



HAL
open science

Cholangiocarcinoma: what are the options in all comers and how has the advent of molecular profiling opened the way to personalised medicine ?

G.S. Roth, C. Neuzillet, M. Sarabi, J. Edeline, D Malka, Astrid Lièvre

► To cite this version:

G.S. Roth, C. Neuzillet, M. Sarabi, J. Edeline, D Malka, et al.. Cholangiocarcinoma: what are the options in all comers and how has the advent of molecular profiling opened the way to personalised medicine ?. European Journal of Cancer, 2023, 179, pp.1-14. 10.1016/j.ejca.2022.11.006 . hal-03931293

HAL Id: hal-03931293

<https://hal.science/hal-03931293v1>

Submitted on 25 Jan 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Cholangiocarcinoma: what are the options in all comers and how has the advent of molecular profiling opened the way to personalized medicine ?

Gael S Roth¹, Cindy Neuzillet², Matthieu Sarabi^{3,4}, Julien Edeline⁵, David Malka⁶, Astrid Lièvre⁷

Affiliations:

- 1- Univ. Grenoble Alpes / Hepato-Gastroenterology and Digestive Oncology department, CHU Grenoble Alpes / Institute for Advanced Biosciences, CNRS UMR 5309-INSERM U1209, Grenoble, France
- 2- Institut Curie, Versailles Saint-Quentin University - Paris Saclay University, Saint-Cloud, France
- 3- Medical Oncology Department, Centre Léon Bérard, 28 rue Laennec, Lyon 69008, France
- 4- Tumor Escape, Resistance and Immunity Department, Centre de Recherche en Cancérologie de Lyon, INSERM 1052, CNRS 5286, Lyon, France
- 5- Medical Oncology, Centre Eugene Marquis, Rennes, France
- 6- Medical oncology, Institut Mutualiste Montsouris, Paris, France
- 7- Department of Gastroenterology, Rennes University Hospital, University of Rennes 1, INSERM Unité 1242, Rennes, France

Corresponding author :

Dr Gael S Roth, MD-PhD

Hepato-Gastroenterology and Digestive Oncology department

University Hospital of Grenoble-Alpes, France

Team Immunology and Cancer - Institute for Advanced Biosciences - Grenoble

INSERM U1209 - CNRS UMR 5309 - University Grenoble-Alpes, France

Email : groth@chu-grenoble.fr

Tel: +33 4 76 76 51 68

Keywords: cholangiocarcinoma, bile tract cancer, molecular profiling, personalized medicine, IDH1 mutation, FGFR2 fusion, HER2 amplification

Abstract

Cholangiocarcinoma is a deadly cancer comprising very heterogeneous subtypes with a limited therapeutic arsenal in all comers. However, recent significant advances were made with immunotherapy in the first line treatment of advanced cholangiocarcinoma, with the addition of durvalumab to CISGEM (cisplatin-gemcitabine) chemotherapy showing a survival benefit. In the second line setting, only FOLFOX (5FU/folinic acid-oxaliplatin) is validated by a phase 3 trial, yet with a very modest benefit on survival; new options using 5FU with nanoliposomal-irinotecan may emerge in the next few years. The advent of molecular profiling in advanced cholangiocarcinoma in the last decade revealed frequent targetable alterations such as IDH1 mutations, FGFR2 fusions or rearrangements, HER2 amplification, BRAF V600E mutation and others. This strategy opened the way to personalized medicine for patients which are still fit after first line treatment and the use of targeted inhibitors in first line constitutes a huge challenge with many ongoing trials to improve patients' care.

This review exposes the recent clinical trial findings in non-molecularly selected advanced cholangiocarcinoma, offers a focus on how systematic molecular screening should be structured to allow patients to access to personalized medicine, and details which are the therapeutic options accessible in case of actionable alteration.

Introduction

Cholangiocarcinoma (CCA) corresponds to a very heterogeneous group of invasive cancers developed from the epithelium of the biliary tree. Anatomically, four main groups are distinguished as follows: intrahepatic cholangiocarcinomas (iCCA) arising from small intrahepatic bile ducts upstream of the right and left hepatic ducts (around 20% of CCAs); perihilar cholangiocarcinomas (pCCA), previously called Klastkin's tumors, developed from second biliary ducts segmentation down through common hepatic duct (50-60% of CCAs); distal cholangiocarcinomas (dCCAs), located in the main biliary tract downstream of the insertion of the cystic duct (20-30% of CCAs); and adenocarcinomas of the gallbladder (1). The pCCAs and dCCAs were grouped as extrahepatic CCAs (eCCAs) according to former classifications but the trend is to separate these 2 subtypes (1). In addition, ampullary adenocarcinoma constitutes a distinct entity with specific morphologic and molecular features and are considered separately from CCAs, although it is regularly included in clinical trials of biliary tract cancers.

Cholangiocarcinoma is a rare disease that represents 3% of digestive cancers with an annual incidence rate of approximately 2 per 100,000 inhabitants in Western countries. Worldwide, CCA incidence is very variable and can reach up to 80 cases per 100,000 inhabitants in certain regions such as Northern Thailand (endemic area for liver flukes) (1-3). The global trend is towards an increase in the number of CCAs, particularly in Western countries (4). This rising incidence seems to be mainly related to the increase of iCCA with an incidence that has increased from 0.44 to 1.18 per 100,000 population over the last 30 years (5, 6). This increase is related to various factors such as the better radiological and histological characterization of hepatic nodules leading to a reclassification of ACUP (adenocarcinoma of unknown origin) into iCCAs which account for about 30-35% of ACUP with intrahepatic predominance (7), and the reclassification of certain hepatocellular carcinomas (HCC) in patients with chronic liver disease due to increasing recommendations to perform tumor and non-tumor liver biopsy in front of any primary liver cancer suspicion (8, 9). In addition, there is an overall increase in primary liver tumors (HCC and iCCA) in relation to the increasing incidence of chronic liver disease, mostly related to alcohol consumption and metabolic syndrome (3).

Cholangiocarcinoma is one of the deadliest cancers with a median overall survival (OS) of less than 12 months (10) and a 5-year OS of less than 5% (11). At the diagnosis, the vast majority (60-70%) of patients have an unresectable disease. When resection is possible, the 5-year OS is still low, varying between 15 and 40% for iCCAs, 8 and 47% for pCCAs and 20 and 54% for dCCAs, with a strong negative impact of R1 margins or lymph node involvement (10, 12).

Very few therapeutic options are available in CCA with only one approved first line as well as one second line chemotherapy until 2021. This review aims to expose the recent advances in systemic treatments for all-comers CCAs, as well as the advent of molecular profiling, which allows access to personalized medicine and reshuffle the cards of CCA patients' care.

Systemic treatments: What are the standards of care and what is new?

First-line treatment

Since 2010, the only standard of care for first-line treatment is the combination of CISGEM (cisplatin-gemcitabine) administered for 24 weeks (8 cycles). The latter has shown superiority compared to gemcitabine alone with an OS of 11.7 vs. 8.1 months (HR: 0.64; 95% confidence interval (CI) [0.52-0.80]; $p < 0.001$), independent of tumor stage and CCA location, in the ABC-02 phase 3 trial (13). These results were confirmed in an Asian population in the BT-22 phase 2 trial (CISGEM versus gemcitabine, for 48 weeks). GEMOX and CAPOX represent alternative with comparable performances on the basis of several studies including prospective phase 2 trials (14-16), but their use tends to decrease due to recent validated oxaliplatin-based second-line option in patients who have failed CISGEM.

Other gemcitabine-based combinations showed promising results in single-arm phase 2 trials such as gemcitabine-nivolumab-S1 in Asia (objective response rate (ORR)= 41.7%, disease control rate (DCR) > 12 weeks = 77.1%, PFS= 8.0 months (95%CI : 5.8-not reached) and OS not reached (95%CI : 10.7-not reached) or CISGEM-nab-paclitaxel (ORR= 45%, DCR= 84%, PFS= 11.8 months (95%CI: 6.0-15.6), OS= 19.2 months (95%CI:13.2 months-not reached). They may represent news options but need further studies (17, 18).

However, the NuTide:121 trial comparing cisplatin-NUC-1031, an optimized gemcitabine derivative, with CISGEM (19) was stopped prematurely in January 2022 by the study's independent data monitoring committee due to futility at interim analysis with no published results to date, despite promising results in phase 1 (20).

Regarding the use of 5-fluorouracil (5FU)-based regimens in first line, the AMEBICA-PRODIGE 38 trial comparing modified FOLFIRINOX to CISGEM, recently failed to meet its phase 2 objective (hypothesis of a 6-month progression-free survival (PFS) rate of 59%) with a 6-month PFS of 44.6% (90% CI:[35.7-53.7]) in modified FOLFIRINOX arm versus 47.3% (90% CI: [38.4-56.3]) in CISGEM arm (21).

The NIFE trial, a German randomized non-comparative phase 2 study, compared 5FU/leucovorin-Naliri (nano-liposomal irinotecan) with a CISGEM control arm in 93 patients. The primary objective was met with a 4-month PFS rate of 51% in the 5FU/leucovorin-Naliri arm, but was lower than the control arm (59.5% with the CISGEM regimen) (22). PFS and OS data are immature at this stage. Interestingly, a differential effect was observed between iCCA and eCCA, where CISGEM and 5FU-Naliri seemed to be more active, respectively;

however, this result should be taken with caution, due to low number in these subgroups. This study suggests that 5FU-Naliri may be of interest as a first-line treatment for biliary tract cancer, but the results have not yet been published and need to be confirmed by larger studies.

Finally, 2022's breakthrough in advanced CCA is the arrival of immunotherapy in first-line setting with the phase 3 TOPAZ-1 trial studying CISGEM in combination with durvalumab, an anti-PD-L1 (Programmed death 1 ligand) checkpoint inhibitor, or a placebo, for 8 cycles, followed by a maintenance therapy with durvalumab or placebo. As presented at ASCO GI 2022 congress and recently published, the primary objective was met with an OS of 12.8 months in the CISGEM-Durvalumab arm versus 11.5 months in the CISGEM-placebo arm (HR = 0.80; 95%CI: [0.66-0.97]; p=0.021) following the interim analysis considered as the final analysis. Besides, the estimated 24-month OS seems promising with a rate of 24.9% in durvalumab arm versus 10.4% for placebo even though long-term follow-up data are needed. The response rate and PFS were also higher in the CISGEM-durvalumab arm. Nonetheless, due to limited duration of follow-up, it is difficult to determine if there is a long-term survival benefit of responders as typical with immunotherapy. The benefit appears to be smaller in patients of non-Asian origin and in gallbladder localization, with the caveat of subgroup analyses. Survival analysis according to PD-L1 expression showed that the CISGEM-durvalumab combination was associated with better PFS when the PD-L1 TAP (tumor area positivity) was greater than or equal to 1%, but without any significant impact on OS (23, 24). Overall, more translational research is required to identify more discriminating predictive biomarkers of response to immune therapy.

After 12 years without a positive phase 3 trial in first-line treatment of advanced CCA, the TOPAZ-1 trial, which was positive on all endpoints and showed no signal of overtotoxicity, places the combination CISGEM-durvalumab as the new standard in advanced CCA. Thus, in September 2022, durvalumab has been approved by the US Food and Drug Administration (FDA) in this indication. The European Medicines Agency (EMA) is pending but its reimbursement was already allowed in European countries such as France. However, the magnitude of the benefit is modest in an unselected population, relaunching the debate on the need for relevant selection criteria to predict which subgroups of patients benefit more from immunotherapy based strategies in bile tract cancers. Besides, the results of the phase 3 KEYNOTE-966 study evaluating pembrolizumab *versus* placebo in combination with CISGEM (followed by a maintenance with gemcitabine plus pembrolizumab or placebo) should be released soon and are seriously expected to better understand if immunotherapy really brings an added value in advanced cholangiocarcinoma.

Second-line treatment

Until 2019, no phase 3 study was available to assess the input of second-line (L2) chemotherapy in CCA even though retrospective studies were already in favor of a benefit of L2 in patients with good performance status after first line chemotherapy. Data from retrospective series and systematic reviews suggest that around 30-40% of patients are fit for L2, with a wide range of estimated rates of eligible patients from 15% after CISGEM first-line in ABC-02 trial, to 75% based on retrospective analyses in high volume anticancer centers (13, 25-27).

In 2020, the ABC-06 phase 3 study showed an OS increase with FOLFOX when compared with best supportive cares alone in ECOG PS of 0-1 (28). However, this gain was inferior to 1 month in median OS (6.2 vs. 5.3 months, HR: 0.69, 95%CI [0.50-0.97], $p=0.031$). The response rate was also low, around 5%. Interestingly, FOLFOX was not less effective in patients who progressed rapidly under first-line CISGEM. Moreover, results of quality of life and value of health analyses were recently presented at ESMO congress 2022 and revealed that FOLFOX was stabilizing quality of life (29). Despite a very limited magnitude of benefit, FOLFOX is the only second-line standard to date in all comers advanced CCA with good performans status.

Other therapeutic schemas were recently tested with interesting results of irinotecan based combination such as XELIRI (capecitabine-irinotecan) compared with irinotecan alone in a small single-center Chinese randomized phase 2 trial, which showed a survival benefit of the doublet (PFS: 3.7 vs. 2.4 months, OS: 10.1 vs. 7.3 months) at the price of an acceptable toxicity (30). A South Korean randomized phase 2 study enrolling 120 patients showed that mFOLFIRI was not superior to mFOLFOX with a PFS of 2.1 months (95%CI: 1.3-2.9) in mFOLFIRI arm *versus* 2.8 months (95%CI: 2.3-3.3) with mFOLFOX ($p = 0.682$) and an OS of 5.9 months (95%CI: 4.3-7.5) *versus* 6.6 months (95%CI:5.6-7.6) ($p = 0.887$) (31). Even though this trial may suggest that mFOLFIRI does not constitute a good challenger of mFOLFOX in an Asian population, these results need to be confirmed in a Western countries population. Besides, advances may be made with the nanoliposomal galenic of irinotecan which showed interesting results in another South Korean randomized phase II study, the NIFTY trial, comparing the combination of 5FU/leucovorin-Naliri *versus* 5FU alone. 5FU-Naliri showed an improvement in PFS (primary endpoint) with a median of 7.1 months vs. 1.4 months in the control arm, HR 0.56, 95%CI: [0.39-0.81], $p=0.0019$). There was also a benefit in OS (median: 8.6 vs. 5.5 months HR 0.68, 95%CI: [0.48-0.98], $p=0.0349$) and objective response rate (14.8% vs 5.8%) compared with the 5FU-leucovorin regimen alone (32). These results are very promising but need to be confirmed in a Western population, which is the purpose of the ongoing European phase 2 study NallIRICC (NCT03043547). Moreover, to date, no phase 3 trial compared the benefit of 5FU-based doublets versus 5FU alone in second-line setting of advanced CCA and data from prospective European cohorts suggest

that doublets do not bring a benefit when compared with 5FU alone (33). This question need to be addressed by randomized phase 3 trials.

Beyond L2, no randomized trial has demonstrated the value of systemic treatment in all-comers advanced CCAs, i.e. CCAs not selected according to specific molecular characteristics. On the other hand, multiple studies have demonstrated the interest to detect molecular alterations in patients still in good general condition after one or two lines of systemic treatment in order to allow access to targeted therapies directed against these so-called "actionable" alterations.

Molecular profiling: an essential step to offer personalized medicine

Several high throughput sequencing studies integrating DNA next generation sequencing (NGS) and RNA sequencing (RNAseq) have highlighted the huge molecular heterogeneity of CCAs, with multiple tumor gene alterations including a significant proportion of actionable targets (34-37). Indeed, the most frequent alterations found in CCA are mutations of the genes encoding isocitrate dehydrogenases 1 and 2 (IDH1 and IDH2) in 10-20% of iCCAs and rearrangements and fusions of the fibroblast growth factor receptor 2 (FGFR2) gene in 10 to 15% of iCCAs. Amplification and/or overexpression of the ERBB2 gene encoding the protein HER2 (human epidermal growth factor receptor 2) is also found in about 15% of perihilar, distal and gallbladder CCAs. Other alterations such as the presence of microsatellite instability (MSI), BRAF V600E mutation, NRTK (neurotrophin receptor tyrosine kinase) fusion, KRAS G12C mutation are less frequent (1 to 5%) but also open the access to targeted therapies thus enlarging the therapeutic arsenal for patients with advanced or metastatic CCA (38, 39) (Figure 2).

The benefit of personalized medicine has been demonstrated by several molecular profiling studies including the MOSCATO-1 trial which included 1035 patients, of whom 43 had a CCA (67% iCCA). Molecular profiling could be performed in 79% of patients by DNA and RNA extraction from biopsies. Among analyzable patients, 91% had at least one molecular alteration, 68% had an alteration theoretically accessible to a targeted therapy, and 53% received a targeted treatment in fine, i.e. 42% of the whole CCA cohort. A clinical benefit (defined as a ratio PFS under the matched targeted therapy/PFS under previous systemic treatment > 1.3) was found in 9/18 (50%) CCA patients vs only 7% of overall hard-to-treat advanced cancers cohort and a survival benefit was observed in patients treated with personalized medicine compared with patients who did not have access to it (HR = 0.29; 95%CI: [0.11-0.76]; p = 0.008) (40, 41).

Thus, from the initial diagnostic phase, the preservation of tissue for complementary molecular analyses must be anticipated by taking optimal quality samples and by sparing the

material available for histological diagnosis. Indeed, in recent years, molecular profiling of CCAs has become more and more systematic, and is now recommended in parallel with the first line of chemotherapy in patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1 in order to organize the subsequent lines of treatment according to tumor molecular alterations.

Molecular profiling should be performed as early as possible for several reasons: 1) A majority of patients are not suitable for L2 due to tumor aggressivity with rapid general status deterioration as above mentioned. 2) The delay in the delivery of profiling results can be long and therefore inappropriate for the treatment of patients when initiated too late. Moreover, samples may need to be repeated due to insufficient quality or quantity and further increase the delay. As an example, the delay between the performance of a biopsy and the delivery of the molecular screening results was 21 days in the MOSCATO-01 study (40). Outside of a clinical trial, data from daily life show lower performances (42) and this time is probably greater than 1 month as it includes time to de-archive and send samples to a molecular platform, notably if it is outside of the healthcare center in which the patient is treated, time of analyses (2 to 4 weeks for high-throughput DNA and RNA sequencing), and time to screen and include patients in a clinical trial or initiate a matched targeted therapy. 3) Dominant oncogenic alterations called "drivers" occur from the earliest stages of oncogenesis, and persist during tumor growth, suggesting that early molecular mapping remains relevant after 1 to 2 lines of chemotherapy (43).

Molecular profiling of tumors should allow the detection of all alterations accessible to treatment, which corresponds to class I to III molecular targets according to the European ESCAT (ESMO Scale for Clinical Actionability of Molecular Target) classification (44). It must therefore detect mutations of genes such as IDH1, BRAF and KRAS by NGS DNA sequencing, and fusions or rearrangements of genes such as FGFR2 or more rarely NTRK by RNAseq. Overexpression of HER2 protein can be observed by immunohistochemistry (IHC) but with no consensus on the scoring score, therefore requiring confirmation by FISH (fluorescent in situ hybridization) if overexpression is less than 3+; in addition, most of DNA NGS panels include the search for amplification/overexpression of ERBB2, by studying the copy number variant of the gene (45). Finally, DNA sequencing panels often include the detection of microsatellite instability (MSI), ideally, the NCI-Pentaplex panel (BAT25, BAT26, NR21, NR22 or NR27/Mono-27, NR24) as recommended (46) to allow access to immunotherapy in rare cases of MSI tumors. Alternatively, the Mismatch Repair System (MMR) proteins can be stained in IHC to detect MMR deficiency (dMMR), but this type of finding must be systematically confirmed by molecular biology.

Because good quality tissue samples are often hard to get, especially in eCCAs, liquid biopsy may represent an alternative to screen patients for molecular alterations. It may also

be of particular value for inaccessible tumours or in case of tissue biopsies at high risk of complications. Liquid biopsy is often referring to circulating tumor DNA (ctDNA) which is the most studied technique but peripheral blood of cancer patients carries other sources of genetic information such as circulating tumor cells (CTCs), circulating cell-free noncoding RNAs (cfRNAs) and circulating exosomes available in fluids.(47-49). These analyses are not well validated to date but they may offer an easy and non-invasive way of getting initial molecular profiling as well as monitoring tumour response along therapy (50, 51). Among alterations of interest in CCA, IDH mutations can be detected on ctDNA from peripheral blood either by NGS or digital droplet PCR with a sensitivity of 85%. Besides, its quantitative analysis might bring valuable information to assess tumor response as an increase of circulating IDH1 mutation has already been associated with tumor progression in IDH-mutated tumors while a tendency of longer survival was observed in patients with a IDH-mutant decrease (52). KRAS mutations including G12C and BRAF mutations can be detected on cfDNA as well, and FGFR2 fusions detection was also described as feasible in CCA (50, 53, 54). Moreover, in the latter, ctDNA may be an interesting tool to detect acquired resistance in FGFR2-rearranged CCAs treated by FGFR inhibitors. Interestingly, the number of FGFR alterations associated with resistance suggests a polyclonal mechanism that only ctDNA analysis can reveal (55). Even though liquid biopsy, mostly based on ctDNA analysis, seems of interest in bile tract cancers, further investigations are required to better assess its diagnostic performances and harmonize its use, in order to make it suitable for routine care.

Therefore, today, in the context of screening patients with advanced CCA, it is recommended to perform first a DNA and RNA NGS panel from tissue samples, to cover all actionable alterations and offer the best chances to patients of access to personalized medicine.

Personalized medicine: which targets are currently actionable ?

IDH1 mutations (ESCAT I-A)

Isocitrate dehydrogenases are key enzymes of the Krebs cycle, which in physiological conditions catalyze the oxidative decarboxylation of isocitrate to α -ketoglutarate. Somatic point mutations in IDH1 and IDH2 genes confer a gain of function for cancer cells, resulting in the nonreversible secretion and accumulation of an oncometabolite, D2-hydroxyglutarate (D-2HG) that promotes histone methylation, DNA methylation, and impacts cell differentiation. IDH1 mutations are found in approximately 13% of iCCAs compared to only

0.8% of pCCAs and dCCAs. The most frequent IDH1 mutations are R132C (68-74% of cases), R132L (11-17%), and R132G (10-14%)(56).

Ivosidenib, an oral drug inhibiting the mutated form of IDH1, was studied in a large phase 1 of 73 patients with IDH mutated CCA, followed by the randomized phase 3 ClarIDHy trial (n=185) (57, 58). In the latter, ivosidenib significantly improved PFS compared with placebo (2.7 vs. 1.4 months; HR: 0.37; 95%CI: 0.25-0.54, $p < 0.001$) in patients with advanced CCA previously treated with one or two lines of systemic therapy. OS was 10.8 months in the ivosidenib arm versus 9.7 months (HR: 0.69, $p = 0.06$) in the placebo arm. However, as 57% of patients in the placebo arm had access to ivosidenib after tumor progression, an a priori planned statistical analysis incorporating the impact of this crossover on OS showed a significant increased OS of 10.8 months with ivosidenib versus 6.0 months with placebo (HR: 0.46, $p = 0.0008$). The safety profile was acceptable with mostly grade 1-2 adverse events (AEs) such as nausea, diarrhea, fatigue, and cough in 33%, 31%, 23%, and 21%, respectively, and few grade 3 AEs (58). Ivosidenib should therefore be proposed to patients with IDH1-mutated CCA in L2 and more.

FGFR2 fusions and rearrangements (ESCAT I-B)

The FGFR2 pathway is involved in cell proliferation, survival, migration and differentiation. A fusion or rearrangement of the FGFR2 gene is a potent oncogenic signal and is observed in approximately 15% of CCAs, almost exclusively iCCA. Several FGFR2 inhibitors have already shown benefit in phase 2 trials in patients with FGFR2 fusion/rearrangement CCA who have failed at least one line of systemic therapy, such as pemigatinib, futibatinib, infigratinib, or derazantinib (59-62) (Table 1). These inhibitors achieve objective response rates of 20-35%, with median PFS of 6-7 months. Toxicity profile mainly includes hyperphosphatemia requiring the use of low-phosphorus diet \pm phosphorus chelators, skin disorders, marked mucocutaneous dryness, and ophthalmologic disorders requiring specialized follow-up. Currently, pemigatinib, infigratinib and futibatinib were approved by the FDA and only pemigatinib and futibatinib were approved by the EMA for use in patients with advanced CCA with FGFR2 fusion or rearrangement previously treated by at least one line of systemic therapy. The approval of pemigatinib followed the results of the FIGHT-202 trial (59), a phase 2 studying pemigatinib in 147 patients with unresectable CCA, including 107 with FGFR2 fusion or rearrangement, 20 with another FGF/FGFR alteration and 18 without any FGF/FGFR alteration. The objective response rate was 35.5% in the FGFR2 fusion/rearrangement group (3 complete responses and 35 partial responses), while no objective response was observed in the other groups. The PFS rate at 12 months was 29% in the FGFR2 fusion/rearrangement group versus 0% in the other groups. These results clearly confirm that the theoretical benefit of FGFR2 inhibitors, although significant in case of

FGFR2 fusion or rearrangement, seems to drop in case of other FGF/FGFR alterations, as well as in the absence of alterations. Safety profile was acceptable with among all grade treatment-related AEs, hyperphosphatemia as the most frequent AE (55%), followed by alopecia (46%), dysgeusia (38%), diarrhea (34%), asthenia (31%), stomatitis (27%) and dry mouth (29%). Among grade 3 or higher treatment-related AEs, the most frequent were hypophosphatemia (7%), stomatitis (5%), arthralgias (4%), and palmoplantar erythodysesthesia (4%). There was no toxic death (59). Other inhibitors are being studied, and several randomized phase 3 trials versus CISGEM in first-line therapy are underway, such as the FIGHT-302 trial (pemigatinib; NCT036536), and the FOENIX-CCA3 trial (Futibatinib; NCT04093362) or the PROOF trial (Infigratinib; NCT03773302). However, because of a strong industrial competition and a complex organization of the molecular profiling before starting L1, conducting phase 3 randomized trial in FGFR2 rearranged CCAs represents a huge challenge. Indeed, PROOF trial was recently prematurely closed and FOENIX-CCA3 discontinuation has also been announced.

To finish, it has been shown that activity of the pan-FGFR inhibitor futibatinib extends to FGFR mutations, including efficacy in patients with acquired resistance mutation to other FGFR inhibitors. Indeed, in futibatinib's phase 1, 36% of patients with a solid tumor harboring FGF/FGFR aberration were previously treated by FGFR inhibitors and 17.9% experienced objective response (63). These results pave the way for sequential treatment strategy in FGFR2 altered CCAs.

Alterations of the ERBB2 gene (ESCAT II-B)

Alterations of the ERBB2 or HER/Neu gene may correspond to amplifications, overexpression or more rarely mutations. They are mainly observed in perihilar, distal and gallbladder CCAs with a frequency of around 15% as previously mentioned, they are also found in adenocarcinomas of the ampulla and are more rarely detected in iCCA. The non-randomized phase II trial MyPathway studied the combination of two humanized anti-HER2 monoclonal antibodies, trastuzumab and pertuzumab, in a cohort of patients with multiple primary ERBB2 overexpression or amplification. Of these patients, 39 had HER2+ metastatic CCA (detected by IHC, FISH, or NGS), previously treated with one to two lines of systemic therapy, with an ECOG PS of 0-2. An objective response rate of 23% and tumor control of 51% were observed. The safety profile was acceptable, with grade 1-2 diarrhea and grade 3 hypertransaminasemia among the most frequent toxicities in 33% and 13% of cases respectively (64). To date, these interesting results remain preliminary, but the association trastuzumab-pertuzumab may represent a new option in HER2 amplified CCA patients.

Recently the combination modified FOLFOX with trastuzumab tested in the single-arm phase 2 trial KCSG-HB19-14 (NCT04722133) reinforced the signal of the interest of anti-HER2 therapies in second line of HER2-amplified CCA patients after progression under CISGEM. Based on unpublished results, tolerance was acceptable, ORR, DCR and PFS were respectively 29.4% (95%CI 15.1-47.5), 79.4% and 5.1 months (95%CI 3.6-6.7). Median OS was not reached (95%CI 7.1-NR) and 12-months OS rate was 50.6% (95%CI 29.3-63.6) (65).

New therapies are under investigation such as the zanidatamab, a novel bispecific antibody that targets HER2 domains ECD2 and ECD4, resulting in increased antibody binding density and improved receptor internalization and downregulation relative to trastuzumab. We expect the final results of the phase I ZWI-ZW25-101 (NCT02892123), in which zanidatamab was well tolerated with promising anti-tumor as a single-agent (ORR= 47%, DCR = 65%, duration of response = 6.6 months), as well as the results of the ongoing single-arm phase 2b trial HERIZON-BTC-01 (NCT04466891) evaluating zanidatamab in monotherapy in patients with HER2-amplified, inoperable, advanced or metastatic CCA (66, 67).

As well, trastuzumab deruxtecan (T-DXd), an antibody-drug conjugate composed of a humanized monoclonal anti-HER2 antibody, a cleavable linker, and a topoisomerase I inhibitor, also showed very promising results in the single-arm phase 2 study DS-8201/HERB trial in patients with HER2-expressing unresectable or recurrent biliary tract cancer. ORR, DCR, median PFS and OS were respectively 36.4% (90%CI: 19.6–56.1; $p = 0.01$), 81.8% (95%CI: 59.7–94.8), 4.4 months (95%CI: 2.8–8.3), and 7.1 months (95%CI: 4.7–14.6). Safety was manageable with grade 3 and more AEs in 81.3% (26/32), the most common being anemia (53.1%), neutropenia (31.3%), and leukopenia (31.3%). Interstitial lung disease and drug discontinuation both occurred in 25.0% of patients (68) (Table 1).

Even though no phase 3 trial has been published yet HER2 in CCA, many options are emerging in HER2-amplified CCA, confirming the interest to target this pathway.

NRTK fusions (ESCAT I-C)

Fusions of one of the three neurotrophic tyrosine receptor kinase genes (NTRK) 1, 2, 3 encoding the tropomyosin receptor kinase (TRK) A, B, C are rare alterations in biliary tract cancers (<1%). Nevertheless, as they are associated with a powerful oncogenic signal whose pharmacological inhibition seems promising, they should be systematically sought (69, 70). Larotrectinib, an oral TRK A/B/C inhibitor, was evaluated in a phase 1-2 study including 55 patients aged 4 months to 76 years with 17 tumor types with NTRK fusion. Objective response rate was 75% and tumor response was found in 1 of the 2 CCA patients. Safety profile was acceptable with grade 1-2 hypertransaminasemia and dizziness in respectively 38 and 25% of cases (71). Entrectinib, another TRK A/B/C inhibitor, showed an

objective response rate of 57% including 7% of complete response in an analysis integrating 3 phase 1-2 trials pooling a total of 54 patients with NTRK fusion-positive advanced cancer. The only CCA included was among these responders (72). These 2 inhibitors have FDA and EMA approval for the treatment of NTRK fusion-positive solid tumors and patients with this type alteration should have access to these promising therapies.

RET fusions (ESCAT I-C)

The proto-oncogene RET encodes a transmembrane tyrosine kinase receptor which plays a physiological role in the embryonic development of the nervous system and the kidneys. RET mutation or alteration induce oncogenic transformation with an aberrant activation of RET receptor. RET fusions are found in various cancers including CCA, with a prevalence around 1%, except for non small cell lung cancer (NSCLC) and papillary thyroid cancers in which prevalence reaches respectively 2 and 20% RET fusions (73, 74). To date, 2 orally bioavailable potent selective RET TKI-inhibitors showed promising preliminary results in solid tumors. The pralsetinib (BLU-667) was tested in the phase 1/2 trial ARROW (NCT03037385) including 29 patients with RET-fusion positive solid tumors. An objective response rate of 57% was observed, with a tumor shrinkage in 91% of the evaluable patients according to RECIST 1.1 criteria. Two of the 3 CCAs included, experienced tumor response. Safety was acceptable with neutropenia (29%), anemia (14%) and increased aspartate transaminase (AST ; 10%), as the most common grade 3 and more TRAEs (75). The selpercatinib (LOXO-292), which first showed interesting results in RET-fusion positive thyroid cancer and NSCLC within the pivotal phase 1/2 LIBRETTO-001 (NCT03157128) (76, 77), was then evaluated in another cohort of 45 patients with other RET fusion-positive tumors including 2 CCAs. The objective response rate was 43.9% and the only evaluable CCA experienced tumor response. The duration of response and the PFS were respectively 24.5 (9.2-not evaluable) and 13.2 (7.4–26.2) months. The most common grade 3 and more TRAEs were hypertension (22%) increased alanin transaminase (16%), and increased AST (13%). Treatment-emergent serious adverse events occurred in 40% of patients and no treatment-related deaths occurred (78). In September 2022, the FDA granted selpercatinib for an accelerated approval in locally advanced or metastatic RET-fusion positive solid tumors.

Microsatellite instability and immunotherapy (ESCAT I-C)

As in most digestive tumors, mismatch repair deficiency and/or microsatellite instability should be investigated as they are present in < 5% of CCAs and may allow access to immunotherapy. The dMMR can be part of either a Lynch syndrome or be a sporadic alteration, corresponding to a constitutional or acquired mutation in one of the MMR protein-coding genes, respectively. The non-randomized phase II KEYNOTE-168 trial evaluated the

pembrolizumab, an anti-PD-1 monoclonal antibody, in 233 patients with 27 types of MSI/dMMR tumors, previously treated with at least one line of systemic therapy, and with ECOG PS 0-1. In this cohort, 22 patients had advanced CCA, a subgroup in which an objective response rate of 40.9%, a PFS of 4.2 months and an OS of 24.3 months were observed (79). Immunotherapy thus represents a promising therapeutic option in MSI CCAs within a clinical trial or in daily care according to countries practices and standards, as pembrolizumab has been approved by both the FDA and the EMA in advanced dMMR/MSI cholangiocarcinoma.

BRAFV600E mutation (ESCAT II-B)

The V600E mutation of the BRAF gene is observed in approximately 3-7% of biliary cancers with a predominance of intrahepatic cancers (38). The non-randomized phase II ROAR trial evaluated the safety and efficacy of the combination of the BRAF inhibitor dabrafenib and the mitogen-activated protein kinase kinase (MEK) inhibitor trametinib in 43 previously treated patients with an advanced BRAF^{V600E}-mutated CCA with an ECOG PS of 0-2. An objective response rate of 47% and a control rate of 82% were observed (80). The AEs were mostly grade 2 with hyperthermia (60%), nausea (42%), vomiting (33%), asthenia (33%), diarrhea (30%), and chills (28%) as the most frequent. Thus, this combination shows promising preliminary results and constitutes a new option for BRAF^{V600E}-mutated CCA patients.

KRASG12C mutation (ESCAT II-B)

An activating mutation of the KRAS oncogene is found in 15-25% of biliary tract cancers. To date, only the KRASG12C mutation is accessible to pharmacological inhibition. This mutation is found in only 1% of CCAs but the results are particularly promising and should strongly motivate the inclusion of patients in clinical trials offering access to this type of inhibitor. Indeed, the phase 1/2 KRYSTAL-1 trial studied the safety and antitumor activity of adagrasib, a KRASG12C inhibitor, in 42 patients including 8 advanced CCAs, pre-exposed to at least two lines of systemic treatment, in which an objective response rate of 50% and a tumor control rate of 100% were observed. The main AEs were nausea, vomiting, diarrhea and fatigue in 48%, 43% and 29% of cases, respectively (81). At this moment, only sotorasib, another oral inhibitor specific for KRASG12C mutations, has been approved in non-small cell lung cancer by FDA and EMA, but no data is available for this latter in CCA. At this time, no KRASG12C inhibitor is considered as a standard of care in CCA but the presence of this type of mutation must lead to patients' inclusion in dedicated clinical trials.

Conclusion

CCA is a rare disease with an increasing incidence, a very poor prognosis with a 5-year survival rate of less than 15% for all stages combined, and a limited therapeutic arsenal. Even though recently a significant advance was made in all comers CCA with the arrival of the CISGEM-durvalumab combination in L1, the real change comes from molecular profiling which opens the way to personalized medicine. This profiling is now recommended from the time of the diagnosis due to the frequency of actionable alterations such as IDH1 mutations and FGFR2 rearrangements/fusions in iCCA, as well as HER amplification/overexpression in gallbladder cancers, pCCAs and dCCAs. Even though no direct comparative data are available *versus* FOLFOX, regarding the oncological results of matched targeted therapies, these treatments should be proposed from the second line in patients with actionable alterations. Moreover, many upcoming trials will aim to demonstrate the value of these targeted treatments from L1 such as in FGFR2 rearranged cholangiocarcinomas or the ambitious European randomized phase 3 trial SAFIR/ABC-10 which will compare chemotherapy *versus* maintenance by matched therapy according to profiling results, after 3 months of L1. These studies should help to prove the benefit of personalized medicine from the first steps of patients' therapeutic pathway. Thus, as integration of personalized medicine in the treatment of CCA is now unavoidable, molecular profiling structuring represents a huge challenge to improve patients' care and homogenize the access to innovative therapies worldwide.

Acknowledgements: none

Funding: none

Conflict of interest statement:

Gael S Roth declares consulting or advisory role for Servier, AstraZeneca, Bristol Myers Squibb, MSD, Servier, Amgen, Ipsen, Viatris, Accord Healthcare, Sanofi; travel, accommodations or expenses from Servier, AstraZeneca, Bristol Myers Squibb, MSD, Roche, Amgen, Ipsen.

Cindy Neuzillet declares consultancy/honoraria from Amgen, AstraZeneca, Baxter, Bristol-Myers Squibb, Fresenius Kabi, Incyte Biosciences, Merck, MSD, Mylan, Novartis, Nutricia, Pierre Fabre, Roche, Sanofi, Servier, Viatris; Research funding from Roche; clinical trials sponsored by OSE Immunotherapeutics, AstraZeneca, Bristol-Myers Squibb, Fresenius Kabi, Nutricia, Viatris

Matthieu Sarabi declares consultancy/honoraria AstraZeneca, Servier, Roche and accommodations or expenses from Ipsen.

Julien Edeline declares consulting or advisory role for BTG, Bristol Myers Squibb, AstraZeneca, Bayer, Ipsen, AstraZeneca, MSD, Eisai, Boston Scientific, Roche, Basilea, Merck Serono, Servier ; research Funding from Bristol Myers Squibb (Inst), BeiGene (Inst); travel, accommodations or expenses from Amgen, Bristol Myers Squibb, Roche

David Malka declares honoraria for Roche, Amgen, Bayer, Merck Serono, Servier, Sanofi, Pierre Fabre, Viartis, Bristol Myers Squibb, MSD Oncology, LEO Pharma, Incyte, AstraZeneca; consulting or advisory role: Roche, Sanofi, Merck Serono, MSD, Servier, Bayer, Incyte, Amgen, Bristol Myers Squib, Taiho Oncology, AbbVie, AstraZeneca, Pierre Fabre; travel, accommodations or expenses from Roche, Bayer, Sanofi, Merck Serono, Amgen, Servier, Pierre Fabre, Bristol Myers Squibb/Pfizer, MSD, Viartis

Astrid Lièvre declares honoraria for lectures from AAA, Amgen, Bayer, BMS, Incyte, Ipsen, Leo-pharma, Mylan, Novartis, Pierre Fabre, Roche, Sandoz , Sanofi, Servier and Viartis; consulting/advisory relationship from AAA, Astellas, BMS, Incyte, Pierre Fabre and Servier; travel, accomodations or congress registration support from Bayer, Boehringer, Ipsen, Mylan, MSD, Pierre Fabre, Roche and Servier; research funding from Bayer (Inst), Lilly (Inst), Novartis (Inst).

No other potential conflicts of interest were reported.

References :

1. Valle JW, Kelley RK, Nervi B, Oh D-Y, Zhu AX. Biliary tract cancer. *The Lancet* 2021;397(10272):428-444.
2. Izquierdo-Sanchez L, Lamarca A, La Casta A, Buettner S, Utpatel K, Klumpen H-J, et al. Cholangiocarcinoma landscape in Europe: Diagnostic, prognostic and therapeutic insights from the ENSCCA Registry. *Journal of Hepatology* 2022.
3. Clements O, Eliahoo J, Kim JU, Taylor-Robinson SD, Khan SA. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma: A systematic review and meta-analysis. *Journal of Hepatology* 2020;72(1):95-103.
4. Vithayathil M, Khan SA. Current epidemiology of cholangiocarcinoma in western countries. *Journal of Hepatology* 2022.
5. Saha SK, Zhu AX, Fuchs CS, Brooks GA. Forty-Year Trends in Cholangiocarcinoma Incidence in the U.S.: Intrahepatic Disease on the Rise. *The Oncologist* 2016;21(5):594-599.
6. Neuzillet C, Emery C, Teissier C, Bouée S, Lièvre A. Patient healthcare trajectories of intrahepatic cholangiocarcinoma in France: A nationwide retrospective analysis. *The Lancet Regional Health - Europe* 2022;15:100324.
7. Conway A-M, Morris GC, Smith S, Vekeria M, Manoharan P, Mitchell C, et al. Intrahepatic cholangiocarcinoma hidden within cancer of unknown primary. *British Journal of Cancer* 2022.

8. Blanc JF, Debaillon-Vesque A, Roth G, Barbare JC, Baumann AS, Boige V, et al. Hepatocellular carcinoma: French Intergroup Clinical Practice Guidelines for diagnosis, treatment and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, AFEF, SIAD, SFR/FRI). *Clinics and Research in Hepatology and Gastroenterology* 2021;45(2):101590.
9. Galle PR, Forner A, Llovet JM, Mazzaferro V, Piscaglia F, Raoul J-L, et al. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *Journal of Hepatology* 2018;69(1):182-236.
10. Khan SA, Thomas HC, Davidson BR, Taylor-Robinson SD. Cholangiocarcinoma. *The Lancet* 2005;366(9493):1303-1314.
11. Mosconi S, Beretta GD, Labianca R, Zampino MG, Gatta G, Heinemann V. Cholangiocarcinoma. *Crit Rev Oncol Hematol* 2009;69(3):259-70.
12. Bridgewater J, Galle PR, Khan SA, Llovet JM, Park J-W, Patel T, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *Journal of Hepatology* 2014;60(6):1268-1289.
13. Valle J, Wasan H, Palmer DH, Cunningham D, Anthony A, Maraveyas A, et al. Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer. *New England Journal of Medicine* 2010;362(14):1273-1281.
14. Harder J, Riecken B, Kummer O, Lohrmann C, Otto F, Usadel H, et al. Outpatient chemotherapy with gemcitabine and oxaliplatin in patients with biliary tract cancer. *British Journal of Cancer* 2006;95(7):848-852.
15. André T, Tournigand C, Rosmorduc O, Provent S, Maindrault-Goebel F, Avenin D, et al. Gemcitabine combined with oxaliplatin (GEMOX) in advanced biliary tract adenocarcinoma: a GERCOR study. *Annals of Oncology* 2004;15(9):1339-1343.
16. Fiteni F, Nguyen T, Vernerey D, Paillard M-J, Kim S, Demarchi M, et al. Cisplatin/gemcitabine or oxaliplatin/gemcitabine in the treatment of advanced biliary tract cancer: a systematic review. *Cancer Medicine* 2014;3(6):1502-1511.
17. Chiang N, L. Bai, C. Huang, S. Chen, C. Hsiao, Y. Shan, et al. A phase II trial of nivolumab and gemcitabine and S-1 as the first-line treatment in patients with advanced biliary tract cancer. *Annals of Oncology* 2021;32 (suppl_5): S376-S381. 10.1016/annonc/annonc685.
18. Shroff RT, Javle MM, Xiao L, Kaseb AO, Varadhachary GR, Wolff RA, et al. Gemcitabine, Cisplatin, and nab-Paclitaxel for the Treatment of Advanced Biliary Tract Cancers: A Phase 2 Clinical Trial. *JAMA Oncol* 2019;5(6):824-830.
19. Knox JJ, McNamara MG, Goyal L, Cosgrove D, Springfield C, Sjoquist KM, et al. Phase III study of NUC-1031 + cisplatin vs gemcitabine + cisplatin for first-line treatment of patients with advanced biliary tract cancer (NuTide:121). *Journal of Clinical Oncology* 2021;39(3_suppl):TPS351-TPS351.
20. McNamara MG, Bridgewater J, Palmer DH, Faluyi O, Wasan H, Patel A, et al. A Phase Ib Study of NUC-1031 in Combination with Cisplatin for the First-Line Treatment of Patients with Advanced Biliary Tract Cancer (ABC-08). *The Oncologist* 2021;26(4):e669-e678.
21. Phelip Jm, Desrame J, Edeline J, Barbier E, Terrebonne E, Michel P, et al. Modified FOLFIRINOX Versus CISGEM Chemotherapy for Patients With Advanced Biliary Tract Cancer (PRODIGE 38 AMEBICA): A Randomized Phase II Study. *Journal of Clinical Oncology* 2022;40(3):262-271.
22. Perkhofer L, Striefler JK, Sinn M, Opitz B, Goetze TO, Gallmeier E, et al. LBA10 Nal-IRI with 5-fluorouracil (5-FU) and leucovorin or gemcitabine plus cisplatin in advanced biliary tract cancer: Final results of the NIFE-trial (AIO-YMO HEP-0315), a randomized phase II study of the AIO biliary tract cancer group. *Annals of Oncology* 2021;32:S1282.
23. Oh D-Y, He AR, Qin S, Chen L-T, Okusaka T, Vogel A, et al. A phase 3 randomized, double-blind, placebo-controlled study of durvalumab in combination with gemcitabine plus cisplatin (GemCis) in patients (pts) with advanced biliary tract cancer (BTC): TOPAZ-1. *Journal of Clinical Oncology* 2022;40(4_suppl):378-378.

24. Oh D-Y, Ruth He A, Qin S, Chen L-T, Okusaka T, Vogel A, et al. Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer. *NEJM Evidence* 2022.
25. Brieau B, Dahan L, De Rycke Y, Boussaha T, Vasseur P, Tougeron D, et al. Second-line chemotherapy for advanced biliary tract cancer after failure of the gemcitabine-platinum combination: A large multicenter study by the Association des Gastro-Entérologues Oncologues. *Cancer* 2015;121(18):3290-3297.
26. Lamarca A, Hubner RA, David Ryder W, Valle JW. Second-line chemotherapy in advanced biliary cancer: a systematic review. *Annals of Oncology* 2014;25(12):2328-2338.
27. Lowery MA, Goff LW, Keenan BP, Jordan E, Wang R, Bocobo AG, et al. Second-line chemotherapy in advanced biliary cancers: A retrospective, multicenter analysis of outcomes. *Cancer* 2019;125(24):4426-4434.
28. Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, et al. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. *The Lancet Oncology* 2021;22(5):690-701.
29. Lamarca A, Palmer D, Wasan HS, Ross P, Ma YT, Arora A, et al. 54MO Quality of life (QoL) and value of health (V-He) in advanced biliary cancers (ABC) treated with second-line active-symptom-control (ASC) alone or ASC with oxaliplatin/5-FU chemotherapy (ASC+FOLFOX) in the randomised phase III, multi-centre, open-label ABC-06 trial. *Annals of Oncology* 2022;33:S564-S565.
30. Zheng Y, Tu X, Zhao P, Jiang W, Liu L, Tong Z, et al. A randomised phase II study of second-line XELIRI regimen versus irinotecan monotherapy in advanced biliary tract cancer patients progressed on gemcitabine and cisplatin. *British Journal of Cancer* 2018;119(3):291-295.
31. Kim JW, Suh KJ, Kim J-W, Park JH, Kim KH, Kim YJ, et al. A randomized phase II study of oxaliplatin/5-FU (mFOLFOX) versus irinotecan/5-FU (mFOLFIRI) chemotherapy in locally advanced or metastatic biliary tract cancer refractory to first-line gemcitabine/cisplatin chemotherapy. *Journal of Clinical Oncology* 2020;38(15_suppl):4603-4603.
32. Yoo C, Kim K-p, Jeong JH, Kim I, Kang MJ, Cheon J, et al. Liposomal irinotecan plus fluorouracil and leucovorin versus fluorouracil and leucovorin for metastatic biliary tract cancer after progression on gemcitabine plus cisplatin (NIFTY): a multicentre, open-label, randomised, phase 2b study. *The Lancet Oncology* 2021;22(11):1560-1572.
33. Neuzillet C, Casadei - Gardini A, Brieau B, Vivaldi C, Brandi G, Tougeron D, et al. Fluropyrimidine single agent or doublet chemotherapy as second line treatment in advanced biliary tract cancer. *International Journal of Cancer* 2020;147(11):3177-3188.
34. Lowery MA, Ptashkin R, Jordan E, Berger MF, Zehir A, Capanu M, et al. Comprehensive Molecular Profiling of Intrahepatic and Extrahepatic Cholangiocarcinomas: Potential Targets for Intervention. *Clinical Cancer Research* 2018;24(17):4154-4161.
35. Voss JS, Holtegaard LM, Kerr SE, Fritcher EGB, Roberts LR, Gores GJ, et al. Molecular profiling of cholangiocarcinoma shows potential for targeted therapy treatment decisions. *Human Pathology* 2013;44(7):1216-1222.
36. Montal R, Sia D, Montironi C, Leow WQ, Esteban-Fabrá R, Pinyol R, et al. Molecular classification and therapeutic targets in extrahepatic cholangiocarcinoma. *Journal of Hepatology* 2020;73(2):315-327.
37. Nepal C, O'Rourke CJ, Oliveira DVNP, Taranta A, Shema S, Gautam P, et al. Genomic perturbations reveal distinct regulatory networks in intrahepatic cholangiocarcinoma. *Hepatology* 2018;68(3):949-963.
38. Valle JW, Lamarca A, Goyal L, Barriuso J, Zhu AX. New Horizons for Precision Medicine in Biliary Tract Cancers. *Cancer Discovery* 2017;7(9):943-962.
39. Verlingue L, Hollebecque A, Boige V, Ducreux M, Malka D, Féré C. Matching genomic molecular aberrations with molecular targeted agents: Are biliary tract cancers an ideal playground? *European Journal of Cancer* 2017;81:161-173.
40. Verlingue L, Malka D, Allorant A, Massard C, Féré C, Lacroix L, et al. Precision medicine for patients with advanced biliary tract cancers: An effective strategy within the prospective MOSCATO-01 trial. *European Journal of Cancer* 2017;87:122-130.

41. Massard C, Michiels S, Ferté C, Le Deley M-C, Lacroix L, Hollebecque A, et al. High-Throughput Genomics and Clinical Outcome in Hard-to-Treat Advanced Cancers: Results of the MOSCATO 01 Trial. *Cancer Discovery* 2017;7(6):586-595.
42. Lamarca A, Kapacee Z, Breeze M, Bell C, Belcher D, Staiger H, et al. Molecular Profiling in Daily Clinical Practice: Practicalities in Advanced Cholangiocarcinoma and Other Biliary Tract Cancers. *Journal of Clinical Medicine* 2020;9(9):2854.
43. MacConaill LE, Garraway LA. Clinical Implications of the Cancer Genome. *Journal of Clinical Oncology* 2010;28(35):5219-5228.
44. Mateo J, Chakravarty D, Dienstmann R, Jezdic S, Gonzalez-Perez A, Lopez-Bigas N, et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). *Annals of Oncology* 2018;29(9):1895-1902.
45. Javle M, Churi C, Kang HC, Shroff R, Janku F, Surapaneni R, et al. HER2/neu-directed therapy for biliary tract cancer. *Journal of Hematology & Oncology* 2015;8(1).
46. Boland CR, Thibodeau SN, Hamilton SR, Sidransky D, Eshleman JR, Burt RW, et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. *Cancer Res* 1998;58(22):5248-57.
47. Rompianesi G, Di Martino M, Gordon-Weeks A, Montalti R, Troisi R. Liquid biopsy in cholangiocarcinoma: Current status and future perspectives. *World Journal of Gastrointestinal Oncology* 2021;13(5):332-350.
48. Barile L, Vassalli G. Exosomes: Therapy delivery tools and biomarkers of diseases. *Pharmacology & Therapeutics* 2017;174:63-78.
49. Cescon DW, Bratman SV, Chan SM, Siu LL. Circulating tumor DNA and liquid biopsy in oncology. *Nature Cancer* 2020;1(3):276-290.
50. Mody K, Kasi PM, Yang J, Surapaneni PK, Bekaii-Saab T, Ahn DH, et al. Circulating Tumor DNA Profiling of Advanced Biliary Tract Cancers. *JCO Precis Oncol* 2019;3:1-9.
51. Merker JD, Oxnard GR, Compton C, Diehn M, Hurley P, Lazar AJ, et al. Circulating Tumor DNA Analysis in Patients With Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. *Journal of Clinical Oncology* 2018;36(16):1631-1641.
52. Lapin M, Huang HJ, Chagani S, Javle M, Shroff RT, Pant S, et al. Monitoring of Dynamic Changes and Clonal Evolution in Circulating Tumor DNA From Patients With IDH-Mutated Cholangiocarcinoma Treated With Isocitrate Dehydrogenase Inhibitors. *JCO Precision Oncology* 2022(6):e2100197.
53. Thein KZ, Biter AB, Banks KC, Duda AW, Saam J, Roszik J, et al. Identification of KRASG12C Mutations in Circulating Tumor DNA in Patients With Cancer. *JCO Precision Oncology* 2022(6):e2100547.
54. Goyal L, Meric-Bernstam F, Hollebecque A, Morizane C, Valle JW, Karasic TB, et al. Updated results of the FOENIX-CCA2 trial: Efficacy and safety of futibatinib in intrahepatic cholangiocarcinoma (iCCA) harboring FGFR2 fusions/rearrangements. *Journal of Clinical Oncology* 2022;40(16_suppl):4009-4009.
55. Varghese AM, Patel J, Janjigian YY, Meng F, Selcuklu SD, Iyer G, et al. Noninvasive Detection of Polyclonal Acquired Resistance to FGFR Inhibition in Patients With Cholangiocarcinoma Harboring FGFR2 Alterations. *JCO Precis Oncol* 2021;5.
56. Boscoe AN, Rolland C, Kelley RK. Frequency and prognostic significance of isocitrate dehydrogenase 1 mutations in cholangiocarcinoma: a systematic literature review. *Journal of Gastrointestinal Oncology* 2019;10(4):751-765.
57. Lowery MA, Burris HA, Janku F, Shroff RT, Cleary JM, Azad NS, et al. Safety and activity of ivosidenib in patients with IDH1-mutant advanced cholangiocarcinoma: a phase 1 study. *The Lancet Gastroenterology & Hepatology* 2019;4(9):711-720.
58. Abou-Alfa GK, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. *The Lancet Oncology* 2020;21(6):796-807.

59. Abou-Alfa GK, Sahai V, Hollebecque A, Vaccaro G, Melisi D, Al-Rajabi R, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *The Lancet Oncology* 2020;21(5):671-684.
60. Goyal L, Meric-Bernstam F, Hollebecque A, Morizane C, Valle JW, Karasic TB, et al. Abstract CT010: Primary results of phase 2 FOENIX-CCA2: The irreversible FGFR1-4 inhibitor futibatinib in intrahepatic cholangiocarcinoma (iCCA) with FGFR2 fusions/rearrangements. *Cancer Research* 2021;81(13_Supplement):CT010-CT010.
61. Javle M, Lowery M, Shroff RT, Weiss KH, Springfield C, Borad MJ, et al. Phase II Study of BGJ398 in Patients With FGFR-Altered Advanced Cholangiocarcinoma. *J Clin Oncol* 2018;36(3):276-282.
62. Javle MM, Abou-Alfa GK, Macarulla T, Personeni N, Adeva J, Bergamo F, et al. Efficacy of derazantinib in intrahepatic cholangiocarcinoma patients with FGFR2 mutations or amplifications: Interim results from the phase 2 study FIDES-01. *Journal of Clinical Oncology* 2022;40(4_suppl):427-427.
63. Meric-Bernstam F, Bahleda R, Hierro C, Sanson M, Bridgewater J, Arkenau H-T, et al. Futibatinib, an Irreversible FGFR1–4 Inhibitor, in Patients with Advanced Solid Tumors Harboring FGF/FGFR Aberrations: A Phase I Dose-Expansion Study. *Cancer Discovery* 2022;12(2):402-415.
64. Javle M, Borad MJ, Azad NS, Kurzrock R, Abou-Alfa GK, George B, et al. Pertuzumab and trastuzumab for HER2-positive, metastatic biliary tract cancer (MyPathway): a multicentre, open-label, phase 2a, multiple basket study. *The Lancet Oncology* 2021;22(9):1290-1300.
65. Lee C-k, Chon HJ, Cheon J, Lee MA, Im H-S, Jang J-S, et al. Trastuzumab plus FOLFOX for gemcitabine/cisplatin refractory HER2-positive biliary tract cancer: A multi-institutional phase II trial of the Korean Cancer Study Group (KCSG-HB19-14). *Journal of Clinical Oncology* 2022;40(16_suppl):4096-4096.
66. Pant S, Ducreux M, Harding JJ, Javle MM, Oh D-Y, Wasan HS, et al. A phase IIb, open-label, single-arm study of zanidatamab (ZW25) monotherapy in subjects with advanced or metastatic HER2-amplified biliary tract cancers. *Journal of Clinical Oncology* 2021;39(3_suppl):TPS352-TPS352.
67. Meric-Bernstam F, Hanna DL, El-Khoueiry AB, Kang Y-K, Oh D-Y, Chaves JM, et al. Zanidatamab (ZW25) in HER2-positive biliary tract cancers (BTCs): Results from a phase I study. *Journal of Clinical Oncology* 2021;39(3_suppl):299-299.
68. Ohba A, Morizane C, Kawamoto Y, Komatsu Y, Ueno M, Kobayashi S, et al. Trastuzumab deruxtecan (T-DXd; DS-8201) in patients (pts) with HER2-expressing unresectable or recurrent biliary tract cancer (BTC): An investigator-initiated multicenter phase 2 study (HERB trial). *Journal of Clinical Oncology* 2022;40(16_suppl):4006-4006.
69. Drilon A. TRK inhibitors in TRK fusion-positive cancers. *Annals of Oncology* 2019;30:viii23-viii30.
70. Marchiò C, Scaltriti M, Ladanyi M, Iafrate AJ, Bibeau F, Dietel M, et al. ESMO recommendations on the standard methods to detect NTRK fusions in daily practice and clinical research. *Annals of Oncology* 2019;30(9):1417-1427.
71. Drilon A, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, et al. Efficacy of Larotrectinib in TRK Fusion–Positive Cancers in Adults and Children. *New England Journal of Medicine* 2018;378(8):731-739.
72. Doebele RC, Drilon A, Paz-Ares L, Siena S, Shaw AT, Farago AF, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1–2 trials. *The Lancet Oncology* 2020;21(2):271-282.
73. Kato S, Subbiah V, Marchlik E, Elkin SK, Carter JL, Kurzrock R. RET Aberrations in Diverse Cancers: Next-Generation Sequencing of 4,871 Patients. *Clinical Cancer Research* 2017;23(8):1988-1997.
74. Thein KZ, Velcheti V, Mooers BHM, Wu J, Subbiah V. Precision therapy for RET-altered cancers with RET inhibitors. *Trends in Cancer* 2021;7(12):1074-1088.

75. Subbiah V, Cassier PA, Siena S, Garralda E, Paz-Ares L, Garrido P, et al. Pan-cancer efficacy of pralsetinib in patients with RET fusion–positive solid tumors from the phase 1/2 ARROW trial. *Nature Medicine* 2022;28(8):1640-1645.
76. Wirth LJ, Sherman E, Robinson B, Solomon B, Kang H, Lorch J, et al. Efficacy of Selpercatinib in RET-Altered Thyroid Cancers. *New England Journal of Medicine* 2020;383(9):825-835.
77. Drilon A, Oxnard GR, Tan DSW, Loong HHF, Johnson M, Gainor J, et al. Efficacy of Selpercatinib in RET Fusion–Positive Non–Small-Cell Lung Cancer. *New England Journal of Medicine* 2020;383(9):813-824.
78. Subbiah V, Wolf J, Konda B, Kang H, Spira A, Weiss J, et al. Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial. *The Lancet Oncology* 2022;23(10):1261-1273.
79. Marabelle A, Le DT, Ascierto PA, Giacomo AMD, Jesus-Acosta AD, Delord J-P, et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair–Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. *Journal of Clinical Oncology* 2020;38(1):1-10.
80. Subbiah V, Lassen U, Élez E, Italiano A, Curigliano G, Javle M, et al. Dabrafenib plus trametinib in patients with BRAFV600E-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial. *The Lancet Oncology* 2020;21(9):1234-1243.
81. Bekaii-Saab TS, Spira AI, Yaeger R, Buchsacher GL, McRee AJ, Sabari JK, et al. KRYSTAL-1: Updated activity and safety of adagrasib (MRTX849) in patients (Pts) with unresectable or metastatic pancreatic cancer (PDAC) and other gastrointestinal (GI) tumors harboring a KRASG12C mutation. *Journal of Clinical Oncology* 2022;40(4_suppl):519-519.

Table 1: Published studies evaluating targeted therapies against most frequent actionable alterations in cholangiocarcinoma (IDH1 mutation, FGFR2 fusions and HER amplification/overexpression).

Abbreviations: Ab: antibody, chemo: chemotherapy, ESCAT: ESMO Scale for Clinical Actionability of molecular Targets, FGFR: fibroblast growth factor receptor, IDH1: isocitrate dehydrogenase 1, L: line, L2+: line 2 and more, m: month, mut: mutation, n: number, ORR: objective response rate, OS: overall survival, PFS: progression-free survival, pts: patients TOP1: topoisomerase 1

| Actionable alteration ESCAT class | Drug name Drug class | Trial (Name, ClinicalTrials.gov Identifier or other, reference) | Phase and study design | Population (number, line of treatment) | Primary objectives | Results (final results, intermediate analyses) | | |
|--|---|---|--|---|--|--|---|---|
| | | | | | | ORR | mPFS | mOS |
| IDH1 mutation ESCAT I-A | Ivosidenib (AG-120) <i>IDH1mut -inhibitor</i> | ClarIDHy NCT02989857 Lancet 2020 (58) | Randomized (2 :1) multicenter phase 3 versus Placebo | n=185 pts L2-L3 | OS | Ivosidenib vs Placebo : 2 vs 0% | Ivosidenib vs Placebo : 2.7 vs 1.4 m (HR:0.37; 95%CI:0.25-0.54, p<0.001) | Ivosidenib vs Placebo : 10.8 vs 9.7 m (HR 0.69, 95%CI: 0.44–1.10 p=0.060) Placebo (RPSFT-adjusted OS): 6.0 m (HR 0.46 95%CI:0.28–0.75; p=0.0008) |
| | FGFR2 alterations ESCAT I-B | Pemigatinib <i>FGFR1/2/3 inhibitor</i> | FIGHT-202 NCT02924376 Lancet Oncol 2020 (59) | Single-arm multicenter phase 2 | n=147 pts (107 pts with FGFR2-fusions) L2+ | ORR | Cohort fusion: 35.5% Other alterations: 0% | 12m-PFS: 29% in fusion cohort (0% in other cohorts) |
| Futibatinib <i>FGFR1-4 inhibitor</i> | | FOENIX-CCA2 NCT02052778 Cancer Res 2021 (Abst) (60) | Single-arm multicenter phase 2 | n=103 pts (78% of pts with FGFR2-fusion) L2+ | ORR | 41.7% | 9.0m | 21.7m |
| Infigratinib (BGJ398) <i>FGFR1/2/3 inhibitor</i> | | CBGJ398X2204 NCT02150967 J Clin Oncol 2017 (61) | Single-arm multicenter phase 2 | n=61 pts (48 pts with FGFR2-fusions) L2+ | | 14.8% Cohort fusion: 18.8% | 5.8m | N/A |
| Derazantinib (ARQ 087) <i>FGFR1/2/3 inhibitor</i> | | FIDES-01 NCT03230318 J Clin Oncol 2022 (Abst) (62) | Single-arm multicenter phase 2 | n=28 pts L2+ | 3m-PFS | 8.7% | 7.3m 3m-PFS: 76.3% 6m-PFS: 50.3% | N/A |
| HER amplification / overexpression ESCAT II-B | Trastuzumab-pertuzumab <i>Anti-HER2 Ab</i> | myPathway NCT02091141 Lancet Oncol 2021 (64) | Single-arm multicenter phase 2 | n=39 pts L2+ | ORR | 23% | 4.0m | 10.9m |
| | FOLFOX-trastuzumab <i>Chemo + anti-HER2 Ab</i> | KCSG-HB19-14 NCT04722133 J Clin Oncol 2022 (Abst) (65) | Single-arm multicenter phase 2 | n=34pts L2-L3 | ORR | 29.4% | 5.1m | not reached |
| | Trastuzumab-deruxtecan (T-DXd; DS-8201) <i>Anti-HER2 Ab conjugated</i> | HERB trial JMA-IIA00423 J Clin Oncol 2022 (Abst) (68) | Single-arm multicenter phase 2 | n=32pts (24 HER2-positive and 8 HER2-low) L2+ | ORR in HER-positive | HER-positive: 36.4% HER2-low: 12.5% | HER-positive: 4.4m HER2-low: 4.2m | HER-positive: 7.1m HER2-low: 8.9m |

| | | | | | | | | |
|--|--|---|-----------------------------------|----------------|--------------------------|-----|-----|-----|
| | <i>with TOP1 inhibitor</i> | | | | | | | |
| | Zanidatamab <i>Bi specific anti-HER2 Ab</i> | ZWI-ZW25-101 NCT02892123 J Clin Oncol 2021 (Abst) (67) | Single-arm multicenter phase 1 | n=20pts L2+ | Safety / tolerability | 47% | N/A | N/A |

Journal Pre-proof

Figure 1: Cholangiocarcinomas subtypes: epidemiology, clinical presentation, management principles and most frequent molecular alterations.

Journal Pre-proof

Figure 2: Molecular actionable alterations' landscape in cholangiocarcinoma with corresponding targeted therapeutic options. This pie chart presentation aims to offer a rapid overview of actionable alterations in iCCA and eCCA with their respective relative frequency without taking into account the possibility of overlap of several alterations.

Abbreviations: ESCAT: ESMO Scale for Clinical Actionability of Molecular Targets, FGFR2 : Fibroblast growth factor receptor 2, FISH: fluorescent in situ hybridation, IDH1: Isocitrate dehydrogenase 1, IHC: immunohistochemistry, HER2 : human epidermal growth factor receptor 2, MSI : Microsatellite instability, NGS: next generation sequencing, NTRK: neurotrophic tyrosine receptor kinase, RNAseq: RNA sequencing

Journal Pre-proof

Intrahepatic cholangiocarcinoma (iCCA) : 20% of CCA

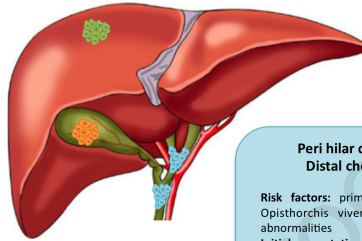
Risk factors: primary sclerosing cholangitis, cirrhosis, obesity, diabetes, chronic hepatitis B and C, hepatolithiasis, Opisthorchis viverrini or Clonorchis sinensis, biliary papillomatosis, morphological abnormalities of the bile duct

Initial presentation: incidental finding of one or more liver lesions

Treatment:

- localized stage: surgery + adjuvant capecitabine
- locally advanced stage: radioembolization may be considered
- advanced stage: systemic treatment (molecular screening for actionable gene alterations)

Most frequent actionable alterations: IDH 1/2 mutations, FGFR2 rearrangements/fusions

**Gallbladder carcinoma: < 10% of CCA**

Risk factors: gallstones, gallbladder polyps, chronic cholecystitis, Salmonella typhi, obesity, diabetes, sex ratio: female > male

Initial presentation: incidental finding after cholecystectomy (localized stage) or abdominal pain at an advanced stage

Treatment:

- localized stage: surgery + adjuvant capecitabine
- advanced stage: systemic treatment

Most frequent actionable alterations: HER amplification/overexpression

**Peri hilar cholangiocarcinoma (pCCA) : 50-60% of CCA
Distal cholangiocarcinoma (dCCA) : 20-30% of CCA**

Risk factors: primary sclerosing cholangitis, gallstones, Lynch syndrome, Opisthorchis viverrini or Clonorchis sinensis, bile duct morphological abnormalities

Initial presentation: obstructive jaundice

Treatment:

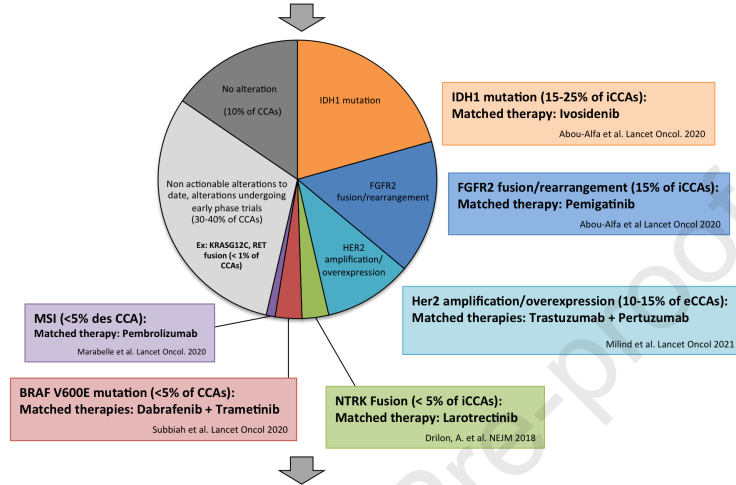
- localized stage: surgery + adjuvant capecitabine
- advanced stage: systemic treatment

Most frequent actionable alterations: HER amplification/overexpression

L1: CISGEM-durvalumab

Screening for actionable alterations: all patients with advanced CCA, ECOG 0-1

| Molecular profiling | | |
|-----------------------------|---|---------------------------|
| Sequencing technique | NGS DNA | RNAseq |
| Main ESCAT I-II alterations | IDH1/2 mutations, ERBB2 amplification, BRAF mutation, MSI | FGFR2 fusion, NTRK fusion |
| Confirmation technique | ERBB2 amplification: HER2 expression confirmation by IHC and/or by FISH | |



L2 options: FOLFOX or initiation of a matched targeted therapy

Title: Cholangiocarcinoma: what are the options in all comers and how the advent of molecular profiling has opened the way to personalized medicine ?

Highlights (3 to 5 bullet points, 85 characters including spaces)

- CISGEM-durvalumab is a new standard in advanced cholangiocarcinoma in first line
- Actionable alterations are present in up to 40-50% of patients, especially in iCCA
- Molecular profiling should be proposed to every ECOG 0-1 patients from the diagnosis
- Molecular profiling should integrate DNA and RNA next generation sequencing techniques

Title: Cholangiocarcinoma: what are the options in all comers and how the advent of molecular profiling has opened the way to personalized medicine ?

Conflict of interest statement:

Gael S Roth declares consulting or advisory role for Servier, AstraZeneca, Bristol Myers Squibb, MSD, Servier, Amgen, Ipsen, Viatris, Accord Healthcare, Sanofi; travel, accommodations or expenses from Servier, AstraZeneca, Bristol Myers Squibb, MSD, Roche, Amgen, Ipsen.

Cindy Neuzillet declares consultancy/honoraria from Amgen, AstraZeneca, Baxter, Bristol-Myers Squibb, Fresenius Kabi, Incyte Biosciences, Merck, MSD, Mylan, Novartis, Nutricia, Pierre Fabre, Roche, Sanofi, Servier, Viatris; Research funding from Roche; clinical trials sponsored by OSE Immunotherapeutics, AstraZeneca, Bristol-Myers Squibb, Fresenius Kabi, Nutricia, Viatris

Matthieu Sarabi declares consultancy/honoraria AstraZeneca, Servier, Roche and accommodations or expenses from Ipsen.

Julien Edeline declares consulting or advisory role for BTG, Bristol Myers Squibb, AstraZeneca, Bayer, Ipsen, AstraZeneca, MSD, Eisai, Boston Scientific, Roche, Basilea, Merck Serono, Servier ; research Funding from Bristol Myers Squibb (Inst), BeiGene (Inst); travel, accommodations or expenses from Amgen, Bristol Myers Squibb, Roche

David Malka declares honoraria for Roche, Amgen, Bayer, Merck Serono, Servier, Sanofi, Pierre Fabre, Viatris, Bristol Myers Squibb, MSD Oncology, LEO Pharma, Incyte, AstraZeneca; consulting or advisory role: Roche, Sanofi, Merck Serono, MSD, Servier, Bayer, Incyte, Amgen, Bristol Myers Squib, Taiho Oncology, AbbVie, AstraZeneca, Pierre Fabre; travel, accommodations or expenses from Roche, Bayer, Sanofi, Merck Serono, Amgen, Servier, Pierre Fabre, Bristol Myers Squibb/Pfizer, MSD, Viatris

Astrid Lièvre declares honoraria for lectures from AAA, Amgen, Bayer, BMS, Incyte, Ipsen, Leo-pharma, Mylan, Novartis, Pierre Fabre, Roche, Sandoz , Sanofi, Servier and Viatris; consulting/advisory relationship from AAA, Astellas, BMS, Incyte, Pierre Fabre and Servier; travel, accomodations or congress registration support from Bayer, Boehringer, Ipsen, Mylan, MSD, Pierre Fabre, Roche and Servier; research funding from Bayer (Inst), Lilly (Inst), Novartis (Inst).

No other potential conflicts of interest were reported.