SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Immunohistochemistry test, DNA mismatch repair (MMR) Protein assay
Device Trade Name:	VENTANA MMR RxDx Panel
Device Procode	QNH
Applicant's Name and Address:	Ventana Medical Systems, Inc. (Roche Tissue Diagnostics) 1910 East Innovation Park Drive Tucson, AZ 85755
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P210001
Date of FDA Notice of Approval:	August 17, 2021

II. INDICATIONS FOR USE

VENTANA MMR RxDx Panel is a qualitative immunohistochemistry test intended for use in the assessment of mismatch repair (MMR) proteins (MLH1, PMS2, MSH2 and MSH6) in formalin-fixed, paraffin-embedded (FFPE) tissue specimens by light microscopy. The OptiView DAB IHC Detection Kit is used for MLH1, MSH2 and MSH6, and the OptiView DAB IHC Detection Kit with the OptiView Amplification Kit is used for PMS2 on a VENTANA BenchMark ULTRA instrument.

VENTANA MMR RxDx Panel includes VENTANA anti-MLH1 (M1) Mouse Monoclonal Primary Antibody, VENTANA anti-PMS2 (A16-4) Mouse Monoclonal Primary Antibody, VENTANA anti-MSH2 (G219-1129) Mouse Monoclonal Primary Antibody, and VENTANA anti-MSH6 (SP93) Rabbit Monoclonal Primary Antibody.

VENTANA MMR RxDx Panel is indicated as an aid in identifying patients eligible for treatment with the therapy listed in Table 1 for the indication and MMR status in accordance with the approved therapeutic product labeling.

Table 1. VENTANA MMR RxDx Panel companion diagnostic indications

Indication for use	Therapy	Status
Solid Tumors	JEMPERLI (dostarlimab-gxly)	deficient MMR (dMMR)

Results of the VENTANA MMR RxDx Panel 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 associated with these tests.

IV. WARNINGS AND PRECAUTIONS

Warnings and precautions can be found in the anti-MLH1 (M1) Mouse Monoclonal Primary Antibody, anti-PMS2 (A16-4) Mouse Monoclonal Primary Antibody, VENTANA anti-MSH2 (G219-1129) Mouse Monoclonal Primary Antibody, and VENTANA anti-MSH6 (SP93) Rabbit Monoclonal Primary Antibody product labeling.

V. DEVICE DESCRIPTION

A. Device Kit Components

The VENTANA MMR RxDx Panel is comprised of four primary antibodies used to detect the MMR proteins MLH1, PMS2, MSH2 and MSH6 in solid tumor tissue specimens. The primary antibodies are used in combination with individually optimized detection reagents and in conjunction with ancillary reagents in order to complete specimen testing. The VENTANA MMR RxDx Panel is optimized to run on the VENTANA BenchMark Ultra platform with OptiView DAB detection kit or in the case of PSM2 antibody the OptiView DAB detection Kit with the OptiView Amplification Kit. The presence or absence of target proteins is determined by visual examination of the specimen slide under light microscope by a qualified pathologist.

The VENTANA MMR RxDx Panel antibodies are packaged as individual products in single ready to use reagent dispensers. The VENTANA MMR RxDx Panel uses four separate intended use tissue slides that are stained on the BenchMark ULTRA instrument. The primary antibody reagents are listed below.

1. VENTANA anti-MLH1 (M1) Mouse Monoclonal Primary Antibody

The anti-MLH1 (M1) antibody is a mouse monoclonal antibody produced against a full-length recombinant MLH1 protein with a glutathione-S-transferase tag. The antibody binds to the MLH1 protein in FFPE tissue sections, where it can be localized using the OptiView DAB immunohistochemistry (IHC) Detection Kit. Antibody concentration is ~1 µg/mL.

2. **VENTANA anti-PMS2 (A16-4) Mouse Monoclonal Primary Antibody**

The VENTANA anti-PMS2 (A16-4) antibody is a mouse monoclonal antibody raised against a recombinant PMS2 protein. The antibody binds to PMS2 protein in FFPE tissue sections, where it can be localized using the OptiView DAB IHC Detection Kit and OptiView Amplification Kit. Antibody concentration is ~1 µg/mL.

3. **VENTANA anti-MSH2 (G219-1129) Mouse Monoclonal Primary Antibody**

The anti-MSH2 (G219-1129) antibody is a mouse monoclonal antibody produced against a recombinant human MSH2 protein. The antibody binds to the MSH2 protein in FFPE tissue sections, where it can be localized using the OptiView DAB IHC Detection Kit. Antibody concentration is ~ 20 µg/mL.

4. **VENTANA anti-MSH6 (SP93) Rabbit Monoclonal Primary Antibody**

The VENTANA anti-MSH6 (SP93) antibody is a rabbit monoclonal antibody raised against a recombinant MSH6 protein. It binds to MSH6 protein in FFPE tissue sections, where it can be localized using the OptiView DAB IHC Detection Kit. Antibody concentration is ~1 µg/mL.

Detection and ancillary reagents required but not provided with VENTANA MMR RxDx Panel are listed below:

- OptiView DAB IHC detection Kit has the following components
  - OptiView peroxidase Inhibitor
  - OptiView HQ universal Linker
  - OptiView HRP Multimer
  - OptiView H_2O_2
  - OptiView DAB
  - OptiView Copper
- OptiView Amplification kit
  - OptiView Amplification (0.003% HQ conjugated tyramide complex)
  - OptiView H_2O_2
  - OptiView Multimer
- Hematoxylin II
- Bluing Reagent
- Reaction Buffer (10x)
- EZ Prep Reagent (10x)
- ULTRA Cell Conditioning (CC1) (Pre-dilute)
- ULTRA Liquid Cover Slip (LCS) (Pre-dilute)
- Negative reagent control mouse monoclonal antibody
- Negative reagent control rabbit monoclonal antibody

B. Device Instrument and Software

The VENTANA MMR RxDx Panel test is fully automated. The VENTANA MMR RxDx panel antibodies are for use on the BenchMark ULTRA instrument using Ventana System Software (VSS) software version 12.5.4 or earlier.

C. Specimen Preparation

Routinely processed, formalin-fixed, paraffin-embedded (FFPE) tissues are suitable for use with the MMR primary antibodies when used with VENTANA OptiView DAB detection kit (with OptiView Amplification Kit for PMS2) 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 the MMR antibodies. 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.

D. 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:
Pre-qualified solid tumor tissue including endometrial cancer (EC) tissue with an MMR status of intact or tonsil may be used as a positive system-level control for MMR antibodies to detect the intact protein. Alternatively, pre-qualified normal endometrial tissue fixed and processed in the same manner as the patient tissue can also be used as a positive system-level control. Normal endometrium will stain positive for all antibodies in the MMR IHC Panel. Since the MSH6, PMS2, MSH2 and MLH1 proteins are expressed in all tissues, a normal negative tissue control does not exist for these biomarkers. For a negative system level control, EC tissue with loss of an MMR protein can be used as an appropriate tissue control for mismatch repair protein deficiency status. However, lymphocytes, fibroblast and epithelial cells should exhibit staining and serve as positive internal control cells in EC samples with MMR protein deficiency (dMMR).

1. Internal Positive Controls

Normal tissue elements (e.g., lymphocytes, fibroblasts, or normal epithelium) in the immediate vicinity of the tumor may serve as internal positive controls. Unequivocal nuclear staining in these cells validates the staining run. If the internal positive controls fail to demonstrate appropriate staining, results with the test specimen should be considered invalid.

2. Negative Reagent Control

Negative reagent control should be used to stain an adjacent section of the patient specimen tissue on a separate slide from the VENTANA MMR antibody stained

slides. A negative reagent control mouse monoclonal antibody (for MLH1, PMS2, and MSH2) and a negative reagent control rabbit monoclonal antibody (for MSH6) is recommended for use in place of the primary antibodies to evaluate nonspecific staining.

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

E. Principles of Procedure

The VENTANA MMR RxDx Panel is an immunohistochemistry test system used to stain FFPE solid tumor specimens to detect expression of the MMR proteins (MLH1, PMS2, MSH2 and MSH6). The 4 antibodies of the VENTANA MMR RxDx Panel have individualized staining protocols that are created using available staining parameters provided in staining procedures in the VSS software that drives the BenchMark ULTRA automated staining platform. The panel test is run individually on 4 separate tissue sections and the test process involves sequential application of specific primary antibodies against the panel protein, followed by detection reagents and chromogen deposition for visualization of the target protein expression.

The VENTANA MMR RxDx Panel 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% H2O2). After the endogenous peroxidase block, the 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 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 PMS2 test uses the OptiView amplification in addition of to the OptiView DAB detection system for signal amplification. The OptiView Amplification Kit includes an HQ hapten conjugate (OptiView Amplifier), corresponding substrate (OptiView Amplification H2O2), 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.

Table 1. VENTANA MMR RxDx Panel Staining Protocol

Protocol Parameter	MLH1	PMS2	MSH2	MSH6
Deparaffinization	Selected	Selected	Selected	Selected
Cell Conditioning	Cell Conditioning 1, 64 minutes, 100°C	Cell Conditioning 1, 92 minutes, 100°C	Cell Conditioning 1, 40 minutes, 100°C	Cell Conditioning 1, 48 minutes, 100°C
Pre-primary antibody peroxidase	Selected	Selected	Selected	Selected
Antibody Incubation or Negative Reagent Control	24 minutes, 36°C	32 minutes, 36°C	12 minutes, 36°C	16 minutes, 36°C
OptiView HQ Linker	8 minutes (default)	8 minutes (default)	8 minutes (default)	8 minutes (default)
OptiView HRP Multimer	8 minutes (default)	8 minutes (default)	8 minutes (default)	8 minutes (default)
OptiView Amplification	Not Selected	Selected	Not Selected	Not Selected
Amplifier and Amplification H_2O_2	Not Selected	4 minutes	Not Selected	Not Selected
Amplification Multimer	Not Selected	4 minutes	Not Selected	Not Selected
Hematoxylin II	4 minutes	4 minutes	4 minutes	4 minutes
Bluing Reagent	4 minutes	4 minutes	4 minutes	4 minutes

F. Staining Interpretation

Stained slides are interpreted by a qualified pathologist and the MMR status (intact or loss) for each of the MMR proteins (MLH1, PMS2, MSH2 and MSH6) is assigned based on the presence or absence of specific nuclear staining in the tumor. An MMR status of "Intact" is assigned to cases with unequivocal nuclear staining in viable tumor cells in the presence of acceptable internal positive controls (nuclear staining in lymphocytes, fibroblasts or normal epithelium in the vicinity of the tumor). An MMR status of "Loss" is assigned to cases with unequivocal loss of nuclear staining or focal weak equivocal nuclear staining in the viable tumor cells in the presence of internal positive controls.

If unequivocal nuclear stain is absent in internal positive controls and/or background staining interferes with interpretation, the assay should be considered unacceptable and repeated. Punctate nuclear staining of tumor cells should be considered negative.

MMR Intact (or proficient) Status: Detection of all four proteins (MLH1, PMS2, MSH2 and MSH6) in the tumor.

MMR Loss (or deficient) Status: Loss of expression of at least one protein (MLH1, PMS2, MSH2 and MSH6) in the tumor.

Interpretation of Challenging Cases: The VENTANA MMR RxDx Panel scoring algorithm for each of the four MMR antibodies is binary: either the protein is expressed (a clinical status of Intact) or it is not expressed (a clinical status of Loss). Once each of the four antibodies is interpreted, the case may be assigned an overall status of proficient (all four antibodies are intact) or deficient (at least one antibody is a loss). As a result, there are no true "borderline" cases. While the vast majority of cases stained with VENTANA MMR RxDx Panel are clearly proficient or deficient in their staining results, a few cases have been observed that present a challenge in interpretation. These cases

may be challenging due to the following issues: Non-specific background staining, focal staining, punctate staining, speckling, and tissue or staining artifacts resulting from sample processing and microtomy processes.

Interpretation for MMR proteins status is detailed in Table 2 below.

Table 2. Interpretation of MMR Protein Expression in Solid Tumor Tissue Stained with the VENTANA MMR RxDx Panel

Clinical Status	Description
Intact MMR Protein Expression	Unequivocal nuclear staining in viable tumor cells, in the presence of acceptable internal positive controls (e.g. nuclear staining in lymphocytes, fibroblasts, or normal epithelium in the vicinity of the tumor)
Loss of MMR Protein Expression	Unequivocal loss of nuclear staining or focal weak equivocal nuclear staining in the viable tumor cells in the presence of acceptable internal positive controls. Punctate nuclear staining will be considered negative.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are currently no FDA approved companion diagnostic devices to assess MMR status in solid tumors for treatment with JEMPERLI. This device is also approved for the EC indication. See Summary of Safety and Effectiveness Data for P200019.

VII. MARKETING HISTORY

VENTANA MMR RxDx Panel is currently marketed globally in several countries, including in the United States as a Class II device for the identification of Lynch syndrome (DEN170030) and as a Class III device for identifying patients with dMMR EC for treatment with JEMPERLI. The device in the US and ex-US products contain the same reagents. The device has not been withdrawn to date from the market in any country for reasons relating to safety and effectiveness of the device.

The VENTANA MMR RxDx Panel to assess MMR status in solid tumors for treatment with JEMPERLI is not marketed in any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

As with any IVD test, the potential risks are associated with an incorrect test result or incorrect interpretation of results, rather than with the device itself. Failure of the device to perform as expected or failure to correctly interpret results may lead to improper patient management decisions.

IX. SUMMARY OF NON-CLINICAL STUDIES

Non-clinical studies were performed using the VENTANA MMR RxDx Panel to support the analytical performance of the device for the solid tumor indication. These studies were performed using a variety of solid tumor tissue. 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.

Terminology used in the analysis:

An MMR status (intact or loss) was assigned to cases for each of the 4 individual MMR protein status (MLH1, PMS2, MSH2 and MSH6). Panel-level status (proficient or deficient) was assigned to cases where proficient status implies detection of all four proteins (MLH1, PMS2, MSH2 and MSH6) in the tumor, and a deficient status implies loss of expression of at least one protein (MLH1, PMS2, MSH2 or MSH6) in the tumor.

A. Laboratory Studies

1. Analytical Sensitivity Study

See Summary of Safety and Effectiveness Data for P200019.

An additional analytical sensitivity study for solid tumors will be performed in the post-market setting.

2. Analytical Specificity

a. Western Blot

See Summary of Safety and Effectiveness Data for P200019.

b. Peptide Inhibition

See Summary of Safety and Effectiveness Data for P200019.

c. Immunoreactivity in Human Tissues

See Summary of Safety and Effectiveness Data for P200019.

3. Robustness

a. Tissue Thickness

See Summary of Safety and Effectiveness Data for P200019.

b. Protocol Limitations and Failure Modes

See Summary of Safety and Effectiveness Data for P200019.

4. **Precision**

The purpose of this study was to evaluate precision of the VENTANA MMR RxDx Panel in solid tumors. Assay precision was evaluated for each of the 4 panel antibodies individually using identical study design.

The sample distribution was as follows:

MLH1: 33 solid tumors (21 intact and 18 loss): urinary (6 cases: 4 intact and 2 loss), reproductive (9 cases: 6 intact and 3 loss), gastrointestinal (6 cases: 1 intact and 5 loss), hepato-pancreatobiliary (3 cases: 2 intact and 1 loss) soft tissue (1 case: 1 intact), and thoracic (2 cases: 1 intact and 1 loss), EC (6 cases: 3 intact and 3 loss).

PMS2: 32 solid tumors (17 intact and 15 loss): urinary (3 cases: 1 intact and 2 loss), reproductive (9 cases: 4 intact and 5 loss), gastrointestinal (7 cases: 2 intact and 5 loss), endocrine (2 cases: 2 intact), hepato-pancreatobiliary (1 case: 1 intact), soft tissue (2 cases: 2 intact), and thoracic (2 cases: 2 intact), EC (6 cases: 3 intact and 3 loss).

MSH2: 33 solid tumors (18 intact and 15 loss): urinary (6 cases: 4 intact and 2 loss), reproductive (12 cases: 4 intact and 8 loss), gastrointestinal (4 cases: 2 intact and 2 loss), hepato-pancreatobiliary (1 case: 1 intact), soft tissue (2 cases: 2 intact), and thoracic (2 cases: 2 intact), EC (6 cases: 3 intact and 3 loss).

MSH6: 34 solid tumors (18 intact and 16 loss): urinary (4 cases: 1 intact and 3 loss), reproductive (11 cases: 5 intact and 6 loss), gastrointestinal (2 cases: 2 intact), endocrine (3 cases: 1 intact and 2 loss), hepato-pancreatobiliary (2 cases: 2 intact) soft tissue (4 cases: 2 intact and 2 loss), and thoracic (2 cases: 2 intact), EC (6 cases: 3 intact and 3 loss).

Total number of observations for each test condition is shown in Tables 4-8 below.

The following parameters were tested:

- Three lots of antibody (between-antibody lots)
- Three lots of OptiView DAB IHC Detection Kits (between-detection kits) and OptiView Amplification (where applicable)
- Three ULTRA instruments (between-instruments)
- Across 3 days (between-day)
- Across all intermediate precision conditions (within-run).

Each case was assigned one mode (optimal prediction) based on the samples aggregated per test condition for:

- Between-antibody lots
- Between-detection kit lots
- Between-instruments

- Between-day

Each case was compared within its duplicate samples per test run for the within-run precision study.
For each case there were 4 antibody components of the MMR RxDx Panel and a negative reagent control (NRC) antibody. For the combined intermediate precision studies, the number of non-evaluable slides and the reasons for non-evaluable observations were as follows:
MLH1: 3 slides (no staining in any cells).
PMS2: 9 slides (insufficient internal controls staining for evaluation).
MSH2: 1 slide (no internal control cells staining).
MSH6: 0

Analyses included evaluation of overall percent agreement (OPA), positive percent agreement (PPA) for Loss cases, and negative percent agreement (NPA) for Intact cases between antibody lot, between detection kit lot, between day, between instrument and within run.

Table 4. Precision, Between-antibody lots

	MLH1		PMS2		MSH2		MSH6	
	%(n/N)	95% CI	%(n/N)	95% CI	%(n/N)	95% CI	%(n/N)	95% CI
Overall	100.0 (162/162)	(97.7, 100.0)	100.0 (156/156)	(97.6, 100.0)	100.0 (162/162)	(97.7, 100.0)	100 (168/168)	(97.8, 100.0)
Intact	100.0 (96/96)	(96.2, 100.0)	100.0 (84/84)	(95.6, 100)	100.0 (90/90)	(95.9, 100.0)	100 (90/90)	(95.9, 100.0)
Loss	100.0 (66/66)	(94.5, 100.0)	100.0 (72/72)	(94.9, 100)	100.0 (72/72)	(94.9, 100.0)	100 (78/78)	(95.3, 100.0)

Table 5. Precision, Between-detection kit lots

	MLH1		PMS2		MSH2		MSH6	
	%(n/N)	95% CI	%(n/N)	95% CI	%(n/N)	95% CI	%(n/N)	95% CI
Overall	100.0 (160/160)	(97.7, 100.0)	100.0 (147/147)	(97.5, 100.0)	100.0 (162/162)	(97.7, 100.0)	100 (168/168)	(97.8, 100.0)
Intact	100.0 (95/95)	(96.1, 100.0)	100.0 (82/82)	(95.5, 100.0)	100.0 (90/90)	(95.9, 100.0)	100 (90/90)	(95.9, 100.0)
Loss	100.0 (65/65)	(94.4, 100.0)	100.0 (65/65)	(94.4, 100.0)	100.0 (72/72)	(94.9, 100.0)	100 (78/78)	(95.3, 100.0)

Table 6. Precision, Between-instruments

	MLH1		PMS2		MSH2		MSH6	
	%(n/N)	95% CI	%(n/N)	95% CI	%(n/N)	95% CI	%(n/N)	95% CI
Overall	100.0 (160/160)	(97.7, 100.0)	100.0 (156/156)	(97.6, 100.0)	100.0 (162/162)	(97.7, 100.0)	100 (168/168)	(97.8, 100.0)

Intact	100.0 (96/96)	(96.2, 100.0)	100.0 (84/84)	(95.6, 100)	100.0 (90/90)	(95.9, 100.0)	100 (90/90)	(95.9, 100.0)
Loss	100.0 (64/64)	(94.3, 100.0)	100.0 (72/72)	(94.9, 100)	100.0 (72/72)	(94.9, 100.0)	100 (78/78)	(95.3, 100.0)

Table 7. Precision, Between-day

	MLH1		PMS2		MSH2		MSH6	
	%(n/N)	95% CI	%(n/N)	95% CI	%(n/N)	95% CI	%(n/N)	95% CI
Overall	100.0 (160/160)	(97.7, 100.0)	100.0 (156/156)	(97.6, 100.0)	100.0 (162/162)	(97.7, 100.0)	100 (168/168)	(97.8, 100.0)
Intact	100.0 (96/96)	(96.2, 100.0)	100.0 (84/84)	(95.6, 100)	100.0 (90/90)	(95.9, 100.0)	100 (90/90)	(95.9, 100.0)
Loss	100.0 (64/64)	(94.3, 100.0)	100.0 (72/72)	(94.9, 100)	100.0 (72/72)	(94.9, 100.0)	100 (78/78)	(95.3, 100.0)

Table 8. Precision, Within-Run

	MLH1		PMS2		MSH2		MSH6	
	%(n/N)	95% CI	%(n/N)	95% CI	%(n/N)	95% CI	%(n/N)	95% CI
Overall	98.8 (240/243)	(97.3, 100.0)	100.0 (228/228)	(98.3, 100.0)	100.0 (243/243)	(98.4, 100.0)	100.0 (252/252)	(98.5, 100.0)
Intact	99.3 (143/144)	(97.8, 100.0)	100.0 (125/125)	(97.0, 100.0)	100.0 (135/135)	(97.2, 100.0)	100.0 (135/135)	(97.2, 100.0)
Loss	98.0 (97/99)	(94.9, 100.0)	100.0 (103/103)	(96.4, 100.0)	100.0 (108/108)	(96.6, 100.0)	100.0 (117/117)	(96.8, 100.0)

Between-Day Precision for VENTANA MMR RxDx Panel

In addition to the between-day precision described above, a supplemental between-day precision to assess the test performance of VENTANA MMR RxDx Panel on solid tumor samples over 5 non-consecutive days was also performed. Agreement results are presented in Table 9 below.

The between-day precision study over 5 non-consecutive days consisted of 24 FFPE solid tumor cases distributed as follows:

MLH1: 12 intact cases [4 endometrium, 1 bladder (a challenging case), and 7 gastric (including 2 challenging cases)] and 12 loss cases (3 endometrium, 1 bladder, 5 gastric (including 1 challenging case), 1 ureter, 1 kidney (a challenging case) and 1 melanoma (a challenging case)].

PMS2: 12 intact cases (4 gastric, 3 endometrium, 1 ovary, 3 bladder, and 1 pancreas) and 12 loss cases (5 gastric, 3 endometrium, 3 bladder, and 1 pancreas). The agreement results are presented below.

MSH2: 12 intact cases [3 endometrium, 1 bladder, 5 gastric (including 1 challenging case), 1 kidney, 1 ureter (a challenging case), and 1 melanoma] and 12 loss cases [3 endometrium, 1 bladder, 5 gastric (including 1 challenging case), 1 ureter, 1 kidney (a challenging case), and 1 melanoma (a challenging case)].

MSH6: 12 intact cases [4 endometrium (including 1 challenging case), 1 ovary, 1 bladder, 3 gastric (including 1 challenging case), 1 kidney, 1 ureter, and 1 melanoma] and 12 loss cases [4 endometrium, 1 ovary, 1 bladder, 3 gastric (including 1 challenging case), 1 kidney, 1 ureter, and 1 melanoma (a challenging case)].

For this supplemental between-day precision study for solid tumor cases, there was one non-evaluable slide:
MSH2: 1 slide (no internal control cells staining).

Table 9. Precision, Between-Day for VENTANA MMR RxDx Panel – Solid Tumor Cases

Overall Agreement Between-Days							
Antibody	Slide-Level Marker Status	Marker Mode Status			Measure	%(n/N)	95% CI
		Loss	Intact	Total			
MLH1	Loss	120	0	120	PPA	100.0 (120/120)	(96.9, 100.0)
	Intact	0	120	120	NPA	100.0 (120/120)	(96.9, 100.0)
	Total	120	120	240	OPA	100.0 (240/240)	(98.4, 100.0)
PMS2	Loss	120	0	120	PPA	100.0 (120/120)	(96.9, 100.0)
	Intact	0	120	120	NPA	100.0 (120/120)	(96.9, 100.0)
	Total	120	120	240	OPA	100.0 (240/240)	(98.4, 100.0)
MSH2	Loss	119	0	119	PPA	100.0 (119/119)	(96.9, 100.0)
	Intact	0	120	120	NPA	100.0 (120/120)	(96.9, 100.0)
	Total	119	120	239	OPA	100.0 (239/239)	(98.4, 100.0)
MSH6	Loss	120	0	120	PPA	100.0 (120/120)	(96.9, 100.0)
	Intact	0	120	120	NPA	100.0 (120/120)	(96.9, 100.0)
	Total	120	120	240	OPA	100.0 (240/240)	(98.4, 100.0)

5. **Reader Precision**

Between-Reader and Within-Reader precision was assessed by evaluating concordance of VENTANA MMR RxDx Panel status between 3 readers and within individual readers using 162 (100 proficient and 62 deficient) cases from a variety of solid tumors as follows:

Urinary system-15 cases (9 proficient and 6 deficient), reproductive system- 48 cases, gastrointestinal system- 56 cases (28 proficient and 28 deficient, endocrine system- 7 cases (7 proficient), hepato-pancreatobiliary system-13 cases (9 proficient and 4 deficient), soft tissue/skin- 9 cases (7 proficient and 2 deficient), thoracic- 9 cases (7 proficient and 2 deficient) and head and neck cancer- 5 cases (5 proficient).

Specimens were blinded and randomized prior to evaluation of each of the 4 individual antibody status (intact or loss) and panel-level status (proficient or deficient) for each case using the VENTANA MMR RxDx Panel scoring algorithm (Staining Interpretation Section F of the Device Description Section V, and Table 2 above). Readers scored all specimens twice, with a minimum of two weeks wash-out period between reads. The agreement rates between the readers and within-reader are summarized in Table 10.

For the reader precision studies, the number of non-evaluable slides and the reasons for non-evaluable observations were as follows:

Case 1: Unevaluable for PMS2 (no internal control cells staining).

Case 2: Unevaluable for all 4 antibodies (high DAB staining on NRC). Due to unacceptable NRCs, each antibody-stained slide was not evaluated.

Case 3: same as above.

Case 4: Unevaluable for all 4 antibodies (internal control very minimally present).

Table 10. Within-Reader and Between-Reader Precision of the VENTANA MMR RxDx Panel on solid tumor tissues, by MMR Status (Proficient/ Deficient)

Precision	Clinical Status	Agreement			
		Type	n/N	%	95% CI
Within-Reader	Deficient	APA	(364/366)	99.5	(98.6 ,100.0)
	Proficient	ANA	(598/600)	99.7	(99.2 ,100.0)
	Total	OPA	(481/483)	99.6	(99.0 ,100.0)
Between-Reader	Deficient	APA	(364/366)	99.5	(98.3 ,100.0)
	Proficient	ANA	(596/598)	99.7	(99.0 ,100.0)
	Total	OPA	(480/482)	99.6	(98.8 ,100.0)

Precision	Clinical Status	Agreement			
		Type	n/N	%	95% CI

Note: Average Positive Agreement (ANA), Average Negative Agreement (ANA), Overall Percent Agreement (OPA).

2-sided 95% confidence interval (CI) was calculated using the percentile bootstrap method from 2000 bootstrap samples.

Table 11. Within-Reader and Between-Reader Precision of the VENTANA MMR RxDx Panel on solid tumor tissues, by marker (Intact/ Loss)

Marker	Parameter	Clinical Status	Agreement			
			Type	n/N	%	95% CI
MLH1	Within-Reader	Loss	APA	288/290	99.3	(98.2 ,100.0)
		Intact	ANA	676/678	99.7	(99.3 ,100.0)
		Total	OPA	482/484	99.6	(99.0 ,100.0)
	Between-Reader	Loss	APA	286/290	98.6	(96.4 ,100.0)
		Intact	ANA	674/678	99.4	(98.5 ,100.0)
		Total	OPA	480/484	99.2	(97.9 ,100.0)
PMS2	Within-Reader	Loss	APA	292/294	99.3	(98.3 ,100.0)
		Intact	ANA	670/672	99.7	(99.3 ,100.0)
		Total	OPA	481/483	99.6	(99.0 ,100.0)
	Between-Reader	Loss	APA	292/294	99.3	(97.8 ,100.0)
		Intact	ANA	668/670	99.7	(99.1 ,100.0)
		Total	OPA	480/482	99.6	(98.8 ,100.0)
MSH2	Within-Reader	Loss	APA	48/50	96.0	(90.2 ,100.0)
		Intact	ANA	916/918	99.8	(99.0 ,100.0)
		Total	OPA	482/484	99.6	(99.0 ,100.0)
	Between-Reader	Loss	APA	44/50	88.0	(69.0 ,100.0)
		Intact	ANA	912/918	99.3	(98.5 ,100.0)
		Total	OPA	478/484	98.8	(97.1 ,100.0)
MSH6	Within-Reader	Loss	APA	72/73	98.6	(95.5 ,100.0)
		Intact	ANA	894/895	99.9	(99.7 ,100.0)
		Total	OPA	483/484	99.8	(99.4 ,100.0)
	Between-Reader	Loss	APA	66/72	91.7	(81.4 ,100.0)
		Intact	ANA	890/896	99.3	(98.4 ,100.0)
		Total	OPA	478/484	98.8	(97.1 ,100.0)

Note: Average Positive Agreement (ANA), Average Negative Agreement (ANA), Overall Percent Agreement (OPA).

2-sided 95% confidence interval (CI) was calculated using the percentile bootstrap method from 2000 bootstrap samples.

Reader precision study met all the requirements and acceptance criteria for Within-Reader and Between-Reader precision studies.

6. **External Reproducibility**

The reproducibility of VENTANA MMR RxDx Panel was evaluated in 3 independent Inter-Laboratory Reproducibility (ILR) studies (diverse solid tumors, EC only and CRC only) conducted using the same study design. In each study, a set of de-identified FFPE tumor specimens was stained on a BenchMark ULTRA instrument at each of 3 external laboratories on each of 3 non-consecutive days (spanning at least 20 days in total). Each staining day at each site produced a 5-slide panel [4 biomarker antibody-stained slides and 1 slide stained with mouse NRC using the PMS2 staining protocol] that was independently evaluated for the status of each marker (Intact or Loss) and for MMR status (Deficient or Proficient) by 2 pathologists at the site.

The solid tumor ILR study used 60 diverse solid tumor cases (30 dMMR cases and 30 pMMR cases), of which 6 were considered challenging; EC only and CRC only ILR studies used 30 EC cases and 30 CRC cases respectively. The EC and CRC studies each used 15 dMMR cases and 15 pMMR cases, and each included 4 cases that were considered challenging.

The specimen distribution is shown the Table 12 below.

Table 12. Specimen Distribution, External Reproducibility Study

Study	Total Number of Cases in the Study	Organ System	Tissue Type	MMR Panel Clinical Status		Total number of Cases
				Number of Proficient Cases	Number of Deficient Cases	
Solid tumor	60	Gastrointestinal	Gastric/Stomach	6	9	15
			Esophagus	0	2	2
			Colon	0	5	5
		Urinary	Bladder	5	1	6
			Renal Pelvis	1	0	1
		Reproductive	Endometrium	0	5	5
			Cervix	1	0	1
			Ovary	5	5	10
		Hepato-pancreatobiliary	Pancreas	3	1	4
			Liver	0	1	1
			Lung	3	1	4
		Endocrine	Pancreas (Neuroendocrine)	1	0	1
			Thyroid	1	0	1
		Soft Tissue/ Skin	Soft tissue	1	0	1
			Skin	3	0	3
EC	30	Reproductive	EC	15	15	30

CRC	30	Gastrointestinal	CRC	15	15	30

Note: The solid tumor study cohort represented a diverse range of histologies and organ systems, including 5 CRC cases and 5 EC cases.
One sample was common between the solid-tumor and EC ILR studies, but is being counted as separate for analysis purposes.

Each set of 5 stained slides per case per staining day (4 biomarker-stained slides and 1 mouse NRC stained with PMS2 staining protocol) was combined with a case-matched hematoxylin and eosin (H&E)-stained slide and provided as a 6-slide panel to 2 trained, blinded pathologists (readers) at the site. Each pathologist independently interpreted each case panel for the marker status (Intact or Loss) for each of the 4 VENTANA MMR RxDx Panel biomarkers (MLH1, PMS2, MSH2 and MSH6) and for the overall MMR panel status of the case (dMMR or pMMR). As noted above in section V.F. (Staining Interpretation), a case was considered pMMR if all 4 biomarkers were Intact and was considered dMMR if any one of the four biomarkers had a Loss status.

PPA and NPA rates for MMR status (dMMR or pMMR) across all evaluable observations, using the case-level reader modes for MMR status as the reference were assessed (see below for a description of non-evaluable observations and reasons for non-evaluable). Study results are presented for panel-level status (dMMR or pMMR), and for marker-level status (for 4 VENTANA MMR RxDx Panel biomarkers MLH1, PMS2, MSH2 and MSH6) for Solid Tumor, EC and CRC indications in Tables 13-20 below.

For the external reproducibility studies, the number of non-evaluable slides and the reasons for non-evaluable observations were as follows:

Case 1: Solid tumor ILR study (site C; day 1, reader 2): Unevaluable for PMS2 (Internal control not acceptable.

Case 2: CRC ILR study (site A; day 1, readers 1 and 2): Unevaluable for MSH2 (No tissue on slide). The backup slide was used, and repeat staining was evaluable.

Case 3: CRC ILR study (site C; day 2, reader 1): Unevaluable for PMS2 (Internal control not acceptable.

Table 13. External Reproducibility, VENTANA MMR RxDx Panel, Solid Tumors**

	Overall		Between-Site		Between-Reader	
Analysis	**% (n/N)**	**95% CI***	**% (n/N)**	**95% CI***	**% (n/N)**	**95% CI***
PPA	99.6 (537/539)	(99.1, 100.0)	99.6 (537/539)	(99.1, 100.0)	99.6 (537/539)	(99.1, 100.0)
NPA	99.3 (536/540)	(98.3, 100.0)	99.3 (536/540)	(98.3, 100.0)	99.3 (536/540)	(98.3, 100.0)
OPA	99.4 (1073/1079)	(99.0, 99.9)	99.4 (1073/1079)	(99.0, 99.9)	99.4 (1073/1079)	(99.0, 99.9)

* Two-sided 95% CIs for point estimates (PEs) of 100% were calculated using the Wilson score method; for other PEs, they were calculated using the percentile bootstrap method with 2000 replicates.

** Does not include EC ILR study and CRC ILR study tumors

Table 14. External Reproducibility Study for VENTANA MMR RxDx Panel on Solid Tumor* tissue, by each marker

		Agreement with Mode [b]					
		PPA		NPA		OPA	
	Marker	% (n/N)[a]	95% CI [c]	% (n/N)	95% CI	% (n/N)	95% CI
Agreement of Reader Biomarker Status with the Case-Level Reader Modal Status	MLH1	99.7 (359/363)	(99.1, 100.0)	99.4 (716/717)	(98.7, 100.0)	99.5 (1075/1080)	(99.1, 99.9)
	PMS2	98.6 (354/357)	(97.3, 99.7)	99.6 (717/722)	(99.1, 100.0)	99.3 (1071/1079)	(98.7, 99.7)
	MSH2	98.3 (177/185)	(96.7, 100.0)	99.1 (892/895)	(98.0, 99.9)	99.0 (1069/1080)	(98.0, 99.7)
	MSH6	97.0 (192/195)	(94.4, 99.1)	99.7 (879/885)	(99.3, 100.0)	99.2 (1071/1080)	(98.6, 99.6)
Within Site Agreement of Biomarker Status with the Case-Level Mode	MLH1	99.7 (359/363)	(99.1, 100.0)	99.4 (716/717)	(98.7, 100.0)	99.5 (1075/1080)	(99.1, 99.9)
	PMS2	98.6 (354/357)	(97.3, 99.7)	99.6 (717/722)	(99.1, 100.0)	99.3 (1071/1079)	(98.7, 99.7)
	MSH2	98.3 (177/185)	(96.7, 100.0)	99.1 (892/895)	(98.0, 99.9)	99.0 (1069/1080)	(98.0, 99.7)
	MSH6	97.0 (192/195)	(94.4, 99.1)	99.7 (879/885)	(99.3, 100.0)	99.2 (1071/1080)	(98.6, 99.6)
Within-Reader Agreement of Biomarker Status with the Case-Level Mode	MLH1	99.7 (359/363)	(99.1, 100.0)	99.4 (716/717)	(98.7, 100.0)	99.5 (1075/1080)	(99.1, 99.9)
	PMS2	98.6 (354/357)	(97.3, 99.7)	99.6 (717/722)	(99.1, 100.0)	99.3 (1071/1079)	(98.7, 99.7)
	MSH2	98.4 (180/185)	(96.7, 100.0)	99.4 (892/895)	(98.9, 99.9)	99.3 (1072/1080)	(98.7, 99.7)
	MSH6	97.0 (192/195)	(94.4, 99.1)	99.7 (879/885)	(99.3, 100.0)	99.2 (1071/1080)	(98.6, 99.6)

NPA = negative percent agreement; PPA = positive percent agreement OPA = overall percent agreement
[a] Counts indicate numbers of reader observations, not numbers of unique cases.
[b] For the purpose of agreement rate calculations, a biomarker status of Loss was considered Positive and a biomarker status of Intact was considered Negative.
[c] Two-sided 95% CIs were calculated using the percentile bootstrap method with 2000 replicates, except that those for point estimates of 100% were calculated using the Wilson score method.
*Does not include EC ILR study and CRC ILR study tumors

Table 15. External Reproducibility, VENTANA MMR RxDx Panel, Endometrial cancer

	Overall		Between-Site		Between-Reader	
Analysis	% (n/N)	95% CI*	% (n/N)	95% CI*	% (n/N)	95% CI*
PPA	98.1 (263/268)	(95.5, 100.0)	98.1 (263/268)	(95.5, 100.0)	99.2 (263/265)	(98.1, 100.0)
NPA	100.0 (269/269)	(98.6, 100.0)	100.0 (269/269)	(98.6, 100.0)	100.0 (272/272)	(98.6, 100.0)
OPA	99.1 (532/537)	(97.8, 100.0)	99.1 (532/537)	(97.8, 100.0)	99.6 (535/537)	(99.1, 100.0)

* Two-sided 95% CIs for point estimates (PEs) of 100% were calculated using the Wilson score method; for other PEs, they were calculated using the percentile bootstrap method with 2000 replicates.

Table 16. External Reproducibility Study for VENTANA MMR RxDx Panel on EC tissue, by each marker

		Agreement with Mode [b]					
		PPA		NPA		OPA	
	Marker	% (n/N)[a]	95% CI [c]	% (n/N)	95% CI	% (n/N)	95% CI
Agreement of Reader Biomarker Status with the Case-Level Reader Modal Status	MLH1	98.8 (160/162)	(97.2, 100.0)	100.0 (377/377)	(99.0, 100.0)	99.6 (537/539)	(99.1, 100.0)
	PMS2	98.1 (159/162)	(96.3, 100.0)	100.0 (377/377)	(99.0, 100.0)	99.4 (536/539)	(98.9, 100.0)
	MSH2	96.2 (102/106)	(90.0, 100.0)	99.5 (429/431)	(98.9, 100.0)	98.9 (531/537)	(97.6, 99.8)
	MSH6	88.9 (96/108)	(78.9, 98.1)	99.3 (428/431)	(98.6, 100.0)	97.2 (524/539)	(95.2, 99.3)
Within Site Agreement of Biomarker Status with the Case-Level Mode	MLH1	98.8 (160/162)	(97.2, 100.0)	100.0 (377/377)	(99.0, 100.0)	99.6 (537/539)	(99.1, 100.0)
	PMS2	98.1 (159/162)	(96.3, 100.0)	100.0 (377/377)	(99.0, 100.0)	99.4 (536/539)	(98.9, 100.0)
	MSH2	96.2 (102/106)	(90.0, 100.0)	99.5 (429/431)	(98.9, 100.0)	98.9 (531/537)	(97.6, 99.8)
	MSH6	94.1 (96/102)	(88.2, 98.6)	99.3 (434/437)	(98.6, 100.0)	98.3 (530/539)	(97.0, 99.3)
Within-Reader Agreement of Biomarker Status with the Case-Level Mode	MLH1	98.8 (160/162)	(97.2, 100.0)	100.0 (377/377)	(99.0, 100.0)	99.6 (537/539)	(99.1, 100.0)
	PMS2	98.1 (159/162)	(96.3, 100.0)	100.0 (377/377)	(99.0, 100.0)	99.4 (536/539)	(98.9, 100.0)
	MSH2	99.0 (102/103)	(96.9, 100.0)	99.5 (432/434)	(98.9, 100.0)	99.4 (534/537)	(98.9, 100.0)
	MSH6	97.0 (96/99)	(94.4, 100.0)	99.3 (437/440)	(98.7, 100.0)	98.9 (533/539)	(98.1, 99.6)

NPA = negative percent agreement; PPA = positive percent agreement OPA = overall percent agreement
[a] Counts indicate numbers of reader observations, not numbers of unique cases.
[b] For the purpose of agreement rate calculations, a biomarker status of Loss was considered Positive and a biomarker status of Intact was considered Negative.
[c] Two-sided 95% CIs were calculated using the percentile bootstrap method with 2000 replicates, except that those for point estimates of 100% were calculated using the Wilson score method.

Table 17. External Reproducibility, VENTANA MMR RxDx Panel, Colorectal Cancer

Analysis	Overall		Site-Stratified		Reader-Stratified	
	% (n/N)	95% CI*	% (n/N)	95% CI*	% (n/N)	95% CI*
PPA	99.3 (267/269)	(98.1, 100.0)	99.3 (267/269)	(98.1, 100.0)	99.3 (267/269)	(98.1, 100.0)
NPA	100.0 (270/270)	(98.6, 100.0)	100.0 (270/270)	(98.6, 100.0)	100.0 (270/270)	(98.6, 100.0)
OPA	99.6 (537/539)	(99.1, 100.0)	99.6 (537/539)	(99.1, 100.0)	99.6 (537/539)	(99.1, 100.0)

* Two-sided 95% CIs for point estimates (PEs) of 100% were calculated using the Wilson score method; for other PEs, they were calculated using the percentile bootstrap method with 2000 replicates.

Table 18. External Reproducibility Study for VENTANA MMR RxDx Panel on CRC tissue as measured for each marker

		Agreement with Mode [b]					
		PPA		NPA		OPA	
	Marker	% (n/N)[a]	95% CI [c]	% (n/N)	95% CI	% (n/N)	95% CI
Agreement of Reader Biomarker Status with the Case-Level Reader Modal Status	MLH1	98.6 (142/144)	(96.7, 100.0)	100.0 (396/396)	(99.0, 100.0)	99.6 (538/540)	(99.1, 100.0)
	PMS2	98.6 (142/144)	(96.7, 100.0)	100.0 (395/395)	(99.0, 100.0)	99.6 (537/539)	(99.1, 100.0)
	MSH2	92.1 (116/126)	(78.9, 100.0)	99.3 (411/414)	(98.2, 100.0)	97.6 (527/540)	(94.2, 99.8)
	MSH6	91.7 (132/144)	(79.9, 99.1)	100.0 (396/396)	(99.0, 100.0)	97.8 (528/540)	(94.3, 99.8)
Within-Site or Within-reader Agreement of Biomarker Status with the Case-Level Mode	MLH1	98.6 (142/144)	(96.7, 100.0)	100.0 (396/396)	(99.0, 100.0)	99.6 (538/540)	(99.1, 100.0)
	PMS2	98.6 (142/144)	(96.7, 100.0)	100.0 (395/395)	(99.0, 100.0)	99.6 (537/539)	(99.1, 100.0)
	MSH2	96.7 (116/120)	(91.3, 100.0)	99.3 (417/420)	(98.3, 100.0)	98.7 (533/540)	(97.4, 99.8)
	MSH6	95.7 (132/138)	(90.7, 99.1)	100.0 (402/402)	(99.1, 100.0)	98.9 (534/540)	(97.6, 99.8)

NPA = negative percent agreement; PPA = positive percent agreement OPA = overall percent agreement
[a] Counts indicate numbers of reader observations, not numbers of unique cases.
[b] For the purpose of agreement rate calculations, a biomarker status of Loss was considered Positive and a biomarker status of Intact was considered Negative.
[c] Two-sided 95% CIs were calculated using the percentile bootstrap method with 2000 replicates, except that those for point estimates of 100% were calculated using the Wilson score method.

The MMR results for all cases in the 3 ILR studies (solid tumors, EC and CRC) were combined (120 cases in total) and analyzed for the same cases to assess the performance of VENTANA MMR RxDx Panel as a diagnostic device for determining MMR status in diverse solid tumor specimens. The combined analysis of MMR status across all readers, sites, and days included a total of 2155 observations. The summary of MMR status agreement rates across all evaluable observations vs the reader modes, using the reader modes as the reference, is shown in Table 19. The agreement rates for the pooled within-site and within-reader analyses vs the reader modes, using the within-site and within-reader modes as the references, are also shown in Table 20.

Table 19. Inter-Laboratory Reproducibility for overall agreement rates for VENTANA MMR RxDx Panel in variety of solid tumor tissues including EC

Inter-Laboratory Reproducibility	Agreement			
	Type	n/N	%	95% CI
Overall	PPA	1066/1076	99.1	(98.3, 99.6)
	NPA	1075/1079	99.6	(99.2, 100.0)
	OPA	2141/2155	99.4	(98.9, 99.7)
Within-Site	PPA	1066/1076	99.1	(98.3, 99.6)
	NPA	1075/1079	99.6	(99.2, 100.0)

Inter-Laboratory Reproducibility	Agreement			
	Type	n/N	%	95% CI
	OPA	2141/2155	99.4	(98.9, 99.7)
Within-Reader	PPA	1066/1073	99.3	(98.9, 99.7)
	NPA	1078/1082	99.6	(99.2, 100.0)
	OPA	2144/2155	99.5	(99.2, 99.8)

Note: Positive Percent Agreement (PPA), Negative Percent Agreement (NPA), Overall Percent Agreement (OPA).
Note: Two-sided 95% CIs were calculated using the percentile bootstrap method with 2000 replicates.
Note: For the purposes of this study, a sample with a MMR Panel status of deficient was considered positive and a sample with a MMR Panel status of proficient was considered negative.

In addition, pairwise comparisons were made Between-site, Between-Reader and Between-Day for panel level MMR status. A summary of the results can be found in Table 20.

Table 20. Inter-Laboratory Reproducibility Pairwise Agreement Rates for the VENTANA MMR RxDx Panel in a variety of solid tumor tissues including EC

Inter-Laboratory Reproducibility	Agreement			
	Type	n/N	%	95% CI
Between-Site	APA	12628/12794	98.7	(97.8, 99.4)
	ANA	12840/13006	98.7	(97.8, 99.4)
	OPA	12734/12900	98.7	(97.8, 99.4)
Between-Reader	APA	1056/1068	98.9	(98.1, 99.5)
	ANA	1072/1084	98.9	(98.1, 99.5)
	OPA	1064/1076	98.9	(98.1, 99.5)
Between-Day	APA	2110/2132	99.0	(98.3, 99.5)
	ANA	2146/2168	99.0	(98.3, 99.5)
	OPA	2128/2150	99.0	(98.3, 99.5)

Note: Average Positive Agreement (APA), Average Negative Agreement (ANA), Overall Percent Agreement (OPA)
Note: Two-sided 95% confidence interval (CI) was calculated using the percentile bootstrap method from 2000 bootstrap samples.
Note: For the purposes of this study, a sample with an MMR Panel status of deficient was considered positive and a sample with a MMR Panel status proficient was considered negative.
Note: The same sites and readers were used for EC and CRC ILR studies. For the solid tumor ILR study, two sites were different from the EC and CRC ILR.

7. **Stability Studies**

a. Cut Slide Stability

See Summary of Safety and Effectiveness Data for P200019.

b. Real Time Stability

See Summary of Safety and Effectiveness Data for P200019.

An additional analytical stability study for solid tumors will be performed in the post-market setting.

B. Animal Studies

None

C. Additional Studies

1. **Fixative Type and Time**

See Summary of Safety and Effectiveness Data for P200019.

2. **Tissue Heterogeneity**

This study evaluated the prevalence of case heterogeneity in various solid tumor tissue blocks from the same case when stained with VENTANA MMR RxDx Panel Assay on the BenchMark ULTRA instrument.

For the sample set of 300 tissues (150 pairs) evaluated, 10 of 44 EC tissues, 6 of 54 CRC tissues, and 2 of 202 of the solid-tumor tissues demonstrated dMMR status. All 150 pairs across all indications exhibited equivalent marker and panel level MMR status for an OPA of 100%. Therefore, case heterogeneity was not observed in any of patient pairs for overall panel level nor marker-level MMR status. Due to the difficulty of procuring matched patient samples from commercial vendors and the overall low prevalence of MMR biomarkers, the sample distribution for MMR status in this study was unequal, with only 18 of 300 cases representing a dMMR status. Although the trend in this study indicates, case heterogeneity is unlikely to be observed in EC, CRC, and solid-tumor tissues, the small sample size of the available dMMR tissues provide a limited assessment of case heterogeneity for MMR panel status.

3. **Primary versus Metastatic**

This study evaluated the concordance of MMR panel status between FFPE matched primary and metastatic solid tumors when stained with the MMR RxDx Panel assay on the BenchMark ULTRA instrument.

In this characterization study, matched primary vs. metastatic solid tumor tissue specimens were stained and compared to show either concordance or discordance in overall MMR panel status between each pair. For the sample set of 156 tissue cases (78 pairs) evaluated, 152 of these cases (76 pairs) were concordant. Out of these 152 cases, 4 cases (2 pairs) exhibited an MMR status of deficient (dMMR), 146 (73 pairs) cases exhibited an MMR status of proficient (pMMR), and 2 cases (1 pair) exhibited an MMR status of non-evaluable. Four cases (2 pairs) exhibited discordance between the matched primary and metastatic tumor tissue pairs.

X. SUMMARY OF CLINICAL STUDIES

The clinical performance of VENTANA MMR RxDx Panel as a CDx device for the solid tumor indication for JEMPERLI was based on the GARNET clinical trial (NCT02715284) Subpart 2B. The primary efficacy population for the drug was based on Cohorts A1 and F.

A. Study Design

GARNET is a multicenter, open-label, study with Subpart 2B, designed to evaluate the antitumor activity of JEMPERLI in patients with recurrent or advanced mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) cancers, including dMMR/MSI-H EC (Cohort A1) and recurrent or advanced dMMR/MSI-H solid tumors (Cohort F). The clinical bridging study for the VENTANA RxDx Panel included retesting the biomarker positive (dMMR) patients (Cohorts A1 and F) and a subset of biomarker negative EC patients from cohort A2 (pMMR) (intact or biomarker-negative) EC, and CRC negative (pMMR) samples that were procured from outside the trial, to evaluate the positive and negative percent agreement between the enrolling tests and the final CDx. Refer to the clinical bridging study in the Effectiveness Results in Section D below for further details.

1. GARNET Clinical Inclusion and Exclusion Criteria

Key Trial Inclusion Criteria

1. Patient has proven recurrent or advanced solid tumor and has disease progression after treatment with available anti-cancer therapies or is intolerant to treatment that meets the requirements for the part of the study, they will participate in per clinical trial protocol.
2. Patients who have progressed on or after platinum doublet therapy
3. Patients have received no more than 2 lines of anti-cancer therapy for recurrent or advanced (≥Stage IIIB) disease. Prior treatment with hormone therapies is acceptable and does not count towards the number of anti-cancer therapies noted in the criterion above for this cohort.
4. Patients must submit 2 scans demonstrating increase in tumor measurement that meet criteria for Progressive Disease (PD) on or after the latest systemic anticancer therapy based on RECIST 1.1 to Central Radiology prior to the first dose of JEMPERLI.

5. Presence of at least 1 measurable lesion on baseline scan will be confirmed by central radiology review.
6. Status of tumor MMR status as determined by immunohistochemistry (IHC) testing.
7. Tumor MMR/MSI or POLE status: Patients can be screened based on local MMR/MSI testing results using IHC, polymerase chain reaction (PCR), or next generation sequencing (NGS) performed in a certified local laboratory, but patient eligibility is determined by MMR IHC results. For patients with available local MMR IHC results for the respective cohort(s), tumor samples have to be submitted to a central IHC laboratory and its quality has to be checked and cleared prior to Day 1 of chemotherapy treatment Cycle 1(C1D1). For patients without available local MMR IHC test results (patients with local PCR or NGS test results), tumor samples have to be submitted directly to central IHC laboratory and central IHC results have to confirm eligibility prior to proceeding with other screening procedures. After the central IHC test is completed, remaining tumor tissue may be sent to a central NGS laboratory for further testing.
8. Patients who are considered for the study based on POLE mutation must have the local results available showing tumor mutation(s) in the exonuclease domain of the POLE gene (amino acid residues 268-471) to begin screening. Patients must have the quality of submitted tumor samples checked and cleared by a central IHC laboratory prior to receiving study treatment.

Key Trial Exclusion Criteria

1. Patient has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
2. Patient has known uncontrolled central nervous system metastases and/or carcinomatous meningitis.
3. Patient has a known additional malignancy that progressed or required active treatment within last 2 years.

2. Follow-up Schedule

Up to 2 years, or until the subject meets protocol specific discontinuation criteria.

3. Clinical Endpoints

Primary endpoints:

1. The primary efficacy endpoint is ORR, defined as the proportion of patients achieving complete response (CR) or partial response (PR) per RECIST v1.1 for dMMR/MSI-H (Cohorts A1 and F).
2. Duration of response (DOR) based on independent blinded central review using RECIST v1.1 for Cohorts A1 and F will be evaluated as a secondary endpoint.

Secondary endpoints:

1. Disease control rate will be assessed for Cohorts A1, A2, and F as a secondary endpoint and is defined as the proportion of patients achieving CR, PR, or stable disease (SD) as assessed per RECIST v1.1
2. Immune-related duration of response will be evaluated as a secondary endpoint for all cohorts in Part 2B and is defined as the time from first documentation of CR or PR by irRECIST until the time of first documentation of PD (subsequently confirmed) per irRECIST
3. Progression-free survival will be assessed as a secondary endpoint and is defined as the time from date of first dose to the earlier date of assessment of progression or death by any cause in the absence of progression based on: (1) the time of first documentation of PD per RECIST v1.1 (for cohorts A1, A2, and F only); and (2) the time of first documentation of PD (subsequently confirmed) per irRECIST for all cohorts in Part 2B
4. OS will be assessed as a secondary endpoint and is defined as the time from date of first dose of study treatment to the date of death by any cause.

B. Accountability of PMA Cohorts

Accountability of EC Cohorts A1 and A2

Study participants with recurrent or advanced endometrial carcinoma in the GARNET study comprise one of the primary analysis population for this application. Out of the 126 patients in EC Cohort A1, 103 were in the efficacy population and 23 were in the non-efficacy safety population. Out of the 103, 57 were available for retesting using the CDx test (EC population). Additionally, 16 were available for retesting that were not derived from the efficacy population but instead from the Safety Population. This resulted in an overall available sample for retesting of 73 subjects (Concordance Population).

Table 21. Accountability of EC Cohorts A1 and A2 (EC)

Analysis Population	Clinical Trial Assay [a] MMR Status		
	dMMR (n)	pMMR (n)	Unknown (n)
Total Enrolled in Study [b]	126	145	4
Efficacy Population	103	142	3
Available Sample for Retesting from Efficacy Population Population	57	74	0
Concordance Population from Safety Population	16	N/A	N/A
Concordance Population	73	75	0

[a] Any IHC MMR test performed at a local or central laboratory for the purpose of GARNET enrollment screening.
[b] All patients enrolled in GARNET Cohort A1 and A2 (EC) who received study treatment prior to the 01-March-2020 clinical data cutoff date (CCOD) for solid-tumor and had an evaluable clinical trial assay (CTA) testing result or were tested with VENTANA MMR RxDx Panel (the CDx assay).

Accountability of Solid Tumor Cohort F

Study participants with recurrent or advanced solid tumors in cohort F of the GARNET study comprise the primary analysis population for this application. Out of the 141 patients in non-EC Cohort F dMMR, 106 were included in the Efficacy population after exclusion due to 35 being in the Non-efficacy safety population. Out of the 106, 53 were available for retesting using the CDx test (EC population). A further 30 were available for retesting that were not derived from the Efficacy population but instead the Safety population. This resulted in an overall available sample for retesting of 83 subjects (Concordance Population).

Table 22. Accountability of Solid Tumor Cohort F (non-EC)

Analysis Population	Clinical Trial Assay [a] MMR Status		
	dMMR (n)	pMMR (n) [b]	Unknown (n)
Total Enrolled in Study [c]	141	4	6
Efficacy Population	106	2	4
Available Sample for Retesting from Efficacy Population Population[c]	53	0	0
Concordance Population from Safety Population	30	N/A	N/A
Concordance Population	83	1	0

[a] Any IHC MMR test performed at a local or central laboratory for the purpose of GARNET enrollment screening.

[b] Includes 1 patient who received a pMMR result from the CTA but also an MSI-H result and 3 patients who received a pMMR result from the CTA but also a POLE-mut result.

[c] All patients enrolled in GARNET Cohort F (non-EC) who received study treatment prior to the 01-March-2020 clinical data cutoff date (CCOD) for the solid tumor BLA and had an evaluable clinical trial assay (CTA) testing result or were tested with VENTANA MMR RxDx Panel (the CDx assay).

C. Study Population Demographics and Baseline Parameters

The table below summarizes patient characteristics by presence/absence of evaluable CDx results for dMMR solid-tumor patients tested with VENTANA MMR RxDx Panel (Efficacy population).

Table 23. Patient Characteristics by Presence/Absence of Evaluable CDx Results – Efficacy Population[a] – dMMR Solid Tumor[b]

Characteristic	Evaluable VENTANA MMR RxDx Panel Result Obtained?		
	Yes (N=110)	No (N=99)	Overall (N=209)
Age (yr)			
n	110	99	209
Mean (SD)	61.8 (11.03)	62.2 (10.68)	62.0 (10.84)
Median	62.0	65.0	63.0
Min, Max	24, 85	25, 80	24, 85
Missing	0	0	0
Age Group (yr)			
n	110	99	209
<65 years	63 (57.3%)	47 (47.5%)	110 (52.6%)
>=65 years - <75 years	36 (32.7%)	43 (43.4%)	79 (37.8%)
>=75 years	11 (10.0%)	9 (9.1%)	20 (9.6%)
Sex			
n	110	99	209
Female	86 (78.2%)	75 (75.8%)	161 (77.0%)
Male	24 (21.8%)	24 (24.2%)	48 (23.0%)
Ethnicity			
n	110	99	209
Hispanic or Latino	5 (4.5%)	2 (2.0%)	7 (3.3%)
Not Hispanic or Latino	72 (65.5%)	63 (63.6%)	135 (64.6%)
Not Reported	31 (28.2%)	31 (31.3%)	62 (29.7%)
Unknown	2 (1.8%)	3 (3.0%)	5 (2.4%)
Race			
n	110	99	209
American Indian or Alaska Native	2 (1.8%)	1 (1.0%)	3 (1.4%)
Asian	4 (3.6%)	2 (2.0%)	6 (2.9%)
Black	1 (0.9%)	3 (3.0%)	4 (1.9%)
White	71 (64.5%)	61 (61.6%)	132 (63.2%)
Other	0	1 (1.0%)	1 (0.5%)
Not Reported	30 (27.3%)	31 (31.3%)	61 (29.2%)
Unknown	2 (1.8%)	0	2 (1.0%)
Organ System			
n	110	99	209
Endocrine	1 (0.9%)	0	1 (0.5%)
Gastrointestinal	47 (42.7%)	43 (43.4%)	90 (43.1%)
Hepatopancreatobiliary	2 (1.8%)	6 (6.1%)	8 (3.8%)
Reproductive	59 (53.6%)	48 (48.5%)	107 (51.2%)
Thoracic	0	1 (1.0%)	1 (0.5%)
Urinary	1 (0.9%)	0	1 (0.5%)
Unknown	0	1 (1.0%)	1 (0.5%)
Tumor Site			
n	110	99	209
Adrenal Cortical	1 (0.9%)	0	1 (0.5%)
Biliary Neoplasm	1 (0.9%)	0	1 (0.5%)

Characteristic	Evaluable VENTANA MMR RxDx Panel Result Obtained?		
	Yes (N=110)	No (N=99)	Overall (N=209)
Breast Cancer	0	1 (1.0%)	1 (0.5%)
Carcinoma of Unknown Primary Origin	0	1 (1.0%)	1 (0.5%)
Colorectal Cancer	32 (29.1%)	37 (37.4%)	69 (33.0%)
Endometrial Cancer	57 (51.8%)	46 (46.5%)	103 (49.3%)
Esophageal Cancer	0	1 (1.0%)	1 (0.5%)
Gallbladder	1 (0.9%)	0	1 (0.5%)
Gastric Cancer	5 (4.5%)	3 (3.0%)	8 (3.8%)
Genital Neoplasm Malignant Female	0	1 (1.0%)	1 (0.5%)
Liver Cancer	0	2 (2.0%)	2 (1.0%)
Ovarian Cancer	2 (1.8%)	0	2 (1.0%)
Pancreatic Carcinoma	0	4 (4.0%)	4 (1.9%)
Pleural	0	1 (1.0%)	1 (0.5%)
Renal Cell Carcinoma	1 (0.9%)	0	1 (0.5%)
Small Intestinal Cancer	10 (9.1%)	2 (2.0%)	12 (5.7%)
Stage at Initial Diagnosis			
n	110	99	209
Stage I	23 (20.9%)	21 (21.2%)	44 (21.1%)
Stage II	9 (8.2%)	8 (8.1%)	17 (8.1%)
Stage III	41 (37.3%)	30 (30.3%)	71 (34.0%)
Stage IV	36 (32.7%)	39 (39.4%)	75 (35.9%)
Unknown	1 (0.9%)	1 (1.0%)	2 (1.0%)
Cancer Stage (Most Recent) [d]			
n	53	53	106
Locoregional (Unresectable)	1 (1.9%)	4 (7.5%)	5 (4.7%)
Metastatic	52 (98.1%)	49 (92.5%)	101 (95.3%)
Missing	57	46	103
Baseline ECOG Performance			
n	110	99	209
0	36 (32.7%)	46 (46.5%)	82 (39.2%)
1	74 (67.3%)	53 (53.5%)	127 (60.8%)
Histology [c]			
n	57	46	103
Adenocarcinoma	48 (84.2%)	40 (87.0%)	88 (85.4%)
Clear Cell Carcinoma	1 (1.8%)	0	1 (1.0%)
Mixed Carcinoma	3 (5.3%)	1 (2.2%)	4 (3.9%)
Serous Carcinoma	3 (5.3%)	1 (2.2%)	4 (3.9%)
Squamous Carcinoma	0	1 (2.2%)	1 (1.0%)
Undifferentiated Carcinoma	1 (1.8%)	3 (6.5%)	4 (3.9%)
Unknown	1 (1.8%)	0	1 (1.0%)
Missing	53	53	106

[a]VENTANA MMR RxDx Panel (CDx) results associated with exclusionary diagnostic (Dx) protocol deviations (PDs) [ie, IU CDx results] were treated as missing.

[b] All patients in the Efficacy Population who had a dMMR CTA MMR result.

[c] Variable(s) for EC patients only.

[d] Variable(s) for non-EC patients only.

D. Safety and Effectiveness Results

1. Safety Results

Adverse events (AEs) in the GARNET trial were specific to the toxicity of the investigational agent. There were no device-specific adverse events in the diagnostic study. In this trial, observed AEs included events that were in line with those expected in subjects with recurrent or advanced solid tumors, as well as those consistent with reported safety profiles of monoclonal antibodies blocking the PD 1 interactions.

2. Effectiveness Results

The analysis of effectiveness was based on the efficacy population (209 in cohorts A1 and F (dMMR)).

Efficacy in dMMR solid tumors was performed in 209 patients with dMMR tumors (103 dMMR EC and 106 dMMR non-EC). The tumor response summary for the dMMR solid-tumor population overall is summarized in Table 24 below. The overall response rate (ORR) from the drug trail was 41.6%.

Table 24. Efficacy Results in GARNET dMMR Recurrent or Advanced Solid Tumors

Endpoint	JEMPERLI N = 209
Confirmed overall response rate	
Overall response rate	41.6%
(95% CI)	(34.9, 48.6)
Complete response rate	9.1%
Partial response rate	32.5%
Duration of response	
Median in months	34.7
(range)[a]	2.6, 35.8+
Patients with duration ≥6 months	95.4%

Clinical Bridging Study

Bridging study was performed to evaluate agreements of MMR status (PPA for dMMR status, and NPA for pMMR status) between VENTANA MMR RxDx Panel and the CTA (local or central testing using an IHC assay other than VENTANA MMR RxDx Panel) and to assess the estimated clinical efficacy (ORR, DOR) of the patients enrolled in the GARNET Study, had the CDx been the enrolling device.

The agreement of MMR status between CTA and CDx results was calculated in the Concordance (EC = 73 and non-EC = 83) population using the CTA results as reference. For the purpose of the analyses, a pMMR status was considered negative, and dMMR status was considered positive.

Concordance between the CTA and CDx [VENTANA MMR RxDx Panel (Solid Tumors)]

PPA rates for the dMMR EC (n = 73), non-EC (n = 83), and solid tumor (n = 156) groups were 93.2% (95% CI: 84.9, 97.0), 83.1% (95% CI: 73.7, 89.7), and 87.8% (95% CI: 81.8, 92.1), respectively. NPA rates for the pMMR EC group (n = 75) was 98.7% (95% CI: 92.8, 99.8), and the NPA in the non-EC group (n = 1) was 100% (95% CI: 20.7, 100.0) and in the solid tumor group (n = 76) it was 98.7% (95% CI: 92.9, 99.8), respectively.

Table 25.: Solid Tumor MMR Status Concordance between the GARNET Clinical Trial Assay and VENTANA MMR RxDx Panel

	CDx MMR	CTA Status			Agreement		
Group	Status	dMMR	pMMR	Total	Measure	% (n/N)	95% CI [a]
EC	dMMR	68	1	69	PPA	93.2 (68/73)	84.9, 97.0
	pMMR	5	74	79	NPA	98.7 (74/75)	92.8, 99.8
	Total	73	75	148	OPA	95.9 (142/148)	91.4, 98.1
Non-EC	dMMR	69	0	69	PPA	83.1 (69/83)	73.7, 89.7
	pMMR	14	1	15	NPA	100 (1/1)	20.7, 100
	Total	83	1	84	OPA	83.3 (70/84)	73.9, 89.8
dMMR Solid tumors	dMMR	137	1	138	PPA	87.8 (137/156)	81.8, 92.1
	pMMR	19	75	94	NPA	98.7(75/76)	92.9, 99.8
	Total	156	76	232	OPA	91.4(212/232)	87.1, 94.4

[a] Two-sided 95% CIs were calculated using the Wilson score method.

A sensitivity analysis was conducted to evaluate the robustness of the ORR estimates in dMMR patients in the GARNET clinical trial. Multiple imputation using logistic regression was conducted separately for EC, non-EC and solid tumor. In an examination of covariates between samples that were evaluable and non-evaluable with the VENTANA MMR RxDx Panel, distribution of the covariates supports missing at random assumption. In the bridging study, since a large proportion of dMMR in solid tumor includes EC and CRC, the NPA for solid tumors was calculated based on lower bound 95% CI of NPA from EC and CRC cohorts. The imputation-based ORR for solid tumor population was 31.8% with 95% CI (26.1%, 37.6%) with CTA+ prevalence of 9% under the worst-case scenario (no drug efficacy in CDx+|CTA- population) and 48.7% with 95% CI (41.6%, 55.7%) under the best-case scenario (full drug efficacy in CDx+|CTA-

population). The range of these results include the observed ORR for the GARNET clinical trial (41.6% [34.9%, 48.6%]).

3. **Subgroup Analyses**

There was no subgroup analysis performed.

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 1 principal investigator. 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 did not raise any new safety and effectiveness questions compared with information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM THE STUDIES

A. Effectiveness Conclusions

Effectiveness of the of VENTANA MMR RxDx Panel in determining MMR status (proficient or deficient) is based on the clinical performance and benefit to patients with recurrent or advanced solid tumors as assessed in the GARNET study which evaluated the safety and the efficacy of JEMPERLI in these patients who have no satisfactory alternative treatment options. The clinical benefit of the VENTANA MMR RxDx Panel was demonstrated for patients enrolled in GARNET clinical study, in which the MMR status was determined using CTA. Overall, the observed clinical benefit in the subset of patients tested with the VENTANA MMR RxDx Panel Assay was comparable to that observed in the BLA efficacy population. Additional sensitivity analyses combined with

multiple imputation approaches for missing CDx values consistently support the clinical benefit of the VENTANA MMR RxDx Panel.

The performance of the VENTANA MMR RxDx 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 MMR RxDx Panel is an *in vitro* diagnostic device, which involves tumor specimens collected from patients with recurrent or advanced solid tumors. 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 MMR RxDx Panel are associated with failure of the device to perform as expected or failure to correctly interpret test results. As VENTANA MMR RxDx Panel is intended for use to identify patients for JEMPERLI 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 JEMPERLI without much clinical benefit and may experience adverse reactions associated with JEMPERLI therapy. Patients with false negative results may not be considered for treatment with JEMPERLI, and therefore, may receive other treatment options. There is also a risk of delayed results, which may lead to a delay in treatment with JEMPERLI.

C. Benefit-Risk Determination

The probable benefits of this device are based on the data collected in the GARNET clinical study. When the VENTANA MMR RxDx Panel is used in the designated intended use population, recurrent or advanced dMMR solid tumors, according to the approved instructions for use, and whose tumors demonstrate deficient MMR with this device, the benefits of the use of JEMPERLI are expected to be an overall response rate of approximately 31.8% (estimate based on worst-case scenario) to 48.7% (estimate based on best case scenario) with acceptable duration of response and with evidence of probable benefit.

The potential risk associated with the use of the device, mainly due to 1) false positive, false negative or failure to provide a result. The risk of use of the VENTANA MMR RxDx Panel in the designated intended use population, for the proposed indication for use include the risks of a false positive device result and subsequent use of JEMPERLI include a failure of the patient's tumor to respond to this therapy, and the experiencing of toxicity/adverse events. With respect to a false negative device result, such a patient could be deprived of a potentially beneficial solid tumor treatment and associated overall response rate and durability.

In this trial, observed AEs included events that were in line with those expected in subjects with recurrent or advanced solid tumors and endometrial cancer, as well as those

consistent with reported safety profiles of monoclonal antibodies blocking the PD 1 interactions.

In addition to a false positive device result, a failure to respond could also be due to the particular biology of the patient's tumor, or other idiosyncratic biological issues specific to the individual patient, even if the device result is a true positive, as not all true positives will respond to this therapy. With respect to a false negative device result, such a patient could be deprived of a potentially beneficial solid tumor or endometrial cancer treatment and associated overall response rate and durability. The risks are mitigated by the expected poor prognosis of recurrent or advanced solid tumors. The risks of false results are partially mitigated by the analytical validation results summarized above.

The overall clinical and analytical data support that for the VENTANA MMR RxDx Panel, and the indications noted in the intended use statement, the probable benefits outweigh the probable risks

Patient Perspectives

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

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Study 4010-01-001 (GARNET) is a multi-center, open-label ongoing clinical study of JEMPERLI efficacy and safety in adult patients who have recurrent or advanced solid tumors with limited available treatment options. Data from this study support the use of the MMR RxDx Panel as an aid in selecting patients with MMR deficient solid tumors who are likely to benefit from JEMPERLI therapy. The response rate in patients with solid tumors that have deficient MMR expression is better than what would be expected of available therapy and represents an improvement that is reasonably likely to predict clinical benefit.

XIV. CDRH DECISION

CDRH issued an approval order on August 17, 2021.

The final conditions of approval cited in the approval order are described below.

1. Ventana Medical Systems, Inc. must provide additional data from an appropriately designed analytical sensitivity study for the VENTANA RxDx Panel for the solid tumor indication. For each marker (MLH1, PMS2, MSH2 and MSH6), ensure that the relevant solid tumors are adequately represented. The data from this study must be adequate to support analytical sensitivity of the 4 markers of the VENTANA MMR RxDx Panel in the intended use population.

2. Ventana Medical Systems, Inc. must provide additional data from well-designed stability studies (shelf-life, in-use and shipping) to support stability claims for the VENTANA MMR RxDx Panel for the solid tumor indication. These studies should use intended use specimens and the data from these studies must be adequate to support stability claims for the VENTANA MMR RxDx Panel in the intended use population.

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.