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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 Cancers Guidelines Panel consider the following requested updates pertaining to the evaluation and management of patients with esophageal and esophagogastric junction cancers.

Requested Update: Please consider *recommending* comprehensive genomic profiling via a validated next-generation sequencing (NGS) assay, using tumor tissue or cell free DNA in plasma (liquid biopsy), as an option for identification of HER2 amplification, microsatellite instability (MSI) status, tumor mutational burden and *NTRK* fusions as opposed to following testing for MSI and HER2 status if sufficient tissue is available. (ESOPH-1, ESOPH-10, ESOPH-19).

Rationale: Comprehensive genomic profiling (CGP) using next-generation sequencing (NGS) technology of tumor tissue or cell free DNA (cfDNA) in plasma (liquid biopsy) provides complementary approaches for biomarker testing in patients with advanced/metastatic esophageal and esophagogastric cancers.

- **FDA-approved and validated comprehensive genomic profiling (CGP) tests, using tissue or plasma (liquid biopsy) are available for use in all advanced or metastatic solid tumors, providing clinicians with information to inform patient prognosis, targeted therapy options, and clinical trial eligibility.**[1,2,3,4] CGP utilizes NGS technology to examine entire exonic regions of cancer-relevant genes (in contrast to limited "hot spot" tests), simultaneously identifying the 4 main classes of genomic alterations (base substitutions, insertions or deletions, copy number alterations, and gene rearrangements). Further, CGP assays can assess genomic alteration patterns across related genes in established cancer pathways to report complex biomarkers such as tumor mutational burden and microsatellite instability to inform cancer treatment decisions using a single assay.

- **Liquid biopsy provides an alternative to tissue biopsy in certain clinical situations.** As noted in "Principles of Pathologic Review and Biomarker Testing" (ESOPH-B, 5 of 6), the role of liquid biopsy has become increasingly well-established in the management of patients with advanced disease who are unable to undergo biopsy. Lack of evaluable tumor tissue results may also occur due to insufficient tumor tissue, and/or low tumor cellularity, low DNA quantity and/or low quality, failed library preparation or other technical issues.[5] Liquid biopsy may also provide advantages to tissue biopsy in reduced time from sample to result because a biopsy procedure is not needed; provision of information on intratumor heterogeneity or information on the molecular biology of multiple metastatic lesions; and the detection of clinically actionable treatment and resistance-related genomic alterations.[6]

Requested Update: Please consider removing statement, "It should be noted that NGS has several inherent limitations and thus, whenever possible, the use of gold-standard assays (IHC/ISH) should be performed first and if sufficient tissue is available, NGS testing may be considered" from Principles of Pathologic Review and Biomarker Testing, Assessment of Overexpression or Amplification of HER2 in Esophageal and Esophagogastric Junction Cancers (ESOPH-B, 3 of 6) and Next Generation Sequencing (NGS) (ESOPH-B, 5 of 6).

Rationale: CGP using NGS technology can reliably identify *ERBB2* amplifications in addition to other guideline recommended biomarkers, supporting the efficient use of tissue.

- 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%.[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.[9,10]

- A genomic analysis of patients with advanced gastroesophageal adenocarcinoma identified *ERBB2* amplification (defined as predicted copy number ≥ 5 with > 80% of exons amplified) in 15% (1,920/12,749). For a subset of cases in also included in the real-world (rw) database, 101 patients were treated with first line anti-HER2 therapy. Higher *ERBB2* copy number was a significant predictor as a continuous variable of longer rwPFS.[11]

- CGP also allows for quantitative assessment of *HER2* copy number, which has demonstrated the level of ERBB2 amplification to be predictive of the degree of trastuzumab response and overall survival benefit in gastric cancer.[12] *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.[13] 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.[14]

- 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.[15] 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.[15]

Requested Update: Include option for MSI testing by a validated NGS-based assay in addition to MSI by polymerase chain reaction (PCR) or MMR by IHC in Principles of Pathologic Review and Biomarker Testing, Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing (ESOPH-B, 4 of 6).

Rationale: CGP using NGS technology can reliably identify MSI in addition to other guideline recommended biomarkers, supporting the efficient use of tissue.

- 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.[1,2] 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.[16] 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 2.2021, COL-B, 4 of 8)**

Thank you for your consideration of this submission.

Sincerely,

Geoffrey Oxnard, M.D.
Vice President and Global Medical Lead, Liquid Franchise
Foundation Medicine Inc.

[1]FDA Label: Foundation Medicine Inc. FoundationOne® CDx Technical Information. Found at f1cdxlabel.com

[2]FDA Label: Foundation Medicine Inc. FoundationOne®Liquid CDx Technical Information. Found at f1lcdxlabel.com

[3]Woodhouse R, Li M, Hughes J, Delfosse D, Skoletsky J, Ma P, Meng W, Dewal N, Milbury C, Clark T, Donahue A, Stover D, Kennedy M, Dacpano-Komansky J, Burns C, Vietz C, Alexander B, Hegde P, Dennis L. Clinical and analytical validation of FoundationOne Liquid CDx, a novel 324-Gene cfDNA-based comprehensive genomic profiling assay for cancers of solid tumor origin. PLoS One. 2020 Sep 25;15(9):e0237802. doi: 10.1371/journal.pone.0237802. PMID: 32976510; PMCID: PMC7518588.

[4] FDA Label: Guardant360® CDx Technical Information. Found at: https://www.accessdata.fda.gov/cdrh_docs/pdf20/P200010C.pdf

[5]Razavi P, Li BT, Brown DN, Jung B, Hubbell E, Shen R, Abida W, Juluru K, De Bruijn I, Hou C, Venn O, Lim R, Anand A, Maddala T, Gnerre S, Vijaya Satya R, Liu Q, Shen L, Eattock N, Yue J, Blocker AW, Lee M, Sehnert A, Xu H, Hall MP, Santiago-Zayas A, Novotny WF, Isbell JM, Rusch VW, Plitas G, Heerdt AS, Ladanyi M, Hyman DM, Jones DR, Morrow M, Riely GJ, Scher HI, Rudin CM, Robson ME, Diaz LA Jr, Solit DB, Aravanis AM, Reis-Filho JS. High-intensity sequencing reveals the sources of plasma circulating cell-free DNA variants. Nat Med. 2019 Dec;25(12):1928-1937. doi: 10.1038/s41591-019-0652-7. Epub 2019 Nov 25. PMID: 31768066; PMCID: PMC7061455.

[6]Ignatiadis M, Sledge GW, Jeffrey SS. Liquid biopsy enters the clinic - implementation issues and future challenges. Nat Rev Clin Oncol. 2021 May;18(5):297-312. doi: 10.1038/s41571-020-00457-x. Epub 2021 Jan 20. PMID: 33473219.

[7] Bartley AN, et al. HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma: Guideline from the College of American Pathologists, American Society of Clinical Pathology, and American Society of Clinical Oncology. *American Journal of Clinical Pathology*, Volume 146, Issue 6, December 2016, Pages 647–669

[8] Lee He et al Eur J Cancer 2013 Lee HE, Park KU, Yoo SB, et al. Clinical significance of intratumoral HER2 heterogeneity in gastric cancer. *Eur J Cancer*. 2013;49(6):1448-1457.

[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] Klempner poster, ASCO 2021: https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.4045

[12] 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

[13] 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

[14]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

[15] Stein S, et al. Association of real-world agreement between HER2 expression and ERBB2 amplification with trastuzumab therapy benefit in advanced gastric/esophageal (adv GE) cancer patients (pts). Journal of Clinical Oncology 38, no. 4_suppl (February o1, 2020). Published online February 04, 2020.

[16] 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