Myriad myChoice® CDx PLUS Technical Specifications

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CE IVD

Intended Use Statement

Myriad myChoice® CDx PLUS is used to detect Homologous Recombination Deficiency (HRD) by assessing the GIS Status and the Tumor Mutation *BRCA1/BRCA2* Status in genomic DNA extracted from tumor specimens. Results are used as an aid to determine the eligibility of patients with ovarian cancer for treatment with certain Poly-ADP Ribose Polymerase (PARP) inhibitors in accordance with the approved therapeutic product labeling.

Additionally, sequencing and large rearrangement analyses are performed on all analyzable regions of the following genes that have been analytically validated using multiple cancer types: *ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D,* and *RAD54L*.

Note: *Analytical concordance studies have been performed with the FDA approved myChoice CDx test.*

Limitations

- For *in vitro* diagnostic use
- For professional use only
- For prescription use only
- The myChoice® CDx PLUS assay identifies germline and somatic variants in the tumor but does not distinguish between the two.
- Reduced hybridization efficiency of DNA fragments spanning long insertions and deletions (indels) or rearrangements may result in under-representation of mutant DNA molecules in the final sequencing library. This will result in a reduction in the observed frequency of sequence reads spanning the mutation.
- Indels > 25 bp in length can be detected by the myChoice® CDx PLUS assay. However, the ability to detect any particular indel may be impacted by the location and nature of the mutation, the local sequence context, the DNA quality, and the non-tumor DNA content in the sample provided.
- The myChoice® CDx PLUS assay has been designed to detect genomic rearrangements including large rearrangements (LRs) involving the promoter and coding exons of *BRCA1* and *BRCA2*, however, the detection of large rearrangement deletions and duplications is dependent on the quality of the submitted specimen.
- Whole gene duplications and deletions may not be detected by the myChoice® CDx PLUS assay.
- Other terminal duplications are reported as variants of uncertain significance.

- This analysis is believed to rule out the majority of abnormalities in the genes analyzed. There may be uncommon genetic abnormalities such as specific insertions, inversions, and certain regulatory mutations that will not be detected by the myChoice® CDx PLUS assay.

Description of Analysis

Myriad myChoice® CDx PLUS uses next generation sequencing to assess tumor genomic instability and detects sequence variants and large rearrangements in 15 genes (*ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*). This analysis is performed on genomic DNA isolated from fixed tumor tissue.

The myChoice® CDx PLUS *in vitro* diagnostic laboratory developed test includes the following components:

Genomic Instability Score (GIS)

A comprehensive signature for Homologous Recombination Deficiency (HRD) is identified by testing genome-wide single nucleotide variants. The GIS is determined by measuring several elements including loss of heterozygosity, (LOH), telomeric allelic imbalance (TAI), and large-scale state transitions (LST).

Sequence Analysis

Gene coding regions and portions of non-coding intronic regions are analyzed by sequence analysis and typically do not extend more than 20 base pairs (bp) proximal to the 5' end and 10 bp distal to the 3' end of each exon.

Large Rearrangement Analysis

Dosage analysis is used to determine copy number abnormalities indicative of deletion or duplication mutations. Coding exons and limited flanking intronic regions are examined for evidence of deletions and duplications (see Limitations section for any exceptions). Large rearrangement (LR) detection utilizes the number of reads that map to each nucleotide, normalized to the run median depth of coverage of the same nucleotide.

Description of Method

Genomic DNA from fixed tumor tissue is extracted using standard extraction reagents and methods to prepare DNA for library amplification. Following amplification, DNA is hybridized to a custom hybridization capture panel which has biotinylated probes for over 26,000 single nucleotide polymorphism sites that are distributed across the human genome. The hybridized DNA mixture is amplified via standard PCR amplification method. The DNA libraries are then run on the next-generation sequencing instrument to generate sequences to be analyzed by Myriad's proprietary algorithm and software.

Sequence reads are mapped to targeted sequences of a pre-specified panel of genes. Allele specific copy number (ASCN) at each SNP location is determined using an algorithm to identify sequencing and LR variants. Each variant is compared to a list of previously classified variants stored in the Myriad Variant Classification database, and the classification in the database is applied accordingly. Variants are classified in accordance with the recommendations of the American College of Medical

Genetics and Genomics (ACMG) for standards in the interpretation and reporting of sequence variations. Clinically significant variants will be identified as "deleterious" or "suspected deleterious".

Additionally, the patient's Genomic Instability Score (GIS) is assessed. The GIS is calculated based upon an aggregate analysis of Loss of Heterozygosity, (LOH), Telomeric Allelic Imbalance (TAI), and Large-scale State Transitions (LST). A GIS is considered to be positive if the score is at or above the current pre-specified threshold.

A positive Myriad HRD Status result can be due to either a positive Tumor Mutation *BRCA1/BRCA2* Status or a positive GIS Status. The HRD Status is used to aid in identifying patients who may be eligible for treatment with PARP inhibitors, in accordance with the approved therapeutic product labeling.

This test has also been validated to detect sequencing variants and large rearrangements within 13 additional genes: *ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D,* and *RAD54L*. Results of the analysis of the 13 additional genes may be used to provide additional information to the physician.

Performance Characteristics

Analytical Specificity: The incidence of a false report of a genetic variant or mutation resulting from technical error or errors in specimen handling and tracking is estimated from validation studies to be less than one percent (<1%).

The validation studies demonstrated a Negative Percent Agreement (NPA) of all valid sequence non-variant base calls to be 953,408/953,409 (99.9999%).

Analytical Sensitivity: Failure to detect a genetic variant or mutation in the analyzed DNA regions may result from errors in specimen handling and tracking, hybridization, amplification and sequencing reactions, or computer-assisted analysis and data review. The rate of such errors is estimated from validation studies to be less than one percent (<1%).

The analytical sensitivity of next-generation sequencing for *BRCA1* and *BRCA2* was demonstrated to be 100%, based on complete concordance of results between the test and comparator assays, using 56 individual anonymized breast, ovarian, and prostate fixed tumor samples.

The comparator assay, which was performed by a second Myriad Genetic laboratory, detected 421 sequence variants observed at ≥ 10% allele frequencies. All 421 sequence variants were also detected by the myChoice® CDx PLUS assay, corresponding to a positive percent agreement (PPA) of 100%. The PPA of all valid variant calls (at allele frequencies ≥ 2%) was 425/426 (99.8%).

For the *BRCA1* and *BRCA2* large rearrangement (LR) portion of the assays, 108/108 concordant valid gene LR calls were obtained corresponding to an overall LR agreement of 100%.

Comparisons were also made between the GISs generated by both assays for each of the 56 samples. The Total Analytical Error calculated for all valid GISs generated by both assays was 3.83.

The lower Limit of Detection (LoD) for sequence variants was determined by using a total of three cell lines with multiple known sequence variants selected as "tumor" samples and one cell line with as few sequence variants as possible selected as the "normal" sample. The designated "tumor" DNA was mixed with various amount of "normal" DNA to create three sets of simulated "tumor":"normal" DNA mixtures with six levels of "tumor"-to-"normal" mix ratios. The resulting DNA mixtures were tested

in multiple replicates. The results from this study revealed that the LoD for the sequencing portion of the myChoice® CDx PLUS assay is at 10% variant allele frequency.

For large rearrangement analysis, two cell lines with large rearrangements (one single exon deletion and one multi-exon deletion) were selected as "tumor" samples and one cell line that did not carry any large rearrangements was selected as the "normal" sample. The designated "tumor" DNA was mixed with various amount of "normal" DNA to create two sets of simulated "tumor":"normal" DNA mixtures with 6 levels of "tumor"-to-"normal" dosage ratios. The resulting DNA mixtures were tested in triplicate. The results from this study demonstrate that the LoD of the LR portion of the myChoice® CDx PLUS assay is at 20% allele frequency for both the single exon deletion and multi-exon deletion.

For the GIS portion of the myChoice® CDx PLUS assay, three pairs of matched "tumor" and "normal" cell lines were evaluated in this study. Each cell line sample pair consisted of DNA from a breast cancer cell line and DNA from the corresponding, matched normal cell line that was established from the same affected individual. The resulting paired "tumor" and "normal" DNAs were mixed at eight different levels of "tumor" to "normal" dosage ratios ranging from 100% "tumor" to 100% "normal" (0% "tumor") to create three sets of simulated "tumor":"normal" DNA mixtures. These DNA mixtures were subsequently tested in multiple replicates. The Limit of Quantitation of the GIS portion of the assay was determined to be 30% tumor DNA content.

Test Reproducibility: Analytical validation studies included a reproducibility study for NGS. In a separate study, seven fixed tumor samples (comprised of ovarian, breast and prostate samples) were analyzed by the myChoice® CDx PLUS assay. Each sample was run in duplicate on four independent runs performed over different days, using two sets of different instruments, reagents lots, and operators. This study demonstrated 1,157/1,160 (99.74%) concordance for all valid sequence variant calls at allele frequencies ≥ 2%, 3,256,283/3,256,291 (99.9998%) concordance for all valid sequence non-variant base calls, and 834/834 (100%) concordance for all valid large rearrangement calls across all samples and replicates evaluated.

GISs were also assessed across the same samples and demonstrated an overall standard deviation of 2.20 for valid scores across all replicates evaluated.

Interpretive Criteria:

Myriad's myChoice® CDx PLUS assay is used to detect Homologous Recombination Deficiency (HRD). A positive Myriad HRD Status result can be due to either a positive Tumor Mutation *BRCA1/BRCA2* Status or a positive GIS Status. The HRD Status is used to aid in identifying patients who may be eligible for treatment with certain Poly-ADP Ribose Polymerase (PARP) inhibitors in accordance with the approved therapeutic product labeling.

This test has also been validated to detect sequencing variants and large rearrangements within 13 additional genes: *ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L*. Results of the analysis of the 13 additional genes may be used to provide additional information to the physician.

"GIS Status: Positive"

The test results demonstrate homologous recombination deficiency based on the Genomic Instability Score.

"GIS Status: Negative"

The test results demonstrate homologous recombination proficiency based on the Genomic Instability Score.

"Tumor Mutation BRCA1/BRCA2 Status: Positive for a Clinically Significant Mutation"

The test results demonstrate the presence of a deleterious or suspected deleterious sequencing mutation or large rearrangement in *BRCA1* and/or *BRCA2*.

"Tumor Mutation BRCA1/BRCA2 Status: Negative for a Clinically Significant Mutation"

The test results do not demonstrate the presence of a deleterious or suspected deleterious sequencing mutation or large rearrangement in *BRCA1* or *BRCA2*. This category includes genetic variants for which published data demonstrate absence of substantial clinical significance and truncating mutations in *BRCA2* that occur at and distal to amino acid 3.326 (Mazoyer S et al., *Nature Genetics* 1996, 14:253-254). It also includes variants in the protein-coding region that neither alter the amino acid sequence nor are predicted to significantly affect exon splicing, and base pair alterations in non-coding portions of the gene that have been demonstrated to have no pathogenic effect on the length or stability of the mRNA transcript. There may be uncommon genetic abnormalities that will not be detected by the myChoice® CDx PLUS assay (see **Limitations**).

Variant Interpretations

"Deleterious": Includes most nonsense and frameshift mutations that occur at/or before the last known deleterious amino acid position of the affected gene. In addition, specific missense mutations and non-coding intervening sequence (IVS) mutations are recognized as deleterious on the basis of data derived from linkage analysis of high-risk families, functional assays, biochemical evidence, statistical evidence, and/or demonstration of abnormal mRNA transcript processing. Deletions and duplications of an entire exon(s) identified by the myChoice® CDx PLUS test may also be interpreted to be deleterious. Deleterious large genomic rearrangements include single exon and multi-exonic deletions that are out-of-frame. Out-of-frame single or multi-exonic duplications are classified as deleterious if the orientation is determined to be in tandem and head-to-tail. In-frame deletions/duplications are interpreted on an individual basis and the specific evidence supporting the classification of these mutations is included in the individual patient report.

"Suspected Deleterious": Includes genetic variants for which the available evidence indicates a high likelihood, but not definitive proof, that the mutation is deleterious. The specific evidence supporting an interpretation will be summarized for individual variants in the patient report.

"***Complex Large Rearrangement***": a large rearrangement involving one or more exons where there is insufficient data to definitively determine its precise structure but has a significant potential to result in abnormal protein production and/or function.

"Special Interpretation": describes variants that would be typically interpreted as pathogenic according to the recommendations of the American College of Medical Genetics and Genomics (Richards S et al., Genet Med, 17(5):405-24); however, Myriad internal data suggest that these particular variants may not fully impair gene function in comparison to other pathogenic variants. Therefore, the effect of this variant on homologous recombination is currently unknown. These variants are reported under the category of "Additional Non-Clinically Significant Findings".

"***Uncharacterized Large Rearrangement***": a large rearrangement involving one or more exons where there is insufficient data to definitively determine its structure, breakpoints and location within the

genome. It is not known if transcription and/or translation are affected by this large rearrangement. This finding should not be used for clinical management of this patient. These large rearrangements are reported under the category of "Additional Non-Clinically Significant Findings".

"Genetic variant of Uncertain Significance": Includes missense variants and variants that occur in analyzed intronic regions whose functional significance has not yet been determined, as well as nonsense and frameshift mutations that occur distal to the last known deleterious amino acid positions of the affected genes. These variants are reported under the category of "Additional Non-Clinically Significant Findings".

"Favor Polymorphism" and "Polymorphism": Includes genetic variants for which available evidence indicates that the variant is highly unlikely to alter protein production and/or function. Variants of this type are not reported.

Change of Interpretation and Issuance of Amended Reports

The classification and interpretation of all variants identified in the assay reflect the current state of scientific understanding at the time the report is issued. In some instances, the classification and interpretation of such variants may change as new scientific information becomes available. Whenever there is a change in the classification of a variant that affects the overall interpretation of a patient's test result, an amended report will be provided by Myriad Genetic Laboratories.

Clinical Significance

The clinical utility of the Myriad myChoice® CDx PLUS for use as a companion diagnostic has been evaluated in multiple clinical studies.

Summary of Clinical Study - Olaparib D0817C00003 (PAOLA-1)

Overview

A phase III, randomized, double-blind, placebo-controlled, multicenter study was conducted in 806 patients (537 patients in the olaparib/bevacizumab group, 269 patients with placebo/bevacizumab) with newly diagnosed, advanced (FIGO stage IIIB-IV), high grade epithelial ovarian, fallopian tube or primary peritoneal cancer treated with standard first-line treatment, combining platinum-taxane chemotherapy and bevacizumab concurrent with chemotherapy and in maintenance to evaluate the efficacy and safety of olaparib (tablet) 300 mg given twice daily in combination with bevacizumab) in comparison with placebo in combination with bevacizumab.

Additionally, progression free survival (PFS) was investigated in exploratory biomarkers subgroups using the Myriad myChoice® HRD Plus test, a research use assay, to further understand the consistency of treatment effect of olaparib across potential predictive and prognostic factors.

Myriad HRD status is based on the Genomic Instability Score (GIS) and/or Tumor Mutation *BRCA1/BRCA2* Status (*tBRCAm)*. A positive Myriad HRD status is determined either by presence of a *tBRCA1/2* mutation or by a GIS at or above cut-off of 42 in the absence of a *tBRCA1/2* mutation.

Of the 806 randomized patients in PAOLA-1, 755 (93.7%) had a Myriad *tBRCA1/2* mutation status available and 664 (82.4%) had an available Myriad HRD status with the myChoice® HRD Plus test. With the myChoice® CDx test, a total of 755/806 (93.7%) patients were considered for testing. A total

of 700/806 (86.8%) patients had a valid *tBRCA1/2* mutation status result and 643/806 (79.8%) had a valid HRD status result.

Concordance between the Myriad myChoice® HRD plus RUO test and the Myriad myChoice® CDx in PAOLA-1

The concordance between the myChoice® HRD Plus test and the myChoice® CDx test for HRD status at a cut-off 42 for patients with a valid result for both tests, was as follows:

- OPA: 97.8% (95% CI 96.3%, 98.8%)
- PPA: 98.6% (95% CI 96.8%, 99.6%)
- NPA: 96.6% (95% CI 93.7%, 98.4%)

Comparison of efficacy between PAOLA-1 full analysis set and the subgroups determined by Myriad myChoice® CDx

PAOLA-1 met its primary objective, demonstrating a statistically significant and clinically meaningful improvement in PFS in the Full Analysis Set (FAS) for olaparib vs placebo when added to bevacizumab (HR 0.59; 95% CI 0.49 to 0.72; p<0.0001). Olaparib prolonged PFS by a median of 5.5 months over placebo. The clinical outcome data for the FAS and the efficacy data from post-database lock exploratory analyses performed in the subset of patients for whom Myriad HRD status for cut-off ≥42 defined by the Myriad myChoice® CDx test are shown in the following table.

Clinical outcome (PFS by investigator assessment) of PAOLA-1

FAS		**myChoice® CDx Myriad HRD status positive**		**myChoice® CDx Myriad HRD status negative**		**myChoice® CDx Myriad HRD status unknown**	
Olaparib/ bevacizumab (n=537)	**Placebo/ bevacizumab (n=269)**	**Olaparib/ bevacizumab (n=251)**	**Placebo/ bevacizumab (n=125)**	**Olaparib/ bevacizumab (n=180)**	**Placebo/ bevacizumab (n=87)**	**Olaparib/ bevacizumab (n=106)**	**Placebo/ bevacizumab (n=57)**
Number of events/total number of patients (%)							
280/537 (52.1)	194/269 (72.1)	87/251 (34.7)	86/125 (68.8)	135/180 (75.0)	68/87 (78.2)	58/106 (54.7)	40/57 (70.2)
Median PFS (months)							
22.1	16.6	39.3	17.7	16.6	16.2	22.1	15.3
HR (95% CI)							
0.59 (0.49, 0.72)		0.35 (0.26-0.48)		1.00 (0.75-1.34)		0.68 (0.45-1.02)	

Summary of Clinical Study – Olaparib D0818C00001 (SOLO1)

The olaparib clinical study D0818C00001 (SOLO1) was a Phase III, randomized, double blind, placebo controlled, multicenter study to assess the efficacy of olaparib maintenance monotherapy in advanced ovarian cancer patients (including patients with primary peritoneal and/or fallopian tube cancer) who had responded following first-line platinum based chemotherapy and carrying *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). A total of 391 patients were enrolled 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, or from prospective testing performed by Myriad (Salt Lake City, UT) using the Myriad Integrated BRAC*Analysis*® or for Chinese patients by BGI Clinical Laboratories (Shenzhen, China) using a local validated test.

A post-randomisation analysis of a subset of the SOLO1 tumor samples was performed to identify the population that would be defined as tumor *BRCA1/2 (tBRCA1/2)* by the Myriad myChoice® CDx test. The clinical performance of the myChoice® CDx test for the SOLO1 study was based on the Tumor Mutation *BRCA1*/*BRCA2* (t*BRCAm*) Status and was established based on available residual extracted DNA generated from tumor FFPE samples collected from patients enrolled on the SOLO1 study.

Accountability of PMA Cohort

Out of the 391 patients randomized in the SOLO1 study, extracted FFPE DNA samples from 333 patients were available for retrospective myChoice® CDx testing. Samples from 298 patients were tested using myChoice® CDx test, and valid *tBRCA1/2* mutation status results were reported for 292 patients. Among those, 284 patients were confirmed to carry a deleterious or suspected deleterious *tBRCA1/2* mutation and 8 patients were not confirmed to carry a deleterious or suspected deleterious *tBRCA1/2* mutation by the myChoice® CDx test. The PMA cohort represented 74.7% (292/391) of the full analysis set in SOLO1.

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 Tumors (RECIST (version 1.1)) of olaparib maintenance monotherapy compared with placebo in *BRCA* mutated high risk advanced ovarian cancer patients who are in clinical complete response (CR) or partial response (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 BRAC*Analysis*® test, BRACAnalysis CDx® test, BGI test or local test results. A statistically significant and clinically relevant improvement in investigator-assessed PFS, 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 (HR 0.30; 95% CI 0.23-0.41; p<0.0001), with a median PFS not reached in the olaparib arm vs 13.8 months for placebo. Median follow-up for PFS defined as time from randomisation to date of censoring was approximately 41 months on both arms.

The effectiveness of the *tBRCA1/2* mutation status of the Myriad myChoice® CDx test was based on a subset of 284 confirmed ovarian cancer patients with deleterious or suspected deleterious *tBRCA1/2* mutations.

The clinical outcome data for the 284 patients with a confirmed *tBRCA1*/2 mutation was as follows: a 71% reduction in the risk of disease progression or death at any point in time for olaparib vs placebo treated patients (HR 0.29; 95% CI 0.21-0.41; p<0.0001), with a median PFS not reached in the olaparib arm vs 13.8 months for placebo. Median follow-up for PFS defined as time from randomisation to date of censoring was approximately 41 months on both arms. Taken together, these results are very similar to those observed in the 391 patients in the SOLO1 study, which supports the effectiveness of the test.

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

	SOLO1		**Myriad myChoice® CDx**	
	Olaparib 300 mg bd[a]	**placebo**	**Olaparib 300 mg bd[a]**	**placebo**
PFS				
Number of events: total number of patients (%)	102/206 (39)	96/131 (73)	75/191 (39.3)	69/93 (74.2)
Median PFS (months)	not reached	13.8	not reached	13.8

	SOLO1		Myriad myChoice® CDx	
	Olaparib 300 mg bd[a]	**placebo**	**Olaparib 300 mg bd[a]**	**placebo**
HR (95% CI)	0.30 (0.23-0.41)		0.29 (0.21-0.41)	
P-value (2-sided)	<0.0001		<0.0001	

a- tablet formulation

Summary of Clinical Study - Niraparib PR-30-5020-C (QUADRA)

The niraparib clinical study PR-30-5020-C (QUADRA) was a multicenter, open-label, single-arm clinical trial designed to evaluate the safety and efficacy of niraparib in patients with advanced, relapsed, high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who had received three or more previous chemotherapy regimens.

Accountability of Premarket Approval (PMA)

To determine patient eligibility, a tumor sample was sent to a centralized laboratory for immediate testing by Myriad. Archival or fresh tumor tissue was required. (*Note: for patients enrolled after implementation of protocol version 3 [amendment 2; 24 May 2016], the sample was required prior to enrollment and could be sent in advance of the protocol-defined screening period in order to facilitate the screening and enrollment process*). Patients were to wait for the results from the on-study centralized HRD testing prior to enrollment unless they had a previously detected germline breast cancer gene (*BRCA*) mutation (g*BRCA*m). Blood samples were also collected for all patients during screening for determination of g*BRCA*m status. If g*BRCA* status was previously confirmed positive, then it was not necessary to wait for HRD testing results for enrollment into the study; however, confirmatory HRD testing still needed to be performed.

Effectiveness Results

The primary efficacy endpoint was investigator-assessed confirmed objective response rate (ORR) as defined by RECIST (version 1.1). The primary analysis population for this endpoint included all patients with HRD positive tumors who received 3 or 4 prior lines of therapy (LOT) and whose disease was platinum-sensitive to the last platinum-based therapy. Patients with prior poly (ADP-ribose) polymerase (PARP) inhibitor (PARPi) treatment were not included in the primary analysis population. The patient's best overall response (BOR) was determined based on the overall responses at all timepoints between the date of the first dose and the date of first documented radiological disease progression, the date of subsequent anticancer therapy, or the date of study discontinuation, whichever occurred first. Patients with a BOR of either confirmed CR or confirmed PR were considered to have responded to treatment ("responders"). All other patients were considered not to have responded to treatment ("non-responders").

Post hoc analyses were also conducted in subgroups defined by platinum sensitivity and biomarkers.

Investigator-assessed confirmed ORR as defined by RECIST (version 1.1) was analyzed for the biomarker-defined population overall and in the following biomarker subsets:

- t*BRCAm* (regardless of platinum sensitivity)
- Non-t*BRCAm*/GIS positive, platinum-sensitive

In the biomarker-defined population, meaningful ORR and duration of response (DOR) were observed among all subgroups, including the following:

- In the HRD positive cohort (n=98), the ORR was 24.4% and the median DOR was 8.3 months.
- In patients with t*BRCAm* tumors (n=63), the ORR was 28.6% and median DOR was 9.2 months. When this group was analyzed by platinum sensitivity status, patients with t*BRCAm* platinum-sensitive disease (n=18) had an ORR of 38.9%; patients with t*BRCAm* platinum-resistant disease (n=21) had an ORR of 28.5%; and patients with t*BRCAm* platinum-refractory disease (n=16) had an ORR of 18.8%.
- In patients with non-t*BRCAm*/GIS positive, platinum-sensitive disease (n=35); the ORR was 20.0% and median DOR was 6.6 months.

Conclusions

In summary, the efficacy results from the PR-30-5020-C (QUADRA) clinical study demonstrated that the magnitude of clinical benefit expected from niraparib treatment can be predicted by the clinical benefit continuum defined by clinical and molecular biomarkers. In line with the continuum of benefit based on molecular and clinical biomarkers, the highest response rates were observed among patients with tumors that were GIS positive and platinum-sensitive or t*BRCA*m regardless of platinum sensitivity status.

Summary of Clinical Study - Niraparib PR-30-5017-C (PRIMA) for maintenance treatment.

The niraparib clinical study PR-30-5017-C (PRIMA) was a randomized, double-blind, placebo-controlled, multicenter Phase 3 study design in subjects with ovarian, fallopian tube, and primary peritoneal cancer, collectively referred to as ovarian cancer. The objective of PRIMA was to evaluate the therapeutic effect of maintenance niraparib treatment following response to first-line platinum-based chemotherapy in patients with advanced ovarian cancer.

Accountability of PMA Cohort

A total of 733 patients were screened into the PRIMA study for homologous recombination deficiency (HRD) testing. Test results were required prior to randomization. Subjects with a documented deleterious germline (gBRCA) or somatic (sBRCA) BRCA mutation by local results were considered to have homologous recombination deficient tumors for stratification and randomization purposes; the tumor test was performed concurrently to confirm local results. Of these 733 randomized patients, 487 niraparib-treated and 246 placebo-treated patients were included in the PMA cohort. The retrospective analysis included the testing of 713 ovarian FFPE tumor specimens (7 samples were retests from existing patients and 4 samples from 4 patients who were identified as screen failures after re-matching ID with clinical database) from PRIMA, where biomarker calls from the CTA were compared with those from the CDx. Therefore, the final PMA cohort by CTA/CDx includes a total of 733 patients: 373 HRD positive patients, 249 HRD negative patients, 80 patients who had inconclusive results from HRD testing, and 31 patients without sufficient sample for HRD testing.

Effectiveness Results

The primary endpoint was PFS, defined as the time from treatment randomization to the

earlier date of assessment of progression (by BICR) or death by any cause in the absence of progression. PFS was based on radiology assessment using RECIST v1.1 criteria. Efficacy analyses were primarily conducted on the intent to treat (ITT) population, in the overall and homologous recombination deficient populations.

Conclusions

The main efficacy conclusions for the prespecified primary analysis population were as follows:

- The study met its primary efficacy objective; treatment with niraparib prolonged median PFS by 11.5 months compared to placebo in subjects with homologous recombination deficient advanced ovarian cancer following response to front-line platinum-based chemotherapy. Median PFS as determined by BICR based on RECIST (version 1.1) was 21.9 months in the niraparib arm and 10.4 months in the placebo arm (HR 0.43 [95% CI: 0.310,0.588]; p<0.0001).
- In the overall population, treatment with niraparib prolonged median PFS by 5.6 months compared to placebo. Median PFS as determined by BICR based on RECIST (version 1.1) was 13.8 months in the niraparib arm and 8.2 months in the placebo arm (HR 0.62 [95% CI: 0.502, 0.755]; p<0.0001).

Table 3 Efficacy Results[a] in PRIMA (Biomarker-Defined Population)

	HRD Positive Population		**Overall Population[b]**	
	ZEJULA (N=247)	Placebo (N=126)	ZEJULA (N=487)	Placebo (N=246)
PFS events, n (%)	81 (33)	73 (58)	232 (48)	155 (63)
PFS Median (95% CI), in months	21.9 (19.3, NE)	10.4 (8.1, 12.1)	13.8 (11.5, 14.9)	8.2 (7.3, 8.5)
Hazard Ratio (HR)[c] (95% CI)	0.43 (0.31, 0.59)		0.62 (0.50, 0.76)	
p-value[d]	<0.0001		<0.0001	

[a] efficacy analysis was based on blinded independent central review (BICR).
[b] In the HR proficient (HRD negative) population (N=249), a hazard ratio of 0.68 (95% CI [0.49, 0.94]) was observed.
In the HR not determined (HRnd) population (N=111), a hazard ratio of 0.85 (95% CI [0.51,1.43]) was observed.
[c] based on a stratified Cox proportional hazards model
[d] based on a stratified log-rank test
NE=Not Evaluable

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The Myriad myChoice® CDx PLUS test was developed and performance characteristics were determined by Myriad Genetic Laboratories, Inc. and in compliance to In-Vitro Diagnostic Device Directive (98/79/EC) and is CE marked. Myriad is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform high complexity clinical laboratory testing. Myriad is compliant with multiple international standards including, ISO 13485:2016 and ISO 15189: 2012 as applicable.