VENTANA MET (SP44) RxDx Assay

REF 740-7064

08866856001

IVD Σ 50

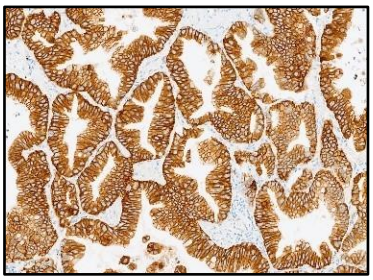

Figure 1. VENTANA MET (SP44) RxDx Assay staining of MET on non-squamous non-small cell lung cancer.

INTENDED USE

VENTANA MET (SP44) RxDx Assay is a qualitative immunohistochemical assay using rabbit monoclonal anti-MET, clone SP44, intended for use in the assessment of MET protein in formalin-fixed paraffin embedded (FFPE) non-squamous non-small cell lung cancer (NSCLC) specimens by light microscopy. This assay is for use with OptiView DAB IHC Detection Kit for staining on a BenchMark ULTRA or BenchMark ULTRA PLUS instrument.

MET protein expression clinical cut-off is ≥ 50% of tumor cells exhibiting strong membrane and/or cytoplasmic staining (3+) in non-squamous NSCLC.

VENTANA MET (SP44) RxDx Assay is indicated as an aid in identifying non-squamous NSCLC patients who may be eligible for treatment with EMRELIS™ (telisotuzumab vedotin-tllv).

The results of VENTANA MET (SP44) RxDx 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.

SUMMARY AND EXPLANATION

VENTANA MET (SP44) RxDx Assay (MET (SP44) Assay) is a rabbit monoclonal antibody, clone SP44, produced against the carboxyl region of the human MET protein. It recognizes MET proto-oncogene, receptor tyrosine kinase (MET), also known as hepatocyte growth receptor and sometimes abbreviated as c-Met.

The MET (SP44) Assay demonstrates membrane and cytoplasmic staining, which are both evaluated for the determination of MET status in non-squamous NSCLC.

PRINCIPLE OF THE PROCEDURE

MET (SP44) Assay binds to the MET protein in sections of formalin-fixed, paraffin-embedded tissue. The specific antibody can be localized using a haptenated secondary antibody followed by a multimer anti-hapten-HRP conjugate (OptiView DAB IHC Detection Kit, Cat. No. 760-700 / 06396500001). The specific antibody-enzyme complex is then visualized with a precipitating enzyme reaction product. Refer to the OptiView DAB IHC Detection Kit method sheet for further information. Results are interpreted using a light microscope.

Clinical cases must be evaluated with appropriate tissue controls. In addition to staining with VENTANA MET (SP44) RxDx Assay, a second slide should be stained with Rabbit Monoclonal Negative Control Ig (Cat. No. 790-4795 / 06683380001). This slide must be negative for specific staining to be considered acceptable.

MATERIAL PROVIDED

MET (SP44) Assay contains sufficient reagent for 50 tests.

One 5 mL dispenser of MET (SP44) Assay contains approximately 17.5 µg of a recombinant rabbit monoclonal MET (SP44) antibody.

The antibody is diluted in Tris-HCl with carrier protein and 0.10% ProClin 300, a preservative.

Specific antibody concentration is approximately 3.5 µg/mL. There is no known non-specific antibody reactivity observed in this product.

MET (SP44) Assay is a recombinant rabbit monoclonal antibody produced as purified cell culture supernatant.

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

MATERIALS REQUIRED BUT NOT PROVIDED

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

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

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

1. Recommended control tissue
2. Microscope slides, positively charged
3. Rabbit Monoclonal Negative Control Ig (Cat. No. 790-4795 / 06683380001)
4. OptiView DAB IHC Detection Kit (Cat. No. 760-700 / 06396500001)
5. EZ Prep Concentrate (10X) (Cat. No. 950-102 / 05279771001)
6. Reaction Buffer Concentrate (10X) (Cat. No. 950-300 / 05353955001)
7. ULTRA LCS (Predilute) (Cat. No. 650-210 / 05424534001)
8. ULTRA Cell Conditioning Solution (ULTRA CC1) (Cat. No. 950-224 / 05424569001)
9. Hematoxylin II (Cat. No. 790-2208 / 05277965001)
10. Bluing Reagent (Cat. No. 760-2037 / 05266769001)
11. General purpose laboratory equipment
12. BenchMark ULTRA or BenchMark ULTRA PLUS instrument
13. Permanent Mounting Medium
14. Cover glass
15. Automated coverslipper

STORAGE AND STABILITY

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

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

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

SPECIMEN PREPARATION

Routinely processed FFPE non-squamous NSCLC tissues are suitable for use with this primary antibody when used with OptiView DAB IHC Detection Kit and BenchMark ULTRA and ULTRA PLUS instruments. The recommended fixative is 10% neutral buffered formalin (NBF).[1] Fix samples in formalin for 6-72 hours. Fixation times less than 6 hours have demonstrated a loss of specific MET immunoreactivity. Zinc formalin fixative is also acceptable for a fixation time of 6-72 hours.

Fixatives such as AFA, PREFER fixative, Z-fix, Alcohol Formalin and 95% ethanol are not acceptable for use with this assay and have demonstrated a significant loss of specific MET immunoreactivity.

Cut sections at approximately 4-5 µm in thickness and mount on positively charged slides. Stain slides immediately or store at 2-8 °C for no more than 45 days, as antigenicity of cut tissue sections can diminish over time.

It is recommended that positive and negative controls be run simultaneously with every IHC run.

WARNINGS AND PRECAUTIONS

1. For in vitro diagnostic (IVD) use.
2. For professional use only.
3. Do not use beyond the specified number of tests.
4. ProClin 300 solution is used as a preservative in this reagent. It is classified as an irritant and may cause sensitization through skin contact. Take reasonable precautions when handling. Avoid contact of reagents with eyes, skin, and mucous membranes. Use protective clothing and gloves.
5. Positively charged slides may be susceptible to environmental stresses resulting in inappropriate staining. Ask your Roche representative for more information on how to use these types of slides.

6. Materials of human or animal origin should be handled as biohazardous materials and disposed of with proper precautions. In the event of exposure, the health directives of the responsible authorities should be followed.[2,3]
7. Avoid contact of reagents with eyes and mucous membranes. If reagents come in contact with sensitive areas, wash with copious amounts of water.
8. Avoid microbial contamination of reagents as it may cause incorrect results.
9. For further information on the use of this device, refer to the BenchMark ULTRA or BenchMark ULTRA PLUS instrument User Guide, and instructions for use of all necessary components located at navifyportal.roche.com.
10. Consult local and/or state authorities with regard to recommended method of disposal.
11. Product safety labeling primarily follows EU GHS guidance. Safety data sheet available for professional user on request.
12. To report suspected serious incidents related to this device, contact the local Roche representative and the competent authority of the Member State or Country in which the user is established.

This product contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

Table 1. Hazard information.

Hazard	Code	Statement
WARNING 	H317	May cause an allergic skin reaction.
	H412	Harmful to aquatic life with long lasting effects.
	P261	Avoid breathing mist or vapours.
	P273	Avoid release to the environment
	P280	Wear protective gloves.
	P333 + P313	If skin irritation or rash occurs: Get medical advice/ attention.
	P362 + P364	Take off contaminated clothing and wash it before reuse.
	P501	Dispose of contents/ container to an approved waste disposal plant.

This product contains CAS # 55965-84-9, a reaction mass of: 5-chloro-2-methyl-2H-isothiazol-3-one and 2-methyl-2H-isothiazol-3-one (3:1).

STAINING PROCEDURE

VENTANA primary antibodies have been developed for use on BenchMark ULTRA and BenchMark ULTRA PLUS instruments in combination with VENTANA detection kits and accessories. Refer to Table 2 for recommended staining protocol.

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

The parameters for the automated procedures can be displayed, printed and edited according to the procedure in the instrument User Guide. Refer to the appropriate VENTANA detection kit method sheet for more details regarding immunohistochemistry staining procedures.

For more details on the proper use of this device, refer to the inline dispenser method sheet associated with P/N 740-7064.

Table 2. Recommended staining protocol for MET (SP44) Assay with OptiView DAB IHC Detection Kit on BenchMark ULTRA and BenchMark ULTRA PLUS instruments.

Procedure Type	Method
	ULTRA or ULTRA PLUS
Staining Procedure	U VENTANA MET (SP44) RxDx Assay
Baking*	Optional**
Deparaffinization	4 minutes (default), 72 °C
Cell Conditioning (Antigen Unmasking)	ULTRA Cell Conditioning 1 64 minutes, 100 °C
Pre-antibody peroxidase inhibitor	4 minutes, 36 °C
Antibody (Primary)*	VENTANA MET (SP44) RxDx Assay (16 minutes, 36 °C) Or Rabbit Monoclonal Negative Control Ig (16 minutes, 36 °C)
OptiView HQ Linker	8 minutes (default), 36 °C
OptiView HRP Multimer	8 minutes (default), 36 °C
Counterstain*	Hematoxylin II, 4 minutes
Post Counterstain*	Bluing, 4 minutes

*Selectable by customer

** May be performed on-board the instrument (4-32 minutes, 60 °C) or performed offline (up to 60 minutes, 60 °C)

NEGATIVE REAGENT CONTROL

In addition to staining with MET (SP44) Assay, a second slide should be stained with the appropriate negative control reagent.

POSITIVE AND NEGATIVE TISSUE CONTROL

A tissue control must be included with each staining run. Optimal laboratory practice is to include a positive control section on the same slide as the test tissue. This helps identify any failures in applying reagents to the slide. Tissue with weak positive staining is best suited for quality control. Control tissue may contain both positive and negative staining elements and serve as both the positive and negative control. Control tissue should be fresh autopsy, biopsy, or surgical specimen, prepared or fixed as soon as possible in a manner identical to test sections.

Known positive tissue controls should be utilized only for monitoring performance of reagents and instruments, not as an aid in determining specific diagnosis of test samples. If the positive tissue controls fail to demonstrate positive staining, results of the test specimen should be considered invalid.

An example of positive control tissue for this antibody is non-neoplastic gallbladder tissue, which demonstrates moderate staining of the membrane in epithelial cells and an absence of staining within cells of stromal tissue. Gallbladder tissue contains positive and negative staining elements for the MET protein and is therefore suitable for use as a tissue control. The positive and negative staining elements should be examined to ascertain if all reagents are functioning properly. If these elements fail to demonstrate appropriate

staining, any results with the test specimens included in the same staining run should be considered invalid. Refer to Table 3.

Table 3. System-Level Control Non-neoplastic Gallbladder for VENTANA MET (SP44) RxDx Assay

Acceptable	Unacceptable
Presence of moderate* membrane staining in the epithelium AND Absence of specific MET staining within cells of stromal tissue	Absence of moderate* membrane staining in the epithelium OR Excessive background staining of the stromal tissue that interferes with interpretation

* Moderate staining intensity is characterized by rich brown thickened membranes that are detectable at low magnifications such as 4x or 10x.

STAINING INTERPRETATION / EXPECTED RESULTS

The cellular staining pattern for MET (SP44) Assay is membranous and/or cytoplasmic with varying ranges of stain intensity. The stained slide(s) are interpreted using light microscopy. A qualified pathologist experienced in IHC staining interpretation must evaluate tissue controls before interpreting patient results.

Refer to VENTANA MET (SP44) RxDx Assay Interpretation Guide for NSCLC (P/N 1018336US) for specifics and images.

Negative Reagent Control

Non-specific staining, if present, may 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. Refer to Table 5 for the acceptability criteria for non-specific staining.

Patient Tissue

Patient specimens should be examined last and must be evaluated according to the VENTANA MET (SP44) RxDx Assay scoring algorithm provided in Table 4 and Table 5. Refer to the VENTANA MET (SP44) RxDx Assay Interpretation Guide for NSCLC (P/N 1018336US) for representative images and instructions for scoring.

The cellular staining pattern for VENTANA MET (SP44) RxDx Assay is membranous and/or cytoplasmic staining of tumor cells in non-squamous NSCLC tissue with varying ranges of stain intensity. The percentage of tumor cells staining at each intensity (negative, weak, moderate, strong) will be assessed from specimens containing a minimum of approximately 100 viable tumor cells. Only strong intensity membranous and/or cytoplasmic staining will contribute to the MET status determination using the scoring method.

Strong (3+) signal intensity is characterized by dark brown to black hue with saturated DAB. Membranes/cytoplasm exhibiting strong signal are easily detectable at low power magnifications such as 2x or 4x. Non-squamous NSCLC tissue cases are considered positive for MET status if ≥ 50% of viable tumor cells (TC) demonstrate strong membranous and/or cytoplasmic staining. Non-squamous NSCLC tissue is evaluated for MET IHC Status according to the VENTANA MET (SP44) scoring algorithms (Table 4) and the non-specific background scoring criteria (Table 5).

Table 4. VENTANA MET (SP44) RxDx Assay Scoring Algorithm for NSCLC for the 50% Strong Tumor Cell Staining Cutoff.

MET IHC Status	Staining Criteria
Positive*	≥ 50% of tumor cells with strong membrane and/or cytoplasmic staining intensity.
Negative*	< 50% of tumor cells with strong membrane and/or cytoplasmic staining intensity
Not Evaluable (N/E)	Interpretation is not possible, e.g., no tissue present, presence of staining artifacts or poor tissue quality

*Re-reading by Additional Pathologists for MET Scoring

Table 5. Non-specific background scoring criteria for VENTANA MET (SP44) RxDx 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.

To decrease variability of MET results for cases with %TC near the threshold of 50% (40% to 60%) or with staining intensity near the strong (3+) versus moderate (2+) threshold, re-reading of the slide by a second pathologist is recommended. A case result with %TC between 40-60% or borderline strong versus moderate intensity by a pathologist should be adjudicated by one or two independent pathologists. The patient's final result with regard to MET staining (positive or negative) should be obtained by consensus among the pathologists. In NSCLC samples, weak to moderate MET staining can also occur in type II pneumocytes and the normal epithelium of bronchi and bronchioles, which may serve as an internal control. If the internal controls show no staining, this can suggest a staining failure.

SPECIFIC LIMITATIONS

This antibody demonstrates the following specific limitations:

1. The VENTANA MET (SP44) RxDx Assay has been optimized on the BenchMark ULTRA and BenchMark ULTRA PLUS instruments in combination with the OptiView DAB IHC Detection Kit at a 16 minute primary antibody incubation time. Incubation times and temperatures other than those specified may give erroneous results.
2. Immunohistochemistry is a multiple step diagnostic process that requires specialized training in the selection of the appropriate reagents, tissue selections, fixation, processing, preparation of slides, and interpretation of staining results.
3. Tissue staining is dependent on the handling and processing of the tissue before staining. Improper fixation, freezing, thawing, washing, drying, heating, sectioning or contamination with other tissues or fluids may produce artifacts or false negative results. Inconsistent results may arise from variations in fixation and embedding methods.
4. The recommended fixative is 10% NBF. Fix samples in formalin for 6-72 hours. Zinc formalin is also acceptable for fixative time of 6-72 hours. Samples fixed in formalin and zinc formalin for fixation times less than 6 hours have demonstrated a loss of specific MET immunoreactivity and can lead to a false negative result.
5. Fixatives such as AFA, PREFER fixative, Z-fix, Alcohol Formalin and 95% ethanol are not acceptable for use with this assay and have demonstrated a significant loss of specific MET immunoreactivity and can lead to a false negative result. When fixative type and/or fixation duration are unknown or outside of the recommended parameters, and a negative test result is obtained, consider including a statement in the pathology report that re-testing with a new sample collected and prepared according to the recommended device specifications may be warranted.
6. Cytology specimen processing requirements for the use of cytology fixatives such as CytoLyt® and SurePath™ collection media have not been established. Cytology specimens may be collected into and rinsed in 10% NBF and cell blocks may be fixed in 10% NBF.
7. Patient tissue sections should be refrigerated (5 ºC ± 3 ºC) and stained within 45 days of sectioning from the tissue block. Storage outside of recommended conditions have demonstrated a loss of specific MET immunoreactivity and can lead to a false negative result. Please refer to IX.A.5.b Section in SSED for more details.
8. For optimal results, consultation with a second pathologist with reporting on the consensus result is recommended for cases scored near the %TC and staining intensity cutoffs for companion diagnostic indications.
9. This assay has not been validated for use with cytology smears or decalcified specimens.

All assays might not be registered on every instrument. Please contact your local Roche representative for more information.

PERFORMANCE CHARACTERISTICS

ANALYTICAL PERFORMANCE

Staining tests for sensitivity, specificity, and precision were conducted and the results are listed below.

Sensitivity and Specificity

In a commercial cohort of 100 unique NSCLC (resection, biopsy (core needle biopsy (CNB)) and cell block [fine needle aspirate (FNA)]) cases were evaluated for MET staining. Of the 100 cases, 91 were described as having both membrane and cytoplasmic staining and 8 had cytoplasmic staining only. One case had no staining present. MET positive status was observed in 12% (12/100) of cases. MET negative status was observed in 88% (88/100) of cases.

Analytical sensitivity and specificity was evaluated using arrays and tissue resections containing a variety of non-neoplastic and neoplastic tissues stained with VENTANA MET (SP44) RxDx Assay and evaluated for presence of membranous and/or cytoplasmic MET staining as listed in Table 6 and Table 7.

Off-target focal nuclear staining was observed in <1.0% of evaluable samples (4/606), including non-neoplastic fallopian tube and heart and squamous cell carcinoma (esophagus and lung).

Table 6. Sensitivity/Specificity of MET (SP44) Assay was determined by testing FFPE non-neoplastic tissues.

Tissue	# positive / total cases	Tissue	# positive / total cases
Cerebrum	0/7	Esophagus[c]	3/4
Cerebellum	0/7	Stomach[g,h]	7/7
Adrenal gland	0/7	Small intestine[g]	5/7
Ovary	0/7	Colon[g]	5/6
Pancreas[a]	1/7	Liver[i]	2/7
Parathyroid gland	0/5	Salivary gland[j]	5/6
Pituitary gland	0/5	Kidney[k]	5/9
Testis	0/7	Prostate[c]	5/7
Thyroid[b]	3/7	Cervix[c]	3/5
Breast[c]	2/5	Skin[c]	2/5
Spleen	0/6	Mesothelium[l]	3/4
Tonsil[d]	5/6	Appendix[g]	3/3
Endometrium[c]	3/6	Bladder[m]	4/5
Skeletal muscle	0/6	Fallopian tube[c]	4/7
Nerve	0/5	Rectum[g]	3/4
Thymus[e]	0/6	Ureter[n]	2/2
Myeloid (bone marrow)	0/5	Lymph node (reactive)	0/1
Lung[f,g]	13/16	Placenta[o]	5/6
Heart	0/6	Spinal cord	0/2

[a] acinar cells (focal staining), [b] follicular cells, [c] epithelial cells (weak staining), [d] germinal center lymphocytes (weak staining), [e] epithelial cells (focal staining), [f] type II pneumocytes, [g] epithelial cells, [h] fundic glands, [i] focal hepatocyte staining, [j] serous glands and striated duct epithelium, [k] renal tubular epithelial cells, [l] mesothelial cells, [m] urothelial cells, [n] urothelial cells (weak staining), [o] cytotrophoblastic and syncytiotrophoblastic cells

Table 7. Sensitivity/Specificity of MET (SP44) Assay was determined by testing FFPE neoplastic tissues.

Pathology	# positive / total cases
Adenoma, cortical (Adrenal gland)	0/1
Adrenocortical carcinoma (Adrenal gland)	0/1
Urothelial carcinoma (Bladder)	2/2
Fibroadenoma (Breast)	0/1
Osteosarcoma (Bone)	0/1
Chondrosarcoma (Bone)	0/1
Meningioma (Cerebellum)	0/2
Meningioma (Cerebrum)	1/1
Astrocytoma (Cerebrum)	0/1
Squamous cell carcinoma (Esophagus)	2/2
Adenocarcinoma (Stomach)	3/3
Adenoma (Small intestine)	1/1
Adenocarcinoma (Small intestine)	1/1
Adenoma (Colon)	1/1
Adenocarcinoma (Colon)	3/3
Adenocarcinoma (Rectum)	3/3
Clear cell carcinoma (Kidney)	2/2
Hepatocellular carcinoma (Liver)	2/4
Squamous cell carcinoma (Lung)	105/145
Adenocarcinoma (Lung)	96/116
Small cell carcinoma (Lung)	0/1
Adenosquamous carcinoma (Lung)	1/1
Adenocarcinoma in-situ (Lung)	12/13
Mucinous adenocarcinoma (Lung)	8/8
Papillary carcinoma (Lung)	5/6
Neuroendocrine tumor, typical carcinoid (Lung)	3/11
Neuroendocrine carcinoma (Lung)	5/5
Large cell carcinoma (Lung)	8/9
Large cell neuroendocrine carcinoma (Lung)	3/3
Pleomorphic carcinoma (Lung)	5/5
Mucoepidermoid carcinoma (Lung)	1/1
Hodgkin lymphoma (Lymph node)	0/1
B-cell lymphoma, NOS (Lymph node)	0/1

Pathology	# positive / total cases
Anaplastic large cell lymphoma (Lymph node)	0/1
Adenocarcinoma (Oral cavity)	0/1
Squamous cell carcinoma (Oral cavity)	1/1
Nasopharyngeal carcinoma (Nasopharynx)	1/1
Granulosa cell tumor (Ovary)	0/1
Adenocarcinoma (Ovary)	1/1
Endometrioid adenocarcinoma (Ovary)	0/1
Adenocarcinoma (Pancreas)	0/1
Adenocarcinoma (Prostate)	0/2
Pleomorphic adenoma (Salivary gland)	0/1
Adenoid cystic carcinoma (Salivary gland)	1/1
Squamous cell carcinoma (Skin)	1/1
Melanoma (Nasal cavity)	1/1
Seminoma (Testis)	0/2
Adenoma (Thyroid)	2/3
Follicular carcinoma (Thyroid)	1/1
Papillary carcinoma (Thyroid)	1/1
Squamous cell carcinoma (Cervix)	2/2
Adenocarcinoma (Endometrium)	2/2
Metastatic Colon adenocarcinoma (Liver)	1/1
Metastatic Breast ductal carcinoma (Lymph Node)	1/1
Metastatic Colon signet ring cell carcinoma (Ovary)	1/1
Metastatic Esophageal squamous cell carcinoma (Lymph Node)	1/1

Precision- NSCLC 50% Strong Tumor Cell Staining

The precision of the VENTANA MET (SP44) RxDx Assay was evaluated in multiple precision studies: Repeatability and Intermediate Precision study, Between Day Precision study and Reader (pathologist) Precision study.

Repeatability and Intermediate Precision- NSCLC 50% Strong Tumor Cell Staining

Twenty-four unique NSCLC resection tissue cases were enrolled (12 MET Positive and 12 MET Negative) in the intermediate precision study. The study design for evaluation of staining precision on NSCLC stained with MET (SP44) Assay included:

- Three lots of MET antibody
- Three lots of OptiView DAB IHC Detection Kits
- Three BenchMark ULTRA instruments
- Three non-consecutive day precision on the BenchMark ULTRA
- Within run repeatability on the BenchMark ULTRA

Twenty-eight unique NSCLC resection tissue cases were enrolled (12 MET Positive and 16 MET Negative) in the intermediate precision study. The study design for evaluation of staining precision on NSCLC stained with MET (SP44) Assay included:

- Three BenchMark ULTRA PLUS instruments
- Three non-consecutive day precision on the BenchMark ULTRA PLUS
- Within run repeatability on the BenchMark ULTRA PLUS

Twenty-eight unique NSCLC resection tissue cases were enrolled (12 MET Positive and 16 MET Negative) in the intermediate precision study. The study design for evaluation of staining precision on NSCLC stained with MET (SP44) Assay included:

- Five non-consecutive day precision on the BenchMark ULTRA
- Five non-consecutive day precision on the BenchMark ULTRA PLUS

All slides were blinded, randomized and then evaluated using the VENTANA MET (SP44) RxDx Assay scoring algorithm for the 50% Strong TC staining cutoff (Table 4).

All studies met their acceptance criteria. Results are summarized in Table 8.

Table 8. Repeatability and intermediate precision of the VENTANA MET (SP44) RxDx Assay staining of NSCLC specimens for the 50% Strong TC Staining cutoff.

Repeatability/Intermediate Precision Parameter	Agreement			
	Type	n/N	%	95% CI
Between antibody lot precision	PPA	76/78	97.4	(91.7, 100.0)
	NPA	64/64	100.0	(94.3, 100.0)
	OPA	140/142	98.6	(95.7, 100.0)
Between detection kit lot precision	PPA	75/78	96.2	(90.3, 100.0)
	NPA	61/65	93.8	(83.3, 100.0)
	OPA	136/143	95.1	(89.5, 99.3)
Between ULTRA instrument precision	PPA	78/78	100.0	(95.3, 100.0)
	NPA	65/65	100.0	(94.4, 100.0)
	OPA	143/143	100.0	(97.4, 100.0)
Between 3 non-consecutive day intermediate precision-ULTRA	PPA	75/78	96.2	(89.7, 100.0)
	NPA	63/65	96.9	(89.8, 100.0)
	OPA	138/143	96.5	(91.7, 100.0)
Within run repeatability-ULTRA	PPA	230/232	99.1	(97.9, 100.0)
	NPA	196/198	99.0	(97.5, 100.0)
	OPA	426/430	99.1	(98.1, 99.8)
Between ULTRA PLUS instrument precision	PPA	54/54	100.0	(93.4, 100.0)
	NPA	114/114	100.0	(96.7, 100.0)
	OPA	168/168	100.0	(97.8, 100.0)
Between 3 non-consecutive day intermediate precision-ULTRA PLUS	PPA	54/54	100.0	(93.4, 100.0)
	NPA	114/114	100.0	(96.7, 100.0)
	OPA	168/168	100.0	(97.8, 100.0)
Within run repeatability-ULTRA PLUS	PPA	45/45	100.0	(92.1, 100.0)
	NPA	95/95	100.0	(96.1, 100.0)
	OPA	140/140	100.0	(97.3, 100.0)
Between 5 non-consecutive day intermediate precision-ULTRA	PPA	120/130	92.3	(85.5, 98.0)
	NPA	144/147	98.0	(94.7, 100.0)
	OPA	264/277	95.3	(91.8, 98.2)
Between 5 non-consecutive day intermediate precision-ULTRA PLUS	PPA	129/130	99.2	(97.7, 100.0)
	NPA	148/149	99.3	(97.8, 100.0)
	OPA	277/279	99.3	(98.2, 100.0)

Note: Positive Percent Agreement (PPA), Negative Percent Agreement (NPA), Overall Percent Agreement (OPA).

Between Day Intermediate Precision Biopsies- NSCLC 50% Strong Tumor Cell Staining

Twenty unique NSCLC biopsy cases were enrolled (9 MET Positive and 11 MET Negative) in the between day precision study on the BenchMark ULTRA. The study evaluated the staining precision on NSCLC biopsy cases stained with MET (SP44) Assay across three non-consecutive days. All slides were blinded, randomized and then

evaluated using the VENTANA MET (SP44) RxDx Assay scoring algorithm for the 50% Strong TC staining cutoff (Table 4).

All studies met their acceptance criteria. Results are summarized in Table 9.

Table 9. Between day intermediate precision of the VENTANA MET (SP44) RxDx Assay staining of NSCLC biopsy specimens for the 50% Strong TC staining cutoff.

Intermediate Precision Parameter	Agreement			
	Type	n/N	%	95% CI
Between day intermediate precision biopsies	PPA	40/42	95.2	(85.2, 100.0)
	NPA	77/78	98.7	(95.8, 100.0)
	OPA	117/120	97.5	(93.3, 100.0)

Note: Positive Percent Agreement (PPA), Negative Percent Agreement (NPA), Overall Percent Agreement (OPA).

Between Day Intermediate Precision Cell Blocks- NSCLC 50% Strong Tumor Cell Staining

Twenty-one unique NSCLC cell block (FNA) cases were enrolled (10 MET Positive and 11 MET Negative) in the between day precision study on the BenchMark ULTRA. The study evaluated the staining precision on NSCLC FNA cell block cases stained with MET (SP44) Assay across three non-consecutive days.

Sixteen unique NSCLC cell block (pleural effusion) cases were enrolled (2 MET Positive and 14 MET Negative) in the between day precision study on the BenchMark ULTRA. The study evaluated the staining precision on NSCLC pleural effusion cell block cases stained with MET (SP44) Assay across three non-consecutive days.

All slides were blinded, randomized and then evaluated using the VENTANA MET (SP44) RxDx Assay scoring algorithm for the 50% Strong TC staining cutoff (Table 4).

All studies met their acceptance criteria. Results are summarized in Table 10.

Table 10. Between day intermediate precision of the VENTANA MET (SP44) RxDx Assay staining of NSCLC cell blocks specimens for the 50% Strong TC staining cutoff.

Intermediate Precision Parameter	Agreement			
	Type	n/N	%	95% CI
Between day intermediate precision - FNAs	PPA	54/54	100.0	(93.4, 100.0)
	NPA	72/72	100.0	(94.9, 100.0)
	OPA	126/126	100.0	(97.0, 100.0)
Between day intermediate precision - pleural effusions	PPA	11/11	100.0	(74.1, 100.0)
	NPA	84/84	100.0	(95.6, 100.0)
	OPA	95/95	100.0	(96.1, 100.0)

Note: Positive Percent Agreement (PPA), Negative Percent Agreement (NPA), Overall Percent Agreement (OPA).

Reader Precision- NSCLC 50% Strong Tumor Cell Staining

In the Reader Precision study for the MET (SP44) Assay, Within-Reader and Between-Reader components of precision for NSCLC tissue reads were evaluated. The study included 100 unique NSCLC (resection and biopsy) specimens (50 MET Positive and 50 MET Negative) that were stained with MET (SP44) Assay. Specimens were blinded and randomized prior to evaluation for MET status using the VENTANA MET (SP44) RxDx Assay scoring algorithm for the 50% Strong TC staining cutoff (Table 4). The study included three readers (pathologists). Readers scored all specimens twice, with a minimum of two weeks between reads. Each case had 6 reads (2 reads by each of the three readers). The following precision components were calculated: within-reader and between-reader. Results are summarized in Table 11 below.

Table 11. Within-Reader and Between-Reader Precision of the VENTANA MET (SP44) RxDx Assay for NSCLC specimens for the 50% Strong TC Staining cutoff.

Precision	Agreement			
	Type	n/N	%	95% CI
Within-Reader	APA	288/293	98.3	(96.6, 99.6)
	ANA	302/307	98.4	(96.6, 99.7)
	OPA	295/300	98.3	(96.7, 99.7)
Between-Reader	APA	278/292	95.2	(91.3, 98.2)
	ANA	294/308	95.5	(91.9, 98.4)
	OPA	286/300	95.3	(92.0, 98.0)

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

Reader Precision Cell Blocks- NSCLC 50% Strong Tumor Cell Staining

In the Reader Precision study for the MET (SP44) Assay, Within-Reader and Between-Reader components of precision for NSCLC tissue reads were evaluated. The study included 40 unique NSCLC cell block (FNA and pleural effusion) specimens (20 MET Positive and 20 MET Negative) that were stained with MET (SP44) Assay. Specimens were blinded and randomized prior to evaluation for MET status using the VENTANA MET (SP44) RxDx Assay scoring algorithm for the 50% Strong TC staining cutoff (Table 4). The study included four readers (pathologists). Readers scored all specimens twice, with a minimum of two weeks between reads. Each case had 8 reads (2 reads by each of the four readers). The following precision components were calculated: within-reader and between-reader. Results are summarized in Table 12 below.

Table 12. Within-Reader and Between-Reader Precision of the VENTANA MET (SP44) RxDx Assay for NSCLC specimens for the 50% Strong TC Staining Cutoff.

Precision	Agreement			
	Type	n/N	%	95% CI
Within-Reader	APA	164/165	99.4	(98.1, 100.0)
	ANA	154/155	99.4	(98.0, 100.0)
	OPA	159/160	99.4	(98.1, 100.0)
Between-Reader	APA	234/246	95.1	(90.5, 98.8)
	ANA	222/234	94.9	(89.5, 98.8)
	OPA	228/240	95.0	(90.0, 98.8)

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

Inter-laboratory Reproducibility and Method Comparison Study- NSCLC 50% Strong Tumor Cell Staining

The Inter-laboratory Reproducibility (ILR) and Method Comparison (MC) study for the VENTANA MET (SP44) RxDx Assay was conducted to evaluate the reproducibility of the VENTANA MET (SP44) RxDx Assay on the BenchMark ULTRA and the BenchMark ULTRA PLUS platforms independently. Additionally, a method comparison between the BenchMark ULTRA and BenchMark ULTRA PLUS was performed to determine if the performance of the VENTANA MET (SP44) RxDx Assay is equivalent on both BenchMark platforms. The study included 60 NSCLC specimens (30 MET Positive and 30 MET Negative, including several cases which exhibited borderline/challenging staining relative to the diagnostic cutoff) run across three BenchMark ULTRA and three BenchMark ULTRA PLUS instruments on 3 non-consecutive days at three external laboratories. For each BenchMark platform a set of 3 stained slides per sample per staining day was randomized and evaluated by a total of 6 readers (2 readers per site). Each case had 6 results per site per BenchMark platform (18 results per platform, 36 results in total). Performance was evaluated and the following precision components were calculated: between-reader, between-site and total. Results are presented in the tables below.

Table 13. Results of the Inter-Laboratory Reproducibility Study (ULTRA)

Case ID	Majority MET (SP44) Status	Median % Strong TC	Standard Deviation					Percent Positive Results n/N (%)			
			Range of % Strong TC (Min., Max.)	Between Reader	Between Day	Between Site	Total	Site A	Site B	Site C	Total
1	Negative	0	0, 0	0	0	0	0	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
2	Negative	0	0, 1	0	0	0	0.24	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
3	Negative	0	0, 2	0.41	0.33	0.10	0.63	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
4	Negative	2.5	0, 15	0.58	0.85	2.72	3.97	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
5	Negative	2.5	0, 5	1.33	0	1.65	2.26	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
6	Negative	2.5	0, 20	1.84	2.27	2.34	5.74	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
7	Negative	3.5	0, 15	2.67	1.67	2.61	4.79	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
8	Negative	4.5	0, 35	5.33	3.81	7.44	10.97	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
9	Negative	5.0	0, 15	1.08	0	4.08	5.14	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
10	Negative	5.0	0, 15	2.01	0	3.06	5.42	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
11	Negative	7.5	0, 20	1.99	2.79	5.32	6.80	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
12	Negative	7.5	0, 20	3.19	2.79	5.84	8.00	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
13	Negative	7.5	0, 35	4.58	6.00	6.21	10.20	0/4 (0.0)	0/6 (0.0)	0/6 (0.0)	0/16 (0.0)
14	Negative	7.5	0, 65	20.24	4.65	8.98	23.24	2/6 (33.3)	0/6 (0.0)	0/4 (0.0)	2/16 (12.5)
15	Negative	10.0	1, 20	3.55	3.70	3.42	7.02	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
16	Negative	10.0	0, 20	0	0.00	7.34	9.07	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
17	Negative	12.5	0, 40	6.28	3.73	12.46	15.41	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
18	Negative	17.5	5, 25	2.47	0	6.25	8.11	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
19	Negative	17.5	0, 50	9.94	0	12.73	18.06	0/6 (0.0)	0/6 (0.0)	1/6 (16.7)	1/18 (5.6)
20	Negative	20.0	0, 40	7.83	0	14.16	16.40	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
21	Negative	22.5	0, 45	6.00	5.41	9.67	15.66	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
22	Negative	25.0	0, 50	12.08	5.77	0	16.16	1/6 (16.7)	1/6 (16.7)	0/6 (0.0)	2/18 (11.1)
23	Negative	27.5	10, 50	8.58	0	5.00	12.25	1/6 (16.7)	0/6 (0.0)	0/6 (0.0)	1/18 (5.6)
24	Negative	27.5	5, 60	15.94	5.53	0	18.18	0/6 (0.0)	0/6 (0.0)	3/6 (50.0)	3/18 (16.7)
25	Negative	27.5	1, 60	0	0	7.68	22.28	2/6 (33.3)	1/6 (16.7)	2/6 (33.3)	5/18 (27.8)
26	Negative	30.0	5, 60	6.12	6.67	10.65	17.02	1/6 (16.7)	0/6 (0.0)	1/6 (16.7)	2/18 (11.1)
27	Negative	40.0	20, 55	7.99	5.53	0	11.96	2/6 (33.3)	0/6 (0.0)	1/6 (16.7)	3/18 (16.7)
28	Negative	40.0	20, 50	12.58	4.25	0	13.99	1/6 (16.7)	1/6 (16.7)	2/6 (33.3)	4/18 (22.2)
29	Negative	40.0	5, 70	12.47	7.55	14.73	22.70	4/6 (66.7)	0/6 (0.0)	3/6 (50.0)	7/18 (38.9)
30	Negative	40.0	5, 70	15.86	0	0	19.86	3/6 (50.0)	3/6 (50.0)	2/6 (33.3)	8/18 (44.4)
31	Negative	45.0	5, 75	12.75	8.25	13.39	22.64	3/6 (50.0)	1/6 (16.7)	3/6 (50.0)	7/18 (38.9)
32	Positive	50.0	10, 70	4.08	6.87	10.18	15.17	6/6 (100.0)	2/6 (33.3)	3/6 (50.0)	11/18 (61.1)
33	Positive	50.0	5, 90	9.43	14.85	11.67	25.33	6/6 (100.0)	3/6 (50.0)	5/6 (83.3)	14/18 (77.8)
34	Positive	50.0	0, 70	9.99	15.85	0	20.27	5/6 (83.3)	3/6 (50.0)	2/6 (33.3)	10/18 (55.6)
35	Positive	50.0	10, 70	8.38	0	9.57	20.94	5/6 (83.3)	2/6 (33.3)	2/5 (40.0)	9/17 (52.9)
36	Positive	50.0	25, 90	22.82	6.97	0	25.90	4/6 (66.7)	3/6 (50.0)	4/6 (66.7)	11/18 (61.1)
37	Positive	50.0	1, 90	17.91	0	0	35.25	4/6 (66.7)	2/6 (33.3)	4/6 (66.7)	10/18 (55.6)
38	Positive	50.0	25, 75	9.35	6.01	4.71	13.39	6/6 (100.0)	1/6 (16.7)	4/6 (66.7)	11/18 (61.1)
39	Positive	50.0	1, 90	20.13	0	18.73	29.47	5/6 (83.3)	1/6 (16.7)	5/6 (83.3)	11/18 (61.1)
40	Positive	50.0	5, 80	22.42	4.08	0	23.66	5/6 (83.3)	3/6 (50.0)	5/6 (83.3)	13/18 (72.2)

Case ID	Majority MET (SP44) Status	Median % Strong TC	Standard Deviation					Percent Positive Results n/N (%)			
			Range of % Strong TC (Min., Max.)	Between Reader	Between Day	Between Site	Total	Site A	Site B	Site C	Total
41	Positive	57.5	20, 80	12.19	9.28	6.40	19.98	6/6 (100.0)	3/6 (50.0)	3/6 (50.0)	12/18 (66.7)
42	Positive	62.5	10, 90	17.32	0	6.22	23.27	6/6 (100.0)	3/6 (50.0)	5/6 (83.3)	14/18 (77.8)
43	Positive	65.0	25, 98	13.47	0	3.55	20.84	6/6 (100.0)	4/6 (66.7)	5/6 (83.3)	15/18 (83.3)
44	Positive	72.5	1, 95	11.53	9.40	17.36	28.86	6/6 (100.0)	3/6 (50.0)	6/6 (100.0)	15/18 (83.3)
45	Positive	82.5	20, 100	20.96	7.17	8.04	25.28	6/6 (100.0)	4/6 (66.7)	6/6 (100.0)	16/18 (88.9)
46	Positive	85.0	5, 99	15.65	11.90	0	23.25	6/6 (100.0)	5/6 (83.3)	6/6 (100.0)	17/18 (94.4)
47	Positive	90.0	10, 100	0	5.11	11.94	22.38	6/6 (100.0)	5/6 (83.3)	6/6 (100.0)	17/18 (94.4)
48	Positive	92.5	5, 100	15.86	6.95	6.90	24.98	6/6 (100.0)	4/6 (66.7)	6/6 (100.0)	16/18 (88.9)
49	Positive	95.0	70, 100	3.81	3.33	2.06	7.22	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
50	Positive	95.0	65, 100	8.23	2.79	0	10.13	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
51	Positive	95.0	80, 100	5.68	0	0	8.80	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
52	Positive	95.0	70, 100	8.64	0.00	0	9.92	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
53	Positive	97.5	90, 100	4.56	1.67	0	5.40	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
54	Positive	97.5	85, 100	6.01	0	0	6.67	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
55	Positive	97.5	80, 100	5.89	0.00	0	6.87	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
56	Positive	100.0	90, 100	2.53	0.75	0	3.04	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
57	Positive	100.0	90, 100	2.64	0	0	3.73	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
58	Positive	100.0	90, 100	3.91	0.00	0	4.56	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
59	Positive	100.0	90, 100	2.64	0	0	3.33	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
60	Positive	100.0	65, 100	5.89	6.24	0	10.74	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)

Table 14. Results of the Inter-Laboratory Reproducibility Study (ULTRA PLUS)

Case ID	Majority MET (SP44) Status	Median % Strong TC	Standard Deviation					Percent Positive Results n/N (%)			
			Range of % Strong TC (Min., Max.)	Between Reader	Between Day	Between Site	Total	Site A	Site B	Site C	Total
1	Negative	0	0, 0	0	0	0	0	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
2	Negative	0	0, 1	0	0	0	0.24	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
3	Negative	0	0, 5	0.67	0.58	0.00	1.22	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
4	Negative	1.0	0, 15	3.82	1.91	0	4.66	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
5	Negative	1.0	0, 15	4.62	0.53	0	4.92	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
6	Negative	1.5	0, 15	3.82	1.13	1.32	4.81	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
7	Negative	5.0	0, 15	4.49	1.05	4.53	7.01	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
8	Negative	5.0	0, 25	6.77	1.05	0	7.63	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
9	Negative	5.0	0, 25	6.14	0	3.69	7.86	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
10	Negative	5.0	0, 40	9.96	0	4.31	12.00	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
11	Negative	5.0	0, 40	10.55	3.16	3.43	13.05	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
12	Negative	5.0	0, 80	25.30	8.38	11.64	29.86	2/5 (40.0)	0/6 (0.0)	2/5 (40.0)	4/16 (25.0)
13	Negative	6.5	0, 25	4.81	2.53	5.43	8.17	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
14	Negative	7.0	2, 25	2.01	5.15	0	7.50	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
15	Negative	7.5	0, 40	8.42	4.25	2.68	11.36	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)

Case ID	Majority MET (SP44) Status	Median % Strong TC	Standard Deviation					Percent Positive Results n/N (%)			
			Range of % Strong TC (Min., Max.)	Between Reader	Between Day	Between Site	Total	Site A	Site B	Site C	Total
16	Negative	10.0	1, 40	8.57	5.73	5.65	11.97	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
17	Negative	10.0	2, 25	5.71	2.84	3.11	7.39	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
18	Negative	10.0	0, 70	21.52	0	7.91	23.43	0/6 (0.0)	0/6 (0.0)	3/6 (50.0)	3/18 (16.7)
19	Negative	15.0	0, 40	8.03	0	12.30	15.98	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
20	Negative	19.0	5, 30	3.69	2.98	4.30	7.38	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)	0/18 (0.0)
21	Negative	20.0	5, 50	7.26	0	9.35	15.28	0/6 (0.0)	0/6 (0.0)	2/6 (33.3)	2/18 (11.1)
22	Negative	20.0	1, 50	12.45	3.42	11.42	18.03	1/6 (16.7)	0/6 (0.0)	1/6 (16.7)	2/18 (11.1)
23	Negative	20.0	5, 75	17.54	5.75	0	22.98	1/6 (16.7)	1/6 (16.7)	3/6 (50.0)	5/18 (27.8)
24	Negative	24.5	1, 70	14.11	0	11.56	20.68	3/6 (50.0)	0/6 (0.0)	1/6 (16.7)	4/18 (22.2)
25	Negative	25.0	1, 90	22.66	8.37	0	28.30	3/6 (50.0)	1/6 (16.7)	2/6 (33.3)	6/18 (33.3)
26	Negative	25.0	5, 65	14.45	8.08	14.92	23.91	4/6 (66.7)	0/6 (0.0)	3/6 (50.0)	7/18 (38.9)
27	Negative	25.0	5, 70	17.95	3.12	0	19.97	3/6 (50.0)	0/6 (0.0)	3/6 (50.0)	6/18 (33.3)
28	Negative	30.0	5, 50	9.72	9.57	0	16.29	0/6 (0.0)	2/6 (33.3)	2/6 (33.3)	4/18 (22.2)
29	Negative	32.5	20, 55	5.89	5.65	7.67	11.98	3/6 (50.0)	0/6 (0.0)	0/6 (0.0)	3/18 (16.7)
30	Negative	37.5	5, 70	19.97	7.45	0	23.57	2/6 (33.3)	3/6 (50.0)	2/6 (33.3)	7/18 (38.9)
31	Negative	40.0	15, 60	1.88	0	9.82	13.91	4/5 (80.0)	0/6 (0.0)	0/6 (0.0)	4/17 (23.5)
32	Negative	40.0	10, 90	19.22	2.89	7.98	24.88	3/6 (50.0)	1/6 (16.7)	3/6 (50.0)	7/18 (38.9)
33	Negative	42.5	20, 50	11.06	4.56	0	13.74	1/6 (16.7)	0/6 (0.0)	1/6 (16.7)	2/18 (11.1)
34	Positive	42.5	1, 98	30.70	9.50	11.60	35.69	4/6 (66.7)	1/6 (16.7)	4/6 (66.7)	9/18 (50.0)
35	Positive	50.0	5, 98	26.67	9.31	0	29.60	4/6 (66.7)	2/6 (33.3)	4/6 (66.7)	10/18 (55.6)
36	Positive	50.0	10, 95	13.89	10.80	5.11	24.35	5/6 (83.3)	3/6 (50.0)	4/6 (66.7)	12/18 (66.7)
37	Positive	50.0	15, 90	13.02	10.27	8.18	19.37	6/6 (100.0)	3/6 (50.0)	3/6 (50.0)	12/18 (66.7)
38	Positive	50.0	35, 70	6.35	5.00	5.38	10.46	6/6 (100.0)	4/6 (66.7)	3/6 (50.0)	13/18 (72.2)
39	Positive	50.0	15, 98	25.39	1.29	0	27.11	4/6 (66.7)	3/6 (50.0)	3/6 (50.0)	10/18 (55.6)
40	Positive	50.0	5, 80	17.04	0	0	28.48	3/6 (50.0)	4/6 (66.7)	3/6 (50.0)	10/18 (55.6)
41	Positive	52.5	25, 70	6.24	0	1.73	10.35	6/6 (100.0)	5/6 (83.3)	5/6 (83.3)	16/18 (88.9)
42	Positive	55.0	25, 90	19.40	0	0	21.21	6/6 (100.0)	5/6 (83.3)	3/6 (50.0)	14/18 (77.8)
43	Positive	65.0	8, 99	24.03	13.11	0	29.60	5/6 (83.3)	6/6 (100.0)	4/6 (66.7)	15/18 (83.3)
44	Positive	80.0	50, 95	13.64	7.07	0	17.83	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
45	Positive	85.0	50, 100	19.87	5.06	0	21.49	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
46	Positive	90.0	60, 100	12.50	3.50	0	13.52	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
47	Positive	90.0	70, 100	9.79	0	0	10.14	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
48	Positive	90.0	50, 100	12.22	5.27	1.38	15.18	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
49	Positive	92.5	30, 100	7.36	1.18	4.00	16.69	6/6 (100.0)	5/6 (83.3)	6/6 (100.0)	17/18 (94.4)
50	Positive	92.5	25, 100	13.33	4.56	0	20.55	6/6 (100.0)	5/6 (83.3)	6/6 (100.0)	17/18 (94.4)
51	Positive	95.0	80, 100	6.45	0.00	0	6.87	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
52	Positive	95.0	70, 100	8.47	0	0	9.30	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
53	Positive	96.5	85, 100	5.92	1.49	0	6.35	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
54	Positive	97.0	10, 100	15.95	2.74	0	22.80	6/6 (100.0)	6/6 (100.0)	5/6 (83.3)	17/18 (94.4)
55	Positive	98.0	65, 100	5.57	1.49	0	9.02	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
56	Positive	100.0	80, 100	4.71	1.67	0	6.24	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)

Case ID	Majority MET (SP44) Status	Median % Strong TC	Standard Deviation					Percent Positive Results n/N (%)			
			Range of % Strong TC (Min., Max.)	Between Reader	Between Day	Between Site	Total	Site A	Site B	Site C	Total
57	Positive	100.0	75, 100	7.73	0.00	0	8.42	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
58	Positive	100.0	90, 100	4.25	0	0	4.56	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
59	Positive	100.0	90, 100	2.64	1.67	0	4.08	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)
60	Positive	100.0	85, 100	5.89	0.00	0	6.24	6/6 (100.0)	6/6 (100.0)	6/6 (100.0)	18/18 (100.0)

Table 15. Results of the Inter-Laboratory Reproducibility Study for VENTANA MET (SP44) RxDx Assay on BenchMark ULTRA and ULTRA PLUS Instruments.

Case ID	Majority MET (SP44) Status	Median % Strong TC	Standard Deviation					Percent Positive Results n/N (%)			
			Range of % Strong TC (Min., Max.)	Between Reader	Between Day	Between Site	Total	Site A	Site B	Site C	Total
1	Negative	0	0, 0	0	0	0	0	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
2	Negative	0	0, 1	0.10	0	0	0.24	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
3	Negative	0	0, 5	0.56	0.51	0	0.98	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
4	Negative	1.5	0, 20	2.89	0	2.28	5.33	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
5	Negative	2.0	0, 15	1.77	0	2.06	4.21	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
6	Negative	2.0	0, 15	2.52	0	1.67	3.85	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
7	Negative	4.5	0, 15	3.64	0.51	3.65	6.07	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
8	Negative	5.0	0, 25	2.65	0	4.75	6.89	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
9	Negative	5.0	0, 25	4.49	0	1.33	6.38	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
10	Negative	5.0	0, 25	4.64	1.62	5.03	7.87	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
11	Negative	5.0	0, 40	7.23	0	6.40	11.42	0/10 (0.0)	0/12 (0.0)	0/12 (0.0)	0/34 (0.0)
12	Negative	5.0	0, 40	7.99	3.59	4.42	11.85	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
13	Negative	5.0	0, 80	22.74	7.57	12.86	28.25	4/11 (36.4)	0/12 (0.0)	2/9 (22.2)	6/32 (18.8)
14	Negative	9.5	1, 25	2.75	2.25	0	6.70	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
15	Negative	10.0	0, 40	7.22	3.78	8.58	13.51	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
16	Negative	10.0	0, 25	3.48	1.24	4.85	7.31	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
17	Negative	10.0	0, 40	4.42	2.41	6.22	10.19	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
18	Negative	12.5	0, 70	16.00	0	10.91	20.85	0/12 (0.0)	0/12 (0.0)	4/12 (33.3)	4/36 (11.1)
19	Negative	19.0	5, 30	2.81	0.60	5.55	7.61	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
20	Negative	20.0	0, 40	4.81	0	13.97	16.25	0/12 (0.0)	0/12 (0.0)	0/12 (0.0)	0/36 (0.0)
21	Negative	20.0	0, 50	7.60	0	11.21	16.94	1/12 (8.3)	0/12 (0.0)	1/12 (8.3)	2/36 (5.6)
22	Negative	21.5	1, 75	11.29	0	5.42	21.20	3/12 (25.0)	2/12 (16.7)	5/12 (41.7)	10/36 (27.8)
23	Negative	22.5	0, 50	8.47	2.26	4.85	15.05	1/12 (8.3)	1/12 (8.3)	2/12 (16.7)	4/36 (11.1)
24	Negative	25.0	1, 70	14.38	0	7.43	19.19	3/12 (25.0)	0/12 (0.0)	4/12 (33.3)	7/36 (19.4)
25	Negative	30.0	5, 60	6.88	0	4.38	15.43	1/12 (8.3)	2/12 (16.7)	3/12 (25.0)	6/36 (16.7)
26	Negative	35.0	10, 60	6.24	0.48	7.81	13.02	5/11 (45.5)	0/12 (0.0)	0/12 (0.0)	5/35 (14.3)
27	Negative	35.0	5, 70	13.57	3.64	15.44	23.43	8/12 (66.7)	0/12 (0.0)	6/12 (50.0)	14/36 (38.9)
28	Negative	35.0	5, 75	14.31	3.44	10.30	21.54	6/12 (50.0)	1/12 (8.3)	6/12 (50.0)	13/36 (36.1)
29	Negative	37.5	20, 55	6.12	0	3.83	11.33	5/12 (41.7)	0/12 (0.0)	1/12 (8.3)	6/36 (16.7)
30	Negative	40.0	0, 90	15.18	4.70	0	23.49	8/12 (66.7)	4/12 (33.3)	4/12 (33.3)	16/36 (44.4)
31	Negative	40.0	20, 50	11.29	2.80	0	13.51	2/12 (16.7)	1/12 (8.3)	3/12 (25.0)	6/36 (16.7)

Case ID	Majority MET (SP44) Status	Median % Strong TC	Standard Deviation					Percent Positive Results n/N (%)			
			Range of % Strong TC (Min., Max.)	Between Reader	Between Day	Between Site	Total	Site A	Site B	Site C	Total
32	Negative	40.0	5, 70	17.63	3.83	0	21.32	5/12 (41.7)	6/12 (50.0)	4/12 (33.3)	15/36 (41.7)
33	Negative	45.0	10, 90	16.88	4.95	5.82	22.71	8/12 (66.7)	3/12 (25.0)	5/11 (45.5)	16/35 (45.7)
34	Positive	50.0	10, 70	5.49	0	6.85	13.14	12/12 (100.0)	7/12 (58.3)	8/12 (66.7)	27/36 (75.0)
35	Positive	50.0	5, 98	17.58	8.13	8.79	26.52	10/12 (83.3)	5/12 (41.7)	9/12 (75.0)	24/36 (66.7)
36	Positive	50.0	10, 95	18.40	0	0	24.75	9/12 (75.0)	6/12 (50.0)	8/12 (66.7)	23/36 (63.9)
37	Positive	50.0	1, 98	26.39	0	0	33.93	8/12 (66.7)	3/12 (25.0)	8/12 (66.7)	19/36 (52.8)
38	Positive	50.0	25, 75	7.52	0	5.41	12.20	12/12 (100.0)	5/12 (41.7)	7/12 (58.3)	24/36 (66.7)
39	Positive	50.0	1, 98	22.88	0	8.83	27.33	9/12 (75.0)	4/12 (33.3)	8/12 (66.7)	21/36 (58.3)
40	Positive	50.0	5, 80	19.95	0	0	25.67	8/12 (66.7)	7/12 (58.3)	8/12 (66.7)	23/36 (63.9)
41	Positive	52.5	15, 90	12.43	0	9.33	19.90	12/12 (100.0)	6/12 (50.0)	6/12 (50.0)	24/36 (66.7)
42	Positive	60.0	10, 90	17.96	0	0	21.10	12/12 (100.0)	8/12 (66.7)	8/12 (66.7)	28/36 (77.8)
43	Positive	65.0	8, 99	19.02	7.19	0	25.19	11/12 (91.7)	10/12 (83.3)	9/12 (75.0)	30/36 (83.3)
44	Positive	75.0	1, 95	12.38	2.03	4.44	22.76	12/12 (100.0)	9/12 (75.0)	12/12 (100.0)	33/36 (91.7)
45	Positive	85.0	20, 100	18.68	0	0	23.44	12/12 (100.0)	10/12 (83.3)	12/12 (100.0)	34/36 (94.4)
46	Positive	90.0	10, 100	10.27	6.05	5.65	17.97	12/12 (100.0)	11/12 (91.7)	12/12 (100.0)	35/36 (97.2)
47	Positive	90.0	5, 100	14.66	0	0	22.45	12/12 (100.0)	10/12 (83.3)	12/12 (100.0)	34/36 (94.4)
48	Positive	90.0	5, 100	14.08	0	6.41	20.94	12/12 (100.0)	10/12 (83.3)	12/12 (100.0)	34/36 (94.4)
49	Positive	95.0	80, 100	6.33	0.36	0	6.77	12/12 (100.0)	12/12 (100.0)	12/12 (100.0)	36/36 (100.0)
50	Positive	95.0	30, 100	6.41	0	3.52	13.30	12/12 (100.0)	11/12 (91.7)	12/12 (100.0)	35/36 (97.2)
51	Positive	95.0	65, 100	9.16	2.43	0	10.16	12/12 (100.0)	12/12 (100.0)	12/12 (100.0)	36/36 (100.0)
52	Positive	95.0	70, 100	7.48	0	0	8.81	12/12 (100.0)	12/12 (100.0)	12/12 (100.0)	36/36 (100.0)
53	Positive	95.0	10, 100	11.90	0	0	17.62	12/12 (100.0)	12/12 (100.0)	11/12 (91.7)	35/36 (97.2)
54	Positive	96.5	80, 100	6.02	0	0	6.61	12/12 (100.0)	12/12 (100.0)	12/12 (100.0)	36/36 (100.0)
55	Positive	100.0	80, 100	3.40	0	0	5.10	12/12 (100.0)	12/12 (100.0)	12/12 (100.0)	36/36 (100.0)
56	Positive	100.0	75, 100	6.19	0.55	0	7.01	12/12 (100.0)	12/12 (100.0)	12/12 (100.0)	36/36 (100.0)
57	Positive	100.0	90, 100	3.50	0.36	0	4.17	12/12 (100.0)	12/12 (100.0)	12/12 (100.0)	36/36 (100.0)
58	Positive	100.0	65, 100	5.04	0.26	0	7.17	12/12 (100.0)	12/12 (100.0)	12/12 (100.0)	36/36 (100.0)
59	Positive	100.0	90, 100	2.80	1.41	0	3.78	12/12 (100.0)	12/12 (100.0)	12/12 (100.0)	36/36 (100.0)
60	Positive	100.0	65, 100	5.80	2.98	0	8.71	12/12 (100.0)	12/12 (100.0)	12/12 (100.0)	36/36 (100.0)

The data were analyzed for positive percent agreement (PPA), negative percent agreement (NPA), and overall percent agreement (OPA) across all evaluable observations, and a summary is presented in the tables below.

Table 16. Overall, Site-Stratified, and Reader-Stratified Reproducibility Analyses of MET Status vs. Mode for BenchMark ULTRA Instrument for 50% Strong TC Staining Cutoff.

ULTRA External Reproducibility	Agreement			
	Type	n/N	%	95% CI
Overall	PPA	438/521	84.1	(81.4, 86.8)
	NPA	509/554	91.9	(88.5, 95.1)
	OPA	947/1075	88.1	(86.3, 89.9)
Within Site	PPA	436/498	87.6	(85.3, 89.8)
	NPA	530/577	91.9	(89.6, 94.1)
	OPA	966/1075	89.9	(88.2, 91.5)
Within Reader	PPA	445/473	94.1	(92.7, 95.7)
	NPA	564/602	93.7	(92.2, 95.2)
	OPA	1009/1075	93.9	(92.9, 94.8)

Note: Positive Percent Agreement (PPA), Negative Percent Agreement (NPA), Overall Percent Agreement (OPA).

Table 17. Overall, Site-Stratified, and Reader-Stratified Reproducibility Analyses of MET Status vs. Mode for BenchMark ULTRA PLUS Instrument for 50% Strong TC Staining Cutoff.

ULTRA PLUS External Reproducibility	Agreement			
	Type	n/N	%	95% CI
Overall	PPA	424/468	87.2	(83.9, 91.3)
	NPA	525/591	88.8	(85.8, 91.9)
	OPA	949/1077	88.1	(86.2, 90.1)
Within Site	PPA	441/509	86.6	(83.9, 89.6)
	NPA	519/568	91.4	(88.9, 93.9)
	OPA	960/1077	89.1	(87.5, 91.0)
Within Reader	PPA	465/491	94.7	(93.2, 96.2)
	NPA	561/586	95.7	(94.5, 97.0)
	OPA	1026/1077	95.3	(94.4, 96.1)

Note: Positive Percent Agreement (PPA), Negative Percent Agreement (NPA), Overall Percent Agreement (OPA).

The performance equivalence analysis (method comparison) of the VENTANA MET (SP44) RxDx Assay on the BenchMark ULTRA and BenchMark ULTRA PLUS was evaluated twice using each instrument platform as a reference. Each reader at each site produced 180 reads (1080 total reads). Results of the method comparison study are presented in Table 18 and Table 19 below. Please note that, due to an observed decrease in precision for cases with borderline expression, consultation with a second pathologist is recommended per standard medical practice for cases with borderline expression and/or intensity levels. Please refer to the limitation in the Scoring Algorithm and the Specific Limitations section.

Table 18. Overall Method Comparison Study Results

Rate	ULTRA as Reference		ULTRA PLUS as Reference	
	% (n/N)	95% CI	% (n/N)	95% CI
PPA	87.2 (421/783)	(84.7, 89.8)	86.3 (421/488)	(83.8, 88.6)
NPA	88.6 (523/590)	(86.3, 90.7)	89.4 (523/585)	(87.4, 91.6)
OPA	88.0 (944/1073)	(86.3, 89.5)	-	-

Note: Positive Percent Agreement (PPA), Negative Percent Agreement (NPA), Overall Percent Agreement (OPA).

Table 19. Overall Method Comparison Study Results (Reader 1, Day 1)

Rate	ULTRA as Reference		ULTRA PLUS as Reference	
	% (n/N)	95% CI	% (n/N)	95% CI
PPA	81.3 (65/80)	75.3, 87.2	85.5 (65/76)	78.7, 92.0
NPA	88.9 (88/99)	83.2, 94.0	85.4 (88/103)	80.6, 90.2
OPA	85.5 (153/179)	81.5, 89.4	-	-

Note: Positive Percent Agreement (PPA), Negative Percent Agreement (NPA), Overall Percent Agreement (OPA).

CLINICAL PERFORMANCE

LUMINOSITY: Previously Treated EGFR Wild-Type Non-squamous NSCLC with MET Protein Overexpression

The efficacy of EMRELIS™ (telisotuzumab vedotin-tllv) as monotherapy was evaluated in the LUMINOSITY study (NCT03539536), a multicenter, open-label, single-arm study. Eligible patients were required to have locally advanced or metastatic non-squamous NSCLC with MET protein overexpression and treatment with prior systemic therapy (including no more than one line of prior chemotherapy). The major efficacy outcome measure was overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as assessed by a blinded independent central review (BICR). An additional efficacy outcome measure was duration of response (DOR) by BICR. The primary endpoint of ORR was calculated based on the Primary Efficacy population (n=84).

As part of enrollment screening, archived or post-progression/recent NSCLC tumor samples from prospective study participants were assessed for the presence or absence of MET protein overexpression at a central laboratory using an IHC clinical trial assay (CTA) based on the MET-directed monoclonal antibody clone SP44 [MET (SP44)]. For patients with non-squamous NSCLC, subjects were enrolled on the basis of MET protein expression CTA result demonstrating strong IHC staining (3+ intensity) in ≥25% of tumor cells (a "CTA^{+}_{25}" result). Tumor specimens from enrolled subjects were also assessed for high MET expression, defined as strong CTA IHC staining (3+ intensity) in ≥50% of tumor cells (designated "CTA^{+}_{50}"). Efficacy was evaluated in 84 EGFR wild-type non-squamous NSCLC patients with CTA result indicating high MET expression (≥50% tumor cells with strong (3+) membrane staining) who received telisotuzumab vedotin at 1.9 mg/kg intravenously every two weeks until disease progression or unacceptable toxicity (the primary efficacy population).

The median age was 64 years (range: 38 to 83 years); 75% were male; 61% were White, 1.2% were Black or African American, 38% were Asian; none were Hispanic or Latino. Twenty-five percent had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 and 74% had ECOG PS of 1; 19% were never smokers, 68% were former smokers, and 13% were current smokers; 99% had Stage IV disease; and 19% of patients had previously treated brain metastases. The median number of lines of prior therapies was 1 (range 1 - 3); 73% of patients had

one line, 24% had two lines, and 3.6% had three lines of prior systemic therapy; 96% of patients had prior platinum therapy, 82% had prior immunotherapy (anti-PD-1/PD-L1), 6% had prior targeted therapy, and 3.6% had prior MET tyrosine kinase inhibitor therapy. Efficacy results for Study LUMINOSITY are summarized below.

The primary efficacy endpoint was overall response rate (ORR) determined by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as assessed by Independent Central Review (ICR). Efficacy results, for patients selected based on the CTA, are summarized in Table 20.

Table 20. Clinical Benefit of MET Patient Population in LUMINOSITY

	CTA+ (n=84)	CTA+/CDx+ (n=32)	CTA+/CDx- (n=5)	CTA+/CDx unevaluable (n=47)
ORR (95% CI)	34.5 (24.5, 45.7)	34.4 (18.6, 53.2)	20 (0.5, 71.6)	36.2 (22.7, 51.5)
Complete response (CR), n (%)	0	0	0	0
Partial response (PR), n (%)	29 (34.5)	11 (34.4)	1 (20)	17 (36.2)
Duration of Response (DOR)				
Median DoR, months (95% CI)	7.2 (4.2, 12.0)	7.2 (2.8, 13.0)	4.2 (-,-)	10.0 (3.8, 18.9)
% with DoR ≥6 months, n (%)	17 (58.6)	7 (63.6)	0	10 (58.8)
% with DoR ≥12 months, n (%)	6 (20.7)	2 (18.2)	0	4 (23.5)

The clinical performance of the VENTANA MET (SP44) RxDx Assay as a companion diagnostic (CDx) device to aid in the identification of patients with non-squamous non-small cell lung cancer (NSCLC) who are likely to benefit from EMRELIS™ (telisotuzumab vedotin-tllv) treatment was demonstrated through a clinical bridging study using specimens from patients screened for enrollment into the LUMINOSITY study using the CTA. Remnant specimens from patients previously screened for LUMINOSITY were retrospectively assessed for MET protein expression using VENTANA MET (SP44) RxDx Assay (978 patients) at central laboratories. The re-tested patient set included 37 of 84 patients with outcome data available from the LUMINOSITY trial and 830 individuals representative of LUMINOSITY screen-failed subjects.

The agreement of MET status between the CTA results and VENTANA MET (SP44) RxDx Assay (CDx) was calculated at the 50% strong tumor cell staining cutoff using the CTA results as the reference. The concordance analysis results for the patients included in the bridging efficacy analysis are shown in Table 21.

Table 21. MET status concordance at the 50% strong tumor cell staining cutoff between LUMINOSITY study CTA and the CDx in the bridging intended use population.

LUMINOSITY Study		MET CTA Status		
		Positive	Negative	Total
MET CDx Status	Positive	32	42	74
	Negative	5	461	466
	Unknown[1]	47	327	374
	Total	84	830	914
	PPA: 86.5% (32/37) [95% CI: 71.23, 95.46]			
	NPA: 91.7% (461/503) [95% CI: 88.88, 93.92]			
	OPA: 91.3% (493/540) [95% CI: 88.59, 93.53]			

[1]CDx unknown includes: 1) protocol deviations, incident events, and/or screen failures for reasons other than CTA result, 2) CDx not evaluable.

LUMINOSITY Study	MET CTA Status		
	Positive	Negative	Total

CDx = VENTANA MET (SP44) assay; CI = confidence interval; CTA = clinical trial assay; NPA = negative percent agreement; PPA = positive percent agreement; OPA = overall percent agreement

Note: Concordance was estimated in only those patients who had an evaluable CDx result.

Sensitivity analysis with regard to the missing CDx test results were conducted to evaluate the robustness of the ORR estimates considering VENTANA MET (SP44) RxDx Assay (CDx) unevaluable patients enrolled in the LUMINOSITY trial. Samples's CDx results were considered missing if the samples were not tested by the CDx, or if they were tested but returned an invalid result, or if they were excluded from the analysis due to protocol deviations, incident events, and/or because they were screen failures for reasons other than CTA result. Under the reasonable assumption of missing at random (MAR), the missing CDx results were imputed. A multiple imputation approach was utilized to impute the missing CDx MET status. The CTA MET result, treatment outcome variable, patient characteristics variables, and sample characteristics variables were considered. Amongst all CTA+ patients, 56% did not have VENTANA MET (SP44) RxDx Assay result (47/84).

The imputed ORR was estimated to be 32.4% (95% CI: 24.23, 40.51), which is comparable to the ORR for the CTA-positive population [34.5% (24.5, 45.7)]. Thus, the sensitivity analysis demonstrated the robustness of the clinical efficacy estimate to the missing VENTANA MET (SP44) RxDx Assay results.

TROUBLESHOOTING

If a problem cannot be attributed to any of these causes, or if the suggested corrective action fails to resolve the problem, consult your local support representative.

Table 22. Troubleshooting guidance for VENTANA MET (SP44) RxDx Assay.

Problem	Probable Cause	Suggested Action
Light or no staining of slides	Incorrect staining protocol selected	Verify that U VENTANA MET (SP44) RxDx Assay procedure was used.
		Verify that VENTANA MET (SP44) RxDx Assay was selected for Primary Antibody
	Degradation of tissue	Verify tissue was stained within the recommended time frame following sectioning.
	Dispenser malfunction	Verify nozzle cap is removed.
		Ensure dispenser is primed
		Check the priming chamber for foreign materials or particulates, such as fibers or precipitate
		Refer to inline dispenser method sheet associated with P/N 740-7064 located at navifyportal.roche.com
	Inappropriate fixation method used	Ensure that only recommended fixatives and fixation times are used.
	Incorrect or missing bulk reagent	Ensure bulk reagents are correctly filled.
Excessive background staining of slides	Incorrect staining protocol selected	Verify that U VENTANA MET (SP44) RxDx Assay procedure was used.
	Incorrect of missing bulk reagent	Ensure bulk reagents are correctly filled.
	Inappropriate fixation method used	Ensure that only recommended fixatives and fixation times are used.
Tissue detachment from slides	Use of incorrect microscope slides	Ensure positively charged microscope slides are used.

REFERENCES

1. Carson FL, Cappellano C. Histotechnology; A Self-Instructional Text, 5th edition. American Society for Clinical Pathology Press; 2020, 2022.
2. Occupational Safety and Health Standards: Occupational exposure to hazardous chemicals in laboratories. (29 CFR Part 1910.1450). Fed. Register.
3. Directive 2000/54/EC of the European Parliament and Council of 24 June 2020 on the protection of workers from risks related to exposure to biological agents at work.

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

Symbols

Ventana uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see elabdoc.roche.com/symbols for more information).

GTIN	Global Trade Item Number
Rx only	For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

INTELLECTUAL PROPERTY

For USA: Rx only

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