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Date of request: September 18, 2020
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' in algorithm for clinical presentation on pages OV-1, OV-2, and OV-3 to state "Germline and/or somatic *BRCA1/2* informs maintenance therapy. *Consider tumor molecular testing with validated, next-generation sequencing (NGS)-based assay to include at least: BRCA1/2, MSI, NTRK gene fusions, TP53, and tumor mutational burden. Tumor molecular testing can be performed as part of a single, NGS-based broad molecular profiling assay to inform patient treatment options, including clinical trials*."

Requested Update #2: Update footnote 'z' in algorithm for recurrent disease on pages OV-6, OV-7 to state "*Tumor molecular testing is recommended prior to initiation of therapy for recurrent or persistent disease with validated NGS-based assay to include at least: BRCA1/2, MSI and/or DNA mismatch repair, NTRK gene fusions, TP53, and tumor mutational burden . Evaluation of homologous recombination deficiency can be considered. Tumor molecular testing can be performed as part of a single, NGS-based broad molecular profiling assay to inform patient treatment options, including clinical trials."*

Requested Update #3: In "Principles of Pathology," under Tumor Molecular Analyses (OV-B 1 of 3), indicate that MSI testing can be performed through a validated NGS panel, similar to the NCCN® Colon and Rectal Cancer Guidelines (COL-B page 4 of 8; REC-B page 5 of 8). Also, under Tumor Molecular Analysis (page OV-B 1 of 3), recommend tumor molecular testing via a single, validated NGS-based broad molecular profiling assay to include at least: *BRCA1/2*, MSI and/or DNA mismatch repair, *NTRK* gene fusions, *TP53* and tumor mutational burden to inform patient treatment options, including clinical trials.

Requested Update #4: In "Principles of Systemic Therapy," (OV-C, 3 of 10) indicate that tumor molecular testing is recommended prior to initiation of therapy for recurrent or persistent disease with validated NGS-based assay to include at least: *BRCA1/2,* MSI and/or DNA mismatch repair, *NTRK* gene fusions, *TP53*, and tumor mutational burden . Evaluation of homologous recombination deficiency can be considered. Tumor molecular testing can be performed as part of a single, NGS-based broad molecular profiling assay to inform patient treatment options, including clinical trials.

Requested Update #5: In "Principles of Systemic Therapy," (OV-C 7,8 of 10), add pembrolizumab as an acceptable recurrence therapy for patients with tumor mutational-high (TMB-H) ≥10 mutations/mega base tumors who have progressed following prior treatment and have no satisfactory treatment options. Add footnote recommending that tumor mutational burden (TMB) should be determined by a validated and/or FDA-approved assay to inform the use of pembrolizumab for metastatic disease, referencing published validated standards (Merino, DM, et al. J Immunother Cancer 2020;8:e0014[1]). Amend footnote 't' to "*recommend tumor molecular testing prior to initiation of therapy for recurrent or persistent disease with validated NGS-based assay to include at least: BRCA1/2, MSI and/or DNA mismatch repair, NTRK gene fusions, TP53, and tumor mutational burden . Evaluation of homologous recombination deficiency can be considered. Tumor molecular testing can be performed as part of a single, NGS-based broad molecular profiling assay to inform patient treatment options, including clinical trials."*

KEYNOTE-158 (NCT02628067) was a multicohort, single-arm, open-label phase 2 study evaluating pembrolizumab monotherapy in 1066 patients with selected previously treated advanced solid tumors, who were administered pembrolizumab 200 mg once every 3 weeks by intravenous infusion[1]. 805/1066 patients had an evaluable tissue TMB (tTMB) score (efficacy population), and 105 (13%) were tTMB-high, defined as ≥10 mutations/megabase per the FoundationOne CDx panel, and were assessed for safety. 1050 (98%) of 1066 patients enrolled by at least 26 weeks before data cutoff, of whom 790 (75%) were evaluable for TMB and included in efficacy analyses. 102 (13%) of 790 patients had tTMB-high status. tTMB-high status was associated with a clinically meaningful improvement as demonstrated by an objective response rate (ORR) of 29% (95% CI, 21-39), compared to 6% (95% CI, 5-8) in the non-tTMB-high group (primary endpoint). Median follow-up was 37.1 months (IQR 35.0-38.3) and median duration of response was not reached in the tTMB-high group and was 33.1 months in the non-tTMB-high group. Additional secondary outcomes at landmark timepoints include the 2-year PFS rate of 22% (95% CI 14-30) in the tTMB-high group vs. 7% (95% CI 5-9) in the non–tTMB-high group, and the 3-year OS rate of 32% (95% CI 23-41) in the tTMB-high group versus 22% (95% CI 19-25) in the non–tTMB-high group. The predictive value of tTMB was independent of other biomarkers, including microsatellite instability (MSI)-high and PD-L1 expression. Additionally, the predictive value of tTMB did not appear to be driven by a particular tumor type, with an increased response rate for TMB-high patients observed across most tumor types. Based on the results of KEYNOTE-158, pembrolizumab is now FDA-approved for patients with unresectable or metastatic solid tumors with tTMB-high (≥10 mutations/megabase), as determined by an FDA-approved test, who have progressed following prior treatment and who have no satisfactory alternative treatment options[2,3].

Rationale:

- **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[5.] In particular, trametinib extended PFS of low-grade serous carcinoma to 13.0 months with a hazard ratio of 0.48[6] and *KRAS* mutations predicted a higher response rate of 24% to binimetinib[7]. Additionally, *TP53* loss has recently been shown to predict worse outcomes in patients with ovarian clear cell carcinoma[8].

- **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[9].
  - A meta-analysis of 22 studies of 1234 ovarian cancer cases showed that 8% of serous and 12-20% of non-serous 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[11].
  - TMB is a complex continuous biomarker and TMB estimation provided by next generation sequencing (NGS) targeted panels can vary across laboratories due to factors such as differences in panel size, gene coverage, and bioinformatics pipelines. Because of the important role TMB now plays in clinical decision-making and the potential for variation across laboratories, the Friends of Cancer Research convened a consortium of key stakeholders to recommend best practices and approaches for TMB measurement, validation, alignment and reporting[1]. Stakeholders, including the FDA, the National Cancer Institute, diagnostic manufacturers, academics, and pharmaceutical companies published detailed recommendations around TMB reporting consistency, standardization of analytical validation studies for TMB estimation, and alignment of panel TMB values to a whole exome sequencing (WES)-derived universal reference standard[1]. All tests that report a TMB value should comply with the recommendations as published and/or be FDA-approved for TMB measurement and reporting purposes[3,11].

1. 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[12,13]. 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%)[14].
- Comprehensive genomic profiling is an approved testing platform for both 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.
  - Subprotocol H of the NCI-MATCH platform trial investigated the selective BRAF inhibitor dabrafenib and the MEK1/2 inhibitor trametinib in patients with solid tumors, lymphomas, or multiple myeloma whose tumors harbored a $BRAF^{V600}$ mutation. The study met its primary endpoint with an ORR of 38%, and of 29 patients included in the efficacy analysis, five had low-grade serous ovarian carcinoma (LGSOC), perhaps the largest report to date regarding the efficacy dabrafenib and trametinib in LGSOC. Four of 5 patients with LGSOC had a partial response, and 1 patient had stable disease. Three of the PRs lasted 12 months or longer and the fourth patient was progression free at 10.7 months[15].

Thank you for your review of this submission.

Sincerely,

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Chief Medical Officer
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