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NCCN guidelines panel: Ovarian Cancer

On behalf of Myriad Genetics, I respectfully request that the NCCN Ovarian Cancer Guideline Panel review the enclosed request for changes to the current guideline.

Specific changes requested:

1. In the decision tree on page OV-5, for women who have received bevacizumab as part of their primary therapy, we recommend that an indication be added that shows the utilization of bevacizumab + olaparib is now based on a *BRCA1/2* mutation and/or genomic instability. A new footnote can also be added to state genomic instability as defined by Myriad myChoice® CDx.
2. OV-C pages 7 and 8, please change footnote O to include the underlined: "For patients treated with three or more prior chemotherapy regimens and whose cancer is associated with HRD defined by either: 1) deleterious or suspected deleterious BRCA mutation; or 2) genomic instability as defined by Myriad myChoice® CDx and progression >6 months after response to the last platinum-based chemotherapy."
3. Define HRD consistently throughout the guidelines (pages OV-1,2,3,5) using language in #2 above.

FDA Clearance: Myriad myChoice® CDx is the only HRD assay with a companion diagnostic FDA indication for any PARP inhibitor[1].

Rationale:

Regarding #1 above, the request is to align with the recent FDA biomarker decision on May 8th, 2020. Myriad myChoice® CDx was the only biomarker used in the PAOLA-1 trial[2]. In addition, it is the only biomarker named in the ASCO Guideline for PARP Inhibitors in the Management of Ovarian Cancer for this indication[3]. Regarding #2 and #3 above, the request is to create a consistent definition of HRD throughout the guidelines based on the FDA biomarker approval. This will be consistent for treatment regimens based on the QUADRA[4], PRIMA[5], and PAOLA-1[2] trials, in which Myriad myChoice® CDx was the only biomarker utilized.

There are several ways to test for HRD, however not all testing is interchangeable. Posters presented at the 2020 SGO[6] and ASCO Annual Meetings[7] made *in silico* comparisons between the Myriad myChoice® CDx genomic instability score to Foundation Medicine's percent loss of heterozygosity (%LOH) assay. Results showed significant discordance between the two assays, and %LOH alone would miss 34% of women with *BRCA1/2* wild type status that have genomic instability who would qualify for, or preferentially benefit from, PARP inhibitor therapy.

We acknowledge there are currently no companion diagnostic commercial brand names in the ovarian treatment guidelines. Brand names are used in many other NCCN guidelines, for instance, the Breast Cancer[8] (i.e., Oncotype Dx, EndoPredict, etc.) and Prostate Cancer guidelines[9] (i.e., Prolaris). Since the FDA approval of Myriad myChoice® CDx in 2019, the number of laboratories providing LOH testing as a claim to comprehensive HRD has more than doubled. To thoroughly evaluate HRD, Myriad myChoice® CDx goes beyond LOH by also evaluating large-scale state transitions and telomeric allelic imbalance, for which no other laboratories have a comparable test. The assay distinction, robust clinical trial data, and FDA approvals lead to Myriad myChoice® CDx being uniquely named in the recent ASCO guidelines as the test to determine tumor genomic instability[3]. It is similarly crucial for the NCCN to not only provide situationally appropriate therapeutic treatment guidance for PARP inhibitors, but also situationally appropriate companion diagnostic guidance for determination of HRD.

References:

The following data are submitted in support of this proposed change. We would like to acknowledge the contributions of NCCN panel members who are also co-authors and co-contributors of some of these publications.

1. https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools [pleasesee Myriad myChoice CDx approvals]
2. Ray-Coquard I, Pautier P, Pignata S, et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. *N Engl J Med* 2019; 381:2416-2428. PMID: 31851799.
3. Tew WP, Lacchetti C, Ellis A, et al. PARP Inhibitors in the Management of Ovarian Cancer: ASCO Guideline. *Journal of Clinical Oncology*. doi: 10.1200/JCO.20.01924
4. Moore KN, Secord AA, Geller MA, et al. Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol*. 2019;20(5):636-648. doi: 10.1016/S1470-2045(19)30029-4.
5. Gonzalez-Martin A, Pothuri B, Vergote I, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. [published online September 28, 2019]. *N Engl J Med*. doi: 10.1056/NEJMoa1910962
6. Mills G, et al. Comparison of Genomic Instability Scores for Predicting PARP Activity in Ovarian Cancer. SGO 2020 Annual Meeting on Women's Cancer (*Manuscript in preparation*).
7. Mills G, et al. Comparison of Genomic Instability Scores for Predicting PARP Activity in Ovarian Cancer. ASCO Annual Meeting 2020 (*Manuscript in preparation)*.
8. Gradishar W et al. NCCN Clinical Practice Guidelines in Oncology®: Breast Cancer. V 5.2020. July 15. Available at http://www.nccn.org.
9. Schaeffer E et al. NCCN Clinical Practice Guidelines in Oncology®: Prostate Cancer. V 2.2020. May 21. Available at http://www.nccn.org.

Sincerely,

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