BRACAnalysis CDx® Technical Information

www.myriad.com/technical-specifications

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NOTE: Test results should be communicated to the patient in a setting that includes appropriate counseling

Intended Use

BRACAnalysis CDx® is an *in vitro* diagnostic device intended for the qualitative detection and classification of variants in the protein coding regions and intron/exon boundaries of the *BRCA1* and *BRCA2* genes using genomic DNA obtained from whole blood specimens collected in EDTA. Single nucleotide variants and small insertions and deletions (indels) are identified by polymerase chain reaction (PCR) and Sanger sequencing. Large deletions and duplications in *BRCA1* and *BRCA2* are detected using multiplex PCR.

Results of the test are used as an aid in identifying patients who are or may become eligible for treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling.

Table 1: Companion diagnostic indications

Tumor Type	**Biomarker**	**Therapy**
Breast Cancer	Deleterious or suspected deleterious mutations in *BRCA1* and *BRCA2* genes	Lynparza® (olaparib)
		Talzenna® (talazoparib)
Ovarian Cancer	Deleterious or suspected deleterious mutations in *BRCA1* and *BRCA2* genes	Lynparza® (olaparib) - treatment/maintenance
		Rubraca® (rucaparib)
Pancreatic Cancer	Deleterious or suspected deleterious mutations in *BRCA1* and *BRCA2* genes	Lynparza® (olaparib)
Prostate Cancer	Deleterious or suspected deleterious mutations in *BRCA1* and *BRCA2* genes	Lynparza® (olaparib)

Detection of deleterious or suspected deleterious germline *BRCA1* and *BRCA2* mutations by the BRACAnalysis CDx test in ovarian cancer patients is also associated with enhance progression-free survival (PFS) from Zejula® (niraparib) or Rubraca® (rucaparib) maintenance therapy.

This assay is for professional use only and is to be performed only at Myriad Genetic Laboratories, a single laboratory site located at 320 Wakara Way, Salt Lake City, UT 84108.

Contraindication

- Patients who have undergone a previous allogeneic bone marrow transplant should not be tested with the BRACAnalysis CDx® test.

BRACAnalysis CDx® Technical Information

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Warnings and Precautions

- When drawing blood for the BRACAnalysis CDx® test, universal precautions for bloodborne pathogens should be observed.
- Patients under consideration for testing who have been diagnosed with a hematologic malignancy, such as leukemia, could generate a positive (deleterious or suspected deleterious) result that is somatic, and not germline, due to chromosome instability. The classification and interpretation of all variants identified reflects the current state of scientific understanding at the time the result report is issued. In some instances, the classification and interpretation of variants may change as scientific information becomes available.

Limitations

- For *in vitro* diagnostic use
- For professional use only
- For prescription use only
- Limitation: In Ovarian Cancer, ~70% of tumor *BRCA1* or *BRCA2* mutation positive patients are estimated to have a germline mutation while ~30% of patients are estimated to have a somatic mutation. The BRACAnalysis CDx test detects germline mutations only, not somatic mutations from patient's blood sample. A negative result using the BRACAnalysis CDx blood test in ovarian cancer patients does not rule out the possibility of a somatic *BRCA1* or *BRCA2* mutation in tumor tissue from these patients.
- Limitation: In Prostate Cancer, ~50% of tumor *BRCA1* or *BRCA2* mutation positive patients are estimated to have a germline mutation while ~50% of patients are estimated to have a somatic mutation. The BRACAnalysis CDx test detects germline mutations only, not somatic mutations from patient's blood sample. A negative result using the BRACAnalysis CDx blood test in prostate cancer patients does not rule out the possibility of a somatic *BRCA1* or *BRCA2* mutation in tumor tissue from these patients.
- The test has been designed to detect genomic rearrangements (i.e., deletions or duplications) involving the promoter and coding exons of *BRCA1* and *BRCA2*, but the test will not detect some types of errors in RNA transcript processing. Insertions that do not result in duplications will generally not be detected. Also, the test may not accurately differentiate between duplications and triplications.
- Unequal allele amplification may result from rare polymorphisms under primer sites and lead to false negative results.
- There are limited portions of either *BRCA1* or *BRCA2* for which sequence determination can be performed only in the forward or reverse direction. Approximately 0.25% of interrogated sequences are analyzed in multiple runs in either the forward or reverse direction.
- The test is intended to be performed on specific serial number-controlled instruments at Myriad Genetic Laboratories, Inc.

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Test Principle

BRACAnalysis CDx® is performed by a single laboratory, Myriad Genetic Laboratories, Inc. (Myriad), located in Salt Lake City, UT. The test is intended to detect germline *BRCA1* and *BRCA2* variants and provide a clinical interpretation of the identified variants. Results of the test are used as an aid in identifying breast, ovarian, pancreatic, and prostate cancer patients with deleterious or suspected deleterious germline *BRCA1* and *BRCA2* mutations, who are or may become eligible for treatment with Lynparza® (olaparib). In addition, results of the test are used as an aid in identifying breast cancer patients with deleterious or suspected deleterious germline *BRCA1* and *BRCA2* mutations, who are or may become eligible for treatment with Talzenna® (talazoparib). Results of the test are also used as an aid in identifying epithelial ovarian cancer (EOC), fallopian tube cancer (FTC), or primary peritoneal cancer (PPC) cancer patients with deleterious or suspected deleterious germline *BRCA1* and *BRCA2* mutations, who are or may become eligible for treatment with Rubraca® (rucaparib).

Detection of deleterious or suspected deleterious germline *BRCA1* and *BRCA2* mutations by the BRACAnalysis CDx test in ovarian cancer patients is also associated with enhanced progression-free survival (PFS) from Zejula® (niraparib), Rubraca® (rucaparib) maintenance therapy.

The BRACAnalysis CDx® test is composed of the following major processes:

- Whole Blood Collection and Shipping
- Genomic DNA Extraction
- DNA Processing using the following primary assays:
    - BRACAnalysis CDx® Sanger Sequencing - used to detect sequence variants
    - BRACAnalysis CDx® Large Rearrangement Test (BART® CDx) - used to identify genomic rearrangements (i.e., large deletions and duplications)
- Variant Classification
- Results Reporting

Reportable variants are confirmed by repeat analysis and, in some cases, by confirmatory testing. Approximately 98% of all reportable variants detected by the BRACAnalysis CDx® are confirmed by repeat testing alone; the remaining reportable variants (about 2%) require confirmatory analysis by the following tests, in addition to repeat testing:

- Alternate Primer Sequencing (APS) - used to identify potential heterozygous base changes under the primers used in the BRACAnalysis CDx® Sanger Sequencing test or the BART® CDx test
- Confirmatory PCR Analysis (CPA) - used to confirm a subset of *BRCA1* and *BRCA2* large rearrangements detected initially by the BART® CDx test.

Summary and Explanation

The BRACAnalysis CDx® device is an *in vitro* diagnostic device intended for the qualitative detection and classification of variants in the protein coding regions and intron/exon boundaries of the *BRCA1* and *BRCA2* genes using genomic DNA obtained from whole blood specimens collected in EDTA. Results of the test are used as an aid in identifying breast,

ovarian, pancreatic, and prostate cancer patients with deleterious or suspected deleterious germline *BRCA1* and *BRCA2* mutations, who are or may become eligible for treatment with Lynparza® (olaparib). In addition, results of the test are used as an aid in identifying breast cancer patients with deleterious or suspected deleterious germline *BRCA1* and *BRCA2* mutations, who are or may become eligible for treatment with Talzenna® (talazoparib). Results of the test are also used as an aid in identifying epithelial ovarian cancer (EOC), fallopian tube cancer (FTC), or primary peritoneal cancer (PPC) cancer patients with deleterious or suspected deleterious germline *BRCA1* and *BRCA2* mutations, who are or may become eligible for treatment with Rubraca® (rucaparib).

Detection of deleterious or suspected deleterious germline *BRCA1* and *BRCA2* mutations by the BRACAnalysis CDx test in ovarian cancer patients is also associated with enhanced progression-free survival (PFS) from Zejula® (niraparib), or Rubraca® (rucaparib) maintenance therapy. Cells that possess at least one normal *BRCA1* and *BRCA2* allele are relatively resistant to PARP inhibition. *BRCA1* or *BRCA2* dysfunction, defined as mutant cells lacking wild-type *BRCA1* or *BRCA2*, sensitizes cells to PARP inhibition leading to chromosomal instability, cell cycle arrest and apoptosis. [Bryant et al. Specific killing of *BRCA2*-deficient tumors with inhibitors of poly (ADP-ribose) polymerase.

Nature 2005;434(7035):913-7., Farmer et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature* 2005;434(7035):917-21.]

Test Kit Contents

A sample collection kit provided by Myriad is used by the ordering laboratories/physicians. The collection kits contain the following components:

- Monoject™ Blood Collection Tube, Silicone Coated Lavender Stopper, buffered EDTA(K2 and K3) 0.10 mL 15.0% Solution, or equivalent
    - The shelf life is printed on each individual tube. Prior to using a tube for blood collection, check the expiration date.
- Test Request Form (TRF)
- Example TRF
- Collection Instructions
- Mailing Instructions

Instruments

The BRACAnalysis CDx® device is intended to be performed with the following instruments, as identified by specific serial numbers:

- QIASymphony SP (Not Specific to Serial Number)
- MasterCycler EP & MasterCycler Pro 384 & 96 well
- ABI 3730xl

Sample Collection and Test Ordering

To order BRACAnalysis CDx® testing, the Test Request Form (TRF) included in the test kit must be fully completed.

Please refer to the BRACAnalysis CDx® Collection Instructions and Mailing Instructions for

further details about collecting blood samples and mailing the samples to Myriad.

Test Results and Interpretation

Patients evaluated with the BRACAnalysis CDx® test that are determined to carry a deleterious or suspected deleterious germline *BRCA1* and *BRCA2* mutations can be considered for treatment with Lynparza® (olaparib) or Rubraca® (rucaparib) or Talzenna® (talazoparib) as shown in Table 1 under the supervision of a physician. Detection of deleterious or suspected deleterious germline *BRCA1* and *BRCA2* mutations by the BRACAnalysis CDx test in ovarian cancer patients is also associated with enhanced progression-free survival (PFS) from Zejula® (niraparib), Rubraca® (rucaparib) maintenance therapy.

Upon completion of testing at Myriad, a test report will be sent to the designated physician. The results of each test component, along with the interpretation of the variant(s) identified, are provided. If multiple variants are detected, the overall test interpretation most relevant to patient management is based on the most severe variant identified (as reported in the Test Results and Interpretation section of the report). Standard interpretative information included in test reports is listed below. Note that variants determined to have a classification of polymorphism are not included on the test report.

- **Positive for a deleterious mutation:** All mutations (nonsense, insertions, deletions) that prematurely terminate the protein product before the last documented deleterious mutation of the gene. In addition, some specific missense mutations and non-coding intervening sequence mutations are recognized as deleterious on the basis of compelling scientific data derived from linkage analysis of high risk families, functional assays, biochemical evidence and/or demonstration of abnormal mRNA transcript processing.

- **Genetic variant, suspected deleterious:** Genetic variants for which available evidence indicates a strong likelihood, but not definitive proof, that the mutation is deleterious.

- **Genetic variant, favor polymorphism:** Genetic variants for which available evidence indicates that the variant is highly unlikely to contribute substantially to compromised protein function.

- **Genetic variant of uncertain significance:** Genetic variants whose clinical significance has not yet been determined. These can include certain missense variants, variants that occur in analyzed intronic regions, as well as terminating variants that truncate the gene distal to the last known deleterious mutation.
- **No mutation detected:** This includes results with no variants differing from the wildtype sequence, or polymorphic genetic variants. Polymorphisms include variants in the protein coding region that neither alter the amino acid sequence nor are predicted to significantly affect exon splicing, and alterations in the non-coding portions of the gene that have no deleterious effect on the mRNA transcript. These also include genetic variants for which published data demonstrate absence of clinical significance.

Whenever there is a change in the interpretation of a patient's test result, an amended report will be provided by Myriad.

All mutations and genetic variants are named according to the convention of Beaudet and Tsui. (Beaudet AL, Tsui LC. A suggested nomenclature for designating mutations. *Hum Mut* 1993; 2:245-248). Nucleotide numbering starts at the first transcribed base of *BRCA1* and *BRCA2* according to GenBank entries U14680 and U43746, respectively. (Under these conventions, the two mutations commonly referred to as "185delAG" and "5382insC" are named 187delAG and 5385insC, respectively.)

Performance Characteristics

The analytical validation studies described in Sections 1-9 included samples from individuals with personal and/or a family history of breast and/or ovarian cancers.

1. Accuracy

   a. BRACAnalysis CDx® Sanger Sequencing Test Accuracy

      The accuracy of the BRACAnalysis CDx® Sanger Sequencing assay was evaluated by comparing its sequencing results with those of a validated Next Generation Sequencing (NGS)-based assay on a set of 110 blinded, patient blood-derived DNA samples. The CDx Sanger sequencing assay identified a range of *BRCA1* and *BRCA2* variants/mutations in this sample set, including samples with deletions ranging from 1-40 basepairs, insertions ranging from 1-10 basepairs, and single nucleotide variants, including variants in homopolymer runs.

      After variant and non-variant calls (relative to wild-type sequences) were made for the set of samples tested, a total of 982 variant bases (representing 883 variant calls as not all variants are single base substitutions) and 1,906,122 non-variant bases were identified by the NGS-based test. For each sample tested with the BRACAnalysis CDx® Sanger Sequencing test, successful calls were made for all amplicons that are part of the assay, and the no call rate was 0%. All variant and non-variant base calls for common interrogated regions between the two tests were concordant. The agreement analysis between the results from both tests demonstrated a positive percent agreement (PPA), negative percent agreement (NPA), and overall agreement of 100%. The lower bounds of the 95% confidence intervals for PPA and NPA were 99.6954% and 99.9998%, respectively. Overall, these results demonstrate that results from the BRACAnalysis CDx® Sanger Sequencing assay are highly concordant with those from a validated NGS assay.

   b. BART® CDx Test Accuracy

      The accuracy of the BRACAnalysis CDx® Large Rearrangement (BART® CDx) assay was evaluated by comparing its large rearrangement results with those of a validated microarray assay on a set of 103 blinded, blood-derived DNA samples.

      Accuracy of the results from the BART® CDx test was demonstrated by comparison against the positive and negative calls from the microarray test.

Based on the microarray results, 29 samples were positive for a large rearrangement in *BRCA1* or *BRCA2*, and 74 samples were negative. For the BART® CDx test, 98 samples yielded valid results and 5 samples did not yield a callable result. The sample set covered the range of *BRCA1* or *BRCA2* large rearrangements identified by the BART® CDx assay including samples containing single-exon deletions, single-exon duplications, multi-exon deletions, multi-exon duplications/triplications, and those carrying the Portuguese founder mutation (insertion of Alu sequence in Exon 3 of *BRCA2).* Among the 98 samples with callable results, 97 samples had results that matched those from the microarray assay, while one did not. The miscalled, or discordant, variant was identified as a multi-exon duplication by the BART® CDx test and a multi-exon triplication by the microarray test. Although both tests detected an increase in dosage of the same region and the corresponding test result did not differ, the BART® CDx test is not designed to differentiate between duplications and triplications, and therefore, this is a limitation of the BART® CDx test.

Overall, the results demonstrate that the BART® CDx test generates analytical calls that are highly concordant with the results from a validated microarray assay, for the identification of *BRCA1* and *BRCA2* large rearrangements.

2. Analytical Sensitivity – DNA Input

   a. BRACAnalysis CDx® Sanger Sequencing Test

   PCR Amplification is the critical step in the BRACAnalysis CDx™ Sanger Sequencing test for generating high levels of specific amplicons for the sequencing reactions. To assess the acceptable range of genomic DNA input to achieve the PCR performance requirements of the test, DNA extracted from 5 specimens were each diluted to evaluate 6 DNA input concentrations (0.2 ng, 1 ng, 4 ng, 20 ng, 40 ng, and 100 ng) per PCR reaction. The rate of successful calls at each DNA input level was assessed, in addition to the concordance between tests and the expected results from the optimal input level of 20 ng per reaction, specified in the SOP for the BRACAnalysis CDx® test. At the 20 ng input level, all of the results for each sample met the quality criteria, and the duplicate results for each amplicon were fully concordant for all of the variant and non-variant calls. The performance of the BRACAnalysis CDx® Sanger Sequencing test was not significantly affected by DNA input levels from 1 ng to 100 ng.

   b. BRACAnalysis CDx® Large Rearrangement Test (BART® CDx)

   The BART® CDx test is a multiplex PCR assay that amplifies specific regions in the *BRCA1* and *BRCA2* genes. To evaluate the DNA input range for the PCR step, DNA concentrations higher and lower than the 8 ng per reaction optimal DNA input amount specified in the assay protocol were tested. The rate of successful calls per DNA input level was assessed, as well as the concordance between tests and the expected results from the optimal input level. DNA input levels ranging from 2 ng to 12 ng produced callable results for all samples tested, and the results were fully concordant.

3. Analytical Specificity – Cross Reactivity

   a. BRACAnalysis CDx® Sanger Sequencing Test

      The ability of the BRACAnalysis CDx® Sanger Sequencing test to detect sequence variants is highly dependent upon the specificity of the primers for PCR amplification. To assess the potential for amplification of non-specific products from human genomic DNA, *in silico* analysis of the PCR primers used in the assay was performed. No non-standard primer combinations were evaluated since the assay consists of only singleplex PCR reactions. Non-specific products were not predicted for any of the primer pair combinations.

   b. BRACAnalysis CDx® Large Rearrangement Test (BART® CDx)
      A specificity analysis was conducted to determine if the PCR primers used in the BART® CDx test have the potential to amplify non-target sequences in the human genome. A bioinformatics program was used to align primer pairs against genomic sequence to predict if there may be any non-specific amplicons. Every possible primer pair combination per multiplex reaction was evaluated. In total, 3,016 combinations were assessed. No non-specific products were predicted for any of the potentially cross-reactive primer pairs, in any of the BART® multiplex PCR reactions.

4. Interference

   To evaluate how potential interfering substances may impact the performance of the BRACAnalysis CDx® test, the effects of three classes of substances were assessed:

   a. endogenous substances normally present in human whole blood (i.e. hemoglobin, albumin, Immunoglobulin G (IgG), and bilirubin);
   b. an exogenous substance (i.e. K3EDTA, the anti-coagulant in the blood collection tube); and
   c. substances used in the standard process of the device (i.e. ethanol and bleach).

   At least eight whole blood samples were evaluated for each of these substances. The sample set was comprised of samples with deleterious *BRCA1/2* mutations, including insertions and deletions ranging from 1-40 basepairs, as well as multi-exon deletions. The sample set also included variants of lower clinical severity across *BRCA1* and/or *BRCA2*. All of the samples were processed with the BRACAnalysis CDx® test.

   The variant and non-variant calls were compared across treated and untreated aliquots of these samples to determine if the potential interferents may lead to alterations in the test results. All untreated samples yielded results that passed the acceptance criteria for both the BRACAnalysis CDx® Sanger Sequencing test and the BART® CDx test. With the exception of IgG at 60 g/L added into whole blood, treatment with each potentially interfering substance at the maximum concentration tested did not affect the performance of either test (i.e. hemoglobin added at 20 g/dL, albumin added at 50 g/L,

conjugated bilirubin added at 5 mg/dL, K_3EDTA added at 5%). Two method-specific potential interferents, ethanol at a final concentration of 12.75% and 10% bleach at a final concentration of 0.5%, were added to extracted DNAs and produced fully successful, concordant *BRCA1/2* sequence and LR results. The 60 g/L added IgG tests displayed partial inhibition as final *BRCA1/2* sequencing results were not generated for 1/21 of the treated samples and final *BRCA1/2* LR results were not generated for 4/21 of the treated samples (note: the other 17 samples treated at 60 g/L added IgG produced fully concordant sequencing and LR calls). As such, additional tests were performed at tests levels of 9.5 g/L, 30 g/L, and 45 g/L of IgG added to whole blood samples, where at least 8 samples were tested for each test level. When these samples were treated at these lower IgG test levels, all samples met the quality criteria for each test and generated callable results matching those of the corresponding untreated samples.

5. Reproducibility and Repeatability

   Combined Reproducibility

   Reproducibility of the BRACAnalysis CDx® test was assessed by testing a combined panel of 49 whole blood and whole blood-derived DNA samples in replicate over 6 independent runs. Six sources of variability of the device were evaluated in this combined reproducibility study: inter-run, intra-run, inter-instrument, inter-reagent lot, inter-operator, and inter-day. The CDx Sanger sequencing assay identified a range of *BRCA1* and *BRCA2* variants/mutations in this 49 sample panel; including several samples with insertions ranging from 1-28 basepairs, deletions ranging from 1-133 basepairs and single nucleotide variants, including six in homopolymer runs. A total of 14 samples with large rearrangements in *BRCA1* or *BRCA2* were identified by the BART® CDx assay, including samples containing single-exon deletions, single-exon duplications, multi-exon deletions, multi-exon duplications/triplications, and the Portuguese founder mutation (insertion of Alu sequence in Exon 3 of *BRCA2*). The 6 runs were conducted over non-consecutive days. The confirmatory assays were also performed, in accordance with the standard protocols.

   For the BRACAnalysis CDx® Sanger Sequencing test concordance among all successful replicates of each of the 49 samples was:

   Inter-run
   99.91% PPA, lower bound of 95% confidence interval for 3,174 total variant bases called.
   99.99982% NPA, lower bound of 95% confidence interval for 5,069,175 total non-variant bases called.

   Intra-run
   99.95% PPA, lower bound of 95% confidence interval for 5,770 total variant bases called.
   99.9999% NPA, lower bound of 95% confidence interval for 9,075,511 total non-variant bases called.

For the BART® CDx assay, 100% concordance was observed among all called replicates for each of the 49 samples. For inter-run reproducibility, 279/279 total LR calls were concordant across the set of samples/replicates tested. For intra-run reproducibility, 494/494 total LR calls were concordant across the set of samples/replicates tested.

These results met the acceptance criteria for combined reproducibility of the BRACAnalysis CDx® device.

6. Guardband / Robustness
   a. BRACAnalysis CDx® Sanger Sequencing Test

      Guard-banding studies were performed to evaluate if the performance of the BRACAnalysis CDx® Sanger Sequencing test is robust to withstand process variations around two key parameters: PCR annealing temperature, and sequencing annealing temperature. Five samples were tested in duplicate per tested condition, and variant types such as single nucleotide variants and small deletions (up to 5 bp) were represented.

      i. PCR Annealing Temperature

         The thermal cycling profile was guard-banded by varying the PCR annealing temperature by ± 1°C, ± 2°C and ± 3°C. For three test conditions (+ 1°C, - 2°C and - 3°C), all replicates for each amplicon tested per sample yielded successful results that matched the expected call. Similar results were observed for the other test conditions (- 1°C, + 2°C and + 3°C), with the exception that only one replicate of one of the tested amplicons for one sample generated no call. In all cases, the acceptance criteria were met, and all test conditions were tolerated.

      ii. Sequencing Reaction Annealing Temperature

         The annealing temperature for the sequencing reaction was challenged by varying the temperature by ± 1°C, ± 2°C and ± 3°C. For three test conditions (- 1°C, + 2°C and - 3°C), all replicates for each amplicon tested per sample yielded successful results that were in agreement with the expected call. For the other test conditions (+ 1°C, - 2°C and + 3°C), one replicate for one of the tested amplicons for one sample generated no call, while all other replicates generated results that matched the expected call. Thus, all of the tested temperature variations did not appear to affect the performance of the sequencing reactions.

   b. BRACAnalysis CDx® Large Rearrangement Test (BART® CDx)

      The robustness of two critical parameters of the BART® CDx test was assessed: PCR annealing temperature and injection time of the PCR product input for capillary electrophoresis. In both cases, the same set of 28 unique samples was assessed and analyzed, of which two were run in duplicate. Two samples were positive for BRCA multi-exon deletions.

      i. PCR Annealing Temperature

The PCR annealing temperature was varied by ± 1°C, ± 2°C, and ± 3°C. Four test conditions (± 1°C, - 2°C, and - 3°C) yielded successful and concordant calls for all samples. At the two other conditions (+ 2°C and + 3°C), one sample yielded an initial positive deletion result for one interrogated *BRCA2* exon on the BART® CDx assay. Per standard BART® CDx procedures, sequencing results were obtained for all BART® primer sites for the putatively affected exon, which revealed a single-nucleotide variant affecting one of the primer binding sites. These sequencing data indicated that the apparent dosage decrease observed on BART® at the + 2°C and + 3°C test conditions was an artifact caused by decreased primer binding efficiency, rather than the presence of a true deletion. Therefore, the initial positive was refuted and concluded to be a false-positive, and all final BART® CDx results for this sample were concordant with the expected results.

ii. Electrokinetic Injection Time

Different levels of PCR product injected onto the ABI 3730xl platform were assessed by altering the injection time of the PCR product. The injection time was set at 2, 4, 5, 6, 7, 10, or 20 seconds, while the voltage was held constant (2 kV), resulting in 4,
8, 10, 12, 14, 20 or 40 kV·s, respectively. All conditions except 40 kV·s resulted in successful, concordant results for all samples. At 40 kV·s, calls of acceptable quality were not obtained for any sample, indicating that this setting falls outside of the acceptable range for the BART® CDx assay. Thus, the optimal condition of 12 kV·s was within the acceptable PCR input injection conditions from 4 kV·s to 20 kV·s.

7. Carryover

The potential for carryover within a run and between runs was evaluated at 3 processes of BRACAnalysis CDx® test:

a. DNA extraction from whole blood specimens;
b. the BRACAnalysis CDx® Sanger Sequencing test; and
c. the BART® CDx test.

Specimens with different *BRCA1*/*2* genotypes (for sequence variants and large rearrangements) were processed adjacent to each other in microtiter plate formats to maximize the potential for carryover between wells within a plate and between plates in consecutive batch runs. Two consecutive batches were evaluated for inter-run carryover, and each run was evaluated separately for intra-run carryover.

a. DNA Extraction

DNA extraction from whole blood samples is an automated process on the QIASymphony robotic platform. For all samples in all batches, successful results were generated. All replicates were fully concordant within each run and between

runs. Thus, carryover events were not detected.

b. BRACAnalysis CDx® Sanger Sequencing test

Two samples with unique BRCA sequence variants were set up within one PCR plate in a checkerboard pattern at alternating high (20ng for the first sample) and low (4 ng for the second sample) DNA input levels. In the first run, there were 84/90 (93%) successful calls and 6/90 no calls for the two samples tested. All callable results were concordant. In the second run, there were 89/90 (99%) successful calls, all of which were concordant. All replicates were fully concordant within each run and between runs. Thus, carryover events were not detected.

c. BRACAnalysis CDx® Large Rearrangement Test (BART® CDx)

For the BART® CDx test, a total of 10 samples were evaluated. The samples were arranged such that 8 unique BRCA large rearrangement-negative samples, along with two samples positive for BRCA large rearrangements, were tested in each batch. For all replicates of all samples in each batch, the results were of acceptable data quality and were fully concordant with the expected results. All replicates were fully concordant within each run and between runs. Thus, carryover events were not detected.

8. Stability

Verification studies were performed to evaluate the stability of whole blood specimens, reagents, standards and controls. Testing supports the following expiration dating:

a. Specimen Stability

Whole Blood Specimens in EDTA blood collection tubes: up to 30 days at 4 °C and up to 7 days at 30 °C.

b. Reagents Stability

i. Sanger Sequencing PCR Reagent Plates: up to 6 months at -20 °C.

ii. Sanger Sequencing Oligo Reagent Plates: up to 6 months at -80 °C and up to 60 days at 4 °C.

iii. Sanger Sequencing CAPSeq Reagent Plates: up to 6 months at -20 °C.

iv. BART® PCR Reagent Plates: up to 6 months at -80 °C.

v. Quantification Standards: up to 30 days at 4 °C.

c. Controls Stability

i. Sanger M13 F+R Negative Control: up to 6 months at -80 °C.

ii. BART® Cell Line Positive Control: up to 2 months at 4 °C.

iii. BART® Alternate Positive Control: up to 3 months at 4 °C.

iv. BART® Amplicon Negative Control: up to 6 months at -80 °C.

v. CPA PCR Amplification Controls: up to 2 months at 4°C.

vi. CPA No Genomic DNA Controls: up to 12 months at -20 °C.

Stability testing of whole blood specimens, reagents, standards and controls supports the performance of the BRACAnalysis CDx® device under the specified storage conditions and stability/expiration times for the listed device components.

9. Mock Shipping-Stressed Whole Blood Specimens

Clinical specimens have the potential to be compromised during shipment from the collection site to the testing site. Whole blood specimens treated with EDTA were subjected to various stresses mimicking those that can be encountered in real-world shipping. The robustness and precision of the BRACAnalysis CDx® device was assessed by comparing the *BRCA1*/*2* sequencing and large rearrangement results generated from stressed whole blood samples with the results of un-stressed controls.

Whole blood specimens produced full successful, expected results under the following mock-shipping stress conditions:

i. Storage at -20 °C for up to 10 days
ii. Storage at 42 °C for up to 12 hours
iii. One, two and three freeze-thaws

Storage of specimens at 60 °C and 42 °C resulted in complete coagulation after 2 hours and 24 hours, respectively; and extraction of genomic DNA could not be performed according to standard procedures. This coagulation is a clearly observable phenotype of incoming patient specimens that would be rejected.

10. Variant Classification Study

To evaluate the robustness and reliability of the variant classification process, a set of 262 unique BRCA variants was subjected to classification as if they were new variant observations. The variants were classified in a blinded manner according to defined classification criteria. The resulting classifications for each variant were compared to the existing classifications in Myriad's database, and the concordance rate was determined. One variant that was not previously observed at Myriad, and therefore was not previously classified, was excluded from the study. The majority of variants (185/262) were identified from clinical studies for Lynparza® (olaparib), and the remaining variants (77/262) were selected for inclusion into the study to adequately cover the spectrum of variant types for classification. The results are summarized in the tables below.

Comparison of the new classifications to the previous classifications resulted in agreement for 245 variants (93.9%; 95% CI: 90.2% to 96.5%). The criteria and current evidence provided opportunity to update the classification for 16 of the 262 variants. Of the 16 variants with inconsistent results, 14 would not affect treatment eligibility for Lynparza® (olaparib). Of the remaining two, one is a missense variant classified in the study as suspected deleterious (SD), but the previous classification was a variant of uncertain

significance (VUS). The change in classification resulted from new structural and functional evidence, which recently became available, to support the SD classification. The other was an intronic splicing variant classified as VUS in this study, but previously was SD. The classification changed due to available evidence. This variant has only been observed twice in the population tested at Myriad since 1996. Thus, by comparing results from two separate and independent variant classifications, the concordance rate - as defined as leading to the same eligibility status for treatment with Lynparza® (olaparib) – is 99.2% (95% CI: 97.2% to 99.9%).

Summary of Clinical Studies

1. Summary of Clinical Study - Olaparib D0810C00042 (Study 1)

   The olaparib clinical study D0810C00042 (Study 1) was an open-label, non-randomized study to assess the safety and efficacy of olaparib treatment in patients with ovarian cancer who have a deleterious or suspected deleterious germline BRCA mutation (*gBRCAm*) and who have been previously treated with at least 3 lines of prior chemotherapy. Patients were enrolled from 13 centers in six countries, including the United States. Local test results for BRCA status were used to assess patient eligibility for the trial. Samples from a subset of enrolled patients were retrospectively evaluated at one laboratory, Myriad (Salt Lake City, UT) using the BRACAnalysis CDx® test. The clinical utility of the BRACAnalysis CDx® test was established by comparing the mutation results and the associated clinical outcomes for the overall population to those for the subset of patients with confirmed *g*BRCA status upon retrospective testing with the BRACAnalysis CDx® test. Lynparza® (olaparib) demonstrated a robust overall response rate with a clinically meaningful duration of response in *gBRCAm* patients with ovarian cancer who had received three or more prior lines of chemotherapy. The magnitude of response in the population tested with the BRACAnalysis CDx® test was comparable to that in the overall population. Data from this bridging study were used to support PMA approval.

   a. Accountability of PMA Cohort

      Based on local test results, a total of 317 patients with advanced cancers were enrolled in the study. There were 193 patients with deleterious or suspected deleterious germline BRCA mutation (*gBRCAm*)-associated ovarian cancer, among whom 137 had measureable disease and had received three or more lines of prior chemotherapy. Out of the 137 patients, specimens from 61 patients were available for retrospective testingwith the BRACAnalysis CDx® test in the clinical bridging study.

   b. Effectiveness Results

      The analysis of efficacy analysis was based on objective response rate (ORR) and duration of response (DoR) observed in 137 patients with deleterious or suspected deleterious germline BRCA mutation (*gBRCAm*)-associated ovarian cancer who had received three or more prior lines of chemotherapy and who had measurable disease. In this cohort, the ORR was 34% (95% CI: 26% - 42%) with a median DoR of 7.9 months. The results are listed in the table below. The observed ORR represents an improvement over existing therapies and is reasonably likely to predict clinical benefit in the indicated population. Confirmatory studies are in progress.

      The effectiveness analysis for the BRACAnalysis CDx® test was based on a subset of 61 *gBRCAm* patients with ovarian cancer who had received three or more prior lines of chemotherapy, who had measurable disease, and for whom specimens were available for retesting with BRACAnalysis CDx®. The level of concordance between the local test results, as reported in the Case Report Form,

and the results from the BRACAnalysis CDx® test was determined to be 96.7% (59/61). Among the discordant results, one sample did not yield a callable result with BRACAnalysis CDx® test, and another sample had different classification results between the local test and the BRACAnalysis CDx® test (deleterious vs. variant of unknown significance, respectively), although the specific variant that was detected by both tests matched. In addition, the clinical outcome data for the 59 patients with confirmed *gBRCAm* status was as follows: ORR was 41% (95% CI: 28% - 54%), and median DoR was 8.0 months. Taken together, the results in the subset of *gBRCAm* patients tested with the BRACAnalysis CDx® test were comparable to those observed in the cohort of 137 patients, which supports effectiveness of the device. The results are summarized in the table below.

Clinical Study Results

Subset*	Subjects with response	ORR	95% CI	Progressed n (%)	Median DoR (months)	95% CI
All	46 (33.6)	0.34	(0.26, 0.42)	30 (65.2)	7.9	(5.6, 9.6)
With BRACAnalysis	24 (40.7)	0.41	(0.28, 0.54)	14 (58.3)	8.0	(3.8, NC)
Without BRACAnalysis	22 (28.2)	0.28	(0.19, 0.40)	16 (72.7)	7.9	(6.0, 9.6)

*Ovarian cancer patients with measureable disease who had received at least 3 lines of prior chemotherapy

c. Robustness Analyses

Additional robustness analyses were conducted to consider the potential impact of missing data arising from patients with a positive BRACAnalysis CDx® test result, but who may have been negative by the local test. Patients with such test results are part of the intended use population of the BRACAnalysis CDx® test; however, they were excluded from the clinical trial due to negative results upon local test screening. To account for this missing data, the efficacy of olaparib treatment (based on ORR) in patients with positive results from the BRACAnalysis CDx® test was estimated assuming different combinations for multiple parameters.

The confidence intervals were calculated based on the imputed ORR from the subset of 137 patients with deleterious or suspected deleterious germline BRCA mutation *(gBRCAm)*-associated ovarian cancer who had received 3 or more prior lines of chemotherapy and who had measurable disease in the study. The smallest estimated ORR value estimated for the BRACAnalysis CDx® test-positive population is 34% (95% CI: 26% - 43%), which is not significantly different from that observed for the overall subpopulation of patients (n=137) who had measurable disease and who had received 3 or more lines of prior chemotherapy (34%, 95% CI: 26% - 42%). These results support the finding that the observed improvement in ORR in the indicated population is robust.

The data describing the performance characteristics above, as well as the clinical study endpoints, support the clinical utility of BRACAnalysis CDx® as a companion diagnostic to Lynparza® (olaparib).

2. Summary of Clinical Study – Olaparib D0819C00003 (OlympiAD)

The olaparib clinical study D0819C00003 (OlympiAD) was a Phase III randomized, open label, controlled, multi-center study of olaparib monotherapy versus healthcare provider's choice of chemotherapy (capecitabine, eribulin, or vinorelbine, at standard dose) in the treatment of metastatic HER2-negative breast cancer patients with germline *BRCA1/2* mutations. A total of 302 patients were enrolled from 125 centers in 19 countries, including the United States. Patients were required to have documented evidence of a deleterious or suspected deleterious mutation in either *BRCA1* or *BRCA2* to be enrolled into the study. Evidence of a qualifying *BRCA* mutation could be from either an existing *BRCA* mutation result from local testing or from prospective testing performed by Myriad (Salt Lake City, UT) using either the Myriad Integrated BRAC*Analysis*® or BRACAnalysis CDx® test, or by BGI Clinical Laboratories (Shenzhen, China) for Chinese patients. Samples from 29 patients were tested prospectively using the BRACAnalysis CDx® test, and samples from 270 patients who were randomized based on local, BGI or Myriad Integrated BRAC*Analysis*® testing were retrospectively evaluated using the BRACAnalysis CDx® test. The clinical performance of the BRACAnalysis CDx® test was established by comparing the mutation results and the associated clinical outcomes for the overall study population to those for the subset of patients with confirmed germline *BRCA* status upon prospective or retrospective testing with the BRACAnalysis CDx® test. Lynparza® (olaparib) demonstrated a clinically relevant improvement in progression-free survival (PFS) for olaparib-treated patients compared to chemotherapy-treated patients in metastatic HER2-negative breast cancer patients with germline *BRCA1/2* mutations. The magnitude of response in the population tested with the BRACAnalysis CDx® test was comparable to that in the overall population.

a. Accountability of PMA Cohort

Of the 302 patients randomized in OlympiAD, 29 patients were randomized on the basis of the BRACAnalysis CDx® test. The remaining 273 cases were randomized on the basis of an Integrated BRAC*Analysis*® test result (n=65), an alternative test performed in China (n=41), or local test results (n=167). Retrospective testing using the BRACAnalysis CDx® test was performed for 270 of the 273 cases randomized on the basis of results from tests other than the BRACAnalysis CDx® test.

Overall, of the 302 patients randomized onto OlympiAD, 299 were tested with the BRACAnalysis CDx® test and 297 patients were confirmed to carry a deleterious or suspected deleterious germline *BRCA* mutation. The PMA cohort represented 98% of the full analysis set in OlympiAD.

b. Effectiveness Results

The primary efficacy endpoint of the therapeutic study was progression-free survival (PFS) determined by blinded independent central review assessed by Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). The study population consisted of 302 metastatic breast cancer patients with a deleterious or suspected deleterious germline *BRCA* mutation as detected by the Myriad Integrated BRAC*Analysis*® test, BRACAnalysis CDx® test, or local test results. In this study, the

PFS improvement was statistically significant and clinically meaningful, as evidenced by a 42% reduction in the risk of progression or death, and a median PFS of 2.8 months longer for olaparib-treated patients (7.0 months) compared with chemotherapy-treated patients (4.2 months). These results are shown in the table below.

The effectiveness of the BRACAnalysis CDx® test was based on a subset of 297 confirmed metastatic breast cancer patients with deleterious or suspected deleterious germline *BRCA1/2* mutations for whom prospective or retrospective testing was performed with the BRACAnalysis CDx® test. Five cases among the 302 randomized patients were not confirmed to have a germline *BRCA* mutation using the BRACAnalysis CDx® test. In 3 cases no BRACAnalysis CDx® result was available, and in 2 cases the BRACAnalysis CDx® result reported a variant that was not deleterious or suspected deleterious.

The clinical outcome data for the 297 patients with a confirmed germline BRCA1/2 mutation was as follows: a 43% reduction in the risk of progression or death, and a median PFS of 3.2 months longer for olaparib-treated patients compared with chemotherapy-treated patients. Taken together, these results are very similar to those observed in the 302 patients in the OlympiAD study, which supports the effectiveness of the device.

The clinical outcome results for cases classified as having a deleterious or suspected deleterious germline *BRCA* mutation by the BRACAnalysis CDx® test are shown in the table below.

	OlympiAD		**BRACAnalysis CDx® test**	
	Olaparib 300 mg bd[a]	**Comparator[b]**	**Olaparib 300 mg bd[a]**	**Comparator[b]**
PFS				
Number of events: total number of patients (%)	163:205 (80)	71:97 (73)	160:202 (79)	71:95 (75)
Median PFS (months)	7.0	4.2	7.4	4.2
HR (95% CI)	0.58 (0.43-0.80)		0.57 (0.41-0.78)	
P-value (2-sided)	p=0.0009		p=0.0005	

a- tablet formulation, b - Comparator consisting of either capecitabine, eribulin or vinorelbine

3. Summary of Clinical Study – Olaparib D0818C00001 (SOLO1)

The olaparib clinical study D0818C00001 (SOLO1) was a Phase III, randomised, double blind, placebo controlled, multicentre study to assess the efficacy of olaparib maintenance monotherapy in newly diagnosed advanced ovarian cancer patients (including patients with primary peritoneal and/or fallopian tube cancer) with BRCA mutations (documented mutation in *BRCA1* or *BRCA2*) that were predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss

of function) who had responded following first-line platinum based chemotherapy. A total of 391 patients were randomized from 118 centers in 15 countries, including the United States. Patients were required to have documented evidence of a deleterious or suspected deleterious mutation in either *BRCA1* or *BRCA2* to be enrolled into the study. Evidence of a qualifying BRCA mutation could be from either an existing BRCA mutation result from local testing (n=210) or from prospective testing (n=181) performed by Myriad (Salt Lake City, UT) using the Myriad Integrated BRACAnalysis® or by BGI Clinical Laboratories (Shenzhen, China).

Out of 181 samples enrolled, 178 patients were tested prospectively using the Myriad Integrated BRACAnalysis® test and 3 patients were tested prospectively using the BGI test. Out of 210 enrolled by local testing, 208 patients were retrospectively evaluated using the Myriad Integrated BRACAnalysis® (n=205) or the BRACAnalysis CDx® (n=3) test. Samples from 2 patients who were randomized based on local testing in China could not be exported for testing at Myriad. A total of 383 patients were tested with the Myriad Integrated BRACAnalysis® and 3 patients were tested with the BRACAnalysis CDx®. Concordance studies between the Integrated BRACAnalysis® and BRACAnalysis CDx® have demonstrated a 100% agreement between the two tests. Thus, for simplification, the terminology Myriad BRACAnalysis test will be used if either the Integrated BRACAnalysis® or BRACAnalysis CDx® was used.

The clinical performance of the Myriad BRACAnalysis test was established by comparing the mutation results and the associated clinical outcomes for the overall study population to those for the subset of patients with confirmed germline BRCA status upon prospective or retrospective testing with a Myriad BRACAnalysis test. The data from SOLO1 demonstrated a substantial improvement in investigator-assessed progression-free survival (PFS) that was statistically significant and clinically relevant for olaparib compared with placebo treated patients with newly diagnosed BRCA-mutated advanced ovarian cancer. The magnitude of response in the population tested with a Myriad BRACAnalysis test was comparable to that in the overall population.

a. Accountability of PMA Cohort

   Of the 391 patients randomized in the global SOLO1 cohort, 178 patients were randomized on the basis of the Integrated BRACAnalysis® test and 3 on the basis of the BGI test. The remaining 210 cases were randomized on the basis of local test results; 208 out of the 210 cases with a local result were retrospectively tested using either the Integrated BRACAnalysis® test (n=205) or the BRACAnalysis CDx® (n=3).

   Overall, of the 391 patients randomized in the global SOLO1 cohort, 386 were tested with either the Integrated BRACAnalysis® test or the BRACAnalysis CDx® test and 383 patients were confirmed to carry a deleterious or suspected deleterious germline BRCA mutation. The PMA cohort represented 98% of the

full analysis set in the global SOLO1 cohort.

b. Effectiveness Results

The primary objective of this study was to determine the efficacy by PFS (using investigator assessment of scans according to modified Response Evaluation Criteria in Solid Tumours [RECIST] 1.1) of olaparib maintenance monotherapy compared with placebo in newly diagnosed BRCA mutated advanced ovarian cancer patients who were in clinical CR or PR following first line platinum-based chemotherapy. The study population consisted of 391 ovarian cancer patients with a deleterious or suspected deleterious germline BRCA mutation as detected by the Myriad Integrated BRACAnalysis® test, BRACAnalysis CDx® test, BGI test or local test results (Full Analysis Set – FAS). A statistically significant and clinically relevant improvement in investigator-assessed PFS was observed, as evidenced by the magnitude of effect: a 70% reduction in the risk of disease progression or death at any point in time for olaparib vs placebo treated patients (Hazard Ratio [HR] 0.30; 95% CI 0.23-0.41; p<0.0001; Table 1). After a median follow-up of 41 months, median PFS was not reached on the olaparib arm vs 13.8 months for placebo.

The effectiveness of the Myriad BRACAnalysis test was based on a subset of 383 confirmed ovarian cancer patients with deleterious or suspected deleterious germline *BRCA1* or *BRCA2* mutations for whom prospective or retrospective testing was performed with either the Myriad Integrated BRACAnalysis® test or the BRACAnalysis CDx® test. Three cases among the 386 randomized patients were not confirmed to have a germline BRCA mutation using the Myriad test. In 1 case, the Myriad BRACAnalysis test result reported a variant that was not deleterious or suspected deleterious and in the other 2 cases, the Myriad BRACAnalysis test result did not report any variant.

The clinical outcome data for the 383 patients with a confirmed germline *BRCA1* or *BRCA2* mutation was as follows: a 70% reduction in the risk of disease progression or death at any point in time for olaparib vs placebo treated patients (HR 0.30; 95% CI 0.22-0.40; p<0.0001; Table 1). After a median follow-up of 41 months, median PFS was not reached on the olaparib arm vs 13.8 months for placebo. Taken together, these results are very similar to those observed in the 391 patients in the SOLO1 study, which supports the effectiveness of the Myriad BRACAnalysis device.

The clinical outcome results for cases classified as having a deleterious or suspected deleterious germline BRCA mutation by the Myriad BRACAnalysis test (Myriad gBRCAm subset) are shown in Table below.

SOLO1	**FAS**		**Myriad *gBRACAm* subset**	
	Olaparib 300 mg bd[a]	**Placebo**	**Olaparib 300 mg bd[a]**	**Placebo**
			PFS	
Number of events: total number of patients (%)	102:260 (39)	96:131 (73)	99:253 (39)	95:130 (73)

Median PFS (months)	Not reached	13.8	Not reached	13.8
HR (95% CI)	0.30 (0.23-0.41)		0.30 (0.22-0.40)	
P-value (2-sided)	<0.0001		<0.0001	

a- tablet formulation

4. Summary of Clinical Study – Olaparib D081FC00001 (POLO)

The olaparib clinical study D081FC00001 (POLO) was a Phase III, randomized, double-blind, placebo-controlled, multicenter trial to assess the efficacy of Lynparza maintenance treatment in patients with metastatic adenocarcinoma of the pancreas who have a deleterious or suspected deleterious germline *BRCA* mutation (*gBRCAm*) and whose disease had not progressed after at least 16 weeks of first-line platinum-based chemotherapy. The study randomized 154 patients (3:2 randomization: 92 olaparib and 62 placebo). Patients were enrolled from 59 centers in twelve countries, including the United States. Patients with germline *BRCA* mutations were identified from prior local testing results or by central testing using the Myriad BRAC*Analysis*® or Myriad BRACAnalysis CDx® test. The g*BRCAm* status of all patients identified using prior local testing results was confirmed, if a sample was available, using the Myriad BRAC*Analysis*® or Myriad BRACAnalysis CDx® test at one laboratory, Myriad Genetic Laboratories (Salt Lake City, UT). The clinical performance of the Myriad BRACAnalysis test was established by comparing the mutation results and the associated clinical outcomes for the overall study population to those for the subset of patients with confirmed germline *BRCA* status upon prospective or retrospective testing with a Myriad BRACAnalysis test. Lynparza® (olaparib) demonstrated an improvement in progression free survival for olaparib compared to placebo.

a. Accountability of PMA Cohort

Of the 154 patients randomised in the global POLO cohort, 106 patients were randomized on the basis of a Myriad *gBRCAm* result using either the Myriad BRAC*Analysis*® (n=6) or Myriad BRACAnalysis CDx® test (n=100). The remaining 48 cases were randomized on the basis of local test results; 44 out of the 48 cases with a local result were retrospectively tested using either the Myriad BRAC*Analysis*® test (n=3) or the Myriad BRACAnalysis CDx® (n=41).

Overall, of the 154 patients randomized in the global POLO cohort, 150 were tested with either the Myriad BRAC*Analysis*® test (n=9) or the Myriad BRACAnalysis CDx® test (n=141) and 150 patients were confirmed to carry a deleterious or suspected deleterious germline *BRCA* mutation. The PMA cohort represented 97.4% of the full analysis set in the global POLO cohort.

b. Effectiveness Results

The primary endpoint of POLO was Progression-Free Survival (PFS), defined as time from randomisation to progression determined by Blinded Independent Central Review (BICR) using modified Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1), or death.

The study population consisted of 154 pancreatic cancer patients with a deleterious or suspected deleterious germline *BRCA* mutation as detected by the Myriad BRAC*Analysis*® test, Myriad BRACAnalysis CDx® test or local test results (Full Analysis Set – FAS). The study demonstrated a clinically meaningful and statistically significant improvement in PFS for olaparib compared to placebo, with a HR of 0.53 (95% CI 0.35 – 0.81; p=0.0035; the median was 7.4 months for olaparib vs 3.8 months for placebo). The results are shown in the table 1.

The PFS data for the 150 patients in the confirmed Myriad *gBRCAm* subset was as follows: HR of 0.55 (95% CI 0.36-0.84; p=0.0060; the median was 7.4 months for olaparib vs 3.8 months for placebo).

These results are consistent to those observed in the 154 patients in the POLO study, which supports the effectiveness of the Myriad BRACAnalysis device.

The POLO PFS results for the FAS and the confirmed Myriad *gBRCAm* subset of patients are shown in Table 1.

Table 1: Clinical Study Results

POLO	**FAS**		**Myriad *gBRCAm* subset**	
	Olaparib 300 mg bd[a]	**Placebo**	**Olaparib 300 mg bd[a]**	**Placebo**
PFS				
Number of events: total number of patients (%)	60:92 (65)	44:62 (71)	59:89 (66)	44:61 (72)
Median PFS (months)	7.4	3.8	7.4	3.8
HR (95% CI)	0.53 (0.35-0.81)		0.55 (0.36-0.84)	
P-value (2-sided)	p=0.0035		p=0.0060	

a- tablet formulation.

The effectiveness analysis for the Myriad BRACAnalysis test was based on a subset of 150/154 metastatic pancreatic adenocarcinoma patients who were confirmed with a deleterious or suspected deleterious germline *BRCA1/2* mutation by either the Myriad BRAC*Analysis*® test or the Myriad BRACAnalysis CDx® test. Four patients were not confirmed to have a germline *BRCA* mutation by the Myriad test as no sample was submitted for testing. The data demonstrated that the Myriad test supports the efficacy conclusions obtained with the ITT population.

5. Summary of Clinical Study-Olaparib D081DC00007 (PROfound)

BRACAnalysis CDx® Technical Information

https://myriadmyrisk.com/documents-and-forms/technical-specifications/

The clinical benefit of BRACAnalysis CDx® test was demonstrated in a retrospective analysis of efficacy and safety data obtained from the Phase III randomized, open label, randomized study to assess the efficacy and safety of olaparib (Lynparza™) versus enzalutamide or abiraterone acetate (physician's choice of new hormonal agent [NHA]) in men with metastatic castration-resistant prostate cancer who have failed prior treatment with a new hormonal agent and have homologous recombination repair gene mutations.

Patients were required to have documented evidence of a deleterious or suspected deleterious mutation in one of 15 genes with a direct or indirect role in homologous recombination repair (HRR) to be enrolled into the study. The 15 gene panel included *BRCA1* and *BRCA2*. HRR gene mutation status was prospectively determined using a tumour tissue test. Patients were enrolled from 206 study centers in 20 countries (of these, 139 centers randomized patients) including the United States. Patients were randomized into 2 cohorts: Cohort A included 245 patients with *BRCA1*, *BRCA2* and *ATM* mutations (162 patients received olaparib, 83 patients received physician's choice of NHA), Cohort B included 142 patients with mutations in the remaining 12 HRR genes (94 patients received olaparib, 47 patients received physician's choice of NHA).

Determination of the germline *BRCA* mutation status was performed by testing blood samples from patients randomized onto the PROfound study retrospectively using the BRACAnalysis CDx® test performed by Myriad (Salt Lake City, UT)

The clinical utility of the BRACAnalysis CDx® test was established by comparing the mutation results and the associated clinical outcomes for the Cohort A PROfound population to those for the subset of patients with confirmed *gBRCAm* status by retrospective testing with the BRACAnalysis CDx® test. Lynparza™ (olaparib) demonstrated a clinically relevant improvement in Progression Free Survival for olaparib treated patients compared to physician's choice NHA treated patients in HRRm metastatic castration resistant prostate cancer patients. The PFS improvement in Cohort A patients was statistically significant and clinically relevant. The magnitude of response in the population tested with the BRACAnalysis CDx® test was comparable to that in the overall population. Data from this bridging study were used to support PMA approval.

a. Accountability of PMA Cohort

Of the 387 patients randomised in PROfound, 288 patients reported a successfully *gBRCAm* status using the BRACAnalysis CDx® test. For 98 patients, no retrospective BRACAnalysis CDx® test result was obtained due to no sample being provided for retrospective testing (n=39), consent not being granted for diagnostic development (n=55), samples being unsuitable for testing (n=4). In addition, in one patient also reported an inconclusive result.

Of the 288 patients with a *gBRCA* status reported by the BRACAnalysis CDx® test, 114 carried a tumor *BRCA1*/2 mutation and 174 patients were tumor non-*BRCA* mutation positive. In total, 62 patients were reported as germline *BRCA*

mutation positive by the BRACAnalysis CDx® test. The PMA cohort represented 25.3% (62/245) of Cohort A and 16.0% (62/387) of Cohort A+B in PROfound. Germline *BRCA* mutations were seen in 53.5% (61/114) of tumor *BRCA* mutation positive patients. Additionally, one patient who was tumor non-*BRCA* mutation positive reported a germline *BRCA* mutation.

b. Effectiveness results

The analysis of efficacy was based on the primary endpoint of the study of radiological progression free survival determined by blinded independent central review observed in the 245 metastatic castration resistant prostate cancer cases with *BRCA1/2* or *ATM* mutations (Cohort A). In this study the PFS improvement was statistically significant and clinically relevant, as evidenced by the magnitude of effect: a 66% reduction in the risk of progression or death, and a median PFS of 3.84 months longer for olaparib-treated patients (7.39 months) compared with NHA-treated patients (3.55 months). A key secondary endpoint of radiological progression free survival determined by blinded independent central review in the overall HRRm treated population (Cohort A+B) also demonstrated a statistically significant and clinically relevant improvement in olaparib treated patients compared with NHA-treated patients (rPFS HR=0.49, median PFS: 5.82mo [olaparib], 3.52mo [NHA]). These results are shown in the table below.

Within the PROfound study, there were 160 patients who carried a *BRCA1/2* mutation according to the tissue test, 15 patients carried a t*BRCA1* mutation and 145 patients carried a t*BRCA2* mutation. No patients carried both t*BRCA1* and t*BRCA2* mutations. Of the 160 t*BRCAm* patients in PROfound, 114 patients had a valid result reported by BRACAnalysis CDx® test and 46 patients were not tested/did not have a valid result. One (1) patient excluded as they were tested using the tissue test that did not meet inclusion criteria. Of these, 113 patients had a valid result reported by BRACAnalysis CDx® test, and 61 germline *BRCA1/2* mutations were identified in these cases. Additionally, 1 patient was reported as germline *BRCA1/2* mutation positive which did not report a *BRCA1/2* mutation in the tissue test. Overall therefore, 62 patients randomised in PROfound were germline *BRCA1/2* mutation positive. These 62 patients were used to generate the efficacy estimates for patients with *BRCAm* status defined by BRACAnalysis CDx®.

The effectiveness of the BRACAnalysis CDx® test was based on a subset of 62 confirmed *gBRCAm* metastatic castration resistant prostate cancer cases for whom retrospective testing was performed with the BRACAnalysis CDx® test and a *gBRCAm* result identified (43 patients received olaparib, 19 patients received physician's choice of NHA).

The clinical outcome data for the 62 patients with confirmed *gBRCAm* status was as follows: a 92% reduction in the risk of progression or death, and a median PFS of 8.25 months longer for *gBRCAm* olaparib-treated patients (10.12 months)

compared with NHA-treated patients (1.87 months). Taken together, the results in the subset of *gBRCAm* patients tested with the BRACAnalysis CDx® test were comparable to those observed in the 245 Cohort A patients and 387 Cohort A+B patients in the overall PROfound study, which supports the effectiveness of the device.

The clinical outcome data for cases classified as *gBRCAm* by the BRACAnalysis CDx® test is shown in the table below.

	PROfound Cohort A (n=245)		**PROfound Cohort A+B (n=387)**		**BRACAnalysis CDx® test *gBRCAm* confirmed (n=62)**	
	Olaparib 300 mg bd[a]	**Physicians choice NHA[b]**	**Olaparib 300 mg bd[a]**	**Physicians choice NHA[b]**	**Olaparib 300 mg bd[a]**	**Physicians choice NHA[b]**
Number of events: total number of patients (%)	106:162 (65.4)	68:83 (81.9)	180:256 (70.3)	99:131 (75.6)	25:43 (58.1)	17:19 (89.5)
Median PFS (months)	7.39	3.55	5.82	3.52	10.12	1.87
HR (95% CI)	0.34 (0.25, 0.47)		0.49 (0.38, 0.63)		0.08 (0.03, 0.18)	
P-value (2-sided)	<0.0001		<0.0001		<0.0001	

a- tablet formulation, b - Physician's choice of NHA consisting of either enzalutamide or abiraterone acetate

6. Summary of Clinical Study - Niraparib PR-30-5011-C (NOVA)

The niraparib clinical study PR-30-5011-C (NOVA) was a double-blind, 2:1 (niraparib: placebo) randomized, placebo-controlled, multicenter, global clinical trial designed to evaluate the efficacy and safety of niraparib in patients with ovarian cancer who had received at least two platinum-based regimens and were in response to their last platinum-based chemotherapy. Patients were required to have received a minimum of four cycles of treatment and, following treatment, have an investigator-defined complete or partial response to their last platinum regimen with no observable residual disease of <2 cm and cancer antigen 125 (CA-125) values either within the normal range, or a CA-125 decrease of more than 90% that was stable for at least 7 days.

a. Accountability of PMA Cohort

Enrollment into cohorts was determined by the results of Myriad's BRACAnalysis CDx® test. Randomization was stratified by time to progression after the penultimate platinum therapy before study enrollment (6 to <12 months or ≥12 months); use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes/no); and best response during the last platinum regimen (complete response [CR] or partial response [PR]).

Patients were enrolled from 128 centers in 15 countries, including the United States. All testing for germline BRCA was conducted centrally using the BRACAnalysis CDx® test. Overall, 553 patients were randomized. A total of 203 patients were assigned to the BRACAnalysis CDx positive cohort and 350

patients were assigned to the BRACAnalysis CDx negative cohort.

b. Effectiveness Results

The evaluation of efficacy was based on serial assessments of disease using radiographs of the abdomen/pelvis and other clinically indicated areas, physical examinations, and CA-125 testing; PRO questionnaires; and post-treatment information on follow-up anti-cancer therapy (including progression on that therapy), and survival status.

The primary efficacy endpoint was progression-free survival (PFS), defined as the time from the date of treatment randomization to the date of first documentation of progression (by blinded IRC review according to RECIST 1.1) or death by any cause in the absence of documented progression, whichever occurred first. There were several secondary and exploratory endpoints.

Patients receiving niraparib exhibited significantly longer PFS than those receiving placebo. Within the BRACAnalysis CDx positive cohort, the median PFS was 21.0 months versus 5.5 months with placebo (HR: 0.27; 95% CI: 0.173 to 0.410) (p<0.0001). PFS was statistically significantly longer with niraparib than with placebo in the overall BRACAnalysis CDx negative cohort (median, 9.3 months versus 3.9 months; HR: 0.45; 95% CI: 0.338 to 0.607) (p<0.0001).

Progression-Free Survival in the Primary Efficacy Cohorts (ITT Population, N=553)

Treatment	Median PFS[a] (95% CI) (Months)	Hazard Ratio[b] (95% CI) p-value[c]
BRACAnalysis CDx Positive Cohort		
Niraparib (N=138)	21.0 (12.9, NR)	0.26 (0.17, 0.41) p<0.0001
Placebo (N=65)	5.5 (3.8, 7.2)	
BRACAnalysis CDx Negative Cohort		
Niraparib (N=234)	9.3 (7.2, 11.2)	0.45 (0.34, 0.61) p<0.0001
Placebo (N=116)	3.9 (3.7, 5.5)	

Abbreviations: BRCA=breast cancer susceptibility gene; CI=confidence interval; BRACAnalysis CDx positive=germline BRCA mutation; ITT=intent-to-treat; BRACAnalysis CDx negative=without a germline BRCA mutation; PFS=progression-free survival; NR=not reached.
[a] Progression-free survival is defined as the time in months from the date of randomization to progression or death.
[b] Niraparib:Placebo, based on the stratified Cox Proportional Hazards Model using randomization stratification factors.
[c] Based on stratified log-rank test using randomization stratification factors.

7. Summary of Clinical Study – EMBRACA (NCT01945775)

The talazoparib clinical study EMBRACA was a Phase III randomized, open label, study of talazoparib versus protocol specified healthcare provider's choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) and was designed to assess the safety and efficacy of talazoparib in patients with deleterious or suspected deleterious germline *BRCA1/2*-mutated HER2-negative locally advanced or metastatic breast cancer who received no more than 3 prior cytotoxic chemotherapy regimens for

locally advanced or metastatic breast cancer. A total of 431 patients were enrolled from 145 study sites across 16 countries, including the United States.

Patients were required to have documentation of a deleterious, suspected deleterious, or pathogenic germline *BRCA1* or *BRCA2* mutation from Myriad Genetics (Myriad; Salt Lake City, UT) or another laboratory approved by the Sponsor. Myriad used a combination of Integrated BRAC*Analysis*® and BRACAnalysis CDx® test results for study enrollment. The concordance studies between the Integrated BRACAnalysis®and BRACAnalysis CDx® for the OlympiAD and NOVA trials demonstrated a 100% agreement between the two tests. For data obtained regarding a BRCA1/2 mutation from a non Myriad laboratory, the pathology report was submitted to and approved by the Sponsor and a blood sample was sent to Myriad for analysis before randomization.

The clinical performance of the BRACAnalysis CDx® test was established by comparing the mutation results and the associated clinical outcomes for the overall (Intent-to-Treat) study population to those for the subset of patients with confirmed deleterious or suspected deleterious germline *BRCA1/2* status by the BRACAnalysis CDx® test.

Talazoparib treatment demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint of progression-free survival (PFS) over healthcare provider's choice of chemotherapy patients with deleterious or suspected deleterious germline *BRCA1/2* -mutated HER2-negative locally advanced or metastatic breast cancer. The magnitude of benefit in the population tested with the BRACAnalysis test was comparable to that in the overall population.

a. Accountability of PMA Cohort

   Based on central testing conducted by Myriad and on local testing, a total of 431 patients were randomized into the EMBRACA study. Of the 431 patients randomized into the clinical study, 408 (95%) patients were tested centrally (114 were tested with the Integrated BRAC*Analysis*® test and 294 with the BRACAnalysis CDx). Of the 114 samples tested with the Integrated BRAC*Analysis*® test, 60 were retested with the BRACAnalysis CDx® test and shown to have 100 % agreement. The remaining 23 patients (5.3%) were enrolled using a non-Myriad laboratory test.

b. Effectiveness Results

   The primary efficacy endpoint was PFS evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and assessed by blinded independent central review (BICR). The study population consisted of 431 patients with deleterious or suspected deleterious germline *BRCA1* or *BRCA2* -mutated (as detected by central testing conducted by Myriad or local test results) HER2-negative locally advanced or metastatic breast cancer.

   In the EMBRACA study, talazoparib treatment demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint of PFS over chemotherapy in patients with deleterious or suspected deleterious

germline *BRCA1* or *BRCA2*-mutated HER2-negative locally advanced or metastatic breast cancer, with a 46% relative risk reduction of disease progression or death (hazard ratio [HR]: 0.54 [95% confidence interval {CI}: 0.41, 0.71]; p<0.0001). The median PFS by BICR assessment was 8.6 months (95% CI: 7.2, 9.3) in the talazoparib arm and 5.6 months (95% CI: 4.2, 6.7) in the chemotherapy arm. These results are shown in the table below.

The effectiveness of the BRACAnalysis CDx® test was based on a subset of 354 (82%) patients with deleterious or suspected deleterious germline *BRCA1/2* mutations for whom prospective and retrospective testing was performed with the BRACAnalysis CDx® test. For the remaining 77 patients (18%) whose samples were not available for testing with the BRACAnalysis CDx® test, *BRCA1* or *BRCA2* status was determined with the Integrated BRAC*Analysis*® test for 54 patients (18%) or by local assessment for 23 patients (5.3%). As shown in the table below, the clinical outcome data for the 354 patients with confirmed deleterious or suspected deleterious *BRCA1/2* mutation by the BRACAnalysis CDx® test was as follows: a 47% reduction in the risk of progression or death, and a median PFS of 8.5 months for talazoparib-treated patients compared with 5.6 months for chemotherapy treated patients. These PFS results are comparable to those observed in the 431 patients in the EMBRACA study, which supports the effectiveness of the device.

PFS by BICR (Intent-to-Treat Population) in the EMBRACA Study		
	Talazoparib	Chemotherapy[a]
Number of patients analyzed, N	N=287	N=144
Events, n (%)	186 (65%)	83 (58%)
Median (95% CI), months	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
Hazard Ratio (95% CI); 2-sided P-value	**0.54 (0.41, 0.71); <0.0001**	
PFS by BICR in BRACAnalysis CDx® Test Population		
Number of patients analyzed, N	N=238	N=116
Events, n (%)	144 (61%)	67 (58%)
Median (95% CI)	8.5 (7.0, 9.3)	5.6 (3.9, 6.7)
Hazard Ratio (95% CI); p-value	**0.53 (0.39, 0.72); <0.0001**	
a - comparator consisting of healthcare provider's choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine).		

8. Summary of Clinical Studies- Treatment Indication for rucaparib
The rucaparib treatment indication is supported by data pooled from Study CO-338-010 (Study 10; NCT01482715) and CO-338-017 (ARIEL2; NCT01891344).

Study 10 is an ongoing 3-part, Phase 1/2 open-label, safety, pharmacokinetic (PK), and preliminary efficacy study of oral rucaparib administered once, twice, or three times a day for continuous 21-day cycles. Only patients from Part 2A were included in this analysis. Part 2A is a Phase 2 portion, which includes patients with platinum-sensitive, relapsed, highgrade serous or endometrioid epithelial ovarian cancer (EOC), fallopian tube cancer (FTC), or primary peritoneal cancer (PPC) associated with a gBRCA mutation (as recorded in the patient's medical record) and who have

progressed after at least 2, but no more than 4, prior regimens.

ARIEL2 is an ongoing two-part open-label, study of rucaparib monotherapy treatment for relapsed, platinum-sensitive, high-grade EOC, FTC, and PPC. Participants were required to have disease that could be biopsied and was measurable. Patients who met the enrollment criteria were enrolled regardless of molecular testing results. However, results from the tissue-based clinical trial assay (CTA) placed patients into molecularly defined groups for the purpose of analysis. One of these group included patients who were identified as tumor BRCA positive [tBRCA, i.e., harboring a deleterious and suspected deleterious germline (gBRCA) and or somatic BRCA mutation (sBRCA)].

The primary efficacy population for drug indication included 106 patients with BRCA positive mutations (BRCA, inclusive of germline and or somatic deleterious mutations) pooled from Study 10 and ARIEL2 who were enrolled at sites in North America (including the United States), Europe and Australia. However, 53 available germline BRCA mutant population was assessed for companion diagnostic indication. The primary outcome measure was ORR. Patient blood samples from a subset (53) of the primary efficacy population were retrospectively evaluated at one laboratory, Myriad (Salt Lake City, UT) using the BRACAnalysis CDx® test. The clinical utility of the BRACAnalysis CDx® test was established by comparing the test results and associated clinical outcomes for the primary efficacy population (inclusive of both germline and somatic deleterious and suspected deleterious BRCA mutations) with the subset of patients with confirmed *g*BRCA status upon retrospective testing with the BRACAnalysis CDx® test. Rubraca® (rucaparib) demonstrated a robust overall response rate with a clinically meaningful duration of response in gBRCA positive patients with ovarian cancer who had received two or more prior lines of chemotherapy.

a. Accountability of PMA Cohort

Out of the 106 patients, specimens from 53 patients were available for retrospective testing with the BRACAnalysis CDx® test in the clinical bridging study.

b. Effectiveness Results

The primary efficacy analysis was based on objective response rate (ORR) and duration of response (DoR) observed in 106 patients with deleterious BRCA mutation -associated ovarian cancer who had received two or more prior lines of chemotherapy and who had measurable disease. In this cohort, the ORR was 54% (95% CI: 44% - 64%) with a median DoR of 9.2 months. The magnitude of response in the population tested with the BRACAnalysis CDx® test was comparable to that in the primary efficacy population, as shown in the table below.

ORR by gBRCA subgroup (Study10/ARIEL2)

ORR Rate	**gBRCA Results (N=53)**	**gBRCA Positive (N=38)**	**gBRCA Negative** (N=15)**	**gBRCA Unknown (N=53)**	**gBRCA Overall* (N=106)**

Confirmed Response Rate (95% CI)	25 / 53 47.2% (33.3 - 61.4)	18 / 38 47.4% (31.0 - 64.2)	7 / 15 46.7% (21.3 - 73.4)	32 / 53 60.4% (46.0 - 73.5)	57 / 106 53.8% (43.8- 63.5)

*70% were gBRCA positive and 30% were sBRCA positive

** gBRCA negative are sBRCA positive

9. Summary of Clinical Studies- Maintenance Indication for rucaparib

The rucaparib maintenance indication is supported by data from Study CO-338-014 (ARIEL3; NCT01968213).

Study CO-338-014 is an ongoing, double-blind, placebo-controlled, randomized study of rucaparib as switch maintenance treatment in patients with relapsed platinum-sensitive, highgrade EOC, FTC, or PPC who achieve a response to platinum-based chemotherapy. The primary efficacy population included 564 patients who were enrolled at sites in North America (including the United States), Europe Australia, and Israel.

The primary endpoint for this study is to evaluate PFS, as assessed by the investigator (invPFS), in molecularly-defined HRD subgroups. Patients were assigned to molecularly-defined HRD subgroups for the final analysis of invPFS. The nested populations are ITT, HRD, and tBRCA.

Patient blood samples from a subset of the primary efficacy population were retrospectively evaluated at one laboratory, Myriad (Salt Lake City, UT) using the BRACAnalysis CDx® test. The clinical utility of the BRACAnalysis CDx® test was established by comparing the test results and associated clinical outcomes tBRCA group (inclusive of both germline and somatic deleterious BRCA mutations) with the subset of patients with confirmed *g*BRCA status upon retrospective testing with the BRACAnalysis CDx® test. Rubraca® (rucaparib) demonstrated a robust overall invPFS in gBRCA positive patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who were in a complete or partial response to platinum-based chemotherapy.

a. Accountability of PMA Cohort

Of the patients randomized, samples from 535/564 patients were available for testing using the BRACAnalysis test. Six patients did not have a sufficient amount of DNA for analysis; therefore, results from BRACAnalysis are available for 529/564 of the randomized patients.

b. Effectiveness Results

The primary efficacy analysis was based on invPFS in 196 patients in the tBRCA population. The primary efficacy endpoint showed a statistical significant benefit with rucaparib in the tBRCA population An analysis of the 146 patients classified as gBRCA positive by the BRACAnalysis CDx® test

showed that the statistically significant benefit of rucaparib in this subgroup, as measured by the hazard ratios, was similar to that in the tBRCA primary efficacy population, as shown in table below.

Analysis Population	**PFS by Investigator Assessment (Primary Endpoint)**	
Group	**Hazard Ratio**	**Median PFS (months) Rucaparib vs. Placebo**
gBRCA positve (n=146)	0.25 (95% CI 0.16-0.39) p<0.001	15.7 vs 5.4
tBRCA (n=196)	0.23 (95% CI: 0.16-0.34) p<0.0001	16.6 vs. 5.4

In addition, invPFS showed a statistically significant benefit with rucaparib in patients classified as gBRCA negative by the BRACAnalysis CDx test compared to placebo (median, 9.1 months versus 5.4 months; HR: 0.393; 95% CI: 0.303 to 0.510) (p<0.0001).