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NCCN Clinical Practice Guidelines in Oncology
(NCCN Guidelines®)

Biliary Tract Cancers

Overall management of Biliary Tract Cancers is described in the full NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Biliary Tract Cancers. Visit NCCN.org to view the complete library of NCCN Guidelines®.

NCCN National Comprehensive Cancer Network®

PRINCIPLES OF SYSTEMIC THERAPY[a,k]
TARGETED THERAPY

Primary Treatment for Unresectable and Metastatic Disease

Useful in Certain Circumstances

- **For *NTRK* gene fusion-positive tumors:**
  - **Entrectinib[13,14]**
  - **Larotrectinib[15]**
  - **Repotrectinib[16]**
- **For MSI-H/dMMR tumors:**
  - **Pembrolizumab[g,l,17-20]**
- **For TMB-H tumors:**
  - **Nivolumab + ipilimumab (category 2B)[g,21]**
- **For *RET* gene fusion-positive tumors:**
  - **Pralsetinib (category 2B)[22]**
  - **Selpercatinib (category 2B)[23]**

Subsequent-Line Therapy for Biliary Tract Cancers if Disease Progression[i]

Useful in Certain Circumstances

- **For *NTRK* gene fusion-positive tumors[m]:**
  - **Entrectinib[13,14]**
  - **Larotrectinib[15]**
  - **Repotrectinib[16]**
- **For MSI-H/dMMR tumors:**
  - **Pembrolizumab[g,h,l,17-20]**
  - **Dostarlimab-gxly (category 2B)[g,h,n,24]**
- **For TMB-H tumors:**
  - **Nivolumab + ipilimumab[g,h,o,21]**
  - **Pembrolizumab[g,h,l,17,25]**
- **For *BRAF* V600E-mutated tumors**
  - **Dabrafenib + trametinib[26,27]**
- **For CCA with *FGFR2* fusions or rearrangements[p]:**
  - **Futibatinib[28]**
  - **Pemigatinib[29]**
  - **Erdafitinib[q,30]**
- **For CCA with *IDH1* mutations**
  - **Ivosidenib (category 1)[31,32]**
- **For HER2-positive tumors:**
  - **Fam-trastuzumab deruxtecan-nxki (IHC3+)[33]**
  - **Trastuzumab + pertuzumab (IHC3+/ISH+/NGS amplification)[34]**
  - **Tucatinib + trastuzumab (IHC3+/ISH+/NGS amplification)[35]**
  - **Zanidatamab-hrii (IHC3+)[36]**
- **For *RET* gene fusion-positive tumors:**
  - **Selpercatinib[23]**
  - **Pralsetinib (category 2B)[22]**
- **For *KRAS* G12C mutation-positive tumors:**
  - **Adagrasib[37]**

[a] Order does not indicate preference.
[g] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[h] For patients who have not been previously treated with a checkpoint inhibitor when used as subsequent-line therapy because there is a lack of data for use of immunotherapy in patients who have previously been treated with a checkpoint inhibitor.
[i] Treatment selection depends on clinical factors including previous treatment regimen/agent, somatic molecular testing results, and extent of liver dysfunction.
[k] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[l] There are limited clinical trial data to support pembrolizumab in this setting.
[m] Repotrectinib is an option if there was progression on a prior therapy, which may include prior NTRK inhibitors. Entrectinib and larotrectinib should not be used if there was progression on prior NTRK inhibitors.
[n] Dostarlimab-gxly is a recommended treatment option for patients with MSI-H/dMMR recurrent or advanced tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.
[o] For patients with disease refractory to standard therapies or who have no standard treatment options available.
[p] Futibatinib and pemigatinib are preferred over erdafitinib.
[q] The data available for this agent are from a smaller trial.

References on BIL-C 4 of 5

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SYSTEMIC THERAPY
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Note: All recommendations are category 2A unless otherwise indicated.

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NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

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