INTRODUCTION

BRACAnalysis CDx® is the FDA approved companion diagnostic test for AstraZeneca’s drug Lynparza™ (olaparib), a poly ADP-ribose polymerase (PARP) inhibitor. BRACAnalysis CDx is intended to detect germline BRCA1 and BRCA2 variants and provide a clinical interpretation of the identified variants. Results of the test identify deleterious or suspected deleterious germline BRCA variants in patients with ovarian cancer and/or HER2-negative metastatic breast cancer. These patients are therefore eligible or may become eligible for treatment with Lynparza.¹ The Food and Drug Administration (FDA) announced approval of BRACAnalysis CDx for patients with ovarian cancer on December 19, 2014.² On January 12, 2018 the FDA approved BRACAnalysis CDx for patients with HER2-negative metastatic breast cancer.³

IMPACT OF PARP INHIBITORS BASED ON BRCA STATUS

Early studies with PARP inhibitors (PARPi) demonstrate that cells possessing at least one normal BRCA1 and BRCA2 allele are relatively resistant to PARP inhibition, while cells with BRCA1 or BRCA2 dysfunction lacking wild-type BRCA1 or BRCA2 (homologous recombination deficient mutant cells) are profoundly sensitized to PARP inhibition leading to chromosomal instability, cell cycle arrest and apoptosis.⁴,⁵ Based on these findings, many clinical trials with PARPi, including Lynparza trials, have looked at BRCA mutation status as part of outcome subgroup analysis and/or inclusion criteria.⁶,⁷

BRACAnalysis CDx is the first FDA approved laboratory developed companion diagnostic test. It is indicated 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 Ethylenediaminetetraacetic acid (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 breast and ovarian cancer patients with deleterious or suspected deleterious germline BRCA variants, who are or may become eligible for treatment with Lynparza. Detection of deleterious or suspected deleterious germline BRCA variants by the BRACAnalysis CDx test in ovarian cancer patients is also associated with enhanced progression free survival (PFS) from Zejula® (niraparib) maintenance therapy.⁸

STUDIES & INDICATIONS

Women with HER2-negative metastatic breast cancer at any age who have a deleterious variant identified by BRACAnalysis CDx are now candidates for treatment with Lynparza. This represents a new treatment option for this patient population and is based on the findings of the OlympiAD trial, designed to compare the efficacy and safety of olaparib with the efficacy and safety of standard therapy with single agent chemotherapy of the physicians choice among patients with HER2-negative metastatic breast cancer and a germline BRCA mutation.¹ The multi-center, international randomized phase 3 trial had PFS as the primary endpoint, which was assessed by blinded independent central review and analyzed on an intention to treat basis. PFS was significantly longer in the olaparib group than in the standard therapy group, 7.0 months vs 4.2 months (hazard ratio for disease progression or death, 0.58; 95% CI 0.43 to 0.80; P<0.0001). To learn about the adverse events associated with the OlympiAD trial, please visit myriad.com/managed-care/bracanalysis-cdx/.
The NCCN (National Comprehensive Cancer Network) updated their breast cancer treatment guidelines to include all patients with HER2-negative metastatic breast cancer as appropriate candidates for germline BRCA testing in order to evaluate for Lynparza treatment eligibility.

In addition to this new indication, BRACAnalysis CDx continues to be the companion diagnostic to Lynparza for treatment of patients with ovarian cancer. In the primary clinical study, Lynparza demonstrated an objective response rate (ORR) of 34% (95% CI: 28-54%), and a median duration of response (DoR) of 7.9 months in ovarian cancer patients previously treated with at least three lines of prior chemotherapy and who had deleterious or suspected deleterious germline BRCA mutations. The results are summarized in the table below.

<table>
<thead>
<tr>
<th>Subset</th>
<th>Total Subjects n</th>
<th>Subjects with Response n (%)</th>
<th>ORR</th>
<th>95% CI</th>
<th>Median DoR (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>137</td>
<td>46 (33.6)</td>
<td>0.34</td>
<td>(0.26, 0.42)</td>
<td>7.9</td>
<td>(5.6, 9.6)</td>
</tr>
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</table>

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The performance characteristics as well as clinical study endpoints support the clinical utility of BRACAnalysis CDx as a companion diagnostic to Lynparza.

There are additional indications in which knowing a germline BRCA status demonstrates increased PFS. Patients with ovarian cancer may benefit from Lynparza or Zejula for second line maintenance therapy. The table below demonstrates the difference in PFS for those patients who use PARPi who have or do not have a BRCA mutation.⁸

<table>
<thead>
<tr>
<th>NOVA Cohort</th>
<th>BRACAnalysis CDx Result</th>
<th>Prolonged PFS Benefit (Niraparib vs. Placebo)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-Value</th>
</tr>
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<tbody>
<tr>
<td>Germline BRCA Positive</td>
<td>BRACAnalysis CDx positive (n=203)</td>
<td>15.5 months (21.0 vs. 5.5 months)</td>
<td>0.27 (0.17-0.41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Germline BRCA Negative</td>
<td>Overall germline BRCA negative cohort (n=350)</td>
<td>5.4 months (9.3 vs. 3.9 months)</td>
<td>0.45 (0.34-0.61)</td>
<td>&lt;0.001</td>
</tr>
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THE FDA APPROVAL PROCESS

When the FDA approved BRACAnalysis CDx as a companion diagnostic for Lynparza, it did so based on evaluation of Myriad’s established laboratory processes, validation and verification studies, and variant classification program. As part of the FDA pre-market approval process for BRACAnalysis CDx, the following validation and verification studies were performed and submitted to the FDA by Myriad Genetic Laboratories: 17 non-clinical studies for analytical verifications, six comparator studies, variant classification validation, clinical bridging study, two extraction studies, process validation study, equipment qualifications, software validation, facilities validation, and clinical validation studies.¹¹

Myriad’s myVision™ variant classification program is committed to accurately identify and interpret variants to promote responsible healthcare spending and medical management. A dedicated staff of genetic experts analyzes and reclassifies genetic variants to confidently catalogue variants as deleterious disease-causing mutations or benign. To strengthen the accuracy of Myriad’s variant classification, Myriad developed proprietary tools that augment accuracy and speed to classify variants. These tools are validated in peer reviewed publications that demonstrate a greater than 99% confidence in the statistical methods that are utilized to classify variants.¹²,¹³ This provides your appropriate members with the lowest variant of uncertain significance rate available (more actionable answers for your members). As a part of the myVision program, Myriad has a lifetime commitment to inform providers and patients of reclassifications. This new information is essential to patients’ medical management and their overall care. Myriad is committed to provide the right information to the right patient at the right time — all with the intention to mitigate overall healthcare spend while improving personalized medical outcomes.
BRACAnalysis CDx is the first and only germline BRCA gene test that has been critically evaluated and approved by the FDA as a companion diagnostic to Lynparza for the treatment of HER2-negative metastatic breast cancer and for maintenance therapy of recurrent platinum-resistant ovarian cancer. BRACAnalysis CDx is appropriate for any woman diagnosed with HER2-negative metastatic breast cancer at any age and will determine eligibility for treatment with the PARPi, Lynparza. HER2-negative metastatic breast cancer as an indication for BRCA testing differs from most medical policy criteria for BRCA testing which are focused on the evaluation of hereditary breast and ovarian cancer syndrome (HBOC) and typically requires either a young age of onset or additional personal/family history of HBOC-related cancers.

If we can help provide information to aid in the development of a medical policy for BRACAnalysis CDx for your members eligible for PARPi, contact Myriad and ask for the Hereditary Cancer Manager in Managed Markets at 1-800-4-MYRIAD.

REFERENCES

10. FDA Labeling http://www.accessdata.fda.gov/cdrh_docs/pdf14/P140020c.pdf