

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 Express Test
Device Procode:	PQP
Applicant's Name and Address:	Life Technologies Corporation 7305 Executive Way Frederick, MD 21704
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P240040/S005
Date of FDA Notice of Approval:	September 9, 2026

The original PMA (P240040) for Oncomine™ Dx Express Test was approved on July 2, 2025, for the detection of genetic alterations from formalin-fixed paraffin-embedded (FFPE) tumor specimens in patients who may benefit from treatment with an FDA-approved therapy for non-small cell lung cancer (NSCLC). The SSED to support the original indication is available on the CDRH website and is incorporated by reference [here](#).

The current panel-track supplement was submitted to expand the indications for use of Oncomine™ Dx Express Test to include a companion diagnostic indication for the identification of *ERBB2/HER2* activating mutations (SNVs in exons 18-21 within the tyrosine kinase domain and exon 20 insertions) in patients with NSCLC who may benefit from treatment with HYRNUO® (sevabertinib).

II. INDICATIONS FOR USE

The Oncomine™ Dx Express Test is a qualitative *in vitro* diagnostic test that uses targeted next-generation sequencing (NGS) technology to detect substitutions, insertions, and deletions in 42 genes from DNA, copy number variants (CNVs) in 10 genes from DNA, and fusions or splice variants in 18 genes from RNA isolated from formalin-fixed,

paraffin-embedded (FFPE) tumor samples, using the Genexus™ Dx Integrated Sequencer.

The test is intended to be used as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling.

Table 1. Companion Diagnostic Indications

Tissue Type	Gene	Variant	Targeted Therapy
Non-small cell lung cancer (NSCLC)	<i>EGFR</i>	<i>EGFR</i> exon 20 insertions	ZEGFROVY™ (sunvozertinib)
	<i>ERBB2/HER2</i>	<i>ERBB2/HER2</i> activating mutations (SNVs in exons 18-21 within the tyrosine kinase domain and exon 20 insertions)	HYRNUO® (sevabertinib)

Additionally, the test is intended to provide tumor mutation profiling information to be used by qualified health care professionals in accordance with professional guidelines in oncology for cancer patients with solid malignant neoplasms. Genomic findings other than those listed in Table 1 are not prescriptive or conclusive for labeled use of any specific therapeutic product.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

The Oncomine Dx Express Test (ODxET) is a distributed *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™ Genexus Dx System (including Ion Torrent™ Genexus Dx Integrated Sequencer, Ion Torrent™ Genexus Dx Purification System, and Reagents & Consumables) for detection of alterations in deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) isolated from FFPE tumor specimens. The test is intended to detect substitutions, insertions, and deletions in 42 genes; CNVs in 10 genes; and fusions or splice variants in 18 genes, as outlined in Table 2, across solid tumors.

ODxET Panel provides a set of Ion AmpliSeq HD primers that target key regions of 46 cancer-related genes. The ODxET reports targeted variants from the following genes:

Table 2. ODxET Reportable Gene List

Alteration Type	Genes
Deletions, insertions, substitutions from DNA (42 genes)	<i>AKT1, AKT2, AKT3, ALK, AR, ARAF, BRAF, CDK4, CHEK2, CTNNB1, EGFR, ERBB2, ERBB3, ERBB4, ESRI, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, GNAS, HRAS, IDH1, IDH2, KEAP1, KIT, KRAS, MAP2K1, MAP2K2, MET, NRAS, NTRK1, NTRK2, NTRK3, PDGFRA, PIK3CA, PTEN, RAF1, RET, ROS1, STK11, TP53</i>
Copy number variants from DNA (10 genes)	<i>AR, EGFR, ERBB2, ERBB3, FGFR1, FGFR2, FGFR3, KRAS, MET, PIK3CA</i>
Gene fusions and splice variants from RNA (18 genes)	<i>ALK, AR, BRAF, EGFR, ESRI, FGFR1, FGFR2, FGFR3, MET, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, RET, ROS1, RSPO2, RSPO3</i>

A. Test Output

The test report includes variants reported in the following levels:

- Level 1: Companion Diagnostics (CDx) biomarkers noted in Table 1 of the Intended Use
- Level 2: Cancer mutations with evidence of clinical significance
- Level 3: Cancer mutations with potential clinical significance

Genomic findings (i.e., Levels 2 and 3) other than those listed in Table 1 of the companion diagnostic indications table of the intended use statement are not prescriptive or conclusive for labeled use of any specific therapeutic product.

B. Test Kit Contents and Instruments

The ODxET consists of the following:

- Oncomine™ Dx Express Test and Controls Kit:
 - Oncomine™ Dx Express Test Panel
 - Oncomine™ Dx Express Test FFPE DNA Control
 - Oncomine™ Dx Express Test FFPE RNA Control
 - Oncomine™ Dx Express Test No Template Control
- Genexus™ Dx FFPE DNA/RNA Purification Combo Kit:
 - Genexus™ Dx FFPE DNA/RNA Purification Combo Kit Ion Torrent™ Dx cDNA Synthesis Kit
 - Genexus™ Dx Nucleic Acid Quantitation
 - Genexus™ Dx Purification Supplies 2
- Genexus™ Dx Integrated Sequencer Reagents and Consumables:
 - Genexus™ Dx Library Strips 1 and 2-HD
 - Genexus™ Dx Templating Strips 3-GX5 and 4

- Genexus™ Dx Sequencing Kit
- Genexus™ Dx Barcodes 1-32 HD
- Genexus™ Dx GX5 Chip and Genexus Coupler
- Genexus™ Dx Pipette Tips
- Genexus™ Dx Filter
- Genexus™ Dx Conical Bottles
- Instrumentation and Software:
 - Genexus™ Dx Purification System
 - Genexus™ Dx Integrated Sequencer
 - Genexus™ Dx Software

The ODxET User Guide and ADF are provided as electronic files delivered to users through Thermo Fisher Connect (TFC). Users receive the specific ODxET product SKUs they have ordered. The packaging label includes URLs for further information: www.thermofisher.com/GXDxDocs and www.thermofisher.com/ODxETDocs, which direct users to an online PDF with detailed instructions on accessing the User Guides and ADF.

C. Test Workflow

a. Sample and Assay Run Setup

Information about each sample is entered into Genexus™ Dx Software, which directs the progress of the sample from creation of a run plan through automated sample preparation (as applicable), library preparation, template preparation, sequencing, and analysis. During creation of a run plan, samples are selected and assigned to the run plan. The assay selected in the run plan specifies instrument run and analysis parameters and directs the reporting output of sample results.

b. Nucleic Acid Extraction

Nucleic acid extraction is performed with the Genexus™ Dx Purification System or other IVD-labeled extraction chemistries. When using the Genexus™ Dx Purification System specimens are treated with protease, then loaded into a sample input plate. The Genexus™ Dx Purification System is loaded with the sample plate and consumables specific for the sample and run type. During the automated run, the instrument purifies samples using a magnetic bead-based procedure, quantifies sample concentration, then loads the purified samples in a sequencer-ready output plate.

c. Library Preparation

In the first stage of a Genexus™ Dx Integrated Sequencer run, complementary DNA (cDNA) is prepared from RNA sample, then sample and control amplicon libraries are prepared from DNA or cDNA. Oncomine™ Dx Express Test panel

primers, reagents in Genexus™ Dx Strip 1 and Genexus™ Dx Strip 2-HD, and barcode adapters from the Genexus™ Dx Barcodes 1–32 HD plate are used in library preparation. Each library that is generated in a run has a distinguishing nucleic acid sequence barcode that is incorporated into each amplified molecule.

d. Template Preparation

In the template preparation stage of the automated Genexus™ Dx Integrated Sequencer run, library molecules are bound onto Ion Sphere Particles (ISPs), and each nucleic acid sequence is amplified over the ISP surface using reagents in the Genexus™ Dx Strip 3-GX5™ and Genexus™ Dx Strip 4. The templated ISPs are enriched and collected using magnetic beads, then the enriched ISPs are magnetically loaded into wells of the sequencing chip. A second amplification step is then carried out with ISPs loaded on the chip, one ISP per well. After amplification, sequencing primer is annealed to the single-stranded template, and sequencing enzyme is added.

e. Sequencing

In the sequencing stage of the run, the sequencer flows one of four nucleotides over the Genexus™ Dx GX5™ Chip surface in a programmed series of flows. A base that is incorporated into the newly synthesized strands of an ISP during a flow, results in a release of protons and a concomitant pH change in the well. The change in pH is detected by sensors at the base of each well on the chip. Electrical signals that correspond to pH changes generated in each well during sequencing are processed and stored in data files on the system. Throughout this procedure, as the sample is processed by the instrument, sample and reagent information is recorded and tracked by Genexus™ Dx Software.

f. Data Analysis

On the internal server of the Genexus™ Dx Integrated Sequencer, the initial signals are processed and each base in a sequence is called (identified). Base calls are assembled into files representing the reads, which are strings of nucleotide bases in the order found in the original library molecules. The reads are then mapped to the reference files provided with the test. Finally, Genexus™ Dx Software assesses the mapped reads at specific nucleotide locations and detects variation in sequence information in comparison to a human reference sequence.

D. Assay Validity Criteria—FFPE Samples (DNA and RNA)

Quality control (QC) specifications for the templating control, sample, no-template control (NTC), and purification are provided in Table 3.

Table 3. FFPE Workflow—Quality Control specifications for Templating Control, Sample, No-Template Control, and Purification

Metric	Criteria
Templating Control QC - CF-1 (Run Level Control)	
Average Reads per Lane	≥ 2383
Mean AQ20 Read Length (bp)	≥ 82
Sample QC – DNA	
Median Absolute Pairwise Difference	≤ 0.5
DNA Mapped Reads	$\geq 100,000$
DNA Mean AQ20 Read Length (bp)	≥ 64
Sample QC – RNA	
Mapped Fusion Reads	$\geq 6,000$
RNA Expression Controls Detected	≥ 5
NTC QC – DNA	
Hotspot Calls	0
Average Base Coverage Depth	≤ 15
NTC QC – RNA	
Mapped Reads	≤ 2848
Total Fusion Calls	0
Purification QC	
Sample Concentration DNA	0.5 ng/ μ L minimum – 512 ng/ μ L maximum
Sample Concentration RNA	0.5 ng/ μ L minimum – 512 ng/ μ L maximum

E. Variant Calling Criteria

In addition to the run and clinical sample validity criteria listed above, several variant calling criteria established separately for different biomarkers are used to determine which biomarkers are reportable in a passing sample in a successful run.

Primary parameters evaluated to produce each variant call include number of reads supporting a variant call, allele frequency, chromosomal strand coverage, and ultimately, alignment with known and targeted hotspots by the panel included in the ADF. The variant caller algorithm calls variants using either read-based evidence or molecular family-based evidence.

a. Variant Calling Criteria for Companion Diagnostic Biomarkers

EGFR exon 20 insertions:

A targeted *EGFR* exon 20 insertion mutation will be called ‘positive’ if it meets the variant calling criteria specified in the ADF. The ODxET covers codons E762 to R776 and Q787 to L814 of *EGFR* exon 20. The *EGFR* exon 20 insertion annotation is applied only to in-frame insertions (or in-frame block substitutions with a net nucleotide gain) affecting codons 762–775.

ERBB2/HER2 activating mutations (SNVs in exons 18-21 within the tyrosine kinase domain and exon 20 insertions):

A targeted *ERBB2/HER2* activating mutation will be called ‘positive’ if it meets the variant calling criteria specified in the ADF. The *ERBB2/HER2* exon 20 insertion annotation is applied only to in-frame insertions (or in-frame block substitutions with a net nucleotide gain) affecting codons 770-778. The *ERBB2/HER2* single nucleotide variant (SNV) annotation is applied only to variants occurring at specified codons in exons 18-21 within the tyrosine kinase domain: codon 733 in exon 18; codons 755, 767, and 769 in exon 19; codons 776, 777, and 798 in exon 20; and codons 842, 868, and 869 in exon 21.

b. Variant Calling Criteria for Tumor Profiling Variants

The variant calling approach for tumor profiling incorporates multiple algorithms tailored to each variant class. Single nucleotide variants (SNVs), insertions, and deletions are identified by the variant caller algorithm using criteria such as read depth, quality score, and allele frequency. Copy number variants (CNVs) are evaluated using a separate algorithm that considers sample-specific tumor cellularity. Gene fusions and RNA splice variants are detected based on minimum thresholds for unique molecule counts or reads. In certain cases, variant-specific criteria are also applied.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are other FDA approved CDx alternatives for the detection of genetic alterations using NSCLC FFPE tissue specimens, compared to those listed in Table 1 of the ODxET intended use statement. These approved alternative CDx tests are shown in Table 4 below. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

Table 4. FDA-Approved CDx Alternatives for Genes and Therapies Targeted by ODxET for NSCLC

Gene	Variant	Device	Company	Technology	Therapy
<i>EGFR</i>	EGFR exon 20 insertion	Oncomine Dx Target Test	Thermo Fisher Scientific	Next Generation Sequencing (NGS)	RYBREVANT™ (amivantamab-vmjw) (P160045/S027)
<i>ERBB2/HER2</i>	<i>ERBB2/HER2</i> activating mutations (SNVs in exons 18-21 within the tyrosine kinase domain and exon 20 insertions)	Oncomine Dx Target Test	Thermo Fisher Scientific	Next Generation Sequencing (NGS)	HYRNUO® (sevabertinib) (P160045/S050)
<i>ERBB2/HER2</i>	<i>ERBB2</i> activating mutations (SNVs and exon 20 insertions)	Oncomine Dx Target Test	Thermo Fisher Scientific	Next Generation Sequencing (NGS)	ENHERTU (fam-transtuzumab deruxtecan-nxki) (P160045/S035)
<i>ERBB2/HER2</i>	activating mutations in the tyrosine kinase domain (SNVs in exons 18-21 and exon 20 insertions)	Oncomine Dx Target Test	Thermo Fisher Scientific	Next Generation Sequencing (NGS)	HERNEXEOS (zongertinib) (P160045/S049)

For additional details, see FDA List of Cleared or Approved Companion Diagnostic Devices at: <https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools>.

VII. MARKETING HISTORY

The ODxET was introduced into interstate commerce in the United States (US) on July 2, 2025, and is commercially available in 17 countries in Europe (Austria, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Malta, Netherlands, Norway, Poland, Romania, Slovenia, Spain, Sweden, and United Kingdom), and Malaysia. The ODxET has not been withdrawn from these markets for any reasons related to its safety or effectiveness.

The expansion of the indications for use of ODxET described above in Section I have not been previously marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Failure of the device to perform as expected or failure to correctly interpret test results may lead to incorrect ODxET results and subsequently improper patient management and

treatment decisions for patients with NSCLC. Patients with false positive results may undergo treatment with the therapies listed in the intended use statement without clinical benefit and may experience adverse reactions associated with the therapies. Patients with false negative results may not be considered for treatment with the indicated therapies. There is also a risk of delayed results, which may lead to delay of treatment with the indicated therapies.

No device-related adverse events were reported in connection with the clinical studies used to support the original PMA or this supplement as the studies were performed retrospectively using banked samples.

For the specific adverse events that occurred in the clinical studies, please see the FDA approved package inserts available at Drugs@FDA.

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Laboratory Studies

Analytical validation studies demonstrating the performance of the ODxET for the detection of *ERBB2/HER2* activating mutations (SNVs in exons 18-21 within the tyrosine kinase domain and exon 20 insertions) in FFPE specimens are listed below. All studies were performed using intended use specimens and sample blends.

1. Analytical Accuracy/Concordance – Comparison to an Orthogonal Method

The accuracy of the ODxET for detecting *ERBB2/HER2* activating mutations in the tyrosine kinase domain (TKD) in FFPE tumor specimens from patients with NSCLC was evaluated by comparing the test results of the ODxET with those of a validated NGS-based orthogonal method. A total of 92 tissue samples were obtained from subjects enrolled in the HYRNUO[®] (sevabertinib) clinical trial (SOHO-01; NCT05099172). Additionally, 150 tissue samples were procured from commercial vendors and screened using NGS-based assays representative of the technologies commonly used for patient enrollment in the SOHO-01 trial to identify *ERBB2/HER2* activating mutation-negative cases. Of these, 130 samples that were negative were included for the analysis.

A total of 219 samples were tested with the ODxET: 89 *ERBB2/HER2* variant-positive samples (three samples were invalid) and 130 variant-negative samples. All 89 variant-positive samples were confirmed as positive and all 130 variant-negative samples were confirmed as negative.

All 219 samples tested with the ODxET were submitted for testing with the orthogonal method. Of these, only 61 variant-positive samples and 125 variant-negative samples produced valid results.

The analytical concordance between the ODxET and the orthogonal method for detecting *ERBB2/HER2* activating mutations, based on a total of 222 samples (92 *ERBB2/HER2* variant-positive samples and 130 *ERBB2/HER2* variant-negative samples) is summarized in Table 5.

Table 5. Analytical Concordance Between ODxET and Orthogonal Method for *ERBB2/HER2* TKD Activating Mutations in FFPE-Tumor Specimens

		Orthogonal Method				Total
		Positive	Negative	TNP ¹	Invalid ²	
ODxET	Positive	58	3	25	3	89
	Negative	0	125	0	5	130
	TNP ¹	0	0	3	0	3
Total		58	128	28	8	222
¹ TNP= Test Not Performed due to DNA concentration fail, tumor content fail, insufficient material, or DNA.						
² Invalid considered unknown or unevaluable.						

All three discordant samples were detected by the ODxET at frequencies below the LoD of the orthogonal method which likely accounts for the observed discordance. The positive percent agreement (PPA), negative percent agreement (NPA), overall percent agreement (OPA), and their corresponding two-sided 95% Wilson Score confidence intervals (CIs), using the orthogonal method as the reference, are provided in Table 6.

Table 6. Agreement Between ODxET and Orthogonal Method for *ERBB2/HER2* TKD Activating Mutations in FFPE-Tumor Specimens

Parameter	Agreed	Total	Percent Agreement (Wilson Score 95% CIs)
PPA Excluding or Including Unknowns	58	58	100.0% (93.8%, 100.0%)
NPA Excluding or Including Unknowns	125	128	97.7% (93.3%, 99.2%)
OPA Excluding or Including Unknowns	183	186	98.4% (95.4%, 99.4%)

In the SOHO-01 trial, the study population was enriched for cases positive for *ERBB2/HER2* TKD activating mutations. Consequently, the analytical concordance between ODxET and the orthogonal method was re-evaluated by calculating prevalence-adjusted values for PPA and NPA, with corresponding two-sided 95% CI calculated using the percentile-bootstrap method, except for when the point estimate was 100%, in which case the Wilson Score method was used with adjusted proportions. At a prevalence of 1.8%, the adjusted point estimates for PPA and NPA were 100.0% (95% CI: 93.8%, 100.0%) and 99.1% (95% CI: 95.4%, 100.0%), respectively, demonstrating high analytical concordance between the ODxET and the comparator method.

2. Analytical Sensitivity

a. Limit of Blank

A Limit of Blank (LoB) study was conducted for the ODxET for P240040. Please refer to Section IX.A.2.a of the Summary of Safety and Effectiveness Data of P240040 for study details. Data from the LoB study was reanalyzed for 43 *ERBB2/HER2* SNV variants and 44 *ERBB2/HER2* exon 20 insertion variants. No false positive variants were detected, establishing a false positive rate of zero. The LoB of ODxET for *ERBB2/HER2* SNVs and *ERBB2/HER2* exon 20 insertions is therefore zero.

b. Limit of Detection

The limit of detection (LoD) of the ODxET for *ERBB2/HER2* SNV and exon 20 insertion variants was previously determined for a total of 5 clinical NSCLC specimens. The variants included four exon 20 insertions (3, 6, 9, and 12 bp) and one TKD SNV in exon 20. The LoD for these samples ranged from 2.98% VAF to 4.07% VAF (Table 7). Please refer to the Summary of Safety and Effectiveness Data of P240040 (Section IX.A.2.b) for study details.

Table 7. Summary of LoD Results for *ERBB2/HER2* SNVs and Exon 20 Insertion Variants

Variant Type	Gene	Exon	Variant ID	COSMIC ID	LoD (%VAF)
Insertion	<i>ERBB2/HER2</i>	20	Exon 20 insertion (3bp)	COSM12553	2.98
Insertion	<i>ERBB2/HER2</i>	20	Exon 20 insertion (6bp)	COSM303939	3.91
Insertion	<i>ERBB2/HER2</i>	20	Exon 20 insertion (9bp)	COSM12556	4.07
Insertion	<i>ERBB2/HER2</i>	20	Exon 20 insertion (12bp)	COSM12558	3.87
SNV	<i>ERBB2/HER2</i>	20	p.G776V	COSM18609	3.24

The previously determined LoD of the ODxET for platform level SNVs (ranging from 3.24% to 4.78% VAF), robust sequencing coverage of the *ERBB2/HER2* regions of interest amongst NSCLC samples, and the established LoD for a single TKD SNV (Table 7) collectively provided sufficient evidence to support the LoD for TKD SNVs in NSCLC.

c. DNA Input

Please refer to the Summary of Safety and Effectiveness Data of P240040 (Section IX.A.2.c) for platform level DNA input data for ODxET.

d. Tissue Input

Please refer to the Summary of Safety and Effectiveness Data of P240040 (Section IX.A.2.d) for platform level tissue input data for ODxET.

e. **Tumor Content**

Please refer to the Summary of Safety and Effectiveness Data of P240040 (Section IX.A.2.e) for platform level tumor content data for ODxET.

3. **Analytical Specificity**

a. **Interference**

Please refer to the Summary of Safety and Effectiveness Data of P240040 (Section IX.A.2.e) for platform level interference data for ODxET.

b. **Tumor Necrosis**

Please refer to the Summary of Safety and Effectiveness Data of P240040 (Section IX.A.3.b) for platform level necrosis data for ODxET.

c. **Carryover and Cross-Contamination**

Please refer to the Summary of Safety and Effectiveness Data of P240040 (Section IX.A.3.c) for platform level carryover and cross-contamination data for ODxET.

d. **Primer Specificity – *in-silico* Analysis**

Please refer to the Summary of Safety and Effectiveness Data of P240040 (Section IX.A.3.d) for platform level primer specificity data for ODxET.

4. **Precision**

Two reproducibility studies were conducted to evaluate the precision and reproducibility of the ODxET: a sample processing reproducibility study and an external panel reproducibility study. The sample processing reproducibility study began with the nucleic acid extraction step to assess the reproducibility and repeatability of the entire sample processing workflow. The panel reproducibility study began with extracted nucleic acid.

a. **Panel Reproducibility**

Panel reproducibility, starting from DNA, was previously established for three NSCLC FFPE clinical samples with *ERBB2/HER2* exon 20 insertions (3bp, 6bp and 12bp), and two NSCLC FFPE clinical samples WT for *ERBB2/HER2*. Please see Tables 8-10 for variant data and refer to the Summary of Safety and Effectiveness Data of P240040 (Section IX.A.4.b) for study details.

Table 8. Call Rates for *ERBB2/HER2* Exon 20 Insertions by Sample

Variant	Variant ID	Variant Level (xLoD)	Total Calls	Positive Calls	Negative Calls	No Calls	Positive Call Rate (95%CI)		Negative Call Rate (95%CI)	
							No Calls included	No Calls excluded	No Calls included	No Calls excluded
<i>ERBB2/HER2</i> Exon 20 insertion (3bp)	COSM12553	1.38	72	72	0	0	100% (94.9%-100.0%)	100% (94.9%-100.0%)	0.0% (0.0%-5.1%)	0.0% (0.0%-5.1%)
		2.66	72	72	0	0	100% (94.9%-100.0%)	100% (94.9%-100.0%)	0.0% (0.0%-5.1%)	0.0% (0.0%-5.1%)
<i>ERBB2/HER2</i> Exon 20 insertion (9bp)	COSM12556	1.31	72	72	0	0	100% (94.9%-100.0%)	100% (94.9%-100.0%)	0.0% (0.0%-5.1%)	0.0% (0.0%-5.1%)
		2.53	72	72	0	0	100% (94.9%-100.0%)	100% (94.9%-100.0%)	0.0% (0.0%-5.1%)	0.0% (0.0%-5.1%)
<i>ERBB2/HER2</i> Exon 20 insertion (12bp)	COSM20959	1.00	72	72	0	0	100% (94.9%-100.0%)	100% (94.9%-100.0%)	0.0% (0.0%-5.1%)	0.0% (0.0%-5.1%)
		1.41	72	72	0	0	100% (94.9%-100.0%)	100% (94.9%-100.0%)	0.0% (0.0%-5.1%)	0.0% (0.0%-5.1%)
95% CI calculated with Wilson Score Method										

Table 9. Within Run Repeatability Estimates for *ERBB2/HER2* Exon 20 Insertions

Variant	Variant ID	Variant Level (xLoD)	Total Pairs		Concordant Pairs		Within-Run Repeatability (95% CI)	
			No Calls Included	No Calls Excluded	No Calls Included	No Calls Excluded	No Calls included	No Calls Excluded
<i>ERBB2/HER2</i> Exon 20 insertion (3bp)	COSM12553	1.38	36	36	36	36	100.0% (90.3%-100.0%)	100.0% (90.3%-100.0%)
		2.66	36	36	36	36	100.0% (90.3%-100.0%)	100.0% (90.3%-100.0%)
<i>ERBB2/HER2</i> Exon 20 insertion (9bp)	COSM12556	1.31	36	36	36	36	100.0% (90.3%-100.0%)	100.0% (90.3%-100.0%)
		2.53	36	36	36	36	100.0% (90.3%-100.0%)	100.0% (90.3%-100.0%)

Variant	Variant ID	Variant Level (xLoD)	Total Pairs		Concordant Pairs		Within-Run Repeatability (95% CI)	
			No Calls Included	No Calls Excluded	No Calls Included	No Calls Excluded	No Calls included	No Calls Excluded
<i>ERBB2/HER2</i> Exon 20 insertion (12bp)	COSM20959	1.00	36	36	36	36	100.0% (90.4%-100.0%)	100.0% (90.4%-100.0%)
		1.41	36	36	36	36	100.0% (90.4%-100.0%)	100.0% (90.4%-100.0%)
95% CI Calculated with Wilson Score method								

Table 10. Variant Component Analysis for *ERBB2/HER2* Exon 20 Insertions

Variant	Variant ID	Variant Level (xLoD)	Operator / Instrument		Reagent Lot		Within-Run (Repeatability)		Between-Run (Between operator)		Overall (Within-Lab)	
			SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV
<i>ERBB2/HER2</i> Exon 20 insertion (12 bp) [3]	COSM20959	1.00	0	0.00	0	0.00	0.95	18.30	0	0.00	0.95	18.30
		1.41	0	0.00	0.3	4.06	0.93	12.56	0	0.00	0.98	13.20
<i>ERBB2/HER2</i> Exon 20 insertion (9 bp)	COSM12556	1.31	0	0.00	0.33	6.46	0.93	18.16	0	0.00	0.99	19.27
		2.53	0	0.00	0	0.00	0.93	11.27	0	0.00	0.93	11.27
<i>ERBB2/HER2</i> Exon 20 insertion (3 bp)	COSM12553	1.38	0	0.00	0.37	9.05	0.56	13.60	0	0.00	0.73	17.71
		2.66	0.05	0.66	0.16	2.07	0.97	12.24	0	0.00	0.98	12.43

An additional study was conducted, starting from DNA, to further evaluate the repeatability and reproducibility of the ODxET workflow for detecting

ERBB2/HER2 SNVs in FFPE tissue samples. The study included two FFPE clinical samples harboring *ERBB2/HER2* SNVs in exon 20 and exon 22, and two NSCLC FFPE clinical samples WT for *ERBB2/HER2* variants. One of the variant positive samples was from a NSCLC FFPE clinical specimen (exon 20 [TKD]), and the other (exon 22 [non-TKD]) was from non-NSCLC tissue blended with DNA from an NSCLC FFPE clinical specimen WT for *ERBB2/HER2* variants. Robust sequencing coverage of the *ERBB2/HER2* regions of interest amongst NSCLC samples and across TKD and non-TKD *ERBB2/HER2* regions supported the use of a non-NSCLC, non-TKD SNV for this rare biomarker. The study was designed to assess reproducibility (variability across three testing sites, operators, and instruments) and repeatability (within-run variability) using three lots of ODxET reagents, controls, and Genexus™ Dx Integrated Sequencer reagents and consumables. Each of the three test sites included two operators, two instruments, and used two of the three lots. DNA blends containing *ERBB2/HER2* SNVs were prepared to represent two variant levels: 1–1.5x LoD and 2–3x LoD. For each DNA sample blend, a total of 72 replicates were generated per LoD level.

The call rate, no call rate, positive call rate, and negative call rate were calculated for each variant of interest (summarized in Table 11). The positive call rate was 100% for the *ERBB2/HER2* SNV, with no instances of no calls observed. The negative call rate, evaluated using two WT NSCLC samples and calculated for relevant hotspots, ranged from 99.6% to 100%, excluding no-calls.

Table 11. Call rates for *ERBB2/HER2* SNVs by Sample

Variant	Variant ID	Total Calls	Positive Calls	Negative Calls	No Calls	Variant Level (xLoD)	Positive Call Rate (95%CI)		Negative Call Rate (95%CI)	
							No Calls included	No Calls excluded	No Calls included	No Calls excluded
<i>ERBB2/HER2</i> Exon 20 SNV (p.G776V)	COSM18609	72	72	0	0	1.7	100% (94.9%, 100.0%)	100% (94.9%, 100.0%)	0% (0.0%, 5.1%)	0% (0.0%, 5.1%)
		72	72	0	0	3.0	100% (94.9%, 100.0%)	100% (94.9%, 100.0%)	0% (0.0%, 5.1%)	0% (0.0%, 5.1%)
<i>ERBB2/HER2</i> Exon 22 SNV (p.R896H)	COSM119971	72	72	0	0	1.2	100% (94.9%, 100.0%)	100% (94.9%, 100.0%)	0% (0.0%, 5.1%)	0% (0.0%, 5.1%)
		72	72	0	0	2.6	100% (94.9%, 100.0%)	100% (94.9%, 100.0%)	0% (0.0%, 5.1%)	0% (0.0%, 5.1%)
WT1	N/A	144	1	142	1	N/A	0.7% (0.1%, 3.8%)	0.7% (0.1%, 3.9%)	98.6% (95.1%, 99.6%)	99.3% (96.1%, 99.9%)
WT2	N/A	144	0	144	0	N/A	0% (0.0%, 2.6%)	0% (0.0%, 2.6%)	100% (97.4%, 100.0%)	100% (97.4%, 100.0%)

Repeatability for the detection of *ERBB2/HER2* SNVs was evaluated across within-run, between run / day, between tech / system, between-lot, between-site, within-site, and total variability. When including or excluding no calls from the reproducibility study data, the within-run repeatability was 100% (Table 12).

Table 12. Within Run Repeatability Estimates for *ERBB2/HER2* SNVs

Variant	Variant ID	Variant Level (xLoD)	Total Pairs		Concordant Pairs		Within-Run Repeatability (95%CI)	
			No Calls Included	No Calls excluded	No Calls Included	No Calls excluded	No Calls included	No Calls excluded
ERBB2/HER2 exon 20 SNV (p.G776V)	COSM18609	1.7	36	36	36	36	100% (90.4%, 100.0%)	100% (90.4%, 100.0%)
		3.0	36	36	36	36	100% (90.4%, 100.0%)	100% (90.4%, 100.0%)
ERBB2/HER2 exon 22 SNV (p.R896H)	COSM119971	1.2	36	36	36	36	100% (90.4%, 100.0%)	100% (90.4%, 100.0%)
		2.6	36	36	36	36	100% (90.4%, 100.0%)	100% (90.4%, 100.0%)
WT1	COSM119971	N/A	36	36	34	35	94.4% (90.4%, 100.0%)	97.2% (85.8%, 99.5%)
	COSM18609	N/A	36	36	36	36	100% (90.4%, 100.0%)	100% (90.4%, 100.0%)
WT2	COSM18609	N/A	36	36	36	36	100% (90.4%, 100.0%)	100% (90.4%, 100.0%)
	COSM119971	N/A	36	36	36	36	100% (90.4%, 100.0%)	100% (90.4%, 100.0%)

Variance component analysis for target variants is summarized in Table 13.

Table 13. Variance Component Analysis Results for *ERBB2/HER2* SNVs

Variant	Variant ID	Variant Level (xLoD)	Within Run		Between Run / Day		Between Tech / System		Between Lot		Within Site (Intermediate Precision)		Between Site		Overall	
			SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV
<i>ERBB2/HER2</i> exon 20 SNV (p.G776V)	COSM18609	1.7	0.82	15.3	0.00	0.0	0.00	0.0	0.00	0.0	0.82	15.3	0.26	4.8	0.86	16.0
		3	1.06	10.8	0.00	0.0	0.00	0.0	0.00	0.0	1.06	10.8	0.17	1.8	1.08	11.0

Variant	Variant ID	Variant Level (xLoD)	Within Run		Between Run / Day		Between Tech / System		Between Lot		Within Site (Intermediate Precision)		Between Site		Overall	
			SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV
<i>ERBB2/HER2</i> exon 22 SNV (p.R896H)	COSM119971	1.2	0.81	17.6	0.00	0.0	0.00	0.0	0.03	0.7	0.81	17.7	0.00	0.00	0.81	17.7
		2.6	0.91	9.6	0.33	3.5	0.32	3.3	0.40	4.2	1.10	11.6	0.00	0.00	1.10	11.6

b. Sample Processing Reproducibility

ODxET sample processing reproducibility was previously evaluated for three NSCLC FFPE clinical samples with *ERBB2/HER2* exon 20 insertions (3bp, 6bp and 12bp) and two NSCLC FFPE clinical samples WT for *ERBB2/HER2* (Table 14). As the sample processing reproducibility study began at the nucleic acid extraction step, it was conducted using neat (undiluted) samples. Consequently, the VAF levels in these samples were relatively high, and samples with VAFs near the LoD were not assessed in this study. To evaluate reproducibility at or near the assay's LoD, samples with variant levels close the LoD (1-1.5x LoD) were evaluated separately in the panel reproducibility study. Please refer to Section IX.A.4.a for details on the panel reproducibility study. Please refer to the Summary of Safety and Effectiveness Data of P240040 (Section IX.A.4.a) for study details.

Table 14. Sample Reproducibility Results for *ERBB2/HER2* Exon 20 Insertions

Variant ID	COSMIC ID	Variant Level (xLoD)	Total Calls	Positive Calls	Negative Calls	No Calls	No Calls Excluded	
							Positive Call Rate (95% CI)	Negative Call Rate (95% CI)
<i>ERBB2/HER2</i> Exon 20 insertion (12bp) [1]	COSM20959	4.29	12	12	0	0	100.0% (75.8%, 100.0%)	0.0% (0.0%, 24.2%)
<i>ERBB2/HER2</i> Exon 20 insertion (3bp)	COSM12552	2.17	12	12	0	0	100.0% (73.5%, 100.0%)	0.0% (0.0%, 26.5%)

Variant ID	COSMIC ID	Variant Level (xLoD)	Total Calls	Positive Calls	Negative Calls	No Calls	No Calls Excluded	
							Positive Call Rate (95% CI)	Negative Call Rate (95% CI)
<i>ERBB2/HER2</i> Exon 20 insertion (6bp)	COSM303939	6.11	12	12	0	0	100.0% (73.5%, 100.0%)	0.0% (0.0%, 26.5%)
<i>ERBB2/HER2</i> Exon 20 insertion (12bp) [2]	COSM20959	1.92	12	12	0	0	100.0% (73.5%, 100.0%)	0.0% (0.0%, 26.5%)
WT	N/A	N/A	132	0	132	0	0.0% (0.0%, 2.8%)	100.0% (97.2%, 100.0%)

Platform-level SNV reproducibility data, reproducibility data from two *ERBB2/HER2* SNVs in non-NSCLC tissues, and robust sequencing coverage of *ERBB2/HER2* regions of interest amongst NSCLC samples collectively provided sufficient evidence to support sample processing reproducibility for *ERBB2/HER2* TKD SNVs in NSCLC. Please refer to the Summary of Safety and Effectiveness Data of P240040 (Section IX.A.4.a) for platform-level SNV data for the ODxET.

5. Stability

a. Stability of Assay Intermediates

Please refer to the Summary of Safety and Effectiveness Data of P240040 (Section IX.A.5.a) for platform level stability of assay intermediates data for ODxET.

b. FFPE Tissue Block, Curl, and Slide Stability

The platform level stability of FFPE tissue blocks, tissue sections (curls), and slide-mounted sections was evaluated for P240040. Please refer to the

Summary of Safety and Effectiveness Data of P240040 (Section IX.A.5.b) for full study details.

c. Extracted Nucleic Acid Stability

Please refer to the Summary of Safety and Effectiveness Data of P240040 (Section IX.A.5.b) for platform-level nucleic acid stability.

d. Reagent Stability

Please refer to the Summary of Safety and Effectiveness Data of P240040 (Section IX.A.5.d) for platform level reagent stability data for ODxET.

6. Reagent Lot Interchangeability – ODxET and Genexus Sequencing Reagents

Please refer to the Summary of Safety and Effectiveness Data of P240040 (Section IX.A.6) for platform level reagent lot interchangeability data for ODxET.

7. Contrived Sample Functional Characterization Study

Please refer to the Summary of Safety and Effectiveness Data of P240040 (Section IX.A.7).

8. FFPE Slide vs Curl Equivalency Study

Please refer to the Summary of Safety and Effectiveness Data of P240040 (Section IX.A.8) for platform level FFPE slide vs. curl equivalency data for ODxET.

9. Extraction Method Equivalency Study

Please refer to the Summary of Safety and Effectiveness Data of P240040 (Section IX.A.9) for platform level extraction level equivalency data for ODxET.

B. Animal Studies

No animal studies were conducted using ODxET.

X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

Life Technologies Corporation conducted a clinical validation study to support the reasonable assurance of safety and effectiveness of the ODxET for detecting *ERBB2/HER2* activating mutations (SNVs in exons 18-21 within the tyrosine kinase domain and exon 20 insertions) in tumor tissue specimens to identify patients with NSCLC who may benefit from treatment with HYRNUO[®] (sevabertinib). A summary of the clinical study is provided below.

A. Study Design

The clinical performance of ODxET was established through a retrospective analysis of samples from patients enrolled in the SOHO-01 clinical trial (NCT05099172), an open-label, multicenter study that evaluated the safety, tolerability, pharmacokinetics, and anti-tumor activity of sevabertinib in participants with advanced non-squamous NSCLC and documented *ERBB2/HER2* TKD activating mutations.

A clinical bridging study was performed to assess the concordance between *ERBB2/HER2* TKD activating mutation results generated by the ODxET and those obtained from clinical trial assays (CTAs) used for patient enrolment in the SOHO-01 trial. The study also evaluated the clinical effectiveness of ODxET in identifying patients with *ERBB2/HER2* TKD activating mutations who were likely to benefit from treatment with HYRNUO[®] (sevabertinib).

Retrospective testing was performed using ODxET on *ERBB2/HER2* TKD activating mutation positive samples from SOHO-01 trial participants as well as on commercially sourced NSCLC samples that were negative for *ERBB2/HER2* TKD activating mutations as screened using NGS-based assays representative of the CTAs.

The clinical bridging study included a total of 242 FFPE tissue samples: 92 samples positive for *ERBB2/HER2* activating mutations from subjects enrolled in the SOHO-01 trial and 150 commercially sourced biomarker negative samples.

1. Clinical Inclusion and Exclusion Criteria

Inclusion criteria for FFPE clinical trial samples consisted of the following:

- FFPE sample is available from a patient who was enrolled in the SOHO-01 study, Group D or E, received at least one dose of sevabertinib treatment at 20 mg BID and was included in the sevabertinib NDA full analysis set;
- Sample meets ODxET samples requirement criteria (tumor presence and content);
- Sample meets ODxET tissue input requirements;
- Extracted DNA meets ODxET minimum nucleic concentration requirements.

Inclusion criteria for FFPE supplemental biomarker negative samples consisted of the following:

- Pathology diagnosis of NSCLC;
- FFPE sample is available and meets ODxET sample and tissue input requirement criteria;
- Extracted DNA meets ODxET minimum nucleic concentration requirements;
- Mutation status screening result is *ERBB2/HER2* negative.

Exclusion criteria for FFPE samples consisted of the following:

- Samples with patient consent restrictions for participation in the clinical bridging study.

2. **Follow-up Schedule**

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

3. **Clinical Endpoints**

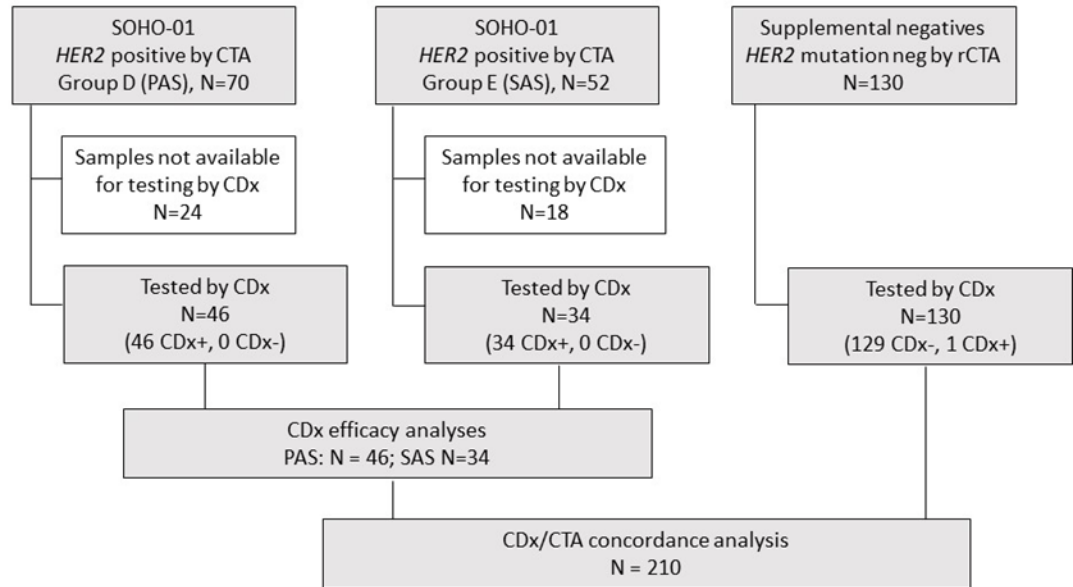
The primary clinical endpoint used to assess HYRNUO[®] (sevabertinib) efficacy in the SOHO-01 clinical study was objective response rate (ORR; complete response [CR] or partial response [PR]). ORR was based on Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1), as assessed by blinded independent central review, and was calculated for patients with non-squamous NSCLC who were treated with sevabertinib in Group D or Group E of SOHO-01.

The clinical effectiveness of the ODxET in the SOHO-01 clinical trial was evaluated by measuring the SOHO-01 primary clinical trial endpoint, ORR, for patients that tested positive for *ERBB2/HER2* TKD activating mutations by the ODxET.

B. **Accountability of PMA Cohort**

A total of 122 subjects were enrolled in the primary analysis set (PAS) [Group D] and the supportive analysis set (SAS) [Group E] of the SOHO-01 clinical trial. Subjects were enrolled based on detection of *ERBB2/HER2* TKD activating mutations using various NGS-based or PCR-based CTAs. Of these, 80 samples were tested with ODxET, and 42 samples were not available for testing (Figure 1). An additional 150 commercially sourced NSCLC FFPE tissue samples were screened using representative CTAs to identify specimens negative for *ERBB2/HER2* TKD activating mutations- for use in the clinical validation of ODxET. Of these, 130 samples were tested with ODxET (Figure 1).

Figure 1. Tissue Sample Accountability Chart for Clinical Bridging Study Samples



C. Study Population Demographics and Baseline Parameters

A comparison of subject demographics, disease characteristics, and prior cancer treatment showed that the ODxET-evaluable and ODxET-unevaluable populations were similar. Data summaries for biomarker positive subjects are presented in Table 15 and Table 16. All commercially sourced biomarker negative NSCLC FFPE tissue samples were ODxET-evaluable.

Table 15. Baseline Demographic Characteristics of ODxET Evaluable and ODxET Non-Evaluable CTA *ERBB2*/HER2 Positive Patients.

	ODxET Evaluable N=80	ODxET Unevaluable N=42	P-value	Total N=122
Age group 1	-	-	0.794	
18-64	50 (62.5%)	24 (57.1%)	-	74 (60.7%)
65-84	29 (36.3%)	17 (40.5%)	-	46 (37.7%)
>=85	1 (1.3%)	1 (2.4%)	-	2 (1.6%)
Age group 2	-	-	0.566	
<65	50 (62.5%)	24 (57.1%)	-	74 (60.7%)
>=65	30 (37.5%)	18 (42.9%)	-	48 (39.3%)
Gender	-	-	0.686	
Female	55 (68.8%)	27 (64.3%)	-	82 (67.2%)
Male	25 (31.3%)	15 (35.7%)	-	40 (32.8%)
Ethnicity	-	-	0.350	
Hispanic or Latino	1 (1.3%)	2 (4.8%)	-	3 (2.5%)
Not Hispanic or Latino	74 (92.5%)	36 (85.7%)	-	110 (90.2%)
Not Reported	5 (6.3%)	4 (9.5%)	-	9 (7.4%)

	ODxET Evaluable N=80	ODxET Unevaluable N=42	P-value	Total N=122
Race	-	-	0.453	
Asian	56 (70.0%)	25 (59.5%)	-	81 (66.4%)
Black or African American	3 (3.8%)	1 (2.4%)	-	4 (3.3%)
White	18 (22.5%)	12 (28.6%)	-	30 (24.6%)
Not Reported	3 (3.8%)	4 (9.5%)	-	7 (5.7%)
P-values were calculated using the two-sided Fisher's exact test.				

Table 16. Baseline Clinical Characteristics of ODxET Evaluable and ODxET Non-Evaluable CTA *ERBB2/HER2* Positive Patients

	ODxET Evaluable N=80	ODxET Unevaluable N=42	P-value	Total N=122
Smoking habits at informed consent	-	-	0.591	-
Current	1 (1.3%)	1 (2.4%)	-	2 (1.6%)
Former	27 (33.8%)	11 (26.2%)	-	38 (31.1%)
Never	52 (65.0%)	30 (71.4%)	-	82 (67.2%)
NSCLC Histology – adenocarcinoma	-	-	NC	-
Yes	80 (97.5%)	42 (100.0%)		122 (100.0%)
Stage at Study Entry	-	-	0.288	-
Stage III A	0	1 (2.4%)	-	1 (0.8%)
Stage III B	1 (1.3%)	1 (2.4%)	-	2 (1.6%)
Stage IV A	24 (30.0%)	9 (21.4%)	-	33 (27.0%)
Stage IV B	46 (57.5%)	29 (69.0%)	-	75 (61.5%)
Missing	9 (11.3%)	2 (4.8%)	-	11 (9.0%)
ECOG Performance Status at Baseline	-	-	0.843	-
0 - Fully Active	27 (33.8%)	15 (35.7%)	-	42 (34.4%)
1 - Restricted Active	53 (66.3%)	27 (64.3%)	-	80 (65.6%)
Prior Brain Metastases at Baseline	-	-	0.823	-
Yes	20 (25.0%)	9 (21.4%)	-	29 (23.8%)
No	60 (75.0%)	33 (78.6%)	-	93 (76.2%)
Prior systemic anti-cancer treatments	-	-	NC	-
Yes	80 (100.0%)	42 (100.0%)	-	122 (100.0%)
Number of prior systemic anti-cancer therapy regimens	-	-	0.397	-
1	37 (46.3%)	15 (35.7%)	-	52 (42.6%)
2	20 (25.0%)	10 (23.8%)	-	30 (24.6%)
>=3	23 (28.8%)	17 (40.5%)	-	40 (32.8%)

	ODxET Evaluable N=80	ODxET Unevaluable N=42	P-value	Total N=122
Best response to the most recent prior systemic anti-cancer therapy	-	-	0.697	-
NA	5 (6.3%)	2 (4.8%)	-	7 (5.7%)
No Response / Treatment Failure	2 (2.5%)	0	-	2 (1.6%)
Not Assessed	0	1 (2.4%)	-	1 (0.8%)
Stable Disease	28 (35.0%)	14 (33.3%)	-	42 (34.4%)
Partial Remission	4 (5.0%)	2 (4.8%)	-	6 (4.9%)
Progressive Disease By Clinical Judgement	2 (2.5%)	0	-	2 (1.6%)
Progressive Disease By Response Assessment Criteria	1 (1.3%)	2 (4.8%)	-	3 (2.5%)
Progressive Disease Measurement Proven	8 (10.0%)	6 (14.3%)	-	14 (11.5%)
Partial Response	23 (28.8%)	9 (21.4%)	-	32 (26.2%)
Unknown	7 (8.8%)	6 (14.3%)	-	13 (10.7%)
Prior <i>EGFR</i> Ex20ins-targeted Therapy	-	-	0.607	-
Yes	2 (2.5%)	2 (4.8%)	-	4 (3.3%)
No	78 (97.5%)	40 (95.2%)	-	118 (96.7%)
Prior <i>ERBB2/HER2</i> Ex20ins-targeted therapy	-	-	0.848	-
Yes	34 (42.5%)	19 (45.2%)	-	53 (43.4%)
No	46 (57.5%)	23 (54.8%)	-	69 (56.6%)
Prior <i>ERBB2/HER2</i> Ex20ins-targeted TKI	-	-	1.000	-
Yes	1 (1.3%)	1 (2.4%)	-	2 (1.6%)
No	79 (98.8%)	41 (97.6%)	-	120 (98.4%)
Prior Surgery Pneumonectomy	-	-	1.000	-
Yes	1 (1.3%)	0	-	1 (0.8%)
No	79 (98.8%)	42 (100.0%)	-	121 (99.2%)
Prior Chemotherapy	-	-	1.000	-
Yes	71 (88.8%)	38 (90.5%)	-	109 (89.3%)
No	9 (11.3%)	4 (9.5%)	-	13 (10.7%)
Use of prior Enhertu	-	-	0.419	-
Yes	24 (30.0%)	16 (38.1%)	-	40 (32.8%)
No	56 (70.0%)	26 (61.9%)	-	82 (67.2%)
Prior Platinum	-	-	0.574	-
Yes	68 (85.0%)	38 (90.5%)	-	106 (86.9%)
No	12 (15.0%)	4 (9.5%)	-	16 (13.1%)

	ODxET Evaluable N=80	ODxET Unevaluable N=42	P-value	Total N=122
Prior Anti-PD(L)1	-	-	0.843	-
Yes	51 (63.8%)	28 (66.7%)	-	79 (64.8%)
No	29 (36.3%)	14 (33.3%)	-	43 (35.2%)

Abbreviations: CDx = Companion Diagnostic, CTA = Clinical Trial Assay (Local Test), ECOG = Eastern Cooperative Oncology Group, *EGFR* = Epidermal Growth Factor Receptor, Ex20ins = Exon 20 Insertion, *ERBB2* = erb-b2 receptor tyrosine kinase 2, *HER2* = Human Epidermal Growth Factor Receptor 2, NSCLC = Non-Small Cell Lung Cancer, PD(L)1 = Programmed Death Ligand1, TKI = Tyrosine Kinase Inhibitor.

P-values were calculated using the two-sided Fisher's exact test.

NC: p-value not calculated due to a single category.

D. Safety and Effectiveness Results

1. Safety Results

Safety with respect to treatment with HYRNUO[®] (sevabertinib) was addressed during the review of the new drug application (NDA) and is summarized in the drug label. Please refer to Drugs@FDA for complete safety information on HYRNUO[®] (sevabertinib).

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

2. Effectiveness Results

a. Concordance Analysis

Concordance between the CTA results and the ODxET results was evaluated using 210 samples: 80 *ERBB2/HER2* activating mutation-positive samples from the SOHO-01 clinical study and 130 biomarker-negative samples from commercial vendors (Table 13. ODxET demonstrated a PPA of 100% (95.4%-100.0%) and NPA of 99.2% (95.8%-99.9%) (Table 17).

Table 17. Concordance Summary of ODxET and CTA results

		CTA		
		Positive	Negative	Total
ODxET	Positive	80	1	81
	Negative	0	129	129
	Total	80	130	210
PPA (95% CI*)		100.0% (95.4%-100.0%)		
NPA (95% CI*)		99.2% (95.8%-99.9%)		
OPA (95% CI*)		99.5% (97.4%-99.9%)		
*95% CI calculated with Wilson score method				

The clinical study samples were enrolled by CTAs, resulting in an enriched CTA-positive population. Therefore, to account for potential bias due to enrichment, the positive predictive value (PPV) and negative predictive value (NPV) were adjusted based on the *ERBB2/HER2* TKD activating mutation frequency of 1.8% in non-squamous NSCLC. The point estimates of PPV and NPV were 70.4% (25.5%-94.4%) and 100.0% (95% CI not evaluable), respectively.

Missing ODxET results for CTA-positive patients were imputed using a logistic regression model. When including imputed values, the PPA was 100% (100.0% - 100.0%), the NPA was 99.2% (97.7% - 100.0%), and the OPA was 99.6% (98.8% - 100.0%).

b. Clinical Efficacy

The efficacy population included 70 patients from Group D, and 52 patients from Group E, with advanced non-squamous NSCLC with *ERBB2/HER2* activating mutations (SNVs in exons 18-21 within the tyrosine kinase domain and exon 20 insertions) based on prospective local testing.

i. NSCLC Previously Treated, Naïve to HER2-Targeted Therapy: Group D

Efficacy was evaluated in 70 patients who had received prior systemic therapy but were naïve to therapy targeting activating *ERBB2/HER2* mutations. As shown in Table 18 below, the ORR in the clinical trial assay (CTA)-positive Group D population was 71.4% (50/70) (95% CI: 59.4%, 81.6%). Among these, 46 patients were both CTA-positive and tested positive for *ERBB2/HER2* TKD activating mutations using the ODxET (ODxET+ | CTA+) with an ORR of 80.4% (37/46) (95% CI: 66.1%, 90.6%). The remaining 24 samples were not available for testing by the ODxET.

The median DOR from Group D was 9.2 months (95% CI: 6.3, 15.0).

Table 18. Group D Objective Response Rates in the Bridging Study Populations

Clinical Efficacy	ODxET+ CTA+	ODxET evaluable CTA+	ODxET unevaluable CTA+	CTA+
Total patients, n	46	See ODxET+ CTA+	24	70
Patients with CR+PR, n	37		13	50
ORR (%) (95% CI)	80.4% (66.1%, 90.6%)		54.2% (32.8%, 74.4%)	71.4% (59.4%, 81.6%)
95% CI for ORR was calculated based on the two-sided Copper-Pearson exact CI method.				

1. Sensitivity Analysis for the Total ODxET+ Population

The ORRs in the total ODxET+ population was estimated using a weighted ORR based on two subgroups: 1) patients who were both CTA-positive and ODxET-positive (CTA+ | ODxET+), and 2) patients who were CTA-negative but ODxET-positive (CTA- | ODxET+). The ORRs for the CTA+ | ODxET+ subgroup was directly observed from the clinical study. Because clinical trial enrollment required CTA positivity, no efficacy data were available for the CTA-/ODxET+ subgroup. Therefore, a sensitivity analysis was conducted to evaluate the potential impact of this unobserved subgroup on the overall efficacy estimate in the total ODxET+ population. The sensitivity analysis explored a range of scenarios (sensitivity factor, c ranging from 0 to 1), assuming the efficacy in CTA- | ODxET+ patients to be equivalent to that in CTA+ | ODxET+ patients (best-case scenario, c=1), or that there would be no therapeutic effect (worst-case scenario, c=0).

The ORR for the total ODxET+ population was calculated using an assumed frequency of *ERBB2/HER2* activating mutations in non-squamous NSCLC of 1.8%, and the observed PPA of 100.0% and NPA of 99.2% (as determined from the concordance analysis). As c increased from 0 to 1, the estimated ORRs with two-sided CIs ranged from 56% (22% to 90%) at c=0 to 80% (71% to 90%) at c=1 (Table 19).

Table 19. Estimated efficacy for ODxET+ population (Group D)

Estimated ORR in the total ODxET+ population with 95% CIs*				
c=0	c=0.25	c=0.5	c=0.75	c=1
56% (22%, 90%)	62% (36%, 88%)	68% (49%, 87%)	74% (62%, 87%)	80% (71%, 90%)
*The two-sided 95% CI was calculated using the delta method				

2. Sensitivity Analysis for Clinical Efficacy in the total ODxET+ Population after Imputation for Missing ODxET results

To assess the potential impact of missing data on drug efficacy estimates, additional sensitivity analyses were conducted. These analyses addressed both unevaluable ODxET results (n=24) and the absence of efficacy data for CTA- | ODxET+ population. Missing ODxET results were estimated using a multiple imputation approach, incorporating covariates associated with the imbalance between ODxET-evaluable and ODxET-unevaluable patients, covariates associated with clinical response, and covariates associated with ODxET results. The ORRs in the ODxET+ population were then re-estimated under various scenarios based on the imputed data. As the sensitivity factor (c) increased from 0 to 1, the estimated ORRs with two-sided 95% CIs ranged from 50% (19%, 80%) at c=0 to 71% (61%, 82%) at c=1.

ii. NSCLC Previously Treated, Including Prior HER2 Targeted Antibody Drug Conjugates (ADCs): Group E

Efficacy was evaluated in 52 patients who had received prior systemic therapy and had documented progression with *ERBB2/HER2*-targeted antibody-drug conjugates. As shown in Table 20 below, the ORR in the clinical trial assay (CTA)-positive population was 38.5% (20/52) (95% CI: 25.3%, 53.0%). Among these, 34 patients were both CTA-positive and tested positive for *ERBB2/HER2* activating mutations using the ODxET (ODxET+ | CTA+) with an ORR of 41.2% (14/34) (95% CI: 24.6%, 59.3%).

Table 20. Group E Objective Response Rates in the Bridging Study Populations

Clinical Efficacy	ODxET+ CTA+	ODxET evaluable CTA+	ODxET unevaluable CTA+	CTA+
Total patients, n	34	See ODxET+ CTA+	18	52
Patients with CR+PR, n	14		6	20
ORR (%) (95% CI)	41.2% (24.6%, 59.3%)		33.3% (13.3%, 59.0%)	38.5% (25.3%, 53.0%)
95% CI for ORR was calculated based on the two-sided Copper-Pearson exact CI method.				

1. Sensitivity Analysis for the Total ODxET+ Population

Using the same methodology described above for Group D (Section X.D.b.i.1), the ORR for the total ODxET+ population was calculated using an assumed frequency of *ERBB2/HER2* activating mutations in non-squamous NSCLC of 1.8%, and the observed PPA of 100.0% and NPA of 99.2% (as determined from the concordance analysis). As c increased from 0 to 1, the estimated ORRs with two-sided CIs ranged from 29% (8% to 49%) at c=0 to 41% (28% to 55%) at c=1 (Table 21).

Table 21. Estimated efficacy for ODxET+ population (Group E)

Estimated ORR in the total ODxET+ population with 95% CIs*				
c=0	c=0.25	c=0.5	c=0.75	c=1
29% (8%, 49%)	32% (13%, 50%)	35% (19%, 51%)	38% (24%, 52%)	41% (28%, 55%)
*The two-sided 95% CI was calculated using the delta method				

2. **Sensitivity Analysis for Clinical Efficacy in the total ODxET+ Population after Imputation for Missing ODxET results**

Using the same methodology described above for Group D (Section X.D.b.i.2), the potential impact of missing data on drug efficacy estimates were assessed. These analyses addressed both unevaluable ODxET results (n=18) and the absence of efficacy data for CTA- | ODxET+ population. The estimated ORRs with two-sided 95% CIs ranged from 27% (7%, 46%) at c=0 to 39% (25%, 52%) at c=1.

3. **Pediatric Extrapolation**

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

Patients aged 18 years and older were eligible for enrollment into the SOHO-01. trial if they fulfilled other inclusion criteria. The youngest patient included in the primary or supportive analysis set was 29 years old. For the SOHO-01 study, data from adult patients aged 29 and older are considered generalizable to the pediatric population aged 18-21 years and can be relied on to establish safety and effectiveness within the 18-21 years age group.

XI. 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 one was a full-time employee of the sponsor and 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.

XII. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Not applicable.

XIII. 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 Clinical and Genetics Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIV. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The effectiveness of ODxET in identifying *ERBB2/HER2* activating mutations (SNVs in exons 18-21 within the tyrosine kinase domain and exon 20 insertions) in patients with non-squamous NSCLC who may benefit from treatment with HYRNUO[®] (sevabertinib) was demonstrated through a clinical bridging study using specimens from patients enrolled in the SOHO-01 trial. Data from both nonclinical (analytical) and clinical validation studies provide a reasonable assurance of the safety and effectiveness of ODxET when used in accordance with the indications for use. Results from the SOHO-01 trial showed that patients with locally advanced or metastatic non-squamous NSCLC harboring *ERBB2/HER2* activating mutations (SNVs in exons 18-21 within the tyrosine kinase domain and exon 20 insertions) and who have received a prior systemic therapy derived clinical benefit from treatment with HYRNUO[®] (sevabertinib). These findings support the addition of the CDx indication to ODxET.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory studies as well as data collected in a clinical study conducted to support PMA approval as described above. The ODxET is an in vitro diagnostic test, which involves testing of DNA and RNA extracted from FFPE tumor samples.

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 a therapy 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 an indicated therapy. There is also a risk of delayed results, which may lead to delay of treatment with indicated therapy.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in the SOHO-01 clinical study, the analytical validation, and the clinical bridging study conducted to support PMA approval as described above. Treatment with HYRNUO[®] (sevabertinib) is anticipated to provide meaningful clinical benefit to previously treated adult patients with locally advanced or metastatic non-squamous NSCLC with *ERBB2/HER2* activating mutations (SNVs in exons 18-21 within the tyrosine kinase domain and exon 20 insertions) selected for therapy based on the results of testing with the ODxET. Based on the data provided in the clinical concordance study which compared the agreement between results of the ODxET with those of the CTAs and the efficacy analysis, the ODxET has clinically acceptable performance in the selection of patients for treatment and the efficacy observed in the clinical trial is maintained in the efficacy analysis for ODxET. Therefore, there is probable benefit for the use of the ODxET to select non-squamous NSCLC patients with *ERBB2/HER2* activating mutations (SNVs in exons 18-21 within the tyrosine kinase domain and exon 20 insertions) for administration of HYRNUO[®] (sevabertinib).

The probable risks of the device are also based on data collected from the described studies, as conducted to support PMA approval. The risks associated with the use of this device are mainly due to 1) false negatives, false positives, and failure to provide a result and 2) incorrect interpretation of test results. Erroneous device results could adversely influence clinical interpretation and consultation for/management of patients. 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 of patients with non-squamous NSCLC. Patients with false positive results may be treated with HYRNUO[®] (sevabertinib) without clinical benefit and may experience adverse reactions associated with the therapy. A false negative result may prevent a patient from accessing appropriate treatment. There is also a risk of delayed results/failure to provide a result, which may lead to delay of treatment with appropriate and indicated therapy. These risks are partially mitigated by the analytical and clinical performance of the device and device labeling; therefore, the risk of this device is considered to be clinically acceptable for the indication listed.

Patient Perspective

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

In conclusion, given the available information above, the data support that for the indications of the ODxET 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 nonclinical and clinical validation studies support the performance of ODxET as an aid for the identification of *ERBB2/HER2* TKD activating mutations in patients with non-squamous NSCLC for whom HYRNUO[®] (sevabertinib) may be indicated.

XV. CDRH DECISION

CDRH issued an approval order for the PMA (P240040/S005) on September 9, 2026.

The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820), which was in effect at the time of the inspection. As of February 2, 2026, the revised part 820, referred to as the Quality Management System Regulation (QMSR), is effective.

XVI. 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.

XVII. REFERENCES

None.