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**Diagnosis and treatment of cholangiocarcinoma in Italy: a Delphi consensus
statement**

Abstract

Background: Clinical practice guidelines for the management of cholangiocarcinoma (CCA)/biliary tract cancer recommend genomic profiling to guide treatment decisions. Variable access to such profiling across Italy means many oncologists are unfamiliar with when and how to conduct genetic testing and prescribe targeted treatments.

Methods: A Scientific Board of Italian oncologists who treat CCA (the authors) developed recommendations, based on recent clinical evidence, for using molecular testing in diagnosing, assessing, and treating CCA in Italy. The Delphi process was used to reach consensus on these recommendations among 38 Italian oncologists. Consensus was considered to be met if $\geq 66.7\%$ of the panel agreed or strongly agreed with each statement.

Findings: Consensus was reached on 28 statements across four themes: (1) epidemiology and risk factors; (2) diagnosis, including molecular diagnosis; (3) treatment selection; and (4) treatment safety.

Interpretation: These recommendations should aid Italian clinicians in selecting appropriate treatment options for their patients.

Key words: biliary tract cancer, cholangiocarcinoma, Delphi consensus, gene expression profile, molecular targeted therapies

1. Introduction

Cholangiocarcinoma (CCA) is a cancer that arises from the biliary tree, whereas biliary tract cancers that arise from the gallbladder or cystic duct are referred to as gall bladder carcinomas (Vogel et al., 2023). CCAs are generally classified as intrahepatic (iCCA; i.e. those occurring in the bile ducts that are proximal to second-order ducts) or extrahepatic (i.e. those occurring between the second-order ducts and the Ampulla of Vater) (Valle et al., 2021). Extrahepatic CCAs (eCCAs) are further classified as either perihilar (pCCA) or ductal (dCCA) (Cholangiocarcinoma Working Group, 2020). pCCAs arise between the second-order ducts and the insertion of the cystic duct, while dCCAs develop in the epithelium distal to the cystic duct.

CCA remains a relatively rare gastrointestinal cancer in most industrialised countries, although its incidence is increasing, mostly because of the intrahepatic component (Valle et al., 2021).

The rise in iCCA numbers has been ascribed in part to better diagnostic tools (including the recent resolution on the misclassification of iCCA in the ICD-11 coding), in part to the increased incidence of chronic liver diseases, and also in part to changes in the environmental risk factors (Khan et al., 2019).

For many years, the prognosis of patients with advanced or metastatic CCA remained poor, and treatment options were limited to surgery (where possible), conventional chemotherapy and locoregional treatments, such as radioembolisation and radiofrequency ablation, or a combination thereof (Brandi et al., 2020; Edeline et al., 2020; Koch et al., 2020; Valle et al., 2021). In recent years, targeted therapies have demonstrated favourable improvements in the survival of CCA patients with relevant gene alterations, including ivosidenib in patients with isocitrate dehydrogenase-1 (*IDH1*) mutations (Abou-Alfa et al., 2020a), pemigatinib, infigratinib, and futibatinib in patients with fibroblast growth factor receptor-2 (*FGFR2*) fusions or rearrangements (Abou-Alfa et al., 2020b; Goyal et al., 2023; Javle et al., 2021b), pertuzumab

and trastuzumab in patients with human epidermal growth factor receptor 2 (*HER2*) amplifications or mutations (Javle et al., 2021a), and dabrafenib and trametinib in patients with v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*)^{V600E} mutations (Subbiah et al., 2020). Other targeted therapies that have demonstrated anti-tumour activity in patients with solid tumours include neurotrophic receptor tyrosine kinase (*NTRK*) inhibitors, such as entrectinib and larotrectinib (Zhang et al., 2022). Furthermore, additional genomic alterations in patients with CCAs (and their associated targeted therapies) have been potentially identified, and include BReast CAncer gene (*BRCA*)1/2 mutations (olaparib), partner and localiser of *BRCA2* (*PALB2*) mutations (rucaparib), kirsten rat sarcoma virus (*KRAS*) G12C mutations (adagrasib) and microsatellite instability (MSI; pembrolizumab) (Vogel et al., 2023).

Putatively targetable genetic alterations are common in CCA (45–48% of patients) (Lowery et al., 2018; Silverman et al., 2021). In this respect, the prevalence of targetable mutations in CCA is lower than in melanoma or lung adenocarcinoma, similar to the prevalence in colorectal cancer and breast cancer, and higher than in many other common solid tumours including gastric cancer, ovarian or uterine cancer, clear-cell renal cell carcinoma, squamous cell carcinoma of the lung, head and neck cancer, thyroid cancer and bladder cancer (Dienstmann et al., 2015). Moreover, some CCA patients harbour more than one type of targetable genetic alteration (Javle et al., 2016; Silverman et al., 2021). Therefore, the European Society for Medical Oncology (ESMO) guideline on the management of biliary tract cancer now recommends molecular testing for patients with advanced disease eligible for systemic treatment, to identify potentially targetable genetic alterations (Vogel et al., 2023). This guideline provides a comprehensive list of targetable alterations based on the ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) (Vogel et al., 2023).

Several targeted therapies have been approved for use in patients with CCA in the United States (US) (pemigatinib, infigratinib, futibatinib and ivosidenib), the European Union (EU)

(pemigatinib) and the United Kingdom (UK) (pemigatinib), and for use in MSI-high or mismatch repair deficient (dMMR) tumours, both of which include CCAs (pembrolizumab) (**Table 1**). The IDH1 inhibitor ivosidenib has received a positive opinion from the European Medicine Agency's (EMA) Committee for Medicinal Products for Human Use for the treatment of locally advanced or metastatic CCA (European Medicines Agency, 2023), and approval is expected soon. Targeted agents that have been granted orphan drug status in the EU include futibatinib (FGFR1–4 inhibitor) and zanidatamab (HER2-targeted monoclonal antibody), which are available in Italy under named patient or expanded access programmes. Pemigatinib is the only reimbursed targeted therapy for CCA in Italy, indicated for adults with locally advanced or metastatic CCA with *FGFR2* fusions or rearrangements who have progressed after at least one previous line of systemic therapy. Tumour-agnostic targeted agents that could be used in patients with CCA with the relevant gene alterations that are approved in Italy (and other EU countries), as well as the UK and US, include the NTRK1-3 receptor tyrosine kinase inhibitors entrectinib and larotrectinib (**Table 1**).

The current Italian guidelines on CCA recommend molecular profiling be performed for patients who are to be treated with targeted therapies, or if required for enrolment of patients into clinical trials, but do not currently recommend profiling at diagnosis (Associazione Italiana per lo Studio del Fegato (AISF) et al.). Expert guidelines on molecular testing from the Federation of Italian Cooperative Oncology Groups (FICOG) and the Istituto Superiore di Sanità (ISS) recommend molecular profiling using next-generation sequencing (NGS) for a number of cancers, including CCA, and advise that this be conducted on the most recent available tumour sample (whether at diagnosis or later) (Pinto et al., 2021). They further specify that NGS should be conducted prior to starting first-line therapy when targeted therapies are available for a particular cancer (Pinto et al., 2021).

Because access to tumour gene profiling is limited in Italy, the majority of Italian oncologists

have not adopted molecular analysis into their routine clinical practice and have to rely exclusively on tumour/node/metastasis (TNM) staging – without the added knowledge of the tumour’s genomic profile – to make clinical treatment decisions (Pinto et al., 2021). In our experience, many Italian oncologists may also be unfamiliar with when and how to implement targeted therapies and genetic testing for CCA in clinical practice. Therefore, our aim was to use a Delphi process to develop consensus recommendations around the use of molecular testing in the diagnosis, assessment, and treatment of CCA, in the Italian clinical setting.

2. Methods

A Scientific Board of five individuals, who are either clinicians treating patients with CCA or experienced molecular biologists, from main Italian oncology treatment centres in Bologna, Naples, Milan, and Verona was established; all five are the authors of this consensus statement. An initial web-based meeting of the Scientific Board was held on October 5th, 2021 to define the scope of the consensus statement, and the parameters for the literature search. Four key topics related to advanced CCA were identified: (1) epidemiology and risk factors; (2) diagnosis, including molecular diagnosis; (3) selection of treatment; and (4) safety of treatment. Each Board member chose particular topics for research (some topics had more than one Board member assigned to them). After the meeting, literature searches of the PubMed and Embase databases for relevant articles published in the last 5 years on each topic were conducted (see Supplementary Material for search strategies).

A second meeting of the Board was held on February 16th, 2022, during which the Board developed 27 statements, which were then critically reviewed and approved by two senior oncologists who are experts in CCA management and NGS sequencing, before being circulated to a voting panel of oncologists. The voting panel consisted of 38 clinicians around Italy (**Appendix**), selected by members of the Scientific Board based on their clinical

experience/expertise, and the geographic location and size of their hospital (representation from all regions of Italy and of all sizes of hospitals).

This panel was emailed a questionnaire in which they were asked to rate their agreement with each statement on the following scale: 1=strongly disagree, 2=disagree, 3=neither agree nor disagree, 4=agree and 5=strongly agree. Participants could also provide free-text feedback on the statements. Consensus was considered to be met if $\geq 66.7\%$ of the panel gave the statement a score of ≥ 4 .

After the first round of voting, the Board held another web meeting on June 27th, 2022 to discuss the results; some of the statements were revised as the Board thought necessary, a new statement was added (new total: 28 statements), and the questionnaire was re-circulated for a second round of voting to the same clinicians who had responded to the first questionnaire. The statements were finalised in a web meeting on August 29th, 2022 after receipt of the second round of voting results.

Ethical approval and informed consent were not required for a study of this nature.

3. Consensus Results

3.1 Epidemiology and risk factors

Six statements on the epidemiology and risk factors of CCA received consistent agreement during both rounds of voting (statements 1–6; **Table 2**). The first statement regarding the incidence of iCCA acknowledges the growing evidence for a global increase in CCA incidence, particularly iCCA (Florio et al., 2020; Mukkamalla et al., 2018; Parasuraman et al., 2020), especially in countries where there was formerly a low risk (Florio et al., 2020), although CCA remains a relatively rare tumour.

Statement 2 acknowledged the reasons for this increase in incidence including environmental factors, better diagnostic processes, or unknown causes (Florio et al., 2020; Mukkamalla et al., 2018). Consensus was reached on recognising that chronic liver disease is a risk factor for iCCA (statement 3) (Clements et al., 2020), as illustrated by the growing frequency of iCCA in Western countries. This in turn may be partially accounted for by the increasing incidence of metabolic-associated fatty liver disease (Chen et al., 2022; De Lorenzo et al., 2020; Park et al., 2021).

As agreed in statement 4, the risk factors for iCCA may also impact the molecular profile of the tumour. For instance, there is a high rate of telomerase reverse transcriptase (*TERT*) promoter mutations in hepatitis B-related CCA; *IDH1/2*, BRCA1 associated protein-1 (*BAP1*) and *FGFR* alterations are significantly more common in liver fluke-negative iCCA; and tumour protein P53 (*TP53*) mutations and *HER2* amplifications are more common in liver fluke-positive iCCA (Sirica et al., 2021).

The genetic and epigenetic relationship between risk factors and the pathogenesis of CCA is shown in **Figure 1** (Labib et al., 2019). Indeed there is a higher rate of *FGFR2* rearrangements in younger than in older patients with CCA (Jain et al., 2018; Javle et al., 2016), and in female than in male patients (Javle et al., 2016). These associations of age and sex with *FGFR2* alterations were also observed in a subgroup of patients with *FGFR2* fusions/rearrangements in the FIGHT-202 phase 2 study which assessed pemigatinib in patients with previously treated advanced CCA (of whom almost all had iCCA) (Abou-Alfa et al., 2020b). Statements 5 and 6 acknowledge these age and sex associations. Because CCA is generally asymptomatic in its early stages (Valle et al., 2021), patients often have advanced disease at diagnosis (Abou-Alfa et al., 2020b; Alvaro et al., 2011; Izquierdo-Sanchez et al., 2022). Since these patients have fewer treatment options available to them, it is important to identify potentially effective therapies early (Bekaii-Saab et al., 2021).

3.2 Diagnosis and role of genetic alterations

A total of ten statements were related to iCCA diagnosis and genomic profiling (statements 7–16; **Table 2**). There was strong agreement (>94%) that tumour tissue should be used for histological diagnosis of CCA and for genomic profiling (statements 7 and 8) (Carotenuto et al., 2022; Normanno et al., 2022; Pascual et al., 2022; Vogel et al., 2023). Disagreement in round 1 was mainly related to the use of liquid biopsy and led to the revision of three statements (statements 8, 9 and 10 in the final version). Liquid biopsies are an acceptable alternative to tumour tissue biopsies if the tumour tissue is not available or not adequate (statement 9) (Rompianesi et al., 2021). In CCA, inadequate tumour tissue samples can result from the technical challenges associated with collecting sufficient samples from within the bile ducts (Cho et al., 2022; Lamarca et al., 2020). We also note that liquid biopsies have a role in monitoring mutations that may lead to resistance against FGFR inhibitors within research protocols (statement 10).

Irrespective of biopsy sampling method, there was strong (>86%) agreement among the panel for genomic profiling in all patients diagnosed with CCA (statement 11), performed at the time of the initial diagnosis (statement 12), and using NGS technologies (statement 13). These statements are at odds with the 2022 Italian guidelines (Associazione Italiana per lo Studio del Fegato (AISF) et al.), but are broadly consistent with the ESMO guidelines (**Figure 2**) (Mosele et al., 2020; Vogel et al., 2023), 2022 National Comprehensive Cancer Network guidelines (National Comprehensive Cancer Network, 2022), multidisciplinary recommendations from the US (Madoff et al., 2022), and the Italian expert guidelines from FICOG/ISS, which recommend using NGS for genomic profiling of patients with advanced CCA (Pinto et al., 2021). Although the ESMO guidelines do not specifically advocate genomic profiling in every patient diagnosed with CCA, they do recommend genomic profiling prior to any nonsurgical treatment, and particularly for patients with advanced disease prior to systemic treatment (Vogel et al., 2023).

NGS is the recommended technology for genetic analysis (statement 13) because of its ability to undertake parallel sequencing of multiple genes (Bekaii-Saab et al., 2021). Other technologies, such as immunohistochemistry (IHC) or fluorescence *in situ* hybridisation (FISH), are more widely available and less expensive, but can only be used to identify specific genetic alterations, rather than screening for several alterations (Bekaii-Saab et al., 2021; Normanno et al., 2022). The NGS panel should include at least those gene targets categorised as ESCAT Level 1 in the ESMO guidelines (statement 14), which as of November 2022 are *IDH1* mutations (e.g. single nucleotide variants), *FGFR2* fusions, *HER2* amplifications, *BRAF*^{V600E} mutations, *KRAS* mutations, *NTRK* fusions and MSI (Vogel et al., 2023). The NGS panel should also include mutations, fusions, and copy number variations (statement 15).

For CCA, ESMO guidelines define *HER2* and *FGFR2* mutations as level 2, and *IDH2*, *BRCA1/2* mutations and *PALB2* mutations as level 3 genomic alterations (Vogel et al., 2023). We recommend that these genetic alterations are included in the NGS panel if there is no additional cost (statement 16).

3.3 Selection of treatment

Eight statements were developed related to the selection of appropriate systemic treatments for patients (statements 17–24) and each received >79% agreement in the first round of voting and >86% in the second round (**Table 2**). In line with the European and US guidelines that were available at the time of the Delphi consensus (National Comprehensive Cancer Network, 2022; Valle et al., 2016), we recommended first-line therapy with cisplatin + gemcitabine in patients with advanced or metastatic CCA (statement 17). Our recommendation was based on the results of randomised trials (Oh et al., 2022; Okusaka et al., 2010; Valle et al., 2010). In the ABC-02 trial in patients with locally advanced or metastatic biliary tract cancers, first-line cisplatin + gemcitabine significantly increased overall survival (OS) compared with gemcitabine

alone (11.7 vs 8.1 months; hazard ratio [HR] 0.64 [95% confidence interval (CI) 0.52–0.80], $p < 0.0001$) (Valle et al., 2010). Recently, the TOPAZ-1 trial showed that adding durvalumab to cisplatin + gemcitabine as first-line treatment significantly improved OS and progression-free survival (PFS) in patients with advanced iCCA compared with cisplatin + gemcitabine + placebo (respective HR [95% CI] of 0.76 [0.58–0.98] and 0.79 [0.64–0.99]) (Oh et al., 2022), and was acknowledged in statement 18 as a first-line treatment option. Subsequent to the panel voting on this statement, this combination has become the new standard of care and is recommended in the ESMO guidelines as first-line treatment for patients with advanced biliary tract cancer (Vogel et al., 2023), with approval by the European Medicines Agency on December 21, 2022 (European Medicines Agency, 2022a).

There is no clear evidence supporting continued treatment with gemcitabine + cisplatin for more than eight cycles as maintenance therapy in patients who respond to this treatment (statement 19). Only data from a retrospective analysis supports this strategy (Hyung et al., 2019).

Modified FOLFIRINOX (a combination of leucovorin [folinic acid], 5-fluorouracil, irinotecan and oxaliplatin) has been examined as a potential alternative to gemcitabine + cisplatin in the PRODIGE 38 AMEBICA study (Phelip et al., 2022), but did not prolong survival or show improved tolerability. Therefore, modified FOLFIRINOX cannot be recommended for the first-line treatment of advanced CCA (statement 20) and is not recommended in the ESMO guidelines (Vogel et al., 2023).

For patients who do not tolerate or who progress after first-line therapy, second-line treatment choices should be guided by the presence of targetable gene alterations.

Pemigatinib is the recommended second-line therapy for patients with *FGFR2* fusions or rearrangements (Agenzia Italiana del Farmaco, 2022) (statement 21), based on the results of

the FIGHT-202 study (Abou-Alfa et al., 2020b). In this study, objective responses occurred only in patients with *FGFR2* fusions or rearrangements (no responses were seen in patients with no or other *FGFR2* gene alterations) (Abou-Alfa et al., 2020b; Vogel et al., 2022). Median OS in patients with *FGFR2* fusions or rearrangements was 17.5 months, 6.7 months in those with other *FGFR2* gene alterations, and 4.0 months in those with no *FGFR2* alterations (data currently available as a congress abstract) (Vogel et al., 2022). The current ESMO guidelines also suggests pemigatinib for patients with locally advanced or metastatic CCA with an *FGFR2* fusion or rearrangement that has progressed after at least one prior line of therapy (Vogel et al., 2023). For patients with *IDH1* mutations, ivosidenib is a second-line treatment option (statement 22), based on the results of the phase 3 ClarIDHy study (Abou-Alfa et al., 2020a; Zhu et al., 2021). In this placebo-controlled study, ivosidenib significantly prolonged PFS compared with placebo, indicating substantial clinical benefit (Abou-Alfa et al., 2020a). A high proportion of patients from the placebo group crossed over to ivosidenib at disease progression (70% of 59 patients) and when this was taken into account in the OS analysis, there was a significant OS advantage with ivosidenib (median OS 10.3 vs 5.1 months with placebo; HR [95% CI] 0.49 [0.34–0.70], $p < 0.001$) (Zhu et al., 2021).

Targeted therapies have been developed for some of the other gene alterations in CCA, including *NTRK*, *BRAF*, *HER2* and MSI. Our consensus was that these agents can be offered as second-line treatments for CCA patients with these gene alterations in the context of a clinical trial or expanded access programme (statement 23). Notably, the two *NTRK* inhibitors entrectinib and larotrectinib have already been approved in the EU (including Italy) as well as in the US/UK with an agnostic indication, i.e. in patients with solid tumours expressing *NTRK* gene fusions (**Table 1**).

For patients who do not have targetable gene alterations, the recommended second-line therapy after cisplatin + gemcitabine is the combination of leucovorin, 5-fluorouracil and

oxaliplatin, commonly known as FOLFOX (statement 24). In the ABC-06 study, second-line modified FOLFOX was shown to statistically significantly increase survival compared with active symptom control in patients with locally advanced or metastatic biliary tract cancer (Lamarca et al., 2021).

3.4 Treatment safety

Three of the four statements about safety (statements 25, 26 and 28) achieved >87% agreement in round 1 and >97% agreement in round 2 (**Table 2**); all of these statements related to adverse effects (AEs) of FGFR2 or IDH1 inhibitors.

The statement with poor agreement in round 1 (35.9%) related to the prophylactic use of granulocyte-colony stimulating factor (G-CSF) during first-line chemotherapy (gemcitabine + cisplatin); the statement was: “G-CSF prophylactic use is recommended to maintain the adequate dose intensity during first-line chemotherapy”. The likely reason for the low rate of consensus was that the wording of this statement implied that use of G-CSF was recommended *routinely* in *all* patients receiving chemotherapy. Therefore, statement 27 was modified to “G-CSF can be used to maintain adequate dose intensity during first-line chemotherapy in selected patients”, and received 66.7% agreement in round 2, which met the predefined threshold for consensus.

The revised statement 27 is consistent with ESMO recommendations that decisions on G-CSF prophylaxis should be guided by the patient’s likely risk of neutropenia, taking into account the patient’s age, coexisting comorbidities and bone marrow reserve (Klastersky et al., 2016).

As noted above, agreement was high for recommendations on the management of AEs related to FGFR2 and IDH1 inhibitors. Hyperphosphataemia is a common class effect of FGFR2 inhibitors, occurring in 60–76% of patients with various types of cancer across multiple clinical

trials with different FGFR inhibitors (Kommalapati et al., 2021). In the FIGHT-202 study, 60% of patients with CCA receiving pemigatinib developed hyperphosphataemia, but all were grade 1–2 events (Abou-Alfa et al., 2020b); grade ≥ 3 hyperphosphataemia with FGFR2 inhibitors is rare (Kommalapati et al., 2021). Most cases of hyperphosphataemia with FGFR2 inhibitors can be managed with dietary changes and phosphate binders, as reflected in statement 25, which achieved 100% agreement in round 2. With these approaches to phosphate level management, dose reductions or interruptions related to hyperphosphataemia are rarely required (Kommalapati et al., 2021).

FGFR2 inhibitors may also be associated with a specific ocular AE profile, namely serous retinopathy or retinal detachment (Kommalapati et al., 2021). Although potentially serious, serous retinopathy is reversible with drug discontinuation, so regular monitoring for ocular toxicity is recommended (statement 26). Patients who develop changes to their vision during pemigatinib use should be promptly referred for a ophthalmological consultation (Kommalapati et al., 2021).

One of the serious AEs occurring with ivosidenib in the ClarIDHy study was grade 2 QT prolongation on the electrocardiogram (Abou-Alfa et al., 2020a; Zhu et al., 2021). While QT prolongation was not the most common AE with ivosidenib, occurring in $\leq 10\%$ of patients (Abou-Alfa et al., 2020a; Zhu et al., 2021), the potentially serious nature of this AE means that regular monitoring for cardiac toxicity is recommended (statement 28).

4. Conclusions

The advent of targeted therapies for CCA in Italy has highlighted the need for clear guidance on when and how to implement these therapies in clinical practice. These statements were developed to guide clinical practice in Italy, and the relative benefit of testing certain targetable mutations may differ in other countries or regions, depending on the cost of

molecular testing and availability of targeted agents there. Nevertheless, it is hoped that these statements reinforce the importance of identifying potentially targetable gene alterations early in the course of CCA, in order to tailor therapy for the best possible treatment outcomes.

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Data availability statement

The data generated/analysed in the current study are available from the corresponding author upon reasonable request.

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Tables

Table 1. Targeted therapies for cholangiocarcinoma (CCA) or tissue-agnostic targeted therapies suitable for CCA that are marketed in the European Union (EU) including Italy, the United Kingdom (UK), and the United States (US)^a, or that are available via named patient use/expanded access programmes or orphan drug status designation^b

Target	Agent(s) [ESMO-MCBS v1.1 score(European Society of Medical Oncology, 2022)] ^c	Region/country		Indication relevant to CCA
		Approved	Named patient use/ expanded access/ orphan drug status	
BRAF	Dabrafenib + trametinib [3]	US		Patients with unresectable or metastatic solid tumours with <i>BRAF</i> ^{V600E} mutation who have progressed after prior treatment and who have no satisfactory treatment options (Food and Drug Administration, 2022)
FGFR2	Pemigatinib [3]	Italy		Patients with locally advanced or metastatic CCA with <i>FGFR2</i> fusions/rearrangements, who have progressed after at least one prior line of systemic therapy (Agenzia Italiana del Farmaco, 2022)
		EU, US		Patients with inoperable/unresectable, late-stage, or metastatic CCA with <i>FGFR2</i> fusions or rearrangements, as second-line or greater therapy
		UK		Patients with locally advanced or metastatic CCA with <i>FGFR2</i> fusions or rearrangements that have progressed after at least one prior line of systemic therapy

	Infigratinib [3]	US	Patients with previously treated inoperable/unresectable, locally advanced or metastatic CCA with a <i>FGFR2</i> fusion or other rearrangement
	Futibatinib [NA]	Italy	Patients with previously treated, unresectable, locally advanced or metastatic intrahepatic CC with <i>FGFR2</i> gene fusions or other rearrangements ^d
		EU	Patients with biliary tract cancer (European Medicines Agency, 2019)
		US	Patients with previously treated, unresectable, locally advanced or metastatic intrahepatic CCA with <i>FGFR2</i> gene fusions or other rearrangements (Syed, 2022)
HER2	Zanidatamab [NA]	Italy	Patients with <i>HER2</i> positive advanced biliary tract cancer ^e
		EU	Patients with biliary tract cancer (European Medicines Agency, 2021)
IDH1	Ivosidenib [3]	EU^f	Patients with previously treated, locally advanced, or metastatic <i>IDH1</i> -mutated CCA, as second-line or greater therapy (European Medicines Agency, 2018)
		US	Patients with previously treated locally advanced or metastatic CCA that is <i>IDH1</i> mutation positive, as second-line or greater therapy
NTRK	Entrectinib [3]	Italy	Patients with solid tumours expressing <i>NTRK</i> gene fusions (Italian Medicines Agency (AIFA), 2022)
		EU	Patients with solid tumours expressing an <i>NTRK</i> gene fusion who have locally advanced or metastatic disease, who have not received a prior NTRK inhibitor, and who have no satisfactory treatment options (European Medicines Agency, 2022c)
		US	Patients with NTRK+ solid tumours (agnostic), who have late-stage or metastatic disease, as second-line or greater therapy
		UK	Patients with solid tumours expressing an <i>NTRK</i> gene fusion who have a disease that is locally advanced or metastatic, who have not received a prior NTRK inhibitor, and who have

			no satisfactory treatment options (Medicines and Healthcare products Regulatory Agency (UK), 2022a)
	Larotrectinib [3]	Italy	Patients with solid tumours expressing <i>NTRK</i> gene fusions (Italian Medicines Agency (AIFA), 2022)
		EU	Patients with solid tumours expressing <i>NTRK</i> gene fusions, who have late-stage or metastatic disease, as second-line or greater therapy
		US	Patients with solid tumours with <i>NTRK1/2</i> gene fusions, who have late-stage or metastatic disease, as second-line or greater therapy
		UK	Patients with solid tumours with <i>NTRK</i> gene fusions, who have locally advanced or metastatic disease, and who have no satisfactory treatment options (Medicines and Healthcare products Regulatory Agency (UK), 2022b)
MSI-H	Pembrolizumab [3]	EU	Patients with tumours described as MSI-H or dMMR, who have unresectable or metastatic biliary cancer, and who have disease progression on or following at least one prior line of therapy (European Medicines Agency, 2022b)
		US	Patients with solid tumours described as MSI-H or dMMR, who have inoperable/unresectable, late-stage, or metastatic disease, as monotherapy in the second-line or greater line of treatment
		UK	Patients with solid tumours described as MSI-H or dMMR, who have unresectable or metastatic biliary cancer, and who have disease progression on or following at least one prior line of therapy [pembrolizumab approved as monotherapy] (Medicines and Healthcare products Regulatory Agency (UK), 2022c)

BRAF, v-Raf murine sarcoma viral oncogene homologue B; dMMR, mismatch repair deficient; ESMO-MCBS, European Society of Medical Oncology – Magnitude of Clinical Benefit Scale; FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; IDH1, isocitrate dehydrogenase 1; MSI-H, microsatellite instability–high; NA, not available; NTRK, neurotrophic tyrosine receptor kinase.

^aData source: AdisInsight proprietary database, unless stated otherwise.

^bAll drug statuses are up to date at the time of publication but are subject to change.

^cESMO-MCBS scores are shown in square parentheses and are available only for cancer medicines approved by the European Medicines Agency (from January 2016) and the US Food and Drug Administration (from January 2020).

^dFutibatinib is provided for free by Taiho (pharmaceutical company) to eligible patients; physicians must submit a request (Taiho Oncology Inc, 2021) which is then approved on a case-by-case basis.

^eZanidatamab is provided for free by Zymeworks (pharmaceutical company) to eligible patients; physicians must submit a request which is then approved on a case-by-case basis.

^fPositive opinion adopted by the Committee for Medicinal Products for Human Use of the European Medicines Agency (February 2023).

Table 2. Final statements and percentage agreement during each round of voting. Statements in italics were revised between round 1 and round 2.

Agreement percentage refers to the proportion of the panel who gave the statement a score of 4 (agree) or 5 (strongly agree)

No.	Statement	Agreement (%)	
		Round 1 (n=38)	Round 2 (n=36)
Epidemiology and risk factors			
1	The frequency of iCCA, although still a relatively rare tumour, is increasing	97.4	100.0
2	The following causes related to the increase in iCCA have been identified: environmental, better diagnostic procedure, unknown factors	89.7	91.7
3	Chronic liver disease is a risk factor for iCCA	82.1	94.4
4	The risk factors causing iCCA can result in different molecular patterns	82.1	86.1
5	A diagnosis of iCCA is made frequently (70%) after it has reached an advanced stage	92.3	94.4
6	An increasing rate of <i>FGFR</i> rearrangements is found in young female patients with iCCA	76.9	75.0
Diagnosis and role of genetic alterations			
7	The diagnosis of CCA must be performed on a histological tumour sample	94.9	97.2
8	<i>Tumour tissue is the standard for genomic profiling^a</i>	61.5	94.4
9	<i>Liquid biopsy, using NGS technologies, could be used for genomic profiling of iCCA, if tumour tissue is not available or not adequate^b</i>	69.2	88.9
10	<i>Liquid biopsy can be used to monitor mutations leading to resistance to <i>FGFR</i> inhibitors within research protocols^c</i>	56.4	72.2
11	All patients diagnosed with CCA should undergo genomic profiling	89.7	94.4
12	Genomic profiling should be performed at initial diagnosis	87.2	86.1
13	Genomic profiling should be performed using NGS technologies	89.7	97.2

14	According to ESMO guidelines, genomic profiling should include at least those gene targets classified as level 1 ESCAT (as of June 2022: IDH1, FGFR2, NTRK, MSI) ^d	94.9	97.2
15	NGS panels must include mutations, fusions, and copy number variations	92.3	97.2
16	Level 2 and 3 alterations should be tested if there are no additional costs ^e	–	77.8
Selection of treatment			
17	Current first-line standard systemic treatment is represented by the combination of cisplatin and gemcitabine	87.2	91.7
18	Most recent data showed the potential use of first-line combination of cisplatin and gemcitabine plus durvalumab	92.3	100.0
19	There is no evidence to support continuing treatment with cisplatin and gemcitabine beyond 8 cycles and/or maintenance therapy	79.5	86.1
20	mFOLFIRINOX is not recommended for the treatment of advanced CCA	82.1	86.1
21	For patients with FGFR2 fusions or rearrangements progressing after first-line therapy, a treatment with pemigatinib should be considered	92.3	97.2
22	For patients with IDH1 mutations progressing to first-line therapy, a treatment with ivosidenib should be considered	92.3	94.4
23	Other potential molecular targets (MSI, NTRK, BRAF, HER2) should be considered within clinical trials or named patient/expanded access programmes after progression to first-line therapy	94.9	94.4
24	In the absence of an actionable target, second-line suggested systemic treatment is represented by FOLFOX	89.7	94.4
Safety			
25	In most of cases hyperphosphatemia associated with FGFR inhibitors is asymptomatic and manageable with diet and phosphate binders	87.2	100.0
26	Patients treated with FGFR2 inhibitors should be monitored for ocular toxicity	92.3	97.2
27	G-CSF can be used to maintain the adequate dose intensity during first-line chemotherapy, in selected patients ^f	35.9	66.7
28	Patients treated with IDH1 inhibitors should be monitored for cardiac toxicity (abnormal QT interval)	87.2	100.0

BRAF, v-Raf murine sarcoma viral oncogene homologue B; CCA, cholangiocarcinoma; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ESMO, European Society of Medical

Oncology; FGFR, fibroblast growth factor receptor; FOLFOX, folinic acid (leucovorin) + 5-fluorouracil + oxaliplatin; G-CSF, granulocyte colony stimulating factor; HER2, human epidermal growth factor receptor 2; iCCA, intrahepatic cholangiocarcinoma; IDH1, isocitrate dehydrogenase 1; KRAS, Kirsten rat sarcoma virus; mFOLFIRINOX, folinic acid (leucovorin) + 5-fluorouracil + irinotecan + oxaliplatin; MSI, microsatellite instability; NGS, next-generation sequencing; NTRK, neurotrophic tyrosine receptor kinase.

^aIn Round 1, this statement read: "Tumour tissue testing is the standard for genomic profiling; liquid biopsy should be used only if tumour tissue is not available or not adequate."

^bIn Round 1, this statement read: "Liquid biopsy, using NGS technologies, can be used for genomic profiling of intrahepatic CCA."

^cIn Round 1, this statement read: "Liquid biopsy can be used to monitor mutations leading to resistance to FGFR inhibitors."

^dIn Round 1, this statement read: "Genomic profiling should include at least those gene targets classified as level 1 ESCAT (validated in clinical trials and leading treatment decisions) according to ESMO guidelines: IDH1, FGFR2, NTRK, MSI", which was based on the 2016 ESMO guidelines.(Valle et al., 2016) Subsequent to voting on statement 14 in Round 2, new guidelines have been published (November 2022), with new additions of ESCAT Level 1 genetic alterations: *IDH1*, *FGFR2* fusions, *HER2* amplifications, *BRAF*^{V600E} mutations, *KRAS*, *NTRK* fusions, and *MSI*.(Vogel et al., 2023)

^eThis statement was not included in Round 1.

^fIn Round 1, this statement read: "G-CSF prophylactic use is recommended to maintain the adequate dose intensity during first-line chemotherapy."

Figure legends

Figure 1. The molecular pathogenesis of CCA (Labib et al., 2019). The majority of risk factors for CCA cause chronic inflammation and/or cholestasis. Inflammatory mediators, such as IL-6 and TNF α , activate a number of pathways, including JAK-STAT, p38-MAPK and Akt, resulting in increased cell growth, survival and proliferation. Macrophages secrete ligands that activate the Wnt/ β -catenin pathway, leading to TCF/LEF-mediated gene transcription. Although cholestasis causes inflammation, prolonged exposure of bile acids can have direct cellular effects leading to upregulation of COX-2 and Mcl-1, resulting in resistance to apoptosis. Liver flukes can also have direct effects on cholangiocytes via activation of the Akt pathway and upregulation of iNOS, increasing cell survival and proliferation. A number of microRNAs are up- or downregulated in CCA. All these alterations lead to well-established oncogenic mechanisms; genetic mutations, increased cell growth, survival and apoptotic resistance. p38-MAPK, p38 mitogen-activated protein kinase; Akt, protein kinase B; Bcl-2, B-cell lymphoma 2; CCA, cholangiocarcinoma; c-MET, *MET* protooncogene for RTK; COX-2, cyclooxygenase 2; DNMT1, DNA methyltransferase 1; EGFR, epidermal growth factor receptor; ErbB2, erb-b2 receptor tyrosine kinase 2; ERK1/2, extracellular signal-regulated kinase 1/2; FXR, farnesoid X receptor; FZD, frizzled; GLUT1, glucose transporter protein type 1; GPBAR 1, G protein-coupled bile acid receptor 1; IL, interleukin; iNOS, inducible nitric oxide synthase; JAK-STAT, Janus kinase-signal transducer and activator of transcription; lncRNA uc. 158, long non-coding RNA ultra-conserved region 158; LRP, low-density lipoprotein receptor-related protein; Mcl-1, myeloid cell leukemia-1; miR-193b, microRNA 193b; MMP, matrix metalloproteinase; NO, nitric oxide; Notch 1, neurogenic locus notch homolog protein 1; PDGF-D, platelet-derived growth factor - D; PTEN, phosphatase and tensin homolog; Rassf1a, Ras-association domain family 1; RTK, receptor tyrosine kinase; SUZ12, SUZ12 polycomb repressive complex 2 subunit; TCF/LEF, T-cell factor/lymphoid enhancer factor; TGF-beta, transforming growth factor beta; TNF, tumour

necrosis factor; TNFR, TNF receptor; VEGFR, vascular endothelial growth factor receptor; Wnt, wingless/int1. This figure has been reproduced from Labib P, Goodchild LG, and Pereira SP. Molecular pathogenesis of cholangiocarcinoma. *BMC Cancer* 2019;19(1):185 under a Creative Commons CC BY 4.0 License (<https://creativecommons.org/licenses/by/4.0/>).

Figure 2. Treatment algorithm for BTC in Italy. Blue indicates general categories or stratification; orange indicates surgery; white indicates other aspects of management; and green indicates systemic anticancer therapy. All drug statuses are up to date at the time of publication but are subject to change. ^aSpecial considerations: (i) consider the need for preoperative drainage; (ii) avoid percutaneous biopsy in resectable d/pCCA; (iii) assess future liver remnant; (iv) neoadjuvant approach (selected cases); (v) completion surgery for incidental GBC stage T1b; ^bSalvage surgery or local therapies should be considered in responding patients with initially inoperable disease; ^cEMA and FDA approved; ^dDrug available for use under named patient use/expanded accesses/orphan drug status; ^eESMO-MCBS v1.1 was used to calculate scores for 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>); ^fReconsider surgery in the event of adequate response to treatment; ^gMolecular profiling should be carried out before/during first-line therapy. Gene panel should include *IDH1* and *BRAF*, *FGFR2* and *HER2/neu* to test for hotspot mutations, fusions and amplifications, respectively but may also include other genes, such as *NTRK*. The rapidly evolving landscape of drug targets and predictive biomarkers may necessitate larger panels in the future; ^hCisplatin-gemcitabine-durvalumab is recommended for first-line treatment [I, A]. Consider gemcitabine monotherapy in patients with a compromised PS or significant debility who are at risk of toxicity from platinum-containing ChT regimens; ⁱESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the guideline authors and validated by the

ESMO Translational Research and Precision Medicine Working Group. 5-FU, 5-fluorouracil; BRAF, v-raf murine sarcoma viral oncogene homolog B1; BTC, biliary tract cancer; ChT, chemotherapy; dCCA, distal cholangiocarcinoma; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; ESMO, European Society for Medical Oncology; FDA, Food and Drug Administration; FGFR2, fibroblast growth factor receptor 2; FOLFOX, 5-fluorouracileleucovorineoxaliplatin; GBC, gallbladder carcinoma; HER2, human epidermal growth factor receptor 2; iCCA, intrahepatic cholangiocarcinoma; IDH1, isocitrate dehydrogenase 1; MCBS, ESMO-Magnitude of Clinical Benefit Scale; MDT, multidisciplinary team; NTRK, neurotrophic tyrosine receptor kinase; pCCA, perihilar cholangiocarcinoma; PS, performance status. Adapted from *Annals of Oncology*, 27 /Suppl 5, Valle JW, Borbath I, Khan SA, et al., Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up / v28-v37, Copyright (2016), with permission from Elsevier.