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NCCN Guidelines Panel: Hepatobiliary

Dear Panel Members,

On behalf of Foundation Medicine, I respectfully request the NCCN® Hepatobiliary Guideline Panel to consider the requested updates and enclosed references, pertaining to the evaluation and management of patients with cholangiocarcinoma.

Specific Change 1 and Rationale: Amend the algorithm for intrahepatic cholangiocarcinoma (page INTRA-1) and extrahepatic cholangiocarcinoma (page EXTRA-1) to include testing for NTRK gene fusions.

- 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 [15]. 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 including a partial response in one of two patients with cholangiocarcinoma [11].
- Rozyltrek®(entrectinib) is FDA-approved for the treatment adults and pediatric patients 12 years and older with *NTRK* gene fusion positive solid tumors. Results from the first 54 patients in a pooled subgroup of adult patients with unresectable or metastatic solid tumors with a NTRK gene fusion enrolled in one of three multicenter, single-arm, open-label clinical trials showed a 57% overall response rate (50% partial, 7.4% complete). There was one patient with cholangiocarcinoma who had a partial response to entrectinib with 9.3 months duration[16].

Specific Change 2 and Rationale: Amend the algorithm for intrahepatic cholangiocarcinoma (page INTRA-1) and extrahepatic cholangiocarcinoma (page EXTRA-1) to define the recommendation "Consider molecular testing" to indicate that molecular testing is optimally completed as part of a single, validated NGS-based comprehensive genomic profiling (CGP) assay (as opposed to sequential testing of single biomarkers or use of limited molecular diagnostic panels) in order to conserve tissue and to obtain as much information as possible to inform the use of currently available biomarker driven therapies and define/refine clinical trial options.

- FGFR2 fusion or mutation is detected in 21% of cholangiocarcinoma cases [1]. In a Phase 2 study of the FGFR inhibitor BGJ398 for patients with chemotherapy-refractory cholangiocarcinoma containing FGFR2 fusion or mutation, the overall response rate (ORR) was 14.8% (18.8% for FGFR2 fusion) and disease control rate (DCR) was 75.4% (83.3% for FGFR2 fusion) [2]. Similarly, in a Phase 1 trial of the FGFR inhibitor erdafitinib, patients with advanced cholangiocarcinoma whose tumors harbored FGFR alterations had an ORR of 27.3% and DCR of 55.0% [3].
- IDH1/2 mutation is observed in 18% of cholangiocarcinoma [1]. In a Phase 1 study of the IDH1 inhibitor ivosidenib for patients with previously treated cholangiocarcinoma containing an IDH1 mutation, the 6 month progression-free survival was 40%; 6% of patients had a partial response, and 56% experienced stable disease [4].
- ERBB2 (HER2) mutation or amplification is observed in 3%-9% of cholangiocarcinoma [1,5]. In the Phase 2 basket study (MyPathway trial), of the 11 patients with HER2-positive (amplification or

overexpression) refractory metastatic biliary cancer treated with the HER2 targeted antibodies pertuzumab plus trastuzumab, 4/11 had a partial response and 3/11 had stable disease for greater than 4 months [6]. In a basket study of the HER2 kinase inhibitor neratinib, of 8 evaluable patients with biliary tract cancer harboring a HER2 mutation, 2/8 had a partial response and 3/8 had stable disease [7].

- Responses to matched targeted therapy in cholangiocarcinoma have also been reported for patients with mutations in BRAF [12,13] or ERFFI1 [14].
- MSI-High status is observed in 1.4% of cholangiocarcinoma cases[8]. The FDA approval of pembrolizumab for patients with MSI-H solid tumors was based on a basket trial that included patients with cholangiocarcinoma [9]. MSI-H tumors are associated with robust prolongation in overall survival in numerous tumor types treated with pembrolizumab; disease control was achieved in 4/4 patients with MSI-H cholangiocarcinoma (1 had a complete response, 3 had stable disease including 2 patients with tumor shrinkage)[10]. Given the low frequency of MSI-High cholangiocarcinoma, MSI testing is unlikely to be performed as a standalone assay, and routine testing of MSI using CGP, which also identifies other clinically relevant genomic alterations, may be a more efficient use of tissue.
- Tumors with high mutational burden have been shown to be associated with response to immunotherapy across multiple cancer types [17].
- Taken together these data suggest that routine broad-based CGP of tumors of patients with advanced cholangiocarcinoma via a single assay is the most efficient and thorough approach to identify both common genomic alterations and genomic signatures such as TMB and MSI which identify patients for treatment with FDA-approved agents (such as pembrolizumab, larotrectinib, entrectinib) and enrollment into genomically-matched clinical trials.

Thank you for your review of this submission.

Sincerely,

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Chief Medical Officer
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