# SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

## I. GENERAL INFORMATION

| | |
|---|---|
| Device Generic Name: | In vitro diagnostic immunohistochemistry (IHC) for detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) human tissue sections |
| Device Trade Name: | VENTANA PD-L1 (SP263) Assay |
| Device Procode: | PLS |
| Applicant's Name and Address: | Ventana Medical Systems, Inc.<br>1910 E Innovation Park Drive<br>Tucson, AZ 85755 |
| Date(s) of Panel Recommendation: | None |
| Premarket Approval Application (PMA) Number: | P160046/S013 |
| Date of FDA Notice of Approval: | March 1, 2023 |

The original PMA (P160046) was approved on May 1, 2017 and is indicated for the qualitative detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) urothelial carcinoma tissue with OptiView DAB IHC Detection Kit on a VENTANA BenchMark ULTRA instrument.

On October 15, 2021, the indication for VENTANA PD-L1 (SP263) Assay to identify patients with urothelial carcinoma, for treatment with IMFINZI™ (durvalumab) was removed due to the withdrawal of the drug indication.

On October 15, 2021, VENTANA PD-L1 (SP263) Assay was approved as a companion diagnostic (CDx) for identifying patients with non-small cell lung carcinoma (NSCLC) with PD-L1 status of ≥ 1% tumor cells (TC) for treatment with TECENTRIQ. The SSED to support the previously approved 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 (SP263) Assay to include non-small cell lung carcinoma (NSCLC) PD-L1 ≥ 50% TC for treatment with LIBTAYO.

## II. INDICATIONS FOR USE

VENTANA PD-L1 (SP263) Assay is a qualitative immunohistochemistry assay using rabbit monoclonal anti-PD-L1 clone SP263 intended for use in the assessment of the programmed death ligand-1 (PD-L1) protein in formalin-fixed, paraffin-embedded (FFPE) non-small cell lung carcinoma (NSCLC) tissue specimens by light microscopy. The VENTANA PD-L1 (SP263) Assay is used with the OptiView DAB IHC Detection Kit for staining on the BenchMark ULTRA instrument.

PD-L1 protein expression in NSCLC is determined by the percentage of tumor cells (% TC) with any membrane staining above background.

VENTANA PD-L1 (SP263) assay is indicated as an aid in identifying patients eligible for treatment with the therapy listed in Table 1 for the indication and PD-L1 status in accordance with the approved therapeutic product labeling.

**Table 1. VENTANA PD-L1 (SP263) Assay Companion Diagnostic Indication**

| Indication for Use | PD-L1 Cut-off | Therapy |
|---|---|---|
| NSCLC | ≥ 1% TC | TECENTRIQ (atezolizumab) |
| NSCLC | ≥ 50% TC | LIBTAYO (cemiplimab-rwlc) |

Results of the VENTANA PD-L1 (SP263) Assay 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 (SP263) Assay product labeling.

## V. DEVICE DESCRIPTION

### A. Device Kit Components

VENTANA PD-L1 (SP263) 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 Kit. VENTANA PD-L1 (SP263) 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. Table 2 below provides an overview of the VENTANA PD-L1 (SP263) Assay Components.

**Table 2. Overview of the VENTANA PD-L1 (SP263) Assay Components**

| Device Components | Packaged Form | Description |
|---|---|---|
| VENTANA anti-PD-L1 (SP263) Rabbit Monoclonal Primary Antibody | Dispenser: 50 tests | One 5 mL dispenser of VENTANA PD-L1 (SP263) contains approximately 8.05 µg of a rabbit monoclonal antibody. The antibody is diluted in 0.05 M Tris-HCI with 1% carrier protein, and 0.10% ProClin 300, a preservative. Total protein concentration of the reagent is approximately 10 mg/mL. The specific antibody concentration is approximately 1.61 µg/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 horseradish peroxidase (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. |
| BenchMark ULTRA (IHC/ISH) automated staining instrument and VSS system software | Instrument installed with the VSS host system software | A personal computer (PC) that runs on Microsoft Windows controls and monitors the BenchMark ULTRA instrument via the host operating software.<br>The BenchMark ULTRA software has been developed per FDA's guidance on the development of Medical Device 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. |

Ancillary reagents required for the assay are listed below:

- Hematoxylin II
- Bluing Reagent
- Reaction Buffer (10x)
- EZ Prep Reagent (10x)
- ULTRA Cell Conditioning (CC1) (Pre-dilute)

- ULTRA Liquid Cover Slip (LCS) (Pre-dilute)

## B. Device Instrumentation and Software

The VENTANA PD-L1 (SP263) Assay is performed on the BenchMark ULTRA automated staining instrument using the VSS Software versions 12.3 to 12.5.3. The VENTANA PD-L1 (SP263) Assay protocol is assay specific. The software has been designed to recognize and group VENTANA PD-L1 (SP263) Assay, requiring that all system reagents are used together.

## C. Specimen Preparation

Routinely processed, FFPE tissues are suitable for use with this VENTANA PD-L1 (SP263) Assay. Ventana recommends tissue fixation in 10% neutral buffered formalin (NBF) for a period of at least 6 hours and for a maximum of 72 hours. Acceptable fixatives for use with VENTANA PD-L1 (SP263) are Zinc Formalin and Z-5 fixatives when used with at least 6 hours of fixation time. The amount used should be 15 to 20 times the volume of tissue. Fixation can be performed at 15°C - 25°C. Other fixatives, including 95% alcohol, alcohol-formalin-acetic acid (AFA) and PREFER, are not acceptable for use with the VENTANA PD-L1 (SP263) Assay.

Tissue sections approximately 4-5 µm thick mounted on positively charged slides are used for this assay. Slides should be stained promptly, as antigenicity of cut tissue sections may diminish over time and is compromised within 12 months after cutting from the paraffin block for NSCLC specimens and 9 months for placenta specimens used as controls. See device package insert for additional details.

## D. Quality Control Procedures

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

1. Placenta Tissue Control

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

Placental tissue shows moderate to strong uniform staining of the membrane and weak to strong uniform staining of the cytoplasm of trophoblast-lineage cells. Placental stromal tissue and vasculature can be used for assessment of any background staining.

2. 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 is a negative reagent control antibody that is specifically matched for this assay and is used in place of the

primary antibody to evaluate nonspecific staining that may result from reaction with detection chemistry and not the anti PD-L1 primary antibody. 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.

## E. Principles of Operation

The VENTANA PD-L1 (SP263) Assay is fully automated for use on the BenchMark ULTRA automated slide stainer from deparaffinization through counterstaining. Patient FFPE tissue specimens are cut to approximately 4-5 µm 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 HRP) conjugates are blocked with OptiView Inhibitor (3% H2O2). After the endogenous peroxidase block, the VENTANA PD-L1 (SP263) Rabbit Monoclonal Primary Antibody is dispensed during the antibody incubation step and allowed to bind to its antigen. The slides are then incubated with the reagents in the OptiView DAB IHC Detection Kit, which 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 a HRP enzymatic reaction at the antigen site. 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 3 below.

**Table 3. Staining Protocol for VENTANA PD-L1 (SP263) Assay**

| Staining Procedure: VENTANA PD-L1 (SP263) Assay | |
|---|---|
| **Procedure Parameter** | **Selection** |
| **Deparaffinization** | Selected |
| **Baking** | Optional 60ºC 12 minutes |
| **Cell Conditioning** | CC1 Cell Conditioning 64 minutes |
| **Pre-primary Antibody Peroxidase** | Selected |
| **Antibody (Primary)** | VENTANA PD-L1 (SP263) Selected 16 minutes, 36ºC<br>or<br>Negative Control Selected 16 minutes, 36ºC |
| **OptiView HQ Linker** | 8 minutes (default) |
| **OptiView HQ Multimer** | 8 minutes (default) |
| **Counterstain** | Hematoxylin II, 4 minutes |
| **Post Counterstain** | Bluing Reagent, 4 minutes |
| | |

## F. Interpretation of PD-L1 Staining

The VENTANA automated immunostaining procedure results in a brown colored DAB reaction product to precipitate at the antigen sites localized by the VENTANA PD-L1 (SP263) Assay. The stained slide(s) are interpreted by a qualified pathologist using light microscopy. A qualified pathologist experienced in IHC procedures must evaluate tissue controls and qualify the stained product before interpreting results.

1. Placenta Tissue Control Interpretation

The placenta tissue control should be examined for appropriate staining. The stained positive and negative staining elements of the placenta tissue control should be examined to ascertain that all reagents are functioning properly. Examples of positive and negative staining elements of the placenta tissue control can be found in the VENTANA PD-L1 (SP263) Assay Interpretation Guide for NSCLC. Placental Tissue Control Evaluation Criteria are described in Table 4.

**Table 4. Placenta Tissue Control Evaluation Criteria for the VENTANA PD-L1 (SP263) Assay**

| Interpretation | **Staining Description** |
|---|---|
| Acceptable | Moderate to strong uniform membrane staining of trophoblast-lineage cells, and placental stroma and vasculature with no staining. |
| Unacceptable | No to weak uniform membrane staining of trophoblast lineage cells and/or specific staining within placental stromal and vascular tissue. |

If the positive or negative tissue controls fail to demonstrate appropriate staining or demonstrate a change in interpretation, any results with the test specimens should be considered invalid.

2. 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. Examples of background staining for this assay can be found in the VENTANA PD-L1 (SP263) Assay Interpretation Guide for Non-Small Cell Lung Carcinoma.

3. Patient Tissue Interpretation

Patient tissue must be evaluated according to the VENTANA PD-L1 (SP263) Assay scoring algorithm for NSCLC provided in Table 5 and the non-specific background scoring criteria provided in Table 6. Refer to the VENTANA PD-L1 (SP263) Assay Method Sheet and VENTANA PD-L1 (SP263) Assay Interpretation Guide for non-small cell lung carcinoma for additional details.

**Table 5. VENTANA PD-L1 (SP263) Assay Scoring Algorithm for NSCLC**

| PD-L1 Interpretation | Staining Description |
|---|---|
| ≥ 1% | ≥ 1% of tumor cells with membrane positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control. |
| < 1% | < 1% of tumor cells with membrane positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control. |
| ≥ 50% | ≥ 50% of tumor cells with membrane positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control. |
| < 50% | < 50% of tumor cells with membrane positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control. |

Note: For cases scored around the cutoff (40% to 59% TC , consultation with a second pathologist is recommended per standard medical practice. Reporting of the final results based on a consensus score should be considered.

**Table 6. Non-specific Background Scoring Criteria for VENTANA PD-L1 (SP263) Assay**

| Interpretation | Staining Description |
|---|---|
| Acceptable | Non-specific staining that is not obtrusive to interpretation of specific staining. |
| Unacceptable | Non-specific staining that is obtrusive to interpretation of specific staining. |

## VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are FDA-approved companion diagnostic (CDx) alternatives for the detection of PD-L1 in non-small cell lung carcinoma FFPE tissue samples. Currently the PD-L1 IHC 22C3 pharmDx assay is FDA-approved for detection of PD-L1[Tumor Proportion Score (TPS) ≥ 50%] in patients with NSCLC for treatment with LIBTAYO (cemiplimab-rwlc). For additional details see FDA List of Cleared or Approved Companion Diagnostic Devices at: https://www.fda.gov/media/119249/download.

## VII. MARKETING HISTORY

The VENTANA PD-L1 (SP263) Assay for NSCLC is currently marketed in the United States with the intended use to identify patients for treatment with TECENTRIQ (atezolizumab). The VENTANA PD-L1 (SP263) Assay for NSCLC is marketed in the European Union with the intended use to identify patients for treatment with LIBTAYO (cemiplimab-rwlc).

## 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, and an inaccurate estimate of a patient's benefit from LIBTAYO and subsequently improper interpretation of the benefit/risks for patients with NSCLC who are considering treatment with LIBTAYO.

For the specific adverse events that occurred in the LIBTAYO clinical study in NSCLC, please see the LIBTAYO FDA approved package insert which is available at Drugs@FDA.

## IX. SUMMARY OF NONCLINICAL STUDIES

### A. Laboratory Studies

There were no changes to the device design including reagent formulation or kit configuration since the approval of the original PMA (P160046). Studies were performed using the VENTANA PD-L1 (SP263) Assay to establish analytical performance of the device at the 50% TC cutoff for the NSCLC indication. This assay was run using a VENTANA BenchMark ULTRA instrument, using NSCLC tissue samples that had a range of PD-L1 expression levels. 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. The study results detailed below establish sensitivity, specificity, precision, and reproducibility of the device.

1. Analytical Sensitivity
   The VENTANA PD-L1 (SP263) assay was used to assess the prevalence of PD-L1 staining for the 50% TC cutoff on 733 NSCLC specimens. The prevalence of PD-L1 positive cases based on the tumor cell expression ≥ 50% cutoff was 19% (133/733).

2. Analytical Specificity
   The antibody used in the VENTANA PD-L1 (SP263) Assay is Rabbit Anti-Human PD-L1/CD274 Monoclonal Antibody (Clone SP263). The molecular weight of the antibody's target (PD-L1) is 32 kDa, and the SP263 clone specifically targets a 19 amino acid sequence at the cytoplasmic tail of PD-L1. The following studies were conducted with PD-L1 (SP263) antibody to establish antibody specificity.

   a. Western Blot Studies

      Refer to the Summary of Safety and Effectiveness Data P160046/S010 (Section IX.A.2a) for western blot studies.

   b. Blast Results for SP263 Epitope

      Refer to the Summary of Safety and Effectiveness Data P160046/S010 (Section IX.A.2b) for Blast analysis of SP263 epitope.

   c. Peptide Inhibition Studies

      Refer to the Summary of Safety and Effectiveness Data P160046/S010 (Section IX.A.2c) for analytical specificity studies of primary antibody binding to PD-L1.

   d. Immunoreactivity in Human Tissues

      Refer to the Summary of Safety and Effectiveness Data P160046/S010 (Section IX.A.2d) for studies conducted with normal and neoplastic tissues for the presence

of PD-L1 positive staining, staining intensity, and background in tumor cells, tumor infiltrating immune cell, and normal cells.

3. Precision

The repeatability and intermediate precision of VENTANA PD-L1 (SP263) Assay at ≥ 50% TC cutoff was evaluated on the BenchMark ULTRA instrument in combination with OptiView DAB IHC Detection Kit by staining 24 unique cases of patients with NSCLC. The sample distribution was as follows: There were 11 positive cases (including 2 at borderline positive), and 13 negative cases (including 1 at borderline negative). The borderline ranges were, 40-49% as borderline negative, and 50-59% as borderline positive.

For within-day repeatability, 5 replicate slides from each of specimens from patients with NSCLC were stained on a single BenchMark ULTRA instrument within one day.

For between-day precision, 2 replicate slides from each of specimens from patients with NSCLC were stained with VENTANA PD-L1 (SP263) Assay on a single BenchMark ULTRA instrument across 5 non-consecutive days in a span of at least 20 days.

For between-instrument and between-lot precision, 27 slides each from 24 unique NSCLC specimens (11 PD-L1 ≥ 50% and 13 PD-L1 < 50%) were stained with VENTANA PD-L1 (SP263) Assay using three lots of VENTANA PD-L1 (SP263) antibody and three lots of OptiView DAB IHC Detection Kit on three BenchMark ULTRA instruments.

All slides were blinded, randomized, and evaluated using the VENTANA PD-L1 (SP263) Assay scoring algorithm. Analyses included evaluation of overall percent agreement (OPA), positive percent agreement (PPA), and negative percent agreement (NPA). A summary of the results is provided in Table 9.

**Table 9. Repeatability and Intermediate Precision Study of VENTANA PD-L1 (SP263) Assay Staining on Individual NSCLC Specimens at ≥ 50% TC**

| Repeatability/Intermediate Precision Parameter | Agreement % (n/N), (95% CI)* |
|---|---|
| Within-day Repeatability<br>(within a single day) | PPA: 100.0 (65/65), (94.4-100.0)<br>NPA: 100.0 (55/55), (93.5-100.0)<br>OPA: 100.0 (120/120), (96.9-100.0) |
| Between-day Precision<br>(5 non-consecutive days) | PPA: 100.0 (130/130), (97.1-100.0)<br>NPA: 100.0 (110/110), (96.6-100.0)<br>OPA: 100.0 (240/240), (98.4-100.0) |
| Between-instrument and Between-lot Precision<br>(3 instruments, 3 antibody lots, and 3 detection kit lots) | PPA: 97.2 (315/324), (92.6-100.0)<br>NPA: 97.5 (316/324), (94.7-99.4)<br>OPA: 97.4 (631/648), (94.9-99.2) |

* 2-sided 95% confidence intervals (CI) were calculated using the Wilson Score method for agreements of 100% or using the percentile bootstrap method from 2000 bootstrap samples for agreements less than 100%.

4. Reader Precision

Within-reader and between-reader precision was evaluated in a study using three pathologists who evaluated 110 unique NSCLC specimens that were stained with VENTANA PD-L1 (SP263) Assay for comparisons of PD-L1 expression level. The sample distribution was as follows: There were 55 positive cases (including 6 at borderline positive), and 55 negative cases (including 5 at borderline negative). Specimens were blinded and randomized prior to evaluation for PD-L1 expression per the VENTANA PD-L1 (SP263) Assay scoring algorithm at the 50% expression level. Readers scored all specimens twice, with a minimum of two weeks between reads. Within-reader agreement rate between the first and second read was calculated for each reader separately and then averaged across three readers. Between-reader agreement rates were based on the weighted average across all reader permutations for the first set of reads (i.e., Reader 1 vs. Reader 2, Reader 1 vs. Reader 3 and Reader 2 vs. Reader 3). Agreement rates are measured as Average Positive Agreement (APA), Average Negative Agreement (ANA), and Overall Percent Agreement (OPA) and are summarized in Table 10. Inter-reader APA, ANA and OPA for the average of all readers were 94.6%, 95.0% and 94.8% respectively. Additionally, across readers, averages of the three intra-reader agreements rates (APA, ANA, and OPA) were all ≥ 97.0%.

**Table 10. Between- and Within-reader Precision of VENTANA PD-L1 (SP263) Assay staining NSCLC Specimens at ≥ 50% TC**

| Reader Precision | Agreement % (n/N), (95% CI)* |
|---|---|
| Between-reader precision<br>(average of reader-to-reader pairwise comparisons from first read) | APA: 94.6 (298/315), (90.6-97.8)<br>ANA: 95.0 (320/337), (91.1-97.9)<br>OPA: 94.8 (309/326), (91.2-97.8) |
| Within-reader precision<br>(average of all three readers' agreement rates between first and second reads) | APA: 97.2 (310/319), (95.2-98.8)<br>ANA: 97.3 (326/335), (95.2-98.9)<br>OPA: 97.2 (318/327), (95.4-98.8) |

* 2-sided 95% confidence intervals (CI) were calculated using the percentile bootstrap method from 2000 bootstrap samples.

5. External Reproducibility

An inter-laboratory reproducibility study for VENTANA PD-L1 (SP263) Assay staining was conducted to demonstrate reproducibility of the assay in determining PD-L1 protein expression in tissue specimens from patients with NSCLC at the ≥ 50% TC cutoff. Twenty-eight unique specimens from patients with NSCLC with a range of PD-L1 expression (14 < 50% and 14 ≥ 50%, including 2 borderlines positive and 2 borderlines negative cases) were stained at 3 external laboratories on each of 5 non-consecutive days over a period of at least 20 days. The specimens were

randomized before evaluation by 6 readers (2 readers/site) blinded to the sample identity. At each site, the stained slides were independently evaluated using the VENTANA PD-L1 (SP263) Assay scoring algorithm for NSCLC 50% TC cutoff.

Reproducibility of PD-L1 assessments across sites, days and readers was measured as PPA and NPA rates that were determined as the agreement with the modal result among all observations with modal PD-L1 expression '≥50%' or '<50%", respectively. Reproducibility of PD-L1 assessments between readers at a given site, between days at a given site, or between sites, was assessed using APA and ANA rates.

Results are summarized in Table 11.

**Table 11. Inter-laboratory Reproducibility of VENTANA PD-L1 (SP263) Assay Staining of NSCLC Specimens at ≥ 50% TC**

| Inter-laboratory Reproducibility[a] | Agreement % (n/N), (95% CI)[b] |
|---|---|
| Overall agreement[c]<br>(compared to a consensus score, across sites, days and readers) | PPA: 94.3 (395/419), (90.2-98.1)<br>NPA: 90.1 (374/415), (85.1-94.7)<br>OPA: 92.2 (769/834), (89.0-95.2) |
| Between-site agreement[d]<br>(average of site-to-site pairwise comparisons) | APA: 87.5 (7610/8698), (82.2-92.0)<br>ANA: 86.2 (6774/7862), (80.5-91.3)<br>OPA: 86.9 (7192/8280), (81.5-91.7) |
| Between-reader agreement[d]<br>(average of reader-to-reader pairwise comparisons within each site) | APA: 88.5 (386/436), (83.6-92.9)<br>ANA: 87.4 (346/396), (81.5-92.5)<br>OPA: 88.0 (366/416), (82.7-92.7) |

a n = 834 PD-L1 slide observations

b Note: 95% CI = Confidence interval

For PPA/NPA/OPA, 95% CIs were calculated using the Wilson Score method for agreements of 100% or using the percentile bootstrap method for agreements less than 100%

For APA/ANA, 95% CIs were calculated using the transformed Wilson Score method for agreements of 100% or using the percentile bootstrap method for agreements less than 100%

c Agreement of study results with the case-level modal PD-L1 status.

d Pairwise agreement rates.

Based on the results of the study, consultation with a second pathologist is recommended for cases scored around the cutoff (40% to 59% TC), per standard medical practice. Reporting of the final results based on a consensus score should be considered. Please see "Note" in Table 5.

6. Impact of Tissue Specimen Preparation and Treatment Studies

   a. Ischemia Study (Time to Fixation)

      Refer to the Summary of Safety and Effectiveness Data P160046/S010 (Section IX.A.6a) for the study to evaluate the effects of ischemic time on PD-L1 antigenicity as detected by staining with VENTANA PD-L1 (SP263) Assay.

b. Fixation Study

Refer to the Summary of Safety and Effectiveness Data P160046/S010 (Section IX.A.6b) for the study to evaluate the effects of fixative type and fixation time on PD-L1 antigenicity as detected by staining with VENTANA PD-L1 (SP263) Assay.

7. Impact of Tissue Thickness
Refer to the Summary of Safety and Effectiveness Data P160046/S010 (Section IX.A.7) for the study to evaluate the impact of tissue thickness.

8. Impact of Cut Slide (section) Stability
Refer to the Summary of Safety and Effectiveness Data P160046/S010 (Section IX.A. 8) for the study to evaluate the impact of cut slide (section) stability.

9. Real Time Stability Studies
Refer to the Summary of Safety and Effectiveness Data P160046/S010 (Section IX.A.9) for the study to evaluate the real time stability.

## B. Animal Studies

No animal studies were conducted using the VENTANA-PD-L1 (SP263) Assay.

## C. Additional Studies

1. Primary versus Metastatic

This study evaluated the concordance of PD-L1 status between FFPE matched primary and metastatic NSCLC tumors when stained with the VENTANA-PD-L1 (SP263) Assay on the BenchMark ULTRA instrument.

The concordance of PD-L1 expression level at the 50% TC cutoff between 48 commercially sourced patient matched Primary and Metastatic tumor NSCLC samples demonstrated an overall concordance of 83.3% (40 /48) for PD-L1 expression level with 50.0% (4/8) positive percent agreement and 90.0% (36/40) negative percent agreement. Study results indicate that PD-L1 expression may vary between the primary and metastatic sites.

2. Tissue Heterogeneity

This study evaluated the prevalence of case heterogeneity at the 50% TC cutoff in various NSCLC tissue blocks from the same case (multiple blocks from the same case, as well as heterogeneity within a block) when stained with VENTANA-PD-L1 (SP263) Assay on the BenchMark ULTRA instrument.

a. Intra-Block Heterogeneity

The intent of this study was to characterize the intra-block heterogeneity in NSCLC tissue blocks by evaluating the PD-L1 expression level for tumor cells of multiple slide cuts from the same tissue block when stained with

VENTANA PD-L1 (SP263) Assay. Ten FFPE NSCLC cases encompassing the PD-L1 expression range from negative to positive were enrolled in the study. The case distribution consisted of 4 positive cases (including 1 borderline positive case) and 5 negative cases. For each block, approximately every 10th section was stained with VENTANA PD-L1 (SP263) Assay. Cases were sectioned to exhaustion. Nine out of the 10 cases (9/10) maintained the PD-L1 expression level throughout the block. One case with inconsistent PD-L1 expression level was the borderline positive case.

b. Intra-case heterogeneity

The intent of this study was to characterize NSCLC case heterogeneity when multiple blocks from the same patient case were stained with the VENTANA PD-L1 (SP263) Assay. Twenty-four cases with two blocks per case were evaluated in this study. Twenty of the 24 cases (83%) (20/24) maintained the same PD-L1 expression level between blocks. Study results indicate that PD-L1 expression may vary between the different tissue blocks from the same patient case.

## X. SUMMARY OF PRIMARY CLINICAL STUDY

Ventana conducted a clinical bridging study to establish a reasonable assurance of safety and effectiveness of the VENTANA PD-L1 (SP263) assay for determining the PD-L1 expression level in NSCLC FFPE tumor specimens to select patients for treatment with LIBTAYO (cemiplimab-rwlc) monotherapy. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

### A. Study Design

The clinical effectiveness of SP263 assay for detecting the PD-L1 expression level in patients with NSCLC who may benefit from treatment with LIBTAYO was demonstrated in a retrospective analysis of tumor tissue FFPE specimens from patients enrolled in the Regeneron EMPOWER-Lung 1 clinical trial (R2810-ONC-1624). A bridging study was conducted to assess: 1) concordance of results for the PD-L1 expression status between the SP263 assay and an FDA-approved IHC assay (referred to hereafter as Clinical Trial Assay or CTA), which was used to determine patient eligibility for enrollment, and 2) the clinical performance of SP263 assay in identifying patients with PD-L1 positive (TC ≥ 50%) population for treatment with LIBTAYO.

Below is a summary of the clinical study R2810-ONC-1624.

**Therapeutic Study Design**

EMPOWER-Lung 1 is a multicenter, open-label, global, Phase 3 study of cemiplimab-rwlc versus platinum-based chemotherapy in patients with stage IIIB or IIIC, or stage IV squamous or non-squamous NSCLC whose tumors express PD-L1 in ≥ 50% of tumor cells (TPS ≥ 50%) using an FDA-approved IHC assay and who have received no prior systemic treatment for their advanced disease. The primary study objective was to compare the primary endpoints of overall survival (OS) and

progression-free survival (PFS) of cemiplimab -rwlc versus standard-of-care platinum-based chemotherapies in the first-line treatment of patients with advanced or metastatic NSCLC whose tumors express PD-L1 in ≥50% of tumor cells TPS ≥ 50%). The key secondary endpoint in the study was overall response rate (ORR). Patients were screened for PD-L1 expression status (TPS ≥ 50%) in tumor tissue using CTA assay for enrollment. The left-over tissue after the initial screening, was stored for retrospective testing. Eligible patients were randomized to one of two groups for treatment: cemiplimab-rwlc 350 mg monotherapy or platinum-based doublet chemotherapy. The trial demonstrated a statistically significant improvement in OS and PFS for patients randomized to cemiplimab-rwlc as compared with chemotherapy. The EMPOWER-Lung 1 study was used to support the approval of LIBTAYO (cemiplimab-rwlc) under biological license application (BLA) 761097 reviewed by the Center for Drug Evaluation and Research (CDER) at the FDA.

**VENTANA PD-L1 (SP263) assay Clinical Bridging Study**

The objectives of the bridging study were to determine the concordance of results for the PD-L1 expression status (TC ≥ 50%) between the SP263 assay and the CTA, and to establish the clinical validity of SP263 assay in identifying PD-L1 positive (TC ≥ 50%) NSCLC patients for treatment with LIBTAYO.

Clinical performance of the VENTANA PD-L1 (SP263) Assay was evaluated using archived clinical study samples from EMPOWER-Lung 1. A total of 871 clinical trial specimens were retrospectively tested with VENTANA PD-L1 (SP263) Assay, 481 from randomized patients and 390 from a random subset of the screen-failed patients (please see accountability chart for study samples below). Staining acceptability rates for VENTANA PD-L1 (SP263) Assay were evaluated at the subject level.

1. Clinical Inclusion and Exclusion Criteria

The inclusion/exclusion criteria for selection into the clinical bridging study are as follows:

Inclusion Criteria:
A case specimen must have met all the following criteria:

- Tumor biopsy or an archival tumor specimen submitted from patients who were screened for enrollment in the Regeneron Study R2810-ONC-1624
- FFPE NSCLC specimen processed in accordance with standard practice
- Contained sufficient tumor tissue for interpretation
- If an FFPE tissue block was unavailable, unstained FFPE slides were submitted

Exclusion Criteria:
A specimen was excluded if any of the following criteria are met:

- Fine needle aspirate or cytology specimen
- Consisting of tissue that has been decalcified
- Fixed in 95% alcohol, AFA or PREFER™
- Sections from NSCLC specimens stained more than 12 months after being cut from the FFPE block.

2. Follow-up Schedule

The VENTANA PD-L1 (SP263) assay clinical bridging study involved only retrospective testing of FFPE NSCLC specimen samples; as such, no additional patient follow-up was conducted.

3. Clinical Endpoints

The primary clinical efficacy endpoint(s) in this study were the major endpoint(s) defined in EMPOWER-Lung 1, relevant to the efficacy of LIBTAYO (cemiplimab-rwlc) monotherapy versus platinum-based doublet chemotherapy in the first-line treatment of patients with advanced or metastatic NSCLC whose tumors overexpress PD-L1 (≥ 50% TC), and whose tumor PD-L1 expression level was determined with VENTANA PD-L1 (SP263) CDx Assay which were OS and PFS.

## B. Accountability of PMA Cohort

EMPOWER-Lung 1 screened 3,662 patients for study eligibility. Patients underwent a screening evaluation to determine their eligibility to randomization for treatment. PD-L1 expression in tumor tissue was assessed using a validated PD-L1 assay (CTA) in a central laboratory. Patients whose tumors had PD-L1 score of TPS ≥ 50% continued in the trial. Patients whose tumors had PD-L1 score of TPS < 50% were excluded from the study. Of the patients screened, 710 patients [Intent-to-Treat (ITT)] with advanced or metastatic NSCLC whose tumor overexpress PD-L1 were randomized (356 patients to LIBTAYO (cemiplimab-rwlc) and 354 patients to chemotherapy). Among 710 patients, 235 patients who were tested up to August 2018 had their PD-L1 samples impacted by PD-L1 quality testing issues related to the CTA not being used according to the approved labeling, including assay instructions for use (IFU) and were retested for PD-L1 expression in accordance with approved labeling, including assay IFU. Out of the 235 patient samples that were retested, 88 had confirmed PD-L1 score of TPS ≥50%, 56 had PD-L1 score of TPS < 50% and remaining 91 samples were not available for re-testing or invalid test results. As shown in the figure 1 below, a total of 563 patients [modified ITT (mITT) population] had valid PD-L1 score of TPS ≥ 50% results based on the CTA according to the approved labeling.

Since VENTANA PD-L1 (SP263) CDx assay was not the enrollment assay for the study, tumor specimens from patients previously tested with the CTA were retrospectively tested with the SP263 assay. Of the 563 CTA-positive samples, 324 samples had positive results by SP263 assay, 68 samples had negative results, and 171 samples had no results (samples not available for SP263 assay or invalid SP263 results). Among 390 randomly selected screen-failure patients and 56 CTA-negative samples based on testing with the CTA according to the approved labeling, 376 samples had evaluable results by SP263 assay (24 had positive results and 352 had negative results by SP263).

**Figure 1: Sample Accountability Chart for Study Samples**

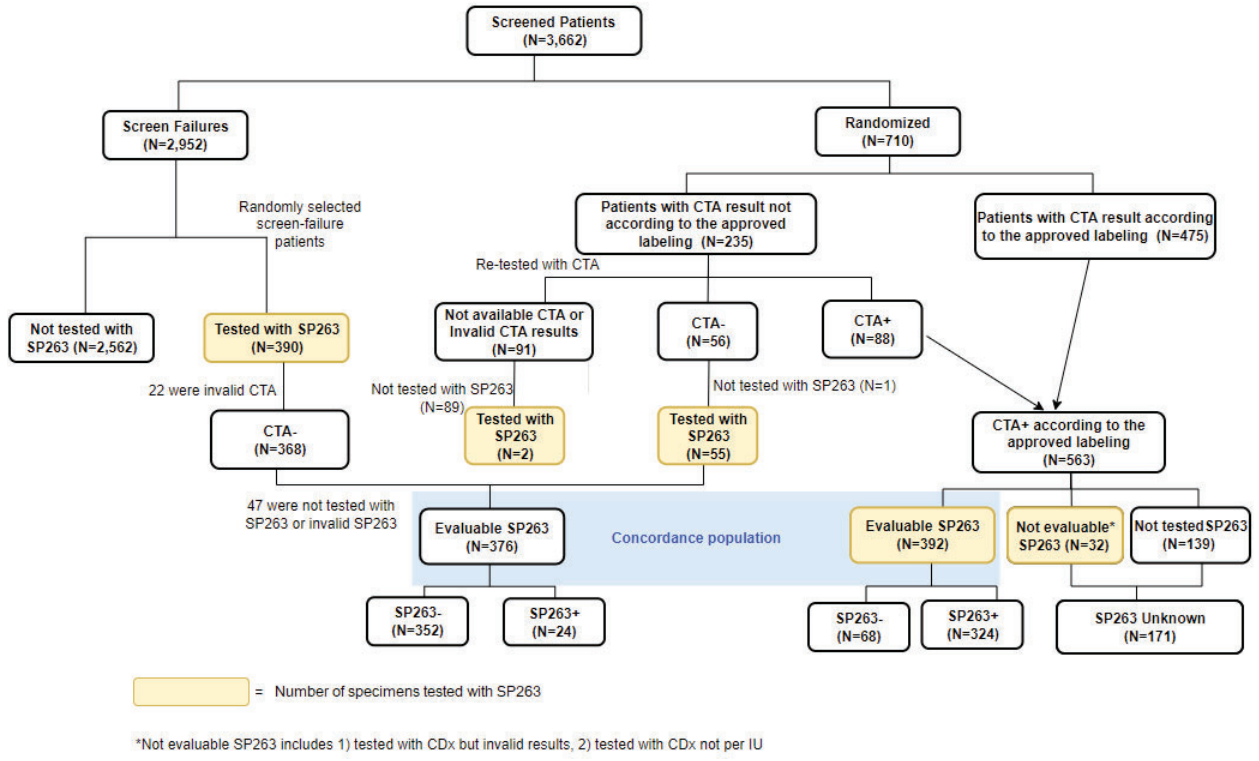


**Table 12. Accountability of Diagnostic Study PMA Cohort**

| Analysis Population | Number of Study subjects |
|---|---|
| All Screened Patients | 3,662 |
| Screen Failures | 2,952 |
| Intent-to-Treat (ITT) population (Randomized) | 710 |
| ITT but excluded from Modified ITT (mITT) Population[a] | 147 |
| Modified ITT (mITT) population[b] | 563 |
| CDx+ | 324 |
| CDx- | 68 |
| CDx unknown | 171 |
| - Tested with CDx but invalid result | 24 |
| - Tested with CDx not per IU | 8 |
| - Not tested with CDx | 139 |

[a] Samples were excluded from mITT population due to sample with no PD-L1 result or PD-L1 score of TPS<50% based on testing with CTA according to the approved labeling.
[b] mITT (N=563) = Samples with a valid PD-L1 score of TPS ≥ 50% results based on testing with CTA according to the approved labeling.

## C. Study Population Demographics and Baseline Parameters

Study population included predominantly white (91% , men (84%) and had a median age of 64 years (range: 22-88 years). Per EMPOWER-Lung 1 study protocol, patients had baseline functional status (ECOG PS 0: 28% vs. 1: 72%), resected Stage IV

(84%), and the majority (64%) had a history of tobacco use. Samples were collected for testing from either primary or metastatic tumors. The table below summarizes patient characteristics between patients with valid CDx (SP263) results and patients without valid CDx (SP263) results.

**Table 13. Clinical Characteristics for Subjects with and without Valid PD-L1 (SP263) Test Result in Clinical Bridging Study population (N=563).**

| Characteristic | Patients With Valid PD-L1 (SP263) Results (N=392) | Patients Without Valid PD-L1 (SP263) Results [a] (N=171) | p-value [b] |
|---|---|---|---|
| **Age (years)** | | | 0.6502 |
| n | 392 | 171 | - |
| Mean (SD) | 63.4 (8.17) | 63.7 (8.69) | - |
| Median | 63.5 | 64.0 | |
| Min, Max | 42, 84 | 31, 81 | |
| Missing | 0 | 0 | |
| **Age groups (years), n (%)** | | | 0.4255 |
| n | 392 | 171 | |
| <65 | 216 (55.1%) | 88 (51.5%) | |
| >=65 | 176 (44.9%) | 83 (48.5%) | |
| **Sex, n (%)** | | | 0.5180 |
| n | 392 | 171 | |
| Male | 331 (84.4%) | 148 (86.5%) | |
| Female | 61 (15.6%) | 23 13.5%) | |
| **Race, n (%)** | | | <.0001 |
| n | 392 | 171 | |
| White | 358 (91.3%) | 125 (73.1%) | |
| Black or African American | 2 (0.5%) | 2 (1.2%) | |
| Asian | 25 (6.4%) | 35 (20.5%) | |
| American Indian or Alaska Native | 7 (1.8%) | 7 (4.1%) | |
| Other | 0 | 2 (1.2%) | |
| **Ethnicity, n (%)** | | | 0.9176 |
| n | 392 | 171 | |
| Not Hispanic or Latino | 351 (89.5%) | 153 (89.5%) | |
| Hispanic or Latino | 40 (10.2%) | 18 (10.5%) | |
| Not Reported | 1 (0.3%) | 0 | |
| **Geographic region, n (%)** | | | <.0001 |
| n | 392 | 171 | |
| Europe | 320 (81.6%) | 111 (64.9%) | |

| | | | |
|---|---|---|---|
| Asia | 25 (6.4%) | 35 (20.5%) | |
| Rest of World (ROW) | 47 (12.0%) | 25 (14.6%) | |
| **Height (cm)** | | | 0.1075 |
| n | 387 | 171 | |
| Mean (SD) | 169.2 (9.24) | 168.0 (8.15) | |
| Median | 170.0 | 168.0 | |
| Min, Max | 143, 197 | 144, 186 | |
| Missing | 5 | 0 | |
| **Body weight (kg)** | | | 0.0024 |
| n | 391 | 171 | |
| Mean (SD) | 71.7 (15.58) | 67.8 (13.64) | |
| Median | 71.0 | 66.0 | |
| Min, Max | 37.6, 138 | 39.6, 112.5 | |
| Missing | 1 | 0 | |
| **BMI (kg/m2)** | | | 0.0065 |
| n | 387 | 171 | |
| Mean (SD) | 25.0 (4.59) | 23.9 (4.02) | |
| Median | 24.5 | 23.7 | |
| Min, Max | 15.53, 43.07 | 16.01, 39.3 | |
| Missing | 5 | 0 | |
| **ECOG performance status, n %)** | | | 0.6546 |
| n | 392 | 171 | |
| 0 | 108 (27.6%) | 44 (25.7%) | |
| 1 | 284 (72.4%) | 127 (74.3%) | |
| **Smoking status, n (%)** | | | 0.4612 |
| n | 392 | 171 | |
| Current Smoker | 141 (36.0%) | 56 (32.7%) | |
| Past Smoker | 251 (64.0%) | 115 (67.3%) | |

[a] Not tested or not evaluable with VENTANA PD-L1 (SP263) CDx assay
[b] P-value from t-test or Fisher's Exact/Chi-Squared.

The distribution of demographic and baseline clinical characteristics of patients randomly selected (N=390) and not selected (N=2,562) from the screen-failed population (N=2952) in the clinical study were in general well-balanced between groups (see below Table 14).

**Table 14. Patient characteristics for screen failure population.**

| Characteristic | Randomly Selected N=390) | Not Selected (N=2562) | Overall (N=2952) |
|---|---|---|---|
| **Age (years)** | | | |

| | | | |
|---|---|---|---|
| n | 390 | 2562 | 2952 |
| Mean (SD) | 63.5 (9.10) | 62.2 (9.32) | 62.4 (9.30) |
| Median | 64.0 | 63.0 | 63.0 |
| Min, Max | 21, 88 | 20, 90 | 20, 90 |
| **Age groups (years), n (%)** | | | |
| n | 390 | 2562 | 2952 |
| <65 | 207 (53.1%) | 1472 (57.5%) | 1679 (56.9%) |
| >=65 | 183 (46.9%) | 1090 (42.5%) | 1273 (43.1%) |
| **Sex, n (%)** | | | |
| n | 390 | 2562 | 2952 |
| Male | 317 (81.3%) | 2035 (79.4%) | 2352  79.7%) |
| Female | 73 (18.7%) | 527 (20.6%) | 600 (20.3%) |
| **Race, n (%)** | | | |
| n | 390 | 2562 | 2952 |
| White | 357 (91.5%) | 2187 (85.4%) | 2544 (86.2%) |
| Black or African American | 3 (0.8%) | 23 (0.9%) | 26 (0.9%) |
| Asian | 16 (4.1%) | 284 (11.1%) | 300 (10.2%) |
| American Indian or Alaska Native | 12 (3.1%) | 46 (1.8%) | 58 (2.0%) |
| Other | 2 (0.5%) | 21 (0.8%) | 23 (0.8%) |
| Unknown | 0 | 1 (0.0%) | 1 (0.0%) |
| **Ethnicity, n (%)** | | | |
| n | 390 | 2562 | 2952 |
| Not Hispanic or Latino | 336 (86.2%) | 2340 (91.3%) | 2676 (90.7%) |
| Hispanic or Latino | 51 (13.1%) | 208 (8.1%) | 259 (8.8%) |
| Not Reported | 3 (0.8%) | 14 (0.5%) | 17 (0.6%) |
| **Region, n (%)** | | | |
| n | 390 | 2562 | 2952 |
| Europe | 318 (81.5%) | 1992 (77.8%) | 2310 (78.3%) |
| Asia | 14 (3.6%) | 282 (11.0%) | 296 (10.0%) |
| ROW | 58 (14.9%) | 288  11.2%) | 346 (11.7%) |
| **Sample Collection Method, n (%)** | | | |
| n | 384 | 1677 | 2061 |
| Resection | 200 (52.1%) | 1117 (66.6%) | 1317 (63.9%) |
| Biopsy | 179 (46.6%) | 527 (31.4%) | 706 (34.3%) |
| Core Needle | 5 (1.3%) | 33 (2.0%) | 38 (1.8%) |
| Missing | 6 | 885 | 891 |
| **Tissue Origin, n (%** | | | |
| n | 389 | 1850 | 2239 |
| Lung | 282 (72.5%) | 1335 (72.2%) | 1617 (72.2%) |
| Other | 107 (27.5%) | 515 (27.8%) | 622 (27.8%) |
| Missing | 1 | 712 | 713 |
| **Fixative Used, n (%)** | | | |
| n | 390 | 1558 | 1948 |
| 10% Neutral Buffered Formalin | 390 (100.0%) | 1323  84.9%) | 1713 (87.9%) |

| | | | |
|---|---|---|---|
| Other | 0 | 235 (15.1%) | 235 (12.1%) |
| Missing | 0 | 1004 | 1004 |

## D. Safety and Effectiveness Results

### 1. Safety Results

The safety with respect to treatment with LIBTAYO (cemiplimab-rwlc) was addressed during the review of the LIBTAYO BLA and is not addressed in detail in this Summary of Safety and Effectiveness Data.

The evaluation of safety was based on the analysis of adverse events (AEs), clinical laboratory evaluations, physical examinations, and vital signs. Refer to the drug label available at Drugs@FDA for complete safety information on LIBTAYO (cemiplimab-rwlc).
No adverse events were reported in connection with the bridging study used to support this PMA supplement, as the study was performed retrospectively using banked samples.

### 2. Effectiveness Results

#### a. Concordance analysis

The agreement between CTA and VENTANA PD-L1 (SP263) CDx assay was calculated using the valid test results (positive or negative). The point estimates of PPA and NPA between the CTA and the SP263 assay, using the CTA results as a reference, were 82.7% (95% CI: 78.6%-86.1%) and 93.6% (95% CI: 90.7%-95.7%), respectively.

The CDx unknown in the following table includes tested with CDx but had invalid CDx results, tested with CDx not per the intended use (IU) and not tested with CDx due to unavailable samples or specimen beyond cut slide stability.

Among samples with PD-L1 expression (TPS ≥ 50%) positive patients by CTA, 416 samples were tested with CDx per IU, and the percent of CDx invalid was 5.8% (24/416). Among samples with PD-L1 expression (TPS < 50%) negative patients by CTA, 411 samples were tested with CDx, and the percent of CDx invalid was 8.5% (35/411).

**Table 15. Concordance between the VENTANA PD-L1 (SP263) CDx Assay and the PD-L1 CTA Results.**

| PD-L1 SP263 | PD-L1 CTA | | | |
|---|---|---|---|---|
| | Positive | Negative | NA[d] | Total |
| CDx+ | 324 | 24 | 2 | 350 |
| CDx- | 68 | 352 | 6 | 426 |
| CDx Unknown[a] | 171 | 48 | 105 | 324 |

| | | | | |
|---|---|---|---|---|
| Total | 563 | 424 | 113 | 1,100 |
| Positive and Negative Percent Agreement[b] | PPA: 82.7% (324/392)<br>95% CI[c]: [78.6%-86.1%] | NPA: 93.6% (352/376<br>95% CI[c]: [90.7%-95.7%] | | |
| Percent of CDx unknown | 30.4% 171/563<br>95% CI[c]: [26.7%-34.3%] | 11.3% 48/424<br>95% CI[c]: [8.7%-14.7%] | | |

[a] CDx unknown includes 1) tested with CDx but invalid results, 2) tested with CDx not per IU, and 3) not tested with CDx, [b] PPA and NPA with 95% CIs are calculated based on valid test results (positive or negative), [c] 95% CIs are calculated based on Wilson-score 2-sided 95% CI, [d] CTA invalid.

b. Clinical Efficacy Results

The primary analyses for the clinical bridging study examined OS and PFS for cemiplimab-rwlc treatment among patients with locally advanced NSCLC who were not candidates for surgical resection or definitive chemoradiation, or with metastatic NSCLC and (i) Who could have been enrolled in EMPOWER-Lung 1 had VENTANA PD-L1 (SP263) Assay been used for enrollment (ii) Who were enrolled in EMPOWER-Lung 1 and had PD-L1 expression.

In the mITT population (N=563), median OS was not yet reached (95% CI: 17.9-NE) in the LIBTAYO (cemiplimab-rwlc) arm and 14.2 months (95% CI: 11.2-17.5) for the chemotherapy arm (P-value 0.0002, HR=0.57 (95% CI: 0.42-0.77)). In this population, median PFS was significantly greater in the LIBTAYO (cemiplimab-rwlc) arm compared with the chemotherapy arm at the time of data cutoff: 8.2 (95% CI: 6.1-8.8) months versus 5.7 (95% CI: 4.5-6.2) months (P-value<0.0001, HR=0.54 (95% CI: 0.43-0.68)). The drug efficacy results (OS and PFS) among whole CTA positive population (N=563) and CTA+/CDx+ population (N=324) in the primary efficacy analysis population are presented in Table 16.

Clinical efficacy (OS, PFS) of LIBTAYO (cemiplimab-rwlc) vs chemotherapy was evaluated among the CTA+/SP263- subgroup (N=68) to compare the response to therapy between CTA+/CDx+ and CTA+/CDx- populations. Efficacy analyses showed that for OS the hazard ratio (HR) among the CTA+/CDx- subgroup was 1.48 (95% CI: 0.67, 3.25) and for PFS the HR was 0.81 (95% CI: 0.42, 1.53) (Table 17). Based on these clinical efficacy data, it can be concluded that there was limited benefit of LIBTAYO (cemiplimab-rwlc) vs chemotherapy among the CTA+/CDx- patient subgroups. The clinical efficacy was also assessed by OS and PFS among the CTA+/CDx unknown subgroup (171) (Table 17).

**Table 16. Primary efficacy results: the overall survival (OS) and progression-free survival (PFS) for PD L1 Expression (≥ 50%TC) positive patients by CTA and SP263 CDx results in the efficacy analysis set.**

| **Endpoints** | **CTA+[a] (N=563)** | **CTA+/CDx+[b] (N=324)** |
|---|---|---|

| | LIBTAYO n=283 | Chemotherapy n=280 | LIBTAYO n=164 | Chemotherapy n=160 |
|---|---|---|---|---|
| Overall Survival | | | | |
| Median in months (95% CI | NR (17.9–NE) | 14.2 (11.2–17.5) | 22.1 (17.7–NE) | 15.5 (11.4–NE) |
| Hazard ratio (95% CI | 0.57 (0.42–0.77)[c] | | 0.52 (0.34–0.80)[c] | |
| P value | 0.0002 | | 0.0022 | |
| Progression-free Survival per BICR | | | | |
| Median in months (95% CI | 8.2 (6.1–8.8) | 5.7 (4.5–6.2) | 9.8 (8.1–14.5) | 5.4 (4.2–6.2) |
| Hazard ratio (95% CI | 0.54 (0.43–0.68)[c] | | 0.43 (0.32–0.59)[c] | |
| P value | <0.0001 | | <0.0001 | |

BICR: blinded independent central review; CI: confidence interval; NE: Not evaluable; NR: Not reached
a Randomized patients with PD-L1 ≥50% by CTA according to approved labeling from EMPOWER-Lung 1 study
b Randomized patients with PD-L1 ≥50% by SP263 and CTA assays, from retested available samples from EMPOWER Lung 1.
c Hazard Ratio based on the stratified Cox proportional hazard model.

**Table 17. Efficacy results in the PD L1 Expression (TPS ≥ 50%) positive patients by CTA but were negative by SP263 CDx and SP263 CDx unknown.**

| Endpoints | CTA+/CDx-[a] (N=68) | | CTA+/CDx unknown[b] (N=171) | |
|---|---|---|---|---|
| | LIBTAYO n=31 | Chemotherapy n=37 | LIBTAYO n=88 | Chemotherapy n=83 |
| Overall Survival | | | | |
| Median in months (95% CI | 7.1 (3.6, NE) | 12.1 (10.5, 23.3) | 18.7 (18.7, NE) | 10.9 (8.2, NE) |
| Hazard ratio (95% CI | 1.48 (0.67–3.25)[c] | | 0.37 (0.21–0.65)[c] | |
| P value | 0.3312 | | 0.0004 | |
| Progression-free Survival per BICR | | | | |
| Median in months (95% CI | 4.5 (2.0, 8.4) | 6.2 (3.4, 7.2) | 6.1 (4.0, 6.4) | 5.9 (4.3, 6.2) |
| Hazard ratio (95% CI | 0.81 (0.42–1.53)[c] | | 0.70 (0.48–1.02)[c] | |
| P value | 0.5054 | | 0.0612 | |

BICR: blinded independent central review; CI: confidence interval; NE: Not evaluable; NR: Not reached
a Randomized patients with PD-L1 ≥50% by CTA and <50% by SP263 assays, from retested available samples from EMPOWER Lung 1.
b Randomized patients with PD-L1 ≥50% by CTA and SP263 unknown (not available for SP263 testing or invalid SP263 test results).
c Hazard Ratio based on the stratified Cox proportional hazard model.

c. Clinical Efficacy Results in CDx-positive (CDx+) population

i. Sensitivity Analysis for Clinical Efficacy in CDx-positive (CDx+) population (Observed)

LIBTAYO efficacy in the population with PD-L1 expression in tumor cells (TC) ≥ 50% identified by the VENTANA PD-L1 (SP263) Assay (CDx+) was calculated as the weighted efficacy of the CDx+/CTA+ and CDx+/CTA- groups. For the subset of CDx+ (PD-L1 [SP263] expression ≥ 50% TC)/ CTA+ (TPS ≥ 50%)) patients, efficacy was estimated based on EMPOWER-Lung 1 study data. For the subset of CDx+/CTA- TPS < 50%) patients (N=24), as efficacy was not assessed in the clinical study, a sensitivity analysis was conducted to assess the impact on the efficacy of the population identified as CDx+. For this purpose, a range of scenarios (c ranging from 0 to 1) were considered where the efficacy for CDx+/CTA- patients was assumed to be the same as that for CDx+/CTA+ population (best-case scenario, c=1) or assumed no therapeutic effect within CDx+/CTA- population (a hazard ratio (HR) = 1 was assumed under the worst-case scenario, c=0). These results are summarized in Table 18.

**Table 18. Estimated efficacy (OS and PFS) for patients selected with SP263 CDx+ patients.**

| **Overall Survival** | | | | | |
|---|---|---|---|---|---|
| LIBTAYO vs. Chemotherapy | HR\|SP263+ Estimates and 95% CI based on multiple c values | | | | |
| | c=0 | c=0.3 | c=0.5 | c=0.8 | c=1 |
| | 0.58 (0.41, 0.84) | 0.56 (0.39, 0.81) | 0.55 (0.39, 0.79) | 0.53 (0.37, 0.77) | 0.52 (0.37, 0.75) |
| **Progression-Free Survival** | | | | | |
| LIBTAYO vs. Chemotherapy | HR\|SP263+ Estimates and 95% CI based on multiple c values | | | | |
| | c=0 | c=0.3 | c=0.5 | c=0.8 | c=1 |
| | 0.50 (0.38, 0.65) | 0.48 (0.37, 0.62) | 0.47 (0.36, 0.60) | 0.45 (0.34, 0.58) | 0.43 (0.33, 0.56) |

ii. Sensitivity Analysis for Clinical Efficacy in CDx-positive (CDx+) population (Observed and Imputed)

Additional sensitivity analyses were performed to account for the impact of missing VENTANA PD-L1 (SP263) Assay results using multiple imputation (MI) method. Samples were considered missing if the samples were not tested, if they were tested but returned an invalid result, or if they tested with CDx not per IU. Among all CTA positive patients, 30.4% (171/563) did not have a VENTANA PD-L1 (SP263) Assay result. Sensitivity analysis against the 171 missing CDx results was conducted to assess the robustness of the clinical efficacy analysis for the SP263 positive patients. In the MI model, CTA status, patient characteristic variables that were imbalanced across CDx evaluable and non-evaluable sets (region, weight, body mass index), clinical

outcome (censor indicator and time to event), and clinically relevant variables (sex, smoking status, and histology) were included.

The missing SP263 results were imputed using the logistic regression via the SAS MI procedure. For each imputed dataset, a concordance table was generated to calculate the weights for the efficacy estimation and results were aggregated across replicates. The clinical efficacy (OS and PFS) for the CDx+ population was estimated under different assumed scenarios based on observed and imputed CDx results. Table 19 shows the estimated clinical efficacy for OS and PFS, respectively in PD-L1 (SP263) positive patients based on the sensitivity analysis after imputing missing SP263 results. In sensitivity analysis, to assess the robustness of the HR estimates to missing SP263 results, the estimated HR (for both OS and PFS in Table 19) including imputed SP263 results were similar to the primary analysis results (without imputation, Table 18). This analysis demonstrated that the drug efficacy in SP263 positive population is robust to missing SP263 results.

**Table 19. Estimated clinical efficacy (OS and PFS) in PD-L1 (SP263) positive (TC ≥ 50%) patients after imputing missing SP263 results**

| **Overall Survival** | | | | | |
|---|---|---|---|---|---|
| LIBTAYO vs. Chemotherapy | HR\|SP263+ Estimates and 95% CI based on multiple c values | | | | |
| | c=0 | c=0.3 | c=0.5 | c=0.8 | c=1 |
| | 0.54 (0.40, 0.74) | 0.52 (0.38, 0.71) | 0.51 (0.37, 0.69) | 0.49 (0.36, 0.66) | 0.48 (0.35, 0.65) |
| **Progression-Free Survival** | | | | | |
| LIBTAYO vs. Chemotherapy | HR\|SP263+ Estimates and 95% CI based on multiple c values | | | | |
| | c=0 | c=0.3 | c=0.5 | c=0.8 | c=1 |
| | 0.56 (0.45, 0.70) | 0.54 (0.44, 0.67) | 0.53 (0.43, 0.66) | 0.51 (0.41, 0.63) | 0.50 (0.40, 0.62) |

3. Subgroup Analyses

   There was no subgroup analysis performed in the clinical bridging study.

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 two (2) 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. 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 primary efficacy data in conjunction with the staining performance support the reasonable assurance of safety and effectiveness of use of VENTANA PD-L1 (SP263) Assay as a companion diagnostic device for LIBTAYO treatment in the target NSCLC patient population.

The data indicate that patients with advanced or metastatic NSCLC with PD-L1 $\geq$ 50% TC expression level (determined using the VENTANA PD-L1 [SP263] CDx Assay), may benefit from LIBTAYO (cemiplimab-rwlc) monotherapy as a first-line treatment and are therefore eligible for treatment. In addition, the staining performance of VENTANA PD-L1 (SP263) Assay demonstrated a high overall staining acceptability rate where the initial and final staining acceptability rates (overall, background and morphology) were all above 90.1%.

The bridging study demonstrated the ability of VENTANA PD-L1 (SP263) Assay in identifying NSCLC patients eligible for treatment with the therapeutic when used in accordance with the instructions for use.

The performance of the VENTANA PD-L1 (SP263) Assay was also supported by the analytical performance validation studies.

### B. Safety Conclusions

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

The VENTANA PD-L1 (SP263) Assay is an in vitro diagnostic device, which tests FFPE tumor specimens collected from patients with NSCLC. The risks of the device are based on data collected in the clinical study. In the context of an in vitro diagnostic test, there are no directly harmful events from testing FFPE NSCLC tissue sections. These tissue sections are routinely removed as part of the diagnosis of NSCLC by pathologists. The test, therefore, presents no additional safety hazard to the patient being tested. Failure of the device to perform as expected may lead to a failure to correctly interpret test results. VENTANA PD-L1 (SP263) Assay is intended for use to identify patients for LIBTAYO (cemiplimab-rwlc) therapy, if incorrect, or false, results are reported, then patients may not receive the proper treatment. Patients with false positive results may undergo treatment with LIBTAYO (cemiplimab-rwlc) without much clinical benefit and may experience adverse reactions associated with LIBTAYO (cemiplimab-rwlc) therapy. Patients with false negative results may not be considered for treatment with LIBTAYO (cemiplimab-rwlc), and therefore, may receive other treatment options. There is also a risk of delayed results, which may lead to a delay in treatment with LIBTAYO (cemiplimab-rwlc).

## C. Benefit-Risk Determination

### Summary of Benefits

The probable benefits of the device are based on data collected in the clinical study EMPOWER-Lung 1conducted to support the supplemental PMA approval as described above.

The clinical performance of the VENTANA PD-L1 (SP263) Assay was demonstrated in the EMPOWER-Lung 1 trial. Collectively, the results from the primary and additional analysis indicate that LIBTAYO (cemiplimab-rwlc) is an effective treatment for the NSCLC population identified by VENTANA PD-L1 (SP263) CDx Assay. The results of the bridging analyses show that the efficacy of LIBTAYO vs chemotherapy is maintained in the PD-L1 (SP263) selected population, supporting the use of the VENTANA PD-L1 (SP263) Assay for identifying patients with NSCLC whose tumors have PD-L1 expression ≥50% TC and who may benefit from first line treatment with LIBTAYO (cemiplimab-rwlc).

### Summary of Risks

The probable risks of the device are also based on data collected in the clinical study EMPOWER-Lung 1 conducted to support the supplemental PMA approval as described above.
The risks of the use of the device relate to false positive and false negative results. Patients who are determined to be false positive by the test may be exposed to a drug that is not beneficial and may lead to adverse events or may have delayed access to other treatments that could be more beneficial. A false negative result may prevent a patient from accessing a potentially beneficial therapeutic regimen. A false positive result could lead to treatment with cemiplimab-rwlc without the possibility of benefit.

This could unnecessarily expose the patient to toxicity of the drug. This is mitigated by the possibility that the patient could nonetheless experience some benefit from the drug even with a result of PD-L1<50%. A false negative result could deprive a patient of the potential benefit of LIBTAYO treatment. Regarding the toxicity profile of cemiplimab-rwlc, please refer LIBTAYO (cemiplimab-rwlc) Label at Drugs@FDA.

**Benefit-Risk Balance**

The data provided demonstrate that, in the context of this population, there is reasonable assurance that the use of the VENTANA PD-L1 (SP263) Assay to identify an appropriate patient population with locally advanced or metastatic EGFR, ALK or ROS1 negative non-small cell lung cancer to be treated with LIBTAYO (cemiplimab-rwlc) is safe and effective.

1. Patient Perspective
   This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support that for the VENTANA PD-L1 (SP263) Assay, and the indications noted in the intended use statement, 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. The provided studies support the use of the VENTANA PD-L1 (SP263) Assay as a companion diagnostic to identify patients with locally advanced or metastatic EGFR, ALK or ROS1 negative non-small cell lung cancer, for treatment with LIBTAYO (cemiplimab-rwlc).

## XIII. CDRH DECISION

CDRH issued an approval order on March 1, 2023.

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.