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NCCN Guidelines Panel: Hepatobiliary

Dear Panel Members,

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.

Specific Changes and Rationale:

1. **Amend the algorithm for intrahepatic cholangiocarcinoma (page INTRA-1) and extrahepatic cholangiocarcinoma (page EXTRA-1) from "Consider additional molecular testing" to "Recommend additional molecular testing" for both unresectable and metastatic disease.**
2. **Indicate in footnote (f) on page INTRA-1 and footnote (j) on page EXTRA-1 that testing should include at least FGFR2 fusions/rearrangements and NTRK fusions/rearrangements performed on assays validated to detect such alterations.**
3. **Add the following to footnote (f) on page INTRA-1 and footnote (j) on page EXTRA-1: "In order to conserve tissue, molecular testing for specific alterations (including *FGFR2* and *NTRK* fusions/rearrangements and *IDH1/2* mutations), microsatellite instability (MSI) status, and tumor mutational burden (TMB) can be achieved via 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).**

CGP can efficiently detect both somatic and germline individual gene alterations (eg *MMR genes, BRCA1/BRCA2, NTRK, FGFR2, IDH1/2),* MSI status, and TMB using a single tumor tissue sample. This allows conservation of tissue while obtaining as much information as possible to inform the use of currently available biomarker driven therapies, immunotherapy, and define/refine clinical trial options, as well as to potentially inform the need for confirmatory germline testing for the patient and their family members when appropriate[1].

FGFR2

FGFR2 fusion or rearrangement is detected in 10-16% of cholangiocarcinoma cases[2-4]. The recently published results of the FIGHT-202 trial demonstrate the antitumor activity of the FGFR-inhibitor, pemigatinib, in patients with known or novel *FGFR2* gene fusions/rearrangements. FIGHT-202, was an international, open-label phase 2 trial evaluating the safety and anti-tumor activity of pemigatinib in 146 previously treated patients with locally advanced or metastatic cholangiocarcinoma. Patients were evaluated for *FGFR2* gene fusions/rearrangements through CGP testing at Foundation Medicine. Of note, patients with both known and novel *FGFR2* fusions/rearrangements were included due to the *FGFR2* fusion partner-agnostic next-generation sequencing CGP test approach in this trial. 107 (9%) of the 1206 prescreened patients had centrally confirmed *FGFR2* fusions or rearrangements. In these 107 patients, 56 different partners were identified, 42 (75%) of which were unique to individual patients. Among patients with *FGFR2* fusions or rearrangements, 38 (36%) achieved an objective response. Three (2.8%) patients had confirmed complete responses and 35 (32.7%) had confirmed partial responses. 88 (82% [95% CI 74–89]) of 107 patients achieved disease control and median duration of response among responders was 7.5 months (95% [CI 5·7–14·5]). No patients with other FGF/FGFR alterations or no FGF/FGFR alterations achieved a response[5]. Based on the results of FIGHT-202, the FDA recently approved the kinase-inhibitor Pemazyre® (pemigatinib) for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (*FGFR2*) fusion or other rearrangement as detected by an FDA-approved test[6]. A CGP assay, **FoundationOne CDx, received simultaneous FDA approval as the first and only companion diagnostic to detect *FGFR2* fusions and rearrangements in patients with cholangiocarcinoma being considered for therapy with pemigatinib[7].**

IDH1/2

IDH1/2 mutations are observed in 18% of cholangiocarcinoma[3]. 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; confidence interval [CI]: 0.25-0.54, P<0.001). The median progression-free survival rate at six months was 32.0% (95% CI 23-42%) and 22% (95% CI 13-32) at 12 months with ivosidenib, while no patients randomized to placebo were free from progression at this timepoint[7].

ERBB2

ERBB2 (*HER2*) mutation or amplification is observed in 3%-9% of cholangiocarcinoma[3,8]. Reported results from the Phase 2 basket study MyPathway (NCT02091141l) include 7 patients with HER2 amplification/overexpression treated with pertuzumab plus trastuzumab; the objective response rate in this cohort was 29%[9]. In the SUMMIT basket study (NCT01953926) 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[10].

MSI

MSI-High status is observed in 1.4% of cholangiocarcinoma cases[11]. The FDA approval of pembrolizumab for patients with MSI-H solid tumors was based on a basket trial that included patients with cholangiocarcinoma[12]. 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)[12]. 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.

TMB

Tumors with high mutational burden have been shown to be associated with response to immunotherapy across multiple cancer types[15]. Recently presented data from KEYNOTE-158 (NCT02628067)showed that tissue tumor mutational burden high (tTMB-high) [≥10 mut/mb] was associated with higher ORR (30.3%;CI 21.5-40.4 vs 6.7%; CI 4.9-9.0) in patients with select advanced solid tumors treated with pembrolizumab monotherapy. The tail of the PFS curve favored the tTMB-high cohort[13]. CGP testing through Foundation Medicine was utilized in KEYNOTE-158 to assess tissue TMB. Based on this study, the FDA has granted priority review of KEYTRUDA monotherapy for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors with tissue tumor mutational burden-high (TMB-H) ≥10 mutations/megabase, as determined by an FDA-approved test, who have progressed following prior treatment and who have no satisfactory alternative treatment options[14].

Clinical Trials

Numerous promising therapeutic approaches are based upon genomic characterization of tumors and therefore many clinical trials require specified genomic alterations for patient enrollment, including trials offered by the NCI (MATCH NCT02465060) and ASCO (TAPUR NCT02693535). Consistent with the NCCN® recommendation to provide patients with opportunities to participate in therapeutic clinical trials, comprehensive genomic profiling assays like FoundationOne® CDx, can potentially match more patients to targeted therapies in clinical trials based on detected alterations. FoundationOne CDx is an approved testing platform for numerous biomarker-driven clinical trials, including NCI-MATCH and ASCO TAPUR, accelerating accrual to these transformative trials using the combination of CGP and clinical trial matching capabilities.

Thank you for your review of this submission.

Sincerely,

Sincerely

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

References

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