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Systemic treatment of patients with locally advanced or metastatic cholangiocarcinoma – an Austrian expert consensus statement

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Key points:

- In der Erstlinientherapie des lokal fortgeschrittenen oder metastasierten Cholangiokarzinoms bildet Cisplatin/Gemcitabin seit mehr als zehn Jahren den Behandlungsstandard. Die Kombination mit dem Immuncheckpoint-Inhibitor Durvalumab bewirkte im Phase-III-Setting eine Effizienz-Verbesserung. Hier ist der absolute Benefit überschaubar, allerdings wurde ein signifikanter und klinisch relevanter Langzeitüberlebensvorteil in einer noch nicht näher charakterisierten Patient:innengruppe beobachtet. Es ist anzunehmen, dass fitte Personen am meisten von der Kombination profitieren werden. Darüber hinaus bietet Durvalumab den Vorteil einer gut verträglichen Erhaltungsoption nach Absetzen des Chemotherapie-Backbones.
- In Bezug auf die Anwendung von Chemotherapie in der Zweitlinie konnten positive Phase-III-Daten bisher nur für FOLFOX generiert werden. Die Evidenzlage zu Nal-IRI

plus 5-FU/LV ist widersprüchlich, in der Praxis existieren jedoch gute Erfahrungen, weswegen beide Optionen valide erscheinen.

- Nach Vorbehandlung können bei Nachweis der molekularen Targets *IDH1*, *FGFR2*, und *NTRK* sowie bei MSI-H zugelassene Therapien angeboten werden. Ebenso zeigte die Gabe von Dabrafenib/Trametinib bei *BRAF*^{V600E}-mutierten Tumoren Wirksamkeit. Diese zielgerichteten Substanzen sind der Zweitlinien-Chemotherapie generell vorzuziehen. Die molekulare Testung sollte bereits bei der Initiierung der Erstlinientherapie bevorzugt aus Tumorgewebe erfolgen und möglichst breit sein. In Einzelfällen kann die Identifikation von Targets den Patient:innen die Teilnahme an klinischen Studien ermöglichen.

Introduction

The term “cholangiocarcinoma” (CCA) comprises a group of heterogeneous malignant tumors arising at any point of the biliary tree. Three subtypes are distinguished according to the anatomical site of origin: intrahepatic, perihilar, and distal CCAs.[1, 2] Although CCA is a rare cancer, epidemiological data suggest an increasing global burden over the last decades, with rising annual rates for incidence (0.3–6/100.000 inhabitants) and mortality (1–6/100.000 inhabitants).[1, 3] Most patients present with advanced disease due to the fact that CCAs are usually asymptomatic in the early stages.[1, 4] In spite of increased awareness and improved therapies, patient prognosis is still poor. The 5-year survival rates range between 7 and 20 %, and recurrence is likely to occur after resection.[5–12]
At present, the systemic treatment landscape is expanding, while the currently available options leave room for discussion with respect to the ideal choice and sequence. Therefore, Austrian experts in the field of medical oncology and liver surgery convened on 9th October, 2022, to reach a consensus on the systemic treatment of non-resectable, locally advanced, or metastatic CCA.

First-line treatment

The phase III ABC-02 trial published in 2010 has established cisplatin plus gemcitabine as the first-line standard in patients with advanced biliary tract cancer.[13] Compared to single-agent gemcitabine, the platinum-based combination improved median overall survival (OS) by 3.6 months (11.7 vs. 8.1 months), which translated into a 36 % mortality reduction (HR: 0.64; $p < 0.001$). All subgroups derived OS benefits.
This long-lasting standard regimen has recently been augmented based on the phase III TOPAZ-1 trial that explored the addition of the anti-PD-L1 antibody durvalumab.[14] The OS

advantage provided by durvalumab plus cisplatin/gemcitabine vs. cisplatin/gemcitabine alone was statistically significant, even though the relative risk reduction did not exceed 20 % (median OS: 12.9 vs. 11.3 months; HR: 0.76 [CI: 0.64–0.91]). In the experimental arm, the Kaplan-Meier curve plateaued beyond 18 months, which gave rise to 2-year OS rates of 23.6 vs. 11.5 %. This indicates that a subgroup of patients derives sustained benefit from the triple combination. Prolonged survival on the combination is most likely in fit patients.
Due to the long-term effect observed in TOPAZ-1, durvalumab plus cisplatin/gemcitabine has been endowed with a 4-point score according to the ESMO-Magnitude of Clinical Benefit Scale (MCBS).[15] However, it must be noted that the regimen would have been classified as score 1 without the ≥ 10 % increase in 2-year survival. Considering the limited statistical power of this comparison based on a total number of 13 patients across the 2 study arms at 24 months, this "upgrade" according to the ESMO-MCBS scoring appears at least debatable.
Nevertheless, the TOPAZ-1 trial has introduced an evidence-based, potentially highly beneficial treatment option after a decade-long standstill with respect to first-line strategies in the advanced CCA setting. Based on the TOPAZ-1 data, durvalumab plus cisplatin/gemcitabine has been approved by the US Food and Drug Administration and recently by the European Medicines Agency for the first-line treatment of biliary tract cancer.
Another aspect favoring the immunotherapy-based approach results from the possibility of durvalumab maintenance after discontinuation of the cisplatin/gemcitabine backbone. This offers increased tolerability compared to continued administration of the platinum-based regimen, whose prolonged use inevitably evokes complications such as neuropathy. In the TOPAZ-1 study, durvalumab use did not add to the overall toxicity, and the rates of grade 3/4 adverse events were similar across the 2 treatment arms.[15] The ESMO Clinical Practice Guideline for the diagnosis and treatment of biliary tract cancer recommends cisplatin/gemcitabine in locally advanced or metastatic biliary tract cancer, while the addition of durvalumab can be considered **(figure)**.[16]
All patients should be reevaluated with respect to potential surgical or locally ablative interventions at regular intervals. It is important for tumor boards to include surgeons specialized in liver surgery, particularly regarding the assessment of resectability, and to repeat multidisciplinary team discussions 2–3 months after treatment initiation.

- The addition of durvalumab to first-line cisplatin/gemcitabine should be considered in patients who can be assumed to experience long-term overall survival benefits, i.e., individuals with ECOG performance status scores of 0 or 1 who are eligible for doublet chemotherapy and have no contraindications to immune checkpoint inhibition.

- In patients who have at least achieved disease stabilization with cisplatin/gemcitabine plus durvalumab, durvalumab can be continued as single-agent maintenance therapy after 6 months (i.e., 8 cycles) of combined treatment.
- Reinduction of cisplatin/gemcitabine can be considered upon progression after a chemotherapy break of at least 6 months.
- In patients with locally advanced disease who are candidates for tumor resection, response evaluation with a view to obtaining resectability is recommended at 2-month intervals. Restaging in the metastatic setting, on the other hand, should be performed every 10–12 weeks.

Second and later lines

Chemotherapy

In the pretreated setting, the ABC-06 trial is the only positive phase III study conducted to date.[17] ABC-06 has demonstrated a significant OS benefit of FOLFOX compared to active symptom control that translated into a 31 % mortality reduction (median OS: 6.2 vs. 5.3 months; HR: 0.69; p = 0.031).
The Korean phase IIB NIFTY trial has established liposomal irinotecan (nal-IRI) plus fluorouracil (5-FU) and leucovorin (LV) as an alternative second-line option.[18] Here, progression-free survival (PFS) was significantly improved compared to 5-FU/LV alone (7.1 vs. 1.4 months; HR: 0.56; p = 0.0019), as was OS (8.6 vs. 5.5 months; HR: 0.68; p = 0.0349). Each treatment arm contained up to 90 patients. However, these findings were not corroborated by the German NALIRICC (AIO-HEP-0116) study that included approximately 50 patients in each arm.[19] Nal-IRI plus 5-FU/LV, as compared to 5-FU/LV, did not prolong PFS (HR: 0.867) nor OS (HR: 1.082), while giving rise to an unexpectedly high adverse event rate. These findings notwithstanding, nal-IRI plus 5-FU/LV is generally preferred over FOLFOX at the Austrian centers and has demonstrated activity in clinical practice. In light of the controversial data, it appears advisable to shorten the intervals of the response assessments.

- Second-line administration of FOLFOX is recommended in patients without targetable driver mutations based on phase III evidence.
- Nal-IRI plus 5-FU/LV represents an alternative option despite controversial phase II data. Early response evaluation after 2 months is recommended.
- The treatment selection should be based on factors such as performance status and toxicities of previous therapies (e.g., neuropathy).

Targeted treatment

The molecular characterization of CCA has revealed several targetable driver aberrations, and a growing array of targeted options is established in clinical routine treatment. The *FGFR2* inhibitor pemigatinib has been approved in pretreated patients with *FGFR2* fusions or rearrangements based on the phase II FIGHT-202 trial that showed an overall response rate of 37 % and a disease control rate of 82 %.[20] Median PFS and OS were 7.0 and 17.5 months, respectively.

In patients with somatic *IDH1* mutations, the phase III ClarIDHy study yielded superiority of the *IDH1* inhibitor ivosidenib over placebo regarding PFS (2.7 vs. 1.4 months; HR: 0.37; $p < 0.0001$) and OS (10.3 vs. 5.1 months after adjustment for crossover; HR: 0.49; $p < 0.0001$).[21, 22] Disease control was obtained in 53.2 vs. 27.9 %.[22]

The single-arm phase II ROAR basket trial, conducted in rare tumor types, showed promising activity of the *BRAF* inhibitor dabrafenib and the MEK inhibitor trametinib in 33 patients with *BRAF*^{V600E}-mutated biliary tract cancer.[23] 41 % responded, and median PFS and OS were 7.2 and 11.3 months, respectively.

Moreover, the PD-1 inhibitor pembrolizumab has been licensed in the setting of previously treated microsatellite instability high (MSI-H) or mismatch-repair-deficient biliary cancer.[24]

Patients with *NTRK*-positive CCA can be treated with the *NTRK* inhibitors larotrectinib or entrectinib that have received tumor-agnostic approval in advanced solid tumors harboring *NTRK* fusions.[25, 26]

The recommendations for the use of next-generation sequencing for patients with metastatic cancers are based on the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT).[27] *IDH1* mutations, *FGFR2* fusions, MSI-H, *NTRK* fusions, *BRAF*^{V600E} mutations and *ERBB2 (HER2)* have been classified as level I and three other aberrations as level III according to the most recent ESMO Guideline for Biliary Tract Cancer **(table)**.[16] At present, no agents are approved for the treatment of patients with level II and III alterations in CCA. Considering the ongoing research efforts in the field of targeted agents, comprehensive testing based on large panels covering driver aberrations beyond those listed by the ESMO Precision Medicine Working Group is encouraged with a view to patient inclusion in future clinical studies. In addition, *BRCA* 1/2 testing can identify families with increased risk of other cancers.

- Molecular testing of a broad range of targets is recommended prior to the initiation of first-line systemic treatment.
- Whenever possible, testing should be performed based on tumor tissue.
- As tissue can be difficult to obtain in the advanced setting, liquid biopsy constitutes a valid alternative. Negative liquid biopsy results do not completely preclude the

presence of driver aberrations and should be confirmed if tissue becomes available later.

- Targeted treatment should be preferred over second-line chemotherapy in patients with ESCAT level I (and II) alterations.
- Patients with level (II and) III targets, in whom evidence-based regimens have been exhausted, should be discussed by the molecular tumor board.
- No standard third-line treatments have been defined to date. Oxaliplatin- or irinotecan-based chemotherapy can be administered upon progression on targeted treatment.

Conclusion

The recommendations on the systemic treatment of locally advanced or metastatic CCA summarized in this paper mirror the availability and reimbursement situation in Austria in autumn 2022 amidst a changing treatment landscape. Data have recently been generated for the addition of first-line durvalumab to the chemotherapy standard, and despite their limited statistical power, the introduction of immunotherapy represents a potential improvement for certain patients. In the second-line setting, targeted treatment based on potential molecular aberrations is the preferred option.
It is strongly recommended to extend molecular testing beyond the established genomic aberrations, as CCA patients – who should be treated at specialized centers as a matter of principle – might be given the opportunity to enter clinical trials investigating new compounds. Innovative agents as well as drugs that have already been implemented in other cancers might become accessible over the coming years, thus redefining the current algorithms and taking the systemic treatment of CCA patients to the next level. For patients without druggable targets, FOLFOX is a potential second-line treatment option with high level of evidence based on a positive clinical phase III trial.[17] Liposomal irinotecan plus chemotherapy is controversial, although this treatment has shown efficacy in clinical trials and daily practice and thus might be considered as a valid second-line treatment option.

Conflicts of Interest

Gerald W. Prager

- Advisory roles or speaker fees: Bayer, Servier, Roche, Merck Serono, Amgen, Lilly, BMS, MSD, PierreFabre, Incyte, AstraZeneca, Takeda

Angela Djanani: no

Wolfgang Eisterer: no

Armin Gerger

- Advisory roles or speaker fees: AstraZeneca, Servier, MSD, Pierre Fabre, Roche, Bayer, Merck, Amgen, Eli Lilly, Incyte, BMS, Daiichii Sankyo

Birgit Gruenberger:

- Amgen, AstraZeneca, BMS, Celgene, Daiichi Sankyo, Eisai, Eli Lilly, Janssen Cilag, Merck, MSD, Novartis, Pierre Fabre, Roche, Sanofi Aventis, Servier

Thomas Gruenberger: no

Holger Rumpold: no

Hossein Taghizadeh

- Honoraria: AstraZeneca, Servier, Ipsen, Eisai, Eli Lilly, MSD, Amgen, Merck

Lukas Weiss

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Thomas Winder

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25 Summary of product characteristics Vitrakvi®
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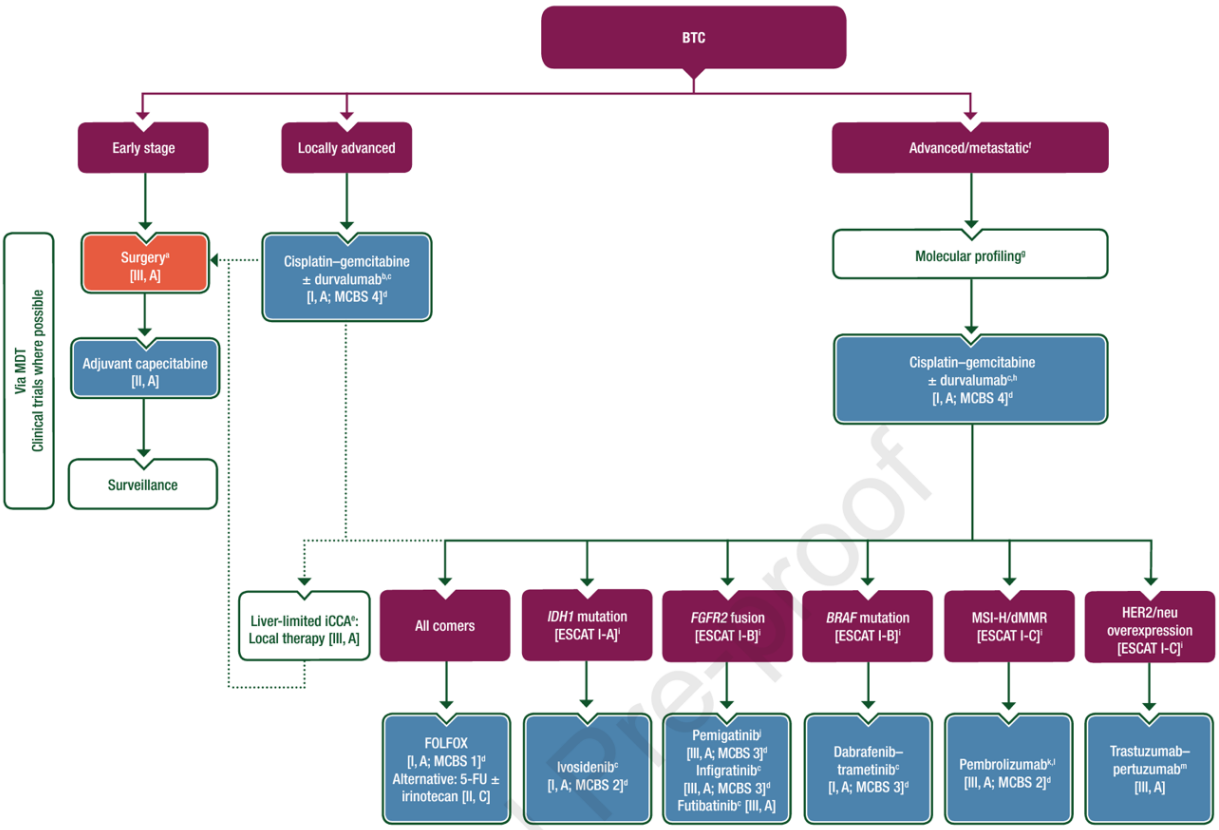
Figure: Treatment algorithm for biliary tract cancer[16]



Last Update as of January 18, 2023: MCBS Score Ivosidenib from 2 to 3
(https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-297-1)

Table: ESCAT levels of genomic alterations according to the ESMO Guideline for Biliary Tract Cancer [16]

Gene	Alteration	Prevalence	ESCAT
IDH1	Mutations	20 %	IA
FGFR2	Fusions	15 %	IB
BRAF^{V600E}	Mutations	5 %	IB
	MSI-H/dMMR	2 %	IC
NTRK	Fusions	2 %	IC
ERBB2	Amplifications Mutations	10 % 2 %	IC –
PIK3CA	Mutations	7 %	IIIA
BRCA 1/2	Mutations	3 %	IIIA
MET	Amplifications	2 %	IIIA