# Chapter 18
# Novel Treatments for Advanced Cholangiocarcinoma


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**Key Learning Points**

1. A modest gain in survival in advanced cholangiocarcinoma using systemic chemotherapy highlights the need for improved therapies at all stages of treatment.
2. Locoregional therapies show promising results in locally advanced and palliative settings; however liver toxicity can occur in up to 40% of patients.
3. The use of targeted therapies remains investigational; to date none have demonstrated an improvement in patient outcomes.
4. The use of antiangiogenic agents has not yet resulted in a significant improvement in survival.
5. As the field of molecular medicine advances, systemic therapies may now focus on targeted therapies and immunotherapies.
6. Further research into novel treatments is warranted and further targeted molecular profiling developments may result in improved survival in advanced cholangiocarcinoma in the future.
7. Palliative care needs to be introduced earlier in the disease for better overall outcomes and quality of life.

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**Areas of Controversy and Uncertainty**

1. High-level evidence for the efficacy of locoregional therapy in cholangiocarcinoma is lacking.
2. Where locoregional therapies will be included in a patient's disease management plan is uncertain.
3. To date, the addition of targeted therapy to the treatment algorithm for cholangiocarcinoma has not resulted in increases in overall survival, and novel agents are needed.
4. The use of immunotherapy has demonstrated encouraging response rates in numerous cancers, and final results of prospective clinical trials in patients with a diagnosis of cholangiocarcinoma are awaited.

## Introduction

Cholangiocarcinoma, which may be intrahepatic, hilar or extrahepatic (distal bile duct), according to primary location, is an aggressive malignancy with unmet treatment needs in advanced stages. The incidence and mortality rates for intrahepatic cholangiocarcinoma (ICC), in particular, have risen steeply over recent decades [1]. Radical surgery with lymphadenectomy (tailored for the site of primary) is the only option which provides the possibility of cure, but most patients have advanced disease at presentation, and disease relapse is common, with 5-year survival rates of only 38.8% [2, 3].

With the rise in cholangiocarcinoma incidence, and the anticipation that novel agents will improve overall survival (OS), symptom palliation will become an ever-increasing challenge. Stenting to relieve biliary obstruction provides essential palliation of cholangiocarcinoma involving the main bile ducts and is associated with improved quality of life, particularly for patients with unresectable disease [4]. Patient education and encouragement of self-reporting of symptoms may help with early detection of obstructive and/or infective disease-related complications and lead to improved outcomes such as OS and quality of life, as has been shown in other cancer types [5]. Early palliative care should be considered for all patients with advanced cholangiocarcinoma, so that optimal benefit with systemic treatment, where appropriate, is achieved.

The current standard treatment for patients with locally advanced or metastatic biliary tract cancer is cisplatin plus gemcitabine (CisGem) chemotherapy [6]. The median survival in patients with advanced biliary tract cancers who receive CisGem is 11.7 months with a median progression-free survival (PFS) of 8 months [6]. There is no second-line therapy with established benefit for patients with advanced cholangiocarcinoma [7].

Whilst there is evidence to support the use of standard-of-care treatments, a number of novel treatments remain in early phases of clinical trial development [8, 9]. These trials are required to establish the efficacy of novel treatments and identify associated toxicity, the role of biomarkers and their place in the patient therapeutic pathway. This chapter will highlight novel treatments and some ongoing clinical

trials in locally advanced and metastatic cholangiocarcinoma and identify where they might be used in the disease trajectory. Locoregional approaches are discussed first, followed by systemic therapy options.

## Locoregional Approaches in Cholangiocarcinoma

Locoregional therapies are used for the treatment of ICC, although high-level evidence for their efficacy is lacking [3]. Transcatheter arterial chemoembolisation (TACE) and radioembolisation have been used for some years to treat cancer in the liver (primary or secondary). Technical advances over the last decade have allowed more precise tumour treatment with focused delivery of chemotherapy and radiotherapy, whilst sparing adjacent normal tissues as much as possible.

Novel approaches such as hepatic arterial-based therapies (HAT) now focus on minimising toxicity and improving quality of life. A meta-analysis of 20 studies of the use of HAT in ICC suggested that hepatic arterial infusion offered the best outcomes in terms of tumour response and survival, compared to other locoregional therapies. However, its use is limited by hepatic toxicity, including raised liver enzymes, hepatic abscess formation and hepatic failure [10].

## Chemotherapy-Based Therapies

### *Chemosaturation*

Most recently, chemosaturation allows delivery of potentially lethal doses of melphalan to the liver via an indwelling hepatic artery catheter, followed by external filtering of the drug before blood is returned to the systemic circulation. By this mechanism, the liver can be exposed to doses of chemotherapy that are not feasible by conventional infusion. It is associated with a degree of bone marrow suppression due to the limited systemic escape of melphalan (approx. 3% of the total delivered dose) [11]. It is resource-intensive, requiring an expert team including interventional radiology, perfusionist and anaesthetist, with oncological and surgical backup, if necessary.

Chemosaturation has resulted in improved PFS in liver metastases in patients with cutaneous or ocular melanoma. A phase III trial comparing the use of chemosaturation with best standard of care reported that patients had an improved median hepatic PFS of 7.0 months compared to 1.6 months with standard-of-care treatment, with an overall PFS of 5.4 months compared to 1.6 months. Median OS, however, was not significantly different [12]. It has been investigated in patients with cholangiocarcinoma [13], as well as primary liver tumours [14] and unresectable hepatic metastases [12]. There has been one documented case of a complete response when used in metastatic cholangiocarcinoma [14]. In order to clarify the potential role of this treatment in cholangiocarcinoma, randomised-controlled trials are needed.

### *Drug-Eluting Bead Transcatheter Arterial Chemoembolisation (DEB-TACE) in Unresectable Cholangiocarcinoma*

Drug-eluting bead transcatheter arterial chemoembolisation is a procedure where drug-eluting microspheres can be delivered directly to the tumour via an arterial catheter. This process allows sustained delivery of chemotherapy into the liver, therefore avoiding peak concentrations which may be associated with toxicity, as well as arterial embolisation. In a small study of 11 patients with ICC using doxorubicin drug-eluting beads (loaded with 100–150 mg), there was a 100% response rate according to response evaluation criteria in solid tumours (RECIST), with a median OS of 13 months [15]. In a further study where 26 patients were given irinotecan DEB-TACE and ten patients were given mitomycin-C DEB-TACE, irinotecan produced a better PFS of 3.9 months and OS of 11.7 months versus a PFS of 1.8 months and OS of 5.7 months in the mitomycin-C group. Doxorubicin appears to be the most effective agent in DEB-TACE. A recognised risk of such therapy is "post-embolisation syndrome" which is characterised by a low-grade fever, nausea and abdominal pain [16].

## Ablative Therapies

### *Irreversible Electroporation in Unresectable Cholangiocarcinoma*

Irreversible electroporation (IRE) is a novel image-guided ablation technique that has been used in the treatment of metastatic or primary tumours in the liver, kidney, lung and prostate [17, 18]. It uses a pulsed electric current to create irreversible pores in the cell membrane causing cell death through non-thermal ablation. Patients who have undergone palliative metal stenting are required to have the metal stent changed for a plastic one before the procedure can be performed, as power conduction tissue heating may lead to thermal complications. Currently, a single-arm pilot clinical trial focussing on the effectiveness of IRE for the treatment of metastatic cholangiocarcinoma or liver cancer is evaluating the response of IRE-treated lesions according to modified RECIST evaluation (clinicaltrials.gov identifier, NCT02807181). Case reports on the use of this technique in cholangiocarcinoma exist, but no randomised trial data is available yet.

### *Radiofrequency Ablation in Unresectable or Advanced Cholangiocarcinoma*

Several small studies in recent years have suggested that percutaneous ultrasound-guided thermal ablation for unresectable ICC is safe and potentially effective, particularly for primary and relatively small tumours (see Table 18.1). The evidence demonstrates that smaller tumours, particularly those <5 cm [19] and a small

**Table 18.1** Retrospective studies including patients with intrahepatic cholangiocarcinoma treated with radiofrequency ablation

| Treatment intent | *N* | Median f/u (months) | No. of nodules | Successful ablation | Largest nodule | OS at 6 months | Median OS (months) |
|---|---|---|---|---|---|---|---|
| Curative /palliative (Giorgio et al.) [19] | 10 | 19.5 | 12 | 8 (75%) | 7 cm | 83.3% | – |
| Curative (Xu et al.) [20] | 18 | 8.7 | 25 | 23 (92%) | 4.3 cm | 30% | – |
| Curative /palliative (Fu et al.) [21] | 17 | 29 | 26 | – | 4.4 cm | – | 33 |
| Curative (Kim et al.) [22] | 13 | 19.5 | 17 | 15 (88%) | 8 cm | 15%. | 38.5 |

*N* number of participants; *f/u* follow-up; *OS* overall survival

number of nodules [20], have a better recurrence-free survival but not OS. Identification of prognostic factors might allow better patient selection and outcomes with this technique [19]. This suggests that radiofrequency ablation may be an option for the treatment of small lesions.

## Radiation-Based Therapies

### *Stereotactic Body Radiation Therapy (SBRT) in Locally Advanced Cholangiocarcinoma*

Stereotactic body radiation therapy allows safe delivery of one to five fractions of high-dose radiotherapy compared with small fractions of daily radiotherapy over many weeks. It has been used in the treatment of unresectable, locally advanced ICC, though experience is limited. There are, to date, no randomised trials comparing this technique with conventional radiotherapy in biliary tract cancer.

Toxicity may limit use, but case reports and retrospective case series have shown that SBRT can give good local control [23, 24]. One report of ten patients with hilar cholangiocarcinoma, where 30 Gy in three fractions was delivered with gemcitabine, resulted in 80% local control and 80% 2-year survival [25]. A phase I study of 41 patients receiving individualised SBRT for unresectable hepatocellular carcinoma and ICC, who were not suitable for standard therapies, received 6 fractions of SBRT over a 2-week period. Seventeen of the 41 patients had received no prior therapy, and patients who had received previous radiotherapy to the right upper abdomen were excluded. This study reported a median survival of 15.0 months in the ICC group. No radiotherapy-induced liver disease or treatment-related grade 4/5 toxicity was seen within 3 months of SBRT [26].

The ongoing multicentre UK randomised phase II, ABC-07, clinical trial randomises patients in a 2:1 ratio between CisGem chemotherapy + SBRT and CisGem chemotherapy alone. If feasibility of recruitment is demonstrated (feasibility phase), the study will then continue to full accrual. It will evaluate the efficacy of six cycles

of CisGem chemotherapy followed by SBRT (experimental arm) compared to eight cycles of CisGem chemotherapy (control arm). The primary endpoint is improvement in PFS at 12 months (EudraCT number 2014-003656-31).

### *Selective Internal Radiation Therapy (SIRT) in Unresectable Cholangiocarcinoma*

Selective internal radiation therapy consists of the injection of millions of tiny beads or microspheres into the hepatic artery feeding the tumour or region of the liver containing malignancy. They embed and irradiate surrounding tissue with yttrium-90, via radioembolisation. A meta-analysis of 12 relevant studies demonstrated a partial radiological-based tumour response in 28% of patients, and stable disease in 54%, at three months, in the setting of unresectable disease. The complication profile of radioembolisation is similar to that of other intra-arterial treatment modalities with elevated liver enzymes, radiotherapy-induced hepatitis and ascites [27]. The SIRCCA trial (clinicaltrials.gov identifier, NCT02807181) is a first-line randomised phase II trial for patients with inoperable ICC, investigating standard of treatment CisGem in one arm versus SIRT preceding CisGem in the other arm; this study is currently recruiting.

### *Proton Beam Irradiation in Locally Advanced Cholangiocarcinoma*

Proton beam therapy, a method of delivering high-dose radiotherapy, minimising normal tissue dose because of the unique physical properties of heavy particles, has been used as a successful method of gaining local control in cholangiocarcinoma. A phase II multi-institutional study of 83 evaluable patients has been conducted to determine the efficacy and safety of proton beam therapy in patients with hepatocellular carcinoma and unresectable ICC. Thirty-seven of these patients had ICC, and OS at 2 years was 46.5% for this patient population [28]. As expected, the larger tumour sizes and worse performance status were associated with inferior survival. The most common associated toxicities were gastrointestinal symptoms and cholangitis (seen in 40% of patients).

## Conclusion on Use of Locoregional Therapies in Cholangiocarcinoma

Locoregional therapies can be used in the locally advanced or palliative settings in cholangiocarcinoma, and Fig. 18.1 demonstrates where they can potentially be included in a patient's disease trajectory. These treatments have only been assessed

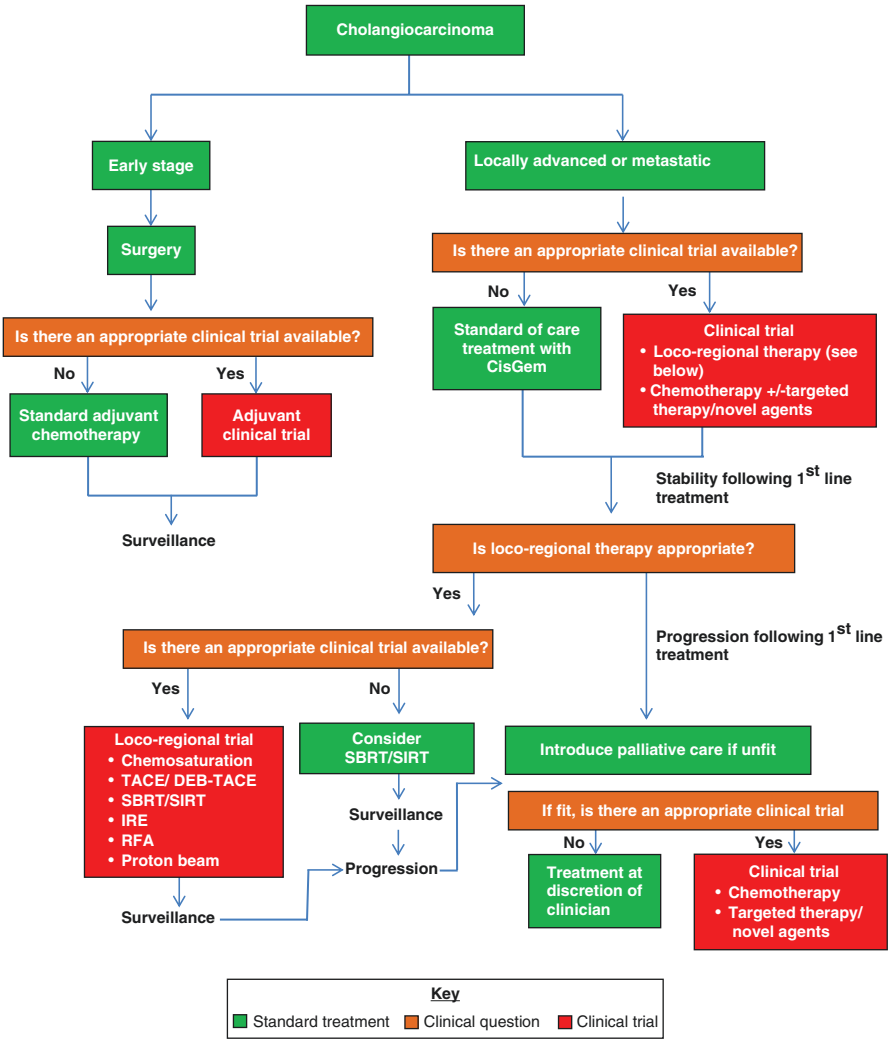


**Fig. 18.1** Algorithm for the potential future management of patients with cholangiocarcinoma (modified from ESMO guidelines, Ann Oncol (2016) 27 (suppl 5): v28-v3, Valle et al.). *TACE* transcatheter arterial chemoembolisation, *DEB-TACE* drug-eluting bead transcatheter arterial chemoembolisation, *SBRT* Stereotactic body radiation therapy, *SIRT* selective internal radiation therapy, *IRE* irreversible electroporation, *RFA* radiofrequency ablation

in small, early phase trials and retrospective series, but have shown some promise in local control and OS. Toxicity to the liver and other abdominal organs is prevalent (occurring in up to 40% of patients). Clinical trials and good patient selection, considering performance status and tumour size, are imperative prior to offering these novel treatments. Results of prospective randomised trials will evaluate the magnitude of benefit compared to currently available options.

## Systemic Therapies in the Treatment of Cholangiocarcinoma

Advances in technology for drug delivery and an improved understanding of advanced cholangiocarcinoma and its microenvironment are aiding researchers in identification of potential future treatment options, including targeted agents and immunotherapies. This section will review the current evidence supporting these potential treatment options. For standard systemic therapy options, please refer to the previous Chap. 16 in this book.

## Some Targeted Therapies Investigated in Biliary Tract Cancers

### *Targeting Epidermal Growth Factor Receptor (EGFR) Mutations in Biliary Tract Cancer*

Common carcinoma-associated gene mutations are found in the epidermal growth factor receptor (*EGFR*), providing a rationale for targeting EGFR-tyrosine kinase *(EGFR-TK*) with novel treatment approaches. The *EGFR-TK* is strictly controlled in normal cells and activated in many tumour cells, and it provides signals that drive dysregulated proliferation, invasion and metastasis, angiogenesis and enhanced cell survival [29]. The use of agents to inhibit this pathway has been investigated as a therapeutic strategy in cholangiocarcinoma [30, 31]. Erlotinib is an oral tyrosine kinase inhibitor which acts on the intracellular kinase domain. Cetuximab and panitumumab are intravenously administered anti-EGFR monoclonal antibodies; they act on the extracellular receptors of the same pathway.

The use of EGFR-TK inhibitors and anti-EGFR antibodies in biliary tract cancers has led to mixed results. Some of the randomised phase II and III studies utilising these agents are summarised in Table 18.2.

Although the data reported in Table 18.2 include all biliary tract cancers, there have been further subgroup analyses of the use of EGFR-TK inhibitors within some of these studies.

An early phase II trial suggested that there could be therapeutic benefit for EGFR blockade with erlotinib as a monotherapy in biliary tract cancer [36]. However, erlotinib compared with standard chemotherapy in a phase III trial [32] showed no OS advantage and no significant difference in PFS. A subgroup analysis of the 180 patients with cholangiocarcinoma reported that those who received erlotinib with gemcitabine and oxaliplatin (GEMOX), versus GEMOX alone, had a significantly better PFS of 5.9 months versus 3 months ($p = 0.049$). Although grade 3 and 4 toxicities were not significantly more frequent in the erlotinib group, toxicity-related dose reductions were more common in the combination therapy arm (64% versus 43%) [32]. In a randomised phase II trial subgroup analysis [34] of the use of panitumumab in cholangiocarcinoma, patients with ICC treated with panitumumab plus

**Table 18.2** Trials using EGFR inhibitors in patients with advanced biliary tract cancers

| Name of study | Drug (dose) | Phase of trial | *N* | Median f/u (months) | EGFR expression | Most common toxicity | PFS (months) | OS (months) | ORR |
|---|---|---|---|---|---|---|---|---|---|
| NCT01149122 | Erlotinib (100 mg) and GEMOX versus GEMOX alone [32] | III | 268 | 15 | Not reported | Febrile neutropenia | 5.8 vs. 4.2 | 9.5 in both groups | 40 (30%) vs. 21 (16%) |
| BINGO | Cetuximab and GEMOX versus GEMOX alone [33] | II | 150 | 31.1 | 23% | Peripheral neuropathy, neutropenia and aminotransferase elevation | 6.1 vs. 5.5 | 11.0 vs. 12.4 | 24% vs. 23% |
| TCOG T1210 | Cetuximab (500 mg/m$^2$) and GEMOX versus GEMOX alone [31] | II | 122 | – | (KRAS)-36.1% | – | 6.7 vs. 4.1 | 10.6 vs. 9.8 | 27% vs. 17% |
| Vecti-BIL | Panitumumab (6 mg/kg) and GEMOX versus GEMOX alone [34] | II | 89 | 10.1 | Not reported | Skin toxicity | 5.3 vs. 4.4 | 9.9 vs. 10.2 | 26.6% vs. 18.1% |
| PICCA | Panitumumab (6 mg/kg) and Cis/Gem versus Cis/Gem alone [35] | II | 93 | – | (p53 34%) | Skin toxicity | 6.7 vs. 8.2 | 12.4 vs. 21.4 | 45% vs. 39% |

Abbreviations: *N* number of participants; *f/u* follow-up; *PFS* progression-free survival; *OS* overall survival; *ORR* objective response rate; *EGFR* epidermal growth factor receptor; *GEMOX* gemcitabine plus oxaliplatin; *Cis/Gem* cisplatin and gemcitabine

chemotherapy had a non-significant survival benefit in comparison with chemotherapy alone (15.1 vs. 11.8 months, $p = 0.13$).

Cetuximab has been associated with improved outcomes in various malignancies including colorectal, lung and head and neck cancer [37]. Cetuximab and panitumumab have shown antitumour activity in *RAS* wild-type colorectal cancer [35, 37]. The *KRAS* or *EGFR* mutation status is not related to outcome in advanced ICC [33, 34].

The use of EGFR-targeted agents in combination with chemotherapy in this disease group has shown no benefit in OS compared to standard chemotherapy, and only one study showed a significant difference in PFS [31]. With no effective targeted therapy for cholangiocarcinoma identified in the face of several negative trials, further investigation of chemotherapy in combination with EGFR-targeted agents is not yet warranted.

## *Targeting Angiogenesis in Biliary Tract Cancer*

Vascular endothelial growth factor (VEGF) is overexpressed in biliary tract cancers and has been proposed as a therapeutic target [38]. It is one of the main growth factors regulating angiogenesis. Receptors for this ligand are also expressed in the adjacent endothelial cells and are named VEGF receptor-1 (VEGFR1) and VEGFR2.

Bevacizumab is a recombinant humanised monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor-A (VEGF-A). It has demonstrated efficacy in a number of other solid tumours, including colorectal cancer, renal cell cancer, non-small cell lung cancer and metastatic breast cancer [39]. In phase I and II trials, bevacizumab in combination with erlotinib demonstrated no pharmacokinetic interaction [40, 41]; but there are no randomised trials to establish whether bevacizumab can improve standard-of-care outcomes in biliary tract cancer. A phase II trial exploring its use in patients diagnosed with advanced cholangiocarcinoma in combination with erlotinib reported a small response rate of just 12%, with a median OS of 9.9 months and median time to disease progression of 4.4 months [39].

Cediranib is an oral tyrosine kinase inhibitor acting on VEGFR1, VEGFR2 and VEGFR3, with additional activity against platelet-derived growth factor (PDGF) receptors and the proto-oncogene c-KIT. A multicentred, placebo-controlled, randomised phase II trial [38] of 124 patients (ABC-03) reported that PFS did not improve with the addition of cediranib to CisGem chemotherapy (median PFS 7.4 months vs. 8.0 months in the standard CisGem and placebo group). The study did not meet its primary endpoint (to detect an improvement in PFS), maybe due to lack of efficacy, but also perhaps due to the fact that patients on cediranib discontinued treatment at a median of 4.6 months, mainly due to toxic effects. The most common grade 3 toxicity was hypertension (37%). The partial response rate of 41% in the cediranib group and improved 6-month PFS of 70.5% in the cediranib group versus 61.3% in the placebo group suggest that cediranib may have had some ben-

eficial effect. However, its toxicity profile, and therefore limited exposure to treatment, prevents longer-term benefit.

The role of VEGF inhibition in addition to chemotherapy for patients with advanced biliary tract cancer remains investigational. Whether a better-tolerated anti-VEGF treatment can improve overall survival in combination with chemotherapy remains to be seen.

## *The Use of Isocitrate Dehydrogenase 1 (IDH-1) Mutation Inhibitors in Cholangiocarcinoma.*

Somatic mutations in *IDH-1* produce the oncometabolite D-2-hydroxyglutarate (2-HG) which promotes oncogenesis. Mutant IDH-1 *(mIDH-1)* was first detected in an integrated genomic analysis of human glioblastoma. Mutations in *IDH-1* occur in up to 25% of ICC [9]. The ongoing ClarIDHy trial is a phase III multicentred, randomised, placebo-controlled trial of AG-120, an inhibitor of the *mIDH-1* enzyme; it plans to enrol 186 patients with an *IDH-1* mutation [9]. In the small phase I trial (500 mg daily versus placebo) in advanced cholangiocarcinoma, AG-120 demonstrated a favourable safety profile and some clinical activity (with 40% PFS rate at 6 months) (clinicaltrials.gov identifier, NCT02073994).

## *The Role of Fibroblast Growth Factor Receptor 2 (FGFR2) Fusion Mutations in Cholangiocarcinoma*

Fibroblast growth factor receptor *(FGFR)* alterations are implicated in the development and progression of ICC. There are four subtypes of *FGFR* identified in multiple cancers, including breast, bladder, lung, gastric, endometrial and multiple myeloma [42]. Using fluorescent in situ hybridisation (FISH) or next-generation sequencing (NGS), mutations are seen in up 20% of ICC [43], with *FGFR2* translocations occurring in approximately 13% of patients [44]. The presence of *FGFR* fusions is therefore a potential therapeutic target and is currently being investigated in clinical trials.

The highly potent and selective irreversible *FGFR* inhibitor, TAS-120, inhibits all four *FGFR* subtypes. It has been shown in vitro to inhibit growth of human cancer cell lines with *FGFR* gene abnormalities selectively, cellular phosphorylation of *FGFR*, intercellular signalling pathways downstream of *FGFR* and tumour growth in human tumour xenograft mouse models [42].

Other *FGFR* inhibitors, such as ARQ 087 and INCB054828 are currently being investigated in clinical trials in this patient group [8, 43]. The pan-*FGFR* inhibitor, ARQ 087, is undergoing a phase I/phase II open-label clinical trial for patients with identified *FGFR2* status positivity in ICC. An interim analysis following

post-treatment radiographic assessment has reported partial response, stable disease and progressive disease in 20%, 57% and 23% of patients, respectively. This indicates encouraging antitumour activity with a manageable safety profile.

A selective *FGFR* inhibitor to *FGFR1, FGFR2* and *FGFR3,* INCB054828 [8] is being investigated in a phase II open-label study recruiting patients with unresectable cholangiocarcinoma.

A phase I study by Nogova et al. has recently reported that oral BGJ398, a selective FGFR1-3 tyrosine kinase inhibitor, demonstrated antitumour activity in several advanced solid tumour types. Common adverse effects at the maximum tolerated dose were hyperphosphataemia (82.5%), constipation (50.9%), decreased appetite (45.6%) and stomatitis (45.6%) [45]. A phase II study has evaluated BGJ398 antitumor activity in patients with advanced or metastatic cholangiocarcinoma containing FGFR2 fusions or other FGFR alterations whose disease had progressed whilst receiving prior therapy, and promising antitumor activity was demonstrated, with an overall response rate of 14.8% (18.8% FGFR2 fusions only), disease control rate of 75.4% (83.3% FGFR2 fusions only) and estimated median PFS of 5.8 months (95% CI, 4.3 to 7.6 months) [46].

### *Mitogen-Activated Protein/Extracellular Signal-Regulated Kinase Kinase (MEK) Inhibitors in Biliary Tract Cancer*

Trametinib is a MEK inhibitor which acts downstream in the mitogen-activated protein kinase (MAPK) pathway. Mitogen-activated protein kinase pathway alterations have been identified in biliary cancers [47]. A randomised phase II trial of 80 patients with cholangiocarcinoma or gallbladder cancer who failed platinum/gemcitabine therapy, and then received oral trametinib versus chemotherapy with oral capecitabine or infusional 5-fluorouracil, reported that survival was not improved in a planned interim analysis of objective response of 14 patients registered to the trametinib arm. Consequently, the study was interrupted early [47]. Further research is required to ascertain if there is a strong enough scientific rationale for pursuing MEK inhibition with or without chemotherapy in this disease group.

## Immunotherapies in Biliary Tract Cancer

Immune checkpoint inhibitors have demonstrated encouraging response rates in numerous cancer groups including melanoma, renal cell cancer, colorectal, bladder and urothelial carcinoma and non-small cell lung cancer [48]. This negative feedback pathway supresses the T-cell immune response and is upregulated in many tumours and their surrounding microenvironment. Expression of programmed death-ligand-1 (PD-L1) and programmed death-ligand-2 (PD-L2) on the surface of tumour cells is important. However, it is not an entirely reliable predictive marker of

response to treatment with immune checkpoint inhibitors [49]. Another factor which may be used as a predictive marker of response is mismatch repair (MMR) deficiency in cholangiocarcinoma, which is strongly associated with therapeutic response to PD-1 blockade in colorectal cancer [50]. The presence of MMR deficiency leads to a high mutational load and microsatellite instability (MSI) (accumulation of numerous insertion/deletion mutations affecting microsatellites). This, in turn, leads to T-cell neoantigen production with a pronounced antitumour immune response resulting in successful immune checkpoint blockade [50]. The MSI phenotype is most frequently found in colorectal and endometrial cancers, but also occurs in a variety of other malignancies [51]. The availability of MSI analysis may open new therapeutic options for biliary tract cancer after (or even prior to) standard treatment.

## *Targeting Programmed Death-1 and Programmed Death-Ligand 1*

Even tumours without PD-L1 expression or dense infiltration with cytotoxic cells can show a good response to immunotherapies. A case series characterising PD-L1 and PD-1 expression and density of tumour-infiltrating lymphocytes (TILs) in 99 cholangiocarcinoma specimens reported that PD-L1 expression by neoplastic cells was observed in only nine patients, but PD-L1 positive inflammatory cell aggregates were identified in 46. Expression of PD-L1 by either neoplastic or inflammatory cells was associated with a high density of CD3-positive TILs. The results highlight that cholangiocarcinomas with dense intra-tumoral lymphocytic infiltration might represent good candidates for PD-L1/PD-1 blocking agents [48].

There is a case report of a patient with extrahepatic cholangiocarcinoma who had a strong and durable response to the immune checkpoint inhibitor pembrolizumab (a highly selective humanised monoclonal antibody against PD-1 and its ligands, PD-L1 and PD-L2) [50]. The patient's tumour displayed deoxyribonucleic acid (DNA) MMR deficiency and MSI, but lacked other features commonly discussed as predictors of response to checkpoint blockade, such as PD-L1 expression or dense infiltration with cytotoxic T cells. Notably, high levels of human leukocyte antigen (HLA) class I and II expression were detected in the tumour, suggesting a potential causal relationship between functionality of the tumour's antigen presentation machinery and the success of immune checkpoint blockade. This suggests that it is worthwhile to determine MSI status in combination with HLA class I and II antigen expression in tumours potentially eligible for immune checkpoint blockade, even in the absence of conventional markers predictive for anti-PD-1/PD-L1 therapy or in entities not commonly linked to MSI phenotype [50]. Defects in HLA class I expression may allow tumour cells to escape immune recognition [52]. A phase II trial to evaluate the clinical activity of pembrolizumab (anti-PD-1 immune checkpoint inhibitor), in patients with progressive metastatic disease, identified MMR deficiency in one case of cholangiocarcinoma; however the response to pembrolizumab was not discussed [53].

No large phase II/III clinical trials have been conducted to ascertain if PD-L1/PD-1 blockade results in improved survival in cholangiocarcinoma. KEYNOTE-028 is a phase Ib multicohort trial designed to assess the safety and antitumour activity of pembrolizumab in patients with PD-L1-positive advanced biliary tract cancer. Preliminary results report that 17% had a partial response, 17% had stable disease, and 52% had progressive disease. The treatment was generally well tolerated, but these data again demonstrate that targeting the PD-L1 ligand does not guarantee response to treatment, even in the presence of PD-L1 expression [54].

## Mesothelin in Cholangiocarcinoma

Mesothelin is a tumour differentiation antigen present at low levels in a restricted set of normal adult tissues and is expressed at high levels in mesothelioma and also in ovarian, pancreatic and lung cancers [55]. Its use as a therapeutic target in cholangiocarcinoma has yet to be fully investigated. An anti-mesothelin recombinant immunotoxin, SS1P, has been found to be active in cholangiocarcinoma in vitro and may be a relevant antigenic target for future immunotherapies [55].

## Conclusion on the Use of Systemic Therapy Options in Cholangiocarcinoma

Understanding of cholangiocarcinoma biology, the oncogenic landscape of this disease and its complex interaction with the tumour microenvironment and immune response could lead to optimum therapies with improvement in patient survival. Studies to characterise the mutational landscape of cholangiocarcinoma further may help to identify appropriate future lines of treatment following standard of care. However, there have been instances where genetic alterations do not stratify risk of disease recurrence or death. More research is required to understand the tumour microenvironment and relevant antigenic targets better. The use of immunotherapy and targeted therapy in cholangiocarcinoma in the UK remains investigational, and therefore these agents remain available only to those patients eligible for clinical trials.

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