PRECISION MEDICINE

Precision Medicine and Immunotherapy Have Arrived for Cholangiocarcinoma: An Overview of Recent Approvals and Ongoing Clinical Trials

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INTRODUCTION

Cholangiocarcinoma (CCA), also known as bile duct cancer, is responsible for more than 7,000 deaths per year in the United States.[1] Estimated mortality because of intrahepatic cholangiocarcinoma (ICC) has significantly increased both globally and in the United States in recent years, while the mortality for extrahepatic cholangiocarcinoma (ECC) has leveled off or decreased.[2] Risk factors for biliary tract cancers (BTCs) include choledochal cysts, cholelithiasis, cirrhosis, and chronic inflammatory conditions of the bile ducts such as primary sclerosing cholangitis or liver fluke infection, but most cases are sporadic or emerge in the setting of weakly associated risk factors such as chronic hepatitis B or C, advanced age, alcohol use, inflammatory bowel disease, or type 2 diabetes.[3]

Traditionally, BTCs have been divided anatomically into intrahepatic, perihilar, and distal bile duct CCAs as well as cancers of the gallbladder. ICC, defined as cancer arising distal to the left and right hepatic ducts, is responsible for approximately two thirds of the annual deaths from CCA in the United States.[1,2]

Although staging and surgical management vary by site, systemic chemotherapies have been developed in clinical trials that include all BTCs. For advanced BTCs, the combination of gemcitabine and cisplatin (GemCis) has been a frontline standard for more than a decade.[4] Recently, the TOPAZ-1 study demonstrated improvements in objective response rate (ORR; 26.7% *v* 18.7%; P = .011), progression-free survival (PFS; median, 7.2 *v* 5.7 months; hazard ratio [HR], 0.75; P = .001), and overall survival (OS, median, 12.8 *v* 11.5 months; HR, 0.80; P = .021) with the addition of the PD-L1 inhibitor durvalumab to GemCis, resulting in US Food and Drug Administration (FDA) approval and establishing a new frontline standard.[5]

National Comprehensive Cancer Network (NCCN) guidelines also include the triplet regimen gemcitabine, cisplatin, and nab-paclitaxel (GAP) as an acceptable option for frontline treatment of advanced BTC on the basis of a median PFS of 11.8 months and an OS of 19.2 months in a single-arm phase II trial.[6] The recently completed phase III SWOG S1815 study comparing GemCis and GAP did not demonstrate an OS advantage for GAP. Subset analyses suggested potential benefit with GAP in patients with locally-advanced tumors or gallbladder cancer.[118]

In the past decade, molecular profiling has shown that ICC is distinct from other BTCs, with rates of targetable driver mutations estimated as high as 40%-50%.[7-12] ICCs arise from the peripheral bile ducts of the liver, and pathologists have further subclassified ICC on the basis of morphologic features into two subtypes—cholangiolar and bile duct—with isocitrate dehydrogenase (IDH) mutations and fibroblast growth factor receptor 2 (*FGFR2*) fusions being more common in the cholangiolar subtype and human epidermal growth factor receptor 2 (*HER2*) amplification/overexpression and *KRAS* mutations being more common in the bile duct subtype.[13,14] The recognition of the potential of personalized medicine for patients with CCA has resulted in many novel treatments directed at molecular subsets (Table 1). In this review, we aim to summarize recent developments in therapeutics for CCA and discuss emerging targets and ongoing clinical trials (Fig 1).

Molecularly Targeted Agents for Cholangiocarcinoma

Large-scale genomic sequencing efforts have elucidated the mutational landscape of CCA and demonstrated distinct molecular profiles on the basis of site of origin.[7,8,10-12,15-17] For example, *FGFR2* fusions and IDH1 mutations nearly exclusively occur in ICC.[10] Some alterations co-occur frequently in ICC, such as *FGFR2* fusions and *BAP1* mutations, while others tend to be mutually exclusive, such as *FGFR2* fusions and *KRAS* mutations.[8] Mutational frequency can vary on the basis of the underlying etiology (eg, liver-fluke–associated *v* non-fluke–associated) and geography, with lower frequencies of *FGFR2* fusions and *IDH1* mutations in Asian populations.[16,18,19]

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CONTEXT

Key Objective

To summarize recent advances in precision medicine and immunotherapy for patients with cholangiocarcinoma.

Knowledge Generated

Targetable alterations are found in up to 40%-50% of patients with intrahepatic cholangiocarcinoma and up to 15%-20% of patients with extrahepatic cholangiocarcinoma. Effective therapies exist for *FGFR2* fusions, *IDH1* mutations, *BRAF* V600E mutations, *NTRK* and *RET* fusions, *HER2* amplification/overexpression, MSI-high tumors, and TMB-high tumors, and data continue to emerge for other potential targets such as *KRAS* G12C mutations, *MDM2* amplifications, and DNA repair deficiencies.

Relevance

The emerging therapies outlined in this review are likely to reshape the treatment landscape for cholangiocarcinoma in the coming years.

The frequency of any given genomic alteration in CCA varies widely among published studies because of differences in sample size, sequencing platform, and proportion of resection versus metastatic samples. More recent analyses of commercial and academic sequencing databases have provided larger sample sizes enriched for advanced disease, which may further refine estimates of mutation prevalence in the relevant treatment population.[8,10,12] A variety of assays exist for the molecular profiling of cholangiocarcinoma, and understanding their coverage and limitations is critical for optimizing selection or clinical use. A recent review by Saab et al[20] summarizes these assays. Increased use of circulating tumor DNA analysis or liquid biopsy, especially in patients with tumor biopsies insufficient for next-generation sequencing, has provided an additional tool to expand molecular profiling and increase understanding of mutational changes during treatment.[21-23]

FGFR2 Fusions and Other Activating Alterations

The fibroblast growth factor (FGF) pathway is composed of four membrane tyrosine kinase receptors (*FGFR1-4*) and 22 FGF ligands involved in cellular growth and development.[24] Wu and colleagues first reported the presence of *FGFR2* fusions in two cases of ICC in 2013, and subsequent studies have shown the transforming potential and oncogenic activity of these alterations in ICC.[25-27] Present in 10%-15% of ICCs, *FGFR2* fusions have emerged as a druggable target in this disease with oral small-molecule FGFR inhibitors demonstrating an ORR of 20.7%-41.7% and a median PFS of 5.7-9.0 months.[28-31] Additional activating *FGFR2* alterations including extracellular domain in-frame deletions (indels) and activating point mutations such as C382R have also demonstrated responsiveness to FGFR inhibition.[32,33]

In April 2020, the reversible FGFR1-3 inhibitor pemigatinib gained accelerated FDA approval for patients with previously treated cholangiocarcinoma harboring an *FGFR2* fusion or rearrangement.[28] Among 107 patients with *FGFR2* fusions or rearrangements, pemigatinib demonstrated an ORR of 35.5%, a median PFS of 6.9 months, and a median OS of 21.1 months. No responses were seen in 20 patients with other FGF/FGFR alterations or in 18 patients without an FGF/FGFR genetic alteration.[34]

Infigratinib, another reversible FGFR1-3 inhibitor, received accelerated FDA approval in May 2021. In 108 patients with an *FGFR2* fusion or rearrangement, the ORR was 23.1%, with a median PFS of 7.3 months and a median OS of 12.2 months.[29]

Futibatinib, an irreversible pan-FGFR inhibitor, received accelerated FDA approval in September 2022. It is the first and only covalently binding FGFR inhibitor to receive an oncology indication. Futibatinib demonstrated an ORR of 41.7%, a median PFS of 9.0 months, and a median OS of 21.7 months in patients with *FGFR2* fusion or rearrangement positive CCA.[30]

The reversible FGFR1-3 inhibitor derazantinib has shown preliminary efficacy in patients with cholangiocarcinoma harboring *FGFR2* fusions (ORR, 20.7%; PFS, 5.7 months) or activating *FGFR2* mutations or *FGFR2* amplification (ORR, 8.7%; PFS, 7.3 months).[31,35] More recently, RLY-4008, a highly selective irreversible inhibitor specific to *FGFR2*, showed early clinical activity in patients with *FGFR2* fusion cholangiocarcinoma, with objective responses in 14 of 17 patients (82.4%) naive to FGFR inhibitors at the recommended phase II dose and activity in patients previously treated with FGFR inhibitors (RLY-4008: ClinicalTrials.gov identifier: NCT04526106).[36-38] Additional FGFR inhibitors are under exploration in ICC, including the multikinase inhibitor TT-00420 (ClinicalTrials.gov identifier: NCT04919642), the bivalent FGFR1-3 inhibitor E7090 (ClinicalTrials.gov identifier: NCT04238715), the FGFR1-3 inhibitor HMPL-453 (ClinicalTrials.gov identifier: NCT04353375), and the irreversible pan-FGFR inhibitors gunagratinib (formerly ICP-192; ClinicalTrials.gov identifier: NCT04565275) and KIN-3248 (ClinicalTrials.gov identifier: NCT05242822).

Given the success of FGFR inhibitors in previously treated patients, an ongoing phase III trial aims to assess the superiority of pemigatinib to frontline GemCis (NCT03656536).

TABLE 1. Efficacy of Targeted Therapies in CCA

Molecular Abnormality	Prevalence	Drug Name	Study Phase	No. of Patients with Molecular Abnormality	ORR	Disease Control Rate	Median PFS (months)	References
FGFR2 fusion	10%-15% (primarily ICC)	Pemigatinib (INCB054828)	II	107	35.5%	82.2%	6.9	[28]
		Infigratinib (BGJ398)	II	108	23.1%	84.3%	7.3	[29]
		Futibatinib (TAS-120)	II	103	41.7%	82.5%	9.0	[30]
		Derazantinib (ARQ087)	I/II	103	21.4%	74.8%	8.0	[35]
IDH1 R132 mutation	13%-20% (primarily ICC)	Ivosidenib	III	124	2.4%	53.2%	2.7	[51]
BRAF V600E mutation	1%-3%	Dabrafenib plus trametinib	II	43	46.5%	85.4%	9.0	[54]
		Vemurafenib	II	9	33.3%	NA	NA	[55]
HER2 overexpression or amplification	ICC 5% ECC 8%-12% GBC 14%-16%	Trastuzumab plus pertuzumab	II	39	23.1%	51.3%	4.0	[57]
		Trastuzumab deruxtecan	II	24	36.4%	81.8%	4.4	[58]
		Zanidatamab	I	17	47%	65%	NA	[61]
HER2 mutation	2%-3%	Neratinib	II	20	10%	30%	1.8	[59]
KRAS G12C mutation	1%	Adagrasib	II	8	50%	100%	NA	[76]
Tumor agnostic indications								
NTRK fusion	0.2%	Larotrectinib Entrectinib						
RET fusion	<1%	Pralsetinib Selpercatinib						
MSI-high	2%	Pembrolizumab						
TMB-high	3%-4%	Pembrolizumab						

Abbreviations: CCA, cholangiocarcinoma; ECC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; ICC, intrahepatic cholangiocarcinoma; MSI, microsatellite instability; ORR, objective response rate; PFS, progression-free survival; TMB, tumor mutational burden.

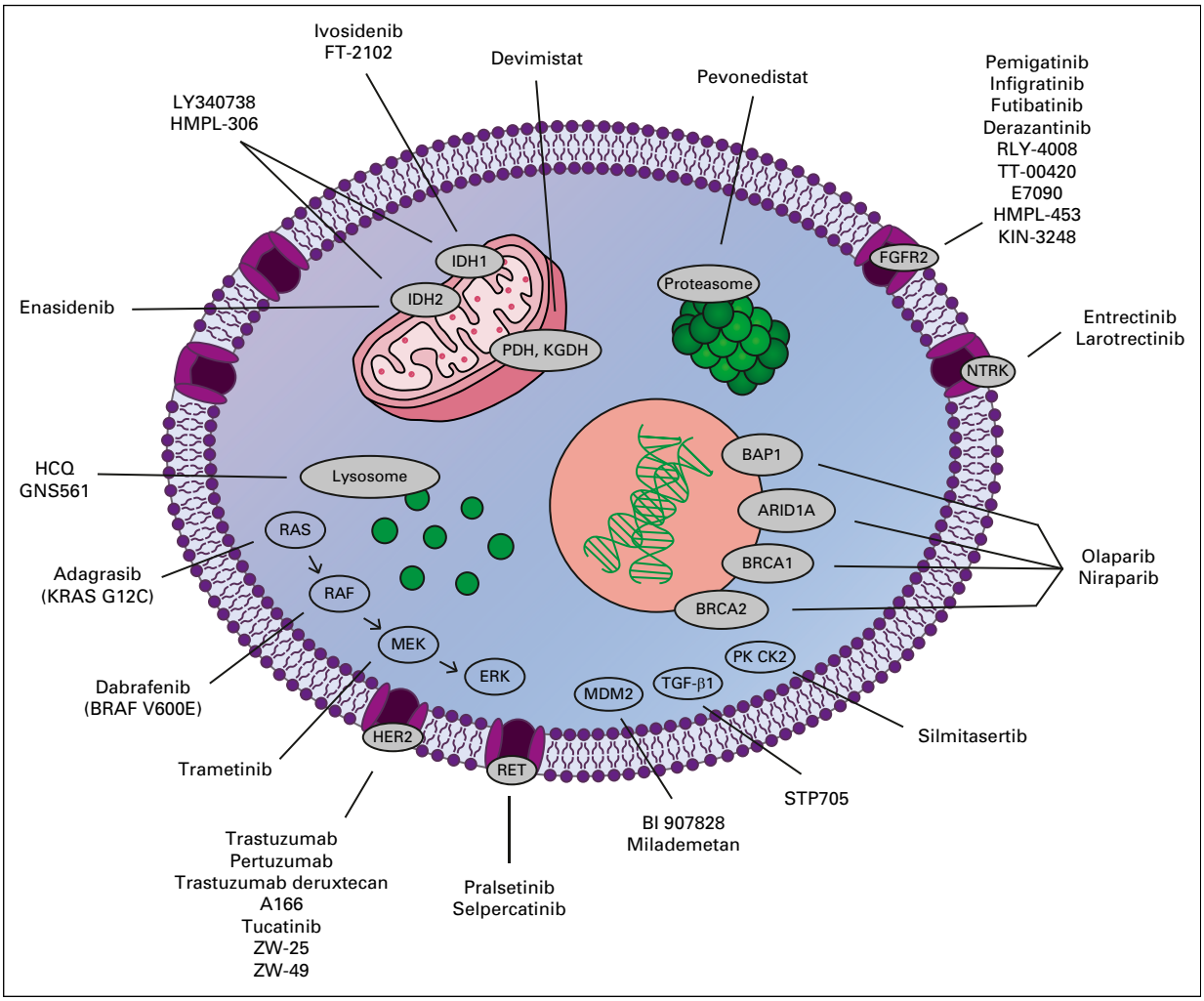

FIG 1. New and emerging targets in cholangiocarcinoma. ARID1A, AT-rich interaction domain 1A; BAP1, BRCA1-associated protein 1; BRAF, v-raf murine sarcoma viral oncogene homolog B1; BRCA, breast cancer gene; ERK, extracellular signal-regulated kinase; FGFR2, fibroblast growth factor receptor 2; HCQ, hydroxychloroquine; HER2, human epidermal growth factor receptor 2; IDH, isocitrate dehydrogenase; KGDH, alpha ketoglutarate dehydrogenase; KRAS, Kirsten rat sarcoma virus; MDM2, mouse double minute 2; MEK, mitogen-activated protein kinase; NTRK, neurotrophic tropomyosin receptor kinase; PDH, pyruvate dehydrogenase; PK CK2, protein kinase CK2; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma virus; RET, rearranged during transfection; TGF-β1, transforming growth factor beta 1.

The similarly designed phase III trials for infigratinib (NCT03773302) and futibatinib (NCT04093362) had modest accrual and are no longer actively recruiting. Combination studies with FGFR inhibitors are also ongoing in cholangiocarcinoma (GemCis plus pemigatinib or ivodesidenib: ClinicalTrials.gov identifier: NCT04088188, futibatinib plus binimetinib: ClinicalTrials.gov identifier: NCT04965818, derazantinib plus atezolizumab: ClinicalTrials.gov identifier: NCT05174650).

Data continue to emerge about resistance mechanisms to FGFR inhibitors in cholangiocarcinoma, with polyclonal secondary mutations in the *FGFR2* kinase domain being a common form of acquired resistance.[33,39-43] Many of these resistance mutations are either gatekeeper mutations (eg, V565F/L/I) that prevent binding of FGFR inhibitors through steric hindrance, or molecular brake mutations (eg, N550K/H/D/T) that lead to ligand-independent kinase activation.[44,45] Futibatinib has shown potent preclinical and clinical activity against multiple of these mutations that arise at progression on reversible, ATP-competitive FGFR inhibitors.[43,46,47]

IDH Mutations

Isocitrate dehydrogenase 1 (*IDH1*) catalyzes the oxidative decarboxylation of isocitrate to α-ketoglutarate in the cytoplasm.[48] Several *IDH1* R132 mutations result in neomorphic activity of the enzyme and consequent abnormal production of 2-hydroxyglutarate (2-HG), an oncometabolite that inhibits histone and DNA demethylases and results in widespread epigenetic alterations and oncogenesis.[49,50] The reported frequency of *IDH1* mutations in ICC versus ECC was 13.1% and 0.8%, respectively, in a systematic review.[18]

Ivosidenib, a specific inhibitor of mutated *IDH1*, gained FDA approval in August 2021 for patients with previously treated *IDH1*-mutated cholangiocarcinoma on the basis of an improvement in PFS versus placebo (HR, 0.37; median, 2.7 *v* 1.4 months; $P < .0001$) in the phase III ClarIDHy trial.[51] Most patients with clinical benefit had stable disease as the ORR was 2%.

The IDH1 inhibitor BAY1436032 was evaluated in 12 patients with CCA, with stable disease in 42% of patients but no objective responses.[52] No further clinical development of BAY1436032 in CCA is planned. Additional agents targeting IDH-mutated cholangiocarcinoma are under development in early-phase trials (FT 2102: ClinicalTrials.gov identifier: NCT03684811, LY3410738: ClinicalTrials.gov identifier: NCT04521686, HMPL-306: ClinicalTrials.gov identifier: NCT04762602)

Isocitrate dehydrogenase 2 (*IDH2*) is a mitochondrial protein which also promotes tumorigenesis via 2-HG through activating mutations in codons 140 and 172. Mutations in *IDH2* occur less frequently in ICC (2%-5%) than mutations in *IDH1*, and the only reported study targeting IDH2 in patients with cholangiocarcinoma enrolled four patients and observed no objective responses with enasidenib.[53]

BRAF V600E

Activating V600E mutations in the oncogene *BRAF* are found in approximately 1%-3% of BTCs. In the phase II ROAR basket trial, 33 patients with previously treated *BRAF* V600E mutant BTC were treated with the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib.[54] Objective responses were seen in 20 of 43 evaluable patients (47%), with a median OS of 14.0 months. The FDA approved dabrafenib and trametinib for all noncolorectal solid tumors harboring a *BRAF* V600E mutation in June 2022. Data are limited with other BRAF inhibitors for BTCs, although vemurafenib monotherapy did demonstrate objective responses in three of nine patients with advanced BTCs.[55]

HER2

HER2 is a receptor tyrosine kinase overexpressed infrequently in ICC (4.8% per a meta-analysis) and more frequently in ECC (17.4%) and gallbladder cancer (19.1%).[56] In the MyPathway basket trial, 39 patients with previously treated BTC with *HER2* amplification and/or overexpression were treated with a combination of two anti-HER2 antibodies, trastuzumab and pertuzumab. Partial responses were seen in nine of 39 (23%) patients, and stable disease for at least 4 months was seen in 11 additional patients (28%).[57] Median PFS was 4.0 months and median OS was 10.9 months. On the basis of this study, the regimen has been included within NCCN guidelines for advanced previously treated *HER2*-positive BTC.

The antibody-drug conjugate (ADC) trastuzumab deruxtecan demonstrated an ORR of 36.4% in patients with previously treated advanced *HER2*-positive BTC, with a median PFS of 4.4 months and a median OS of 7.1 months. One response was also seen among eight patients with *HER2*-low expression.[58] An ongoing international basket study in *HER2*-expressing solid tumors will provide additional data about the efficacy of trastuzumab deruxtecan in BTC (ClinicalTrials.gov identifier: NCT04482309).

For patients with *HER2*-mutated BTC, the pan-HER irreversible tyrosine kinase inhibitor neratinib showed responses in two patients (10%) and stable disease of at least 16 weeks in an additional four patients (20%) in a subgroup of the SUMMIT trial.[59] Trastuzumab in combination with chemotherapy has also demonstrated anecdotal benefit in case series in advanced *HER2* overexpressing and/or amplified BTC.[60]

A variety of novel HER2-targeting agents are under development in BTCs. Zanidatamab, formerly ZW-25, a bispecific antibody targeting the same epitopes as trastuzumab and pertuzumab, demonstrated an interim ORR of 47% in 17 evaluable patients with advanced pretreated BTCs.[61] Further monotherapy expansion in BTC is ongoing for zanidatamab (ClinicalTrials.gov identifier: NCT04466891), as are explorations in combinations with chemotherapy (ClinicalTrials.gov identifier: NCT03929666). The HER2 tyrosine kinase inhibitor tucatinib is being tested in combination with trastuzumab in HER2-positive BTC (ClinicalTrials.gov identifier: NCT04579380). Novel ADCs are also under development in *HER2*-overexpressing solid tumors including CCA (A166: ClinicalTrials.gov identifier: NCT03602079, ZW-49: ClinicalTrials.gov identifier: NCT03821233).

Additional Molecular Targets

Homologous DNA repair deficiencies. Approximately 3%-4% of BTCs harbor mutations in *BRCA1* (0.6%) or *BRCA2* (3%).[62] These mutations result in homologous repair deficiency, which limits cellular repair of double-stranded DNA breaks and connotes sensitivity to platinum chemotherapy and PARP inhibitors.[63] Case reports have shown efficacy of PARP inhibitors in BRCA-mutant cholangiocarcinoma.[64] An additional 10%-15% of ICCs have mutations in BRCA1 associated protein-1 (*BAP1*) and 15%-20% have mutations in *ARID1A*, both of which lead to alterations in homologous DNA repair and sensitivity to PARP inhibition in preclinical studies.[65-67] A trial of niraparib for *BAP1*-mutated solid tumors including CCA was terminated early for lack of efficacy.[68] Olaparib remains under evaluation in cholangiocarcinoma with DNA repair deficiencies (ClinicalTrials.gov identifier: NCT04042831).

***NTRK* and *RET* Fusions.** Oncogenic fusions involving the three tropomyosin receptor kinases TrkA, TrkB, and TrkC (encoded by genes *NTRK1*, *NTRK2*, and *NTRK3*, respectively) occur in approximately 0.2% of BTCs, and are effectively targeted by the NTRK inhibitors larotrectinib and entrectinib.[69] Both agents received FDA approval agnostic of histology on the basis of efficacy across tumor types.[70,71]

RET fusions are also very rare in cholangiocarcinoma but appear sensitive to the RET inhibitors pralsetinib and selpercatinib.[72,73] Pralsetinib is now recommended within NCCN guidelines for patients with previously treated BTC with a *RET* fusion, and selpercatinib is FDA approved for all solid tumors with a *RET* fusion.

***KRAS* G12C.** Activating KRAS mutations are present in approximately 12% of ICCs and 35%-40% of ECCs, but only 1% of cholangiocarcinomas harbor *KRAS* G12C mutations.[10,23,74,75] In the initial phase I/II study of the KRAS G12C inhibitor adagrasib, a 100% disease control rate was observed in eight patients with BTCs, with four partial responses (50%).[76] Further monotherapy expansion and exploration of combination approaches are ongoing with both adagrasib and sotorasib, and additional KRAS G12C inhibitors have entered clinical development (GDC-6036: ClinicalTrials.gov identifier: NCT04449874, JAB-21822: ClinicalTrials.gov identifier: NCT05002270).

One additional approach under development in *KRAS*-mutant BTCs is the combination of the MEK inhibitor trametinib with the autophagy inhibitor hydroxychloroquine (ClinicalTrials.gov identifier: NCT04566133). This approach has shown preclinical and clinical activity in pancreatic adenocarcinoma and is being tested across a variety of tumor types.[77]

***MDM2* Amplification.** Mouse double minute 2 (*MDM2*) amplification is a common driver of certain sarcomas, but has also been reported in up to 6% of ICCs, all bile duct subtype.[78] *MDM2* acts a negative regulator of *TP53*, and novel MDM2 inhibitors such as BI 907828 and milademetan have begun to demonstrate efficacy in *TP53*-wildtype, *MDM2*-amplified solid tumors[79] (BI 907828: ClinicalTrials.gov identifier: NCT03449381; milademetan: ClinicalTrials.gov identifier: NCT05012397).

Immunotherapy for Cholangiocarcinoma

Like pancreatic cancer, CCA is characterized by cancer-associated fibroblasts that produce a desmoplastic stroma as well as a pauci-immune tumor microenvironment rich in immunosuppressive tumor-associated macrophages and myeloid-derived suppressor cells.[80] The immune composition of the surrounding liver also plays an important role, with an immunotolerant environment rich in macrophages (Kupffer cells) and natural killer cells with an active innate immune system that is continually exposed to intestinal microbial products.[81] Tumor agnostic indications for immunotherapy are uncommon in CCA, with approximately 2% being MSI-high and 3.5% having a high tumor mutational burden.[10,82]

Trials of immune checkpoint inhibitors in refractory BTC have shown mixed results to date with response rates ranging from 5%-20% with single-agent PD-1 inhibitors (Table 2). Both nivolumab alone (ORR, 3.3-20%) and lenvatinib combined with pembrolizumab (ORR, 10%) are included within NCCN guidelines for refractory advanced BTCs on the basis of phase II studies.[88,89] Pembrolizumab monotherapy, however, is not included, with an ORR of only 6.8% (eight of 118 patients).[87] Small studies using dual checkpoint blockade have shown promising response rates in pretreated patients, with an ORR of 24% with nivolumab and ipilimumab and 11% with durvalumab and tremelimumab, although ipilimumab + nivolumab was inferior to GemCis + nivolumab for frontline treatment of advanced BTC.[84,86,90]

The global phase III TOPAZ-1 study demonstrated improvements in OS, PFS, and ORR with the addition of durvalumab to frontline GemCis, resulting in FDA approval of durvalumab in combination with chemotherapy for initial treatment of advanced BTC.[83] Chemotherapy was stopped at 6 months in both arms, and a greater improvement in OS with durvalumab was seen after that point (HR, 0.91 up to 6 months; HR, 0.74 after 6 months). Subgroup analyses suggested greater benefit in patients in Asia versus the rest of the world (HR, 0.72 *v* 0.89) and no difference in outcome on the basis of PD-L1 expression. Recently, positive OS results were announced for the global phase III KEYNOTE-966 study, which compared GemCis plus pembrolizumab to GemCis plus placebo in advanced BTC and permitted the use of maintenance gemcitabine chemotherapy.[119]

Other novel immunotherapy agents have also been evaluated in advanced BTC. The bifunctional TGF-β trap and anti–PD-L1 fusion protein bintrafusp alfa demonstrated an ORR of 10.1% in 159 patients in the second-line setting.[91-93] A phase III frontline trial combining bintrafusp alfa with GemCis was terminated early because of lack of efficacy.[94] A phase I study combining bintrafusp alfa with hypofractioned radiation in refractory BTC remains ongoing (ClinicalTrials.gov identifier: NCT04708067).

In patients with previously treated advanced BTC, a phase II trial evaluating the combination of the MEK inhibitor cobimetinib with atezolizumab met its primary end point, with a significantly increased PFS (3.6 *v* 1.9 months; $P = .027$) with the doublet compared with atezolizumab monotherapy. The ORR was low (3%) in both arms.[85] Further preclinical modeling demonstrated that MEK inhibition impaired T-cell activation that was rescued by the addition of either a 4-1BB or a CD27 agonist, and a next-generation trial combining atezolizumab plus the CD27 agonist varlilumab with or without cobimetinib is ongoing[95] (ClinicalTrials.gov identifier: NCT04941287).

Novel targets in ongoing trials for BTCs in combination with immune checkpoint inhibitors include Dickkopf-related protein 1 (DKK1; DKN-01: ClinicalTrials.gov identifier: NCT04057365), CSF-1R (SNDX-6532: ClinicalTrials.gov identifier: NCT04301778), galectin 9 (LYT-200: ClinicalTrials.gov identifier: NCT04666688), and DNA-dependent protein kinase (nedisertib: ClinicalTrials.gov identifier: NCT04068194). In some studies, locoregional therapy

TABLE 2. Efficacy of Immune Checkpoint Inhibitors in Biliary Tract Cancers

Treatment	Study Phase	No. of Patients	% PD-L1–Positive ≥1%	ORR	Disease Control Rate	Median PFS (months)	References
GemCis + durvalumab (arm A) GemCis (arm B)	III	Arm A: 341 Arm B: 344	Arm A: 57.8% Arm B: 59.6%	Arm A: 26.7% Arm B: 18.7%	Arm A: 85.3% Arm B: 82.6%	Arm A: 7.2 Arm B: 5.7	[83]
GemCis + nivolumab (arm A) Ipilimumab + nivolumab (arm B)	II	Arm A: 35 Arm B: 36	NA	NA	NA	Arm A: 7.4 Arm B: 4.1	[84]
Atezolizumab (arm A) *v* atezolizumab + cobimetinib (arm B)	II	Arm A: 37 Arm B: 38	NA	Arm A: 2.9% Arm B: 3.2%	Arm A: 33.4% Arm B: 45.2%	Arm A: 1.9 Arm B: 3.7	[85]
Durvalumab (arm A) Durvalumab + tremelimumab (arm B)	II	Arm A: 42 Arm B: 65	Arm A: 59.4% Arm B: 34.0%	Arm A: 4.8% Arm B: 10.8%	Arm A: 16.7% Arm B: 32.2%	Arm A: 1.5 Arm B: 1.6	[86]
GemCis + durvalumab ± tremelimumab	II	112	NA	50.0%-73.4%	96.7%-100%	11.0-13.0	[110]
Pembrolizumab	II	127	63.3%	7.1%	22.8%	2.0	[87]
Pembrolizumab	II	26	100%	23.1%	50.0%	NA	[111]
Pembrolizumab	II	40	100%	10.0%	47.5%	1.5	[112]
Olaparib + pembrolizumab	II	12	NA	8.3%	41.7%	NA	[113]
Lenvatinib + pembrolizumab	II	31	NA	10.0%	68.0%	6.1	[88]
Nivolumab	II	46	43%	10.9%	50.0%	3.7	[89]
Nivolumab	II	30	36.6%	20.0%	60.0%	3.1	[114]
Nivolumab + ipilimumab	II	39	NA	23.1%	43.6%	2.9	[90]
Nivolumab (arm A) Nivolumab + cisplatin (arm B)	I	30 per arm	NA	3.3% 36.7%	NA	Arm A: 1.4 Arm B: 4.2	[115]
5-FU/Nal-IRI + nivolumab	I/II	30	NA	10.0%	53.3%	5.4	[116]
Durvalumab + tremelimumab	I	12	NA	0%	41.7%	3.1	[117]

Abbreviations: PFS, progression-free survival; ORR, objective response rate.

TABLE 3. Novel Targeted Agents for Biliary Tract Cancers

Agent	Mechanism/Target	Phase	NCT
MVT-5873	CA 19-9 antibody	II	NCT03801915
TC-210	Mesothelin TCR	I/II	NCT03907852
BNT141	Claudin 18.2 ADC	I/II	NCT04683939
AZD8205	B4-H7 ADC	I/II	NCT05123482
SGN-B7H4V	B4-H7 ADC	I	NCT05194072
Pevonedistat	Neddylation	II	NCT04175912
Silmitasertib	Protein kinase CK2	I/II	NCT02128282
GNS561	Lysosome inhibitor	I/II	NCT03316222
BI 905711	TRAILR2 agonist	I	NCT04137289
Devimistat	Mitochondrial metabolism	II	NCT04203160
STP705	TGF-β1/COX2 inhibitor	I	NCT04676633

Abbreviations: ADC, antibody-drug conjugate; CA, 19-9, cancer antigen 19-9; CK2, casein kinase II; TCR, T-cell receptor; TRAILR2, tumor necrosis factor alpha–related apoptosis-inducing ligand receptor 2.

such as transarterial embolization or external beam radiation is combined with checkpoint inhibition to promote antigen release and immune activation. The novel intratumoral injection INT230-6, consisting of an amphiphilic combination of cisplatin and vinblastine, similarly aims to increase tumor immunogenicity in combination with checkpoint inhibitors (ClinicalTrials.gov identifier: NCT03058289).

Additional Therapeutic Approaches

A variety of additional therapies have demonstrated preclinical and/or early clinical evidence of activity in cholangiocarcinoma. These agents target specific proteins or pathways involved in cholangiocarcinogenesis and are undergoing further clinical testing (Table 3).

Antibodies and antibody-drug conjugates for CCA. CCA expresses a variety of cell-surface proteins with limited expression in nontumor tissue, and a variety of new antibodies, ADCs, and cellular immunotherapies have been developed to engage these targets.[96] Improvements in molecular biology have led to improved drug delivery and decreased systemic exposure with ADCs, allowing for combination with more potent cytotoxics.

Cancer antigen 19-9 (CA 19-9) is a sialylated Lewis antigen expressed on the surface of tumor cells as well as in the blood of approximately 80% of patients with advanced cholangiocarcinoma.[97] MVT-5873, an IgG1 antibody targeting an epitope on CA 19-9, has demonstrated safety in combination with gemcitabine and nab-paclitaxel in patients with advanced pancreatic cancer, and is undergoing evaluation as a perioperative therapy in patients with resectable cholangiocarcinoma[98] (ClinicalTrials.gov identifier: NCT03801915).

Mesothelin is a cell-surface protein expressed in mesothelial cells lining the peritoneum, pericardium, and pleural surface that is overexpressed in a variety of cancer types including pancreatic adenocarcinoma, mesothelioma, ovarian cancer, lung cancer, and cholangiocarcinoma.[99] A variety of therapies targeting mesothelin overexpression are in development, including antibody-drug conjugates and cellular immunotherapies.[100]

Additional cell-surface targets found in CCA under investigation include claudin 18.2 (BNT141: ClinicalTrials.gov identifier: NCT04683939) and B7-H4 (AZD8205: ClinicalTrials.gov identifier: NCT05123482, SGN-B7H4V: ClinicalTrials.gov identifier: NCT05194072).

Novel molecular therapies. Pevonedistat is an inhibitor of neddylation, a pathway of intracellular protein catabolism related to ubiquitination that is overactive in CCA.[101] In a phase Ib trial combining pevonedistat with multiple chemotherapy regimens, both patients with previously treated cholangiocarcinoma had partial responses.[102] Further evaluation of pevonedistat as monotherapy or in combination with carboplatin and paclitaxel in previously treated advanced ICC is ongoing (ClinicalTrials.gov identifier: NCT04175912).

Silmitasertib (CX-4945) is a small molecule inhibitor of protein kinase casein kinase II, which has been shown preclinically to inhibit growth of cholangiocarcinoma cell lines and induce lethal vacuolization.[103] A phase Ib/II study in 87 patients with advanced CCA combining silmitasertib with GemCis showed a median PFS of 11.1 months, a median OS of 17.4 months, and an ORR of 32.1%, and a phase III trial is planned.[104]

GNS561 is a small lipophilic molecule that accumulates within lysosomes and causes dysregulation and apoptotic cell death. On the basis of preclinical efficacy in hepatocellular carcinoma and ICC models, a phase I/II trial was launched (ClinicalTrials.gov identifier: NCT03316222). In the initial 19 patients from the 3 + 3 dose escalation updated at ASCO in 2021, no dose-limiting toxicities were observed and two of nine patients with ICC experienced stable disease.[105]

BI 905711 is a novel tetravalent bispecific antibody targeting TRAILR2 and CDH17.[106] TRAIL is a member of the TNFα superfamily, and activation of the TRAIL receptor results in apoptotic cell death, but prior antibodies have been limited by hepatic toxicity.[107] The cell-surface marker CDH17 is expressed in a variety of gastrointestinal cancers but not in normal liver, allowing for specific targeting of tumor cells without engaging hepatocytes. A phase I trial is ongoing, with a planned expansion in cholangiocarcinoma (ClinicalTrials.gov identifier: NCT04137289).

Devimistat (formerly CPI-613) is a lipoate analog that inhibits pyruvate dehydrogenase and a-ketoglutarate dehydrogenase and alters mitochondrial metabolism. In the phase I portion of a phase I/II study of devimistat combined with GemCis in patients with untreated advanced BTC, the regimen demonstrated an ORR of 45% with a median PFS of 14.9 months without excess toxicity. The randomized phase II portion of the

trial testing GemCis with or without devimistat is ongoing[108] (ClinicalTrials.gov identifier: NCT04203160).

STP705 is an injectable combination of small interfering ribonucleic acid targeting TGF-β1 and cyclooxygenase-2 (COX-2) with histidine-lysine polypeptide (siRNA/HKP) in a nanoparticle formulation that has demonstrated efficacy with repeated intratumoral injections in cutaneous squamous cell carcinoma.[109] A phase I study is evaluating serial liver tumor injections in cholangiocarcinoma and other liver tumors (ClinicalTrials.gov identifier: NCT04676633).

DISCUSSION

With the FDA approvals of pemigatinib, infigratinib, futibatinib, and ivosidenib, CCA has entered the era of molecular therapy, and it is likely that additional targeted agents will be approved in the next several years. Data strongly support targeting *FGFR2* fusions, *IDH1* mutations, *HER2* overexpression/amplification, and tissue agnostic targets such as *BRAF* V600E mutations and *NTRK* and *RET* fusions. Among the most promising targeted therapies in development are irreversible FGFR2 inhibitors, which have been shown to overcome resistance to reversible FGFR2 inhibitors, HER2 ADCs such as trastuzumab deruxtecan, and KRAS G12C inhibitors.

Given that 40%-50% of ICCs and 15%-20% of ECCs will have actionable mutations, molecular testing should be conducted in all patients with advanced CCA early in the course of their treatment. CCA is often paucicellular and challenging to biopsy, and liquid biopsy can serve as a complementary approach for molecular profiling.[120] Improved access to rapid biomarker profiling may also facilitate clinical trials in earlier-stage disease to test molecular therapies in the neoadjuvant and adjuvant settings. Serial sequencing of circulating tumor DNA will also elucidate tumor evolution and resistance mechanisms to targeted therapies and advance development of rational combinations and next-generation inhibitors.

The TOPAZ-1 study has led to a new frontline standard of GemCis with durvalumab for patients with advanced disease. Data from the similarly designed KEYNOTE-966 study are expected soon and will further clarify the benefit of frontline immunotherapy. No predictive biomarker for immunotherapy in cholangiocarcinoma has been identified to date, and further research in this area is sorely needed to better identify the subset of patients who experience significant benefit. Immunotherapeutic combinations may enhance the efficacy of PD-1 and PD-L1 inhibitors, but widespread use of durvalumab in the frontline setting will affect enrollment rates of immunotherapy-naive patients in refractory settings and will likely necessitate changes in trial design.

As additional therapies become available for CCA, questions about optimal selection and sequencing in those with targetable mutations will likely arise. No strong data yet exist to guide the choice between initial chemotherapy and highly effective therapies such as NTRK inhibitors for *NTRK* fusions or PD-1 inhibitors for MSI-high tumors. Randomized studies to assess the performance of frontline FGFR inhibitors against GemCis are commendable, but the results may be difficult to interpret with the evolving frontline standard for advanced BTC. With this growing treatment armamentarium, investment in biomarker development to optimize patient selection will enable even bigger strides in precision oncology in cholangiocarcinoma.

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