SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Next generation sequencing oncology panel, somatic or germline variant detection system
Device Trade Name:	Oncomine™ Dx Target Test
Device Product Code:	PQP
Applicant's Name and Address:	Life Technologies Corporation 7305 Executive Way Frederick, MD 21704
Date(s) of Panel Recommendation:	None
PMA Number:	P160045/S025
Date of FDA Notice of Approval:	September 29, 2023

The original PMA (P160045) Oncomine™ Dx Target (ODxT) Test was approved on June 22, 2017, for the detection of genetic alterations in patients who may benefit from one of three FDA-approved therapies for non-small cell lung cancer (NSCLC).

Subsequently, additional PMA supplements were approved for expanding the indications for use of the ODxT Test for detecting *RET* fusions in tumors from NSCLC and thyroid cancer (TC) patients, *EGFR* exon 20 insertions and *ERBB2/HER2* mutations in tumors from NSCLC patients, for the identification of *IDH1* single nucleotide variants (SNVs) in cholangiocarcinoma (CC) patients, and *RET* mutations in medullary thyroid cancer (MTC) patients, for treatment with the corresponding therapeutic products, since its original approval. The SSEDs to support the previously approved indications are available on the CDRH website.

The current panel-track supplement was submitted to expand the indications for use of the ODxT Test to include a companion diagnostic indication for the identification of the BRAF V600E mutations in anaplastic thyroid cancer (ATC) patients who may benefit from the targeted drug therapy, TAFINLAR® (dabrafenib) in combination with MEKINIST® (trametinib).

II. INDICATIONS FOR USE

The Oncomine™ Dx Target Test is a qualitative *in vitro* diagnostic test that uses targeted high-throughput, parallel-sequencing technology to detect single nucleotide variants (SNVs),

insertions, and deletions in 23 genes from DNA and fusions in *ROS1* and *RET* from RNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue samples from patients with non-small cell lung cancer (NSCLC), *IDH1* SNVs from FFPE tumor tissue samples from patients with cholangiocarcinoma (CC), *BRAF* V600E mutations from FFPE tumor tissue samples from patients with anaplastic thyroid cancer (ATC), RET SNVs, multi-nucleotide variants (MNVs), and deletions from DNA isolated from FFPE tumor tissue samples from patients with medullary thyroid cancer (MTC) and RET fusions from RNA isolated from FFPE tumor tissue samples from patients with thyroid cancer (TC) using the Ion PGM™ Dx System.

The test is indicated as a companion diagnostic to aid in selecting NSCLC, CC, ATC, MTC and TC patients for treatment with the targeted therapies listed in **Table 1** in accordance with the approved therapeutic product labeling.

Table 1. List of variants for therapeutic use

Tissue type	Gene	Variant	Targeted therapy
NSCLC	*BRAF*	*BRAF* V600E mutations	TAFINLAR® (dabrafenib) in combination with MEKINIST® (trametinib)
	EGFR	*EGFR* L858R mutation, *EGFR* exon 19 deletions	IRESSA® (gefitinib)
	EGFR	EGFR exon 20 insertions	EXKIVITY™ (mobocertinib) RYBREVANT™ (amivantamab-vmjw)
	ERBB2/HER2	*ERBB2/HER2* activating mutations (SNVs and exon 20 insertions)	ENHERTU® (fam-trastuzumab deruxtecan-nxki)
	RET	*RET* fusions	GAVRETO™ (pralsetinib) RETEVMO® (selpercatinib)
	ROS1	*ROS1* fusions	XALKORI® (crizotinib)
CC	*IDH1*	*IDH1* R132C, *IDH1* R132G, *IDH1* R132H *IDH1* R132L, and *IDH1* R132S mutations	TIBSOVO® (ivosidenib)
ATC	*BRAF*	*BRAF* V600E mutations	TAFINLAR® (dabrafenib) in combination with MEKINIST® (trametinib)
MTC	*RET*	*RET* mutations (SNVs, MNVs, and deletions)	RETEVMO® (selpercatinib)
TC	*RET*	*RET* fusions	RETEVMO® (selpercatinib)

Safe and effective use has not been established for selecting therapies using this device for the variants listed in tissue types other than those in **Table 1**.

Results other than those listed in **Table 1** are indicated for use only in patients who have already been considered for all appropriate therapies (including those listed in **Table 1**). Analytical performance using NSCLC specimens has been established for the variants listed in **Table 2**.

Table 2. List of Variants with Established Analytical Performance Only

Gene	Variant ID/type	Amino acid change	Nucleotide Change
KRAS	COSM512	p.Gly12Phe	c.34_35delGGinsTT
KRAS	COSM516	p.Gly12Cys	c.34G>T
MET	COSM707	p.Thr1010Ile	c.3029C>T
PIK3CA	COSM754	p.Asn345Lys	c.1035T>A

The test is not indicated to be used for standalone diagnostic purposes, screening, monitoring, risk assessment, or prognosis.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Oncomine™ Dx Target Test labeling.

V. DEVICE DESCRIPTION

The Oncomine Dx Target Test is an *in vitro* diagnostic test that provides primer panels, assay controls and interpretative software [an Assay Definition File (ADF)] designed for use with the Ion PGM Dx System and the Ion PGM Dx Reagents for detection of alterations in deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) isolated from NSCLC, CC, MTC, TC and ATC FFPE tumor specimens.

The Oncomine™ Dx Target Test consists of the following: Oncomine™ Dx Target Test and Controls Kit (Combo Kit):

- Oncomine™ Dx Target Test DNA and RNA Panel
- Oncomine™ Dx Target DNA Control Kit
- Oncomine™ Dx Target RNA Control Kit
- Ion Torrent™ Dx No Template Control Kit

Ion Torrent™ Dx FFPE Sample Preparation Kit:

- Ion Torrent™ Dx Total Nucleic Acid Isolation Kit
- Ion Torrent™ Dx cDNA Synthesis Kit
- Ion Torrent™ Dx DNA Quantification Kit
- Ion Torrent™ Dx RNA Quantification Kit
- Ion Torrent™ Dx Dilution Buffer Kit

Ion PGM™ Dx Reagents / Chips:

- Ion PGM™ Dx Library Kit
- Ion OneTouch™ Dx Template Kit
- Ion PGM™ Dx Sequencing Kit
- Ion 318™ Dx Chip Kit

Instrumentation and Software:

- The assay is run on the Ion PGM™ Dx System:
  - Ion OneTouch™ Dx System:
    - Ion OneTouch™ Dx Instrument
    - Ion OneTouch™ ES Dx Instrument
  - Ion PGM™ Dx Sequencer
  - Ion PGM™ Dx Chip Minifuge
  - Ion Torrent™ Server
  - Torrent Suite™ Dx Software
  - Other accessories:
    - Ion PGM™ Wireless Scanner
    - DynaMag™ 16 2mL Dx Magnet
    - DynaMag™ 96 Well Plate Magnet

The system also utilizes specified accessories. The assay's definition files are provided on a USB memory device along with the Oncomine™ Dx Target Test User Guides:

- Oncomine™ Dx Target Assay Definition File (includes interpretive software)
- Oncomine™ Dx Target Test User Guide
- Veriti™ Dx Thermal Cycler Settings
- Electronic Document Instructions (provided to users both as a paper copy and a PDF document on the USB drive)

Nucleic Acid Extraction:

DNA and RNA extraction is performed using the proprietary Ion Torrent Dx FFPE Sample Preparation Kit. The deparaffinized sample is first subjected to protein digestion with Proteinase K at an elevated temperature in a guanidinium thiocyanate solution to facilitate release and protection of RNA and DNA by inhibiting nuclease activity. After a heating step to inactivate the Proteinase K enzyme, the digested sample is transferred into a spin column containing a silica-based filter membrane.

The RNA is selectively eluted and separated from DNA which is retained on the filter. The eluted RNA is mixed with ethanol and captured onto a second spin column containing a silica-based membrane filter. The RNA is retained, and cellular impurities are removed by a series of washes. The bound RNA is treated with DNase to reduce contaminating DNA. Following a series of washes to remove residual deoxyribonuclease (DNase) and DNA degradation products, the purified RNA is eluted from the filter.

The DNA retained on the first filter is similarly subjected to a series of washes to remove cellular impurities and then purified DNA is eluted from the filter. The Elution Solution

provided with the kit is a low ionic strength Tris-buffered solution containing EDTA that facilitates elution of nucleic acids from the silica filter. The solution provides appropriate pH for stability of RNA and DNA and inhibits nucleases by binding metal cofactors.

Quantification:

RNA and DNA quantification is performed using a fluorescence dye-binding assay and a qualified fluorometer/fluorescence reader capable of operating at the specific excitation and emission wavelengths. First, working solutions consisting of buffer and proprietary fluorophores are prepared for both DNA and RNA samples, as well as the DNA and RNA standards supplied at different concentrations in the kit (0 ng/µL to 10 ng/µL). Second, the DNA and RNA samples are incubated with their respective solutions at room temperature where the fluorophores bind to the target DNA and RNA molecules. When bound to the DNA and RNA, the fluorophores exhibit fluorescence enhancement at a specific excitation wavelength. The emitted fluorescent signals are captured and converted into signal fluorescence units. Third, the concentration (in ng/µL) of the DNA and RNA samples are determined by performing a linear regression with the values obtained from the DNA and RNA standards.

Sample Dilution Buffer is provided in the kit to dilute the DNA and RNA samples to a specific concentration required for complementary DNA (cDNA) synthesis and library preparation.

Reverse Transcription (RT) Step (RNA only):

RNA is enzymatically converted to cDNA using the Ion Torrent Dx cDNA Synthesis Kit. Ten nanograms (ng) of RNA is enzymatically converted to cDNA using an enzyme mix containing a proprietary engineered version of Moloney Murine Leukemia Virus (M-MLV) reverse transcriptase (Superscript III RT), an RNase inhibitor, a proprietary helper protein, and a buffer containing random primers, dNTPs, and $MgCl_2$.

Library Preparation Workflow:

The process begins with polymerase chain reaction (PCR) and uses the Oncomine Dx Target Test DNA and RNA Panel and the Ion PGM Dx Library Kit to specifically amplify target regions of interest from cDNA (including cDNA from the RNA control) and DNA (including the DNA Control and No Template Control). For detection of RNA fusions, the device has optimization of the RNA workflow and includes changes to the primer concentrations and the denaturation temperature used in PCR.

Two different libraries are generated and pooled for each sample: one for DNA targets and one for RNA targets. During library preparation for each sample, one of the 16 oligonucleotide barcodes in the Library Kit is used for the DNA-derived library and another oligonucleotide barcode is used for the RNA-derived library. This ensures the correct identification of each respective portion of the assay (DNA and RNA) from each patient sample. After library preparation, the DNA and RNA libraries for all samples and controls may be blended for the templating reaction.

Data Analysis:

This process is executed by the Torrent Suite Dx software, v. 5.12.5, which runs on the Ion Torrent Server. Together, these manage the complete end-to-end workflow from sample to variant call. The DNA reads are 'mapped' to the reference human genome (hg19) followed by detection of single nucleotide variants (SNVs) and deletions (del) using a reference hotspot file. The RNA reads are 'mapped' to a reference containing control sequences and candidate gene fusion sequences. Gene fusions are detected as present if they map to these reference sequences and pass certain filtering criteria provided by the Oncomine Dx Target Test ADF.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are FDA approved companion diagnostic (CDx) alternatives for the detection of genetic alterations using FFPE tumor specimens, to those listed in **Table 1** of the ODxT Test intended use statement. These approved alternative CDx tests are listed in the **Table 3** below. Each alternative has its own advantages and disadvantages. A patient should fully discuss any alternative with his/her physician to select the most appropriate method. For additional details see FDA List of Cleared or Approved Companion Diagnostic Devices at: https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm?source=govdelivery.

Table 3. List of FDA-Approved CDx Assays for Genes Targeted by the ODxT Test

Gene	Variant	Device	Company	Technology	Therapy
BRAF	*BRAF* V600E	FoundationOne CDx	Foundation Medicine, Inc.	NGS	TAFINLAR® (dabrafenib) in combination with MEKINIST® (trametinib)
EGFR	*EGFR* L858R, exon 19 deletions	Therascreen EGFR RGQ PCR Kit	Qiagen Manchester, Ltd.	PCR	IRESSA® (gefitinib)
		Cobas EGFR Mutation Test v2	Roche Molecular Systems, Inc	PCR	
		FoundationOne CDx	Foundation Medicine, Inc.	NGS	
EGFR	*EGFR* Exon 19 Deletions and Exon 21 L858R Substitution	O/RDx- LCCA	Pillar Biosciences, Inc.	NGS	*EGFR* Tyrosine Kinase Inhibitors
ROS1	*ROS1* fusion	FoundationOne CDx	Foundation Medicine, Inc.	NGS	XALKORI® (crizotinib)

VII. MARKETING HISTORY

The ODxT Test was introduced into interstate commerce in the United States on June 22, 2017, and is commercially available in the US, 12 countries in Europe (Austria, Belgium, Switzerland, Germany, Denmark, Spain, France, UK, Scotland, Italy, Netherlands, and Poland), Japan, Korea, Israel, and Saudi Arabia. The ODxT Test has not been withdrawn from the market for reasons related to safety and effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- Failure of the device to perform as expected or failure to correctly interpret test results may lead to incorrect ODxT Test results and subsequently improper patient management decisions in NSCLC, CC, MTC, TC and ATC treatment.

- Patients with false positive results may undergo treatment with the therapy listed in the intended use statement without clinical benefit and may experience adverse reactions associated with the therapy. Patients with false negative results may not be considered for treatment with the indicated therapy.

- There is also a risk of delayed results, which may lead to delay of treatment with the appropriate targeted therapy.

No adverse events were reported in connection with the clinical studies used to support this PMA as the studies were performed retrospectively using banked samples.

For the specific adverse events that occurred in the clinical studies, refer to the drug label (i.e., FDA approved package insert) available at Drugs@FDA.

IX. SUMMARY OF NONCLINICAL STUDIES

The indication for use was modified to include the BRAF V600E detection in ATC FFPE specimens for use as an aid in selecting patients for treatment with dabrafenib and trametinib. To support ATC indication for BRAF V600E, non-clinical studies were leveraged using approved non-clinical data from the original submission, P160045. A summary of additional analytical validation studies demonstrating the performance of the ODxT Test to detect the BRAF V600E mutations are listed below.

A. Laboratory Studies

Analytical validation for BRAF V600E was determined in the original PMA using DNA isolated from NSCLC specimens. Supplemental studies confirming the limit of detection (LoD) and precision (repeatability and reproducibility) were conducted to support the indication for the BRAF V600E mutations in ATC FFPE tissue samples.

1. Limit of Detection (LoD)

A study was conducted to confirm the LoD of the ODxT Test for detection of the BRAF V600E mutation using papillary thyroid cancer (PTC) FFPE tissue. DNA from a BRAF V600E variant-positive thyroid cancer sample was blended with DNA from a BRAF V600E variant-negative sample and used as input DNA for the test. Twenty-four (24) data points were generated by testing 2 reagent lots and 12 replicates (two operators performed 6 runs each). The BRAF V600E mutation was detected in all 24 replicates (24/24) tested from a thyroid-derived DNA blend sample containing the variant and confirmed the previously established (in NSCLC tissue) BRAF V600E mutation LoD level of 6.4% AF (data not shown).

In a supplemental study, ATC clinical samples (one BRAF V600E-positive and one BRAF V600E-negative) were used to prepare DNA sample blends targeting 3 BRAF V600E AF levels near the previously established LoD of 6.4% **(Table 4).** Twenty (20) replicates of each of the 3 DNA sample blends were tested by 2 operators across 2 instrument systems and 2 lots of reagents (10 replicates per blend for each lot) to confirm the LoD. The final estimated LoD for BRAF V600E in ATC FFPE tissue samples was shown to be 6.4%, as determined by the lowest mean AF among the 3 DNA sample blends that produced a BRAF V600E mutation detection rate of at least 95% across both reagent lots combined.

Table 4. LOD confirmation study for BRAF V600E in ATC DNA sample blends

Lot	Sample Blend ID	Total Replicates	Positive Calls	Negative Calls	No Calls	Positive Hit Rate	Mean AF
L1	S1	10	10	0	0	100%	6.27%
	S2	10	10	0	0	100%	6.93%
	S3	10	8	0	2	80%	5.54%
L2	S1	10	10	0	0	100%	6.48%
	S2	10	10	0	0	100%	6.27%
	S3	10	10	0	0	100%	5.51%
L1 and L2 Combined	S1	20	20	0	0	100%	6.38%
	S2	20	20	0	0	100%	6.60%
	S3	20	18	0	2	90%	5.52%

2. Precision (Repeatability and Reproducibility)

The precision testing was conducted by using 2 test samples at each of two levels of analyte concentration. In this study, three (3) samples, including 1 BRAF V600E-negative thyroid cancer FFPE tissue specimen and 2 DNA blends derived from thyroid cancer FFPE tissue specimens with low (LoD level) and high levels of BRAF V600E

mutant allelic frequency, were used for the precision study. Seventy-two (72) data points (24 data points per sample) were collected by 2 operators using 2 different lots of reagents on 2 sets of instruments over a period greater than 20 operational days to assess operator-to-operator, inter- and intra-run precision of the ODxT Test. The point estimate of the average positive agreement (APA), the average negative agreement (ANA), and overall percent agreement (OPA) between the 2 replicates within run across 12 unique runs was calculated.

The assay precision was assessed with 72 valid results from 72 replicates tested in conjunction with the LoD study. For repeatability, the point estimate of APA was 100% on BRAF V600E status between replicates within run for each positive sample; and the point estimate of ANA was 100% on BRAF V600E status between replicates within run for each negative sample. The point of estimate of OPA was 100% on BRAF V600E status within run for all samples. For total precision (within-laboratory precision), the point estimate of the APA was 100% on BRAF V600E status between replicates within laboratory for each positive sample; and the point estimate of ANA was 100% on BRAF V600E status between replicates within laboratory for each negative sample; and the OPA was 100% for all samples within laboratory. For operator-to-operator, instrument-to-instrument, and reagent lot-to-lot precision, the point estimate of the APA for each positive sample and the ANA for each negative sample assessed for the BRAF V600E mutation status were both 100% and the OPA was 100% for all samples.

The results from all samples met the pre-defined acceptance criteria for repeatability and reproducibility.

Results showing precision/reproducibility by operator, instrument, and reagent lot are summarized in **Table 5** below.

Table 5. Results for the assay precision study (operator-to-operator, instrument-to instrument, and lot-to-lot)

BRAF V600E mutation status	Sample	Operator, instrument, or lot	# of positives/total (call rate)	# of negatives/total (call rate)
BRAF V600E-positive	S2	1	12/12 (100%)	0/12 (0%)
		2	12/12(100%)	0/12 (0%)
		Subtotal	24/24 (100%)	0/24 (0%)
BRAF V600E-positive	S3	1	12/12 (100%)	0/12 (0%)
		2	12/12 (100%)	0/12 (0%)
		Subtotal	24/24 (100%)	0/24 (0%)
Wild type	S1	1	0/12 (0%)	12/12 (100%)

BRAF V600E mutation status	Sample	Operator, instrument, or lot	# of positives/total (call rate)	# of negatives/total (call rate)
		2	0/12 (0%)	12/12 (100%)
		Subtotal	0/24 (0%)	24/24 (100%)

Mean AF, between-lot, between-operator, between-instrument, within-run and total standard deviations (SD) and associated coefficients of variation (%CV) are reported in **Table 6** below.

Table 6. Variance components analyses for positive samples

Within-run					Between-instrument		Between-operator		Between-lot		Total	
Sample	**Mean value**	**N**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
S2	7.85	24	1.157	14.7	0.000	0.0	0.133	1.7	0.289	3.7	1.200	15.3
S3	18.04	24	1.539	8.5	0.000	0.0	0.000	0.0	0.000	0.0	1.539	8.5

3. Interference Study

A retrospective analysis was performed to demonstrate that the performance of the ODxT Test in detecting BRAF V600E mutations is not affected by the presence of highly necrotic tissue (defined as having ≥10% necrotic tissue present). A statistical analysis showed that there was 100% agreement for positive percent agreement (PPA), negative percent agreement (NPA), and OPA between the ODxT Test and the clinical trial PCR assay for the detection of BRAF V600E mutations in highly necrotic FFPE thyroid cancer tissue samples. These results demonstrate that the ODxT Test can generate the correct results in the presence of highly necrotic tissue at levels up to 60%.

4. Guard Banding Study

A guard banding study was conducted using 3 BRAF V600E-positive ATC clinical samples to prove that the ODxT Test is adequately robust in the detection of BRAF V600E mutations in ATC tissues by assessing 3 critical conditions of the ODxT Test nucleic acid isolation workflow: Proteinase K enzyme volume, digestion temperature, and digestion time. Additionally, 2 BRAF V600E-negative samples were used to test the same 3 critical conditions to provide evidence that the test protocol deviations do not result in false positive BRAF V600E variant calls. All DNA sample libraries passed QC and met the study acceptance criteria for BRAF V600E variant calling (100% overall call rate). Moreover, all DNA sample library replicates for each ATC BRAF V600E-positive sample produced similar mean AF values across all condition levels tested.

The results demonstrate that the ODxT Test is adequately robust in the detection of the BRAF V600E mutations in ATC FFPE tissue samples with respect to 3 critical conditions of the ODxT Test nucleic acid isolation workflow: PK enzyme volume, digestion temperature, and digestion time.

5. Stability Studies

Due to the rarity of BRAF V600E positive ATC samples, data generated under the standard conditions from five (5) samples tested in the Proteinase K guard-banding study were used for stability studies. FFPE slides from five ATC samples, consisting of three BRAF V600E positive samples and two BRAF V600E negative samples were used for the PK guard-banding study. The three BRAF V600E positive samples were collected as FFPE slides from patients enrolled in the ROAR study, and two BRAF V600E negative samples were procured commercially as blocks. The FFPE slides utilized for the guard-banding study were from the same set of FFPE slides that were utilized in the concordance study. The mutation calls generated under three standard challenging conditions (PK volume, enzyme digestion temperature, and enzyme digestion time) in the guard-banding study from the five samples showed 100% agreement with the test results generated in the concordance study using the same set of FFPE slides.

Overall, the time between the concordance study and the guard-banding study testing is at least 33 months, which demonstrates that all stored ATC FFPE slides were stable from the time the slides were originally cut to the time of testing.

B. Animal Studies

Not applicable.

X. SUMMARY OF PRIMARY CLINICAL STUDY

Clinical validation of the ODxT Test for identification of the BRAF V600E mutations in ATC patients who may benefit from dabrafenib in combination with trametinib was performed by retrospectively testing samples from the 36 patients enrolled in the ATC cohort of the ROAR study (NCT02034110) and additional commercially obtained thyroid cancer samples with both the ODxT Test and another commercially available kit which used a qPCR based technology (hence forth referred to as the ROAR clinical trial central confirmation assay or CTA). Life Technologies Corporation conducted a clinical concordance study to establish the concordance (agreement) between the CTA and the ODxT Test for the detection of the BRAF V600E mutations in thyroid cancer tissue, evaluating the OPA, PPA and NPA, as well as assessing the drug efficacy in the ODxT Test positive population. A summary of the clinical study is presented below.

A. ODxT Test Clinical Concordance Study for the BRAF V600E mutations

The clinical concordance study was conducted to establish the agreement between the clinical trial PCR assay CTA and the ODxT Test for the detection of the BRAF V600E mutations in thyroid cancer tissue.

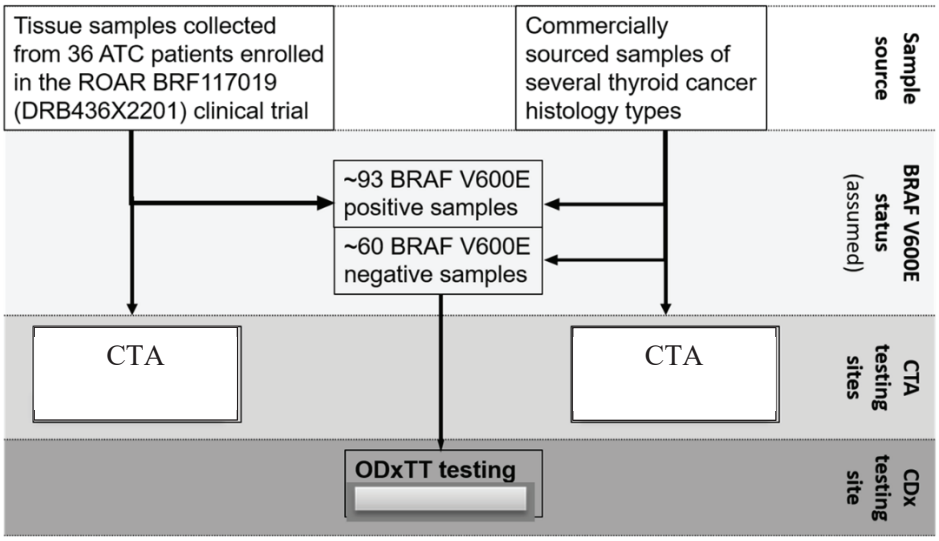
1. Study Design

The ROAR clinical trial was designed to assess the clinical efficacy and safety of the combination of the BRAF inhibitor TAFINLAR (dabrafenib) in combination with the MEK inhibitor MEKINIST (trametinib) in subjects with BRAF V600E-mutant rare cancers, demonstrating a high unmet medical need. The study enrolled 36 subjects with BRAF V600E mutation positive, unresectable, metastatic ATC (including ATC originating from within well-differentiated thyroid cancers or an ATC as part of a thyroid carcinoma of another histologic type). All patients were required to have a BRAF V600E mutation-positive tumor as determined by an approved local laboratory test (LLT) or the clinical trial assay (CTA) at a sponsor designated central reference laboratory. For patients enrolled based on local determination of BRAF V600E mutation positive tumor status, additional tumor tissue was required to be made available for a retrospective confirmatory test performed at the central reference laboratory.

Based on the ROAR clinical trial data, the use of dabrafenib and trametinib in ATC was approved in the US in May 2018, with a post-market commitment to establish, through the use of clinical trial data, an *in-vitro* diagnostic device that is essential to the safe and effective use of dabrafenib and trametinib for patients with BRAF V600E mutations in ATC tumor specimens.

Because of the rarity of the BRAF V600E mutated ATC indication and the resulting small number of ATC patients enrolled to the ROAR trial, a small-scale concordance study was conducted to compare the CTA to the final companion diagnostic. For this clinical concordance study, testing by the proposed CDx assay, ODxT Test, and the CTA was planned to be performed on available thyroid cancer tissue samples from the 36 patients enrolled in the ATC cohort of the ROAR study and approximately 120 commercially obtained thyroid cancer samples, of which approximately 60 were targeted to be BRAF V600E positive and 60 BRAF V600E negative, according to the CTA test result. The commercially sourced samples included several thyroid cancer histologies other than ATC, such as follicular thyroid cancer (FTC), papillary thyroid cancer (PTC), and medullary thyroid cancer (MTC). The clinical validation study plan is shown in Figure 1 below.

Figure 1 Clinical validation study plan



a. ROAR Clinical Trial Key Inclusion Criteria:

- Must have provided informed consent for study participation before performance of any study-specific procedure or test.
- Sex: male or female
- Age:18 years of age at the time of providing informed consent
- Must have advanced disease and no standard treatment options as determined by locally/regionally available standards of care and treating physician's discretion.
- Must have a BRAF V600E mutation-positive tumor as confirmed by an approved local laboratory, or a sponsor designated central reference laboratory.
- Histologically or cytologically confirmed, unresectable, metastatic ATC including ATC originating from within well-differentiated thyroid cancers or an ATC as part of a thyroid carcinoma of another histologic type.
- Has undergone evaluation via indirect or direct laryngoscopy.
- Has undergone prior external beam radiotherapy and/or surgery to the primary tumor.

b. ROAR Clinical Trial Key Exclusion Criteria:

- Prior treatment with BRAF and/or MEK inhibitor(s); Chemotherapy, immunotherapy, biologic therapy or chemoradiation with delayed toxicity within 21 days (or within 42 days if prior therapy contains nitrosourea or

mitomycin C) prior to enrollment; Chemotherapy or biologic therapy without evidence of delayed toxicity within 14 days prior to enrollment; Investigational product(s) within 30 days or 5 half-lives prior to enrollment.

- History of malignancy with confirmed activating RAS mutation at any time.
- Prior radiotherapy less than 7 days prior to enrollment.
- Prior major surgery less than 14 days prior to enrollment.
- Prior solid organ transplantation or allogenic stem cell transplantation
- History of another malignancy
- Presence of brain metastases, symptomatic or untreated leptomeningeal or spinal cord compression, interstitial lung disease or pneumonitis, any serious and/or unstable pre-existing medical disorder, psychiatric disorder, or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures.
- Clinically significant GI abnormalities
- History or evidence of cardiovascular risk
- Pregnancy or lactation
- Presence of thyroid lymphomas, sarcomas, or metastatic disease from other sites of origin to the thyroid.
- Has potentially curable ATC by surgical excision alone or subjects who have not received treatment that might be considered standard of care.

c. Follow-up Schedule

The ODxT Test bridging study involved retrospective testing of samples; as such, no additional patient follow-up was conducted in regard to the clinical bridging study.

d. Clinical Endpoints

The primary clinical efficacy endpoint was to determine the overall response rate (ORR) of dabrafenib in combination with trametinib in patients with rare BRAF V600E mutation as defined by RECIST, v1.1 for solid tumor histologies. The supporting secondary objectives included the evaluation of duration of response, progression free response (PFS), overall survival (OS), and safety of the combination treatment.

B. Accountability of PMA Cohort

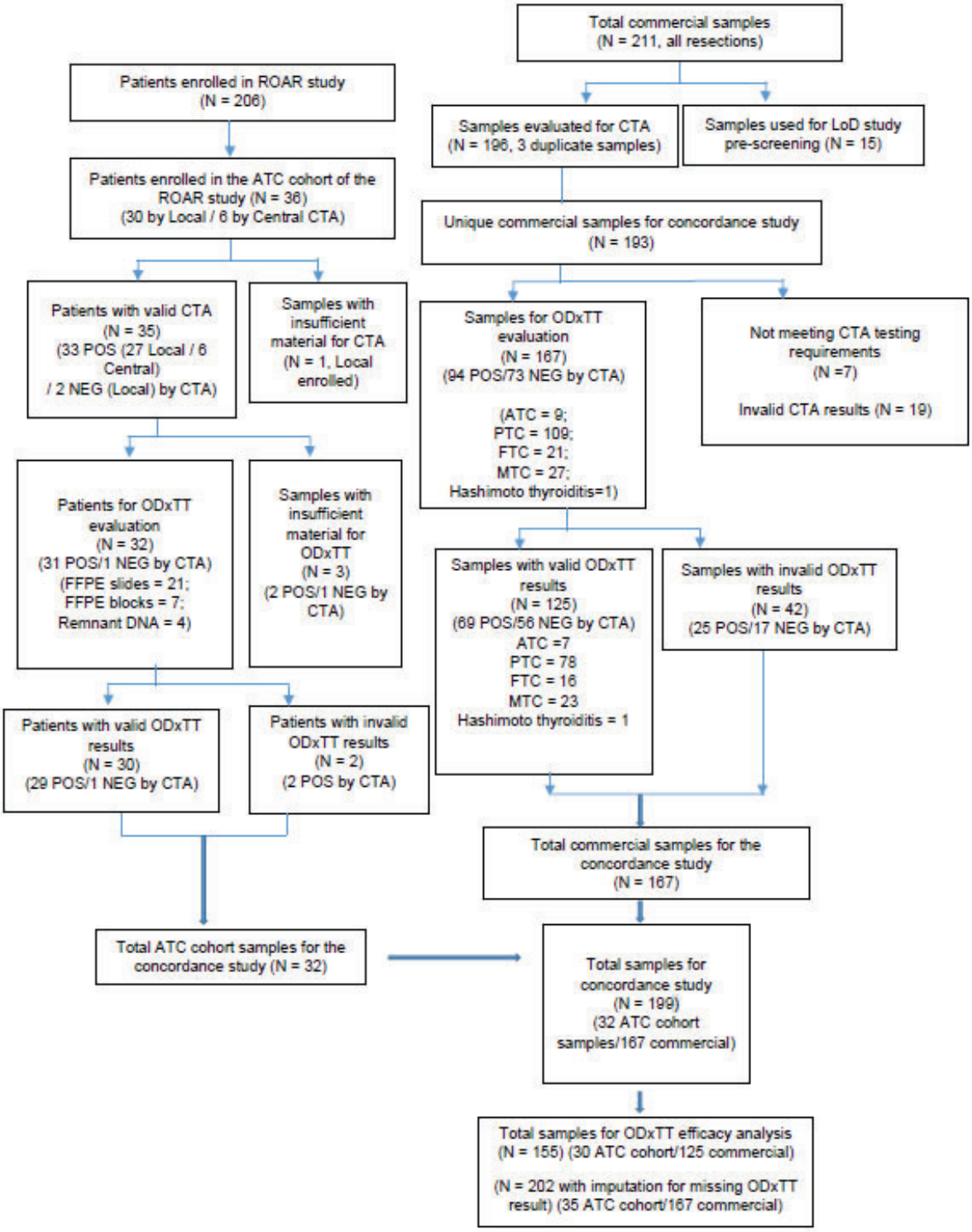
Of the 206 patients enrolled in the Novartis ROAR study, 36 patients with BRAF V600E

positive status were enrolled in the ATC cohort (cohort 1) either by a local laboratory test result (LLT, N = 30) or where a local BRAF test was unavailable, by the CTA (N=6). All 30 patient samples enrolled by a local test result were retrospectively tested with CTA, however, one (1) was deemed to have insufficient material for CTA testing. As a result, 35 samples were available for testing with the ODxT Test [6 samples with central results plus 29 samples with retrospective CTA results yielding 27 positive BRAF V600E results and 2 BRAF negative results (i.e., no mutation detected)]. Of the 35 available ATC samples, 3 samples had insufficient material for ODxT testing, thus 32 samples were tested by the ODxT Test and yielded 29 BRAF V600E positive results, 1 BRAF V600E negative result, and 2 invalid results.

All commercially sourced samples (N = 211) were received as tissue blocks and tested by the CTA and ODxT Test. Among them, 15 samples were used for pre-screening for the LoD study, and 196 samples were used for the concordance study. Of the 196 tissue samples from commercial vendors used for concordance study:

1. Three (3) samples were excluded because they were duplicate blocks from the same patient. In all of these 3 cases, both of the duplicate blocks were tested by CTA before the duplicate issue was noticed. The duplicate block with a higher level of necrosis was selected for the ODxT Test in order to support the interfering substances study. For one set of duplicate blocks, necrosis was equivalent between the blocks and selection was based on the block with higher tumor content.
2. Seven (7) samples did not meet sample eligibility requirements for CTA testing and were excluded from any testing.
3. Nineteen (19) had invalid CTA results and were excluded from the ODxT Test.
4. One hundred sixty-seven (167) had valid CTA results (94 positive/73 negative) and were included in testing by the ODxT Test, resulting in 68 BRAF V600E positive results, 57 BRAF V600E negative results, and 42 invalid results by ODxT.

Figure 2 below shows the sample accountability for the final concordance analysis in detail.



C. Patient Demographics, Disease and Sample Characteristics

The clinical important covariates as well as sample characteristics were compared between the ODxT-evaluable population and the ODxT-unevaluable population in the primary analysis set. Comparison of covariates between the ODxT-evaluable patients and the ODxT-unevaluable patients in ATC patients enrolled in ROAR are reported in **Table 7** and comparison of covariates between the ODxT-evaluable CTA+ patients and the ODxT-unevaluable CTA+ patients in commercially sourced patient samples are reported in **Table 8**.

Table 7. Comparison of baseline and sample characteristics between the ODxT-evaluable patients and the ODxT-unevaluable patients (Primary analysis set, ROAR patients)

Baseline/sample characteristics	ODxT-evaluable patients N=30	ODxT-unevaluable patients N=5	All N=35
Age (years)			
N	30	5	35
Mean (SD)	69.8 (9.86)	69.4 (9.29)	69.7 (9.65)
Median	72.0	71.0	71.0
Q1-Q3	63.0-75.0	65.0-75.0	63.0-75.0
Min-Max	47.0-85.0	56.0-80.0	47.0-85.0
Sex-n (%)			
Female	16 (53.3)	4 (80.0)	20 (57.1)
Male	14 (46.7)	1 (20.0)	15 (42.9)
Race-n (%)			
White	17 (56.7)	1 (20.0)	18 (51.4)
Asian	12 (40.0)	4 (80.0)	16 (45.7)
Missing	1 (3.3)	0	1 (2.9)
ECOG at baseline-n (%)			
0	2 (6.7)	1 (20.0)	3 (8.6)
1	27 (90.0)	3 (60.0)	30 (85.7)
2	1 (3.3)	1 (20.0)	2 (5.7)
Number of prior radiotherapy regimens -n (%)			
0	7 (23.3)	0	7 (20.0)
1	13 (43.3)	5 (100)	18 (51.4)
2	10 (33.3)	0	10 (28.6)
Number of prior systemic therapy regimens -n (%)			
0	10 (33.3)	2 (40.0)	12 (34.3)
1	10 (33.3)	2 (40.0)	12 (34.3)

Baseline/sample characteristics	ODxT-evaluable patients N=30	ODxT-unevaluable patients N=5	All N=35
2	4 (13.3)	0	4 (11.4)
3	4 (13.3)	1 (20.0)	5 (14.3)
>=4	2 (6.7)	0	2 (5.7)
Sample Age			
N	30	2	32
Mean (SD)	44.1 (16.73)	46.0 (27.37)	44.2 (16.92)
Median	40.8	46.0	40.8
Q1-Q3	31.7-60.5	26.6-65.3	31.0-62.0
Min-Max	20.5-75.3	26.6-65.3	20.5-75.3
Tumor Area (%)			
N	29	4	33
Mean (SD)	127.6 (101.17)	10.5 (13.16)	113.4 (102.38)
Median	112.5	5.2	100.0
Q1-Q3	40.0-202.5	2.8-18.2	20.0-180.0
Min-Max	1.2-350.0	1.6-30.0	1.2-350.0
Tumor Content (%)			
N	29	5	34
Mean (SD)	41.9 (19.48)	16.0 (12.94)	38.1 (20.71)
Median	40.0	20.0	35.0
Q1-Q3	25.0-50.0	5.0-25.0	25.0-50.0
Min-Max	20.0-90.0	0.0-30.0	0.0-90.0
Necrosis (%)			
N	29	4	33
Mean (SD)	4.1 (9.26)	15.0 (30.00)	5.5 (13.13)
Median	0.0	0.0	0.0
Q1-Q3	0.0-5.0	0.0-30.0	0.0-5.0
Min-Max	0.0-40.0	0.0-60.0	0.0-60.0

- All percentages calculated using N as denominator.
- SD=standard deviation.

Table 8. Comparison of baseline and sample characteristics between the ODxT-evaluable CTA-positive patients and the ODxT-unevaluable CTA-positive patients (Primary analysis set, commercial samples)

Baseline/sample characteristics	ODxT-evaluable CTA- positive patients N=69	ODxT-unevaluable CTA- positive patients N=25	All N=94
Sex-n (%)			
Female	48 (69.6)	12 (48.0)	60 (63.8)
Male	21 (30.4)	13 (52.0)	34 (36.2)
Sample Age			
N	69	25	94
Mean (SD)	56.4 (30.53)	73.2 (36.51)	60.9 (32.88)
Median	52.4	54.2	53.8
Q1-Q3	27.9-72.5	53.0-100.6	34.5-76.7
Min-Max	15.7-148.7	31.4-148.2	15.7-148.7
Tissue Type (%)			
PTC	67 (97.1)	25 (100)	92 (97.9)
ATC	1 (1.4)	0	1 (1.1)
FTC	1 (1.4)	0	1 (1.1)
Tumor Area (%)			
n	69	25	94
Mean (SD)	123.1 (84.05)	106.8 (72.60)	118.8 (81.10)
Median	100.0	90.0	90.0
Q1-Q3	64.0-160.0	62.5-140.0	62.5-150.0
Min-Max	28.0-448.0	40.0-330.0	28.0-448.0
Tumor Content (%)			
n	69	25	94
Mean (SD)	52.5 (19.28)	41.4 (17.77)	49.6 (19.44)
Median	60.0	30.0	50.0
Q1-Q3	40.0-70.0	30.0-60.0	30.0-65.0
Min-Max	20.0-90.0	20.0-80.0	20.0-90.0
Necrosis (%)			
n	69	25	94
Mean (SD)	0.1 (0.60)	0.0 (0.20)	0.1 (0.52)
Median	0.0	0.0	0.0

Baseline/sample characteristics	ODxT-evaluable CTA- positive patients N=69	ODxT-unevaluable CTA- positive patients N=25	All N=94
Q1-Q3	0.0-0.0	0.0-0.0	0.0-0.0
Min-Max	0.0-5.0	0.0-1.0	0.0-5.0
- All percentages calculated using N as denominator. - SD=standard deviation.			

D. Safety and Effectiveness Results

1. Safety Results

The safety with respect to treatment with TAFINLAR (dabrafenib) in combination with MEKINIST (trametinib) was addressed during the review of the NDA (NDA 202806/S-010 for TAFINLAR dabrafenib capsules and NDA 204114/S-009 for MEKINIST trametinib tablets) and is not addressed in detail in this Summary of Safety and Effectiveness Data. The evaluation of safety was based on the analysis of adverse events (AEs), clinical laboratory evaluations, physical examinations, and vital signs. Please refer to Drugs@FDA for complete safety information on TAFINLAR (dabrafenib) and MEKINIST (trametinib).

No adverse events were reported in connection with the concordance study used to support this PMA supplement, as the study was performed retrospectively using banked samples.

2. Effectiveness Results

The drug efficacy in the ODxT+ population was estimated using samples from ATC patients enrolled in the ROAR study. The endpoints for the efficacy analysis are the confirmed ORR of dabrafenib and trametinib anti-cancer combination therapy by investigator assessment, as well as independent radiology review, where ORR is defined as the percentage of subjects with the best overall response (BOR) of confirmed complete response (CR) or partial response (PR) based on Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.

The Primary analysis set (PAS) includes patients in the full analysis set (FAS) with valid (Positive or Negative) CTA test results (N = 35 from ROAR and N = 167 from commercial samples).

First, descriptive summaries of BOR, as well as the ORR along with the corresponding 95% exact confidence interval were provided within (CTA+, ODxT+) and CTA+ patients based on investigator assessment and independent radiology review in **9** and **10** respectively. The ORR is 65.5% (45.7%, 82.1%) in (CTA+, ODxT+) patients and 60.6%

(42.1%, 77.7%) in CTA+ patients based on investigator assessment, and 58.6% (38.9%, 76.5%) in (CTA+, ODxT+) patients and 57.6% (39.2%, 74.5%) in CTA+ patients based on independent radiology review.

Table 9. Best overall response based on investigator assessment in (CTA+, ODxT+) and CTA+ subjects (Primary analysis set)

	(CTA+, ODxT+) (N = 29)	**CTA+ (N = 33)**
Best overall response		
Complete response (CR)	3 (10.3)	3 (9.1)
Partial response (PR)	16 (55.2)	17 (51.5)
Stable disease (SD)	7 (24.1)	8 (24.2)
Progressive disease (PD)	2 (6.9)	4 (12.1)
Not evaluable (NE)	1 (3.4)	1 (3.0)
Response rate		
CR+PR	19 (65.5)	20 (60.6)
95% Confidence Interval (1)	(45.7, 82.1)	(42.1, 77.1)
(1) Two-sided 95% confidence interval based on Clopper-Pearson exact method.		

Table 10. Best overall response based on independent radiology review in (CTA+, ODxT+) and CTA+ subjects (Primary analysis set)

	(CTA+, ODxT+) (N = 29)	**CTA+ (N = 33)**
Best overall response		
Complete response (CR)	2 (6.9)	2 (6.1)
Partial response (PR)	15 (51.7)	17 (51.5)
Stable disease (SD)	6 (20.7)	6 (18.2)
Progressive disease (PD)	5 (17.2)	7 (21.2)
Not evaluable (NE)	1 (3.4)	1 (3.0)
Response rate		
CR+PR	17 (58.6)	19 (57.6)
95% Confidence Interval (1)	(38.9, 76.5)	(39.2,74.5)
(1) Two-sided 95% confidence interval based on Clopper-Pearson exact method.		

To address the potential bias of bridging CTA and ODxT Test due to the pre-screening with the LLT, an additional concordance analysis was conducted to evaluate the concordance between LLT and CTA using the samples from locally enrolled ATC patients (N = 30) as well as a set of commercially sourced LLT negative samples (N = 58). **Table 11** shows the disposition of the subjects used in this additional concordance analysis and **Table 12** shows the overall concordance between LLT and CTA. One (1) of

the 30 LLT-positive samples and 4 of the 58 LLT-negative samples were not analyzed with CTA due to insufficient testing materials. Twenty-nine (29) of the 30 LLT-positive patients were tested by CTA, yielding 27 CTA-positive results and 2 CTA-negative results. Fifty-four (54) of the 58 LLT-negative samples were tested by CTA, yielding 47 CTA-negative and 7 CTA invalid.

Table 11. Disposition of the subjects (Supplemental concordance set)

	All Subjects	# of Tested by CTA Test	# of Valid CTA Test (%)	# of Invalid CTA Test (%)
Subjects in the Concordance Study	88	83	76 (91.6%)	7 (8.4%)
ROAR	30	29	29 (100%)	0 (0%)
LLT Positive	30	29	29 (100%)	0 (0%)
Commercial	58	54	47 (87%)	7 (13%)
LLT Negative	58	54	47 (87%)	7 (13%)
Invalid means the sample was tested but didn't return a positive/negative result.				

Table 12. Contingency table between LLT and CTA (Supplemental concordance set)

BRAF V600E Mutation CTA Test	LLT		
	Positive	Negative	Total
Positive	27	0	27
Negative	2	47	49
Invalid	0	7	7
Total	29	54	83
- Invalid means the sample was tested by CTA Test but didn't return a positive/negative result.			

PPA, NPA, and OPA between the LLT and the CTA, with and without invalid CTA results, were calculated using the LLT results as reference (**Table 13**). The point estimates of PPA, NPA and OPA were 93.1%, 100% and 97.4% respectively, when excluding CTA invalid results. The results demonstrate the high concordance between LLT, and CTA and we expect the number of patients with (LLT-, CTA+) is very small, therefore the impact of the prescreening by LLT for BRAFV600E mutation detection is negligible.

Table 13. Agreement between LLT and CTA (Supplemental concordance set)

	Without Invalid CTA Test		With Invalid* CTA Test	
Measure of Agreement	**Percent Agreement (N)**	**95% CI (1)**	**Percent Agreement (N)**	**95% CI (1)**
PPA	93.1% (27 /29)	(78.0%,98.1%)	93.1% (27 /29)	(78.0%,98.1%)
NPA	100% (47 /47)	(92.4%, 100%)	87.0% (47 /54)	(75.6%,93.6%)
OPA	97.4% (74 /76)	(90.9%,99.3%)	89.2% (74 /83)	(80.7%,94.2%)
(1) The 95% CI calculated using the Wilson Score method. *Invalid means the sample was tested by CTA Test but didn't return a positive/negative result.				

The clinical efficacy analysis in the ODxT Test-positive population included both the complete case analysis and the sensitivity analysis. The complete case analysis estimated the clinical efficacy in patients with the observed ODxT Test-positive results without considering those patients with the missing ODxT Test results, while the sensitivity analysis evaluated the robustness of the clinical efficacy estimate against the missing ODxT Test results. Patients with missing ODxT Test results (ODxT-unevaluable set) included 1) patients whose samples were not tested by the ODxT test; 2) patients whose samples were tested by the ODxT Test but did not yield valid ODxT result.

Complete Case Analysis

As shown in **Table 14** and **Table 15** below, when excluding invalid ODxT Test results, all 57 samples with negative CTA test results yielded negative ODxT Test results, therefore a 100% NPA. As a result, the positive predictive value (PPV, Pr(CTA+|ODxT+)) was estimated as 100%. The ORR in the ODxT+ population was then estimated as the ORR in the (ODxT+, CTA+), which is 65.5% (45.7%, 82.1%) based on investigator assessment (Table 9), and 58.6% (38.9%, 76.5%) based on independent radiology review (Table 10).

Table 14. Contingency table of test results for concordance study

BRAF V600E mutation ODxT Test (CDx)	**CTA (Comparative method)**		
	Positive	**Negative**	**Total**
Positive	97	0	97
Negative	1	57	58
Invalid	27	17	44
Total	125	74	199
- Invalid means the sample was tested by ODxT Test but did not return a Positive/negative result. - Samples not tested/missing by ODxT Test and/or CTA were excluded from this analysis. - Samples with invalid CTA results were excluded.			

Table 15. Agreement of test results for concordance study

	Without invalid ODxT Test (CDx) results		With invalid ODxT Test (CDx) results	
Measure of Agreement	**Percent Agreement (N)**	**95% CI (1)**	**Percent Agreement (N)**	**95% CI (1)**
PPA	99.0% (97/98)	(94.4%, 99.8%)	77.6% (97/125)	(69.5%, 84.0%)
NPA	100% (57/57)	(93.7%, 100%)	77.0% (57/74)	(66.3%, 85.1%)
OPA	99.4% (154/155)	(96.4%, 99.9%)	77.4% (154/199)	(71.1%, 82.6%)

(1) The 95% CI calculated using the Wilson Score method.
- Invalid means the sample was tested by ODxT Test but did not return a positive/negative result.
- Samples not tested/missing by ODxT Test and/or CTA were excluded from this analysis.
- Samples with invalid CTA results were excluded.

Sensitivity Analysis

To evaluate the robustness of the clinical efficacy, estimate against the missing ODxT Test results including 27 CTA-positives tested by ODxT with invalid results and 17 CTA-negatives tested by ODxT with invalid results (See Table 14), the sensitivity analysis employed the multiple imputation method using fully conditional specification method to impute the missing ODxT Test results.

In the sensitivity analysis for the efficacy in the ODxT-positive population based on investigator assessment and independent radiology review, the ORR estimates ranged from 58.6% to 61.9% for investigator assessment, and 54.8% to 57.9% for independent radiology review (data not shown). For comparison, the ORR (95% CI) in the (CTA+) patients enrolled in ATC cohort of the ROAR trial were 60.6% (42.1%, 77.7%) based on investigator assessment, and 57.6% (39.2%, 74.5%) based on independent radiology review.

3. Pediatric Extrapolation

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

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included two investigators of which none were full-time or part-time employee of the sponsor, and none

had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: [0]
- Significant payment of other sorts: [0]
- Proprietary interest in the product tested held by the investigator: [0]
- Significant equity interest held by investigator in sponsor of covered study:[0]

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

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

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

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

For the intended use to identify the BRAF V600E mutations in ATC patients to be treated with TAFINLAR (dabrafenib) in combination with MEKINIST (trametinib) the effectiveness of the ODxT Test was demonstrated through a clinical bridging / concordance study using specimens from patients enrolled in the ROAR study and commercially sourced samples. The data from the analytical validation and clinical studies support the reasonable assurance of safety and effectiveness of the ODxT Test when used in accordance with the indications for use. Data from the ROAR study show that patients who had qualifying BRAF V600E mutations received benefit from treatment with TAFINLAR (dabrafenib) in combination with MEKINIST (trametinib), and support the addition of the CDx indication to the ODxT Test.

B. Safety Conclusions

The risks of the device are based on data collected in the analytical studies conducted to support sPMA approval as described above. The ODxT Test is an *in vitro* diagnostic test, which involves testing of DNA and RNA extracted from FFPE tumor tissue.

Failure of the device to perform as expected or failure to correctly interpret test results may lead to incorrect test results, and subsequently, inappropriate patient management decisions in cancer treatment. Patients with false positive results may undergo treatment with one of the therapies listed in **Table 1** of the intended use statement without clinical benefit and may

experience adverse reactions associated with the therapy. Patients with false negative results may not be considered for treatment with the indicated therapy. There is also a risk of delayed results, which may lead to delay of treatment with the indicated therapy.

C. Benefit-Risk Determination

Given the available clinical and analytical data provided in the submission, the data supports the conclusion that the ODxT test has probable benefit in selecting patients with the BRAF V600E mutations, for treatment with dabrafenib and trametinib in patients with anaplastic thyroid cancer (ATC). Treatment with TAFINLAR® (dabrafenib) in combination with MEKINIST® (trametinib) provides a meaningful clinical benefit to ATC patients with the BRAF V600E mutations, as demonstrated in the ROAR trial, especially considering the nature of this disease.

The clinical benefit of the Oncomine™ Dx Target Test for the selection of ATC patients with a BRAF V600E mutation was demonstrated in the retrospective analyses of efficacy and safety data obtained from a Phase II, open-label, non-randomized, multi-center study of dabrafenib in combination with oral trametinib in subjects with rare cancers with the BRAF V600E mutation. The ORR along with the corresponding 95% exact confidence interval were provided within (CTA+, ODxT+) and CTA+ patients based on investigator assessment and independent radiology review. The NPA of the ODxT+ test, conditional on the CTA was 100%, resulting in a PPV of 100%; thus, the efficacy of the ODxT+ test was equivalent to the efficacy in the double positive CTA+, ODxT+ group. The ORR was 65.5% (45.7%, 82.1%) in (CTA+, ODxT+) and 58.6% (38.9%, 76.5%) in (CTA+, ODxT+) in patients based on independent radiology review. Thus, the efficacy observed in the clinical trial was maintained with the use of the ODxT+ test. A clinical concordance study between the ODxT Test and the CTA Test was conducted demonstrating the concordance (agreement) between the CTA and ODxT Test for the detection of BRAF V600E mutations in thyroid cancer tissue and has probable benefit in selecting ATC patients for treatment with TAFINLAR® (dabrafenib) in combination with MEKINIST® (trametinib).

There is a potential risk associated with the use of this device, mainly due to 1) false positives, false negatives, and failure to provide a result and 2) incorrect interpretation of test results by the user.

Failure of the device to perform as expected or failure to correctly interpret test results may lead to incorrect test results, and subsequently, inappropriate patient management decisions in treatment. Patients who are determined to be false positive by the test may be exposed to a drug that is not beneficial and may lead to adverse events or may have delayed access to other treatments that could be more beneficial. A false negative result may prevent a patient from accessing a potentially beneficial therapeutic regimen. The risks of erroneous results are partially mitigated by the analytical performance of the device.

The likelihood of false results was assessed by an analytical and clinical validation studies, which partially mitigate the probable risk of the ODxT Test device. Additional factors, including the clinical and analytical performance of the device included in this submission, have been taken into account and demonstrated that the assay is expected to have acceptable performance.

Patient Perspectives

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

In conclusion, given the available information above, the data support that for the indications of the ODxT Test device the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Data from the clinical study support the performance of the ODxT Test as an aid in selecting patients with the BRAF V600E mutations, for treatment with TAFINLAR® (dabrafenib) in combination with MEKINIST® (trametinib) in patients with ATC.

XIII. CDRH DECISION

CDRH issued an approval order for the PMA (P160045/S025) on 09/29/2023.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.