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Date of request: April 29, 2021

NCCN Guidelines Panel: Head and Neck Cancers

On behalf of Kura Oncology, I respectfully request the NCCN Head and Neck Cancers Panel review the enclosed data and publications that support inclusion of a recommendation for next-generation sequencing (NGS) of head and neck malignancies. Such an inclusion could inform the use of available targeted therapies and/or provide the basis to pursue appropriate clinical or therapeutic trials.

Specific Changes: Incorporation of NGS based genomic profiling in Recurrent/Persistent Very Advanced Head and Neck Cancer (ADV-3), Salivary Gland Tumors (SALI-4), and Principles of Systemic Therapy For Non-Nasopharyngeal Cancers (SYST-A). Specifically:

1. ADV-3: Add "NGS genomic profiling for biomarker identification" as a footnote for "Clinical trial preferred" (see rationale below)
2. SALI-4: Change footnote *p* from "For salivary ductal carcinomas and adenocarcinomas, check androgen receptor (AR) status and HER2 status prior to treatment for distant metastases. Check NTRK status for mammary analog secretory carcinoma (MASC)" to "Use NGS profiling and other appropriate biomarker testing to check status of androgen receptor (AR), HER2, NTRK, HRAS, PIK3CA, etc. prior to treatment."
3. SYST-A: Add "NGS genomic profiling for biomarker identification" as part of the first bullet "The choice of systemic therapy should be individualized based on patient characteristics. NGS genomic profiling is recommended to guide patient treatment options including clinical trials".

FDA Clearance: FoundationOne® CDx is currently approved as comprehensive genomic test (NGS) in advanced solid tumors.

Rationale: The recent publication by Hanna, et al. that demonstrated *HRAS* mutation as an actionable biomarker for patients with salivary gland cancer; when treated with an HRAS targeted agent (tipifarnib), participants achieved a clinical benefit rate of 67% and median overall survival of 18 months with approximately 60% of patients alive at 1-year.

A recent publication by Ho, et al. demonstrated *HRAS* mutation as an actionable biomarker for patients with head and neck squamous cell carcinoma (HNSCC), resulting in an objective

response rate of 55% and median overall survival of 15.4 months for patients with *HRAS*-mutant disease yielding a variant allele frequency of ≥20%. A pivotal study (NCT03719690) is currently ongoing to enroll *HRAS*-mutant patients with HNSCC.

A publication by Marret, et al. used the European Society for Medical Oncology (ESMO) Scale of Actionability of Molecular Targets (ESCAT) classification to rank key actionable biomarkers in HNSCC. The mutations include *PIK3CA, HRAS, CDKN2A, EGFR, NTRK*, along with microsatellite instability, and biomarker testing is encouraged for informing clinical trial eligibility. As shown on Clinicaltrials.gov, there is an increasing number of biomarker-driven clinical trials for head and neck cancer, including markers such as *HRAS, TP53, HER2, c-MET*, and PI3K/mTOR/Akt pathways.

These articles are included for your review and consideration.

Precedent for inclusion of similar recommendations include:

- Publications by Hong, et al., Drilon, et al., and Thorpe, et al. that are currently included as NTRK fusion references in the NCCN guideline.
- Publications by Thorpe, et al. and Jhaveri, et al. that are currently included as HER2 references in the NCCN guideline.

Because there is increasing evidence of the benefit of identifying clinically actionable biomarkers in oncology and in head and neck cancer specifically with increasing biomarker-driven clinical trials, we sincerely appreciate your review and consideration of this recommendation.

Sincerely,

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Stephen Dale
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Stephen Dale, MD

Chief Medical Officer
Kura Oncology

The following articles are submitted in support of this proposed change.

1. Drilon et al, Efficacy of Larotrectinib in TRK Fusion–Positive Cancers in Adults and Children. *N Engl J Med*., 2018

2. Hanna et al, Tipifarnib in recurrent, metastatic HRAS-mutant salivary gland cancer, *Cancer, 2020*
3. Ho et al, Tipifarnib in Head and Neck Squamous Cell Carcinoma with HRAS Mutations, *JCO, 2021*
4. Hong et al, Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. *The Lancet Oncology*, 2020
5. Jhaveri et al, Ado-trastuzumab emtansine (T-DM1) in patients with HER2-amplified tumors excluding breast and gastric/gastroesophageal junction (GEJ) adenocarcinomas: results from the NCI-MATCH trial (EAY131) subprotocol Q. *Ann Oncology*, 2019
6. Marret al, Genomic Alterations in Head and Neck Squamous Cell Carcinoma: Level of Evidence According to ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT). *JCO Precision Oncology*, 2021
7. Thorpe et al, Significant and durable clinical benefit from trastuzumab in 2 patients with HER2-amplified salivary gland cancer and a review of the literature. *Head Neck*, 2017

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