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NCCN Guidelines Panels: Gastric Cancer and Esophageal/Esophagogastric Junction Cancers

Dear Panel Members,

On behalf of Foundation Medicine, we respectfully request the NCCN® Gastric Cancer Panel and the Esophageal/Esophagogastric Junction Cancer Guidelines Panel consider the requested updates pertaining to the evaluation and management of patients with gastroesophageal cancers (GEC).

Specific Changes: We respectfully request that the Panels amend the Principles of Pathologic Review (ESOPH-B pg 3 of 5, and GAST-B pg 3 of 5) sections of the guidelines to indicate that testing should be performed for HER2 (*ERBB2*) overexpression or gene amplification, and that comprehensive genomic profiling via a validated next-generation sequencing (NGS) assay be included as a valid methodology. We also request the addition of measuring tumor mutational burden (TMB) as a recommendation together with microsatellite instability (MSI) or mismatch repair (MMR) testing, to identify additional patients who are likely to benefit from immunotherapies (ESOPH-B pg 4 of 5, and GAST-B pg 4 of 5). The option for MSI testing by a validated NGS-based assay should also be noted, as in the updated NCCN Guidelines for Colon Cancer (version 3.2018), particularly for patients with metastatic disease who may benefit from more comprehensive genomic testing.

Further, we respectfully ask the guidelines be amended to recommend testing using a single validated NGS-based comprehensive genomic profiling (CGP) assay, such as FoundationOneCDx (as opposed to sequential testing of single biomarkers or use of limited molecular diagnostic panels). CGP can efficiently detect individual gene alterations (eg. *HER2* amplification and mutation, *EGFR* and *MET* amplification, etc.), TMB, MSI/MMR (*MLH1*, *MLH2*, *MLH6*, *PMS2*) status, and mutations in genes associated with hereditary cancer susceptibility and already included in the current guidelines (*CDH1*, *SMAD4*, *APC*, *STK11*, *BRCA1/2*, *ATM*, *PTEN*, *TP53*, *FANC* genes, etc.) using a single sample. This would allow conservation of tissue while obtaining as much information as possible to inform the use of currently available biomarker driven therapies and define/refine clinical trial options, as well as to potentially recommend germline testing for the patient and their family members.

If tissue is unavailable, we request that the Principles of Pathologic Review sections of the guidelines be updated to suggest genomic testing of a blood-based liquid biopsy using a validated assay, such as FoundationOne Liquid, to identify genomic alterations that may inform the patient's treatment, including the option to enroll in genomically matched clinical trials. An expanded version of the FoundationOne Liquid assay recently received a breakthrough device designation from the U.S. Food and Drug Administration. This assay will include >70 genes including *HER2 (ERBB2)*, *MET*, *EGFR*, *BRAF*, *BRCA1/2*, *CDH1*, *PTEN* and *STK11* as well as MSI and blood TMB¹.

Rationale: CGP allows the molecular diagnostic evaluation of a single sample from a patient with metastatic GEC to identify predictive genomic alterations as a guide for the use of targeted therapies, and as indicators of hereditary cancer susceptibility prompting recommendation for germline testing, as well as TMB, MSI, and MMR gene alterations to guide use of immune checkpoint inhibitors.

Data in multiple solid tumor types suggest that TMB is an important predictive biomarker of response to immunotherapies, and responses to checkpoint inhibitors have been reported in both MSI-high/TMB-high and MS-stable/TMB-high tumors²⁻⁴. Higher TMB has been associated with higher response rate and significantly improved overall survival in patients with GEC treated with immunotherapy⁵. In one study of gastric carcinoma, 10% of patients had TMB >10 mutations/Mb, including 4.4% of patients with MS-stable tumors, whom would therefore not be identified as candidates for immunotherapy based on MSI testing alone⁶. CGP of tissue and

ctDNA samples from GEC patients have shown that MSI-high/TMB-high and Epstein Barr virus-positive (EBV+) status (which are mutually exclusive) each predict response to checkpoint inhibitors, suggesting that future reporting of these biomarkers using CGP assays will have predictive value in GEC, in addition to the established prognostic value of determining EBV status in gastric cancer^{5,7,8}.

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}. Studies in GEC patients treated with trastuzumab have reported that the subset of patients with tumors positive by *HER2* IHC or FISH but negative for *HER2* amplification by CGP have responded poorly to trastuzumab⁵. CGP also allows for quantitative assessment of *HER2* copy number, which has been shown to be predictive of trastuzumab response and overall survival in gastric cancer¹¹. *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 trastuzumab resistance in GEC^{5,13}.

EGFR amplification has been reported in approximately 5% of patients with GEC, with a statistically significant correlation between *EGFR* amplification detected using CGP and *EGFR* expression¹⁴. In a recent 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 months¹⁴. In a phase III trial of gefitinib in esophageal cancer, patients with *EGFR* copy number gain had significantly better OS than those without, and patients with *EGFR*-amplified tumors derived the greatest benefit¹⁵.

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* inhibitors¹⁶.

Data on the performance of liquid biopsy has reported detection of ctDNA in 68%, 100%, and 78% of blood-based circulating tumor DNA (ctDNA) samples from patients with metastatic gastric, esophageal, and gastroesophageal junction carcinomas, respectively, with an average of 2 reportable genomic alteration per sample. Among 7 temporally-matched GEC blood and tissue samples included in this study, 80% (12/15) of alterations detected in tissue were also detected in ctDNA¹⁷. Other studies have reported genomic heterogeneity as an obstacle to effectively identifying genomic alterations and selecting matched targeted therapies in GEC, thus liquid biopsy may help to overcome this potential limitation¹⁸.

Taken together these data suggest that routine, broad-based CGP in patients with GEC via a single assay is the most efficient and thorough approach to identify common genomic alterations and genomic signatures (such as TMB and MSI) enabling treatment with genomics-matched clinical trials and approved therapies, and to identify potential germline alterations known to predispose patients to GEC.

Thank you for your review of this submission.

Sincerely,



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