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 Procode:	PQP
Applicant's Name and Address:	Life Technologies Corporation 5781 Van Allen Way Carlsbad, CA 92008
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P160045/S019
Date of FDA Notice of Approval:	September 4, 2020

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). The SSED to support the indication is available on the CDRH website and is incorporated by reference here.

The current supplement was submitted to expand the indications for use of the ODxT Test to include a companion diagnostic indication for the identification of RET fusions in NSCLC patients who may benefit from the targeted drug therapy, GAVRETO™ (pralsetinib). This supplement also included data supporting an optimized RNA workflow for the detection of RET and ROS1 fusions by the ODxT Test.

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) and deletions in 23 genes from DNA and fusions in ROS1 and in RET from RNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor samples from patients with non-small cell lung cancer (NSCLC) using the Ion PGM™ Dx System.

The test is indicated to aid in selecting NSCLC 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

Gene	Variant Status	Tissue Type	Targeted therapies
BRAF	BRAF V600E	NSCLC	TAFINLAR® (dabrafenib) in combination with MEKINIST® (trametinib)
EGFR	L858R, Exon 19 deletions	NSCLC	IRESSA® (gefitinib)
ROS1	ROS1 fusions	NSCLC	XALKORI® (crizotinib)
RET	RET fusions	NSCLC	GAVRETO™ (pralsetinib)

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

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	Nucleotide Change
KRAS	COSM512	c.34_35delGGinsTT
KRAS	COSM516	c.34G>T
MET	COSM707	c.3029C>T
PIK3CA	COSM754	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 Torrent PGM Dx System and the Ion Torrent PGM Dx Reagents for detection of alterations in DNA and RNA isolated from NSCLCNSCLC formalin-fixed, paraffin-embedded (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 Torrent™ 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 Torrent™ 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 Side Dx 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 and ADF on a USB Memory Device:

- 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 inactive 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 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 cDNA synthesis and library preparation.

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 M-MLV reverse transcriptase (Superscript III RT), an RNase inhibitor, a proprietary helper protein, and a buffer containing random primers, dNTPs, and MgCl2.

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 the detection of RNA fusions, the current device has optimization of the RNA workflow and has 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 (SNV) 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 ADF. The latest software version includes updates to enhance the user interface, ADF, security, and analysis pipeline. Further software updates will be performed post-market (see Section XIII).

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 and Variant	Therapy	Company and Device (PMA #)
BRAF V600E	TAFINLAR® (dabrafenib) in combination with MEKINIST® (trametinib)	Foundation Medicine, Inc. – FoundationOne CDx™ (F1CDx) (P170019)
EGFR L858R and Exon 19 deletions	IRESSA® (gefitinib)	QIAGEN – *therascreen*® EGFR RGQ PCR Kit (P120022/S001) Foundation Medicine, Inc. – F1CDx (P170019) Roche – **cobas**® EGFR Mutation Test v2 (P120019/S019)

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, Poland), Japan, Korea, and Israel. 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 treatment.
- 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.

IX. SUMMARY OF NONCLINICAL STUDIES

The RNA workflow was modified from the original approval of the ODxT Test in order to optimize the performance for the detection of RNA fusions. This RNA workflow modification necessitated the revalidation of the ability of the ODxT Test to detect ROS1. Analytical validation studies demonstrating the performance of the ODxT Test to detect RET and ROS1 fusions using the modified RNA workflow are included below.

A. Laboratory Studies

The evidence in support of the performance of the ODxT Test in detecting RET and ROS1 fusions was from the data presented using intended use specimens and sample blends across all validation studies. Studies evaluating analytical accuracy/concordance, precision studies at the limit of detection (LoD), limit of blank (LoB), tissue input, tissue content, interferents, and stability were conducted to support the indication for RET and ROS1 fusions.

1. **Analytical Accuracy/Concordance**

   Concordance of the ODxT Test for the ability to detect SNVs and deletions was previously established using two externally validated comparator methods (See Secion IX.A.1. in the Summary of Safety and Effectiveness for P160045).

   An analytical accuracy study was performed to demonsrate the concordance between the ODxT Test and an externally validated NGS assay (evNGS) for the detection of RET fusions in NSCLC using 168 NSCLC FFPE specimens. This study evaluated 66 NSCLC FFPE specimens positive for RET fusions from NSCLC patients enrolled in the ARROW clinical trial (please see Section X.A. for study details). RET negative samples consisted of 102 stage-matched commercially sourced NSCLC samples, which were screened with either a local laboratory-validated RET FISH assay, or an NGS-based screening assay.

   The analytical accuracy of the ODxT Test to detect ROS1 fusions (using the modified workflow) was demonstrated using an externally validated FISH assay (evFISH) for the detection of ROS1 fusions in NSCLC using 70 NSCLC FFPE specimens (9 positive and 62 negative for ROS1 fusions).

   Samples were selected by the ODxT Test and then tested by evNGS or evFISH for RET and ROS1 fusions, respectively. A summary of positive percent agreement (PPA) and negative percent agreement (NPA) in reference to an externally validated NGS assay and corresponding 95% two-sided exact confidence intervals (CIs) is provided in Table 4, below. The RNA input requirements of the evNGS assay are higher than the ODxT Test, which resulted in several potential false negative calls by the evNGS assay (possibly due to insufficient amounts of RNA starting material), which ultimately lead to a lower NPA. See Section IX.A.1 of Summary of Safety and Effectiveness Data for P160045 for additional analytical accuracy data.

Table 4: Concordance summary for samples with RNA fusions.

Variant	ODxT+/ evNGS+ or evFISH+	ODxT-/ evNGS+ or evFISH+	ODxT+/ evNGS- or evFISH-	ODxT-/ evNGS- or evFISH-	PPA (95%CI)	NPA (95%CI)
ROS1 Fusions	9	0	0	62	100% (66.4, 100.0)	100% (94.2, 100.0)
RET Fusions	40	4	9	101	90.9% (78.3, 97.5)	91.8% (85.0, 96.2)

2. Analytical Sensitivity

a. Limit of Blank (LoB)

To assess the performance of the ODxT Test in the absence of template and to ensure that a variant-free ("blank") sample does not generate an analytical signal that might be classified as an RNA fusion, 3 FFPE clinical samples known to be negative for RNA fusions (wild-type) were evaluated. The samples were tested using two different lots of the ODxT Test. Each clinical sample was prepared into 24 independent RNA libraries for a total of 144 replicates. There were no positive calls at any of the variant locations analyzed by the test. The false positive rate was therefore 0%, and the limit of blank (LoB) of the test is zero. See Section IX.A.2 of Summary of Safety and Effectiveness Data for P160045 for additional analytical sensitivity data.

b. Limit of Detection (LoD)

The limit of detection (LoD) based on positive calls for the ODxT Test to detect select RNA fusions was estimated to determine the lowest number of RNA fusion reads, at which 95% of the test replicates produced correct calls. The LoD studies evaluated 2 ROS1 and 2 RET fusion positive specimens. At least 6 titration levels were tested and each level was tested with 10 replicates per sample for each of the two reagent lots for a total of 20 replicates per level.

The claimed LoD for the RNA fusions used in this study are noted in Table 5 below. LoDs were confirmed for ROS1 fusions by testing NSCLC samples near the established LoD and for both ROS1 and RET fusions at ~2-3x LoD in the Precision Study (See Section IX.A.4). A post-market precision study near LoD will be performed to confirm the LoD for RET fusions. (see Section XIII).

Table 5: Estimated LoD for clinically RNA fusions.

Gene	LoD* (Total Fusion Reads)
ROS1	516
RET	405

*These values represent the highest LoDs calculated across fusion samples for each gene tested

See Section IX.A.2 of Summary of Safety and Effectiveness Data for P160045 for additional analytical sensitivity data.

c. Tissue Input

This study was performed to validate the use of core needle biopsy (CNB) samples and fine needle aspirate (FNA) samples on the ODxT Test. To validate the use of CNBs, 13 resection samples collected by CNB were used, of which 13/13 passed DNA sample library quality metrics and 11/13 passed RNA sample library quality metrics. To validate FNAs, 12 resection samples collected by FNA were used, which all passed DNA and RNA sample library quality metrics.

See Section IX.A.2.d. of Summary of Safety and Effectiveness Data for P160045 for additional tissue input data.

d. Tumor Content

The minimum tumor content was evaluated for the optimized RNA workflow using the samples included in the clinical validation study. The samples were analyzed using the updated ODxT Test library preparation workflow. The tumor cell content of each specimen and region of interest was estimated before the study by an external pathology lab. The samples generating valid sample results were analyzed with and without macro-dissection. The tumor content distribution for ROS1 confirmed positive and negative samples tested spanned a range of 20%-90%. A total of 9 ROS1 positive and 61 ROS1 negative samples were included in the study analysis. The relationship between a positive variant call (ODxT Test ROS1-positive) and tumor content was observed. Based on an analysis of the results, the corresponding 95% Clopper Pearson Exact CIs of the PPA, NPA, and OPA overlapped between tumor content levels, demonstrating that the fusion detection performance of the ODxT Test was similar at all ranges of tumor content levels; and the tumor content levels of the clinical samples had no impact in fusion detection performance of the ODxT Test.

3. Interference

To evaluate the potential impact of endogenous (necrotic tissue and hemoglobin) and exogenous interferents (paraffin, xylene, ethanol, proteinase K, and wash buffer),this study evaluated clinical FFPE samples in 6 replicates for RNA for every combination of sample and condition taken through the entire test workflow. The impact of potentially interfering substances on assay performance was evaluated, and the results were compared to the control (no interferents) condition. See Section IX.A.4. of Summary of Safety and Effectiveness Data for P160045 for additional interference studies.

a. Endogenous Interference

A review of clinical samples harboring variants detected by the ODxT Test, including ROS1 in the presence of varying levels of tissue necrosis. Hemoglobin was evaluated at 4 mg/mL. The concordance with the control condition (with no calls being excluded) across all samples, for all CDx

RNA fusions tested were calculated to be 100%. The data demonstrate that hemoglobin does not adversely impact the performance of the assay.

b. Exogenous Interference

For the study with exogenous interferents, the concordance with the control condition across all samples and interferents, for all CDx RNA fusions tested were calculated to be 100%. The data support that these interfering substances can be tolerated by the assay at the levels tested.

4. Precision and Reproducibility

a. External Panel Reproducibility Study (Assay Reproducibility)

An external reproducibility study was conducted across 3 sites with 2 operators per site, 3 lots of the ODxTT Controls, NTC Kits, IVD Ion PGM Dx Library Kits, OneTouch Dx Template Kits, Ion PGM Dx Sequencing Kits and Dx Chip Kits used at each site using samples that included RET fusions. All samples and replicates generated a PPA of 100% (90.3%, 100%) and a NPA of 100% (81.5%, 100%), with the exception of two replicates of one RET fusion positive sample, which generated a false negative result across 2 runs, yielding a PPA of 94.4% (81.3%, 99.3%). An investigation into the false negative result determined that operator error resulted in the wrong barcode being added to the RNA libraries during the workflow. As mentioned above, an additional single-site reproducibility study will be performed post-market to confirm the LoD of RET fusions using samples near 1X LoD (see Section XIII).

For the determination of reproducibility for detecting ROS1 fusions, 2 ROS1 fusion positive samples were used, each representing different fusions and 2 wild type samples. Each ROS1 fusion positive sample was tested at two levels, near the estimated LoD and approximately 2X LoD. An additional reproducibility study was performed using 2 RET fusion positive samples and 2 RET fusion blended samples at ~2-3X LoD.

Zero invalids (No Calls) were observed for all samples containing ROS1 RNA fusions at both 1X and 2X LoD tested. Similarly, no invalid calls were observed for all RET fusion positive samples at ~2-3X LoD.

For the ROS1 samples used to determine the reproducibility for detecting ROS1 fusions, all samples and replicates generated a PPA of 100% (90.3%, 100%) and a NPA of 100% (81.5%, 100%) with the exception of one replicate of one WT sample, which generated a false positive result across 2 runs, yielding a NPA of 94.4% (81.3%, 99.3%). An investigation into the false positive result determined that the single replicate was contaminated with the positive RNA control during the generation of the library, prior to barcode ligation.

b. Precision

Precision for the RNA fusion variants was estimated with respect to positive variant locations for within-run, between-system, between-operator, between-site, between-lot and total variability. When including or excluding No Calls from the assay reproducibility study data, the within-run repeatability was 100%, with the exception of one RET fusion positive sample, which had a within run repeatability of 98.1%, with a lower limit of the corresponding 95% CI of ≥ 81.5%, at each of the RNA fusion variant locations.

5. Guard Band Studies

Due to the modifications to the RNA workflow, a subset of the original workflow tolerance studies were repeated. The repeated studies consisted of 8 of the original 20 studies conducted for P160045 based on a risk analysis for the critical assay steps of the workflow from target amplification to library elution using samples to impact assay performance, which included variations in DNA/RNA panel volume, polymerase volume, FuPa reagent volume, barcode switch solution volume, barcode adapter volume, residual ethanol, elution time, and thermal cycling temperature offset). The study was conducted as previously described in Section IX,A.9.a. of the P160045 SSED. To evaluate the workflow tolerances, a RNA blend containing 2 fusions were used as the input material. As a result of these improvements made to the RNA workflow, a new RNA Control dilution strategy was also implemented into the new workflow, in which the RNA fusions in the RNA Control are added to the assay within a range of 1-2x the fusion LoD.

No significant differences between the high and low conditions, relative to the standard operating procedure (SOP), were observed for the new RNA workflow except for the high condition (3 µL) for the Target Amplification RNA Panel Volume for ROS1 [Log(ROS1 fusion reads/total mapped reads)]; however, exhibited a statistically significant difference between SOP (2µL) and 3µL "high" condition (p=0.0356). Although high test conditions showed statistically significant differences from SOP, the level of impact on overall test performance did not alter performance because the high condition also had the highest mean ROS1 fusion reads relative to the number of reads observed under the SOP conditions.

6. Stability Studies

The re-establishing of the shelf-life, in-use, extracted RNA, stored FFPE block, and stored FFPE slide stability of the ODxT Test was required due to the modification of reagents as part of the revision of the RNA workflow.

An in-use stability study was conducted to determine the in-use stability of the ODxT Test and Controls, when used in conjunction with the Ion Torrent Dx FFPE Sample Preparation Kit, the Ion PGM Library Kit, the Ion OneTouch Dx Template Kit, and the Ion PGM Dx Sequencing Kit. Clinical samples carrying

CDx variants, including SNVs, deletions, and RNA fusions were tested with 3 commercial lots of reagents. Samples were tested in duplicate starting from extraction to support the in-use stability of 5 months.

The stability of FFPE cut slides and FFPE blocks used in the clinical study showed a minimum stability of 5 months. Additional stability studies to demonstrate shelf-life, in-use, extracted RNA, stored FFPE block, and stored FFPE slide stability will be completed as conditions of approval (see Section XIII).

7. Kit Lot Interchangeability

A kit lot interchangeability study was conducted as a condition of the original PMA approval and was performed to determine that the performance of the ODxT Test is not affected by the interchanging different kit components of the assay and test system. The study utilized 3 separately manufactured lots each of the Ion PGM Dx System Kit sets, ODxT Test DNA and RNA Panel, and the ODxT Test DNA and RNA Control kits and RNA Control Diluent for a total of 12 combinations.

In order to demonstrate the performance that the interchanging of kit lots does not affect test performance, the sample panel included two blended samples consisting of a DNA blended sample which was comprised of a simple SNV (EGFR L858R), a complex SNV (KRAS G12C), and a deletion (EGFR E746_A750del). In the evaluation of the new optimized RNA workflow and that the performance for the detection of ROS1 fusions, the DNA blended sample served as a Wild Type (WT) sample. The RNA sample blend contained a ROS1 fusion targets. Each of the 12 sequencing runs included 6 replicates of each sample blend for a total of 144 sample sequencing reactions (excluding controls).

Each sample was called correctly in each run with no invalid or no call results for each of the fusions. The overall %CV were 11-12% and the variance component analysis of % allelic frequency of the DNA variants indicated that the %CV's (variations) of the reagent lots (control lot, panel lot and the system lot) observed ranged from 0% to 3%. The overall %CV of log transformed (FusionReads) was 10% for the ROS1 variant. The %CVs of the reagent lots (control lot, panel lot and the system lot) ranged from 2 to 6%. The variation observed between kit lots was minimal and based on the study data, the interchanging of kit lots does not affect the performance of the assay.

B. Animal Studies

Not Applicable

C. Additional Studies

1. **Detection of Fusion Variants using In Vitro Transcripts with Optimized Workflow**

   A study was performed to verify detection of the RNA fusions by the ODxT Test with the optimized workflow. In this study multiple RNA test blends with different numbers of in vitro transcripts (IVTs) RNA fusions were created in combination with WT cellular RNA and one sample with WT cellular RNA alone. While the ODxT Test does not report the individual fusion isoforms, the performance of each isoform was evaluated. The average fusion reads were established for each fusion isoform for the previously approved workflow (SOP) conditions and the optimized workflow. Fold changes were calculated based on the optimized workflow vs. the SOP workflow and a fold change of 1 indicated no change in performance while a fold change greater than 1 or less than 1 would indicate a higher number of fusion reads or lower number of fusion reads, respectively.

   Based on the study results, 100% of the ROS1 fusions interrogated were detected using the IVT samples with 68.6% of the IVTs showed an increase in fusion reads with the optimized workflow conditions and 31.4% of the IVTs tested showed a decrease in the number of fusion reads with the optimized workflow conditions.

   For ROS1, the observed fold changes between the previously approved workflow to the optimized workflow ranged from 0.4 to 7.3 for ROS1. For ROS1 fusions, 11 of the 35 ROS1 fusion isoforms showed a fold change less than 1.

2. **Fine Needle Aspirate Sample Validation:**

   A study was performed to demonstrate the optimal input amount for NSCLC FNA samples. In this study, conducted in two parts, sample input were evaluated based on the number of slides tested for each sample. The results from the first study were used to inform the number of slides tested in the second part of the study.

   The second part of the study was performed to assess FNA and core needle biopsy (CNB) sample sequencing performance and DNA and RNA library sample success rates using the ODxT Test (when minimum concentration specifications for both DNA and RNA were met). In addition to the number of slides, the characteristics of each sample (i.e., block age, tumor cell content, section surface area, and total tumor section surface area) and evaluated in terms of the final DNA and RNA concentration from each sample.

   Based on the results of this study, a minimum of 7 x 5 µm FNA slides with a total section surface area of 66 mm^2, or a total tumor section surface area of 24 mm^2 is recommended.

3. **<u>Verification of Modified Workflow (ROS1)</u>**

   a. **Study Design**

A concordance study was conducted to determine concordance between the original and modified ODxT Test workflows and the ROS1 FISH Assay (ROS1 FISH) using retrospectively collected procured clinical samples the safety and effectiveness of the ODxT Test was not negatively effected for the detection of ROS1 fusions due to the modifications made to the ODxT Test RNA workflow. Prior to testing by the ODxT Test or the comparator ROS1 FISH, the study samples were pre-screened by external vendors to enrich for positive specimens. The pre-screen failure rate of the pre-screen tests used by the external vendors is unknown.

b. Inclusion and Exclusion Criteria:

FFPE clinical tissue specimens previously identified as positive or negative for the presence of ROS1 fusions and were procured from external sources

c. Follow-up Schedule:

As the concordance study was conducted retrospectively to establish safety and effectiveness for selecting patients using the ODxT Test, there was no follow-up conducted.

d. Endpoints:

The primary endpoint of this concordance study was the establishment of PPA and NPA between the FDA approved ODxT Test and the modified ODxT Test RNA workflow.

1. <u>Accountability of Study Cohort</u>

One hundred sixty-nine (169) patient samples were available for this study. Of these, 42 were procured from external vendors as ROS1 fusion-positive (ROS1+), and 127 were identified as ROS1 fusion-negative [ROS1(-)]. ROS1 fusion status of each sample was confirmed, prior to inclusion in the study.

Of the 42 ROS1+ samples, 3 were cancelled due to failed pathology review or failure to meet the RNA concentration cutoff. This resulted in 39 ROS1+ samples eligible for NGS testing. Of the remaining 39 samples expected to be ROS1+, 19 were ROS1(-), 6 were invalid by ODxT Test due to RNA library failures, and 14 ROS1+ samples were called by the optimized ODxT Test workflow.

Of the 127 ROS1(-) samples tested that were initially identified as ROS1(-), 8 were invalid due to below-threshold total RNA mapped reads and 119 were confirmed ROS1(-) samples by ODxT Test.

<u>Validated ROS1 FISH Assay Testing</u>

One hundred and forty-six (146) samples were eligible to be tested by the ROS1 FISH. Of these, 71 tested ROS1(-), 65 were invalid due to lack of reliable hybridization after two attempts, and 10 were ROS1+. Two (2) ROS1(-) results and 5 invalid results were cancelled due to inclusion in another study. Overall, 68 ROS1(-) results, 60 invalid results, and 10 ROS1+ results were available for analyses.

Original ODxT Test RNA Workflow Testing

Following testing by the ODxT Test optimized workflow and ROS1 FISH, 29 expected ROS1+ samples (after excluding samples that failed ODxT Test optimized workflow and/or ROS1 FISH) and 102 ROS1(-) samples remained for testing by the original workflow. Of these 29 samples, 13 were ROS1(-), 11 were valid ROS1+, and 5 were invalid by the original ODxT Test workflow. Of the 102 samples ROS1(-) samples available for testing, 27 yielded invalid results due to failed RNA libraries and 75 were ROS1(-) by the original ODxT Test workflow. Overall, testing by the original ODxT Test workflow yielded 11 ROS1+, 88 ROS1(-), and 32 invalid results.

2. Study Population Demographics and Baseline Parameters:

Of the 50 ROS1+ patients enrolled in the clinical study which supported the original approval of the ROS1 indication for XALKORI, only 19 specimens had sufficient tissue for testing, of those only 11 were evaluable by the ODxT Test, compared to 10 patient samples tested by the ODxT Test in the present study. While the patient breakdowns are comparable with respect to sex, age, and race, smoking status is difficult to compare due to the lack of data for the patient samples acquired (Unknown = 34.9%). Though there is some variability between the histological subtype between the XALKORI patient samples (96% adenocarcinoma) and those acquired for this study (63.3% adenocarcinoma), the differences should be interpreted with caution due to the study sample size limitations (Table 6).

Table 6: Patient demographics and disease characteristics between ODxT test evaluable and unevaluable set for CTA+ patients.

	A8081001 Original Approval						Current Study	
	All Patients N=50		ODxT Test non-evaluable N=39		ODxT Test evaluable N=11		ODxT Test evaluable N=166	
Sex	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Male	22	44.0	15	38.5	7	63.6	77	46.4
Female	28	56.0	24	61.5	4	36.4	84	50.6
Unknown							5	3.0
Age	**median**	**range**	**median**	**range**	**median**	**range**	**median**	**range**
	53	25-77	54	25-77	52	35-77	52	26-77

Race	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Asian	21	42.0	16	41.0	5	45.5	70	42.2
Other	29	58.0	23	59.0	6	54.5	68	41.0
Unknown							28	16.9
Smoking Status	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Ex-Smoker	11	22.0	10	25.6	1	9.1	9	5.4
Smoker							17	10.2
Never Smoked	39	78.0	29	74.4	10	90.9	82	49.4
Unknown							58	34.9
Histological subtype	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Adenocarcinoma	48	96.0	38	97.4	10	90.9	106	63.9
Non-adenocarcinoma	1	2.0	1	2.6	0	0.0	55	33.1
Other	1	2.0	0	0.0	1	9.1	5	3.0

The ODxT Test original workflow showed 78% PPA, 100% NPA, and 97% OPA, compared to the ROS1 FISH. The ODxT Test optimized workflow showed a 100% PPA, NPA, and OPA, compared to the ROS1 FISH. Therefore, the changes to the RNA portion of the ODxT Test workflow do not impact the safety and effectiveness of the ODxT Test for detecting ROS1 fusions.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

Life Technologies conducted a clinical bridging study to establish the reasonable assurance of safety and effectiveness of the ODxT Test for detection of RET fusions in NSCLC FFPE tumor specimens to select patients for treatment with GAVRETO™ (pralsetinib) in the US. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. ODxT Test Clinical Bridging Study for RET Fusions

The safety and effectiveness of the ODxT Test for detecting RET fusions in NSCLC patients who may benefit from treatment with pralsetinib was demonstrated in a retrospective analysis of samples from patients enrolled in the ARROW trial (NCT03037385). A bridging study was conducted to assess the clinical efficacy of the ODxT Test in identifying patients positive for RET fusions for treatment with pralsetinib and the concordance between RET fusions tested with the clinical trial assay (CTA) and the ODxT Test in the intent-to-test population. Retrospective testing with the ODxT Test was done for patients from the drug efficacy population Cohorts 1 and 2, and stage-matched commercially sourced RET fusion negative NSCLC samples, screened with local laboratory-validated (LLT; also referred to as CTA) tests.

For the bridging study analysis, the retrospective testing population consisted of 217 samples (114 samples positive for RET fusions, and 103 samples negative for RET fusions), originally tested by RET fusion CTAs.

1. Study Design

ARROW is a prospectively designed, multi-cohort, open-label, Phase II trial of oral RET inhibitor (pralsetinib) in adult patients with RET fusion positive metastatic NSCLC. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR), as assessed by a blinded independent central review (BICR) assessment according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 to determine the effectiveness of pralsetinib in NSCLC patients. Patients were enrolled into multiple cohorts of the study, out of which the bridging study was focused on the fully-enrolled RET fusion positive Cohorts 1 and 2 (primary efficacy population). Cohort 1 only enrolled RET fusion positive patients previously treated with platinum therapy, Cohort 2 enrolled treatment-naïve RET fusion positive patients only. Patients were screened for enrollment in Cohorts 1 and 2 for RET fusion positive status as detected using RET fusion CTAs. After the initial patient screening, clinical samples were stored for retrospective testing.

ARROW is an ongoing first-in-human (FIH), phase 1/2 trial designed to evaluate the safety, pharmacokinetic and preliminary activity of pralsetinib in patients with RET-altered solid tumors, including NSCLC and medullary thyroid cancer (MTC). The study was initiated on June 11, 2015 with first patient first visit (FPFV). In the dose-escalation, phase 1 portion of the study, patients received pralsetinib up to 600 mg orally, once daily. The recommended phase 2 dose (RP2D) was determined to be 400 mg of pralsetinib orally, once daily. Dose adjustments for pralsetinib were permitted for safety concerns. Efficacy was evaluated every six weeks from the first day of treatment until RECIST 1.1 disease progression. Safety and tolerability were evaluated in all subjects who received at least one dose of pralsetinib by assessment of incidence of adverse events (AEs) and serious adverse events (SAEs), change in vital signs, laboratory results, and electrocardiogram (ECG).

2. <u>Bridging Study</u>

The aim of the bridging study was to determine the concordance between RET fusion results from the enrolling CTAs generated at the time of patient screening for ARROW study and the results of RET fusions using the ODxT Test. The study was also conducted to establish the clinical of the ODxT Test in identifying patients positive for RET fusions for treatment with pralsetinib. Retrospective testing with the ODxT Test was performed for patients from Cohort 1 (87 previously treated with platinum) and Cohort 2 (27 treatment naïve) and commercially procured RET fusion NSCLC samples. The bridging study population consisted of 114 patients in the primary effeciacy population enrolled by CTAs in the ARROW trial and 103 RET fusion negative samples originally tested by the RET fusion CTAs for patient selection. Concordance between the ODxT Test and the CTAs was demonstrated with the companion diagnostic (CDx)-evaluable patient population from the ARROW trial that produced valid ODxT Test results. Clinical validity of the ODxT Test was evaluated by estimation of clinical efficacy in the CTA-enrolled RET fusion positive patient population as assessed by the primary objective of ORR by Blinded Independent Review Committee (BIRC). Baseline demographic and disease characteristics were compared between the CDx-evaluable and CDx-unevaluable populations within all enrolled CTA-positive patients in Cohorts 1 and

2. All the covariates were well balanced between the two groups of patients (See Section X.B below).

3. Study Population Demographics and Baseline Parameters:

The demographics, disease characteristics and specimen characteristics for the CDx-evaluable and CDx-unevaluable patients were similar for all of the CTA-enrolled patients in the ARROW trial. However, for Cohort 1 primary efficacy population, the CTA sample type is not balanced, and the ECOG covariate is not balanced for Cohort 2 primary efficacy population (Table 7).

Table 7: Patient demographics and disease characteristics between CDx evaluable and unevaluable set for CTA+ patients in ARROW; Efficacy Population.

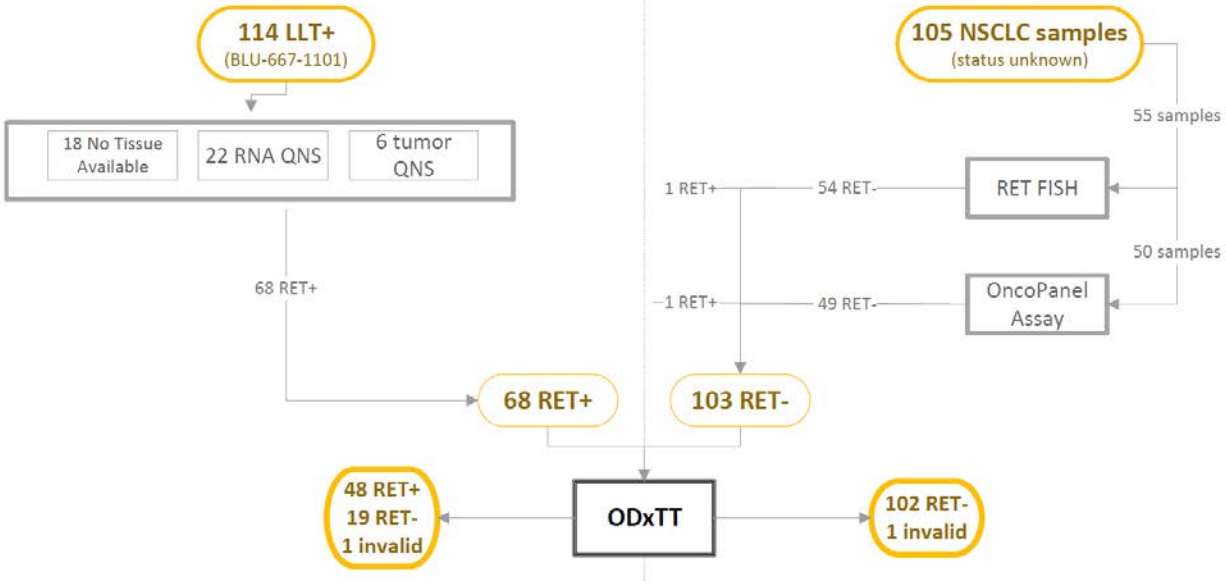
Characteristics		Cohort 1			Cohort 2			Combined Cohorts 1 and 2		
		CDx Evaluable	CDx Uneval.	CTA+	CDx Evaluable	CDx Uneval.	CTA+	CDx Evaluable	CDx Uneval.	CTA+
Subject	(N)	51	36	87	16	11	27	67	47	114
Age	Mean (SD)	58.0 (10.3)	60.9 (11.1)	59.2 (10.7)	59.3 (13.6)	63.0 (14.4)	60.8 (13.8)	58.3 (11.1)	61.4 (11.8)	59.6 (11.4)
Sex	Female	27 (52.9)	16 (44.4)	43 (49.4)	9 (56.3)	5 (45.5)	14 (51.9)	36 (53.7)	21 (44.7)	57 (50.0)
	Male	24 (47.1)	20 (55.6)	44 (50.6)	7 (43.8)	6 (54.5)	13 (48.1)	31 (46.3)	26 (55.3)	57 (50.0)
Race	Asian	18 (35.3)	12 (33.3)	30 (34.5)	6 (37.5)	3 (27.3)	9 (33.3)	24 (35.8)	15 (31.9)	39 (34.2)
	Native Hawaiian or other Pacific	0 (0)	0 (0)	0 (0)	1 (6.3)	0 (0)	1 (3.7)	1 (1.5)	0 (0)	1 (0.9)
	Other	0 (0)	2 (5.6)	2 (2.3)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4.3)	2 (1.8)
	Unknown	4 (7.8)	5 (13.9)	9 (10.3)	1 (6.3)	0 (0)	1 (3.7)	5 (7.5)	5 (10.6)	10 (8.8)
	White	29 (56.9)	17 (47.2)	46 (52.9)	8 (50.0)	8 (72.7)	16 (59.3)	37 (55.2)	25 (53.2)	62 (54.4)
ECOG Baseline	0	16 (31.4)	15 (41.7)	31 (35.6)	10 (62.5)	1 (9.1)	11 (40.7)	26 (38.8)	16 (34.0)	42 (36.8)
	1	31 (60.8)	20 (55.6)	51 (58.6)	6 (37.5)	9 (81.8)	15 (55.6)	37 (55.2)	29 (61.7)	66 (57.9)
	2	4 (7.8)	1 (2.8)	5 (5.7)	0 (0)	1 (9.1)	1 (3.7)	4 (6.0)	2 (4.3)	6 (5.3)
CTA Sample	Plasma	1 (2.0)	8 (22.2)	9 (10.3)	3 (18.8)	2(18.2)	5 (18.5)	4 (6.0)	10 (21.3)	14 (12.3)
	Tissue	37 (72.5)	22 (61.1)	59 (67.8)	11 (68.8)	9 (81.8)	20 (74.1)	48 (71.6)	31 (66.0)	79 (69.3)
	Unknown	13 (25.5)	6 (16.7)	19 (21.8)	2 (12.5)	0 (0)	2 (7.4)	15 (22.4)	6 (12.8)	21 (18.4)

4. Accountability of PMA Cohort

As shown in Figure 1, below, 114 patient samples were available for this study, which included 46 samples that were cancelled due to failed pathology review or failure to meet the RNA concentration cutoff. This resulted in 68 RET+ samples eligible for NGS testing. Of the remaining 68 samples expected to be RET+, 19 were RET(-), 1 was invalid by the ODxT Test due to poor RNA quality, and 48 RET+ samples were called by the ODxT Test

Of the 103 RET(-) samples tested that were initially identified as RET(-), 1 was invalid due to poor RNA quality and 102 were confirmed RET(-) samples by the ODxT Test.

Figure 1: Sample Accountability Chart for Study Samples



B. Safety and Effectiveness Results

1. Safety Results

The safety with respect to treatment with pralsetinib was addressed during the review of the NDA 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 GAVRETO™ (pralsetinib).

The most common adverse reactions (≥25%) were fatigue, constipation, musculoskeletal pain, and hypertension. The most common Grade 3-4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased neutrophils, decreased phosphate, decreased hemoglobin, decreased sodium, decreased calcium (corrected), and increased alanine aminotransferase (ALT). In addition, the safety findings in this study are consistent with the known safety profile of pralsetinib and no new or unexpected safety signals were identified.

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

2. Effectiveness Results

a. Concordance Results

The primary concordance analysis was conducted on 217 (114 RET fusion positive patients, and 103 RET fusion negative stage-matched commercially sourced NSCLC samples) samples tested by CTAs.

Agreement between the ODxT Test and the CTAs was demonstrated (Table 8). The point estimate of PPA between the ODxT Test (CDx) and the CTAs were calculated with and without invalid CDx results, using the CTA results as a reference for the CTA-enrolled patients (Table 9), were 71.6% (59.3, 82) and 42.1% (32.9, 51.7), respectively. Across treatment groups, the point estimate of PPA between the CDx and CTAs with and without invalid CDx results, using th CTA results as a reference for the CTA-enrolled patients (Table 10), were 66.7% (52.1, 79.2) and 39.1 (28.8, 50.1), respectively for Cohort 1 and 87.5% (61.7, 98.4) and 51.9% (31.9, 71.3), respectively for Cohort 2. The reason for the low PPA was likely due to sample quality issues and RET fusions not included in the assay definition file of the ODxT Test. A post-approval study requirement using 57 additional samples from the ARROW study not included in the efficacy population has been planned to supplement the bridging analysis (See Section XIII). The "Invalid" in the following tables includes missing/unknown/invalid CDx results or no CDx results due to insufficient material available to run using the CDx.

Table 8. Accountability table for CDx results for cohorts 1 and 2 of the ARROW trial.

	CTA+			
	Cohort 1	**Cohort 2**	**CTA-**	**Total**
CDx+	34	14	0	48
CDx-	17	2	102	121
CDx Invalid	36	11	1	48
Total	87	27	103	217

Table 9. Positive and Negative Percent agreements between CDx and CTA in reference to CTA results in all patients.

	Without CDx "Invalid"		**With CDx "Invalid"**	
	Agreement % (n/N)	**95% CI (%)**	**Agreement % (n/N)**	**95% CI**
PPA	71.6 (48/67)	(59.3, 82)	42.1(48/114)	(32.9, 51.7)
NPA	100 (102/102)	(96.5, 100)	99.0 (102/103)	(94.7, 100)

Table 10. Positive Percent agreement between CDx and CTA in reference to CTA results in Cohorts 1 and 2.

	Without CDx "Invalid"		With CDx "Invalid"	
	Agreement % (n/N)	95% CI	Agreement % (n/N)	95% CI
Cohort 1	66.7 (34/51)	(52.1, 79.2)	39.1 (34/87)	(28.8, 50.1)
Cohort 2	87.5 (14/16)	(61.7, 98.4)	51.9 (14/27)	(31.9, 71.3)

b. Clinical Efficacy Results in the ARROW RET Fusion Positive Cohort

In the ARROW trial, the confirmed overall response rates (ORR) per BIRC in NSCLC patients previously treated with platinum-based chemotherapy was 57.5% (46.4, 68.0). In 27 treatment-naïve patients with metastatic RET fusion-positive NSCLC, the confirmed ORR was 70.4% (49.8, 86.2). The analyses by BIRC assessment were similar to the analyses by investigator assessment (Table 11). Treatment with pralsetinib was considered efficacious in both Cohort 1 (prior platinum treatment) and Cohort 2 (treatment-naive) (70.6% (52.5, 84.9) and 85.7% (57.2, 98.2), respectively) as demonstrated by an ORR per BIRC. The observed results are judged to be clinically meaningful when considering the intended patient population, patients with metastatic RET fusion-positive NSCLC, and available therapy.

Table 11: Overall response per BIRC assessment in patients by cohort.

ORR (CR + PR)	CTA+/CDx+		CTA+/CDx-		CTA+/CDx Not Evaluable		CTA+	
	ORR% (n/N)	95% CIs	ORR% (n/N)	95% CIs	ORR% (n/N)	95% CIs	ORR% (n/N)	95% CIs
Cohort 1-Prior Platinum Treatment	70.6% (24/34)	(52.5, 84.9)	41.2% (7/17)	(18.4, 67.1)	52.8% (19/36)	(35.5, 69.6)	57.4% (50/87)	(46.4, 68.0)
Cohort 2-No Prior Systemic Treatment	85.7% (12/14)	(57.2, 98.2)	50.0% (1/2)	(1.3, 98.7)	54.5% (6/11)	(23.4, 83.3)	70.4% (19/27)	(49.8, 86.2)

3. <u>Clinical Efficacy Results in the CDx-positive Population</u>

In Table 9, all procured samples that were found to be negative for RET fusions by the CTAs were also tested negative by the CDx (i.e., NPA = pr(CDx+|CTA+) =100%). Therefore, the conditional probability of being CTA positive in the CDx positive population is 100% (i.e., Pr(CTA+|CDx+) = 100%), regardless of the prevalence of RET fusions as determined by the CTAs. Thus, the final estimated drug efficacy (ORR) for the CDx positive patients in the intended use population equals to the estimated drug efficacy of the (CTA+ and CDx+) patients observed in the ARROW clinical trial. So the final estimated drug efficacies (ORR) in CDx test positive patients with no prior platinum therapy and patients with no prior systemic

treatment are the same as the the drug efficacies in the CTA+/CDx+ population in the above Table 11.

A sensitivity analysis, using multiple imputation methods was performed to evaluate the robustness of the clinical efficacy estimate for the 48 patients who were determined to be RET fusion positive by the CTAs, but were missing CDx Test results due to failed pathology review or failure to meet the RNA concentration cutoff (invalid), which included 36 patients treated with prior platinum therapy and 11 patients with no prior systemic treatment Table 12.

Multivariate logistic regression analyses were performed to identify the clinically relevant covariates that were associated with the CDx test device output and clinical outcome, respectively. Given that the sample size is limited in each cohort, a significance level of 0.2 was used as the criteria to select covariates in the logistic regression models. A multiple imputation model was used, which included all the identified covariates and clinical outcomes that were to used to impute the missing CDx test results for the 36 patients treated with prior platinum therapy and the 11 patients with no prior systemic treatment. In total, 2000 imputations were run. The complete imputed datasets were used to estimate the drug efficacy in the CDx RET fusion positive patients, which is the same as the estimated drug efficacy in the CDx+/CTA+ patients calculated from imputed datasets. Both the within imputation variation and between imputation variation have been accounted for when calculating the confidence intervals of the estimated drug efficacy in the final CDx RET fusion positive population. The sensitivity analysis results demonstrated that the estimated final drug efficacy in CDx RET fusion positive patients remains robust with the missing CDx results.

Table 12. Estimated Clinical efficacy results for CDx RET fusion positives based on imputed data

ORR (CR + PR)	Imputed ORR with 95% CI
Cohort 1-Prior Platinum Treatment	67.0% (54.5% - 79.6%)
Cohort 2-No Prior Systemic Treatment	79.9% (62.2% - 97.7%)

4. Pediatric Extrapolation

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

C. 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 4 investigators of which 1 was a full-time or part-time

employee of the sponsor and 1 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: 1
- 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: 1

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 RET fusions in NSCLC patients to be treated with pralsetinib, the effectiveness of the ODxT Test was demonstrated through a clinical bridging study using specimens from patients screened for enrollment into the ARROW study. The data from the analytical validation and clinical bridging 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 ARROW study show that patients who had qualifying RET fusions received benefit from treatment with pralsetinib 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 PMA 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

Treatment with pralsetinib provides a meaningful clinical benefit to NSCLC patients with RET fusions, as demonstrated in the ARROW trial. For the intended use of identifying RET fusions in NSCLC patients to be treated with pralsetinib, the probable benefit of the ODxT Test was demonstrated through a clinical bridging study using specimens from patients screened for enrollment into the ARROW study, showing clinically meaningful ORR response in patients with prior platinum treatment (Cohort 1) and in treatment-naïve patients (Cohort 1) with metastatic RET fusion-positive NSCLC detected by the ODxT test. Given the available information and the analytical data provided in the submission, the data supports the conclusion that the ODxT test has probable benefit in selecting patients with RET fusions, for treatment with pralsetinib in patients with NSCLC.

In addition, for ROS1 fusions, a clinical concordance study between the previously approved version of the ODxT Test and the new optimized version of the ODxT Test RNA workflow, demonstrating that the modification to the RNA workflow has not negatively affected the performance of the ODxT Test to detect ROS1 fusions and demonstrating that the ODxT test has probable benefit in selecting in NSCLC patients for treatment with XALKORI® (crizotinib).

There is 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.

The risks of the OdxT for selection of NSCLC patients with RET fusions or NSCLC patients ROS1 fusions, are associated with the potential mismanagement of patient's treatment resulting from false results of the test. 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 device. Additional factors, including the clinical and analytical performance of the device included in this submission, have been taken into account and demonstrate that the assay is expected to to have acceptable performance. However, conditions of approval are planned to address additional issues.

1. 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 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 bridging study support the performance of the ODxT Test as an aid for the identification of RET fusions in NSCLC patients for whom GAVRETO™ (pralsetinib) may be indicated.

XIII. CDRH DECISION

CDRH issued an approval order on September 4, 2020. The final conditions of approval cited in the approval order are described below.

1. Thermo Fisher Scientific/Life Technologies Corp. must provide data from additional NSCLC samples positive for RET fusions from the ARROW trial to supplement the concordance analysis of the ODxT Test to the clinical trial assays used to select RET fusion positive NSCLC patients for the ARROW trial. The data from this study must be adequate to support robust detection of RET fusions in the intended use population.

2. Thermo Fisher Scientific/Life Technologies Corp. must provide data from a well-designed and well-controlled precision study near LoD using intended use specimens carrying RET fusions detected by your assay. The data from this study must be adequate to support precision near LoD for RET fusions in the intended use population.

3. Thermo Fisher Scientific/Life Technologies Corp. must provide additional data from well-designed and well-controlled stability studies to demonstrate robust RET and ROS1 fusion calling within the ODxT Test stability claims for FFPE slide, FFPE block, extracted RNA, shelf life, and real-time reagent stability. These studies should use intended use specimens carrying RET and ROS1 fusions detected by your assay. The data from these studies must be adequate to support stability claims for RET and ROS1 fusions in the intended use population.

4. Thermo Fisher Scientific/Life Technologies Corp. will provide validation testing, results, and associated software documentation within 1 year of the PMA approval date to confirm the software resolution of existing unresolved anomaly 2687.

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

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.