

Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up

SUPPLEMENTARY MATERIAL

Supplementary Table S1. Biomarkers and molecular targets for precision medicines and corresponding ESCAT scores

Biomarker or genomic alteration	Frequency^a	Method of detection	Drug match	ESCAT score^{b,c}
<i>IDH1</i> mutations ¹⁻⁶	1%-18% (8%-18% iCCA)	NGS	IDH1 inhibitors (e.g. ivosidenib)	I-A ³
<i>IDH2</i> mutations ^{4,6-8}	<5% (<5% iCCA)	NGS	IDH2 inhibitors (e.g. enasidinib)	III-A ⁹
<i>FGFR2</i> fusions ^{2,4,6,10,11}	<10% (5%-15% iCCA)	RNA sequencing	FGFR inhibitors (e.g. pemigatinib, infigratinib)	I-B ^{12,13}
<i>FGFR2</i> mutations ^{2,6,11,14,15}	2% (2% iCCA)	NGS	FGFR inhibitors (e.g. derazantinib, erdafinib)	II-B ^{16,17}
<i>HER2</i> amplifications ^{2,4,6,18-20}	5%-10% (10%-20% dCCA, pCCA, GBC)	NGS, FISH, IHC	Anti-HER2 antibodies (e.g. pertuzumab, trastuzumab)	I-C ²⁰

<i>HER2</i> mutations ^{2,4,6,15,19,21}	3%-5% (more frequent in dCCA, pCCA, GBC)	NGS	Anti-HER2 antibodies (e.g. trastuzumab)	II-B ²⁰
<i>BRAF</i> ^{V600E} mutations ^{2,4-6,15,19,22}	<5% (50% V600E)	NGS	BRAF inhibitors (e.g. dabrafenib) and MEK inhibitors (e.g. trametinib)	I-B ²²
<i>BRCA1/2</i> mutations ^{4-6,19,23-27}	3%-5%	NGS	PARP inhibitors (e.g. olaparib)	III-A ²⁸
<i>PALB2</i> mutations ^{6,25-27}	1%	NGS	PARP inhibitors (e.g. rucaparib)	III-A ²⁹
<i>KRAS</i> ^{G12C4,30}	<1%	NGS	<i>KRAS</i> ^{G12C} inhibitors (e.g. adagrasib)	I-C ³⁰
<i>NTRK</i> fusions ^{6,31}	<1%	RNA sequencing	<i>NTRK</i> inhibitors (e.g. larotrectinib, entrectinib)	I-C ^{31,32 d}
MSI ^{2,4-6}	<1%	IHC	ICIs (e.g. pembrolizumab)	I-C ^{33 e}

dCCA, distal cholangiocarcinoma; dMMR, mismatch repair deficiency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FGFR2, fibroblast growth factor receptor 2; GBC, gallbladder carcinoma; HER2, human epidermal growth factor receptor 2; iCCA, intrahepatic cholangiocarcinoma; ICI, immune checkpoint inhibitor; IDH, isocitrate dehydrogenase 1; IHC, immunohistochemistry; MSI, microsatellite instability; MSI-H, microsatellite instability-high; NGS, next-generation sequencing;

NTRK, neurotrophic tyrosine receptor kinase; PALB2, partner and localiser of BRCA2; PARP, poly (ADP-ribose) polymerase; pCCA, perihilar cholangiocarcinoma.

^a There is substantial heterogeneity across studies in terms of molecular testing methodology and patient population, which limit the precision of these estimates.

^b ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.

^c I-A, alteration–drug match is associated with improved outcome with evidence from randomised clinical trials showing the alteration–drug match in a specific tumour type results in a clinically meaningful improvement of a survival endpoint; I-B, alteration–drug match is associated with improved outcome with evidence from prospective, nonrandomised clinical trials showing that the alteration–drug match in a specific tumour type results in clinically meaningful benefit as defined by ESMO-MCBS v1.1; I-C, alteration–drug match is associated with improved outcome with evidence from clinical trials across tumour types or basket clinical trials showing clinical benefit associated with the alteration–drug match, with similar benefit observed across tumour types; II-B, alteration–drug match is associated with antitumour activity, with evidence from prospective clinical trials showing the alteration–drug match in a specific tumour type results in increased responsiveness when treated with a matched drug, however, no data are currently available on survival endpoints; III-A, alteration–drug match is suspected to improve outcome based on patients with the specific alteration but in a different tumour type, with limited/absence of clinical evidence available for the patient-specific cancer type or broadly across cancer types.⁵

^d Larotrectinib and entrectinib are approved for the treatment of solid tumours that display an *NTRK* gene fusion in patients with locally advanced/metastatic disease or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options.

^e Pembrolizumab is approved for the treatment of MSI-H or dMMR tumours in adults with unresectable or metastatic biliary cancer, who have disease progression on or following at least one prior therapy.

Supplementary Table S2. TNM staging of CCA and GBC according to the UICC 8th Edition^{34-37 a}

CCA						GBC	
iCCA		pCCA		dCCA			
Primary tumour (T)		Primary tumour (T)		Primary tumour (T)		Primary tumour (T)	
TX	Primary tumour cannot be assessed	TX	Primary tumour cannot be assessed	TX	Primary tumour cannot be assessed	TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour	T0	No evidence of primary tumour	T0	No evidence of primary tumour	T0	No evidence of primary tumour
Tis	Carcinoma <i>in situ</i> (intraductal tumour)	Tis	Carcinoma <i>in situ</i>	Tis	Carcinoma <i>in situ</i>	Tis	Carcinoma <i>in situ</i>
T1a	Solitary tumour ≤5 cm in greatest dimension without vascular invasion	T1	Tumour confined to the bile duct, with extension up to the muscle layer or fibrous tissue	T1	Tumour invades bile duct wall to a depth <5 mm	T1	Tumour invades lamina propria or muscular layer
T1b	Solitary tumour >5 cm in greatest dimension without vascular invasion	T2a	Tumour invades beyond the wall of the bile duct to surrounding adipose tissue	T2	Tumour invades bile duct wall to a depth of 5-12 mm	T1a	Tumour invades lamina propria

T2	Solitary tumour with intrahepatic vascular invasion <i>or</i> multiple tumours, with or without vascular invasion	T2b	Tumour invades adjacent hepatic parenchyma	T3	Tumour invades bile duct wall to a depth of >12 mm	T1b	Tumour invades muscular layer
T3	Tumour perforating the visceral peritoneum	T3	Tumour invades unilateral branches of the portal vein or hepatic artery	T4	Tumour involves the coeliac axis, the superior mesenteric artery and/or the common hepatic artery	T2	Tumour invades perimuscular connective tissue; no extension beyond serosa or into liver
T4	Tumour involving local extrahepatic structures by direct hepatic invasion	T4	Tumour invades the main portal vein or its branches bilaterally; or the common hepatic artery; or unilateral second order biliary radicals with contralateral			T2a	Tumour invades perimuscular connective tissue on the peritoneal side with no extension to the serosa

			portal vein or hepatic artery involvement				
						T2b	Tumour invades perimuscular connective tissue on the hepatic side with no extension into the liver
						T3	Tumour perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as stomach, duodenum, colon, pancreas, omentum, extrahepatic bile ducts
						T4	Tumour invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures

Regional lymph nodes (N)		Regional lymph nodes (N)		Regional lymph nodes (N)		Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed	NX	Regional lymph nodes cannot be assessed	NX	Regional lymph nodes cannot be assessed	NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis	N0	No regional lymph node metastasis	N0	No regional lymph node metastasis	N0	No regional lymph node metastasis
N1	Regional lymph node metastasis	N1	Metastases to 1-3 regional lymph nodes	N1	Metastases to 1-3 regional lymph nodes	N1	Metastases to 1-3 regional lymph nodes
		N2	Metastasis to ≥ 4 regional lymph nodes	N2	Metastasis to ≥ 4 regional lymph nodes	N2	Metastasis to ≥ 4 regional lymph nodes
Distant metastasis (M)		Distant metastasis (M)		Distant metastasis (M)		Distant metastasis (M)	
M0	No distant metastasis	M0	No distant metastasis	M0	No distant metastasis	M0	No distant metastasis
M1	Distant metastasis	M1	Distant metastasis	M1	Distant metastasis	M1	Distant metastasis

CCA, cholangiocarcinoma; dCCA, distal cholangiocarcinoma; GBC, gallbladder carcinoma; iCCA, intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma; TNM, tumour–node–metastasis; UICC, Union for International Cancer Control.

^a Reproduced from Brierley et al.³⁴⁻³⁷ with permission.

Supplementary Table S3. Anatomic stage/prognostic groups for CCA and GBC according to the UICC 8th Edition^{34-37 a}

CCA												GBC			
iCCA				pCCA				dCCA							
Stage I	T1	N0	M0	Stage 0	Tis	N0	M0	Stage 0	Tis	N0	M0	Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0	Stage I	T1	N0	M0	Stage I	T1	N0	M0	Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0	Stage II	T2a	N0	M0	Stage IIA	T1	N1	M0	Stage IB	T1b	N0	M0
					T2b	N0	M0		T2	N0	M0				
Stage II	T2	N0	M0	Stage IIIA	T3	N0	M0	Stage IIB	T2	N1	M0	Stage IIA	T2a	N0	M0
									T3	N0	M0				
									T3	N1	M0				
Stage IIIA	T3	N0	M0	Stage IIIB	T4	N0	M0	Stage IIIA	T1	N2	M0	Stage IIB	T2b	N0	M0
									T2	N2	M0				
									T3	N2	M0				
Stage IIIB	T4	N0	M0	Stage IIIC	Any T	N1	M0	Stage IIIB	T4	Any N	M0	Stage IIIA	T3	N0	M0
	Any T	N1													
Stage IV	Any T	Any N	M1	Stage IVA	Any T	N2	M0	Stage IV	Any T	Any N	M1	Stage IIIB	T1	N1	M0
													T2	N1	M0
													T3	N1	M0
				Stage IVB	Any T	Any N	M1					Stage IVA	T4	N0	M0
													T4	N1	M0
												Stage IVB	Any T	N2	M0

Supplementary Table S4. Bismuth–Corlette classification of pCCA^{38 a}

Type I	Tumour involves the common hepatic duct
Type II	Tumour involves the bifurcation of the common hepatic duct
Type IIIa	Tumour involves the right hepatic duct
Type IIIb	Tumour involves the left hepatic duct
Type IV	Tumour involves both the right and left hepatic ducts

pCCA, perihilar cholangiocarcinoma.

^a Reproduced from Bismuth and Corlette³⁸ with permission.

Supplementary Table S5. ESMO-MCBS table for therapies/indications in biliary tract cancer

Therapy	Disease setting	Trial	Control	Absolute survival gain	HR (95% CI)	QoL/toxicity	ESMO-MCBS score ^a
Dabrafenib–trametinib ^b	Adult and pediatric patients ≥6 years of age with unresectable or metastatic solid tumors with <i>BRAF V600E</i> mutation who have progressed following prior treatment and have no satisfactory alternative	ROAR ²² Phase II NCT02034110	Single arm	ORR: 51% Median DoR: 9 months Median PFS: 9 months Median OS: 14 months			3 (Form 3)

	treatment options Biliary tract cancer cohort						
Durvalumab–gemcitabine–cisplatin ^b	Adult patients with locally advanced or metastatic biliary tract cancer	TOPAZ-1 ³⁹ Phase III NCT03875235	Gemcitabine–cisplatin Median PFS: 5.7 months Median OS: 11.5 months	PFS gain: 1.5 months OS gain: 1.3 months 2-year OS gain: 14.5% ^c	PFS: 0.75 (0.63-0.89) OS: 0.80 (0.66-0.97)		4 (Form 2a)
FOLFOX ^d	Second-line treatment of advanced biliary tract cancer	ABC-06 ⁴⁰ Phase III	Symptomatic care				1 (Form 2a)

		NCT01926236	Median OS: 5.3 months	OS gain: 0.9 months	OS: 0.69 (0.50-0.97)		
Infigratinib ^b	Previously treated, unresectable locally advanced or metastatic CCA with an <i>FGFR2</i> fusion or other rearrangement	CBGJ398X2204 ^{13,41} Phase II NCT02150967	Single arm	ORR: 23.1% Median DoR: 5.0 months Median PFS: 7.3 months			3 (Form 3)
Ivosidenib ^b	Locally advanced or metastatic CCA with a susceptible <i>IDH1</i> mutation that has been previously treated	ClarIDHy ^{3,42} Phase III NCT02989857	Placebo Median PFS: 1.4 months	PFS gain: 1.3 months >10% plateau in the tail of the PFS curve	PFS: 0.37 (0.25-0.54)	No global QoL benefit	2 (Form 2b)

Pembrolizumab	Treatment of MSI-H or dMMR tumours in adults with unresectable or metastatic biliary cancer, who have disease progression on or following at least one prior therapy	KEYNOTE-158 ³³ Phase II NCT02628067	Single arm	ORR: 40.90% Median PFS: 4.2 months Median DoR: Not reached (range: 4.1- 24.9)			2 (Form 3)
Pemigatinib	Locally advanced or metastatic CCA with an <i>FGFR2</i> fusion or rearrangement that has progressed after	FIGHT-202 ¹² Phase II NCT02924376	Single arm	ORR: 35.5% Median DoR: 7.5 months			3 (Form 3)

	at least one prior line of systemic therapy			Median PFS: 6.9 months			
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CCA, cholangiocarcinoma; CI, confidence interval; dMMR, mismatch repair deficiency; DoR, duration of response; EMA, European Medicines Agency; ESMO-MCBS, ESMO-Magnitude of Clinical Benefit Scale; FDA, Food and Drug Administration; FGFR2, fibroblast growth factor receptor 2; FOLFOX, folinic acid–fluorouracil–oxaliplatin; HR, hazard ratio; IDH1, isocitrate dehydrogenase-1; MSI-H, microsatellite instability-high; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life.

^a ESMO-MCBS v1.1⁴³ was used to calculate scores for new therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (<https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms>).

^b FDA approved but not EMA approved in this setting.

^c The 2-year OS gain reported was based on 9 patients (2.6% of the experimental group) who were still alive at that time.

^d Regimen without a specific licensed indication in biliary cancer.

**Supplementary Table S6. Levels of evidence and grades of recommendation
(adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System^a)**

Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinions

Grades of recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

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