Submitted by: Brian Alexander, MD
Company: Foundation Medicine, Inc.
Address: 150 Second Street, Cambridge, MA 02141
Phone: **617-418-2200 Ext. 2256**
Email: balexander@foundationmedicine.com
Date of request: October 1, 2019
NCCN Guidelines Panel: Hepatobiliary

Dear Panel Members,

In addition to the previous submission dated September 24, 2019, I respectfully request the NCCN® Hepatobiliary Cancer Guidelines Panel consider the requested updates below and enclosed references, pertaining to the evaluation and management of patients with cholangiocarcinoma. The highlighted information was recently presented at the 2019 European Society of Medical Onocology meeting.

Specific Change 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.

- IDH1/2 mutations are observed in 18% of cholangiocarcinoma [1]. In a global phase III study [ClarIDHy] of advanced cholangiocarcinoma patients with IDH1 alterations who were randomized to ivosidenib or placebo, the median progression-free survival was 2.7 months for patients treated with ivosidenib compared to 1.4 months with placebo (hazard ratio [HR] 0.37; 95% confidence interval [CI]: 0.25-0.54, P<0.001). The median progression-free survival rate at six months was 32.0% with ivosidenib, while no patients randomized to placebo were free from progression at this timepoint [4].
- 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]. In another Phase 2 study, patients with previously treated locally advanced or metastatic cholangiocarcinoma with an FGFR2 rearrangement or fusion who were treated with pemigatinib experienced an ORR of 35.5% and the median duration of response was 7.5 months [18]. 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].

Thank you for your review of this submission.

Sincerely,

Sincerely

Brian Alexander, M.D.
Chief Medical Officer
Foundation Medicine

References

1. Farshidfar F, Zheng S, Gingras M-C et al. Integrative Genomic Analysis of Cholangiocarcinoma Identifies Distinct IDH -Mutant Molecular Profiles. Cell Rep. 2017; 18(11):2780–2794.

2. Javle M, Lowery M, Shroff RT et al. Phase II Study of BGJ398 in Patients With FGFR-Altered Advanced Cholangiocarcinoma. J. Clin. Oncol. 2018; 36(3):276–282.

3. Soria J-C, Strickler JH, Govindan R et al. Safety and activity of the pan-fibroblast growth factor receptor (FGFR) inhibitor erdafitinib in phase 1 study patients (Pts) with molecularly selected advanced cholangiocarcinoma (CCA). J. Clin. Oncol. 2017; 35(15_suppl):4074.

4. Abou-Alfa GK, Mercade M, Javie M, et al. ClarIDHy: A global, phase 3, randomized double-blind study of ivosidenib (IVO) vs placebo in patients with advanced cholangiocarcinoma (CC) with an isocitrate dehydrogenase 1 (IDH1) mutation. Annals of Oncology. Presented at: ESMO Congress 2019. September 27-October 1, 2019. Barcelona, Spain.

18. Vogel A, Sahai V, Hollebecque A, et al. FIGHT-202: a phase 2 study of pemigatinib in patients (pts) with previously treated locally advanced or metastatic cholangiocarcinoma (CCA). Presented at: 2019 ESMO Congress; September 27-October 1, 2019; Barcelona, Spain. Abstract LBA40.