Submitted by: Brian Alexander, MD
Company: Foundation Medicine, Inc.
Address: 150 Second Street, Cambridge, MA 02141
Phone: 617-418-2200 Ext. 2256
Email: balexander@foundationmedicine.com
Date of request: October 2, 2019
NCCN Guidelines Panel: Ovarian Cancer

Dear Panel Members,

On behalf of Foundation Medicine, I respectfully request the NCCN® Ovarian Cancer Guidelines Panel consider the updates below and enclosed references, pertaining to the evaluation and management of patients with ovarian cancer.

Requested Update #1: Update footnote 'e' on pages OV-1, OV-2, and OV-3 to indicate that *NGS-based testing to detect BRCA1 and BRCA2 alterations in tumor tissue is recommended as it may inform maintenance therapy. BRCA1/2 testing can be performed individually or as part of broad molecular profiling that also assesses NTRK gene fusions, TP53, MSI, HRD status, and tumor mutational burden (TMB). If a BRCA1/2 alteration is identified, the patient should be referred to genetic counseling and/or follow up with germline testing of the identified alteration.*

Requested Update #2: Change foot note 'w' in algorithm for recurrent disease (pages OV-6, OV-7) to state that *tumor molecular testing should include at least: BRCA1/2, MSI or DNA mismatch repair if not done previously, NTRK gene fusions, homologous recombination status, and tumor mutational burden. Tumor molecular testing can be performed as part of a single, NGS-based broad molecular profiling assay to inform the patient's treatment options, including clinical trials.*

Requested Update 3: In the Systemic Therapy section (pg OV-C 5 of 9), indicate that *NGS-based tumor molecular testing should include at least: BRCA1/2, MSI or DNA mismatch repair if not done previously, NTRK gene fusions, homologous recombination status, and tumor mutational burden. Tumor molecular testing can be performed as part of a single, NGS-based broad molecular profiling assay to inform the patient's treatment options, including clinical trials.*

Requested Update 4: Under Tumor Molecular Analyses in the Principles of Pathology section (pg OV-B 1 of 3) indicate that *MSI testing can be performed through a validated NGS panel*, similarly to the NCCN® Colon and Rectal Cancer Guidelines (COL-B 4 of 6; REC-B 5 of 7). Also under Tumor Molecular Analysis in the Principles of Pathology section (pg OV-B 1 of 3), indicate that *NGS-based testing for BRCA1/2, TP53, NTRK gene fusions, MSI status, HRD status, and tumor mutational burden could be performed as part of a single assay to inform the patient's treatment options, including clinical trials.*

Requested Update 5: Throughout the guideline (OV-1, OV-2, OV-3, OV-6, OV-7, OV-C 5 of 9, OV-B 1 of 3) change "evaluation of homologous recombination deficiency can be considered" to including HRD in the recommended tumor molecular testing (see language above in requests 1-4).

Rationale:

- ***BRCA* 1/*BRCA* 2**
  - In a study of 235 unselected ovarian cancer patients, somatic *BRCA* testing revealed 44 *BRCA1/2* deleterious alterations. Germline DNA was available for analysis in 28 of the 44 *BRCA* alteration carriers and 11 of the 28 (39.3%) of the *BRCA* alterations were absent in the germline and determined to be somatic in origin[11]. NGS-based comprehensive genomic profiling not only detects *BRCA1/2* alterations that are somatic in origin but has also been shown to be highly concordant (97%) to Sanger sequencing in the identification of *BRCA1/2* germline alterations[12]. Therefore, somatic *BRCA* mutation testing should be offered to women with ovarian cancer as a first-line testing approach to help inform decisions about when to utilize PARPi to maximize clinical benefit[13,14].
- **NTRK**
  - Given that the current NCCN®Guidelines in Ovarian Cancer (v2.2019) list both larotrectinib and entrectinib as targeted treatment options in both platinum-sensitive and platinum-resistant disease (pg OV-C 6 of 9; OV-C 7 of 9), NTRK gene fusion testing should be clearly identified as part of the recommended tumor molecular testing strategy.
- ***TP53***
  - Somatic alterations in the *TP53* gene are associated with high grade epithelial ovarian cancers, mostly high grade serous. The absence of a *TP53* mutation possibly in the presence of other mutations such as *BRAF* and *KRAS*, can reveal misclassified low grade serous tumors, certain other non-serous epithelial subtypes and sex-cord stromal tumors which have distinct treatment approaches from HGSC, and thus plays an important role as a diagnostic tool[1]. In particular, trametinib extended PFS of low grade serous carcinoma to 13.0 months with a hazard ratio of 0.48[15] and *KRAS*

mutations predicted a higher response rate of 24% to binimetinib[16]. Additionally, *TP53* loss has recently been shown to predict worse outcomes in patients with ovarian clear cell carcinoma[17].

- **MSI and TMB**
  - NGS testing to detect high MSI has been validated across tumor types and is shown to be highly concordant (97%, 65/67 cases) with current standard methods for detecting mismatch repair deficiencies, such as MSI testing by PCR and MMR IHC[2].
  - A meta-analyses of 22 studies of 1234 ovarian cancer cases showed that 8% of serous and 12-20% of nonserous ovarian cancers were MSI high[10]. NGS-based CGP of ovarian cancers demonstrates that all MSI-H and some MSS ovarian cancers have an elevated TMB (Feinberg 2018). While more data is needed regarding the clinical utility of TMB in ovarian cancer patients, it has been shown to be an important genomic signature for immunotherapy response across other tumor types[18] and, as an emerging biomarker, may play an important role in clinical trial eligibility regardless of tumor type. Comprehensive genomic profiling assays targeting ~1.1 Mb of coding genome can accurately assess TMB, showing high agreement to TMB calculations based on sequencing the whole exome (gold standard)[3].
- **HRD**
  - High genomic loss of heterozygosity (LOH), related to deficiencies in DNA repair, serves as a marker for potential benefit from PARP inhibitors[4,5].
  - HRD occurs in the setting of both germline and somatic loss of function mutations in *BRCA1* or *BRCA2*, but can also occur through mutations of other HR pathway genes or epigenetic events causing loss of expression of these proteins. Testing for *BRCA1/2* mutations identifies only a subset of patients with HRD ovarian cancer. Additional patients with HRD ovarian cancer who benefit from PARPi therapy can be identified by quantifying the proportion of the genome under loss of heterozygosity (LOH) resulting in a LOH score[5].
  - Several recently published or presented trials demonstrate that HRD assays can enrich for PARPi sensitive patient populations, including demonstrating significant improvement in PFS in patients with HRD-deficient high-grade ovarian cancer, which may be useful in choosing between different 1st and later line treatment and maintenance regimens. Veliparib in addition to first-line carboplatin-paclitaxel chemotherapy was shown to significantly improve PFS in the HRD-deficient cohort compared to placebo (31.9 vs. 20.5 months; HR=0.57; 95 CI, 0.43 to 0.76, P<0.001)[14]. Niraparib significantly extended median PFS in HRD-deficient patients (21.9 vs. 10.4 months: HR=0.43; 95 CI, 0.31 to 0.59, P<0.001) when compared to placebo after response to first-line platinum chemotherapy[13]. Results from the PAOLA-1 trial show that maintenance olaparib plus bevacizumab after response to bevacizumab plus platinum-based chemotherapy showed the highest benefit in advanced ovarian cancer patients with t*BRCA* alterations or HRD-deficient/*BRCA*wt. However, in this trial, HRD-proficient/*BRCA*wt patients had equivalent PFS on bevacizumab alone compared to bevacizumab plus olaparib suggesting HRD evaluation may be used to define populations unlikely to benefit from this combination[9].
- **Clinical Trials**
  - A comprehensive genomic profiling approach to tumor testing supports the NCCN® recommendation for clinical trial participation for all cancer patients by increasing the number of advanced cancer patients who are identified as eligible and enroll in a clinical trial versus the national average[7,8]. In addition, a prospective study of patients with a wide variety of refractory tumors, found that comprehensive genomic profiling nearly doubled the rate of clinical trial enrollment versus a smaller hotspot panel (19% vs 11%)[19].
  - Foundation Medicine has joined both the NCI-MATCH and ASCO TAPUR studies as an approved testing platform, and is accelerating accrual to these transformative trials using the combination of CGP and clinical trial matching capabilities.

Thank you for your review of this submission.

Sincerely

Brian Alexander, M.D.
Chief Medical Officer
Foundation Medicine

References

1. Kohn EC, Romano S, Lee JM, et al. Clinical implications of using molecular diagnostics for ovarian cancers, *Annals of Oncology*, Volume 24, Issue suppl_10, December 2013, Pages x22–x26, https://doi.org/10.1093/annonc/mdt464

2. Trabucco SE, Gowen K, Maund SL, et al. A Novel Next-Generation Sequencing Approach to Detecting Microsatellite Instability (MSI) and Pan-Tumor Characterization of One Thousand MSI-High Cases in 67,000 Patient Samples, The Journal of Molecular Diagnostics (2019), doi: https://doi.org/10.1016/j.jmoldx.2019.06.011

3. Chalmers ZR, Connelly CF, Fabrizio D, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Med. 2017;9(1):34.

4. Coleman RL, Oza AM, Lorusso D, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomized, double-blind, placebo-controlled, phase 3 trial [published correction appears in Lancet. 2017 Oct 28;390(10106):1948]. *Lancet*. 2017;390(10106):1949–1961. doi:10.1016/S0140-6736(17)32440-6

5. Swisher EM, Lin KK, Oza AM, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 part 1): an international, multicenter, open-label, phase 2 trial. Lancet Oncol. 2017 Jan;18(1):75-87. doi: 10.1016/S1470-2045(16)30559-9. Epub 2016 Nov 29.

6. Feinberg J, Elvin J.A., Bellonea S., et al. Identification of ovarian cancer patients for immunotherapy by concurrent assessment of tumor mutation burden (TMB), microsatellite instability (MSI) status, and targetable genomic alterations [Featured Poster Session 70]. Gyn Oncol. June 2018(vol 149); Suppl 1.

7. Sadaps M, Funchain P, Mahdi H, et al. Precision Oncology in Solid Tumors: A Longitudinal Tertiary Care Center Experience. *JCO Precis Oncol*. 2018. DOI: 10.1200/PO.18.00186 JCO Precision Oncology- published online November 27, 2018

8. Powell SF, Dib EG, Bleeker JS, et al. Delivering precision oncology in a community cancer program: results from a prospective observational study. *JCO Precis Oncol.* 2018. DOI: 10.1200/PO.17.00220.

9. LBA2_PR Phase III PAOLA-1/ENGOT-ov25 trial: Olaparib plus bevacizumab (bev) as maintenance therapy in patients (prs) with newly diagnosed, advanced ovarian cancer (OC) treated with platinum-based chemotherapy (PCh) plus bev. *Annals of Oncology*, Volume 30, Supplement 5, October 2019

10. Murphy MA, Wentzensen N. Frequency of mismatch repair deficiency in ovarian cancer: a systematic review This article is a US Government work and, as such, is in the public domain of the United States of America. *Int J Cancer*. 2011;129(8):1914–1922. doi:10.1002/ijc.25835

11. Hennessy BT, Timms KM, Carey MS, et al. Somatic mutations in *BRCA*1 and *BRCA*2 could expand the number of patients that benefit from poly (ADP ribose) polymerase inhibitors in ovarian cancer. *J Clin Oncol*. 2010;28(22):3570–3576. doi:10.1200/JCO.2009.27.2997

12. Dougherty BA, Lai Z, Hodgson DR, et al. Biological and clinical evidence for somatic mutations in *BRCA*1 and *BRCA*2 as predictive markers for olaparib response in high-grade serous ovarian cancers in the maintenance setting. *Oncotarget*. 2017;8(27):43653–43661. doi:10.18632/oncotarget.17613

13. Gonzalez-Martin A, Pothuri B, Vergote I, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. NEJM. September 28, 2019 DOI: 10.1056/NEJMoa1910962

14. Coleman R, Fleming G, Brady M, et al. Veliparib with First-Line Chemotherapy and as Maintenance Therapy in Ovarian Cancer. NEJM. September 28, 2019 DOI: 10.1056/NEJMoa1909707

15. LBA61 A randomized phase II/III study to assess the efficacy of trametinib in patients with recurrent or progressive low-grade serous ovarian or peritoneal cancer. *Annals of Oncology*, Volume 30, Issue Supplement_5, October 2019

16. Grisham R, Monk J B, Banerjee S*, et al* 1 MILO/ENGOT-OV11: Phase-3 study of binimetinib versus physician's choice chemotherapy (PCC) in recurrent or persistent low-grade serous carcinomas of the ovary, fallopian tube, or primary peritoneum *International Journal of Gynecologic Cancer* 2019;**29:**A1.

17. Parra-Herran C, Bassiouny D, Lerner-Ellis J, et a. p53, Mismatch Repair Protein, and *POLE* Abnormalities in Ovarian Clear Cell Carcinoma An Outcome-based Clinicopathologic Analysis. The American Journal of Surgical Pathology: July 19, 2019 - Volume Publish Ahead of Print - Issue - p doi: 10.1097/PAS.0000000000001328.

18. Goodman AM, Kato S, Bazhenova L, et al. Tumor Mutational Burden as an Independent Predictor of Response to Immunotherapy in Diverse Cancers. *Mol Cancer Ther*. 2017;16(11):2598–2608. doi:10.1158/1535-7163.MCT-17-0386.

19. Kopetz S, Mills Shaw K, Lee JJ, et al. Use of a Targeted Exome Next-Generation Sequencing Panel Offers Therapeutic Opportunity and Clinical Benefit in a Subset of Patients With Advanced Cancers. DOI: 10.1200/PO.18.00213 JCO Precision Oncology-published online March 8, 2019.