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NCCN Guidelines Panel: Esophageal/Esophagogastric Junction

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[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 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[20]. 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].
- Rozyltrek®(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[23].

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 tested 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[14]. 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[14]. 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[15].

- *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[16].

- 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[2–4]. Higher TMB has been associated with higher response rate and significantly improved overall survival in patients with GEC treated with immunotherapy[5]. 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[6]. 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].

Thank you for your review of this submission.

Sincerely,

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References

1. Trabucco SE, Gowen K, Maund SL, Sanford E, Fabrizio DA, Hall MJ, Yakirevich E, Gregg JP, Stephens PJ, Frampton GM, Hegde PS, Miller VA, Ross JS, Hartmaier RJ, Huang S-MA, Sun JX, 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

2. 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

3. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science*. 2015;348(6230):124-128. doi:10.1126/science.aaa1348

4. Fabrizio DA, George Jr TJ, Dunne RF, et al. Beyond microsatellite testing: assessment of tumor mutational burden identifies subsets of colorectal cancer who may respond to immune checkpoint inhibition. *J Gastrointest Oncol*. 2018;9(4):610-617.

5. Janjigian YY, Sanchez-Vega F, Jonsson P, et al. Genetic Predictors of Response to Systemic Therapy in Esophagogastric Cancer. *Cancer Discov*. 2018;8(1):49-58. doi:10.1158/2159-8290.CD-17-0787

6. Schrock AB, Devoe CE, McWilliams R, et al. Genomic Profiling of Small-Bowel Adenocarcinoma. *JAMA Oncol*. June 2017. doi:10.1001/jamaoncol.2017.1051

7. Sohn BH, Hwang J-E, Jang H-J, et al. Clinical Significance of Four Molecular Subtypes of Gastric Cancer Identified by The Cancer Genome Atlas Project. *Clin Cancer Res Off J Am Assoc Cancer Res*. July 2017. doi:10.1158/1078-0432.CCR-16-2211

8. Kim ST, Cristescu R, Bass AJ, et al. Comprehensive molecular characterization of clinical responses to PD-1 inhibition in metastatic gastric cancer. *Nat Med*. July 2018. doi:10.1038/s41591-018-0101-z

9. Frampton GM, Fichtenholtz A, Otto GA, et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. *Nat Biotechnol*. 2013;31(11):1023-1031. doi:10.1038/nbt.2696

10. Ross DS, Zehir A, Cheng DT, et al. Next-Generation Assessment of Human Epidermal Growth Factor Receptor 2 (ERBB2) Amplification Status: Clinical Validation in the Context of a Hybrid Capture-Based, Comprehensive Solid Tumor Genomic Profiling Assay. *J Mol Diagn JMD*. 2017;19(2):244-254. doi:10.1016/j.jmoldx.2016.09.010

11. Gomez-Martin C, Plaza JC, Pazo-Cid R, et al. Level of HER2 gene amplification predicts response and overall survival in HER2-positive advanced gastric cancer treated with trastuzumab. *J Clin Oncol Off J Am Soc Clin Oncol*. 2013;31(35):4445-4452. doi:10.1200/JCO.2013.48.9070

12. Ali SM, Sanford EM, Klempner SJ, et al. Prospective comprehensive genomic profiling of advanced gastric carcinoma cases reveals frequent clinically relevant genomic alterations and new routes for targeted therapies. *The Oncologist*. 2015;20(5):499-507. doi:10.1634/theoncologist.2014-0378

13. Lee JY, Hong M, Kim ST, et al. The impact of concomitant genomic alterations on treatment outcome for trastuzumab therapy in HER2-positive gastric cancer. *Sci Rep*. 2015;5:9289. doi:10.1038/srep09289

14. Maron SB, Alpert L, Kwak HA, et al. Targeted Therapies for Targeted Populations: Anti-EGFR Treatment for EGFR-Amplified Gastroesophageal Adenocarcinoma. *Cancer Discov*. 2018;8(6):696-713. doi:10.1158/2159-8290.CD-17-1260

15. Petty RD, Dahle-Smith A, Stevenson DAJ, et al. Gefitinib and EGFR Gene Copy Number Aberrations in Esophageal Cancer. *J Clin Oncol Off J Am Soc Clin Oncol*. 2017;35(20):2279-2287. doi:10.1200/JCO.2016.70.3934

16. Maron SB, Catenacci DVT. Update on Gastroesophageal Adenocarcinoma Targeted Therapies. *Hematol Oncol Clin North Am*. 2017;31(3):511-527. doi:10.1016/j.hoc.2017.01.009

17. Schrock AB, Pavlick DC, Klempner SJ, et al. Hybrid capture-based genomic profiling of circulating tumor DNA from patients with advanced cancers of the gastrointestinal tract or anus. *Clin Cancer Res Off J Am Assoc Cancer Res*. January 2018. doi:10.1158/1078-0432.CCR-17-3103

18. Pectasides E, Stachler MD, Derks S, et al. Genomic Heterogeneity as a Barrier to Precision Medicine in Gastroesophageal Adenocarcinoma. *Cancer Discov*. 2018;8(1):37-48. doi:10.1158/2159-8290.CD-17-0395

19. Drilon A, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, …Hyman DM. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. N Engl J Med. 2018 Feb 22;378(8):731-739. doi: 10.1056/NEJMoa1714448.
20. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210861s000lbl.pdf

21. https://www.gene.com/download/pdf/rozlytrek_prescribing.pdf

22. https://assets.ctfassets.net/vhribv12lmne/3SPYAcbGdqAeMsOqMyKUog/d0eb51659e08d733bf39971e85ed940d/F1L_TechnicalInformation_MKT-0061-04.pdf

23. Maron SB, Chase LM, Lomnicki S, et al. Circulating tumor DNA sequencing analysis of gastroesophageal adenocarcinoma. Clin Cancer Res August 19 2019 **DOI:** 10.1158/1078-0432.CCR-19-1704