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SPECIAL ARTICLE

Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with biliary tract cancer

L.-T. Chen[1,2*], A. Vogel[3,4], C. Hsu[5,6], M.-H. Chen[7], W. Fang[8], E. A. Pangarsa[9], A. Sharma[10], M. Ikeda[11], J. O. Park[12], C. K. Tan[13], E. Regala[14], D. Tai[15], S. Tanasanvimon[16], C. Charoentum[17], C. E. Chee[18], A. Lui[19,20], J. Sow[21], D.-Y. Oh[22], M. Ueno[23], A. Ramaswamy[24], W. S. Jeo[25], J. Zhou[26], G. Curigliano[27,28], T. Yoshino[29], L.-Y. Bai[30], G. Pentheroudakis[31], N.-J. Chiang[7], A. Cervantes[32,33], J.-S. Chen[34] & M. Ducreux[35,36]

[1]Kaohsiung Medical University Hospital, Center for Cancer Research, Kaohsiung Medical University, Kaohsiung; [2]National Institute of Cancer Research, National Health Research Institutes, Tainan, Taiwan; [3]Department of Gastroenterology, Hepatology and Endocrinology, Medical School of Hannover, Hannover, Germany; [4]Division of Gastroenterology and Hepatology, Toronto General Hospital, Medical Oncology, Princess Margaret Cancer Centre, Toronto, Canada; [5]Department of Oncology, National Taiwan University Hospital, Taipei; [6]Department of Medical Oncology, National Taiwan University Cancer Center, Taipei; [7]Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan; [8]Department of Medical Oncology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; [9]Haematology Medical Oncology Division, Department of Oncology, Faculty of Medicine, Diponegoro University/Dr. Kariadi Hospital, Semarang, Indonesia; [10]Department of Medical Oncology, Max Institute of Cancer Care, Max Super Specialty Hospital, Saket, New Delhi, India; [11]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [12]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [13]Department of Oncology and Nuclear Medicine, Thomson Hospital Kota Damansara, Petaling Jaya, Selangor, Malaysia; [14]Clinical Division Building, University of Santo Tomas Hospital, Sampaloc, Manila, Philippines; [15]Division of Medical Oncology, National Cancer Centre Singapore, Singapore, Singapore; [16]Division of Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok; [17]Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; [18]Department of Haematology-Oncology, National University Cancer Institute, National University Health System, Singapore, Singapore; [19]Department of Internal Medicine, Metro Davao Medical and Research Center,Davao City; [20]Section of Medical Oncology, Department of Internal Medicine, Southern Philippines Medical Center, Davao City, The Philippines; [21]Department of Oncology, Curie Oncology Kuala Lumpur, Kuala Lumpur, Malaysia; [22]Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea; [23]Department of Gastroenterology, Kanagawa Cancer Center, Yokohama, Japan; [24]Department of Medical Oncology, Tata Memorial Hospital, Homi Bhabha National Institute, Parel, Mumbai, India; [25]Division of Digestive Surgery, Department of General Surgery, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia; [26]Department of Gastrointestinal Oncology, Peking University Cancer Hospital & Institute, Beijing, China; [27]Istituto Europeo di Oncologia, Milano, IRCCS, Milano; [28]Department of Oncology and Haematology, University of Milano, Milano, Italy; [29]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan; [30]Division of Hematology and Oncology, Department of Internal Medicine, China Medical University Hospital, China Medical University, Taichung, Taiwan; [31]ESMO, Lugano, Switzerland; [32]Department of Medical Oncology, INCLIVA Biomedical Research Institute, University of Valencia, Valencia; [33]CIBERONC. Instituto de Salud Carlos III, Madrid, Spain; [34]Department of Internal Medicine, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan; [35]INSERM U1279, Université Paris-Saclay, Villejuif; [36]Department of Cancer Medicine, Gustave Roussy, Villejuif, France

Available online 6 August 2024

The European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with biliary tract cancer (BTC), published in late 2022 were adapted in December 2023, according to established standard methodology, to produce the Pan-Asian adapted (PAGA) ESMO consensus guidelines for the management of Asian patients with BTC. The adapted guidelines presented in this manuscript represent the consensus opinions reached by a panel of Asian experts in the treatment of patients with BTC representing the oncological societies of China (CSCO), Indonesia (ISHMO), India (ISMPO), Japan (JSMO), Korea (KSMO), Malaysia (MOS), the Philippines (PSMO), Singapore (SSO), Taiwan (TOS) and Thailand (TSCO), co-ordinated by ESMO and the Taiwan Oncology Society (TOS). The voting was based on scientific evidence and was independent of the current treatment practices, drug access restrictions and reimbursement decisions in the different regions of Asia. Drug access and reimbursement in the different regions of Asia are discussed separately in the manuscript. The aim is to provide guidance for the optimisation and harmonisation of the management of patients with BTC across the different countries and regions of Asia, drawing on the evidence provided by both Western and Asian trials, whilst respecting the differences in screening practices and molecular profiling, as well as age and stage at presentation. Attention is drawn to the disparity in the drug approvals and reimbursement strategies, between the different countries.

Key words: ESMO, guidelines, Pan-Asian, biliary tract cancer, treatment

*Correspondence to: Prof. Li-Tzong Chen, Kaohsiung Medical University Hospital, Center for Cancer Research, Kaohsiung Medical University, Kaohsiung, Taiwan. Tel: +886-7-3121101, ext. 7451; Fax: +886-7-3135612

E-mail: leochen@nhri.org.tw (L.-T. Chen).

INTRODUCTION

Biliary tract cancers (BTCs) are a heterogeneous group of tumours which include cholangiocarcinoma (CCA), gallbladder carcinoma (GBC) and cancer of the ampulla of Vater.[1-3] CCA is more frequent in men than women.[2] Arising from any point in the biliary tree, it accounts for ∼3% of all gastrointestinal tumours.[4] CCA can be classified as either intrahepatic CCA (iCCA), which includes all primary intrahepatic carcinomas with a ductal/tubular phenotype and accounts for 10%-20% of all liver cancers, or as extrahepatic CCA (eCCA) which consists of perihilar CCA (pCCA) and distal (dCCA) CCA depending on the site of origin.[4,5]

CCAs are relatively rare globally, with the highest incidences observed in Asia, notably Northeast Asia and Indochina—mainly the Mekong basins of Southeast Asia. The incidence varies geographically, probably due to differences in the prevalence of risk factors, including liver flukes, hepatitis B virus (HBV) and hepatitis C virus infection, liver cirrhosis and hepatolithiasis.[6] Between 1998 and 2003, the age-standardised incidence rates per 100 000 person-years (ASIR) for iCCA in men and women, respectively, were 2.3 and 1.7 in Hong Kong, 4.3 and 3.9 in Taiwan, 5.4 and 2.5 in Korea, 7.4 and 4.9 in Shanghai, and 71.3 and 31.6 in Thailand (Khon Kaen region).[6-9] Liver flukes are the best characterised pathogens for iCCA in the Asia-Pacific regions, and account for the high incidence of iCCA in northeastern Thailand. Owing to improvements in sanitation and agricultural practices, as well as the success of educational and pharmacological interventions, dramatic decreases in the prevalence of the predominant flukes (*Opisthorchis viverrini* in Thailand, and *Clonorchiasis sinensis* in Japan, Korea and Taiwan) have been reported.[10-16] These in turn were accompanied by decreases in the ASIR of iCCA in these regions.[17-19] The public health measures for fluke eradication should now be directed to other high-prevalence areas for liver fluke infection, including Laos PDR, Cambodia, central Vietnam and Myanmar (for *O. viverrini*), and northern Vietnam and southern China (for *C. sinensis).*[20]

Hepatolithiasis, another risk factor for iCCA, is more prevalent in regions of Northeast Asia than in Western countries.[7] Before 1990, the incidence of incidentally found iCCA in patients who underwent hepatectomy for hepatolithiasis was between 5% and 12.5% in Taiwan, Korea, Japan and Shenyang, China.[8-11] A recent, long-term, national survey revealed a trend towards a decrease in the numbers and prevalence of hepatolithiasis in Japan,[17] while a Korean single institute-based study showed a trend towards a decline in the prevalence of hepatolithiasis (from 15.0% to 6.3%) and common bile duct stones (from 30.2% to 5.0%) between the periods of 1986-1990 and 2006-2010.[8]

HBV infection is prevalent in Asia but, with the implementation of nationwide HBV vaccination programmes for all newborns in most regions of Asia, there has been a drastic fall in the incidence rates of hepatitis B surface antigen (HBsAg) carrier status.[12-15] For instance, in 2019 in Taiwan, where a vaccination programme for newborns for HBsAg-carrier mothers established in 1984 was extended to cover all newborns in 1986, the HBsAg-carrier rate in the vaccinated birth cohort was 0.4% compared with 7.7% for those born before 1984.[12] Similarly, in Korea, after the initiation of an expanded immunisation programme in 1995 (which has a 98.9% coverage rate), the HBsAg-positive rate reduced from 2.2% in 1998 for the 10- to 18-year-old cohort to 0.3% in 2016.[14]

According to recent individual national cancer registration reports, those regions of Asia associated with high incidences of iCCA have seen reductions in the ASIR, to 11.0 in Khon Kean, Thailand (2018), 3.2 in Taiwan (2017), 2.7 in China (2015), 2.6 in Korea (2017) and 1.2 in Japan (2016-2018), while the ASIR for all BTCs in the corresponding period was 5.8 in Taiwan (2017), 9.1 in Korea (2017) and 4.4 in Japan (2016-2018).[16,18-21]

Korea, Japan and Thailand had the highest incidences of eCCA between 2008 and 2012 out of 22 countries, with ASIRs of 2.71, 2.67 and 1.07, respectively, while Vietnam had the lowest incidence (ASIR of 0.10).[2] Risk factors for eCCA include primary sclerosing cholangitis, choledochal cyst and choledocholithiasis.[22]

Unlike CCA, GBC is more prevalent in women than men.[2] In 2012, the continent of Asia had the second highest mortality-to-incidence ratio for GBC (0.88) behind Africa (1.00), with a correlation found between the standard of a country's health care system and expenditure and mortality-to-incidence.[23]

Irritation and inflammation of the gallbladder caused by either chronic *Helicobacter pylori* or *Salmonella typhi* infection are risk factors for the development of GBC. *H. pylori* infection showed the greatest association across Asia as a whole, whereas a subgroup analysis carried out according to region found a significant association between *S. typhi* infection and the risk of developing GBC.[24-26] Gallstones as a risk factor for GBC development was highlighted by a Chinese study which found that subjects with gallstones had a 21-fold greater risk of developing GBC compared with control subjects, and that this risk increased to 57-fold if there was a family history of gallstones.[27] Other risk factors for GBC include diabetes mellitus type 2, obesity, raised body mass index and autoimmune disease, including primary autoimmune hepatitis, Crohn's disease, systemic lupus erythematosus, pernicious anaemia and primary sclerosing cholangitis.[28-33]

Recurrent genetic aberrations have been identified in BTC, including actionable mutations in genes such as isocitrate dehydrogenase [NADP(+)] 1 (*IDH1*), fibroblast growth factor receptor 2 (*FGFR2*), B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) and human epidermal growth factor receptor 2 (*HER2/neu*). These plus several rare genetic alterations, such as neurotrophic receptor tyrosine kinase (*NTRK)* fusion, rearranged during transfection (*RET)* fusion, as well as tumours with microsatellite instability-high/mismatch repair deficiency (MSI-H/dMMR) or high tumour mutational burden (TMB-H), have led to a shift in the treatment paradigm for BTC towards precision medicine.[34]

The most recent European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with BTC were published earlier this year.[35] Therefore a decision was taken by ESMO and the Taiwan Oncology Society (TOS) that these latest ESMO guidelines should be adapted to provide updated Pan-Asian guidelines for the management and treatment of BTC in patients of Asian ethnicity. This manuscript summarises the Pan-Asian adapted guidelines developed and agreed upon at a face-to-face working meeting that took place in Singapore on 30 November 2023, hosted by TOS. Each recommendation is accompanied by the level of evidence (LoE), grade of recommendation (GoR) and, where applicable, ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS)[36] and ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT)[37] scores (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103647).

METHODOLOGY

This Pan-Asian adaptation of the current ESMO Clinical Practice Guidelines[35] was prepared in accordance with the principles of ESMO standard operating procedures (https://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology) and was a TOS-ESMO initiative endorsed by the Chinese Society of Clinical Oncology (CSCO), the Indonesian Society of Hematology and Medical Oncology (ISHMO), the Indian Society of Medical and Paediatric Oncology (ISMPO), the Japanese Society of Medical Oncology (JSMO), the Malaysian Oncological Society (MOS), the Philippine Society of Medical Oncology (PSMO), the Singapore Society of Oncology (SSO) and the Thai Society of Clinical Oncology (TSCO). An international panel of experts was selected from the TOS ($n = 6$), the ESMO ($n = 6$ including the co-ordinator of the Pan-Asian Guideline adaptations, TY) and two experts from each of the nine other oncological societies. Only two of the six expert members from the TOS (CH and M-HC) were allowed to vote on the recommendations together with the experts from each of the nine other Asian oncology societies ($n = 20$). All 20 Asian experts provided comments on the pre-meeting survey and one consensus response per society (see Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.103647). Only one voting member per Asian society was present at the face-to-face meeting. None of the additional members and none of the ESMO experts were allowed to vote and were present in an advisory role only (see Supplementary Material: Methodology, available at https://doi.org/10.1016/j.esmoop.2024.103647). All the Asian experts ($n = 20$) approved the revised recommendations.

RESULTS

Scientific adaptations of the ESMO recommendations

In the initial pre-meeting survey, the 20 voting Asian experts reported on the 'acceptability' of the 47 recommendations for the diagnosis, treatment and follow-up of patients with BTC from the most recent ESMO Clinical Practice Guidelines[35] (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.103647), in the five categories outlined in the text below and in Table 1. A lack of agreement in the pre-meeting survey was established for 16 recommendations, 14 of which were discussed at the face-to-face working meeting in Singapore to adapt the recently published ESMO Clinical Practice Guidelines. For each of ESMO 'recommendations 3l, 4f, 4i, 4j and 4l' there were discrepancies relating to their applicability in certain regions of Asia. Of these, 'recommendations 3l and 4f' were not discussed at the face-to-face meeting. ESMO 'recommendation 4b' was also discussed due to the recent Food and Drug Administration (FDA) approvals of durvalumab and pembrolizumab with chemotherapy (ChT) for the treatment of locally advanced unresectable or metastatic BTC.[38,39] Two new recommendations 'recommendations 4p and 4q' were added during the drafting of these guidelines and agreed by all the Pan-Asian panel of experts (see Supplementary Material: Results, and Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2024.103647).

1. DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY—RECOMMENDATIONS 1A-F

The Pan-Asian panel of experts agreed with and accepted completely (100% consensus) the original ESMO recommendations, 'recommendations 1a-f' (Table 1), without change.

2. STAGING AND RISK ASSESSMENT—RECOMMENDATIONS 2A-D

The Pan-Asian panel of experts agreed with and accepted completely (100% consensus) the original ESMO recommendations, 'recommendations 2b and 2d' (Table 1), without change.

For 'recommendation 2a', the Pan-Asian panel of experts agreed with the use of magnetic resonance imaging (MRI) for the examination of eCCA, particularly for the identification of hepatic metastases, but there was discussion regarding the fact that access to MRI is not available for all patients throughout Asia. Furthermore, although MRI is the most sensitive method to detect liver metastases, multiphasic computed tomography (CT) was found to be acceptable for the evaluation of extrahepatic bile duct cancer by the Korean Society of Abdominal Radiology.[40,41] Therefore, the wording of the original ESMO 'recommendation 2a' was modified, as per the bold text below and in Table 1, to include contrast-enhanced CT while highlighting the preference for contrast-enhanced MRI, to read as follows (**100% consensus**):

2a. ***Contrast-enhanced CT and preferably, when available, contrast-enhanced*** *MRI* ***is recommended*** *for local extension of pCCA and dCCA and for identification of hepatic metastases [III, A;* ***consensus*** *=* ***100%****].*

Table 1. Summary of Asian consensus recommendations for the treatment of patients with biliary tract cancer

	Acceptability consensus
1. DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY	
1a. BTC should be classified according to ICD11 criteria [III, A]	100%
1b. A core biopsy should be obtained for diagnostic pathology and molecular profiling before any nonsurgical treatment [III, A]	100%
1c. In patients with d/pCCA without extraductal metastasis, PTC- or ERCP-guided biopsies should be carried out to obtain adequate tissue for diagnostic pathology and molecular profiling [III, A]	100%
1d. Depending on location, EUS-guided FNA or FNB may be an option to obtain biopsies of enlarged regional nodes and to obtain a tumour biopsy if ERCP-guided biopsies are negative or inconclusive [II, B]	100%
1e. Molecular analysis is recommended in advanced disease considered suitable for systemic treatment [I, A]	100%
1f. Elevated CA 19-9 is associated with poorer prognosis and can be useful for assessing response to treatment [III, C]	100%
2. STAGING AND RISK ASSESSMENT	
2a. **Contrast-enhanced CT and preferably, when available, contrast-enhanced** MRI **is recommended** for local extension of pCCA and dCCA and for the identification of hepatic metastases [III, A]	100%
2b. Thoraco-abdomino-pelvic CT remains the reference examination for lymph node and metastatic extension [III, A]	100%
2c. FDG-PET is not recommended for **imaging of the** primary **tumour. However**, **it** may **be considered where there is clinical suspicion** of nodal metastases, distant metastases and disease recurrence [III, C]	100%
2d. Staging is carried out according to the 8th edition of the UICC staging manual and is specific to every subtype of BTC. pCCAs are further subclassified according to the Bismuth-Corlette classification to describe their anatomical location [III, A]	100%
3. MANAGEMENT OF LOCAL AND LOCOREGIONAL DISEASE	
3a. Radical surgery, which includes lymphadenectomy, is the only curative-intent treatment for BTC. The exact nature and extent of surgery will depend on tumour subtype and location and should be agreed at a specialist hepatobiliary multidisciplinary tumour board meeting [III, A]	100%
3b. Radiological imaging should be carried out before ERCP or PTC in patients with jaundice [III, A]	100%
3c. Consideration of non-tumour-related factors (e.g. PS, comorbidities) is important, as resection carries a significant risk of mortality [III, B]	100%
3d. Right portal vein embolisation **should be considered, if clinically indicated,** to induce hypertrophy of the future liver remnant **and only be carried out in high-volume centres** [IV, A]	100%
3e. Liver transplantation is not considered a standard treatment for pCCA and participation in clinical trials should be encouraged [III, D]	100%
3f. In case of incidentally diagnosed GBC (after cholecystectomy), re-operation with radical intent should be offered to sufficiently fit patients with stage ≥T1b disease, provided there is no metastatic spread [IV, A]. Resection of some or all of segment IVb/V of the liver is carried out together with a lymphadenectomy of the hepatoduodenal ligament [II, A]	100%
3g. Resection of the port sites **during open surgery** may be considered if the gallbladder was not removed with a bag or if the gallbladder was perforated [IV, C]	100%
3h. Curative-intent resection of tumours located at the infundibulum requires resection of the bile duct, the duodenal bulb and, potentially, the pancreatic head [III, A]	100%
3i. Adjuvant ChT with **S-1 [I, A] or** capecitabine **[II, A]** should be considered for patients with CCA or GBC following resection	100%
3j. **Following adjuvant S-1 or capecitabine, subsequent** RT **or CRT may** be considered in selected patients (R1 resection **and/or N+** GBC or d/pCCA) [III, C]	100%
3k. Local ablation **could** be considered **as an option** for patients with iCCA ≤3 cm who have contraindications or are otherwise unfit for surgery [III, **B**]	100%
3l. SBRT can be considered for patients with iCCA in case of contraindication to surgery for liver-limited disease in the palliative setting [III, C]	100%
3m. Intraarterial therapies, in combination with **systemic** ChT, can be **an option for** patients with liver-limited iCCA **and discussed by the MDTB according to local availability** [III, C]	100%
3n. External RT or CRT to the primary tumour as definitive treatment should not be used outside of clinical trials for locally advanced CCA [II, D]	100%
3o. Photodynamic therapy and intraductal radiofrequency ablation are considered investigational and should not be used outside of clinical trials for pCCA [II, D]	100%
3p. In case of response following locoregional or systemic treatment of locally advanced tumours, patients should be re-assessed by the MDT to discuss surgery [IV, B]	100%
4. MANAGEMENT OF ADVANCED AND METASTATIC DISEASE	
First-line treatment	100%
4a[a]. The combination of cisplatin-gemcitabine with durvalumab **or pembrolizumab** should be considered **as the standard of care** in first-line BTC [I, A; ESMO-Magnitude of Clinical Benefit (MCBS) v1.1 score **for durvalumab**: 4**; ESMO-MCBS v1.1 score for pembrolizumab: 1**]. **Cisplatin-gemcitabine-S-1 is an alternative therapeutic option for fit patients [II, B]**	100%
4b. Oxaliplatin **or carboplatin** may be substituted for cisplatin when renal **or auditory** function is of concern**, while gemcitabine plus S-1 can be an option for patients who present with or are susceptible to peripheral sensory neuropathy** [II, B]	100%
4c. Gemcitabine monotherapy may be used in patients with a PS of 2 [IV, B]	100%
Second- and later-line treatment	
4d. FOLFOX is the standard of care in the second-line setting after cisplatin-**gemcitabine-based treatment** [**II, B**; ESMO-MCBS v1.1 score: 1; no specific licensed indication in BTC]. **Irinotecan monotherapy or irinotecan- or liposomal irinotecan-based combination therapy may be considered [III, B]**	100%
4e. Ivosidenib is recommended for the treatment of patients with CCA and *IDH1* mutations who have progressed after ≥1 prior line of systemic therapy [I, A; ESMO-MCBS v1.1 score: 2; ESCAT score: I-A; FDA approved, not EMA approved]	100%
4f. FGFR inhibitors are recommended for the treatment of patients with *FGFR2* fusions who have progressed after ≥1 prior line of systemic therapy [III, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-B]	100%
4g. Pembrolizumab is recommended in patients with MSI-H/dMMR who have progressed on or are intolerant to prior **non-immune checkpoint inhibitor-containing** treatment [III, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-C]	100%

Continued

Table 1. Continued

	Acceptability consensus
4h. Dabrafenib-trametinib is recommended for the treatment of patients with BRAFV600E mutations who have progressed after ≥1 prior line of systemic therapy [III, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-B; FDA approved, not EMA approved]	100%
4i. Patients with ***BRCA1/2*** or *PALB2* mutations responding to platinum-based therapy can be considered for treatment with PARP inhibitors, **preferably within clinical trials** [V, B; ESCAT score: III-A]	100%
4j. NTRK inhibitors are recommended in patients with *NTRK* fusions who have progressed on or are intolerant to prior treatment [III, A; ESCAT score: I-C]	100%
4k. HER2-directed therapies can be considered in patients with **HER2 overexpression/amplification** who have progressed on or are intolerant to prior treatment [III, A; ESCAT score: I-C]	100%
4l. Selpercatinib can be considered in patients with *RET* fusions who have progressed on or are intolerant to prior treatment [III; A; ESMO-MCBS v1.1 score for solid tumours with a *RET* fusion: 3; ESCAT score: I-C; FDA approved, not EMA approved]	95%
4m. Pembrolizumab can be considered in patients with TMB-H tumours who have progressed on or are intolerant to prior non-immune checkpoint inhibitor-containing treatment [IV; A; ESMO-MCBS v1.1 score for pembrolizumab in TMB-H solid tumours: 3; ESCAT Score: I-C]	100%
Supportive care	
4n. During systemic and locoregional therapy for advanced disease, follow-up should be conducted at a frequency of 8-12 weeks. In addition to imaging with CT or MRI, CA 19-9 or CEA levels may be used to monitor the course of the disease if one or both are known to be secreted [IV, A]	100%
4o. In patients with biliary obstruction, biliary drainage and subsequent treatment should be carried out; when endoscopic access is not possible, percutaneous transhepatic drainage is recommended [IV, A]. In patients with a life expectancy of >3 months, a metal stent is preferred [IV, B]	100% 100%
4p. Sepsis secondary to biliary obstruction is common and should be treated promptly [IV, A]	100%
4q. Patients should be advised of the likely duration of stent patency and of symptoms and signs which are indicative of biliary obstruction or infection [V, A]	100%
5. FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP	100%
5a. There is no universal follow-up schedule, but as patients develop complications related to treatment as well as cancer recurrence, follow-up is indicated. Surveillance may consist of 3- to 6-monthly visits during the first 2 years and 6- to 12-monthly visits for up to 5 years or as clinically indicated. A combination of clinical examination, laboratory investigation, tumour markers and CT scan of the thorax, abdomen and pelvis may be appropriate [IV, B]	100%
5b. Patients with post-operative biliary obstruction require specialised multidisciplinary evaluation to determine the location of obstruction, evaluate for recurrence and determine the optimal approach to drainage [IV, A]	100%
5c. Rehabilitation to counteract impairments related to cancer and its treatments might help maximise QoL in survivorship [V, A]	100%
5d. Long-term survivors should be followed up using a multidisciplinary approach that is targeted and personalised [V, A]	100%
5e. For younger patients, specific aspects should be considered and monitored, including the impact of treatment on fertility, psychological well-being and the development of secondary tumours [IV, B]	100%

BRCA1/2, breast cancer gene 1 or 2; BTC, biliary tract cancer; CA, carbohydrate antigen; CCA, cholangiocarcinoma; CEA, carcinoembryonic antigen; ChT, chemotherapy; CT, computed tomography; dCCA, distal cholangiocarcinoma; dMMR, mismatch repair deficiency; EMA, European Medicines Agency; ERCP, endoscopic retrograde cholangiopancreatography; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; ESMO, European Society for Molecular Oncology; ESMO-MCBS; ESMO-Magnitude of Clinical Benefit Scale; EUS, endoscopic ultrasonography; FDA, U.S. Food and Drug Administration; FDG-PET, 18F-fluorodeoxyglucose positron emission tomography; FGFR, fibroblast growth factor receptor; FNA, fine needle aspiration; FNB, fine needle biopsy; FOLFOX; 5-fluorouracil, leucovorin and oxaliplatin; GBC, gallbladder carcinoma; HER2, human epidermal growth factor receptor 2; iCCA, intrahepatic cholangiocarcinoma; ICD11, International Classification of Diseases (ICD) 11th revision; IDH1, isocitrate dehydrogenase 1; MDT, multidisciplinary team; MRI, magnetic resonance imaging; MSI-H, microsatellite instability-high; NTRK, neurotrophic tyrosine receptor kinase; PALB2, partner and localiser of BRCA2; PARP, poly (ADP-ribose) polymerase; pCCA, perihilar cholangiocarcinoma; PS, performance status; PTC, percutaneous transhepatic cholangiography; QoL, quality of life; RET, rearranged during transfection; RT, radiotherapy; SBRT; stereotactic body RT; S-1, tegafur, gimeracil and oteracil; TMB-H, tumour mutational burden-high; UICC, Union for International Cancer Control.

[a]Following discussion by the Pan-Asian panel of experts, the original 'recommendation 4a' from the survey (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.103647) was deleted. As a result, all subsequent recommendations were renumbered accordingly.

The use of fluorodeoxyglucose (FDG)-positron emission tomography (PET) for the diagnosis of BTC was discussed for 'recommendation 2c'. Several studies investigating the diagnostic potential of FDG-PET for BTC, including a meta-analysis in GBC, found that PET-CT had higher diagnostic accuracy.[42-44] Moreover, the addition of FDG-PET was found to improve the diagnostic performance of CT for liver metastases and may add diagnostic value.[44] ESMO 'recommendation 2c' was agreed with modification, as per the bold text below and in Table 1, to provide clarification for when FDG-PET may be considered as follows (**100% consensus)**:

*2c. FDG-PET is not recommended for **imaging of the** primary **tumour. However, it** may **be considered where there is clinical suspicion** of nodal metastases, distant metastases and disease recurrence [III, C; **consensus = 100%**].*

3. MANAGEMENT OF LOCAL AND LOCOREGIONAL DISEASE—RECOMMENDATIONS 3A-P

The Pan-Asian panel of experts agreed with and accepted completely (100% consensus) the original ESMO recommendations, 'recommendations 3a-c, 3e, 3f, 3h, 3l and 3n-p' (Table 1), without change.

There was a great deal of discussion around ESMO 'recommendation 3d' regarding the use of right portal vein embolisation (PVE) for patients undergoing extended hepatectomy. Prior PVE improves the safety of extended hepatectomy for patients with advanced primary hepatobiliary tumours with an inadequate future liver remnant.[45,46] As PVE has become more routinely used in high-volume centres, both the rate of mortality and complications, including liver failure, have greatly reduced over time.[47,48] Concerns, however, were raised about local resources and the technical expertise required for carrying out PVE on patients

with inadequate future liver remnants, particularly in smaller medical centres. As a result, it was agreed that PVE should only be carried out in high-volume centres, and ESMO 'recommendation 3d' was modified, as per the bold text below and in Table 1 (**100% consensus**), to read as follows:

*3d. Right portal vein embolisation **should be considered, if clinically indicated,** to induce hypertrophy of the future liver remnant **and only be carried out in high-volume centres** [IV, A; **consensus** = **100%**].*

The majority of GBC cases are discovered by chance (incidentally) on pathologic examination of specimens following elective laparoscopic cholecystectomy.[49,50] In a single US institute database search, 69 out of 113 patients with incidental GBC who presented for definitive resection after laparoscopic cholecystectomy underwent port site resection. Of these, 13 (19%) had port site metastases and the median survival for patients with port site metastases (17 months) was shorter compared with patients without port site metastases (42 months; $P = 0.005$).[51] The incidence of port site metastasis may be higher in the case of gallbladder perforation[52] and ESMO 'recommendation 3g' considered the potential intervention of resection of the port sites for patients whose GBC was incidentally discovered and where the gallbladder was neither removed with a retrieval bag nor perforated. However, several studies have failed to demonstrate either an overall survival (OS) or recurrence-free survival (RFS) benefit for patients who underwent port site resection compared with those who did not undergo the procedure.[51,53,54] As a result, the grade of recommendation (GoR) for 'recommendation 3g' remained 'C' '*insufficient evidence for efficacy or benefit does not outweigh the risk of disadvantages, optional*' (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103647) and it was accepted with **100% consensus** with a modification to the text to improve clarity, as per bold text and in Table 1, to read as follows:

*3g. Resection of the port sites **during open surgery** may be considered if the gallbladder was not removed with a bag or if the gallbladder was perforated [IV, C; **consensus** = **100%**].*

There was a great deal of discussion amongst the Pan-Asian panel of experts regarding ESMO 'recommendation 3i' and the use of adjuvant capecitabine following resection. Part of the discussion centred around the results of the randomised, UK, phase III BILCAP study comparing capecitabine with observation, in patients with resected BTC.[55] The study failed to meet its primary endpoint of OS benefit by intention-to-treat analysis but, despite not being statistically significant, capecitabine did give a clinically meaningful OS benefit of 14.7 months (capecitabine group, median OS = 51.1 months compared with 36.4 months in the observation group, adjusted hazard ratio [HR] 0.81; 95% confidence interval [CI] 0.63-1.04; $P = 0.097$).[55] Furthermore, the median RFS in the capecitabine group was 24.4 months (95% CI 18.6-35.9 months) compared with 17.5 months (95% CI 12.0-23.8 months) in the observation group and the adjusted RFS HR in the first 24 months from randomisation was 0.75 (95% CI 0.58-0.98; $P = 0.033$). Unfortunately, the increases of adjusted HR for OS and progression-free survival (PFS) to 0.84 (95% CI 0.67-1.06) and 0.81 (95% CI 0.65-1.01) in the extension report[56] further weaken the recommendation of adjuvant capecitabine in resected BTC.

In several regions of Asia, tegafur—gimeracil—oteracil (S-1) plus gemcitabine has been used to treat advanced BTC. A recent randomised, Japanese, phase III (JCOG1202/ASCOT) trial in patients who had undergone curative resection compared adjuvant S-1 with observation. The study was terminated early with 41% survival events. In the primary report, the 3-year OS was 77.1% (95% CI 70.9% to 82.1%) in the S-1 group compared with 67.6% (95% CI 61.0% to 73.3%) in the observation group (adjusted HR 0.69; 95% CI 0.51-0.94; one-sided $P = 0.0080$).[57] An improved 3-year RFS was also observed for the adjuvant S-1 group (62.4%) compared with the observation group (57.2%; HR 0.80; 95% CI 0.61-1.04; two-sided $P = 0.088$).[57] Favourable outcomes were seen for both OS and RFS for all subgroups of patients in the adjuvant S-1 group, but notably in those patients with an Eastern Cooperative Oncology Group performance status (PS) = 0, female gender, an R0 resection and a higher risk of recurrence, i.e. pN1 and/or stage III-IVA disease.[58] S-1 has thus become a favoured alternative to adjuvant capecitabine in the treatment of patients with resected BTC in some regions of Asia. As a consequence, it was decided to include adjuvant S-1 in 'recommendation 3i', as per the bold text below and in Table 1, to read as follows (**100% consensus**):

*3i. Adjuvant ChT with **S-1 [I, A] or** capecitabine **[II, A]** should be considered for patients with CCA or GBC following resection (**consensus** = **100%**).*

The Pan-Asian panel of experts felt that ESMO 'recommendation 3j' needed some clarification regarding the use of radiotherapy (RT) following adjuvant ChT for patients with GBC and eCCA. The US, prospective single-arm, phase II SWOG S0809 study of ChT followed by chemoradiotherapy (CRT) in patients with pT2-4, node-positive (N+) or margin-positive, resected eCCA and GBC reported similar median disease-free survival (DFS) (23 versus 26 months) and median OS (35 versus 34 months) rates for patients that were microscopically margin-positive (R1) and margin-negative (R0) after resection.[59,60] There was a difference in the 2-year DFS rate for patients with node-negative (N0) disease compared with N+ disease (62.5% versus 49.8%, respectively) and the distant recurrence was greater for N+ disease than N0 (42.2% versus 25.0%, respectively; HR 2.57; 95% CI 1.04-6.38; $P = 0.04$).[60] In this study, the local recurrence rates were similar (11.1% versus 8.3%; HR 1.13; 95% CI 0.30-4.28) which was in contrast to a large retrospective study from the United States and Netherlands which found positive lymph node status was an

independent prognostic factor (HR 2.65; 95% CI 1.48-4.69) for an initial isolated local recurrence,[61] suggesting improved local control for N+ patients receiving adjuvant radiotherapy.[60,61] The benefit of CRT in Asian patients with eCCA and residual tumour margins following resection were highlighted in a Korean study of 84 patients. Margin-negative (R0) patients received no adjuvant treatment whereas patients with R1 resection margins were treated with either adjuvant CRT or adjuvant RT. In a multivariate analysis, no difference in the 2-year OS rate was observed between the R0 patients (61.5%) and R1 plus CRT patient group (57.9%) but the 2-year OS rate was lower for the R1 + RT group (15.4%; HR 2.417; $P = 0.011$).[62] In a Korean retrospective study of 168 patients with extrahepatic BTC who underwent curative resection, treatment with adjuvant CRT was found to improve outcomes and was a significant prognostic factor for locoregional control, DFS and OS (all $P < 0.05$) compared with outcomes for patients who did not receive CRT.[63] In another Korean retrospective study, the outcomes of 336 patients with eCCA who underwent surgery were assessed.[64] Patients were grouped based on whether they had undergone surgery alone or surgery followed by either ChT, RT or CRT. In a multivariate subgroup analysis comparing outcomes for R1 resection patients, treatment with surgery followed by either RT or CRT had superior locoregional failure-free survival ($P = 0.008$ and $P = 0.001$, respectively) and PFS ($P = 0.017$ and $P = 0.001$, respectively) compared with surgery alone. While surgery with ChT improved distant metastasis-free survival ($P = 0.002$) more than with RT ($P = 0.257$) or CRT ($P = 0.013$), when compared with surgery alone.[64] In a meta-analysis comparing survival outcomes in patients with eCCA who received adjuvant RT to those who did not, a sensitivity pooled analysis was carried out using data from 14 studies with reliable comparability. The sensitivity analysis identified a long-term survival benefit trend for adjuvant RT, with a 5-year OS rate of 34.5% for those treated with adjuvant RT compared with 27.8% for those who were not treated with adjuvant RT ($P = 0.11$) despite patients receiving adjuvant RT having a pooled lower R0 resection rate and higher pN+ rate.[65] As a result of these findings, ESMO 'recommendation 3j', which reads:

3j. RT, after completion of adjuvant capecitabine, might be considered in selected patients (R1 resection of GBC or d/pCCA) [III, C]

was modified for clarity to include S-1, due to its preferred use in certain regions and the lack of approval of capecitabine in some regions of Asia, as per the bold text below and in Table 1, to read as follows (100% consensus):

*3j. **Following adjuvant S-1 or capecitabine, subsequent** RT **or CRT may** be considered in selected patients (R1 resection **and/or N+** GBC or d/pCCA) [III, C; **consensus = 100%**].*

Ablation is an option for patients with unresectable iCCA. In a systematic review and pooled analysis of locoregional therapies in patients with iCCA ablation, the use of either radiofrequency (RFA) or microwave ablation (MWA) was associated with a pooled complete response rate of 93.9% and a median OS of 30.2 months (95% CI 21.8-38.6 months).[66] Although these outcomes were superior to external beam RT, radioembolisation and transarterial chemoembolisation, they could be partially attributed to the smaller median size of tumours seen in patients receiving RFA/MWA.[66] One recent retrospective study to assess outcomes following resection or ablation, using data for patients with stage I-III iCCA from the US National Cancer Database (2010-2018), showed RFA achieved comparable OS to surgical resection in patients with iCCA whose tumours were <3 cm.[67] However, because the data from prospective studies are limited and treatment options vary across the different regions of Asia,[68,69] the Pan-Asian panel of experts downgraded the GoR for ESMO 'recommendation 3k' to '*B*', '*strong or moderate evidence for efficacy but with limited clinical benefit, generally recommended*' (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103647) with modification, as per the text in bold below and in Table 1, with **100% consensus,** to read as follows:

*3k. Local ablation **could** be considered **as an option** for patients with iCCA ≤3 cm who have contraindications or are otherwise unfit for surgery [III, **B; consensus = 100%**].*

Six out of the ten Asian oncological societies disagreed with ESMO 'recommendation 3m' and the use of intra-arterial therapies in combination with systemic ChT for patients with liver-limited iCCA because intraarterial therapy is not available in many regions of Asia and it was felt that there were limited data to support its use in routine clinical practice. However, although larger studies are required to further assess the efficacy of arterial chemoembolisation and transarterial radioembolisation,[70] intra-arterial therapies combined with ChT, including selective internal radiation therapy, transarterial infusion of irinotecan drug-eluting beads and hepatic arterial infusion pump ChT have shown promise for the treatment of iCCA[71-73] and, it was agreed, could be an option for consideration by multidisciplinary tumour boards (MDTB). Thus, ESMO 'recommendation 3m' was modified, as per the bold text below and in Table 1, to read as follows (**100% consensus**):

*3m. Intraarterial therapies, in combination with **systemic** ChT, can be **an option for** patients with liver-limited iCCA **and discussed by the MDTB according to local availability** [III, C].*

A proposed algorithm for the treatment of BTC is shown in Figure 1.

4. MANAGEMENT OF ADVANCED AND METASTATIC DISEASE—RECOMMENDATIONS 4A-O

Following discussion between the Pan-Asian panel of experts, which will be outlined below, the original 'recommendation

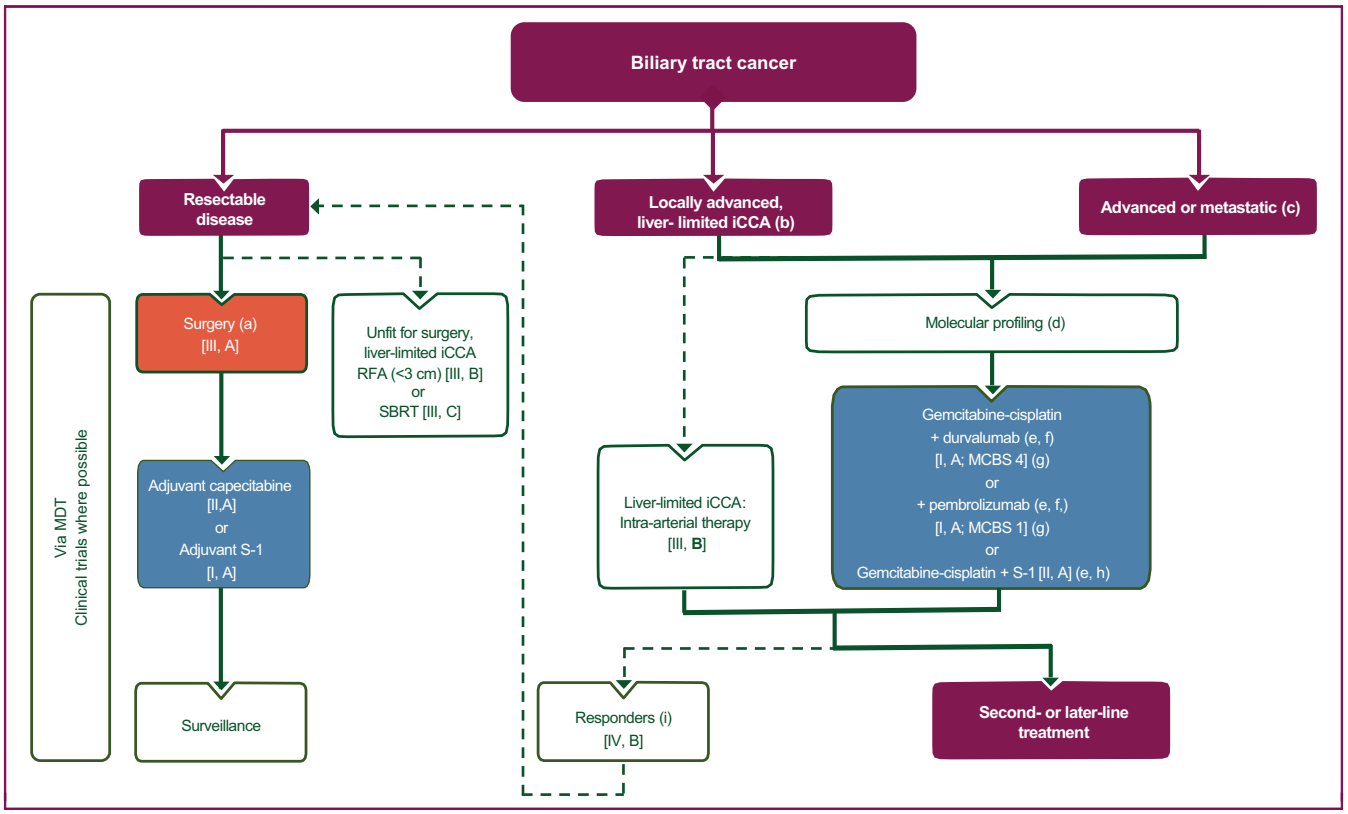

Figure 1. Algorithm for the treatment of biliary tract cancer. Purple boxes: general categories or stratification; red boxes: surgery; white boxes: other aspects of management; blue boxes: systemic anticancer therapy; dashed lines: optional recommendation.
ChT, chemotherapy; dCCA, distal cholangiocarcinoma; EMA, European Medicines Agency; FDA, US Food and Drug Administration; FGFR2, fibroblast growth factor receptor 2; GBC, gallbladder cancer; 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; RFA, radiofrequency ablation; S-1, tegafur, gimeracil and oteracil; SBRT, stereotactic body radiotherapy; RET, rearranged during transfection.
[a] Special 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.
[b] Salvage surgery or local therapies should be considered in responding patients with initially inoperable disease.
[c] Clinical trial recommended when available.
[d] Molecular profiling should be carried out before/during first-line therapy. Gene panel should include *FGFR2*, *IDH1*, *HER2*/neu and *BRAF* to test for hotspot mutations, but may also include genes such as *NTRK* and *c-MET*. The rapidly evolving landscape of drug targets and predictive biomarkers may necessitate larger panels in the future.
[e] Cisplatin-gemcitabine-durvalumab [I, A], cisplatin-gemcitabine-pembrolizumab [I,A] and cisplatin-gemcitabine-S-1 [II, A] are recommended for first-line treatment. Consider gemcitabine monotherapy in patients with a compromised PS or significant debility who are at risk of toxicity from platinum-containing ChT regimens; oxaliplatin or carboplatin can replace cisplatin in the presence of renal insufficiency or ototoxicity; gemcitabine plus S-1 can be considered for patients with or susceptible to peripheral sensory neuropathy.
[f] EMA and FDA approved.
[g] ESMO-MCBS v1.1[36] 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).
[h] Not FDA or EMA approved. (i) Reconsider surgery in the event of adequate response to treatment.

4a' from the pre-meeting survey (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.103647) was deleted and consequently, all subsequent recommendations were renumbered accordingly. Two new recommendations were proposed after the face-to-face meeting and were labelled 'recommendations 4l and 4m'. The original ESMO recommendations 'recommendations 4m-4p' concerned with best supportive care were relabelled 'recommendations 4n-4q'. No further changes were made to these recommendations. Including these, the Pan-Asian panel of experts agreed with and accepted completely (100% consensus) the renumbered ESMO recommendations, 'recommendations 4c, 4e, 4f, 4h, 4k and 4n-4q' (Table 1), without change.

At the face-to-face meeting, the Pan-Asian panel of experts agreed (**100% consensus**) to reject the original ESMO 'recommendation 4a', which reads:

'Cisplatin-gemcitabine is recommended as standard of care in the first-line setting for patients with a PS of 0-1 [I, A]'

because cisplatin-gemcitabine plus durvalumab demonstrated superior OS compared with cisplatin-gemcitabine plus placebo (HR 0.80; 95% CI 0.66-0.97; $P = 0.021$) in the randomised phase III, placebo-controlled TOPAZ-1 study in patients with previously untreated unresectable or metastatic BTC.[74] Addition of durvalumab also improved PFS (HR 0.75; 95% CI 0.6-0.89; $P = 0.001$) and the objective response rate (ORR) was 26.7% compared with 18.7% for

ChT alone.[74] As a result of these findings, the combination of durvalumab plus cisplatin-gemcitabine was given FDA approval in 2022 for the treatment of locally advanced unresectable or metastatic BTC.[39] The triplet combination covered by the original ESMO 'recommendation 4b' was renumbered as 'recommendation 4a' and all subsequent ESMO recommendations were also renumbered accordingly.

In the KEYNOTE-966 randomised, placebo-controlled phase III trial, addition of pembrolizumab to cisplatin-gemcitabine showed a superior survival benefit over the doublet chemotherapy (HR 0.83; 95% CI 0.72-0.95; one-sided $P = 0.0034$) in patients with previously untreated, unresectable, locally advanced or metastatic BTC.[75] As a result of these findings, the triplet of pembrolizumab-cisplatin-gemcitabine was given FDA approval for the treatment of locally advanced unresectable or metastatic BTC[38] and the Pan-Asian panel of experts felt the regimen should be included in the renumbered 'recommendation 4a'. Finally, two Japanese phase III studies investigated the efficacy of S-1 in combination with either gemcitabine or cisplatin-gemcitabine compared with cisplatin-gemcitabine in patients with advanced, unresectable BTC.[76,77] In the FUGA-BT (JCOG1113) trial of chemotherapy-naïve patients with recurrent or unresectable BTC, the median OS was 15.1 months for the gemcitabine-S-1 group compared with 13.4 months for the gemcitabine-cisplatin group (HR 0.945; 90% CI 0.777-1.149; *P* for non-inferiority = 0.046).[77] The 1-year survival for patients in the gemcitabine plus S-1 group was 59.2% compared with 58.3% for those in the gemcitabine-cisplatin group and the median PFS was 6.8 months compared with 5.8 months (HR 0.864; 95% CI 0.697-1.070), respectively. The study met its primary endpoint for the non-inferiority of gemcitabine-S-1 versus gemcitabine-cisplatin combination.[77] In the KHBO1401-MITSUBA trial, patients with BTC with recurrence after surgery or for whom curative surgery was not an option were recruited and randomised to receive cisplatin-gemcitabine with or without S-1. The OS for patients in the triplet group was 13.5 months compared with 12.6 months for patients in the doublet group (HR 0.79; 90% CI 0.628-0.996; $P = 0.046$).[76] The 1-year survival rates for the cisplatin-gemcitabine-S1 and cisplatin-gemcitabine groups were 59.4% and 53.7%, respectively, with median *PFS* of 7.4 months and 5.5 months, respectively.[76] It was felt by the Pan-Asian panel of experts that the triplet of cisplatin-gemcitabine plus S-1 should be the preferred option and included in the modified recommendation. As a result of these discussions, the renumbered 'recommendation 4a' was modified from:

'*The combination of cisplatin-gemcitabine with durvalumab should be considered in first-line BTC [I, A; ESMO-Magnitude of Clinical Benefit (MCBS) v1.1 score: 4]*' to read, with the changes shown in bold text below and in Table 1, to read as follows (**100% consensus**):

4a. The combination of cisplatin-gemcitabine with durvalumab ***or pembrolizumab*** *should be considered* ***as the standard of care*** *in first-line BTC [I, A; ESMO-MCBS v1.1 score* ***for durvalumab****: 4****; ESMO-MCBS v1.1 score for pembrolizumab: 1****]. Cisplatin-gemcitabine-S-1 is an alternative therapeutic option for fit patients [II, B; consensus = 100%].*

Adverse effects of cisplatin treatment include nephrotoxicity and ototoxicity, which can impair auditory function.[78,79] Therefore, alternatives to cisplatin may be required for some patients. In the original ESMO 'recommendation 4c', oxaliplatin was suggested as a substitute (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.103647) and, although a modified gemcitabine-oxaliplatin regimen failed to show equivalence with cisplatin-gemcitabine in an Indian phase III trial of patients with unresectable GBC, the modified gemcitabine-oxaliplatin regimen had a numerically better median OS and lower instances of nephrotoxicity compared with cisplatin-gemcitabine.[80] However, approval and access to oxaliplatin for BTC is an issue in several regions of Asia. An Indian phase II study investigating gemcitabine plus carboplatin in 20 patients with unresectable GBC reported a 43.3% 1-year survival rate and a ORR of 36.7%.[81] The doublet of gemcitabine plus carboplatin also showed efficacy in a US phase II trial in patients with advanced BTC where the OS was 10.6 months, the 12-month OS rate was 43.8% and the ORR was 31.1%.[82] These were reported to be comparable to historical gemcitabine-platinum and gemcitabine-fluoropyrimidine combinations.[82] The frequency of peripheral sensory neuropathy was less frequent in patients with advanced BTC who were treated with gemcitabine plus S-1 (3.4%) compared with those treated with gemcitabine plus cisplatin (15.8%) in the FUGA-BT (JCOG1113) randomised phase III trial.[77] Thus, it was agreed with **100% consensus** to include carboplatin as another treatment option in the renumbered 'recommendation 4b' which was modified, as per the text in bold below and in Table 1, to read as follows:

4b. Oxaliplatin ***or carboplatin*** *may be substituted for cisplatin when renal or auditory function is of concern,* ***while gemcitabine plus S-1 can be an option for patients who present with or are susceptible to peripheral sensory neuropathy*** *[II, B;* ***consensus = 100%****].*

There was a great deal of discussion around the original ESMO 'recommendation 4e' and second- and later-line treatment for advanced and metastatic BTC. While the Pan-Asian panel of experts agreed with the use of the combination of folinic acid, 5-fluorouracil (5-FU) and oxaliplatin (FOLFOX) in this setting based on the ABC-06 phase III randomised study comparing FOLFOX ChT with active symptom control for advanced BTC,[83] it was pointed out that, because the study population did not include Asian patients, the results may be different for this population. Furthermore, FOLFOX treatment showed a limited survival benefit compared with active symptom control (6.2 months for FOLFOX versus 5.3 months for active symptom control). As a result, the GoR was downgraded from '*A*' to '*B*'. Moreover, because the ABC-06 trial is the only positive phase III trial for the second-line treatment of BTC, the LoE

was also downgraded from *'I'* to *'II'*. It was also felt that other treatment options should be taken into consideration because of the lack of approval of FOLFOX for the treatment of BTC in some regions of Asia coupled with the fact that clinical outcomes data are available for other therapeutic regimens, such as those containing irinotecan. A Korean randomised phase II study investigated the superiority of a combination of folinic acid, 5-FU and irinotecan (FOLFIRI) over FOLFOX in the second-line setting in patients with locally advanced or metastatic BTC that were refractory to first-line cisplatin-gemcitabine treatment. The 6-month OS rate was 44.1% for FOLFIRI and 54.1% for FOLFOX ($P = 0.677$). At the 2-year follow-up, the median OS was 5.7 months for the FOLFIRI group and 6.3 months for the FOLFOX group ($P = 0.677$) and the median PFS was 2.1 months and 2.8 months ($P = 0.974$), respectively. Although FOLFIRI was not superior in this setting, it showed comparable efficacy to FOLFOX.[84] Another option discussed was the use of nanoliposomal irinotecan (Nal-IRI) which was assessed in the Korean prospective, randomised phase IIb NIFTY trial where patients with advanced BTC, who had progressed on cisplatin plus gemcitabine, were treated with 5-FU plus folic acid with or without Nal-IRI. The primary endpoint, median PFS as determined by blinded independent central review, was 4.2 months for those patients receiving Nal-IRI compared with 1.7 months in the 5-FU/folic acid-alone group (HR 0.61; 95% CI 0.44-0.86; $P = 0.004$).[85] However, these data contrast with the findings of the German prospective, randomised phase II NALIRICC trial of previously treated patients with GBC and CCA where no difference in clinical benefit was observed between 5-FU plus folic acid alone and in combination with Nal-IRI in terms of median OS (8.21 months versus 6.9 months, respectively) and median PFS (2.3 months versus 2.76 months, respectively), despite an improved ORR (3.9% versus 14.3%, respectively).[86] Irinotecan monotherapy was also discussed and has been investigated as part of the Indian randomised phase II GB-SELECT trial for patients with GBC who had progressed on gemcitabine-based ChT.[87] In this study the efficacy of irinotecan, both alone and in combination with capecitabine, was assessed and the median OS for the capecitabine-irinotecan group was 5.16 months compared with 6.28 months for the irinotecan-alone group (HR 0.98; 95% CI 0.61-1.57; $P = 0.93$) and the 6-month OS rates were 38.4% and 54.2%, respectively. The data outlined above highlight the antitumour efficacy of irinotecan-containing therapeutic regimens for the second-line treatment of BTC and the Pan-Asian panel of experts agreed to include such regimens in the renumbered 'recommendation 4d', as per the text in bold below and in Table 1, to read as follows (**100% consensus**):

*4d. FOLFOX is the standard of care in the second-line setting after cisplatin-gemcitabine-**based treatment** [**II, B**; ESMO-MCBS v1.1 score: 1; no specific licensed indication in BTC]. **Irinotecan monotherapy or irinotecan- or liposomal-irinotecan-based combination therapy may be considered [III, B; consensus = 100%].***

During the drafting of the guidelines, it was suggested that the newly renumbered 'recommendation 4g' be amended to take into account the use of immune checkpoint inhibitors as an option in the first-line setting. The use of immune checkpoint inhibitors in the second- or later-line setting should only be considered in patients who have not previously received immune checkpoint inhibitor-containing treatment. Thus 'recommendation 4g' was amended to include the text shown in bold below and in Table 1, to read as follows (**100% consensus)**:

*4g. Pembrolizumab is recommended in patients with MSI-H/dMMR who have progressed on or are intolerant to prior **non-immune checkpoint inhibitor-containing** treatment [III, A; ESMO-MCBS v1.1 score: 3; ESCAT score: I-C].*

As highlighted in the introduction, BTC has multiple recurrent genetic aberrations. Many of these are actionable, including *IDH1* mutations, *FGFR2*-fusions, *BRAFV600E* mutations, *BRCA1/2* mutations, *PALB2* mutations, *NTRK fusions* and *HER2* aberrations, which are covered by the newly renumbered 'recommendations 4e, 4f and 4i-k', respectively. However, as will be discussed in section B, which covers the applicability of the recommendations below, there is a great discrepancy between the approval and availability of many of these drugs across the different regions of Asia (see also Supplementary Tables S3-S13, available at https://doi.org/10.1016/j.esmoop.2024.103647). Despite this, and following discussion, the Pan-Asian panel of experts agreed the newly renumbered 'recommendation 4h' (Table 1) and the use of the combination of the type I BRAF inhibitor, dabrafenib, with MEK inhibitor, trametinib, for the treatment of *BRAFV600E*-mutated BTC without modification (**100% consensus**).

Discussion around the newly renumbered 'recommendation 4i' and the use of poly (ADP-ribose) polymerase (PARP) inhibitors in the second- and later-line settings for patients with *BRCA1/2*- or *PALB2*-mutated BTC focused on evidence which some members of the Pan-Asian panel of experts felt was sparse and was largely limited to case studies and a retrospective analysis of 18 patients with CCA with either germline or somatic *BRCA1/2* variants where 4 were treated with PARP inhibitors with an OS ranging from 11.01 to 64.76 months.[88,89] However, PARP inhibitors have proven to be efficacious in a number of platinum-sensitive *BRCA1/2*- and *PALB2*-mutated tumours, including ovarian and pancreatic cancer.[90-93] Based on the favourable results from clinical trials in these other solid tumours, the Pan-Asian panel of experts agreed that PARP inhibitors could be a treatment option for patients with *BRCA1/2*- or *PALB2*-mutated BTC who have responded to platinum-based therapy and thus 'recommendation 4i' was agreed with the following modification as per the bold text below and in Table 1, to read as follows (**100% consensus**):

4i. Patients with BRCA1/2 or PALB2 mutations responding to platinum-based therapy can be considered for

*treatment with PARP inhibitors**, preferably within clinical trials** [V, B; ESCAT score: III-A].*

It is estimated that *HER2* is amplified in 10%-15% of cases of GBC.[34] HER2-directed therapies, including the anti-HER2 antibody, trastuzumab, and the antibody—drug conjugate, trastuzumab-deruxtecan, have been approved for the treatment of HER2-positive breast cancer and are being assessed as therapeutic options for other types of cancer including BTC. Indeed, in the DESTINY-PanTumor02 phase II study assessing trastuzumab-deruxtecan in patients with HER2-expressing solid tumours, 41 patients with BTC were treated, for which an ORR of 56.3% was reported for 16 patients with IHC 3+ HER2-expressing disease, a median PFS of 7.4 months and median OS of 12.4 months was seen in these patients.[94] In the MyPathway phase IIa multiple basket study, an ORR of 23% was seen in 39 patients with HER–positive BTC treated with trastuzumab in combination with pertuzumab.[95] The humanised anti-HER2 bi-specific monoclonal antibody zanidatamab was assessed in the phase IIb HERIZON-BTC-01 study where an ORR was seen in 41.3% of patients with IHC 2+ or 3+ HER2-positive BTC who had previously been treated with gemcitabine.[96] Trastuzumab in combination with tucatinib, a tyrosine kinase inhibitor that is highly selective for HER2, showed clinical activity with a confirmed ORR of 46.7% in a phase II study of patients with previously treated, HER2-positive metastatic BTC.[97] Furthermore, in an Indian phase II study, the feasibility of combining trastuzumab with cisplatin-gemcitabine was explored in patients with HER2-positive, treatment-naïve BTC. With a median PFS of 7 months, the study achieved its primary endpoint of improving PFS compared with historical data, and the overall disease control rate was 80%, with 55.5% of patients having either a complete or partial response.[98] As a result of these findings, the Pan-Asian panel of experts agreed with the original ESMO 'recommendation 4l', although there was some discussion around the applicability and testing available in different regions of Asia for HER2-directed therapies in BTC. It was also felt that some clarification was needed regarding which patients could be considered for HER2-directed therapies and, as such, the recommendation was modified as per the text in bold below and in Table 1 to read as follows (**100% consensus**):

*4k. HER2-directed therapies can be considered in patients with **HER2 overexpression/amplification** who have progressed on or are intolerant to prior treatment [III, A; ESCAT score: I-C; **consensus = 100%**].*

During the drafting of the manuscript, two new recommendations for the treatment of patients whose tumours have *RET* fusions and those with TMB-H status were proposed as outlined below. It was thus suggested that they be kept with the other recommendations for the second- and later-line treatment options for BTC. The original ESMO 'recommendations 4m-4p' which cover supportive care were thus relabelled as 'recommendations 4n-4q'. No further changes were made to these recommendations.

Although fusions involving the *RET* gene are rare in BTC, accounting for <1% of tumours,[99,100] the RET kinase inhibitor, selpercatinib, has been approved by the FDA for the treatment of adult patients with locally advanced or metastatic solid tumours with a *RET* gene fusion that have progressed on or following prior systemic treatment.[101] This approval was based on the phase I/II LIBRETTO-001 basket trial where the ORR was 44% and median duration of response was 24.5 months.[102] Following the face-to-face meeting, and as a result of these findings, the Pan-Asian panel of experts retrospectively agreed that the selpercatinib should be included and a new 'recommendation 4p' was proposed to read as follows and in Table 1 (**100% consensus**):

4l. Selpercatinib can be considered in patients with RET fusions who have progressed on or are intolerant to prior treatment [III; A; ESMO-MCBS v1.1 score for solid tumours with a RET fusion: 3; ESCAT score: I-C; FDA approved, not EMA approved; consensus = 100%].

The recommended first-line treatment for patients with advanced BTC is cisplatin-gemcitabine plus either durvalumab or pembrolizumab, although cisplatin-gemcitabine-S1 is also an option (see 'recommendation 4a' above and in Table 1). In a Chinese study that analysed the mutational spectrum of 803 BTC samples, 33 (4.1%) were hypermutated.[103] Furthermore, TMB-H status was found in the tumours of 18.5% of Korean patients with BTC who had been treated with gemcitabine-cisplatin. Although TMB-H status was found not to significantly affect the clinical outcomes of patients receiving gemcitabine-cisplatin treatment, as measured by ORR, disease control rate and OS, a subgroup analysis of 32 patients who had received immune checkpoint inhibitors in the second-line setting found a significant difference between TMB-H tumours and non-TMB-H tumours for ORR (3/5 [60%] versus 3/27 [11.1%]; $P=0.034$) and median PFS (7.4 months versus 2.2 months, respectively; $P=0.025$).[104] The impact of TMB on the response of BTC to immune checkpoint inhibitors was also observed in a US study.[105] These studies highlight the potential of TMB as a biomarker for immune checkpoint inhibitors. Following the face-to-face meeting and because FDA approval has been granted for the tumour-agnostic treatment of patients with unresectable or metastatic TMB-H (≥10 mutations/megabase) solid tumours, the Pan-Asian panel of experts retrospectively agreed that the use of pembrolizumab for the treatment of patients with TMB-H tumours who have not previously been treated with checkpoint inhibitors should be included and a new 'recommendation 4q' was proposed which reads as follows and in Table 1 (**95% consensus**):

4m. Pembrolizumab can be considered in patients with TMB-H tumours who have progressed on or are intolerant to prior non-immune checkpoint inhibitor-containing treatment [IV; A; ESMO-MCBS v1.1 score

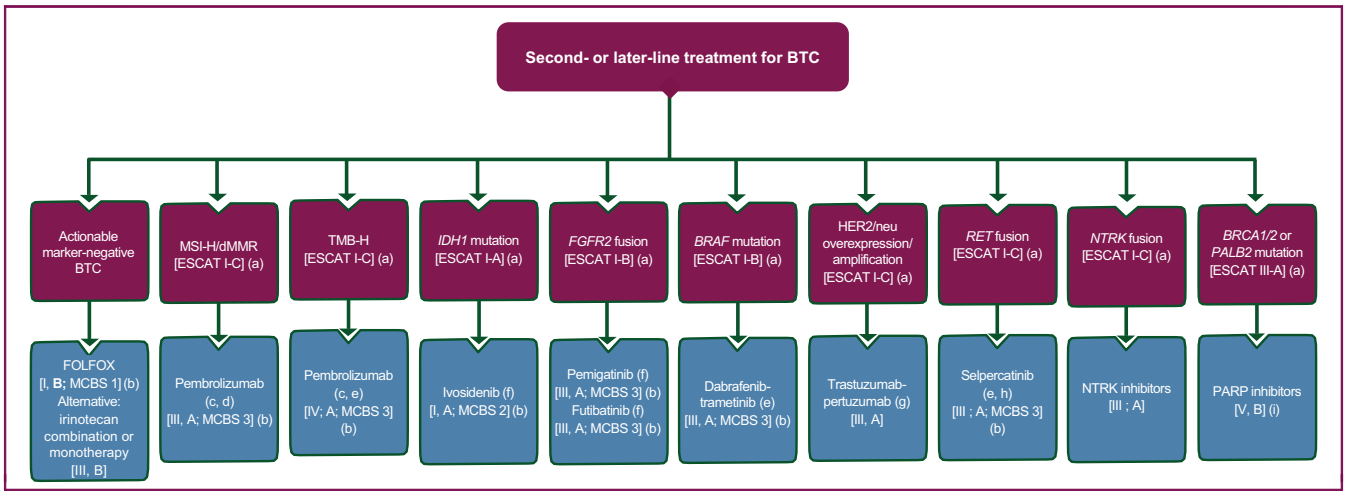

Figure 2. Algorithm for the second- and later-line treatment of biliary tract cancer. Burgundy: general categories or stratification; blue: systemic anticancer therapy. BTC, biliary tract cancer; dMMR, mismatch repair deficiency; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FDA, Food and Drug Administration; FGFR2, fibroblast growth factor receptor 2; FOLFOX, 5-fluorouracileleucovorineoxaliplatin; HER2, human epidermal growth factor receptor 2; IDH1, isocitrate dehydrogenase 1; MCBS, ESMO-Magnitude of Clinical Benefit Scale; MSI-H, microsatellite instability-high; NTRK, neurotrophic tyrosine receptor kinase; PARP, poly (ADP-ribose) polymerase; PD-1, programmed cell death protein 1; RET, rearranged during transfection; TMB-H, tumour mutational burden-high.
[a] ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the authors of the ESMO biliary tract guidelines and validated by the ESMO Translational Research and Precision Medicine Working Group.[35,37]
[b] ESMO-MCBS v1.1[36] 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).
[c] Anti-PD-1 therapy is recommended for patients with MSI-H/dMMR who have not been treated with first-line immunotherapy or for patients with unresectable or metastatic TMB-H (≥10 mutations/megabase) solid tumours that have progressed following prior treatment.
[d] EMA approved for MSI-H/dMMR BTC; FDA approved for all MSI-H/dMMR solid tumours.
[e] FDA approved; not EMA approved.
[f] EMA and FDA approved.
[g] Not EMA approved; not FDA approved.
[h] Selpercatinib is recommended for adult patients with locally advanced or metastatic tumours with a *RET* fusion that have progressed following prior treatment.
[i] Clinical trial recommended when available.

for pembrolizumab in TMB-H solid tumours: 3; ESCAT score: I-C; consensus = 95%].

A proposed algorithm for the second- and later-line treatment of BTC is shown in Figure 2.

5. FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP—RECOMMENDATIONS 5A-E

The Pan-Asian panel of experts agreed with and accepted completely (100% consensus) the original ESMO recommendations, 'recommendations 5a-e' (Table 1), without change.

Applicability of the recommendations

Following the face-to-face meeting in Singapore, the Pan-Asian panel of experts agreed and accepted completely (100% consensus) the revised ESMO recommendations for the diagnosis, treatment and follow-up of BTC in patients of Asian ethnicity (Table 1). However, the applicability of each of the guideline recommendations is impacted by the individual drug and testing approvals and reimbursement policies for each region. The drug and treatment availability for the regions represented by the 10 participating Asian oncological societies is summarised in Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2024.103647, and individually for each region in Supplementary Tables S4-S13, available at https://doi.org/10.1016/j.esmoop.2024.103647.

CSCO. The vast majority of hospitals in mainland China (China) are public and the healthcare system is covered by social insurance for 80%-90% of patients. There are different levels of reimbursement depending on insurance but there are still about 10%-20% of patients who will have no reimbursement for their treatment because of a variety of reasons including poor accessibility to nationwide insurance systems and, to some extent, a lack of insurance awareness. Mutation analysis is limited to sequencing five cancer genes, *RAS, EGFR, HER2, BRCA* and *BRAF,* and 40% of the cost is paid 'out of pocket' (see Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2024.103647). There is no reimbursement for next-generation sequencing (NGS)-based molecular profiling. With the exception of pemigatinib, pembrolizumab and durvalumab, most targeted therapies have not been approved in China for the treatment of BTC and are not reimbursed. Nevertheless, almost all the robust evidence-based targeted and immunotherapy drugs including domestic anti-programmed cell death protein 1 antibody products, such as camrelizumab and toripalimab, are recommended in the national guidelines for first-line treatment in combination with ChT or other specified indications in China. Furthermore, in the same national guideline, the vascular endothelial growth factor receptor inhibitors anlotinib and sulfatinib have been approved for

second-line treatment. It might take between 2 and 5 years for drugs to be approved in China following European Medicines Agency (EMA)/FDA approval, but once approval is granted drugs can be available to patients within 1-3 months. Pricing and insurance coverage can limit access to new treatments, whereas delayed government approval and insurance coverage can limit access to new biomarker-related diagnostic tests and tools.

ISHMO. The Indonesian National Health Insurance (NHI) covers 90% of the population. However, this only covers the minimum standard of care for cancer treatment and, in terms of BTC, only covers infusional 5-FU in combination with platinum-based ChT. This means that all but the 5% of patients who have private insurance will likely contribute 'out of pocket' expenses for their treatment. Access to biomarker-related diagnostic testing in Indonesia is limited and these are not reimbursed. While pembrolizumab and trastuzumab have been approved in Indonesia, most targeted therapies have not (see Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2024.103647), and it can take 1-3 years for approval to be granted following EMA/FDA approval. Once approval has been given in Indonesia, it can take between 3 months and 1 year for drugs to become available because of the price and availability.

ISMPO. In India, there is increasing coverage for systemic therapy, predominantly ChT for first-line treatment, in central and state government health schemes. Government and employers' insurance schemes cover ∼60% of patients for their cancer treatment. These schemes do not cover biomarker-related diagnostic tests, including PCR and NGS assays, meaning that ∼95% of patients will have to pay for these assays in full. With rare exceptions, most insurance schemes do not cover targeted therapy or immunotherapy despite approval being given for some of these (see Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2024.103647). In India, it can take ∼6 months for approval of drugs once approval has been given by the EMA or FDA and this can be longer for orphan drugs. Once national approval has been granted, new drugs are often available to patients with immediate effect.

JSMO. In Japan, universal healthcare is staggered depending on age, with adults aged under 70 required to pay for 30% of their treatment costs, those aged 70-74 pay 20% and those 75 and older, 10%. Nearly all (>99%) patients' treatments are covered by Japanese insurance which typically, depending on income, will reimburse any expenses over ∼¥80,000 (∼ €500) per month. This means that only those patients who do not have insurance will have to cover all of their expenses. All drugs and biomarker-related diagnostic tests and tools need to have been assessed in Japanese patients before being approved by the Japanese Pharmaceuticals and Medical Devices Agency. Therefore, if the EMA or FDA gives approval for a drug based on a global clinical trial which did not involve Japanese patients, then approval in Japan will not be granted until the efficacy and safety has been assessed in a clinical trial involving Japanese patients. For example, despite receiving EMA and FDA approval, the IDH1 inhibitor ivosidenib has not been approved in Japan because there are no data for Japanese patients. Approval of drugs that have been assessed in Japanese patients usually occurs within 1 year of EMA/FDA approval. Once approved, access can be immediate although if a drug has not been given prior approval in Japan, it can take 2-3 months for reimbursement. Adjuvant capecitabine is not approved for the treatment of BTC although S-1 is available for use in the adjuvant setting (Supplementary Table S7, available at https://doi.org/10.1016/j.esmoop.2024.103647). Immunotherapies are approved for the treatment of BTC in Japan as are the FGFR inhibitors, pemigatinib and futibatinib, and NTRK inhibitors. The combination of dabrafenib and trametinib has also recently been approved for hard-to-treat *BRAF*-mutated advanced or relapsed solid tumours including BTC. In Japan, mutational screening is carried out using NGS but, at present, is only reimbursed for patients with BTC who have progressed on or after their first line of treatment.

KSMO. The entire population of Korea is covered by the national health insurance system. For cancer patients, reimbursement for biomarker-related diagnostic testing is tapered depending on the stage of their disease, with patients with stage III/IV disease receiving 50% reimbursement and those with stage I/II disease receiving a reimbursement of 10%. Although many targeted therapies have been approved for the treatment of BTC, only NTRK inhibitors are currently reimbursed, meaning the majority of patients will pay 'out of pocket' for their treatment (Supplementary Table S8, available at https://doi.org/10.1016/j.esmoop.2024.103647). In Korea, national approval can take between 1 and 2 years following EMA or FDA approval but, once national approval has been given, drugs are available immediately. Reimbursement and costs for new drugs is a major limiting factor.

MOS. Malaysia has a two-tier healthcare system consisting of co-existing universal (public sector) health care and private healthcare systems. It is estimated that 60% of patients have private insurance and 10% have employer/social insurance. The remaining 30% of patients will have to pay all their drug costs because they do not have insurance. In Malaysia, the public sector is the largest payer for healthcare, reimbursing payments by patients although there are constraints due to cost. As a result of these constraints, biomarker-related diagnostic testing, including mutational and NGS molecular analysis, are not reimbursed in Malaysia. In terms of drugs available for treating BTC, adjuvant capecitabine is approved and fully reimbursed whereas durvalumab is approved but not reimbursed. At present, no targeted therapies used to treat BTC are currently approved for this indication despite many being approved for other indications in Malaysia (see Supplementary Table S9, available at https://doi.org/10.

1016/j.esmoop.2024.103647). Drug approval in Malaysia can take 1-2 years after approval has been granted by the FDA or EMA. Once approval is given, drugs can be available immediately for private patients.

PSMO. A major challenge for healthcare in the Philippines is in patient accessibility and quality of care. The Philippine health care system is a mix of public and private providers. Philippine NHI covers ∼90% of patients providing the equivalent to ∼$120 USD towards the cost of treatment only. It is estimated that ∼70% of patients have no other insurance beyond NHI meaning they will have to pay for the majority of costs towards any treatments that are not covered by the national formulary. At present, immunotherapies and targeted therapies are not covered by the national formulary for the treatment of BTC or are limited by cost of treatment (see Supplementary Table S10, available at https://doi.org/10.1016/j.esmoop.2024.103647). There is no reimbursement for diagnostic tests such as mutational and molecular analyses with cost and availability, as well as the limited capacity of specialised centres being the biggest limiting factors for accessing new biomarker-related diagnostics. In the Philippines it can take between 1 and 2 years for national approval of a drug once it has been approved by the EMA or FDA. It can then take a further year for new drugs to be available for patients with costs being one of the biggest factors around the access to new treatments.

SSO. The healthcare system of Singapore uses a mixed financing system that includes nationalised insurance schemes (MEDISHIELD LIFE) and deductions from compulsory savings (MEDISAVE). Government subsidies (Medication Assistance Fund) are available for a proportion of drug costs, but this is dependent on monthly per capita household income and only covers the costs of those approved drugs on Singapore's cancer drug list. It is estimated that ∼70% of patients have supplementary private insurance while 10% have employer/social insurance which helps towards the costs of those drugs not on Singapore's cancer drug list and will help to cover the cost of diagnostic tests such as NGS (see Supplementary Table S11, available at https://doi.org/10.1016/j.esmoop.2024.103647). It can take 3-12 months for national approval in Singapore following EMA/FDA approval and once approved, drugs can be available almost immediately although it can take between 3 and 12 months for a drug to appear on the cancer drugs list and be available for reimbursement. Costs are the biggest limiting factors for accessing new treatments and new biomarker-related diagnostics.

TOS. Taiwan's NHI covers >99.9% of the population,[106] providing comprehensive medical care, meaning no patients pay entirely 'out of pocket' for drug costs, once the drugs or tests have been approved for reimbursement by the NHI. However, the system faces challenges related to funding sustainability and rising healthcare costs which can delay reimbursement for new drugs. Certification on genetic testing methods poses a challenge as well. NGS testing for BTC has been adopted through a registration programme supported by the Taiwanese government research funding after August 2021, and will have NHI reimbursement coverage from 2024 Q2 or Q3. NHI covers 100% of costs for first-line gemcitabine plus cisplatin and/or S-1 therapy, and pemigatinib for the second-line and beyond treatment of BTC in Taiwan (see Supplementary Table S12, available at https://doi.org/10.1016/j.esmoop.2024.103647). Other targeted therapies and immunotherapies are not approved for BTC and are not covered by the NHI. In Taiwan it can take 2 years for national approval to be granted following approval by the FDA or EMA but, once approval is given, drugs are typically available within 2 months while NHI reimbursement will be further delayed due to financial impact evaluation.

TSCO. In Thailand, a universal healthcare scheme is structured to provide treatment to the majority of patients without any payment. Access to medications is restricted to those on the national essential drugs list, which are chosen based on economic considerations relative to the gross domestic product of Thailand. Therefore, capecitabine and cisplatin-gemcitabine are the standard of care for patients with early and advanced BTC, respectively, and all targeted therapy and biomarker-related tests are not covered for most patients (see Supplementary Table S13, available at https://doi.org/10.1016/j.esmoop.2024.103647). In Thailand, approval for new drugs can take 2 years once approved by the EMA or FDA, but once approved, the drugs are made immediately available to patients.

CONCLUSIONS

The results of the voting by the Asian experts both before and after the face-to-face meeting in Singapore showed 68.1% concordance with the ESMO recommendations for the treatment of patients with BTC (Supplementary Table S2 and Figure S1, available at https://doi.org/10.1016/j.esmoop.2024.103647). These recommendations therefore constitute the consensus clinical practice guidelines for the treatment of patients with BTC in Asia. The variations in the availability for the patients of diagnostic testing, drugs and therefore treatment possibilities, between the different regions represented, reflect the differences in the organisation of their healthcare systems and their reimbursement strategies, and will have a significant impact on the implementation of the scientific recommendations in certain regions. Thus, policy initiatives are advised, based on this guideline document, in order to improve the access of all BTC patients across all the Asian regions.

ACKNOWLEDGEMENTS

The authors would like to thank the leaders of ESMO and TOS for their support in facilitating this face-to-face meeting. They would also like to thank Klizia Marinoni and Fiona Perdomo from the Scientific and Medical Division of ESMO for the project management and scientific coordination, Kennedy Ng of ESMO Leaders Generation

Programme for his participation, Zarina Othman and Aries Low from the ESMO Singapore Office for the logistical support and Bonnie Z.L. Lai of TOS for the logistic organisation of the face-to-face meeting of experts. Nicola Latino, ESMO Head MSD of Scientific Affairs, is acknowledged for her contribution in confirming the ESMO-MCBS scores. Svetlana Jezdic, ESMO Medical Affairs, is acknowledged for her contribution in confirming the ESCAT scores. Anne Kinsella and Nick Davies of Cancer Communications and Consultancy Ltd, Cheshire, UK are acknowledged for their contribution to the preparation of the manuscript.

FUNDING

All costs relating to this consensus conference were covered by the ESMO and TOS from central dedicated funds. There was no external funding of the event or the manuscript production.

DISCLOSURE

LTC declares speaker's engagement from BMS, C-Stone (TW), Eli Lilly, Ipsen, Novartis, ONO, PharmaEngine (TW) and TTY (TW); steering committee/advisory board role from AstraZeneca, MSD, ONO, Onward, Pfizer, ScinoPharm Taiwan and SynCore (TW); trial chair/DSMC member for clinical trials from Celgene, OBI (TW), SynCore BioPharma and TTY; employment from Kaohsiung Medical University Hospital and the National Institute of Cancer research (Taiwan); licencing fees for alpha-enolase specific antibodies from HuniLife Biotechnology, Inc; non-renumerated PI role from the Taiwan Cooperative Oncology Group; non-renumerated leadership role from the Taiwan NeuroEndocrine Tumor Society (TNETS) and Asian Oncology Society (AOS); non-renumerated International Steering Committee Member (ISCM) from JSMO; product samples from ACTgenomics (TW), SynCore BioPharma and TTY. AV declares speaker's engagement from AstraZeneca, BMS, Eisai, IPSEN, Lilly, MSD and Roche; steering committee/advisory board role from Amgen, AstraZeneca, Beigene, Bohringer Mannheim, Eisai, Incyte, IPSEN, Janssen, Jiangsu Hengrui Medicines, MSD, Roche, Servier, Tahio and Tyra. CH declares speaker's engagement from AstraZeneca, Bayer, BMS/ONO, Eisai, Roche and TTY Biopharm; advisory board role from AstraZeneca; coordinating PI role from BMS/ONO and Roche.

AS declares local PI role from Alembic Pharma; stocks/shares from Dr Reddys Laboratory, Gland Pharma and Zydus Wellness; non-renumerated PI role from Alembic Pharma. MI declares speaker's engagement from Abbott Japan, AbbVie, AstraZeneca, Bristol-Myers Squibb, Chugai Eisai, Eli Lilly Japan, Fujifilm Toyoma Chemical, Guardant Health Japan, Incyte Biosciences Japan, MSD, NIHON SERVIER, Nippon Kayaku, Novartis, ONO, Taiho, Taisho, Takeda, Teijin Pharma and Yakult; steering committee/advisory board role from AstraZeneca, Chugai, Eisai, Eli Lilly Japan, MSD, NIHON SERVIER, Novartis, Rakuten Medical and Takeda; coordinating PI role from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiome Bioscience, Chugai, Delta-Fly Pharma, Eisai, Eli Lilly Japan, Invitae, J-Pharma, Merck Biopharma, Merus N.V., MSD, NIHON SERVIER, Novartis, ONO, Pfizer and Syneos Health. JOP declares advisory board role from Adicet, AstraZeneca, BMS (Celgene), Immune Oncia, MediRama, MedPacto, Merck, Merck Sereno and Servier; research grant from ABL Bio, BMS (Celgene) Eutilex, MedPacto and Servier; travel support from Minneamrita Therapeutics LLC.

ER declares employment/active consultant role from the University of Sano Toma, Diliman Doctors' Hospital and The Medical City Hospital. DT declares advisory board role from Bayer, BMS, Celgene, Eisai, MSD, Novartis and SIRTEX. ST declares speaker's engagement from Amgen, BMS, Eisai, Ipsen, Merck, MSD, Novartis, Pfizer and Roche; local PI role from Amgen, AstraZeneca, MSD and Roche. CC declares local PI role from AstraZeneca, Boehringer Ingelheim, Exelixis, MSD, Novartis and Roche. CEC declares speaker's declaration from Amgen; advisory board role from AstraZeneca, Merck and Roche; educational meeting role from Pierre Fabre. AL declares speaker's engagement from Amgen, AstraZeneca, Eli Lilly, Hi Esai, Johnson and Johnson, Merck, MSD, Nestle, Novartis and Pfizer; consultancy/advisory role from AstraZeneca, Eli Lilly, Merck, MSD, Novartis and Pfizer; funding as local PI from Arcus Biosciences, AstraZeneca, MSD and Roche; institutional funding from Pfizer; non-renumerated activity as member of the Philippine Society of Medical Oncology. DYO declares advisory board role from Arcus Biosciences, ASLAN, AstraZeneca, Basilea, Bayer, BeiGene, BMS/Celgene, Genentech/Roche, Halozyme, IQVIA, Merck Serono, MSD, Novartis, Taiho, Turning Point, Yuhan and Zymeworks; research grant from Array, AstraZeneca, BeiGene, Eli Lilly, Handok, MSD, Novartis and Servier. MU declares speaker's engagement from AstraZeneca, Chugai Pharmaceutical, Daiichi Sankyo, Incyte, MSD, Nihon Servier, Ono Pharmaceutical, Taiho Pharmaceutical and Takeda Pharmaceutical; advisory board role from Nippon Boehringer Ingelheim and Novartis; local PI role from Astellas Pharma, AstraZeneca, Chugai Pharmaceutical, Daiichi Sankyo, DFP, Eisai, Incyte, Merck Biophama, MSD, Novartis, Ono Pharmaceutical and Taiho Pharmaceutical. AR declares institutional research grant from Cipla Health Limited, Dr Reddy Laboratories and Zydus Lifesciences. GC declares speaker's/writer's engagement from AstraZeneca, Daiichi Sankyo, Novartis, Pfizer and Roche; advisory role from AstraZeneca, BMS, Celcuity, Daiichi Sankyo, Ellipsis, Exact Sciences, Gilead, Lilly, Menarini, Merck, Pfizer, Roche and Veracyte; funding as coordinating PI from Relay Therapeutics; institutional funding from Astellas, AstraZeneca, Blueprint Medicine, BMS, Daiichi Sankyo, Kymab, Merck, Novartis, Philogen, Relay Therapeutics, Roche and Sanofi; non-renumerated advisory role for the Italian National Health Council Europa Donna patient advocacy association, EUSOMA and Fondazione Beretta Cancer Research Foundation; non-renumerated activity as chair of ESMO Clinical Practice Guidelines, advisory role from Europa Donna and

Fondazione Beretta; member of board of directors for Lega Italiana Lotta ai Tumori; officer, Italian National Health Council as advisor for Ministry of Health. TY declares speaker's engagement from Bayer Yakuhin, Chugai Pharmaceutical, Merck Biopharma, MSD KK, Ono Pharmaceutical and Takeda Pharmaceutical; consultancy role from Sumitomo Corp; institutional research grant from Amgen KK, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, FALCO Biosystems, Genomedia Inc, Molecular Health GmbH, MSD KK, Nippon Boehringer Ingelheim, Ono Pharmaceutical, Pfizer Japan, Roche Diagnostics, Sanofi K.K., Sysmex Corp and Taiho Pharmaceutical. LYB declares speaker's engagement from ONO; advisory board role from Amgen and Astellas; non-renumerated support of an investigator-initiated clinical trial. GP declares employment by ESMO; non-renumerated membership of ASCO, Hellenic Cooperative Oncology Group (HeCOG) and Hellenic Society of Medical Oncology. AC declares speaker's engagement from Amgen, Foundation Medicine, Merck Serono and Roche; advisory board role from AbbVie, Amgen, AnHeart Therapeutics, GSK, Merck Serono, Roche and Transgene; institutional research grant/funding from Actuate Therapeutic, Adaptimmune, Affimed, Amcure, Amgen, Astellas Pharma, AstraZeneca, Bayer, BeiGene, Bristol Myers Squibb (BMS), F. Star, FibroGen, Genentech, Gilead, Janssen, Lilly, MedImmune, Merck Serono, MSD, Natera, Novartis, Ribon Therapeutics, Roche, Seamless, Servier, Sierra Oncology and Takeda; editorial role from the Annals of Oncology, Cancer Treatment Reviews and ESMO Open; non-remunerated role as General and Scientific Director of INCLIVA Biomedical Research Institute. JSC speaker's engagement from TTY; advisory board role from Astellas, Cstoone and Zai LAB; PI role from Amgen, AstraZeneca, BMS/ONO, Janssen, Merck, MSD, Tohe and Taiho; non-remunerated leadership role from TOS. MD declares speaker's engagement from Amgen, Bayer, Lilly, Merck Kga, MSD, Pfizer, Pierre Fabre, Roche and Servier; advisory board role from AstraZeneca, Basilea, Bayer, Boehringer, Daiichi Sankyo, Glaxo Smith Kline, HalioDx, Ipsen, MSD, Pierre Fabre, Rafael, Roche, Servier, Sotio and Zymeworks; local PI role from Amgen and Rafael; institutional funding from Bayer, Keocyt and Roche; his wife is head of the oncology business unit of the French Affiliate of Sandoz. All other authors declare no conflicts of interest.

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