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:	Guardant360® CDx
Device Procode:	PQP
Applicant's Name and Address:	Guardant Health, Inc. 505 Penobscot Drive Redwood City, CA 94063

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P200010/S026

Date of FDA Notice of Approval: 01/15/2026

The original PMA (P200010) for Guardant360® CDx was approved on August 7, 2020 for the detection of *EGFR* exon 19 deletions, L858R and T790M, in circulating cell-free DNA (cfDNA) from plasma of peripheral whole blood from patients with non-small cell lung cancer (NSCLC). Subsequently, additional PMA supplements were approved for expanding the indications for use of Guardant360® CDx for detecting *EGFR* exon 20 insertions (P200010/S001), *KRAS* G12 mutations (P200010/S002) and *ERBB2/HER2* activating mutations (single nucleotide variants [SNVs] and exon 20 insertions) in patients with NSCLC (P200010/S008) and *ESR1* missense mutations between codons 310-547 (P200010/S010) and *ESR1* mutations (SNVs and V422 deletion) in patients with breast cancer (P200010/S021). The SSEDs to support the previously approved indications are available on the CDRH website.

The current panel-track supplement was submitted to expand the intended use and indications for use of Guardant360® CDx to include a companion diagnostic indication for the detection of *BRAF* V600E in colorectal cancer (CRC) patients who may benefit from treatment with BRAFTOVI (encorafenib) in combination with ERBITUX (cetuximab).

II. INDICATIONS FOR USE

Guardant360® CDx is a qualitative next generation sequencing-based in vitro diagnostic device that uses targeted high throughput hybridization-based capture technology for detection of single nucleotide variants (SNVs), insertions and deletions (indels) in 55 genes, copy number amplifications (CNAs) in two (2) genes, and fusions in four (4) genes. Guardant360® CDx utilizes circulating cell-free DNA (cfDNA) from plasma of

peripheral whole blood collected in Streck Cell-Free DNA Blood Collection Tubes (BCTs). The test is intended to be used as a companion diagnostic to identify patients who may benefit from treatment with the therapies listed in **Table 1** in accordance with the approved therapeutic product labeling.

Table 1. Companion Diagnostic Indications

Indication	Biomarker	Therapy
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions, L858R and T790M*	TAGRISSO® (osimertinib)
	EGFR exon 20 insertions	RYBREVANT® (amivantamab-vmjw)
	ERBB2/HER2 activating mutations (SNVs and exon 20 insertions)	ENHERTU® (fam-trastuzumab deruxtecan-nxki)
	KRAS G12C	LUMAKRAS™ (sotorasib)
Breast cancer	*ESR1* missense mutations between codons 310 and 547	ORSERDU™ (elacestrant)
	ESR1 E380, V422del, S463, >469, *L536, Y537,* and *D538* mutations	INLURIYO™ (imlunestrant)
Colorectal cancer (CRC)	*BRAF V600E*	BRAFTOVI® (encorafenib) in combination with ERBITUX® (cetuximab)

A negative result from a plasma specimen does not assure that the patient's tumor is negative for genomic findings. Patients who are negative for the biomarkers listed in **Table 1** should be reflexed to tissue biopsy testing for **Table 1** biomarkers using an FDA-approved tumor tissue test, if feasible.

*The efficacy of TAGRISSO® (Osimertinib) has not been established in the EGFR T790M plasma-positive, tissue-negative or unknown population and clinical data for *T790M* plasma-positive patients are limited; therefore, testing using plasma specimens is most appropriate for consideration in patients from whom a tumor biopsy cannot be obtained.

Additionally, the test is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for cancer patients with any solid malignant neoplasm. The test is for use with patients previously diagnosed with cancer and in conjunction with other laboratory and clinical findings.

Genomic findings other than those listed in **Table 1** are not prescriptive or conclusive for labeled use of any specific therapeutic product.

Guardant360® CDx is a single-site assay performed at Guardant Health, Inc.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Guardant360® CDx labeling.

V. DEVICE DESCRIPTION

Guardant360® CDx test includes reagents, software, and procedures for testing cfDNA from whole blood samples. The test uses up to 30 ng of cfDNA for library construction and next generation sequencing (NGS). Sequencing data is processed using a customized bioinformatics pipeline designed to detect several classes of genomic alterations, including nucleotide substitutions, indels, copy number amplifications, and genomic fusions / rearrangements. The device is designed to sequence 74 genes but only report pre-defined and de novo alterations within the 55 genes outlined in **Table 2.** The test's reportable range for SNVs and indels covers approximately 46,000 bases.

Table 2. Genes Containing Alterations Detected by the Guardant360® CDx

Alteration Type	Genes
Single Nucleotide Variants (SNVs)	*AKT1, ALK, APC, AR, ARAF, ATM*, BRAF, BRCA1**, BRCA2**, CCND1, CDH1, CDK4, CDK6, CDK12* CDKN2A, CTNNB1, EGFR, ERBB2, ESR1, FGFR1, FGFR2, FGFR3, GATA3, GNA11, GNAQ, HRAS, IDH1, IDH2, KIT, KRAS, MAP2K1, MAP2K2, MET, MLH1, MTOR, MYC, NF1, NFE2L2, NRAS, NTRK1, NTRK3, PDGFRA, PIK3CA, PTEN, RAF1, RET, RHEB, ROS1, SMAD4, SMO, STK11, TERT, TSC1, VHL*

Alteration Type	**Genes**
Indels	*AKT1, ALK, APC, ATM*, BRAF, BRCA1**, BRCA2**, CDH1, CDK12*, CDKN2A, EGFR, ERBB2, ESR1, FGFR2, GATA3, HNF1A, HRAS, KIT, KRAS, MET, MLH1, NF1, PDGFRA, PIK3CA, PTEN, RET, ROS1, STK11, TSC1, VHL*
Copy Number Amplifications (CNAs)	*ERBB2, MET*
Fusions/Rearrangements	*ALK, NTRK1, RET, ROS1*

*Reporting is enabled for pathogenic germline alterations only. Somatic alterations will not be reported.

**Reporting is enabled for both germline and somatic alterations.

Test Output

The test report includes variants reported in the following categories; see **Table 3**.

Table 3. Category Definitions

Category	Guardant360® CDx			Comments
	Prescriptive use for a Therapeutic Product	Clinical Performance	Analytical Performance	
Category 1: Companion Diagnostic (CDx)	**Yes**	**Yes**	**Yes**	ctDNA biomarkers linked to the safe and effective use of the corresponding therapeutic product, for which Guardant360® CDx has demonstrated clinical performance shown to support therapeutic efficacy and strong analytical performance for the biomarker.
Category 2: Biomarkers with Strong Evidence of Clinical Significance in ctDNA	No	No	**Yes**	ctDNA biomarkers with strong evidence of clinical significance presented by other FDA-approved liquid biopsy companion diagnostics for which Guardant360® CDx has demonstrated analytical reliability but not clinical performance.

Category	Guardant360® CDx			Comments
	Prescriptive use for a Therapeutic Product	Clinical Performance	Analytical Performance	
Category 3A: Biomarkers with Evidence of Clinical Significance in tissue supported by: strong analytical validation using ctDNA	No	No	**Yes**	ctDNA biomarkers with evidence of clinical significance presented by tissue-based FDA-approved companion diagnostics or professional guidelines for which Guardant360® CDx has demonstrated analytical performance including analytical accuracy, and concordance of blood based testing to tissue-based testing for the biomarker.
Category 3B: Biomarkers with Evidence of Clinical Significance in tissue supported by: analytical validation using ctDNA	No	No	**Yes**	ctDNA biomarkers with evidence of clinical significance presented by tissue-based FDA-approved companion diagnostics or professional guidelines for which Guardant360® CDx has demonstrated minimum analytical performance including analytical accuracy.
Category 4: Other biomarkers with potential clinical significance	No	No	**Yes**	ctDNA biomarkers with emergent evidence based on peer-reviewed publications for genes/variants in tissue, variant information from well curated public databases, or in-vitro pre-clinical models, for which Guardant360® CDx has demonstrated minimum analytical performance.

Biomarker Rules for *ERBB2* Activating Mutations Reported by Guardant360® CDx
The following *ERBB2* activating mutations will be reported in Category 1 as a companion diagnostic (CDx) for patients with NSCLC for ENHERTU (famtrastuzumab deruxtecan-nxki):

A775_G776insYVMA, Y772_A775dup, P780_Y781insGSP, G778_P780dup, G776delinsVC, G776_V777delinsCVCG, G776delinsLC, V777_S779dup, G776_V777insL, V777_G778insG, G778_S779insLPS, V777_G778insCG, A775_G776insV, A775_G776insTVMA, G776_V777insVGC, G778dup, G778_S779insCPG, L755S, V777L, G776S, S310F, G776V, V777M, S310Y, R678Q, T733I, L755M, L755P, L755W, D769N, D769H, D769Y, L755A, I767M, V842I, T862I, L869R, R896C, R896H, G776C, G776_V777insVC, S779_P780insVGS, I767F, T798I

Biomarker Rules for ESR1 Missense Mutations Reported by Guardant360® CDx
Missense mutations between codons 310 and 347 of *ESR1* will be reported as Category 1 as a companion diagnostic (CDx) for patients with breast cancer for ORSERDUTM (elacestrant).

The following *ESR1* mutations will be reported in Category 1 as a companion diagnostic (CDx) for patients with breast cancer for INLURIYO (imlunestrant):

E380A; E380D; E380K; E380Q; E380V; V422del; S463F; S463P; L469V; L536F; L536G; L536H; L536I; L536K; L536N; L536P; L536Q; L536R; L536V; Y537C; Y537D; Y537G; Y537H; Y537N; Y537P; Y537Q; Y537S; D538E; D538G; D538H; D538N; D538V

Test Kit Contents
The test includes the Guardant360® CDx Blood Collection Kit (BCK), which is sent to ordering laboratories. Each BCK contains two blood collection tubes. The BCK also contains supporting packaging materials, instructions for use and a return shipping label. The BCK contains the following components:

- Streck blood collection tubes for specimen collection, stabilization, and transport of cfDNA; 2 per kit.
- Cushioning materials to prevent breakage of the blood collection tubes; 2 per kit
- Foam tray for protection of collection tubes during transport
- Absorbent sheet to be used during specimen shipping
- Biohazard specimen bag for protection during specimen transport
- Return shipping label for return of specimen to Guardant Health
- Barcodes for specimen identification and shipping instructions
- Instructions for Use for blood draw
- Patient welcome brochure which contains an overview of the test
- Test requisition form to complete to order Guardant360® CDx for a patient.

The test also includes the Guardant360® CDx Sample Preparation Kit (SPK), which is used in the Guardant Health Clinical Laboratory. The SPK contains reagents for library preparation, library enhancement, and cfDNA quantification/qualification. The kit is assembled into six (6) different boxes (referred to as box 1, 2, 3, 4a, 4b, and 4c) based on the usage of the reagents. The division of reagents amongst the boxes reflects different storage conditions and/or locations (e.g. different laboratory spaces).

Instruments
Guardant360 CDx is intended to be performed with serial number-controlled instruments as indicated in **Table 4.** All instruments are qualified by Guardant Health, Inc. under the Guardant Health Quality System.

Table 4. Serial Number Controlled Instruments

Instrument
Agilent Technologies 4200 TapeStation Instrument
Hamilton Company Microlab STAR
Hamilton Company Microlab STARlet
Illumina NextSeq 550 Sequencer
Veriti 96-Well Thermal Cycler

Test Process
Whole Blood Collection and Shipping
The Guardant360® CDx Blood Collection Kit is used by ordering laboratories / physicians to collect whole blood specimens and ship them to the Guardant Health Clinical Laboratory. A minimum of 5 mL whole blood must be received in order to achieve optimal performance for the Guardant360® CDx assay. Underfilling of tubes with less than 5 mL of blood may lead to incorrect analytical results or poor product performance.

Plasma Isolation and cfDNA Extraction
Whole blood specimens are processed in the Guardant Health Clinical Laboratory within 7 days of blood collection. Plasma is isolated from both tubes of whole blood via centrifugation. One tube of plasma is stored, while the second tube is used for cfDNA extraction using the QIAGEN QIAsymphony SP Instrument and reagent system. The resulting cfDNA is quantified using the 4200 TapeStation. Input amounts up to 30 ng of cfDNA are further processed for each sample.

Library Preparation and Enrichment
Reagents from the Guardant360® CDx Sample Preparation Kit are used during library preparation, enrichment, enrichment wash, and quantitation steps using the Veriti 96-Well Thermal Cycler, Microlab STAR and STARlet, and 4200 TapeStation Instruments. During library preparation, cfDNA fragment ends are repaired and library adapters containing inline barcodes are attached using blunt-end ligation. The resulting DNA is amplified by PCR to create libraries suitable for enrichment.

Amplified libraries are enriched for genes of interest using hybrid target capture with custom biotinylated RNA probes. Each enriched library is amplified by PCR using a unique index primer that also contains a sequencing flow cell attachment sequence. Amplified enriched libraries are

pooled in equimolar amounts, denatured, and diluted to appropriate concentration for sequencing.

DNA Sequencing
Paired-end sequencing by synthesis is performed with the Illumina NextSeq 550 Sequencing system. The amplified cfDNA is analyzed by parallel sequencing of amplified target genes to an average depth of coverage of greater than 2,700 unique molecules.

Data Analysis and Reporting
The Guardant360® CDx Software uses a custom-developed analysis bioinformatics pipeline (BIP) software module. The BIP software module uses the raw data (output) from the targeted sequencing, partitions the data based on the sample index sequence (barcode) of each read to separate reads originating from individual samples, and executes a proprietary algorithmic reconstruction of the digitized sequencing signals based on molecular barcodes for high-fidelity molecule-based alteration calling downstream. The sequence data then undergoes an alignment process where it is mapped to the human genome (hg19) and an analysis of sequence alteration data is performed.

Alteration detection is conducted according to alteration calling metrics derived from clinical sample analysis. All alterations must pass alteration calling metrics as described in **Table 5**.

The SNV and indel cut-offs are defined in terms of mutant allele fraction (MAF) estimate, number and type of molecules supporting the alteration, pseudo-gene assessment, and likelihood ratio (LLR). The MAF estimate describes the calculated allelic fraction of an SNV or indel. The number of molecules describes the observed number of molecules meeting requirements for a particular alteration call. The LLR score is a calculated number that reflects how much observed support for the mutation exceeds expectations based on PCR and sequencing induced artifacts.

Table 5. Analytical Alteration Calling Threshold/Cut-Off Metrics

SNV Calling Property	Metric
DNA Molecule Support	≥ 2
MAF Estimate	≥ 0.001%
Log Likelihood Ratio	≥ 0
Indel Calling Property	**Metric**
DNA Molecule Support	≥ 2
MAF Estimate	≥ 0.01%
Log Likelihood Ratio	≥ 10

CNA Calling Property	Metric
ERBB2 copy number	≥ 2.18
ERBB2 Z-score	≥ 10
ERBB2 amplification is not associated with chromosome-arm	TRUE
MET copy number	≥ 2.16
MET Z-score	≥ 10
MET amplification is not associated with chromosome-arm aneuploidy	TRUE
Fusion Calling Property	**Metric**
MAPQ score of supporting molecule to fusion sequence	> 30
Number of unique fusion molecules	≥ 2
Number of unique fusion reads	> 2

The laboratory and physician receive a qualitative alteration-level result. A sample will receive an overall "Failed" result when any QC metric is failed. Samples failing any QC metric are automatically held and not released. The laboratory may attempt to rerun a patient sample that has failed a QC metric by using stored plasma or intermediate products. Results from samples passing all QC metrics are formatted onto an IVD results report with CDx relevant information (Category 1) and all other biomarkers (Categories 2-4).

Quality Control Measures

The Guardant360® CDx Sample Preparation Kit includes the Variant Control, which is engineered to contain known positive and negative alterations and is treated as a sample. Additionally, a no template negative control (NTC) is run in parallel with patient samples.

The Variant Control consists of a mixture of cfDNA from multiple human cancer cell lines containing all four alteration types, SNVs, indels, CNAs and fusions. The control is treated as a sample and processed starting from 15 ng cfDNA input through sequencing where it is analyzed for the presence and absence of the specific alterations.

Although the Variant Control does not contain all the alterations that the test is capable of detecting, concordant detection of alterations targeted in the Variant Control indicates that assay is performing as expected across the panel.

In addition to assessing Variant Control performance within a batch, the test is assessing multiple per-sample in-process and post-sequencing analytical metrics for each of the patient samples tested. These metrics provide in depth analytical QC information that complements Variant Control performance data and is specific and informative to that sample performance.

Due to a lack of DNA template in the NTC samples, cfDNA extraction, library preparation, and enrichment steps are expected to result in background level metrics.

VI. Alternative Practices and Procedures

There are FDA approved companion diagnostic (CDx) alternatives for the detection of some of the genetic alterations using cfDNA isolated from plasma samples to those that are listed in **Table 1** of the Guardant360® CDx intended use statement. These approved alternative CDx tests are listed in **Table 6** below. Each alternative has its own advantages and disadvantages. A patient should fully discuss any alternative with their physician to select the most appropriate method that best meets expectations and lifestyle. For additional details see list of FDA 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

Table 6. List of FDA-Approved CDx Assays for Genes Targeted by Guardant360 CDx

Gene and Variant	Indication	Therapy	Device (PMA #)	Company	Technology
EGFR T790M	NSCLC	TAGRISSO® (osimertinib)	cobas® *EGFR* Mutation Test v2	Roche Molecular Systems, Inc.	Polymerase Chain Reaction
EGFR L858R and exon 19 deletions			FoundationOne® Liquid CDx	Foundation Medicine, Inc.	NGS
BRAF V600E	CRC	BRAFTOVI® (encorafenib) in combination with ERBITUX® (cetuximab)	FoundationOne® Liquid CDx	Foundation Medicine, Inc.	NGS

Note: There are no FDA-approved CDx alternatives using cfDNA isolated from plasma for the detection of *KRAS G12C* mutations for the identification of patients with NSCLC eligible for treatment with LUMAKRAS (sotorasib). However, there is one FDA approved CDx alternative for the detection of *KRAS G12C* mutation in patients with NSCLC using tissue specimens for treatment with LUMAKRAS (sotorasib): QIAGEN *therascreen* KRAS RGQ PCR Kit (See SSED for P110027/S012). Similarly, there are no FDA-approved CDx alternatives using cfDNA isolated from plasma for the detection of *EGFR* exon 20 insertions for the identification of patients with NSCLC eligible for treatment with RYBREVANT (amivantamab-vmjw). There are no FDA-approved CDx alternatives using cfDNA isolated from plasma for the detection of *ERBB2* activating mutations (SNVs and exon 20 insertions) for the identification of patients with NSCLC eligible for treatment with ENHERTU (famtrastuzumab deruxtecan-nxki). There are no

FDA-approved CDx alternatives using cfDNA isolated from plasma for the detection of *ESR1* missense mutations in patients with breast cancer (BC) eligible for treatment with ORSERDU (elacestrant). Also, there are no FDA-approved CDx alternatives using cfDNA isolated from plasma for the detection of specific *ESR1* mutations in patients with BC eligible for treatment with INLURIYO (imlunestrant).

However, there is an FDA approved CDx (Life Technologies Corporation's OncomineDx Target test) alternative for the detection of *EGFR exon 20* insertions in NSCLC patients using tissue specimens for treatment with RYBREVANT (amivantamab-vmjw) (See labeling for P160045/S027). There is also an FDA approved (Life Technologies Corporation's OncomineDx Target test) CDx alternative for the detection of *ERBB2* activating mutations (SNVs and exon 20 insertions) in patients with NSCLC using tissue specimens for treatment with ENHERTU (fam-trastuzumab deruxtecan-nxki) (See SSED for P160045/S035).

VII. Marketing History

The Guardant360® CDx Premarket Approval (PMA) application was FDA-approved on August 7, 2020, and subsequently commercialized in the USA. The approved PMA and its supplements that affected the Intended Use are listed in **Table 7**.

Table 7. Marketing History

Submission No.	Date of Approval	Biomarker	Patient Population	Drug
P200010	August 7, 2020	*EGFR exon 19* deletions, L858R and T790M	NSCLC	TAGRISSO® (osimertinib)
P200010/S001	May 21, 2021	*EGFR exon 20* insertions	NSCLC	RYBREVANT® (amivantamab-vmjw)
P200010/S002	May 28, 2021	*KRAS G12C*	NSCLC	LUMAKRAS™ (sotorasib)
P200010/S008	August 11, 2022	*ERBB2/HER2* activating mutations (SNVs and exon 20 insertions	NSCLC	ENHERTU® (fam-trastuzumab deruxtecan-nxki)
P200010/S010	January 27, 2023	*ESR1* missense mutations between codons 310 and 547	BC	ORSERDU™ (elacestrant)
P200010/S021	September 25, 2025	*ESR1* E380, V422del, S463, L469, L536, Y537, and *D538* mutations	BC	INLURIYO™ (imlunestrant)

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

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Laboratory Studies

The primary evidence for supporting the performance of Guardant360® CDx in detecting *BRAF V600E* was from data presented using intended use specimens across all validation studies. In addition to the existing platform-level validation results, analytical accuracy, limit of detection (LoD), and precision near the LoD studies were conducted using intended use specimens to support the indication for the *BRAF V600E* mutation biomarker.

For Guardant360® CDx platform-level validation (P200010), performance characteristics were established using plasma-derived cfDNA samples from a wide range of cancer types. Each study included CDx variants as well as a broad range of representative alteration types (SNVs, indels, CNAs, and fusions/rearrangements) in various genomic contexts across several genes. The platform validation studies included samples with *BRAF V600E* in plasma specimens from patients with CRC and without CRC. The results from the platform-level validation that have been leveraged to support Guardant360 CDx detection of *BRAF V600E* mutation are referenced below. Additional *BRAF V600E*-specific analytical validation studies are described below.

1. Analytical Accuracy/Concordance with an Orthogonal Method

Accuracy for the detection of *BRAF V600E* was determined relative to an externally validated next generation sequencing (NGS)-based comparator method by comparing the results from 219 samples obtained from patients with CRC.

Of the 219 samples tested, 213 (98.2%) samples passed Guardant360® CDx QC and 209 (95.4%) samples passed comparator QC; 208 (95%) passed QC on both Guardant360® CDx and the comparator. *BRAF V600E* was detected in 103 out of 208 samples (49.5%) with Guardant360® CDx and 102 out of 208 samples (49.0%) with the comparator**. Table 8** summarizes the sample-level agreement between Guardant360® CDx and the comparator for the detection of *BRAF V600E.* Of the 208 evaluable samples, 101 samples (48.6%) were positive for *BRAF V600E* by both Guardant360® CDx and the comparator, while 104 samples (50%) were negative by both devices.

One sample (0.5%) was negative by Guardant360 CDx but positive by the comparator, and two samples (1.0%) were positive by Guardant360® CDx but negative by the comparator. All discordant detections had MAF values that were near or below the limit of detection for both devices (~0.2% MAF at 30 ng input).

A summary of positive percent agreement (PPA) and negative percent agreement (NPA) and corresponding 95% two-sided exact confidence intervals (CIs) is provided in **Table 8**. Since the samples were selected from different sources based on different assays, the unadjusted agreements in **Table 8** may be subject to potential bias. The point estimate for PPA was 99.0% and the lower bound of the two-sided 95% CI was 94.7%. The point estimate for NPA was 98.1%, and the lower bound of the two-sided 95% CI was 93.4%.

Table 8. Sample-Level Agreement of *BRAF V600E* Detection Status between Guardant360® CDx and the Comparator.

Mutation	Guardant360 CDx (+), Comparator (+)	Guardant360 CDx (-), Comparator (+)	Guardant360 CDx (+), Comparator (-)	Guardant360 CDx (-), Comparator (-)	Patients (n)	PPA (95% CI) *	NPA (95% CI) *
BRAF V600E	101	1	2	104	208	99% (94.7%-100%)	98.1% (93.4%-99.8%)

*CI, Clopper-Pearson 95% Confidence Interval. N, Total Sample Number. NPA, Negative Percent Agreement. PPA, Positive Percent Agreement.

2. Analytical Sensitivity

a. Limit of Blank (LoB)

Please refer to the Summary of Safety and Effectiveness Data P200010 (Section IX.A.3.a) for Guardant360® CDx platform-level analytical sensitivity data for LoB. There were no false positives for the *BRAF V600E* mutation among 240 replicates tested across three unique reagent lots.

b. Limit of Detection (LoD)

The LoD of Guardant360® CDx for *BRAF V600E* was previously established in a mixed cancer pool (P200010, Section IX.A.3.b) at a mutant allele fraction (MAF) of 1.8% at 5 ng cfDNA input. A *BRAF V600E* CRC sample was diluted in a background of *BRAF V600E* negative CRC patient cfDNA to target a MAF within 1.0x-1.5x of the established LoD. The samples were tested on Guardant360® CDx at 5 ng cfDNA input. All samples passed QC. At an observed MAF of 2.7%,

which is 1.5x the established LoD of Guardant360 CDx for *BRAF V600E*, the hit rate was 100% (24/24) (**Table 9**)

Table 9. Summary of *BRAF V600E* CRC Positivity Rate at 1.5x LoD

Mutation	Observed MAF (5 ng) at 1.5x LoD
BRAF V600E	2.7%

MAF, Mutant Allele Fraction

These results confirm the established Guardant360 CDx LoD of 1.8% for *BRAF V600E* in CRC patient specimens.

3. **Analytical Specificity**

Please refer to the Summary of Safety and Effectiveness Data P200010 and P200010/S002 (Section IX.A.4) for Guardant360® CDx platform validation of analytical specificity, including endogenous and microbial interfering substances and *in silico* specificity. The effect of potential exogenous interfering substances that may carry over from cfDNA extraction on assay performance was evaluated in the PMA supplement (P200010/S002).

4. **Precision**

The purpose of the study was to evaluate the precision of Guardant360 CDx for *BRAF V600E* using CRC patient samples. *BRAF V600E* positive cfDNA from CRC patients was diluted in a background of *BRAF V600E* negative CRC patient cfDNA to target mutant allele fraction (MAFs) either within 1.0x-1.5x or 2.0x-3.0x of the established LoD.

The samples were tested on Guardant360® CDx at 5 ng of cfDNA input with 24 replicates across 6 unique reagent lot-instrument-operator precision combinations of fully crossed instruments (2) and reagent lots (3) over at least 3 different days. Positive call precision was analyzed at both 1.0-1.5x and 2.0x-3.0x of the established LoD through the assessment of PPA (# positives passing QC/# tested passing QC) across all precision combinations.

One sample with a MAF at 2.0x-3.0x LoD failed enrichment QC and was excluded from sequencing and subsequent analysis. All other samples passed QC. At an observed MAF of 2.7%, which is 1.5x the established LoD of Guardant360® CDx for *BRAF V600E*, the PPA was 100% (24/24) (**Table 10**). At an observed MAF of 5.3%, which is 2.9x the established LoD of Guardant360® CDx for *BRAF V600E*, the PPA was 100% (24/24).

Table 10. Summary of *BRAF V600E* Positive Precision Results

Mutation	Observed MAF%	Relative LoD Level	Number Positive/ Number Tested	PPA (95% CI)
BRAF V600E	2.7%	1.5x	24/24	100.0% (85.8% - 100.0%)
	5.3%	2.9x	23/23	100.0% (85.2% - 100.0%)

*CI, Clopper-Pearson 95% Confidence Interval. MAF, Mutant Allele Fraction.
PPA, Positive Percent Agreement

The PPA at both MAF levels were ≥ 95%. The original PMA (P200010) comprised mutation negative precision data from 72 self- declared cancer-free age-matched healthy donors. In total, 240 replicates were tested at 30 ng inputs across three precision combinations of operator group, instrument combination, reagent lots and start dates. No *BRAF V600E* false positive mutations were detected (NPA 100%, 240/240). These data are leveraged to support this PMA supplement. Please refer to the Summary of Safety and Effectiveness Data for P200010 (Section IX.A.5) for details on precision for mutation-negative samples, precision starting from plasma extraction, and precision studies in support of the Guardant360® CDx platform validation.

5. **Carryover/Cross-Contamination**
   Please refer to the Summary of Safety and Effectiveness Data P200010 (Section IX.A.6) for platform-level carryover/cross-contamination data for Guardant360® CDx.

6. **Reagent Lot Interchangeability**
   Please refer to the Summary of Safety and Effectiveness Data P200010 (Section IX.A.7) for Guardant360® CDx platform validation reagent lot interchangeability**.**

7. **Stability**
   Please see the Summary of Safety and Effectiveness Data P200010 (Section IX.A.8) for Guardant360® CDx platform level reagent and sample stability, including whole blood stability, plasma stability, cfDNA stability, and intermediate sample stability.

8. **Guard Banding/Robustness**
   Please refer to the Summary of Safety and Effectiveness Data P200010/S002 (Section IX.A.6) for Guardant360® CDx platform level Guard Banding/Robustness study.

9. **General Lab Equipment and Reagent Evaluation**
   Please see the Summary of Safety and Effectiveness Data P200010 (Section IX.A.9) for Guardant360® CDx platform validation of general lab equipment and reagents, including for cfDNA extraction as well as other instruments and reagents.

B. **Animal Studies**

No animal studies were conducted using Guardant360® CDx.

C. Other Studies

1. Blood Collection Tube (BCT) Concordance

Please see The Summary of Safety and Effectiveness Data P200010 (Section IX.C.1).

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The safety and effectiveness of the Guardant 360 CDx for identifying colorectal cancer patients with the *BRAF* V600E mutation who may benefit from treatment with BRAFTOVI (encorafenib) in combination with ERBITUX (cetuximab) + mFOLFOX6 (modified fluorouracil, leucovorin, oxaliplatin) was demonstrated through testing of cfDNA in pre-treatment plasma specimens from patients enrolled into the BREAKWATER clinical study (NCT04607421). A summary of the Guardant360® CDx clinical validation study is presented below.

A. BREAKWATER (NCT04607421) Clinical Study Design

The BREAKWATER clinical study was a Phase 3 global, randomized, open-label, 3-arm study of encorafenib in combination with cetuximab (EC) without chemotherapy (Arm A), EC with chemotherapy (Arm B), and standard of care chemotherapy (Arm C) in first line (1L) CRC patients. The study had a safety lead-in portion followed by a Phase 3 portion in which eligible patients were randomized 1:1:1 between the 3 treatment arms with n=158 patients in EC without chemotherapy (Arm A), n= 236 in EC with chemotherapy (Arm B) and n=243 in SOC (Arm C). Enrollment into Arm A was subsequently dropped from the study and enrolled patients were randomly assigned 1:1 to receive either EC + mFOLFOX6 (Arm B) or SOC (Arm C). The BREAKWATER clinical study was used to support the approval of BRAFTOVI (encorafenib) in combination with ERBITUX (cetuximab) + mFOLFOX6 therapy under supplemental new drug application sNDA210496.

For the diagnostic study, pre-treatment plasma samples from 343 of 479 (71.6%) *BRAF* V600E mutation-positive randomized patients in Arm B (n=236) and Arm C (n=243) from the BREAKWATER clinical study were tested with the Guardant360 CDx. Of the 343 pre-treatment plasma samples, those testing positive for *BRAF* V600E by Guardant360® CDx were included in the diagnostic study primary clinical efficacy cohort to assess the clinical validity of Guardant360 CDx to aid in the selection of colorectal cancer patients with *BRAF* V600E mutation for BRAFTOVI (encorafenib) in combination with ERBITUX (cetuximab) + mFOLFOX6 therapy.

The BREAKWATER clinical study only enrolled patients positive for *BRAF* V600E mutations; therefore, the population of patients that would have been negative on the enrolling CTA, but positive on Guardant360® CDx was not represented. As such, additional patients were required to evaluate the enrolling tissue-based CTA *BRAF*

V600E mutation-not detected (CTA-) portion of the Guardant360® CDx-detected (CDx +) intended use population.

To model the hypothetical Guardant360® CDx (+), tissue-based CTA (-) (Guardant360® CDx+/ CTA-) subgroup of the Guardant360 CDx intended use population, supplemental matched tissue and plasma samples were obtained. A sensitivity analysis was performed to evaluate the prevalence of patients positive for *BRAF V600E* mutations by Guardant360® CDx (CDx +), but negative by tissue testing (CTA -) and to evaluate the potential impact of this population on the clinical efficacy in the Guardant360® CDx intended use population.

1. **Clinical Study Inclusion and Exclusion Criteria**

   Patients in the primary BREAKWATER registration population were included in the diagnostic study efficacy cohort if the selection criteria below were met. The key inclusion criteria are summarized below:

   Key BREAKWATER Study Patient Inclusion Criteria:

   - Must be at least 16 years of age (where permitted locally) or 18 years.
   - Must have histologically or cytologically confirmed Stage IV colorectal adenocarcinoma
   - Must have presence of a *BRAF* V600E mutation in tumor tissue or blood
   - Must have no prior systemic regimen(s) for metastatic disease
   - Must have measurable disease as assessed by Investigator and evidenced by available baseline scans
   - Must have Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1
   - Must have adequate bone marrow, hepatic and renal function
   - Must be *RAS* wild type and not be deficiency mismatch repair (dMMR) or microsatellite instability-high (MSI-H) by local confirmation unless the patient is ineligible to receive immune checkpoint inhibitors.

   Guardant360 CDx Diagnostic Study Efficacy Cohort Patient Inclusion Criteria:

   - Patient enrolled in the BREAKWATER clinical study Arm B or Arm C with informed consent for blood sample use for diagnostic development
   - Patient is part of the BREAKWATER NDA registration population
   - Adequate pre-treatment plasma sample available for testing by Guardant360® CDx.

   Guardant360 CDx Study Sensitivity Analysis Prevalence Sub-Study Cohort Patient Inclusion Criteria:

   - The patient has pathologically documented, locally advanced or metastatic CRC
   - Patients must either be previously untreated or have active disease progression and must not be receiving active anti-cancer therapy at the time of blood collection.

- Patients must have archived tumor tissue sample (unstained slides and/or a formalin fixed paraffin embedded tissue block collected within 5 years of the matched plasma sample) with sufficient tumor content and quantity as required by the CTA.
- The patient must have provided a plasma sample that meets the requirements for Guardant360® CDx testing.

2. **Follow-up Schedule**
The Guardant360® CDx diagnostic study involved only the testing and analysis of plasma samples; therefore, no additional patient follow-up was conducted in diagnostic study.

3. **BREAKWATER Study Objective and Endpoints**
The objective of the BREAKWATER study was to evaluate the efficacy of BRAFTOVI (encorafenib) in combination with cetuximab with or without chemotherapy (mFOLFOX6) as a first line treatment for patients with *BRAF V600E*-mutant metastatic colorectal cancer (mCRC).

The primary clinical endpoints used to assess the efficacy in the BREAKWATER clinical study were objective response rate (ORR) by blinded independent central review (BICR) and by progression-free survival (PFS) by BICR. The secondary clinical endpoint was overall survival (OS).

4. **Diagnostic Study Objective and Endpoints**
The primary objective of the diagnostic study was to demonstrate the safety and effectiveness of Guardant360 CDx for aid in selection of metastatic colorectal cancer (mCRC) patients with *BRAF V600E* mutation detected in plasma for treatment with BRAFTOVI (encorafenib) in combination with cetuximab (EC) and chemotherapy [modified fluorouracil/leucovorin/oxaliplatin (mFOLFOX6)].

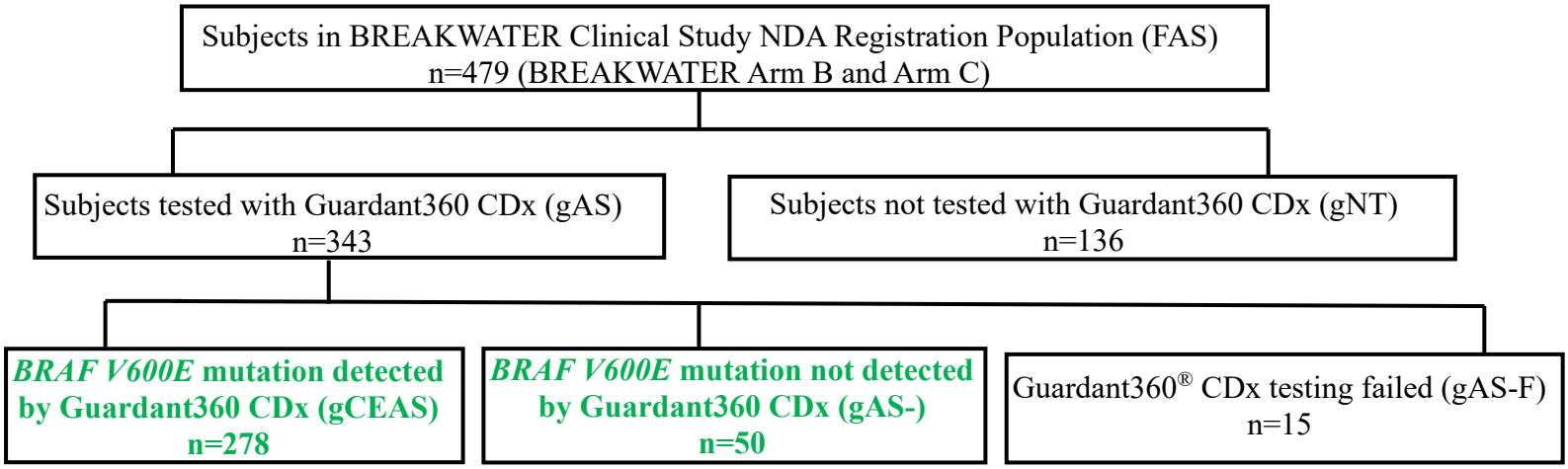
The primary objective was assessed by comparing the clinical efficacy of BRAFTOVI (encorafenib) in combination with cetuximab and chemotherapy to standard of care (SOC) chemotherapy, as measured by objective response rate (ORR) by blinded independent central review (BICR) and by progression free survival (PFS) by BICR in patients with *BRAF V600E* mutation as detected by Guardant360 CDx.

The secondary objectives of the diagnostic study were 1) to compare the clinical efficacy of EC + mFOLFOX6 vs. SOC chemotherapy, as measured by overall survival (OS) in the Guardant360 CDx primary clinical efficacy analysis set (gCEAS); 2) to assess concordance between Guardant360® CDx and enrolling clinical trial assay (CTA) results in patients from the BREAKWATER clinical study and the sensitivity analysis prevalence Sub-Study; and 3) to assess representativeness of the gCEAS relative to the BREAKWATER clinical study registration population (i.e. full analysis set, or FAS) and diagnostic study subgroups as defined by Guardant360® CDx.

B. Accountability of PMA Cohort for Guardant360® CDx for the BREAKWATER Clinical Study

The Guardant360® CDx diagnostic study consisted of 479 patients from Arm B (n=236) and Arm C (n=243) of the BREAKWATER clinical study registration population [full analysis set (FAS)] as shown in **Figure 1** below. Samples from 343 out of 479 (71.6%) randomized patients in EC + mFOLFOX6 (Arm B) and SOC chemotherapy (Arm C) from the phase 3 portion of the BREAKWATER clinical study were tested with Guardant360® CDx (Guardant360 CDx analysis set, or gAS). The *BRAF V600E* mutation was detected in 278 patients (81% of the gAS), the *BRAF V600E* mutation was not detected (defined as the gAS-) in 50 patients (14.6% of the gAS) and 15 (4.4% of the gAS) patient samples failed quality control (QC) and did not generate a valid Guardant360® CDx result (Guardant360® CDx analysis set-failed, or gAS-F). Samples were not available for testing for the remaining 136 randomized patients (Guardant360 CDx not tested, or gNT).

Figure 1. Guardant360 CDx *BRAF V600E* Mutation Efficacy Analysis Patient Accountability and Analysis Set Definitions



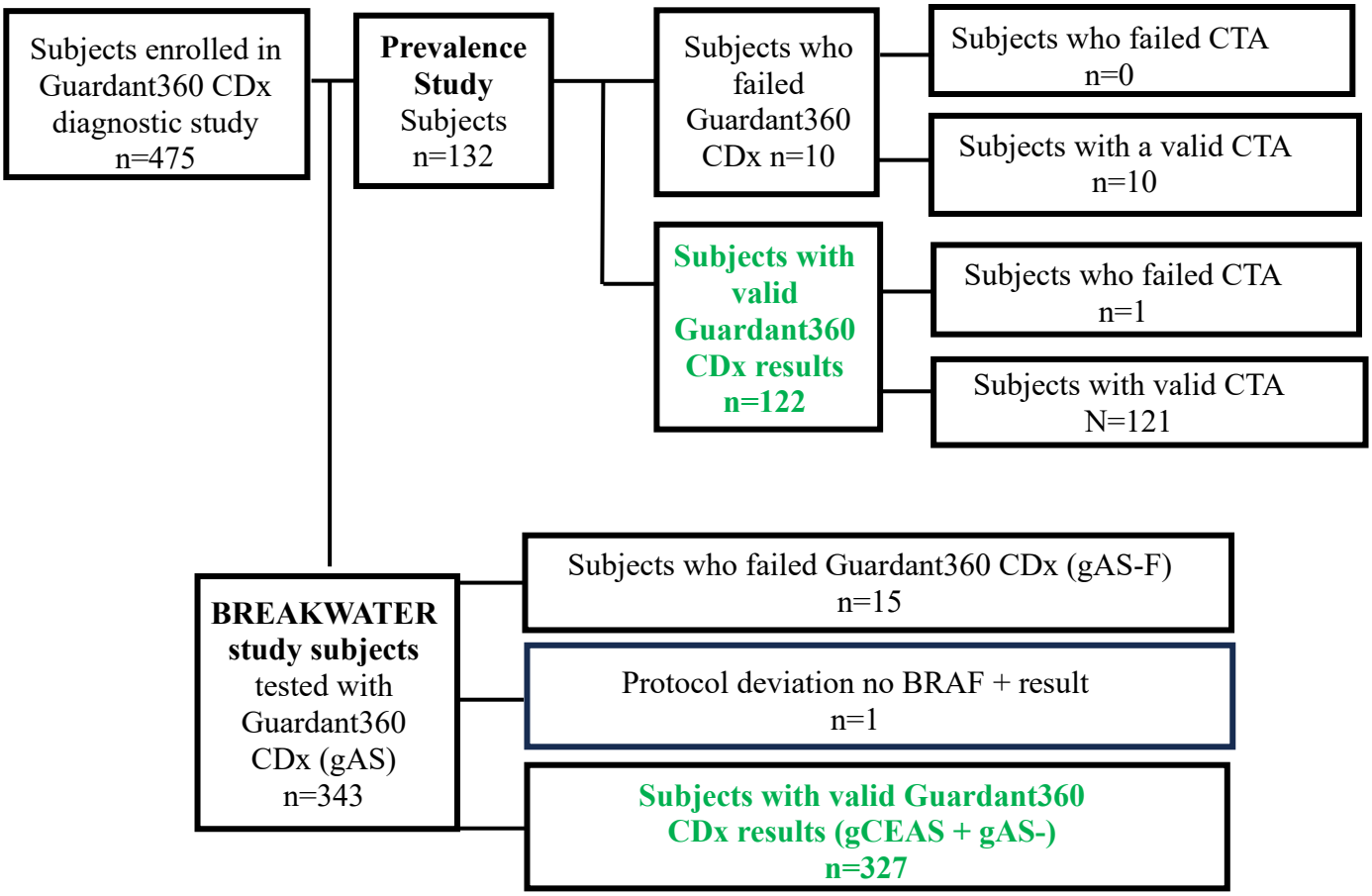
FAS: Full Analysis Set (All randomized patients in the BREAKWATER NDA registration population); **gAS:** Guardant360 CDx Analysis Set (All patients from the FAS tested with Guardant360 CDx; **gNT:** Guardant360 CDx not tested set (All patients in the FAS not tested by Guardant360 CDx); **gCEAS:** Guardant360 CDx primary clinical efficacy analysis set (All patients in the gAS who are *BRAF V600E* positive by Guardant360 CDx); **gAS-:** Guardant360 CDx analysis set-not detected (All patients in the gAS who are *BRAF V600E* negative by Guardant360 CDx); **gAS-F**: Guardant360 CDx analysis set-failed (All patients in the gAS that failed Guardant360 CDx Testing).

Accountability / Patient Disposition of the Diagnostic Study Sensitivity Analysis and Prevalence Sub-Study

The sensitivity analysis prevalence Sub-study set included samples from 132 patients with matched plasma and tissue samples procured from vendors to support the Guardant360® CDx+ CTA- Sub-Study sensitivity analysis (**Figure 2**). Samples from 10 (7.6%) patients failed Guardant360 CDx and a sample from 1 patient failed CTA

testing. No samples failed testing with both Guardant360 CDx and CTA. This resulted in 121 patient samples with valid Guardant360 CDx and tissue CTA results. The BREAKWATER analysis set included 343 BREAKWATER study subjects tested with Guardant360 CDx (gAS) (**Figure 2**). Samples from 15 patients that failed Guardant360 CDx testing (gAS-F), and 1 protocol deviation in which the patient had no BRAF V600 + result and was not treated, resulted in 327 patients with valid Guardant360 CDx results (gCEAS + gAS-). Collectively, the 327 patients from the BREAKWATER study and the 122 patients in the Sub-Study were the sample sets included in the diagnostic study assay agreement analysis set [AAAS (all patients for whom results from both Guardant 360 CDx and enrolling CTA results are available) is equal to [gCEAS (278) + gAS- (49)] 327 patients from the BREAKWATER study + 122 patients from the Sub-Study = 449.

Figure 2. Diagnostic Study Sensitivity Analysis and Prevalence Sub-Study Patient Disposition.



FAS: Full Analysis Set (All randomized patients in the BREAKWATER NDA registration population); **gAS:** Guardant360 CDx Analysis Set (All patients from the FAS tested with Guardant360 CDx; **gNT:** Guardant360 CDx not tested set (All patients in the FAS not tested by Guardant360 CDx); **gCEAS:** Guardant360 CDx primary clinical efficacy analysis set (All patients in the gAS who are *BRAF V600E* positive by Guardant360 CDx); **gAS-:** Guardant360 CDx analysis set-not detected (All patients in the gAS who are *BRAF V600E*

negative by Guardant360 CDx); **gAS-F**: Guardant360 CDx analysis set-failed (All patients in the gAS that failed Guardant360 CDx Testing).

Concordance Between Guardant360® CDx and tissue-based CTA Testing

The concordance study population (AAAS) includes all samples from the gCEAS clinical study population (n= 278 + 49 = 327) and the sensitivity analysis prevalence sub-study set (n=122) with both Guardant360® CDx and tissue-based CTA results.

Concordance between Guardant360® CDx and tissue-based CTA testing in the AAAS population is shown in **Table 11** below. Guardant360® CDx demonstrated a PPA of 85.0% (95% CI 80.7 %, 88.5%) and NPA of 100.0% (95% CI 96.9%, 100.0%) relative to tissue-based CTA results.

Table 11. Concordance Results between Guardant360® CDx and CTA

	CTA Positive [a]	CTA Negative	Total
Guardant360® CDx Positive, n	278	0	278
Guardant360® CDx Negative, n	49	122	171
Total, n	327	122	449
Positive Percent Agreement [b] (95% CI)	85.0 (80.7, 88.5)		
Negative Percent Agreement [b] (95% CI)	100.0 (96.9, 100.0)		

[a] All patients enrolled in the BREAKWATER sNDA registration population are considered to be CTA positive.
[b] Patients with failed response on Guardant360® CDx are excluded from calculations.

C. Study Population Demographics and Baseline Parameters

Demographics and baseline clinical characteristics of patients enrolled in EC + mFOLFOX6 Arm B and the standard of care (SOC) chemotherapy Arm C of the BREAKWATER clinical study were categorized relative to the diagnostic study populations as defined by Guardant360 CDx results and treatment arm.

To assess potential bias from plasma sample availability, demographic and baseline clinical characteristics of the full analysis set (FAS) and all subgroups [Guardant360® CDx primary clinical efficacy analysis set (gCEAS), Guardant360 CDx analysis set (gAS), Guardant360® CDx analysis set-not detected (gAS-) and the Guardant360 CDx unknown set (gAS-UNK)] defined by Guardant360® CDx results were summarized and reported in **Table 12**, **Table 13 (Tumor Site)** and **Table 14 (Tumor Stage)**. Demographic and clinical characteristics of the gCEAS subgroup were similar to those of the FAS. The EC + mFOLFOX6 arms are also similar.

Table 12. Demographic and Baseline Characteristics of Full Analysis Set Population

	gCEAS		gAS		gAS-		gAS-Unk		FAS	
	EC + mFOLFOX6	SOC	EC + mFOLFOX6	SOC	EC + mFOLFOX 6	SOC	EC + mFOLFOX 6	SOC	EC + mFOLFOX6	SOC
n	**143**	**135**	**176**	**167**	**26**	**24**	**67**	**84**	**236**	**243**
Mean (SD)	57.95 (12.67)	60.47 (12.62)	58.30 (12.55)	60.40 (13.05)	61.50 (11.93)	59.21 (15.86)	56.57 (12.99)	57.68 (12.36)	57.95 (12.71)	59.38 (12.89)
Median	61.00	63.00	61.00	63.00	62.50	62.00	60.00	61.00	60.00	62.00
Min, Max	24, 80	30, 84	24, 81	29, 84	32, 81	29, 79	29, 81	28, 81	24, 81	28, 84
Age Category [a] (years) n (%)										
< 18	0	0	0	0	0	0	0	0	0	0
18 to < 65	90 (62.9)	72 (53.3)	110 (62.5)	89 (53.3)	14 (53.8)	13 (54.2)	46 (68.7)	54 (64.3)	150 (63.6)	139 (57.2)
65 to < 75	45 (31.5)	48 (35.6)	55 (31.3)	56 (33.5)	9 (34.6)	5 (20.8)	16 (23.9)	27 (32.1)	70 (29.7)	80 (32.9)
≥ 75	8 (5.6)	15 (11.1)	11 (6.3)	22 (13.2)	3 (11.5)	6 (25.0)	5 (7.5)	3 (3.6)	16 (6.8)	24 (9.9)
Sex, n (%)										
Female	75 (52.4)	73 (54.1)	88 (50.0)	91 (54.5)	10 (38.5)	13 (54.2)	28 (41.8)	38 (45.2)	113 (47.9)	124 (51.0)
Male	68 (47.6)	62 (45.9)	88 (50.0)	76 (45.5)	16 (61.5)	11 (45.8)	39 (58.2)	46 (54.8)	123 (52.1)	119 (49.0)
Race, n (%)										
American Indian or Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	42 (29.4)	35 (25.9)	52 (29.5)	46 (27.5)	9 (34.6)	9 (37.5)	37 (55.2)	47 (56.0)	88 (37.3)	91 (37.4)
Black or African American	0	1 (0.7)	0	1 (0.6)	0	0	0	0	0	1 (0.4)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
White	98 (68.5)	93 (68.9)	119 (67.6)	113 (67.7)	17 (65.4)	15 (62.5)	26 (38.8)	36 (42.9)	141 (59.7)	144 (5.3)
Multiple	0	2 (1.5)	0	2 (1.2)	0	0	0	0	0	2 (0.8)
Not Reported	3 (2.1)	4 (3.0)	5 (2.8)	5 (3.0)	0	0	4 (6.0)	1 (1.2)	1 (1.2)	5 (2.1)
Ethnicity, n (%)										

Hispanic or Latino	14 (9.8)	16 (11.9)	21 (11.9)	17 (10.2)	5 (19.2)	1 (4.2)	9 (13.4)	13 (15.5)	28 (11.9)	30 (12.3)
Not Hispanic or Latino	117 (81.8)	112 (83.0)	141 (80.1)	142 (85.0)	21 (80.8)	23 (95.8)	49 (73.1)	66 (78.6)	187 (79.2)	201 (82.7)
Not Reported	12 (8.4)	7 (5.2)	14 (8.0)	8 (4.8)	0	0	9 (13.4)	5 (6.0)	21 (8.9)	12 (4.9)

Note: The percentages are out of n, the number of patients in each cohort or treatment group. The **FAS** consists of all randomized patients in the BREAKWATER NDA registration population; the **gAS** consists of all patients from the FAS tested with Guardant360 CDx; the **gCEAS** consists of all patients in the gAS who are *BRAF V600E* positive by Guardant360 CDx; the **gAS-** consists of all patients in the gAS who are *BRAF V600E* negative by Guardant360 CDx; the **gAS-UNK** consists of all subjects from the FAS for whom a valid Guardant360 CDx result was not available [includes both gNT (all patients in the FAS not tested by Guardant360 CDx) and gAS-F (all patients in the gAS that failed Guardant360 CDx testing)]. [a] Age at time of informed consent.

Table 13. Baseline Disease Characteristics of Full Analysis Set Population - Tumor Site

	gCEAS		gAS		gAS-		gAS-Unk		FAS	
	EC + mFOLFOX6	SOC	EC + mFOLFOX6	SOC	EC + mFOLFOX6	SOC	EC + mFOLFOX6	SOC	EC + mFOLFOX6	SOC
n	**143**	**135**	**176**	**167**	**26**	**24**	**67**	**84**	**236**	**243**
Body Site, n (%)										
Colon Ascending	50 (35.0)	39 (28.9)	61 (34.7)	52 (31.1)	7 (26.9)	10 (41.7)	21 (31.3)	23 (27.4)	78 (33.1)	72 (29.6)
Colon Descending	11 (7.7)	4 (3.0)	15 (8.5)	7 (4.2)	3 (11.5)	2 (8.3)	4 (6.0)	10 (11.9)	18 (7.6)	16 (6.6)
Colon Recto-sigmoid	9 (6.3)	10 (7.4)	12 (6.8)	12 (7.2)	3 (11.5)	1 (4.2)	5 (7.5)	5 (6.0)	17 (7.2)	16 (6.6)
Colon Sigmoid	16 (11.2)	14 (10.4)	20 (11.4)	18 (10.8)	4 (15.4)	3 (12.5)	10 (14.9)	15 (17.9)	30 (12.7)	32 (13.2)
Colon Transverse	25 (17.5)	26 (19.3)	28 (15.9)	28 (16.8)	2 (8.3)	2 (8.3	12 (17.9)	7 (8.3)	39 (16.5)	35 14.4)
Colon Hepatic Flexure	6 (4.2)	6 (4.4)	6 (3.4)	7 (4.2)	0	1 (4.2)	3 (4.5)	7 (8.3)	9 (3.8)	14 (5.8)
Colon Splenic Flexure	1 (0.7)	5 (3.7)	1 (0.6)	6 3.6)	0	1 (4.2)	0	1 (1.2)	1 (0.4)	7 (2.9)
Rectum	13 (9.1)	15 (11.1)	17 (9.7)	17 (10.2)	4 (15.4)	2 (8.3)	7 (10.4)	10 (11.9)	24 (10.2)	27 (11.1)
Cecum	12 (8.4)	16 (11.9)	16 (9.1)	20 (12.0)	3 (11.5)	2 (8.3)	5 (7.5)	6 (7.1)	20 (8.5)	24 (9.9)
Side of Tumor, n (%)										
Left	50 (35.0)	48 (35.6)	65 (36.9)	60 (35.9)	14 (53.8)	9 (37.5)	26 (38.8)	41 (48.8)	90 (38.1)	98 (40.3)
Right	93 (65.0)	87 (64.4)	111 (63.1)	107 (64.1)	12 (46.2)	15 (62.5)	41 (61.2)	43 (51.2)	146 (61.9)	145 (59.7)

Note: The percentages are out of n, the number of patients in each cohort or treatment group. The **FAS** consists of all randomized patients in the BREAKWATER NDA registration population; the **gAS** consists of all patients from the FAS tested with Guardant360 CDx; the **gCEAS** consists of all patients in the gAS who are *BRAF V600E* positive by Guardant360 CDx; the **gAS-** consists of all patients in the gAS who are *BRAF V600E* negative by Guardant360 CDx; the **gAS-UNK** consists of all subjects from the FAS for whom a valid Guardant360 CDx result was not available [includes both gNT (all patients in the FAS not tested by Guardant360 CDx) and gAS-F (all patients in the gAS that failed Guardant360 CDx testing.

Table 14. Baseline Disease Characteristics of Full Analysis Set Population-Tumor Stage

	gCEAS		gAS		gAS-		gAS-Unk		FAS	
	EC + mFOLFOX6	SOC	EC + mFOLFOX6	SOC	EC + mFOLFOX6	SOC	EC + mFOLFOX6	SOC	EC + mFOLFOX6	SOC
n	**143**	**135**	**176**	**167**	**26**	**24**	**67**	**84**	**236**	**243**
Stage at Initial Diagnosis, n (%)										
Stage I	1 (0.7)	2 (1.5)	2 (1.1)	2 (1.2)	1 (3.8)	0	1 (1.5)	0	3 (1.3)	2 (0.8)
Stage II	9 (6.3)	8 (5.9)	11 (6.3)	9 (5.4)	2 (7.7)	1 (4.2)	2 (3.0)	1 (1.2)	13 (5.5)	10 (4.1)
Stage III	18 (12.6)	12 (8.9)	28 (15.9)	27 (16.2)	9 (34.6)	11 (45.8)	11 (16.4)	22 (26.2)	38 (16.1)	45 (18.5)
Stage IV	115 (80.4)	113 (83.7)	135 (76.7)	129 (77.2)	14 (58.3)	12 (50.0)	53 (79.1)	61 (72.6)	182 (77.1)	186 (76.5)
Presence of Liver Metastasis, n (%)										
Yes	94 (65.7)	98 (72.6)	104 (59.1)	110 (65.9)	8 (30.8)	9 (37.5)	45 (67.2)	53 (63.1)	147 (62.3)	160 (65.8)
No	49 (34.3)	37 (27.4)	72 (40.9)	57 (34.1)	18 (69.2)	15 (62.5)	22 (32.8)	31 (36.9)	89 (37.7)	83 (34.2)
Time Since Initial Diagnosis (months)										
n	143	135	176	167	26	24	67	84	236	243
Mean	7.45	6.34	7.64	7.31	8.82	11.64	4.65	7.49	6.81	7.26
SD	15.62	14.59	14.50	14.41	8.56	13.45	7.66	17.33	13.18	15.51
Median	1.87	1.64	2.14	1.77	4.98	3.19	1.84	2.07	1,94	1.84
Min, Max	0, 112	0, 124	0, 112	0, 124	1, 27	1, 47	0, 37	1, 109	0, 112	0, 124
Time Since Recurrence/Metastatic (months)										
n	142	134	175	166	26	24	67	83	235	241
Mean	2.45	2.05	2.44	2.25	2.24	3.39	1.89	1.61	2.26	2.03
SD	4.44	2.71	4.10	3.50	2.13	6.58	2.13	1.04	3.70	2.97
Median	1.54	1.48	1.58	1.51	1.63	1.86	1.48	1.45	1.54	1.51
Min, Max	0, 40	0, 21	0, 40	0, 34	1, 11	1, 34	0, 16	0, 7	0, 40	0, 34
ECOG Performance Status at Baseline, n (%)										
0	78 (54.5)	81 (60.0)	98 (55.7)	95 (56.9)	17 (65.4)	7 (29.2)	33 (49.3)	43 (51.2)	128 (54.2)	131 (53.9)
1	63 (44.1)	51 (37.8)	75 (42.6)	65 (38.9)	8 (30.8)	13 (54.2)	33 (49.3)	34 (40.5)	104 (44.1)	98 (40.3)
Missing	2 (1.4)	3 (2.2)	3 (1.7)	7 (4.2)	1 (3.8)	4 (16.7)	1 (1.5)	7 (8.3)	4 (1.7)	14 (5.8)

Note: The percentages are out of n, the number of patients in each cohort or treatment group. The **FAS** consists of all randomized patients in the BREAKWATER NDA registration population; the **gAS** consists of all patients from the FAS tested with Guardant360 CDx; the **gCEAS** consists of all patients in the gAS who are *BRAF V600E* positive by Guardant360 CDx; the **gAS-** consists of all patients in the gAS who are *BRAF V600E* negative by Guardant360 CDx; the **gAS-UNK** consists of all subjects from the FAS for whom a valid Guardant360 CDx result was not available [includes both gNT (all patients in the FAS not tested by Guardant360 CDx) and gAS-F (all patients in the gAS that failed Guardant360 CDx testing.

Sensitivity Analysis Prevalence Sub-Study Population Demographics and Baseline Characteristics

Demographic and baseline clinical characteristics of patients whose matched plasma and tissue samples were obtained from vendors to support the Guardant360 CDx+ CTA- Sub-Study sensitivity analysis are shown in **Table 15** next to those for the FAS.

The baseline clinical characteristics of the Prevalence Sub-Study patient population is generally similar to the BREAKWATER patient population, with the exception that there is a higher proportion of patients 18 < 65 years of age in the BREAKWATER FAS as compared with the Sub-Study (60.3 vs. 30.3, respectively), there is a lower proportion of patients ≥ 75 years of age in the BREAKWATER FAS as compared with the Sub-Study (8.4 vs. 39.4, respectively), there is a lower proportion of white patients in the BREAKWATER FAS as compared with the Sub-Study (59.5 vs. 88.6, respectively), while there is a higher proportion of Asian patients in the BREAKWATER FAS as compared to the Sub-Study (37.4 vs 4.5, respectively).

The BREAKWATER FAS also has a lower proportion of patients that were Stage III at initial diagnosis as compared to the Sub-Study (17.3 vs. 71.2, respectively), but the FAS also had a higher proportion of patients that were Stage IV at initial diagnosis, as compared to the Sub-Study (76.8 vs. 28.8, respectively). The differences in age, stage and race between the BREAKWATER study and the Sub-Study are not expected to bias the negative percent agreement (NPA) estimate, as these characteristics do not influence the false positive rate in an analytically validated ctDNA assay.

Table 15. Demographic and Baseline Clinical Characteristics of the Sensitivity Analysis Prevalence Sub-Study Patients and the FAS

	FAS (n=479)	**Sub-Study (n=132)**
Age (years) [a]		
n	479	132
Mean (SD)	58.67 (12.81)	69.32 (12.17)
Median	61.00	72.00
Min, Max	24, 84	30, 94
Age Category (years), n (%) [a]		
< 18	0	0
18 < 65	289 (60.3)	40 (30.3)
65 < 75	150 (31.3)	40 (30.3)
≥ 75	40 (8.4)	52 (39.4)
Sex, n (%)		
Female	237 (49.5)	65 (49.2)
Male	242 (50.5)	67 (50.8)
Race, n (%)		
American Indian or Alaska Native	0	0
Asian	179 (37.4)	6 (4.5)
Black or African American	1 (0.2)	0

Native Hawaiian or Other Pacific Islander	0	0
White	285 (59.5)	117 (88.6)
Multiple	2 (0.4)	1 (0.8)
Not Reported	12 (2.5)	8 (6.1)
Stage at Initial Diagnosis, n (%)		
Stage I	5 (1.0)	0
Stage II	23 (4.8)	0
Stage III	83 (17.3)	94 (71.2)
Stage IV	368 (76.8)	37 (28.8)

Note: Percentages are out of n, the number of patients in each cohort or treatment group. The FAS consists of all randomized patients in the BREAKWATER sNDA registration population. The Sub-Study consists of all patients enrolled in the prevalence Sub-Study. [a] Age at time of informed consent.

D. Safety and Effectiveness Results

1. Safety Results

Data regarding the safety of BRAFTOVI (encorafenib) therapy are presented in the original drug approval. Refer to the BRAFTOVI (encorafenib) label for more information. No adverse events were reported in the conduct of the diagnostic studies used to support this PMA supplement.

For the specific adverse events that occurred in the clinical studies, please see the BRAFTOVI (encorafenib) FDA approved package insert which is available at Drugs@FDA.

2. Effectiveness Results

a. ORR in Patients with *BRAF V600E* Mutation Detected by Guardant360® CDx

The effectiveness of Guardant360® CDx for the selection of CRC patients with *BRAF V600E* mutations for treatment with EC + mFOLFOX6, was assessed by comparing the clinical efficacy of EC + mFOLFOX6 to standard of care (SOC) chemotherapy in the gCEAS, as measured by the primary endpoint of objective response rate (ORR) by blinded independent central review (BICR).

The BICR-assessed ORR among the first 110 randomized patients in Arm B and Arm C with *BRAF* V600E detected by Guardant360® CDx was 66.7% (95% CI, 54.9%, 76.6%) in the EC + mFOLFOX Arm, as compared to 34.5% (95% CI 23.6, 47.3%) in the SOC chemotherapy Arm as shown in **Table 16,** which is similar to the ORR observed in the first 110 randomized patients in the BREAKWATER clinical study [61% (95% CI, 52%, 70%) in the EC + mFOLFOX Arm, as compared to 40% (95% CI, 31%, 49%) in the SOC chemotherapy Arm].

The odds ratio for ORR in the EC + FOLFOX6 Arm compared to the SOC chemotherapy Arm was 4.700 (95% CI, 1.973, 11.046; p<0.0001), indicating a higher likelihood of the benefit with EC + mFOLFOX6. These results are compared with that observed in the full analysis set (FAS) for BREAKWATER, where the ORR odds ratio was 2.443 (95% CI, 1.348, 4.380; p=0.0015.

Table 16. Summary of BICR-assessed ORR for EC + mFOLFOX6 vs. SOC in the BRAF V600E Mutation Detected by Guardant360® CDx

	EC + mFOLFOX6 (N = 69)	**SOC (N = 58)**
Objective Response events, n (%)	46 (66.7)	20 (34.5)
95% CI [a]	(54.9, 76.6)	(23.6, 47.3)
Odds Ratio for Objective Response		
Odds Ratio (95% CI)	4.700 1.973, 11.046)	
2-sided p-value	<0.0001	

The primary objective analysis above demonstrated EC + mFOLFOX6 efficacy in the Guardant360® CDx (+) CTA (+) subset of the Guardant360® CDx intended use population. The sensitivity analysis, modeling efficacy in the Guardant360® CDx (+) intended use population, used an estimate of the positive predictive value of the Guardant360 CDx assay of 1 obtained from the sensitivity analysis prevalence sub-study set. Because the estimated NPA was 100%, the efficacy estimates in the overall Guardant360® CDx (+) intended use population were similar to the efficacy observed in that of the FAS, irrespective of EC + mFOLFOX6 efficacy in the modeled hypothetical Guardant360 CDx (+) CTA (-) sub-population. As a result, the weighted odds ratio remained constant at 4.700 (95% CI, 1.973, 11.0446).

b. PFS in Patients with *BRAF V600E* Mutation Detected by Guardant360 CDx

The effectiveness of Guardant360 CDx for the selection of CRC patients with *BRAF V600E* mutations for treatment with EC + mFOLFOX6, was also assessed by comparing the clinical efficacy of EC + mFOLFOX6 to standard of care (SOC) chemotherapy in the gCEAS, as measured by the primary endpoint of progression free survival (PFS) by BICR.

A total of 156 PFS events were reported in the gCEAS (primary clinical efficacy set n=278), comprising 73 events (51.0%) in the EC + mFOLFOX6 Arm and 83 events (61.5%) in the SOC Arm (Table XX). A total of 254 PFS events were reported in the full analysis set in the BREAKWATER clinical trial (n=479) with similar percentages of events in the EC + mFOLFOX6 Arm 122 (51.7%) and 132 events (54.3%) in the SOC Arm.

The median PFS by BICR in the gCEAS population treated with EC + mFOLFOX6 was 12.5 months (95% CI 9.9, 16.4) compared to SOC 7.0 months (95% CI 5.5, 8.3; **Table 17**), which is similar to the median PFS observed in the

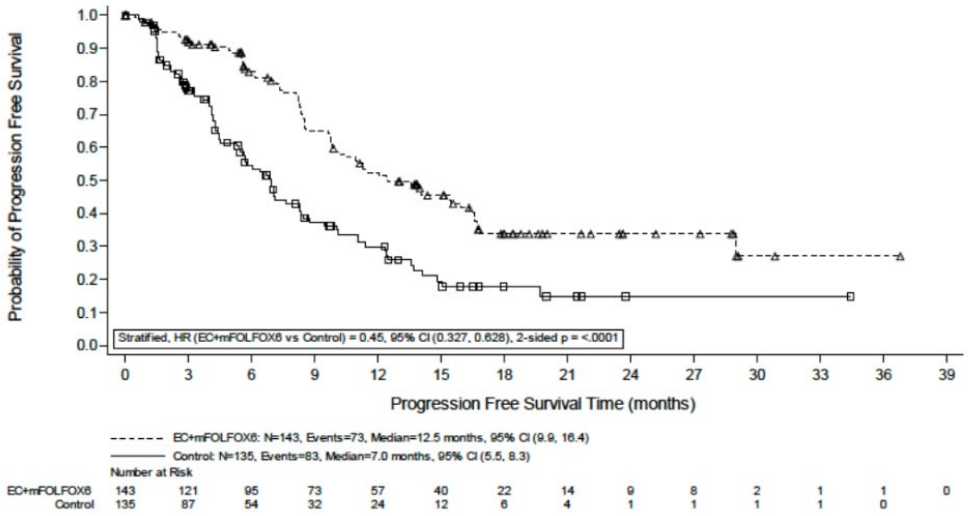
BREAKWATER clinical trial [12.8 months (95% CI, 11.2, 15.9) in the EC + mFOLFOX6 Arm compared with 7.1 months (95% CI, 6.8, 8.5) in the SOC Arm].

The resulting PFS hazard ratio (HR) in the gCEAS population treated with EC + mFOLFOX6 therapy vs. SOC chemotherapy was 0.45 (95% CI 0.327, 0.628; p<0.0001, indicating a reduction in the risk of progression or death with EC + mFOLFOX6 therapy**,** which is similar to the PFS HR of 0.53 reported in the full analysis set (FAS) for the BREAKWATER clinical study (95% CI, 0.41, 0.68), p<0.001 for the EC +mFOLFOX6 Arm vs. SOC chemotherapy. **Figure 3** shows the Kaplan Meier Plot of BICR-Assessed PFS for EC + mFOLFOX6 vs. SOC in the gCEAS Population.

Table 17. Summary of PFS Based on BICR Assessment for EC + mFOLFOX6 vs. SOC in the *BRAF V600E* Mutation Detected by Guardant360 CDx

	EC + mFOLFOX6 (N = 143)	**SOC (N = 135)**
Number of Events, n (%)	73 (51.0)	83 (61.5)
Median months (95% CI)	12.452 (9.9, 16.4)	6.965 (5.5, 8.3)
Hazard ratio (95% CI)	0.45 (0.327, 0.628)	
2-Sided p-value	<0.0001	

Figure 3. Kaplan Meier Plot of BICR-Assessed PFS for EC + mFOLFOX6 vs. SOC in the gCEAS Population



A sensitivity analysis was conducted for PFS, incorporating varying assumptions of CTA (+) prevalence and hypothetical efficacy in a Guardant360® CDx (+) CTA (-) subgroup. In all modeled scenarios, the estimated probability of CTA (-) among Guardant360® CDx (+) patients was zero, as all CTA (-) individuals were also Guardant360® CDx (-) in the study sample. As a result, the weighted hazard ratio remained at 0.453 (95% CI 0.327, 0.628) across all assumptions.

A sensitivity analysis was additionally performed to assess the proportion of patients with missing test results [gNT (n=136) + gAS-F (n=15) =151, (31.5%)], to assess the potential impact of the unrepresented patients, as the number exceeded the 10% of FAS threshold that was pre-specified in the diagnostic statistical analysis plan (dSAP). The sensitivity analysis, conducted among the first 110 patients randomized with *BRAF V600E* mutation detected, as determined by Guardant360 CDx, found that the modeled PFS hazard ratio (HR) (0.50, 95% CI 0.371, 0.674; p<0.0001) with imputation for the missing population (gAS-Unk) was highly similar to the PFS HR in the BREAKWATER study (0.53, 95% CI 0.407, 0.677; p<0.0001)..

c. OS in Patients with *BRAF V600E* Mutation Detected by Guardant360® CDx

The effectiveness of Guardant360® CDx for the selection of CRC patients with *BRAF V600E* mutations for treatment with EC + mFOLFOX6, was also assessed by comparing the clinical efficacy of EC + mFOLFOX6 to standard of care (SOC) chemotherapy in the gCEAS, as measured by the secondary endpoint of overall survival (OS) by BICR.

A total of 152 OS events were reported in the gCEAS with 66 events (46.2%) in the EC + mFOLFOX6 arm and 86 events (63.7%) in the SOC arm. (**Table 18**). A total of 242 OS events were reported in the full analysis set (FAS) for the BREAKWATER study (n=479) with similar percentages of events in the EC + mFOLFOX6 Arm 94 events (39.8%) and 148 events (60.9%) in the SOC Arm.

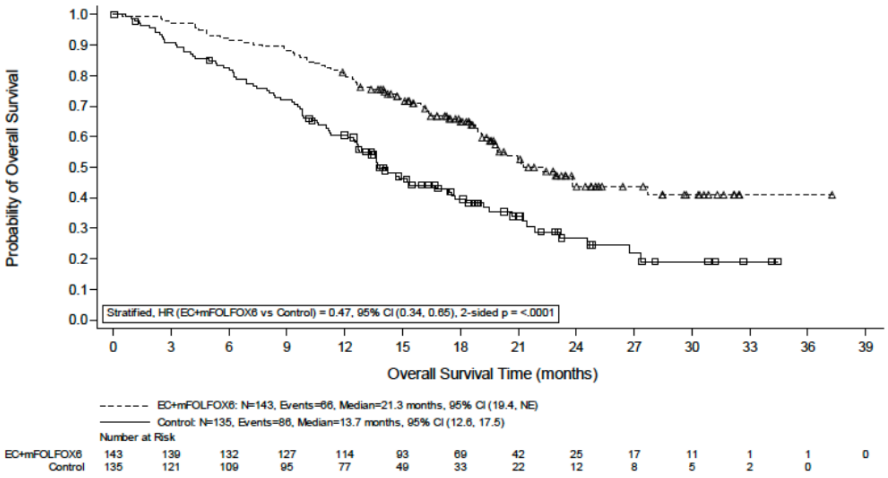
The median overall survival (OS) in the BREAKWATER Study was 30.3 months (95% CI, 21.7, NE) in the EC + mFOLFOX6 Arm, as compared with 15.1 months (95% CI, 13.7, 17.7) in the SOC Arm.

The OS HR in the Guardant360® CDx primary clinical efficacy analysis (gCEAS, N=278) population treated with EC + mFOLFOX6 vs SOC chemotherapy was 0.47 (95% CI 0.34, 0.65; p<0.001), which is similar to the OS HR reported in the full analysis set (FAS) for the BREAKWATER study (0.49, 95% CI 0.375, 0.632; p<0.001). **Figure 4** shows the Kaplan-Meier Plot of BICR-Assessed OS for EC + mFOLFOX6 vs SOC in the gCEAS.

Table 18. Summary of OS HR for EC + mFOLFOX6 vs. SOC in the gCEAS Population

	EC + mFOLFOX6 (N = 143)	**SOC (N = 135)**
Number of Events, n (%)	66 (46.2)	86 (63.7)
Hazard ratio (95% CI)	0.47 (0.340, 0.650)	
2-Sided p-value	<0.0001	

Figure 4. Kaplan-Meier Plot of BICR-Assessed OS for EC + mFOLFOX6 vs SOC in the gCEAS



3. Pediatric Extrapolation

Data from adult patients in the BREAKWATER study is considered generalizable to the pediatric population aged 18-22 years. Additionally, since there is no change in the specimen type (plasma and tissue) to be used or assay workflow prescribed in the Instructions for Use based on the age of the patient, the validation data can be extrapolated to the pediatric population and can be relied upon to establish safety and effectiveness within the 18-22 years age group.

Please see the BRAFTOVI (encorafenib) and ERBITUX (cetuximab) product labels for specific clinical circumstances guiding Guardant360 CDx testing.

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 one investigator who 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: [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.

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

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

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

For the intended use of identifying CRC patients with *BRAF V600E* mutation for treatment with BRAFTOVI (encorafenib) in combination with cetuximab + mFOLFOX6, the effectiveness of Guardant360 CDx was demonstrated through analytical studies using patient samples from the intended use population and a diagnostic clinical study utilizing Guardant360 CDx results and outcome data from the BREAKWATER clinical study. The data from the analytical validation and clinical studies support the reasonable assurance of safety and effectiveness of Guardant360 CDx when used in accordance with the indications for use. Data from the BREAKWATER clinical study show that patients who had qualifying *BRAF V600E* mutation received benefit from treatment with BRAFTOVI (encorafenib) + cetuximab + mFOLFOX6 and support the addition of the CDx indication to Guardant360 CDx.

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. Guardant360 CDx is an *in vitro* diagnostic test, which involves testing of cfDNA extracted from the plasma of whole blood routinely collected as part of the diagnosis and patient care.

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 cancer. 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 that may be beneficial. There is also a risk of delayed results, which may lead to delay of treatment with the indicated therapy.

C. Benefit-Risk Determination

The probable clinical benefit of Guardant360® CDx for the selection of CRC patients with *BRAF V600E* mutation for treatment with BRAFTOVI® (encorafenib) in combination with ERBITUX® (cetuximab) + mFOLFOX6 was demonstrated in a

retrospective bridging analysis of efficacy and safety data obtained from the BREAKWATER clinical Study. The supporting clinical validation analysis demonstrated an ORR of 66.7% (95% CI, 54.9%, 76.6%) in the EC + mFOLFOX6 arm, as compared to 34.5% (95% CI 23.6%, 47.3%) in the SOC chemotherapy arm, as well as a PFS HR 0.45 (95% CI 0.327, 0.628, p<0.0001) and an OS HR 0.47 (95% CI 0.340, 0.650, p<0.0001) for patients in the BREAKWATER clinical study with *BRAF V600E* mutation detected by Guardant360® CDx for treatment with BRAFTOVI® (encorafenib) in combination with ERBITUX® (cetuximab) + mFOLFOX6 relative to standard of care chemotherapy. These data support a clinically meaningful benefit considering that this is a patient population with a serious and life-threatening disease. These results support the use of Guardant360® CDx to identify colorectal cancer patients with *BRAF V600E* mutation for treatment with BRAFTOVI® (encorafenib) in combination with ERBITUX® (cetuximab) + mFOLFOX6.

The potential risks associated with the use of Guardant360® CDx for identification of colorectal cancer patients with *BRAF* V600E mutation for treatment with BRAFTOVI® (encorafenib) in combination with ERBITUX® (cetuximab) + mFOLFOX6 include false positive and false negative results, as well as failure to provide a result and incorrect interpretation of test results by the user.

The risks of Guardant360® CDx are associated with incorrect test results due to false positive and false negative results which could impact appropriate patient management for patients with CRC with a *BRAF V600E* mutation. False positive Guardant360® CDx test results may expose patients to drugs that are not beneficial and may lead to adverse events. False negative Guardant360® CDx test results may result in delays in administration of this effective therapeutic combination and thus, missed opportunities missed beneficial treatment of patients with CRC with a *BRAF* V600E mutation.

The clinical and analytical performance of the Guardant360® CDx demonstrate that the assay is expected to perform with a high degree of accuracy (PPA 99.0%, 95% CI 94.7%, 100% and NPA 98.1%, 95% CI 93.4%, 99.8%) which may mitigate the risks associated with the test.

However, in the analysis of subjects from the BREAKWATER study, this device had false negativity in the Guardant360® CDx, ctDNA based test of 50/328 tested or a 15.2% false negativity rate. This degree of false negativity is expected, given that the majority of the clinical enrollment in the BREAKWATER trial was based on tissue-based testing. Therefore, a negative result from a plasma specimen does not ensure that the patient's tumor is negative for the *BRAF* V600E alteration in tissue and patients who test negative by the Guardant360® CDx should be reflexed to tissue biopsy testing using an FDA-approved tumor tissue test, which will mitigate the risk of false negative results.

The totality of the clinical and analytical data provided in this submission support the use of Guardant360® CDx to identify patients with CRC that harbor the *BRAF* V600E mutation for treatment with BRAFTOVI® (encorafenib) in combination with ERBITUX® (cetuximab) + mFOLFOX6 and the probable benefits of the use of the device for this indication exceed the potential risks.

1. Patient Perspective

   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 indications of use for the Guardant360 CDx discussed above 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 analytical and clinical studies support the use of Guardant360 CDx as an aid for the identification of patients with *BRAF V600E* mutations that may benefit from BRAFTOVI (encorafenib) in combination with ERBITUX (cetuximab) + mFOLFOX6 therapy.

XIV. CDRH DECISION

CDRH issued an approval order on January 15, 2026.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

None.