered for treatment with TECENTRIQ (atezolizumab).

XIII. CDRH DECISION

CDRH issued an approval order on October 18, 2016. The final conditions of approval cited in the approval order are described below.

The applicant’s manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.