Dear Panel Members,

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

Requested Update and Rationale: Add comprehensive genomic profiling via a validated next-generation sequencing (NGS) assay as a valid methodology for the identification of HER2 (ERBB2) overexpression or gene amplification in the Principles of Pathologic Review (ESOPH-B pg 3 of 5) section of the guidelines.

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 trastuzumab\(^5\). 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 cancer\(^13\). 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\(^5,13\).

Requested Update and Rationale: Include the option for MSI testing by a validated NGS-based assay in the Principles of Pathologic Review (ESOPH-B, pg 4 of 5) section, as in the NCCN Guidelines for Colon Cancer (version 2.2019, COL-B pg 4 of 6), 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.\(^1,6\)

Requested Update and Rationale: Recommend testing for NTRK gene fusions to Principles of Pathologic Review and Biomarker Testing (ESOPH-B, pg 4 of 5).

- Vitrakvi® (larotrectinib) is FDA-approved for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment.\(^19\) In a Phase 1/2 trial of the TRK inhibitor larotrectinib in patients with NTRK fusion-positive tumors, which included 17 tumor types, a 75% overall response rate was observed.\(^19\)
- Rozlytrek® (entrectinib) is FDA-approved for the treatment Adults and pediatric patients 12 years and older with NTRK gene fusion positive solid tumors.\(^21\)

Requested Update and Rationale: Amend the Principles of Pathologic Review (ESOPH-B pg 4 of 5) section to indicate that comprehensive genomic testing via a validated, NGS-based liquid biopsy test, such as FoundationOne® Liquid, is an acceptable testing method and may provide unique advantages over tissue-based testing alone.

- Genomic testing of a blood-based liquid biopsy using a validated assay, such as FoundationOne Liquid, to identify genomic alterations may inform the patient’s treatment, including the option to enroll in genomically matched clinical trials. The FoundationOne Liquid assay evaluates four classes of genomic alterations (base substitutions, insertions and deletions, copy number alterations, and rearrangements) in 70 genes including HER2 (ERBB2), MET, EGFR, BRAF, BRCA1/2, CDH1, PTEN and STK11, as well as evaluates and reports MSI-high status.\(^22\)
- 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 ctDNA.\(^17\) 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 limitation.\(^18\)
- In another study of GEC cases with NGS-based ctDNA testing performed, HER2 copy number, after adjustment for overall ctDNA
level detected, was predictive of survival benefit in patients treated with HER2 targeted therapies. Patients with HER2 ctDNA copy number greater than the median trended toward improved overall survival (15.9 vs 9.4 months, p=0.07, HR 0.4) vs those with lower copy number. However, complementary tissue and ctDNA-based NGS testing to detect HER2 amplification was the most robust predictor of response to HER2 targeted therapy, with HER2-amplified patients identified by either ctDNA-NGS or tissue-based NGS demonstrating a profound overall survival benefit (26.3 vs 7.4 months, p=0.002, HR 0.2). The same was observed for a cohort of patients with EGFR amplified (assessed by either tissue or adjusted ctDNA copy number) GEC treated with EGFR targeted therapies.

Requested Update and Rationale: Recommend the option of testing using a single validated NGS-based comprehensive genomic profiling (CGP) assay, such as FoundationOne CDx (as opposed to sequential testing of single biomarkers or use of limited molecular diagnostic panels) in the Principles of Pathologic Review section (ESOPH-B, pg 4 of 5).

CGP can efficiently detect individual gene alterations (e.g. HER2 amplification and mutation, NTRK fusions, 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.

- **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 expression. 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 months. 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 benefit.

- **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.

- 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 tumors. Higher TMB has been associated with higher response rate and significantly improved overall survival in patients with GEC treated with immunotherapy. 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 alone. 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.

Thank you for your review of this submission.

Sincerely,

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


22. https://assets.ctfassets.net/vhribv12lmne/3SPYAcbGdqAeMsOqMyKUog/d0eb51659e08d733bf39971e85ed940df1L_TechnicalInformati on_MKT-0061-04.pdf