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NCCN Guidelines Panel: Esophageal and Esophagogastric Junction Cancers

Dear Panel Members,

On behalf of Foundation Medicine, I respectfully request the NCCN® Esophageal and Esophagogastric Guidelines Panel consider the requested updates pertaining to the evaluation and management of patients with esophageal and esophagogastric junction cancers.

Requested Update and Rationale: Add the following statement to the workup algorithm on page ESOPH-1 : ***If metastatic disease is suspected, consider comprehensive genomic profiling via a validated NGS assay for the identification of MSI, TMB, MMR mutations, HER2 (ERBB2) alterations, and NTRK gene fusions (as opposed to sequential testing of single biomarkers or use of limited molecular diagnostic panels (≤50 genes)).***

For patients with confirmed unresectable locally advanced, locally recurrent, or metastatic disease, add the following: ***Recommend comprehensive genomic profiling via a validated NGS assay for the identification of MSI, TMB, MMR mutations, HER2 (ERBB2) alterations, and NTRK gene fusions as opposed to sequential testing of single biomarkers or use of limited molecular diagnostic panels (≤50 genes)).*** **(ESOPH-10, ESOPH-19)**

Comprehensive genomic profiling (CGP) can efficiently detect individual gene alterations (e.g. *HER2* amplification and mutation, *NTRK* fusions, *EGFR* and *MET* amplification, etc.), TMB, and MSI/MMR (*MLH1*, *MLH2*, *MLH6*, *PMS2*) status using a single sample[2]. This would allow conservation of tissue while obtaining as much information as possible to inform the use of currently available biomarker driven therapies, immunotherapies, and define/refine clinical trial options.

- *EGFR* amplification has been reported in approximately 5%-7 % of patients with GEC, with a statistically significant correlation between *EGFR* amplification detected using CGP and EGFR expression[14]. In a recent prospective study of patients with *EGFR*-amplified GEC treated with anti-EGFR therapies, 4/7 (58%) had objective responses, 7/7 (100%) had disease control, and the median progression free survival was 10 months[14]. Although the large randomized , placebo controlled phase 3 trial of gefitinib (COG) revealed no survival benefit in an unselected patient population (n= 450), additional retrospective analysis suggested a greater survival benefit in patients receiving gefitinib with gained EGFR amplification(7%) , HR for death 0.21,95%CI, 0.07 to 0.64;P=0.006[5].

- The efficacy of combination of immunotherapy in addition to anti-HER targeted therapy is rapidly evolving . In a recent single arm open label study of pembrolizumab with first line trastuzumab plus platinum chemotherapy in gastric, EGJ , and esophageal cancers, at a median follow up of 13 months, 26/37 (70%) patients achieved the primary endpoint of 6 months PFS[4] . Despite the limitations of these data being non randomized , and needing future validation, the ability of CGP to assess multiple biomarkers from a single sample for risk stratification to offer dual targeted inhibition or perform an informed decision on sequential therapy will be important in improving outcome of this disease.

- *MET* amplification has been reported in approximately 5% of GEC tested using CGP. Trials of MET inhibitors in patients selected based on MET expression have been largely negative; however, studies in patients with *MET*-amplified GEC have reported clinical benefit, including multiple cases with durable responses, to treatment with MET inhibitors, suggesting that selection based on amplification rather than expression may allow for identification of a population GEC patients likely to benefit from MET inhibitors[15].

- Numerous promising therapeutic approaches are based upon genomic characterization of tumors and therefore many clinical trials require specified genomic alterations for patient enrollment, including trials offered by the NCI (MATCH NCT02465060) and ASCO (TAPUR NCT02693535). Consistent with the NCCN® recommendation to provide patients with opportunities to participate in therapeutic clinical trials, comprehensive genomic profiling can potentially match more patients to targeted therapies in clinical trials based on detected alterations. Foundation Medicine is an approved testing platform for both NCI-MATCH and ASCO TAPUR and is accelerating accrual to these transformative trials using the combination of CGP and clinical trial matching capabilities.

Requested Update and Rationale: In regard to the assessment of overexpression or amplification of HER2 (ESOPH-B pg 3 and 5 of 6), remove the sentence "It should be noted that NGS has several inherent limitations and thus, whenever possible, the use of gold standard IHC/ISH should be performed."

- The heterogeneity of immunostaining for HER-2 in gastric and GEJ carcinomas and the possibility of intra-tumoral heterogeneity leads to a false-negative test rate of up to 9%[19,20].

- Studies have shown that *HER2* amplification detection using hybridization capture-based NGS assays is highly concordant with HER2 IHC and FISH, including a large study of breast and esophageal samples reporting concordance in 98.4% (248/252) of cases[5,9,10].

- Emerging evidence suggest that the level of ERBB2 amplification as determined by NGS is predictive of trastuzumab benefit. In a large prospective targeted NGS analysis study (n=295), a subset of patients with tumors positive by *HER2* IHC or FISH but negative for *HER2* amplification by CGP have responded poorly to trastuzumab[5] . CGP also allows for quantitative assessment of *HER2* copy number, which has been shown that the level of ERBB2 amplification to be predictive to the degree of trastuzumab response and overall survival benefit in gastric cancer[11]. *HER2* short variant mutations have also been reported in studies utilizing CGP in 3-4% of gastric cancers, largely mutually exclusive with *HER2* amplification, and these mutations would not be detected by HER2 FISH or IHC testing[6,12]. Further, CGP can also simultaneously identify alterations predicted to cause first-line trastuzumab resistance by identifying co-alterations in RTK-RAS-PI3K/AKT pathway GEC[5,13].

- Recently, in a large real world genomic dataset (N=596) of patients with advanced gastro-esophageal cancer in a real-world clinic-genomic database was analyzed[3]. Patients with CGP data for tissue specimens collected before first-line treatment were included. The overall agreement between HER2 status determined by IHC±ISH and ERBB2 amplification by CGP was high (91%) similar to what have been seen in other prospective studies. Both time to treatment discontinuation (TTD) and overall survival (OS) were impacted based on concordance of HER2 status by IHC±ISH and ERBB2 amplification status by CGP. First-line trastuzumab-treated pts with discordant tests (HER2+:ERBB2-) had significantly shorter TTD and OS accounting for better sensitivity utilizing NGS to select patients who drive greater trastuzumab benefit.

Requested Update and Rationale: Include the option for MSI testing by a validated NGS-based assay in addition to MSI by PCR/MMR by IHC in the diagnostic workup (pages ESOPH-1, ESOPH-10, ESOPH-19) and in the Principles of Pathologic Review (ESOPH-B, pg 4 of 6) MSI/MMR testing section, particularly for patients with metastatic disease who may benefit from more comprehensive genomic testing.

- 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 MSI testing including PCR and IHC[1]. High MSI detected using NGS of tumor tissue samples from patients with primarily advanced gastric or esophageal cancer has been reported in 3-4% and 0.4% of cases, respectively[1,6].Other NCCN Guidelines currently list NGS as an acceptable testing methodology for MSI in addition to PCR, especially for patients with metastatic disease who may require additional molecular testing (see **NCCN Guidelines for Colon Cancer (version 2.2019, COL-B pg 4 of 8)**

Previous Requested Updates (6/22/20): please see previous submission and references from Foundation Medicine dated 6/22/20 regarding KEYNOTE-158 (NCT02628067) data and Friends of Cancer Research (FOCR) TMB Harmonization Project recommendations for validation of assays that measure and report TMB for clinical purposes as outlined below.

1. ***Amend the algorithm on pages ESOPH-1, ESOPH-10, ESOPH-19 to recommend tumor mutational burden (TMB) when metastatic disease is documented/suspected as determined by a validated and/or FDA-approved assay to inform the use of pembrolizumab and reference Merino DM, et al. J Immunother Cancer 2020;8:e000147.***
2. ***Add section for TMB in "Principles of Pathologic Review and Biomarker Testing" (page ESOPH-B 4 of 6) including recommendation for TMB measurement and reporting to follow recommendations as outlined in Merino DM, et al. J Immunother Cancer 2020;8:e00147.***
3. ***Add pembrolizumab as a treatment option for patients with unresectable or metastatic tumors with tissue tumor mutational burden-high (tTMB-H) ≥10 mutations/megabase, as determined by an FDA-approved test, who have progressed following prior treatment and who have no satisfactory alternative treatment options. (ESOPH-B 5 of 6, ESOPH-F 4 and 11 of 14)***
    - Pembrolizumab is FDA-approved for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options[7,8].

Thank you for your review of this submission.

Sincerely,

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Chief Medical Officer, Foundation Medicine

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2. FDA Label: Foundation Medicine Inc. FoundationOne® CDx Technical Information. attached

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7. KEYTRUDA (pembrolizumab) FDA approved label found at https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf

8. U.S. Food and Drug Administration List of Cleared or Approved Companion Diagnostic Devices found at https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools

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