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: P160002/S009

Date of FDA Notice of Approval: March 8, 2019

The VENTANA PD-L1 (SP142) Assay was approved on May 18, 2016 for the qualitative detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) urothelial carcinoma tissue and on October 18, 2016 for non-small cell carcinoma (NSCLC) tissue stained with OptiView DAB IHC Detection Kit and OptiView Amplifcation Kit on a VENTANA BenchMark ULTRA instrument. PD-L1 status is determined by the proportion of tumor area occupied by PD-L1 expressing tumor-infiltrating immune cells (% IC) of any intensity in urothelial carcinoma (S006). PD-L1 expression in ≥ 5% IC determined by VENTANA PD-L1 (SP142) Assay in urothelial carcinoma tissue is indicated as an aid in identifying urothelial carcinoma patients for treatment with TECENTRIQ (atezolizumab). PD-L1 expression in ≥ 50% tumor cells (TC) or ≥ 10% IC determined by VENTANA PD-L1 (SP142) Assay in NSCLC tissue may be associated with enhanced overall survival from TECENTRIQ (atezolizumab). The SSEDs to support the indication is available on the CDRH website and is incorporated by reference here.

The current supplement was submitted to expand the indication for the VENTANA PD-L1 (SP142) Assay to include triple negative breast cancer (TNBC) for treatment with TECENTRIQ™ (atezolizumab) in combination with paclitaxel protein-bound. PD-L1 positivity in TNBC is defined as PD-L1 staining of any intensity in IC covering ≥ 1% of tumor area occupied by tumor cells.

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 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 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.

VENTANA PD-L1 (SP142) Assay is indicated as an aid for identifying patients for treatment with the therapies for the respective cutoffs 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	Cut-off
Urothelial Carcinoma	TECENTRIQ	≥ 5% IC
Triple-Negative Breast Carcinoma (TNBC)	TECENTRIQ	≥ 1% IC

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).

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.

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.
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 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 Instrument and Software

The VENTANA PD-L1 (SP142) Assay is performed on the BenchMark ULTRA automated staining instrument using the VSS software version 12.5. 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 TNBC should be used within two months of cutting from the paraffin block when sample sections are stored at 30±5°C, and four months when tissue sample sections are stored at 5±3°C.

Test Controls

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

1) Positive and negative 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.

2) 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.

Additional information about positive and negative controls are avalailable in the product labeling.

Principles of Procedure

The VENTANA PD-L1 (SP142) Assay is 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.

Staining protocol

The VENTANA PD-L1 (SP142) Assay is automated for use on the BenchMark ULTRA automated slide stainer from deparaffinization through counterstaining.

Table 2: Staining Protocol for the BenchMark ULTRA

Protocol Parameter	Selection
Deparaffinization	Selected
Cell Conditioning	CC1 Cell Conditioning, 48 minutes, 100^0C
Pre-primary antibody peroxidase	Selected

Antibody Incubation or Negative Reagent Control	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. See VENTANA PD-L1 (SP142) Assay labeling for additional information on interpretation of control slides.

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 below.

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

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.

Patient tissue interpretation: PD-L1 staining with VENTANA PD-L1 (SP142) Assay in TNBC tissue can be observed in IC as well as TC. IC staining is often seen as

aggregates either in intratumoral or peritumoral stroma (invasive margin) or both locations. IC staining may also be observed as single cells dispersed among TC. The predominant IC staining pattern observed is dark brown punctate. PD-L1 staining TC demonstrates a membranous staining pattern. IC staining is scored as the proportion of tumor area covered with any discernible PD-L1 staining, of any intensity, in IC. The value is provided as a percentage. Tumor area is defined as the area occupied by TC, as well as their associated intratumoral and contiguous peritumoral stroma.

Table 4: VENTANA PD-L1 (SP142) Assay Scoring Algorithm for TNBC

Immune Cell (IC) Staining Assessment*	PD-L1 Expression
Absence of any discernible PD-L1 staining OR Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering	< 1% IC
Presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering ≥ 1% of tumor area occupied by tumor cells, associated intratumoral, and contiguous peritumoral stroma	≥ 1% IC

*PD-L1 staining in tumor cells should not be included in the scoring determination of TNBC patient tissue.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There is currently no alternative FDA-cleared or -approved immunohistochemistry assay available for detection of PD-L1 in FFPE TNBC 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 and in NSCLC since October 18, 2016.

VENTANA PD-L1 (SP142) Assay is globally marketed under two different part numbers. Combined distribution of the VENTANA PD-L1 (SP142) Assay, regardless of part number, includes marketing in the following countries: Algeria, Austria, Bahrain, Belgium, Brunei, Bulgaria, Canada, Chile, Croatia, Cyprus, Czech Republic, Denmark, Egypt, Estonia, Finland, France, Germany, Ghana, Greece, Haiti, Hong Kong, Hungary, Iceland, India, Ireland, Israel, Italy, Jamaica, Japan, Jordan, Kuwait, Laos, Latvia, Lebanon, Libya, Lithuania, Luxembourg, Macao, Macedonia, Malta, Monaco, Morocco, Myanmar, Netherlands, New Zealand, Norway, Philippines, Poland, Portugal, Puerto Rico, Romania, Serbia, Slovakia, Slovenia, South Africa, South Korea, Spain, Sudan, Sweden, Switzerland, Taiwan, Thailand, Tunisia, Turkey, United Arab Emirates, United Kingdom, and Vietnam.

VIII. PROBABLE 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 TNBC patients who are considering treatment with TECENTRIQ (atezolizumab).

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

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

Since approval of the original PMA (P160002), there have been no changes to the device design including reagent formulation or kit configuration. Nonclinical studies were performed using the VENTANA PD-L1 (SP142) Assay to support the analytical performance of the device at ≥1% IC cut-off for the TNBC indication. These studies were performed using TNBC specimens. 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 Sensitivity

Analytical sensitivity of VENTANA PD-L1 (SP142) was assessed based on 2,794 TNBC specimens, including 50 metastatic TNBC specimens. The results are shown in Tables 5 and 6 respectively.

Table 5: Prevalence of IC Satining in TNBC Specimens

PD-L1 Expression	Ratio	Prevalence	PD-L1 Status*
0 %	916/2794	32.8%	Negative
0.5%	490/279	17.5%	Negative
≥ 1%	1388/2794	49.7%	Positive
≥ 5%	490/2794	17.5%	Positive
≥ 10%	209/2794	7.5%	Positive

*Status is based on the IC1 (1%) cut-off

Table 6: Prevalence of IC Staining in Metastatic TNBC Specimens

PD-L1 Expression	Ratio	Prevalence	PD-L1 Status*
< 1%	11/50	22.0%	Negative
≥ 1%	39/50	78.0%	Positive
≥ 5%	13/50	26.0%	Positive
≥ 10%	9/50	18.0%	Positive

*Status is based on the IC1 (1%) cut-off

2. 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
See Summary of Safety and Effectiveness Data for P160002.

b. BLAST Results for SP142 Epitope
See Summary of Safety and Effectiveness Data for P160002.

c. Specificity of PD-L1 (SP142) on Cell Lines with PD-L1 or PD-L2
See Summary of Safety and Effectiveness Data for P160002.

d. Peptide inhibition studies
See Summary of Safety and Effectiveness Data for P160002.

e. Immunoreactivity in Human Tissues
See Summary of Safety and Effectiveness Data for P160002.

3. Robustness

Tissue thickness: This study was conducted to verify the staining performance of the VENTANA anti-PD-L1 (SP142) assay on TNBC tissues sectioned at 2, 3, 4, 5, 6, and 7µm when assessing the ≥1% IC cut-off. Ten (2 replicates each) TNBC samples of varying thickness were stained for each case, and blinded and randomized slides were reviewed by a trained pathologist. A tonsil tissue control slide was also stained for this study. PD-L1 expression status was assessed for each sample for concordance with the PD-L1 expression for the 4µm sections. Acceptance acrteria were as follows: At least 90% of the cases sectioned at 4µm must maintain the original PD-L1status. The assessment of all cases shall demonstrate that at least 90% of sections of a given thickness have a concordant PD-L1 status with that of the 4µm sections. Acceptable, non-specific PD-L1 (SP142) antibody background staining that does not interfere with slide interpretation should be less than or equal to 0.5 points, in at least 90% of sections stained. Study results showed that tissue thickness staining of 2, 3, 5, 6, and 7µm sections had 100% concordant PD-L1 (SP142) status with the reference slides of 4µm sections. Background acceptability rate was 100%**.**

4. Precision

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

a. Intra-day Precision

The sample sets consisted of 5 replicates from 24 unique TNBC specimens (12 positive, 12 negative,) with a range of PD-L1 expression including 4 specimens around the cut-off. 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 IC expression.

b. Inter-day Precision

The sample sets consisted of 2 replicates from 24 unique TNBC specimens (12 positive, 12 negative) with a range of PD-L1 expression including 4 specimens around the cut-off. 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 IC expression.

c. Inter-Instrument/Antibody Lot/Detection Kit Lot Precision

The sample sets consisted of 27 slides from 24 unique TNBC specimens (12 positive, 12 negative) with a range of PD-L1 expression including 4 specimens around the cut-off and 3 lots of the antibody and detection kits/amplification kits and 3 BenchMark ULTRA instruments.

For all studies, all slides were blinded and randomized, and then evaluated by a pathologist using the VENTANA PD-L1 (SP142) Assay TNBC scoring algorithm. Results are summarized in Table 7.

Table 7: Repeatability/Intermediate Precision with TNBC specimens (PD-L1 Expression ≥ 1% IC)

Repeatability/Intermediate Precision Parameter	Agreement % (95% CI)
Intra-day repeatability (within a single day)	PPA: 100.0 (94.0-100.0)* NPA: 95.0 (87.2-100.0) OPA: 97.5 (93.3-100.0)
Inter-day precision (5 non-consecutive days)	PPA: 100.0 (96.9-100.0)* NPA: 96.7 (92.7-100.0) OPA: 98.3 (96.3-100.0)
Inter-instrument and Inter-lot precision (3 instruments, 3 antibody lots, and 3 detection and amplification kit lots)	PPA: 98.3 (96.0-100.0) NPA: 99.2 (97.2-100.0) OPA: 98.6 (97.1-99.8)

C

CI = Confidence Interval, PPA = Positive Percent Agreement, NPA = Negative Percent Agreement, OPA= Overall Percent Agreement
Calculation: Percentile Bootstrap method unless otherwise indicated
*Two-sided Wilson score method CI

5. Reader Precision

To assess Inter- and Intra-Reader Precision, three pathologists evaluated 60 unique

TNBC specimens (30 positive and 30 negative) including 6 specimens around the cut-off 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 TNBC. Readers scored all specimens twice, with a minimum of two weeks between reads. The agreement rates between the readers and between each pathologist's reads are summarized in Table 8 below.

Table 8: Reader Precision with TNBC specimens (PD-L1 Expression ≥ 1% IC)

Reader Precision	Agreement % (95% CI)
Inter-reader Precision* (average of reader-to-reader pairwise comparisons from first read)	APA: 91.1 (86.0, 95.7) ANA: 91.1 (86.1, 95.6) OPA: 91.1 (86.7, 95.6)
Intra-reader Precision (average of all readers' agreement rates between first and second reads)	APA: 93.8 (89.5-97.1) ANA: 93.9 (89.2-97.3) OPA: 93.9 (89.9-97.2)

*Stratified bootstrap analysis

6. External Reproducibility

An inter-laboratory reproducibility (ILR) study was conducted to demonstrate reproducibility of the assay in determining PD-L1 expression in TNBC tissue specimens on the BenchMark ULTRA instrument. Twenty-eight unique TNBC 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 419 slides (140 slides for two sites and 139 slides for the third site). 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 9.

Table 9: ILR with TNBC Specimens (PD-L1 Expression ≥ 1% IC)

Inter-laboratory Reproducibility	Agreement % (95% CI)
Overall agreement (compared to a consensus score, across sites, days and readers)	PPA: 93.2 (90.4-95.2) † NPA: 96.6 (94.4-98.0) † OPA: 94.8 (93.1-96.1) †
Inter-site agreement (average of site-to-site pairwise comparisons)	APA: 91.5 (85.6-96.0)* ANA: 91.3 (86.6-95.7)* OPA: 91.4 (86.4-95.9)*
Inter-reader agreement (average of reader-to-reader pairwise comparisons within each site)	APA: 93.6 (88.2-97.0) ANA: 93.3 (87.8-96.7) OPA: 93.4 (90.6-95.4)†

*Stratified bootstrap analysis
† Two-sided Wilson score method CI

7. Stability Studies

a. Cut Section Stability

The purpose of the cut slide stability study was to determine the time point at which degradation of PD-L1 antigenicity in formalin-fixed, paraffin-embedded (FFPE) TNBC tissue sample sections stored under two different storage conditions, 5±3°C and 30±5°C, impacts staining performance. Five TNBC single-tissue cases were included to represent the range of PD-L1 expression as follows: 1 case IC0 (0-<1% IC), 2 cases IC1 (1-<5% IC), 1 case IC2 (5-<10% IC), and 1 case IC3 (>10% IC). Time points tested wrere as follows: Day 0 (reference), Day 15, one-month intervals till 5 months. The acceptance criteria were as follows: For a cut slide stability time point to be considered acceptable, VENTANA PD-L1 (SP142) assay shall demonstrate staining that does not result in a lower IC Score as compared to that of the Day Zero (baseline) slide.

The study met the acceptance criterion and product requirement of one-month antigen stability on unstained cut slides for both refrigerated and room temperature storage conditions. The data support two months of cut slide stability when TNBC tissue sample sections are stored at 30±5°C, and four months of cut slide stability when TNBC tissue sample sections are stored at 5±3°C.

b. VENTANA PD-L1 (SP142) Assay Stability

The objective of this study was to assess the stability (shelf-life and in-use) and shipping category of the PD-L1 (SP142) Assay for the TNBC indication. Three stability master lots of VENTANA-PD-L1 (SP142) Assay were subjected to different stress conditions and then placed at the intended storage condition (2°C - 8°C). The conditions tested were as follows:

- Ship Stress
  - Intended Storage (2°C -8°C)
  - Hot Ship Stress Cat. A (30°C±5ºC 192 hours)
  - Hot Ship Stress Cat. B (15°C±5ºC 192 hours)
  - Cold Ship Stress Freeze/Thaw (-20°C±5ºC 192 hours)
- On-Board Stability
- Open Vial Stability

FFPE TNBC tissues was tested in triplicate at multiple time points. All lots passed for all conditions to support a 24-month stability claim under intended storage condition (2°C-8°C).

B. Animal Studies

None

C. Additional Studies

1. Impact on Ischemia/Fixation

See SSED for P160002.

2. **Intra-Case Heretogeneity/Intra-Block Heretogeneity**
   This study evaluated existing TNBC heterogeneity data for both case (multiple blocks from the same case) and FFPE block (multiple sections from the same block) heterogeneity by IC 1% PD-L1 expression. PD-L1 expression ranged from no staining to 100% staining for both the immune cells and tumor cells. There were no acceptance criteria as both the tissue and case heterogeneity studies are for characterization only. In addition, total immune cell infiltrate was analyzed. Previously stained slides were analyzed by one pathologist.
   Intra-case heterogeneity: Twelve cases encompassing 37 TNBC FFPE blocks were used in this study. Case heterogeneity was observed in 3 cases (25%) when assessed at the 1% IC cut-off.
   Intra-block heterogeneity: Ten FFPE blocks were used in this study. Block heterogeneity was not observed in any of the TNBC blocks tested for the 1% IC cut-off.

3. **Primary versus Metastatic cancer**
   The intent of this study was to characterize PD-L1 protein expression in tumor infiltrating immune cells in matched primary and metastatic TNBC tumors using the VENTANA anti-PD-L1 (SP142) assay in order to determine if there are changes in PD-L1 protein expression when primary TNBC tumors metastasize. Tissues were evaluated to assess the PD-L1status by one reader (pathologist).

   Four slides were sectioned from each of the 50 matched TNBC cases (4 from the primary and 4 from the metastatic tumors). One slide for each case of primary and metastatic cancer was used for H&E staining (three unstained slides per primary and metastatic cancer remained). Duplicate slides for each block (primary and corresponding metastatic cancer) were stained with VENTANA PD-L1 (SP142) antibody, and one slide was stained with Rabbit Monoclonal Negative Control Ig to test for non-specific background staining. IC scores were assigned.

   There were two primary TNBC tissues where there was no tumor present for evaluation and two more metastatic tissues with insufficient tumor for evaluation. Therefore, four paired cases were excluded from the analysis. Two additional samples required repeat staining due to tissue tearing and/or tissue loss.

   There were 46 sets with scores for both the primary TNBC and metastatic tissue available for comparison. Of these 46 sets, there were 18 sets (18/46, 39%) that exhibited different IC scores between the primary carcinoma vs. metastatic tissues. Of the 18 sets that exhibited different IC scores, 10 exhibited higher IC scores for the primary cancer tissue compared to the metastasis, and 8 exhibited higher IC scores for the metastasis compared to the primary cancer. In the remaining 28 sets, no change in IC was found. This data suggests that there can be changes in PD-L1 protein expression when primary TNBCs metastasize.

4. **Control Cell Line Validation**
   See SSED for P160002.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The clinical performance of the VENTANA PD-L1 (SP142) Assay as a companion diagnostic device for the TNBC indication for atezolizumab was based on the clinical trial WO29522 (IMpassion130).

A. Study Design

IMpassion130 was a phase 3, multicenter, multinational, randomized, placebo controlled study of atezolizumab (anti PD-L1 antibody) in combination with paclitaxel protein-bound compared with placebo with paclitaxel protein-bound for previously untreated unresectable locally advanced or metastatic TNBC patients.

The primary objective of this study was to evaluate progression free survival (PFS) per investigator assessment using RECIST v1.1, and overall survival (OS) in TNBC patients treated with atezolizumab+paclitaxel protein-bound compared with Placebo+paclitaxel protein-bound. Eligible patients were randomized in a 1:1 ratio to receive atezolizumab (840 mg) or placeboIV infusions on Days 1 and 15 of every 28-day cycle plus paclitaxel protein-bound(100 mg/m2) administered via IV infusion on Days 1, 8, and 15 of every 28-day cycle. Randomization was stratified by the following three factors: presence of liver metastases (yes vs. no); prior taxane treatment (yes vs. no); and tumor PD-L1 status ((< 1% IC vs. ≥ 1% IC)). Tumor assessments per RECIST v1.1 were performed.

1. Clinical Inclusion and Exclusion Criteria

   Inclusion Criteria:

   Metastatic or locally advanced, histologically documented TNBC characterized by absence of human epidermal growth factor 2 (HER2), estrogen receptor (ER), and progesterone receptor (PR) expression

   - No prior chemotherapy or targeted systemic therapy for inoperable locally advanced or metastatic TNBC
   - Eligible for taxane monotherapy (i.e., absence of rapid clinical progression, life threatening visceral metastases, or the need for rapid symptom and/or disease control)
   - A representative formalin-fixed, paraffin-embedded tumor specimen in paraffin blocks, or at least 20 unstained slides with an associated pathology report documenting ER, PR, and HER2 negativity. Participants with fewer than 20 unstained slides available at baseline, and not fewer than 12 unstained slides will be eligible upon discussion with Medical Monitor
   - Eastern Cooperative Oncology Group performance status of 0 or 1
   - Measurable disease as defined by RECIST v1.1
   - Adequate hematologic and end-organ function

Exclusion Criteria:

- Known central nervous system (CNS) disease, except for treated asymptomatic CNS metastases
- Leptomeningeal disease
- Pregnancy or lactation
- History of autoimmune disease
- Prior allogeneic stem cell or solid organ transplantation
- Positive test for human immunodeficiency virus
- Active hepatitis B or hepatitis C
- Receipt of a live, attenuated vaccine within 4 weeks prior to randomization, during treatment, or within 5 months following the last dose of atezolizumab/placebo

2. Follow-up Schedule

   Tumor assessments were performed at baseline and approximately every 8 weeks for the first 12 months after Cycle 1, Day 1 and every 12 weeks thereafter until disease progression or treatment discontinuation, whichever was later.

3. Clinical Endpoints

   The following efficacy objectives were evaluated in both the intent-to-treat (ITT) population (i.e., all randomized patients) and the subpopulation with programmed death-ligand 1(PD-L1) - selected tumor status.

   The co-primary efficacy objectives for this study were as follows:

   - To evaluate the efficacy of atezolizumab+paclitaxel protein-bound compared with Placebo+paclitaxel protein-bound as measured by PFS
   - To evaluate the efficacy of atezolizumab+paclitaxel protein-bound compared with Placebo+paclitaxel protein-bound as measured by OS

   The secondary efficacy objectives for this study were as follows:

   - To evaluate the efficacy of atezolizumab+paclitaxel protein-bound compared with Placebo+ paclitaxel protein-bound as measured by objective response rate (ORR; per investigator assessment using RECIST v1.1)
   - To evaluate the efficacy of atezolizumab+paclitaxel protein-bound compared with Placebo+paclitaxel protein-bound as measured by duration of objective response (DOR; per investigator using RECIST v1.1) among patients with an objective response
   - To evaluate patient-reported outcomes (PROs) of health status/health-related quality of life (HRQoL) associated with atezolizumab+paclitaxel protein-bound compared with placebo+paclitaxel protein-bound,as measured by the time to deterioration (TTD) in Items 29 and 30 of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30)

With regard to safety, information about adverse events was collected from time of signed informed consent throughout the treatment period and up to 30 days after their last dose of study drug or until initiation of a new anti-cancer treatment, whichever occured first. The safety analysis was performed in all patients who had received at least 1 dose of study treatment.

With regard to effectiveness, the intent-to-treat (ITT) population were patients with locally advanced or metastatic TNBC and served as the primary population for the efficacy analyses in this trial. Tumor specimens (archival or fresh) were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used as a stratification factor [PD-L1 score (IC0 [PD-L1 expression < 1%] vs. IC1/2/3 [PD-L1 expression ≥ 1% IC]) for randomization and to define the PD-L1 expression subgroups for pre-specified analyses.

B. Accountability of PMA Cohort

The PMA cohort consisted of a total of 902 patients with locally advanced or metastatic TNBC in Study IMpassion130. Additional details are in Table 10 below.

Table 10: Accountability of PMA Cohort

Population	Number of Subjects
All Screened Subjects[1]	1234
Intent-to-Diagnose (ITD) Population[2]	1116
Total Exclusions	118
Screen Failure Prior to Central Testing	110
Sample Characteristics Not Acceptable	8
Intended Use (IU) Population[3]	904
Total Exclusions	330
ITD Population Exclusions	118
WO29522 Inclusion/Exclusion Criteria	212
Intent-to-Treat (ITT) Population[4]	902
Total Exclusions	332
ITD Population Exclusions	118
PD-L1 (SP142) Score Not Evaluated	5
Other Criteria Exclusions (not PD-L1–related)	209

[1]Includes all subjects who signed informed consent for study IMpassion130 enrollment eligibility screening

[2] Includes all subjects for whom a diagnostic assessment was attempted with the VENTANA PD-L1 (SP142) Assay as part of screening for study IMpassion130

[3] Includes all subjects in the ITD population for whom the final staining attempt was performed who met all non-PD-L1 (SP142) assay-related eligibility requirements for study IMpassion130

[4] Includes all randomized patients whether or not the assigned study treatment was received

Sample characteristics by PD-L1 score as determined by the VENTANA PD-L1 (SP142) Assay are shown in Table 11 below.

Table 11: Sample Characteristics by PD-L1 (SP142) Score - ITD Population[1]

Parameter	PD-L1 Score			
	IC0 (N = 533)	IC1/2/3 (N = 369)	Not Evaluated (N = 214)	All Patients (N = 1116)
Collection Point, n (%)				
Archival Tissue	381 (71.5)	295 (79.9)	166 (77.6)	842 (75.4)
Screening/Baseline	152 (28.5)	74 (20.1)	48 (22.4)	274 (24.6)
Collection Type, n (%)				
Resection Specimens	102 (19.1)	144 (39.0)	81 (37.9)	327 (29.3)
Biopsy Specimens	409 (76.7)	212 (57.5)	124 (57.9)	745 (66.8)
Other Specimens	22 (4.1)	13 (3.5)	9 (4.2)	44 (3.9)
Disease Status, n (%)				
Primary Lesion	316 (59.3)	249 (67.5)	157 (73.4)	722 (64.7)
Metastatic Lesion	217 (40.7)	120 (32.5)	57 (26.6)	394 (35.3)

[1]The Intent-to-Diagnose (ITD) population includes all subjects for whom a diagnostic assessment was attempted with VENTANA PD-L1 (SP142) Assay as part of screening for Study IMpassion130

C. Study Population Demographics and Baseline Parameters

Study enrollment occurred at multiple geographic regions, and 187 subjects were in the US. The baseline characteristics are shown in the table below.

Table 12: Subject Characteristics by PD-L1 (SP142) Score - ITT Population[1]

Parameter	PD-L1 Score[2]		All Patients (N = 902)
	IC0 (N = 533)	IC1/2/3 (N = 369)	
Age (yr)			
n	533	369	902
Mean (SD)	55.7 (12.01)	53.6 (12.47)	54.8 (12.23)
Median	56.0	53.0	55.0
Min, max	20, 86	26, 85	20, 86
Age Group (yr)			
n	533	369	902
<65	400 (75.0%)	283 (76.7%)	683 (75.7%)
≥65	133 (25.0%)	86 (23.3%)	219 (24.3%)
Sex			
n	553	369	902
Male	3 (0.6%)	1 (0.3%)	4 (0.4%)
Female	530 (99.4%)	368 (99.7%)	898 (99.6%)
Ethnicity			
n	533	369	902
Hispanic/Latino	83 (15.6%)	60 (16.3%)	143 (15.9%)

Not Hispanic/Latino	422 (79.2%)	287 (77.8%)	709 (78.6%)
Not Reported	14 (2.6%)	12 (3.3%)	26 (2.9%)
Unknown	14 (2.6%)	10 (2.7%)	24 (2.7%)
Race n	533	369	902
American Indian/Alaska Native	23 (4.3%)	17 (4.6%)	40 (4.4%)
Asian	95 (17.8%)	66 (17.9%)	161 (17.8%)
Black/African American	36 6.8%)	23 (6.2%)	59 (6.5%)
Native Hawaiian/Pacific Islander	1 (0.2%)	0 (0.0%)	1 (0.1%)
White	355 (66.6%)	254 (68.8%)	609 (67.5%)
Unknown	18 (3.4%)	9 (2.4%)	27 (3.0%)
Multiple	5 (0.9%)	0 (0.0%)	5 (0.6%)
Country n		369	902
USA	124 (23.3%)	63 (17.1%)	187 (20.7%)
Ex-USA	409 (76.7%)	306 (82.9%)	715 (79.3%)
Region n	533	369	902
North America	142 (26.6%)	88 (23.8%)	230 (25.5%)
Australia	26 (4.9%)	16 (4.3%)	42 (4.7%)
Asia	88 (16.5%)	57 (15.4%)	145 (16.1%)
Europe	197 (37.0%)	151 (40.9%)	348 (38.6%)
Latin America	80 (15.0%)	57 (15.4%)	137 (15.2%)

[1]The Intent-to-Treat (ITT) population includes all randomized patients whether or not the assigned study treatment was received

[2]PD-L1 (SP142) score used for enrollment decision prior to randomization. For the purposes of this study, a case slide with a PD-L1 score of "< 1%" was considered "IC0" and a case slide with a PD-L1 score of "≥ 1%" was considered "IC1/2/3"

D. Safety and Effectiveness Results

1. Safety Results

   In the trial, there were no device related adverse events. TECENTRIQ was discontinued due to adverse reactions in 6% (29/452) of patients in the TECENTRIQ and paclitaxel protein-bound arm. Serious adverse reactions occurred in 23% (103/452) of patients receiving TECENTRIQ and paclitaxel protein-bound arm. The most frequent serious adverse reactions reported included pneumonia (2%), urinary tract infection (1%), dyspnea (1%), and pyrexia (1%). Fatal adverse reactions occurred in 1.3% (6/452) of patients in the TECENTRIQ and paclitaxel protein-bound arm. Safety of the drug was also addressed in the previous drug approvals.

2. Effectiveness Results

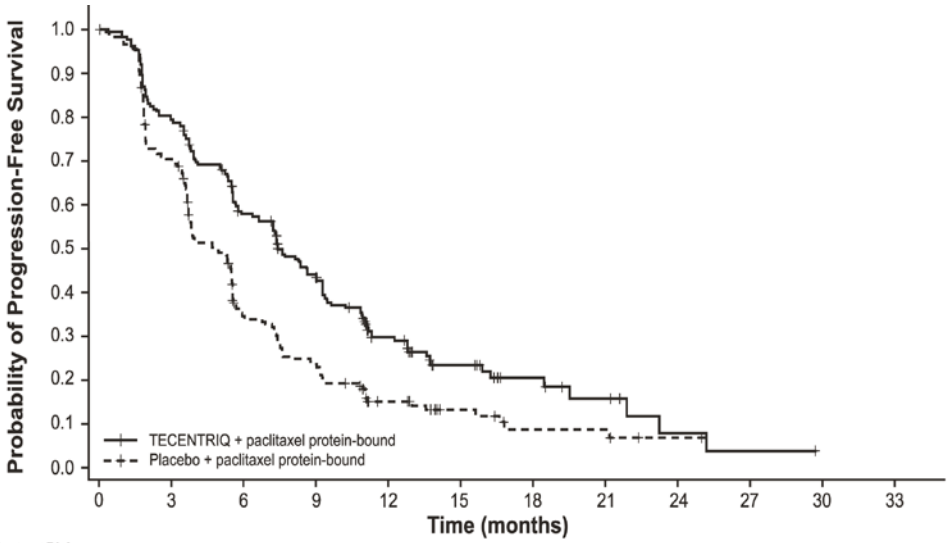
The analysis of effectiveness was based on the 369 evaluable patients who had positive PD-L1 expression (IC ≥1%). Key effectiveness outcomes are presented in Table 13 and Figure 1 below.

Table 13: Efficacy Results from IMpassion130 in Patients with PD-L1 Expression ≥ 1%

	PD-L1 Expression ≥ 1%[1]	
	TECENTRIQ in combination with paclitaxel protein-bound	**Placebo in combination with paclitaxel protein-bound**
Progression-Free Survival[2,3]	(n=185)	(n=184)
Events (%)	136 (74)	151 (82)
Median, months	7.4 (6.6, 9.2)	4.8 (3.8, 5.5)
Stratified Hazard ratio (95% CI)[4]	0.60 (0.48, 0.77)	
p-value	<0.0001	
Objective Response Rate[2,3,5,6]	n=185	n=183
Number of responders (%)	98 (53)	60 (33)
(95% CI)	(45.5, 60.3)	(26.0, 40.1)
Complete response (%)	17 (9)	1 (<1)
Partial response (%)	81 (44)	59 (32)
Duration of Response[2,3,6]	n=98	n=60
Median (months)	9.2	6.2
(95% CI)	(7.5, 11.9)	(5.5, 8.8)

[1] PD-L1 expression in tumor-infiltrating immune cells (IC)
[2] As determined by investigator assessment
[3] per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1)
[4] Stratified by presence of liver metastases, and by prior taxane treatment
[5] Patients with measurable disease at baseline
[6] Confirmed responses
PFS=Progression-Free Survival; CI=Confidence Interval; ORR=Objective Response Rate; DOR=Duration of Response; NE=Not Estimable

Figure 1: Kaplan-Meier Plot of Progression-Free-Survival in IMpassion130 in Patients with PD-L1 Expression ≥1%



3. Subgroup Analyses
   There was no subgroup analyses performed in this trial.

4. Pediatric Extrapolation
   In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

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. The pivotal clinical study included 7 investigators. 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. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Not applicable

XII. 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.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Effectiveness of the of VENTANA PD-L1 (SP142) Assay is based on the clinical performance and benefit to patients with unresectable, locally advanced or metastatic TNBC as assessed in the study IMpassion130 which was conducted to evaluate the safety and the efficacy of TECENTRIQ (atezolizumab) in combination with paclitaxel protein-bound in these patients who had not received chemotherapy for metastaic disease. In this randomized trial, the VENTANA PD-L1 (SP142) Assay was used to determine patient PD-L1 status. TECENTRIQ (atezolizumab) in combination with paclitaxel protein-bound demonstrated a significant improvement in PFS for TNBC patients who had tumors that expressed PD-L1 with a IC $\geq$ 1% [PFS: median months of 7.4 (6.6, 9.2)] who had not received chemotherapy for metastatic disease compared to Placebo in combination with paclitaxel protein-bound [PFS: median months 4.8 (3.8, 5.5)] responses in TNBC patients. The data supports the performance of this device in identifying TNBC cancer patients who will benefit from the therapeutic when used in accordance with the instructions for use.

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

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory studies as well as data collected in a clinical study conducted to support PMA approval as described above.

The VENTANA PD-L1 (SP142) is an *in vitro* diagnostic device, which involves tumor specimens collected from patients with TNBC. The risks of the device are based on data collected in the clinical study conducted to support PMA approval as described above. Risks of the VENTANA PD-L1 (SP142) are associated with failure of the device to perform as expected or failure to correctly interpret test results. As VENTANA PD-L1 (SP142) is intended for use to identify patients for TECENTRIQ (atezolizumab) therapy, if incorrect, or false, results are reported, then TNBC patients may not receive the proper treatment. Patients with false positive results may undergo treatment with TECENTRIQ (atezolizumab) without much clinical benefit, and may experience adverse reactions associated with TECENTRIQ (atezolizumab) therapy. Patients with false negative results may not be considered for treatment with TECENTRIQ (atezolizumab), and therefore, may receive other treatment options. There is also a risk of delayed results, which may lead to a delay in treatment with TECENTRIQ (atezolizumab).

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in the clinical study used to support panel track PMA supplement approval as described above.

The probable risks of the device are also based on data collected in the clinical study, which were used to support panel track PMA supplement approval as described above.

The clinical benefit of TECENTRIQ (atezolizumab) in combination with paclitaxel protein-bound was investigated in a multicenter, open-label, randomized clinical study conducted to assess the safety and efficacy of TECENTRIQ (atezolizumab) in combination with paclitaxel protein-bound in patients with TNBC. Clinical study samples were tested at a US based reference laboratory with VENTANA PD-L1 (SP142) assay. TECENTRIQ (atezolizumab) demonstrated a robust overall response rate with a clinically meaningful duration of response in TNBC patients with positive PD-L1 expression (IC $\geq$ 1%) as determined by the VENTANA PD-L1 (SP142) assay. The response rate in patients with positive PD-L1 expresssing TNBC is better than what would be expected of available therapy and represents an improvement that is reasonably likely to predict clinical benefit.

Additional factors to be considered in determining probable risks and benefits for the VENTANA PD-L1 (SP142) assay included: analytical performance of the device, and the availability of alternative tests. The primary risks associated with the VENTANA PD-L1 (SP142) assay are the possibility of inaccurate or false results that may lead to mismanagement of patient treatment. The performance of the device is supported by analytical validation studies. The VENTANA PD-L1 (SP142) assay is currently FDA-approved for use in the urothelial cancer and non-small cell lung cancer indications. Thus, the probable benefits are based on evaluation that the test performs consistently and provides clinically relevant results for evaluating PD-L1 status (IC $\geq$ 1%) in TNBC patients who are being considered for treatment with TECENTRIQ (atezolizumab).

Together these data support a positive benefit-risk profile for atezolizumab in combination with paclitaxel protein-bound for the treatment of patients with TNBC.

Patient Perspectives

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

In conclusion, given the available information above, the data support that for the use of this device in selecting patients with unresectable locally advanced or metastatic TNBC whose tumors have PD-L1 expression $\geq$ 1% and who have not received prior chemotherapy for metastatic disease for treatment with TECENTRIQ (atezolizumab), the probable benefits outweigh the probable risks.

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. Data from the a phase 3, multicenter, multinational, randomized, placebo controlled clinical study support the use of the VENTANA PD-L1 (SP142) Assay as an aid in selecting patients with unresectable locally advanced or metastatic TNBC that had not received chemotherapy for metastatic disease with PD-L1 IC $\geq$ 1% who may be eligible for treatment with TECENTRIQ (atezolizumab) in combination with paclitaxel protein-bound. These patients showed a significant improvement in PFS when treated with TECENTRIQ (atezolizumab).

XIV. CDRH DECISION

CDRH issued an approval order on March 8, 2019.

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

XV. 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.