

Biliary Tract Cancers¹ Treatment Regimens

Clinical Trials: The NCCN recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced health care team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are provided only to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data become available. The NCCN Guidelines[®] are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines[®] is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

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

► Neoadjuvant Therapy¹

REGIMEN	DOSING
Other Recommended Regimens (no preferred regimens)	
Capecitabine ^{2,4,a}	Days 1-14: Capecitabine 1,250mg/m ² orally twice daily. Repeat cycle every 3 weeks for 8 cycles.
Capecitabine + Oxaliplatin ^{5,a}	Day 1: Oxaliplatin 100-130mg/m ² IV over 2 hours. Days 1-14: Capecitabine 1,000mg/m ² orally twice daily. Repeat cycle every 3 weeks.
Fluorouracil ^{6,a,b}	Days 1-5: Leucovorin 25mg/m ² IV over 2 hours daily, followed by: Days 1-5: Fluorouracil 375mg/m ² IV push over 15 minutes daily. Repeat cycle every 3 or 4 weeks.
Fluorouracil + Oxaliplatin ^{7,8,a-d}	Day 1: Oxaliplatin 85mg/m ² IV over 2 hours, with: Days 1-2: Leucovorin 200mg/m ² IV over 2 hours daily, followed by: Days 1-2: Fluorouracil 400mg/m ² IV push over 15 minutes daily, followed by: Days 1-2: Fluorouracil 600mg/m ² IV continuous infusion over 22 hours daily. Repeat cycle every 2 weeks. OR Day 1: Oxaliplatin 85mg/m ² IV over 2 hours, with: Days 1-2: Leucovorin 500mg/m ² IV over 2 hours daily, followed by: Days 1-2: Fluorouracil 1500-2000mg/m ² IV continuous infusion over 22 hours daily. Repeat cycle every 2 weeks.
Gemcitabine ^{9,12}	Days 1,8,15: Gemcitabine 800-1,000mg/m ² IV over 30 minutes. Repeat cycle every 4 weeks (3 weeks on and 1 week off treatment).
Gemcitabine + Capecitabine ^{13-15,a,e}	Days 1,8: Gemcitabine 1,000mg/m ² IV over 30 minutes. Days 1-14: Capecitabine 750mg/m ² orally twice daily. Repeat cycle every 3 weeks for 4 cycles.
Gemcitabine + Cisplatin ^{9,16-18,f}	Days 1,8: Gemcitabine 1,000mg/m ² IV over 30 minutes. Days 1,8: Cisplatin 25-30mg/m ² IV over 60 minutes. Repeat cycle every 3 weeks OR Days 1,8: Gemcitabine 1,000mg/m ² IV over 30 minutes. Day 1: Cisplatin 70mg/m ² IV over 60 minutes. Repeat cycle every 3 weeks.
Gemcitabine + Cisplatin + Albumin-bound Paclitaxel (Category 2B) ^{19,20,f,g}	Days 1,8: Albumin-bound Paclitaxel 100mg/m ² IV over 30 minutes. Days 1,8: Cisplatin 25mg/m ² IV over 60 minutes. Days 1,8: Gemcitabine 800mg/m ² IV over 30 minutes. Repeat cycle every 3 weeks.
Gemcitabine + Oxaliplatin (Category 2B) ²¹⁻²⁴	Days 1,8: Gemcitabine 1,000mg/m ² IV over 30 minutes Day 1: Oxaliplatin 100mg/m ² IV over 2 hours. Repeat cycle every 3 weeks. OR Days 1,8,15: Gemcitabine 1,000mg/m ² IV over 30 minutes Days 1,15: Oxaliplatin 100mg/m ² IV over 2 hours. Repeat cycle every 4 weeks. OR Day 1: Gemcitabine 1,000mg/m ² IV over 30 minutes. Day 2: Oxaliplatin 100mg/m ² IV over 2 hours. Repeat cycle every 2 weeks. OR Days 1,8: Gemcitabine 900mg/m ² IV over 30 minutes. Days 1,8: Oxaliplatin 80mg/m ² IV over 2 hours. Repeat cycle every 3 weeks.

continued

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► Adjuvant Therapy^{1,25}

REGIMEN	DOSING
Preferred Regimens	
Capecitabine (Category 1) ^{2-4,a}	Days 1-14: Capecitabine 1,250mg/m ² orally twice daily. Repeat cycle every 3 weeks for 8 cycles.
Other Recommended Regimens	
Capecitabine + Cisplatin (Category 3) ^{25,26,a,f}	Day 1: Cisplatin 60mg/m ² IV over 60 minutes. Days 1-14: Capecitabine 1,250mg/m ² orally twice daily. Repeat cycle every 3 weeks.
Capecitabine + Oxaliplatin ^{5,a}	Day 1: Oxaliplatin 100-130mg/m ² IV over 2 hours. Days 1-14: Capecitabine 1,000mg/m ² orally twice daily. Repeat cycle every 3 weeks.
Fluorouracil ^{6,a,b}	Days 1-5: Leucovorin 25mg/m ² IV over 2 hours daily, followed by: Days 1-5: Fluorouracil 375mg/m ² IV push over 15 minutes daily. Repeat cycle every 3 or 4 weeks.
Fluorouracil + Oxaliplatin ^{7,8,a-d}	Day 1: Oxaliplatin 85mg/m ² IV over 2 hours, with: Days 1-2: Leucovorin 200mg/m ² IV over 2 hours daily, followed by: Days 1-2: Fluorouracil 400mg/m ² IV push over 15 minutes daily, followed by: Days 1-2: Fluorouracil 600mg/m ² IV continuous infusion over 22 hours daily. Repeat cycle every 2 weeks. OR Day 1: Oxaliplatin 85mg/m ² IV over 2 hours, with: Days 1-2: Leucovorin 500mg/m ² IV over 2 hours daily, followed by: Days 1-2: Fluorouracil 1500-2000mg/m ² IV continuous infusion over 22 hours daily. Repeat cycle every 2 weeks.
Gemcitabine ⁹⁻¹²	Days 1,8,15: Gemcitabine 800-1,000mg/m ² IV over 30 minutes. Repeat cycle every 4 weeks.
Gemcitabine + Capecitabine ^{13-15,a,e}	Days 1,8: Gemcitabine 1,000mg/m ² IV over 30 minutes. Days 1-14: Capecitabine 750mg/m ² orally twice daily. Repeat cycle every 3 weeks for 4 cycles.
Gemcitabine + Cisplatin ^{9,16-18,f}	Days 1,8: Gemcitabine 1,000mg/m ² IV over 30 minutes. Days 1, 8: Cisplatin 25-30mg/m ² IV over 60 minutes. Repeat cycle every 3 weeks. OR Days 1,8: Gemcitabine 1,000mg/m ² IV over 30 minutes. Day 1: Cisplatin 70mg/m ² IV over 60 minutes. Repeat cycle every 3 weeks.

► Agents Used with Concurrent Radiation

Capecitabine ^{4,15,27,a,b,h}	On the days of radiation: Capecitabine 800-900mg/m ² orally twice daily. OR Days 1-7 (weekly cycle with concurrent radiation): Capecitabine 665mg/m ² orally twice daily.
Fluorouracil ^{28,29,b}	Days 1-3, 29-31: Fluorouracil 500mg/m ² IV push daily. Administer for one 5-week cycle with concurrent radiation.

► Primary Treatment for Unresectable and Metastatic Disease

Preferred Regimens	
Gemcitabine + Cisplatin (Category 1) ^{9,16-18,f}	Days 1, 8: Gemcitabine 1,000mg/m ² IV over 30 minutes. Days 1, 8: Cisplatin 25-30mg/m ² IV over 60 minutes. Repeat cycle every 3 weeks. OR Days 1,8: Gemcitabine 1,000mg/m ² IV over 30 minutes. Day 1: Cisplatin 70mg/m ² IV over 60 minutes. Repeat cycle every 3 weeks.

continued

Biliary Tract Cancers¹ Treatment Regimens

► Primary Treatment for Unresectable and Metastatic Disease (continued)

REGIMEN	DOSING
Other Recommended Regimens	
Capecitabine ^{2-4,a}	Days 1-14: Capecitabine 1,000mg/m ² orally twice daily. Repeat cycle every 3 weeks.
Capecitabine + Cisplatin (Category 2B) ^{26,a,f}	Day 1: Cisplatin 60mg/m ² IV over 60 minutes. Days 1-14: Capecitabine 1,250mg/m ² orally twice daily. Repeat cycle every 3 weeks.
Capecitabine + Oxaliplatin ^{5,a}	Day 1: Oxaliplatin 100-130mg/m ² IV over 2 hours. Days 1-14: Capecitabine 1,000mg/m ² orally twice daily. Repeat cycle every 3 weeks.
Fluorouracil ^{6,a,b}	Days 1-5: Leucovorin 25mg/m ² IV over 2 hours daily, followed by: Days 1-5: Fluorouracil 375mg/m ² IV push over 15 minutes daily. Repeat cycle every 3 or 4 weeks.
Fluorouracil + Cisplatin (Category 2B) ^{30,31,a,b,d,f}	Days 1,4: Cisplatin 3-6mg/m ² IV over 30 minutes Days 1-7: Fluorouracil 160mg/m ² IV continuous infusion over 24 hours daily (1,120mg/m ² IV over 1 week). Repeat cycle every week. OR Days 1, 15, 29: Cisplatin 50mg/m ² IV over 60 minutes Days 1,8,15,22,29,36: Leucovorin 500mg/m ² IV over 2 hours, followed by: Days 1,8,15,22,29,36: Fluorouracil 2,000mg/m ² IV over 24 hours. Repeat cycle every 7 weeks (6 weeks on followed by 1 week off treatment).
Fluorouracil + Oxaliplatin ^{7,8,a,d}	Day 1: Oxaliplatin 85mg/m ² IV over 2 hours, with: Days 1-2: Leucovorin 200mg/m ² IV over 2 hours daily, followed by: Days 1-2: Fluorouracil 400mg/m ² IV push over 15 minutes daily, followed by: Days 1-2: Fluorouracil 600mg/m ² IV continuous infusion over 22 hours daily. Repeat cycle every 2 weeks. OR Day 1: Oxaliplatin 85mg/m ² IV over 2 hours, with: Days 1-2: Leucovorin 500mg/m ² IV over 2 hours daily, followed by: Days 1-2: Fluorouracil 1500-2000mg/m ² IV continuous infusion over 22 hours daily. Repeat cycle every 2 weeks.
Gemcitabine ⁹⁻¹²	Days 1,8,15: Gemcitabine 800-1,000mg/m ² IV over 30 minutes. Repeat cycle every 4 weeks.
Gemcitabine + Albumin-bound Paclitaxel ^{13,2,g}	Days 1,8,15: 125mg/m ² IV over 30 minutes. Days 1,8,15: 1,000mg/m ² IV over 30 minutes. Repeat cycle every 4 weeks.
Gemcitabine + Capecitabine ^{13-15,a,e}	Days 1,8: Gemcitabine 1,000mg/m ² IV over 30 minutes Days 1-14: Capecitabine 650mg/m ² orally twice daily Repeat cycle every 3 weeks.
Gemcitabine + Cisplatin + Albumin-bound Paclitaxel (Category 2B) ^{19,20,f,g}	Days 1,8: Albumin-bound Paclitaxel 100mg/m ² IV over 30 minutes. Days 1,8: Cisplatin 25mg/m ² IV over 60 minutes. Days 1,8: Gemcitabine 800mg/m ² IV over 30 minutes. Repeat cycle every 3 weeks.
Gemcitabine + Oxaliplatin ²¹⁻²⁴	Days 1,8: Gemcitabine 1,000mg/m ² IV over 30 minutes. Day 1: Oxaliplatin 100mg/m ² IV over 2 hours. Repeat cycle every 3 weeks. OR Days 1,8,15: Gemcitabine 1,000mg/m ² IV over 30 minutes. Days 1,15: Oxaliplatin 100mg/m ² IV over 2 hours. Repeat cycle every 4 weeks. OR Day 1: Gemcitabine 1,000mg/m ² IV over 30 minutes. Day 2: Oxaliplatin 100mg/m ² IV over 2 hours. Repeat cycle every 2 weeks. OR Days 1,8: Gemcitabine 900mg/m ² IV over 30 minutes. Days 1,8: Oxaliplatin 80mg/m ² IV over 2 hours. Repeat cycle every 3 weeks.

continued

Biliary Tract Cancers¹ Treatment Regimens

► Primary Treatment for Unresectable and Metastatic Disease (continued)

REGIMEN	DOSING
Useful in Certain Circumstances	
Entrectinib (<i>NTRK</i> gene fusion-positive tumors) ³³⁻³⁶	Days 1-28: Entrectinib 600mg orally once daily. Repeat cycle every 4 weeks.
Larotrectinib (<i>NTRK</i> gene fusion-positive tumors) ^{37,38}	Days 1-28: Larotrectinib 100mg orally twice daily. Repeat cycle every 4 weeks.
Pembrolizumab (MSI-H/MMR tumors) ^{39-46,i,j}	Day 1: Pembrolizumab 200mg IV over 30 minutes Repeat cycle every 3 weeks for up to 2 years. OR Day 1: Pembrolizumab 400mg IV over 30 minutes Repeat cycle every 6 weeks for up to 2 years.

► Subsequent-Line Therapy for Biliary Tract Cancers if Disease Progression^{k,l}

Preferred Regimens	
FOLFOX ^{78,47,a-d}	Day 1: Oxaliplatin 85mg/m ² IV over 2 hours, with: Days 1-2: Leucovorin 200mg/m ² IV over 2 hours daily, followed by: Days 1-2: Fluorouracil 400mg/m ² IV push over 15 minutes daily, followed by: Days 1-2: Fluorouracil 600mg/m ² IV continuous infusion over 22 hours daily. Repeat cycle every 2 weeks. OR Day 1: Oxaliplatin 85mg/m ² IV over 2 hours, with: Days 1-2: Leucovorin 500mg/m ² IV over 2 hours daily, followed by: Days 1-2: Fluorouracil 1500-2000mg/m ² IV continuous infusion over 22 hours daily. Repeat cycle every 2 weeks.
Other Recommended Regimens	
FOLFIRI (Category 2B) ^{48-50,a,b,d,m}	Day 1: Irinotecan 180mg/m ² IV over 30-90 minutes, with: Day 1: Leucovorin 400mg/m ² IV over 30-90 minutes, followed by: Day 1: Fluorouracil 400mg/m ² IV push, followed by: Days 1,2: Fluorouracil 1,200mg/m ² IV continuous infusion daily (2,400mg/m ² IV over 46-48 hours). Repeat cycle every 2 weeks.
Regorafenib (Category 2B) ^{51,52}	Days 1-21: Regorafenib 120mg orally once daily. Repeat cycle every 4 weeks.
Useful in Certain Circumstances^m	
Dabrafenib + Trametinib (<i>BRAF</i> -V600E mutated tumors) ⁵³⁻⁵⁶	Days 1-28: Dabrafenib 150mg orally twice daily. Days 1-28: Trametinib 2mg orally once daily. Repeat cycle every 4 weeks.
Entrectinib (<i>NTRK</i> gene fusion-positive tumors) ³³⁻³⁶	Days 1-28: Entrectinib 600mg orally once daily. Repeat cycle every 4 weeks.
Infigratinib (for cholangiocarcinoma with <i>FGFR2</i> fusions or rearrangements) ^{57,58}	Days 1-21: Infigratinib 125mg orally once daily. Repeat cycle every 4 weeks.
Ivosidenib (for cholangiocarcinoma with <i>IDH1</i> mutations) ^{59,60,n}	Days 1-28: Ivosidenib 500mg orally once daily. Repeat cycle every 4 weeks.
Larotrectinib (<i>NTRK</i> gene fusion-positive tumors) ^{37,38}	Days 1-28: Larotrectinib 100mg orally twice daily. Repeat cycle every 4 weeks.
Lenvatinib + Pembrolizumab (Category 2B) ^{61,62}	Days 1-21: Lenvatinib 20mg orally once daily. Days 1-21: Pembrolizumab 200mg IV over 30 minutes. Repeat cycle every 3 weeks up to 2 years.
Nivolumab (Category 2B) ^{63,64}	Day 1: Nivolumab 240mg IV over 30 minutes. Repeat cycle every 2 weeks for 16 weeks, followed by: Day 1 (Week 16): Nivolumab 480mg IV over 30 minutes. Repeat cycle every 4 weeks.

continued

Biliary Tract Cancers¹ Treatment Regimens

► Subsequent-Line Therapy for Biliary Tract Cancers if Disease Progression^{k,l} (continued)

REGIMEN	DOSING
Useful in Certain Circumstances^m (continued)	
Pembrolizumab (MSI-H/MMR tumors/ TMB-H tumors)^{39-46,i,j}	Day 1: Pembrolizumab 200mg IV over 30 minutes. Repeat cycle every 3 weeks up to 2 years. OR Day 1: Pembrolizumab 400mg IV over 30 minutes Repeat cycle every 6 weeks up to 2 years.
Pemigatinib (for cholangiocarcinoma with FGFR2 fusions or rearrangements)^{65,66,n}	Days 1-14: Pemigatinib 13.5mg orally once daily. Repeat cycle every 3 weeks.

^a Patients with dihydropyrimidine dehydrogenase (DPD) deficiency are unable to metabolize Capecitabine or Fluorouracil normally and may have severe unexpected toxicity.

^b The dose listed above is based on racemic leucovorin product. LEVOleucovorin is not interchangeable, and the product doses are not equivalent.

^c Leucovorin infusion time should match the infusion time of Oxaliplatin when these agents are given concurrently.

^d Fluorouracil IV requires a central venous access device for administration in this regimen.

^e Given before concurrent chemotherapy/radiation (Capecitabine/radiation).

^f Hydration is required with supplemental electrolytes pre- and post-administration of Cisplatin.

^g Albumin-bound PAclitaxel may have altered functional properties relative to standard PAclitaxel. Do not substitute for or with other PAclitaxel formulations. Product doses are not equivalent.

^h Given after 4 cycles of chemotherapy with Gemcitabine/Capecitabine.

ⁱ MSI-H/MMR = Microsatellite instability high/mismatch repair deficient; TMB-H = Tumor mutational burden-high.

^j There are limited clinical trial data to support pembrolizumab in this setting.

^k See also: Preferred and Other Recommended Regimens for Unresectable and Metastatic Disease above.

^l Treatment selection depends on clinical factors including previous treatment regimen/agent and extent of liver dysfunction.

^m Patients who are homozygous for the UGT1A1*28 allele or who have a clinical diagnosis of Gilbert's Syndrome have an increased risk of neutropenia when started on irinotecan, possibly due to a decreased level of glucuronidation of the active metabolite of irinotecan, resulting in its accumulation.

ⁿ Do not administer with a high fat meal.

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