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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 Changes and Rationale

We respectfully request that the Panel consider amending the algorithm for intrahepatic cholangiocarcinoma (page INTRA-1) and extrahepatic cholangiocarcinoma (page EXTRA-1) to change “Consider molecular testing, including MSI testing” to indicate that molecular testing is optimally completed as part of a validated comprehensive genomic profiling (CGP) assay, such as FoundationOne CDx, via a single 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.

CGP can identify genomic alterations in *FGFR2*, *IDH1*, *IDH2*, *ERBB2* and *NTRK*, as well high microsatellite instability status (MSI-H) that may inform the patient’s treatment, including the option to enroll in genomically matched clinical trials.

- *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].
- 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

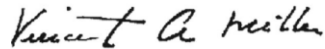
stable disease including 2 patients with tumor shrinkage)[10]. Given the low frequency of MSI-High cholangiocarcinoma, MSI testing is unlikely to be performed as a standalone assay, and routine testing of MSI using CGP, which also identifies other clinically relevant genomic alterations, may be a more efficient use of tissue.

- 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].
- Responses to matched targeted therapy in cholangiocarcinoma have also been reported for patients with mutations in *BRAF* [12, 13] or *ERFF1* [14].

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 approved agents (such as pembrolizumab) and enrollment into genomics-matched clinical trials.

Thank you for your review of this submission.

Sincerely,

A handwritten signature in black ink, appearing to read "Vincent A. Miller".

Vincent A. Miller, M.D.
Chief Medical Officer
Foundation Medicine

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