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Review

Second-line Treatment in Advanced Biliary Tract Cancer: Today and Tomorrow

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Abstract. *Biliary tract cancer (BTC) patients usually have poor prognosis. Whereas combination chemotherapy has been shown to improve survival in the frontline setting, second-line treatment is subject to a lot of debate in the scientific community. Recent data of the ABC-06 trial has provided slight evidence for the use of second-line chemotherapy after progression on cisplatin plus gemcitabine combination. In this study, mFOLFOX plus active symptom control (ASC) improved overall survival (OS) after progression on cisplatin-gemcitabine combination compared with ASC alone, with an increase in 6- and 12-month OS rate. Although genomic studies have paved the way for a new age in cancer management, the "Precision Medicine Era" in BTC is still limited to intrahepatic cholangiocarcinoma and primarily focused on isocitrate dehydrogenase (IDH) and fibroblast growth factor receptor (FGFR) targeted therapies. We herein review recent published data regarding the use of second-line treatment after failure of standard first-line therapies in BTC patients, with a particular focus on ongoing active and recruiting clinical trials.*

Biliary tract cancer (BTC) accounts for 3% of all gastrointestinal malignancies and represents the second most common primary liver cancer, following hepatocellular carcinoma (HCC) (1, 2). BTC comprises a spectrum of malignancies usually classified into intrahepatic cholangiocarcinoma (iCCA), extrahepatic cholangiocarcinoma (eCCA), gallbladder cancer (GBC) and ampulla of Vater cancer (AVC) (3, 4). The term cholangiocarcinoma (CCA) historically embraces iCCA and eCCA, therefore excluding AVC and GBC (5). The incidence of BTC has increased over the past two decades, mainly due to the increase in iCCA in both western and eastern countries and as a result of better disease recognition (6, 7). Despite recent improvements in the field of medical oncology, the prognosis of BTC patients remains dismal since the majority of cases are diagnosed with inoperable disease and, even after radical surgery, the 5-year overall survival (OS) rate is approximately 15% (8, 9).

In the advanced disease setting, first-line systemic chemotherapy is considered the backbone of treatment, following the results of the ABC-02 trial where the cisplatin plus gemcitabine (CisGem) combination was shown to improve OS over gemcitabine alone in 410 patients with locally advanced or metastatic BTC [11.7 *versus* 8.1 months; hazard ratio (HR) 0.64; 95%CI=0.52-0.80; $p<0.001$] (10); moreover, this randomized phase III trial reported improved progression-free survival (PFS) for the combination treatment over single-agent gemcitabine (8.0 months *versus* 5.0 months, $p<0.001$). Although the landmark study by Valle *et al*. certainly represented a historical step forward in the palliative treatment of BTC, the survival advantage of front-line therapy is modest, with nearly all patients developing progressive disease following first-line chemotherapy (11, 12). Nevertheless, some patients still maintain a good general condition after failing first-line therapies, with around 30-35% continuing on second-line treatment, according to previous studies (13, 14). Thus, this subgroup of patients has another chance to control the malignancy, aiming at maintaining an acceptable quality of life and even improving survival.

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The advent of genomic sequencing has led to a better comprehension of the complex molecular mechanisms underlying the pathogenesis of BTC (Figure 1) (15). In fact, several driver genetic alterations have been identified, including fibroblast growth factor receptor (*FGFR*) fusions, isocitrate dehydrogenase (*IDH*) mutations and many others, and targeted therapies are emerging as new promising treatment modalities for BTC (16, 17). Interestingly enough, recent molecular profiling studies have detected that at least 40% of BTC patients present potentially targetable alterations, with relevant differences between different anatomical subgroups (18).

The era of modern cancer care has also been characterized by the introduction of immunotherapy, which has revolutionized the treatment landscape of several hematological and solid tumors (19-21). Although immune checkpoint inhibitors (ICIs) have become the standard treatment of malignancies such as advanced melanoma and non-small cell lung cancer (NSCLC) (22, 23), immunotherapy for BTC is still in the early phases and, as we shall see later, several ongoing trials are investigating the role of ICI monotherapy or combination chemo-immunotherapy in untreated and previously treated patients.

The current review provides an update on the available evidence regarding second-line treatment in locally advanced or metastatic BTC, with a particular focus on recent published data and chief ongoing active and recruiting trials.

Cytotoxic Therapy

While first-line systemic chemotherapy is a generally recognized treatment strategy for improving survival and quality-of-life in advanced BTC (10-12), until the past year, there was no consensus regarding the benefit of second-line systemic chemotherapy. Results concerning the efficacy and safety of second-line treatment in advanced BTC have come previously from retrospective studies with small sample size (24). Second-line fluoropyrimidine monotherapy revealed limited efficacy with a median PFS of 2.5-5.5 months and a median OS of 7.5-13.5 months, respectively (25-27), whereas fluoropyrimidine-based combination therapy with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) showed a median PFS of 1.6-3.9 months and a median OS of 4.4-8.4 months (28-31).

In the last few years, two papers have summarized the results of studies assessing the efficacy of second-line chemotherapy in BTC (32, 33).

First, Lamarca *et al*. in 2014 performed a systematic review to evaluate the level of evidence for the use of second-line therapy in 761 BTC patients (32). This systematic review reported a mean OS of 7.2 months (95%CI=6.2-8.2) in patients receiving second-line treatment while mean PFS, response rate (RR) and disease control rate (DCR) were 3.2 months (95%CI=2.7-3.7), 7.7% (95%CI=4.6-10.9) and 49.5% (95%CI=41.4-57.7), respectively.

In 2019, a meta-analysis by Ying *et al*. evaluated the role of second-line treatment for advanced BTC in terms of response, OS and toxicities, collecting data from 32 published studies including 1391 patients (33). The weighted median PFS and OS for refractory BTCs which received second-line therapy were 2.6 months and 6.5 months, respectively, and combined second-line treatment was not superior to monotherapy in terms of objective response rate (ORR) (33).

Results from the ABC-06, open-label, randomized, multicenter trial comparing 12 cycles of mFOLFOX plus active symptom control (ASC) with ASC alone in the second line setting, were presented at the ASCO 2019 Annual Meeting (34). In a population of 162 patients who had progressed on first-line CisGem, the addition of mFOLFOX improved OS (HR=0.69, p=0.031) with a modest benefit (6.2 months *vs*. 5.3 months) and an increase of 14-15% in OS rates at 6 and 12 months. High-grade toxicities (especially G3-G4 fatigue, neutropenia and infections) were more frequent in the experimental arm (59% *vs*. 39% in control arm), while the frequency of neuropathy and febrile neutropenia remained low (1%). This positive study provided the first level-1 evidence for second-line treatment after standard-of-care first-line therapy. Therefore, although the absolute median OS differences between the two arms were modest, mFOLFOX is actually considered as new standard of care second-line chemotherapy for BTC patients with no driver mutations and whose disease progressed after CisGem.

Lastly, novel chemotherapy combinations have been tested for patients with BTC. Recently, a single-arm two-stage phase II trial evaluated the efficacy of FOLFIRINOX with two different dosages (standard and modified) in 40 patients who had disease progression or unacceptable toxicity after ≥3 cycles of CisGem (35). The median PFS and OS in all patients was 6.2 and 10.7 months, respectively; the most common grade 3-4 adverse events were neutropenia, diarrhea, nausea, vomiting and mucositis.

Targeted Therapy

FGFR2

In iCCA, the FGFR signaling pathway is aberrantly activated in approximately 15 to 20% of cases and the most common FGFR pathway aberrations are gene fusions involving *FGFR2* (36-38). Interestingly, iCCAs harboring *FGFR2* fusions have been historically associated with female sex, younger age and prolonged survival (39). Multiple FGFR tyrosine kinase inhibitors (TKIs) are being assessed as second- or later-line treatment for patients with advanced

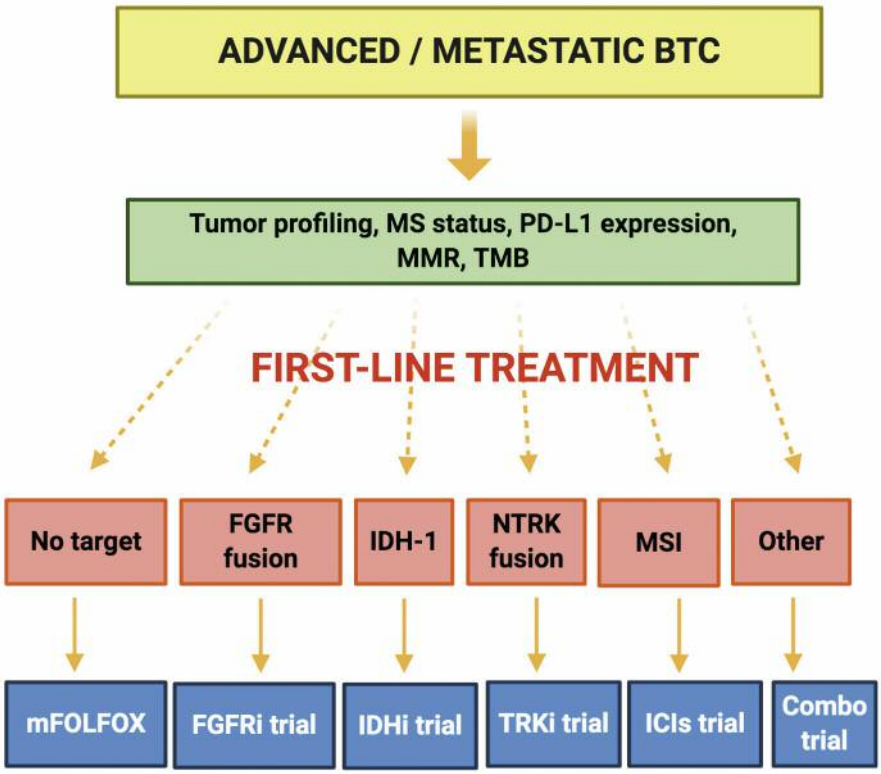

Figure 1. *Current landscape of second-line treatment for biliary tract cancer (BTC).*

FGFR-mutant iCCA, including infigratinib (BGJ398), derazantinib (ARQ-087), erdafitinib, pemigatinib (INCB054828), TAS-120 and rogaratinib (BAY1163877). Infigratinib (BGJ398) showed meaningful clinical efficacy in a phase II trial on chemotherapy refractory iCCA harboring *FGFR* aberrations (40). In this trial, ORR was 14.8% (18.8% in FGFR2 fusion group), DCR 75.4% (83.3% FGFR2 fusions only) and median PFS 5.8 months (95%CI=4.3-7.6) in 61 patients. Most frequent treatment-related adverse events included hyperphosphatemia, alopecia, stomatitis, palmar-plantar erythrodysesthesia and fatigue (40). Another phase II study on infigratinib in second- or later-line setting in patients with advanced CCA harboring *FGFR2* gene fusions or translocations or other *FGFR* genetic alterations is currently ongoing (NCT02150967).

Derazantinib (ARQ087), an orally bioavailable multi-kinase inhibitor with potent activity against FGFR1, FGFR2 and FGFR3 kinases, showed promising anti-tumor activity and a favorable safety profile in patients with advanced *FGFR2* fusion-positive iCCA in a phase I/II trial (41). Twenty-nine patients were enrolled (2 treatment naïve and 27 who had received at least one prior chemotherapy regimen); median PFS was 5.7 months (95%CI=4.04-9.2 months), ORR 20.7% and DCR 82.8%. Commonly observed adverse events were hyperphosphatemia, ocular toxicity, asthenia, and increase in ALT/AST. A phase II trial assessing derazantinib in iCCA patients who received at least one prior regimen of systemic therapy is ongoing (NCT03230318).

In a recent phase I trial, the pan-FGFR inhibitor erdafitinib was associated with promising clinical activity in advanced solid tumors with genomic alterations in the FGFR pathway, including iCCA (42). There are currently ongoing trials evaluating the safety and efficacy of erdafitinib in previously treated solid malignancies (NCT02699606, NCT04083976).

In FIGHT-202 trial, the pan-FGFR inhibitor pemigatinib (INCB054828) showed interesting results in previously treated patients affected by *FGFR2* fusion-positive iCCA (43). More specifically, 38 (35.5%) of 107 patients with *FGFR2* rearrangements or fusions achieved an objective response (35 PRs and 3 CRs) and 88 (82%) of 107 patients achieved disease control, with a median PFS of 6.9 months. Similarly to infigratinib and derazantinib, hyperphosphatemia was the most common all-grade adverse event [88 (60%) of 146 patients], with other common adverse events which included arthralgia, stomatitis, hyponatremia, alopecia, diarrhea and fatigue. A phase II study investigating pemigatinib in patients with advanced/metastatic or surgically unresectable iCCA with

FGFR2 rearrangement and which have failed at least one prior systemic chemotherapy is ongoing (NCT04256980).

TAS-120 is a highly potent, irreversible and selective inhibitor of FGFR1-4. In the dose-escalation phase of a phase I study, TAS-120 showed a tolerable safety profile and preliminary antitumor activity in pretreated patients with FGFR2 fusion-positive iCCA (44). The dose-expansion phase and a phase II trial are currently ongoing (NCT02052778).

Phase I and II trials regarding FGFR inhibitors E7090 (NCT04238715), CPL304110 (NCT04149691), EOC317 (NCT03583125) and INCB062079 (NCT03144661) are ongoing, with the aim to explore novel therapeutic chances in pretreated FGFR-positive iCCA.

Notwithstanding evidence from the initial efficacy of FGFR2 inhibitors, almost all patients develop acquired resistance, something which represents a major concern in FGFR targeted therapy (45).

Table I summarizes ongoing trials on FGFR targeted therapy in BTC registered on clinicaltrials.gov.

IDH1

IDH mutations are reported in 19-36% of iCCAs, representing not only an exclusive mutation to iCCA subtype but also the most frequent in this subgroup (46). *IDH1* and *IDH2* point mutations result in 2-hydroxyglutarate (2-HG) accumulation, which can be directly detected in the bloodstream and seems to play a pivotal role in carcinogenesis (47). From an epidemiological point of view, *IDH* mutations appear to be more common in non Opistorchis Viverrini-related iCCAs compared with noninfectious forms (48).

Following the results of preclinical studies (49, 50), a phase I trial assessed the role of the first-in-class oral IDH1 inhibitor ivosidenib (AG-120) in pretreated, *IDH1*-mutated, metastatic malignancies including 73 cases of iCCA (51). Stable disease (SD) and partial response (PR) were achieved in 56% and 5% of patients, respectively; median PFS was 3.8 months (95%CI=3.6-7.3) and median OS 13.8 months (95%CI=11.1-29.3), with a manageable safety profile and no dose-limiting toxicities. Interestingly, a reduction in Ki67 nuclear staining and in circulating 2-HG levels were detected in ivosidenib responders (51).

The results of the phase III, randomized, placebo-controlled, ClarIDHy trial were presented at the 2019 ESMO Congress (52); in this study, iCCA patients harboring *IDH1* mutations and who had received one or two prior lines of therapy, were randomized to 500 mg ivosidenib once daily or a matched placebo. The ivosidenib arm achieved a median PFS of 2.7 months *versus* 1.4 months of the placebo group, with a median PFS rate at 6 months of 32% and 21.9%, respectively (52). According to the intention-to-treat analysis, median OS was 10.8 months in patients treated with ivosidenib compared to 9.7 months with placebo. Finally, a favorable safety profile was observed in the ivosidenib arm, in concordance with previous studies in this setting. Thus, despite providing a modest OS benefit, ivosidenib represents a promising candidate in future second-line setting for CCA patients harboring *IDH1* mutations.

There are currently ongoing trials testing the safety and efficacy of other IDH inhibitors such as BYA143602, IDH305, FT 21012 and AG-881 (NCT02481154, NCT02746081, NCT02381886, NCT03684811).

Finally, preclinical models recently suggested that 2-HG enhances *IDH*-mutant CCA cells sensitivity to PARP inhibitors, since 2-HG can also prevent homologous recombination inducing a "BRCAness" phenotype (see below) (53). Thus, a phase II trial is currently ongoing with the aim to evaluate the PARP inhibitor olaparib in refractory, *IDH*-mutant solid tumors (NCT03212274).

EGFR/HER2

The epidermal growth factor receptor (EGFR) signaling seems to play a crucial role in BTC tumorigenesis since EGFR is frequently overexpressed in BTC, especially in iCCA (38-100%) (54). Although initial preclinical studies have shown promising results and have paved the way for RCTs in BTC, many trials evaluating EGFR inhibitors as monotherapy or in combination with other anticancer agents have produced modest benefit with short-lived, disappointing responses (55). Moreover, the majority of these studies focused on first-line therapy and only a small part of them assessed EGFR inhibitors in the second-line setting (56).

The EGFR TKI erlotinib was firstly evaluated as monotherapy in a phase II trial enrolling metastatic BTC patients who had received one prior line of therapy (57). In this study, 7 of 42 patients were progression-free at 6 months (17%; 95%CI=7-31%) and 3 patients achieved PR. Erlotinib was also tested in combination with docetaxel and sorafenib, and these combination strategies failed to show any PFS and OS benefit compared with single agent erlotinib (58-60).

Data regarding the EGFR antibodies cetuximab and panitumumab belong only to first-line setting since previous trials have shown disappointing results which do not support further studies on second- or later line of treatment (61-66). Finally, chimeric antigen receptor-modified T (CART)-EGFR cell therapy has been tested on EGFR-positive advanced BTC in a recent phase I trial (67). In this study, 19 patients (14 CCAs and 5 GBCs) received CART-EGFR after conditioning treatment with nab-paclitaxel and cyclophosphamide. Of 17 evaluable patients, 1 subject achieved CR and 10 patients SD; median PFS was 4 months, ranging from 2.5 to 22 months, with a tolerable safety profile (67).

With regard to HER2, HER2 amplification and overexpression are found in approximately 5-15% of eCCAs

Table I. *Current ongoing trials involving FGFR targeted therapy as second-line treatment registered on clinicaltrials.gov.*

NCT04256980	Pemigatinib in treating patients with advanced/ metastatic or surgically unresectable CCA including FGFR2 rearrangement	Not yet recruiting	CCA	Second- or later-line	Drug: Pemigatinib	2	February 2020
NCT04238715	A study of E7090 in participants with unresectable advanced or metastatic CCA with *FGFR2* gene fusion	Recruiting	CCA	Second- or later-line	Drug: E7090	2	January 2020
NCT04233567	Infigratinib for the treatment of advanced or metastatic solid tumors in patients with *FGFR* gene mutations	Recruiting	Advanced FGFR-positive solid malignancies including CCA	Second- or later-line	Drug: Infigratinib	2	January 2020
NCT04149691	Safety, tolerability and pharmacokinetics of oral CPL304110, in adult subjects with advanced solid malignancies	Recruiting	Advanced solid malignancies including CCA	Second- or later-line	Drug: CPL304110	1	July 2019
NCT03583125	Study of EOC317 in Chinese patients with advanced solid tumors	Recruiting	Advanced FGFR-positive solid malignancies including CCA	Second- or later-line	Drug: EOC317	1	May 2018
NCT03230318	Derazantinib in subjects with *FGFR2* gene fusion-, mutation- or amplification-positive inoperable or advanced iCCA	Recruiting	• iCCA • Combined Hepatocellular and Cholangiocarcinoma	Second- or later-line	Drug: derazantinib	2	November 2017
NCT03144661	An open-label safety and tolerability study of INCB062079 in subjects with advanced HCC and othermalignancies	Recruiting	Advanced FGFR-positive solid malignancies including CCA	Second- or later-line	Drug: INCB062079	1	May 2017
NCT02393248	Open-label, dose-escalation study of pemigatinib in subjects with advanced malignancies - (FIGHT-101)	Recruiting	Advanced FGFR-positive solid malignancies including CCA	Second- or later-line	Drug: Pemigatinib (alone or in combination with other anticancer agents)	1/2	January 2015
NCT02699606	A study to evaluate the clinical efficacy of JNJ-42756493 (erdafitinib), a pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor, In Asian participants with advanced NSCLC, urothelial cancer, esophageal cancer or CCA	Recruiting	Advanced FGFR-positive solid malignancies including CCA	Second- or later-line	Drug: Erdafitinib	2	July 2016
NCT04083976	A study of erdafitinib in participants with advanced solid tumors and *FGFR* gene alterations	Recruiting	Advanced FGFR-positive solid malignancies including CCA	Second- or later-line	Drug: Erdafitinib	2	November 2019
NCT02150967	A phase II, single arm study of BGJ398 in patients with advanced CCA	Recruiting	CCA	Second- or later-line	Drug: BGJ398 (infigratinib)	2	July 2014
NCT02052778	A study of TAS-120 in patients with advanced solid tumors	Active, not recruiting	Advanced FGFR-positive solid malignancies including CCA	Second- or later-line	Drug: TAS-120	1 2014	July

CCA: Cholangiocarcinoma; FGFR: fibroblast growth factor receptor.

and GBCs, thus representing a frequent aberration in these two subgroups (68-71). The blockade of HER2 signaling significantly improved the outlook of breast and esophagogastric cancer and targeting the HER2 family pathway has become increasingly attractive in several other malignancies, including BTC (72, 73).

The MyPathway basket trial included 11 patients affected by previously treated BTC harboring HER2 amplification/overexpression (n=8) and mutation (n=3); in this trial, the combination of trastuzumab plus pertuzumab yielded a response rate of 7.5% and 33.3% in HER2 amplified and mutated patients, respectively (74).

The SUMMIT basket trial is currently exploring the efficacy and safety of the pan-HER kinase inhibitor neratinib (NCT01953926) in patients with solid tumors harboring *HER2*, *HER3* or *EGFR* mutations / amplification (75). In this trial, preliminary results have shown an objective response rate of 10% among the subgroup of BTC patients (n=20) included (76), with 74% of the BTC study's population comprising patients whose disease progressed after treatment with gemcitabine and platinum-containing regimens.

Another recent trial showed a PR of 27%, SD of 43% and DCR of 70% in 37 BTC patients receiving the pan-HER TKI varlitinib in combination with cytotoxic chemotherapy (77). The study included patients affected by CCA (74.4%), GBC (16.3%) and AVC (9.3%), of which 32.6% (14 subjects) had received at least one prior line of treatment. Conversely, studies regarding other pan-HER inhibitors such as lapatinib and afatinib have not shown positive results in BTC (78, 79).

There are currently ongoing trials assessing the role of HER2-targeted therapies in BTC, especially as front-line treatment in combination with systemic chemotherapy (NCT03613168, NCT02992340 NCT02836847). With regard to second-line treatment, the TreeTopp (NCT03093870) trial is investigating the efficacy of varlitinib plus capecitabine *versus* capecitabine plus placebo in patients who have received and failed one prior line of systemic treatment. In the same setting, a phase II trial is currently evaluating trastuzumab plus chemotherapy in previously treated HER2 positive patients (NCT03185988).

Angiogenesis Inhibitors

Angiogenesis and lymphangiogenesis are considered essential processes in BTC tumorigenesis (80-83). The importance of angiogenesis in BTC has led to several preclinical and phase I and II trials targeting the vascular endothelial growth factor (VEGF) pathway with antibodies (bevacizumab, ramucirumab, aflibercept) and TKIs (vandetanib, sorafenib, sunitinib, cediranib, regorafenib, selumetinib, apatinib), as monotherapy or in association with chemotherapy or other anticancer agents (84).

A recent phase II trial investigated the association of capecitabine, irinotecan, gemcitabine and bevacizumab as a second-line treatment in 50 patients with metastatic cholangiocarcinoma (85); in this study, median PFS was 3.6 months and median OS 6.4 months.

The role of the TKI sunitinib (86), was assessed in a multicenter phase II study (SUN-CK trial), where second-line treatment sunitinib was administered in 53 patients with advanced iCCA (87). Twenty-four patients experienced SD (71%) and 5 patients PR (15%), with median OS and PFS of 9.6 and 5.2 months, respectively. The most common adverse events were asthenia, mucositis, hypertension, diarrhea and hand-foot syndrome.

Lenvatinib monotherapy was evaluated as second-line treatment in unresectable BTC in a phase II trial (88). In this trial, primary analysis was performed with data on 26 patients, where lenvatinib yielded a DCR of 85% and 46% by an investigator and independent review, respectively. Median PFS was 3.2 months by investigator review and 1.6 months by independent review; lastly, median OS was 7.4 months.

In a phase I trial, the combination of ramucirumab, a human monoclonal antibody against VEGFR-2 (89), plus pembrolizumab suggested limited clinical activity in 26 heavily pretreated CCA patients (90). The most common adverse events were hypertension, fatigue, diarrhea, nausea and hypothyroidism (90). ORR was 4% while median PFS and OS 1.6 months and 6.4 months, respectively (90). A phase II trial evaluating the role of ramucirumab monotherapy in pretreated patients with metastatic CCA is recruiting patients (NCT02520141).

Another VEGFR-2 inhibitor, apatinib, is currently under investigation as second-line therapy in an ongoing phase II study (NCT03521219).

Regorafenib monotherapy was evaluated in a phase II trial on 37 BTC patients whose disease progressed after first-line chemotherapy (91). In this study, 3 patients had PR (10.7%) and 18 experienced SD (4.3%), with DCR of 75%. Median PFS and OS was 3.55 months and 5.55 months, respectively, with a favorable safety profile. The most common adverse events were hypophosphatemia, hand-foot skin reaction, hypertension and increased serum bilirubin. In another phase II trial regorafenib was studied in 39 CCA patients which have failed one prior gemcitabine-based systemic therapy (92). Median PFS was 3.7 months and median OS 9.9 months, with PR achieved in 2 patients (6.2%) and SD in 18 subjects (56.2%). The most common toxicities were fatigue and hypertension, with dose adjustment required in 49% of the patients.

The TKI sorafenib was evaluated in a phase II trial (93) including 46 BTC patients, 26 (56%) of which received sorafenib as second-line treatment. PFS was 2.3 months (range=0-12 months), and median OS was 4.4 months,

showing an overall low activity (93). Performance status was significantly related to PFS since it was 5.7 months for ECOG PS 0 and 2.1 months for ECOG PS 1 subjects (93).

RAF, MEK

The mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK), or Ras-Raf-MEK-ERK pathway, plays a crucial role in cell proliferation and survival (94). Strong activators of this pathway are *BRAF* (v-Raf murine sarcoma viral oncogene homolog B) mutations, the most common of which is *BRAF* V600E (95). With regard to BTC, *BRAF* mutations are more frequent in iCCA compared with eCCA or GBC (96); more specifically, *BRAF* mutations have been reported in 1 to 22% of iCCAs in various population studies or cases series (96).

The *BRAF* V600 kinase inhibitor vemurafenib was tested in a phase II basket trial which enrolled previously treated patients with metastatic *BRAF* V600E mutated non-melanoma cancers (97). In this study, vemurafenib monotherapy showed 12% ORR in *BRAF*-mutant CCA, with 1 out of 8 patients experiencing PR (97).

A phase II trial evaluated the MEK1/2 inhibitor selumetinib in 29 BTC patients, 39% of which had previously received one prior systemic chemotherapy (98). Three objective responses were detected while 17 patients had SD [98]; additionally, median PFS was 3.7 months and median OS 9.8 months.

Trametinib, an oral highly selective inhibitor of MEK1/2, did not show significant activity as second line treatment in the SWOG S1310 trial (99), where trametinib was used in patients with advanced CCA after failure of GemCis chemotherapy. The trial was stopped prematurely given the lack of response observed in the trametinib arm.

The MEK1/2 selective inhibitor binimetinib was tested in a phase Ib trial on 28 CCA patients, in 43% of whom was used as a second-line treatment (100). Two patients experienced objective responses (1 CR, 1 PR) and 12 had SD. The most common adverse events were nausea, rash, vomiting, fatigue, diarrhea, peripheral edema and ocular toxicities. No correlation between mutational status and objective response was observed. In another phase Ib trial, binimetinib was studied in association with capecitabine in gemcitabine-refractory CCA patients (101). Seven out of 34 patients (20.6%) showed PR and 19 (55.9%) SD, with a median OS of 7.8 months. Interestingly, subjects harboring mutations in the RAS/RAF/MEK/ERK pathway showed a better response to therapy (40.0% *vs*. 12.5%), longer PFS (5.4 *vs*. 3.5 months) and better OS (10.8 *vs*. 5.9 months) than wild type patients. On the basis of the well-known improved efficacy of double BRAF and MEK inhibition in melanoma and colorectal cancer, the combination of dabrafenib plus trametinib was evaluated in patients with *BRAF* V600E–mutated CCA in a cohort of the ROAR basket trial. This phase II basket trial regarding 178 patients with *BRAF* V600E mutated malignancies included also 33 patients with refractory BTC (102). In the cohort of BTC patients, promising results were reported since PR was detected in 42% of patients and SD in 45%, with a favorable safety profile. Median PFS and median OS were 7.2 and 11.3 months, respectively.

cMET

The proto-oncogene c-MET plays an important role in carcinogenesis *via* promoting tumor invasion, angiogenesis, increased cell motility and antiapoptotic signals (103-105). MET amplification has been observed in 2-8% of BTCs while high c-MET expression has been described in 15% of eCCA and 12% of iCCA, according to previous studies (106). c-MET overexpression seems to represent a negative prognostic factor in BTC given the association with advanced stage at diagnosis and higher tumor volume (107, 108).

A recent phase II study evaluated the role of cabozantinib, a multikinase TKI targeting MET, in 19 previously treated CCA patients (109). In this trial, cabozantinib showed significant toxicity and limited activity, with a median PFS and OS of 1.8 (95%CI=1.6-5.4) and 5.2 (95%CI=2.7-10.5) months, respectively.

Pi3k/AKT/mTOR

Aberrations involving the PI3K/AKT/mTOR pathway are common in eCCA (40%), iCCA (25%) and GBC (4-16%) patients (110, 111); these aberrations mainly include *PI3KCA* amplifications, *PI3K* mutations, phosphorylated AKT overexpression and phosphorylated mTOR overexpression (112-115). Several trials have investigated the role of PI3K, AKT and mTOR inhibitors in first- and second-line setting in BTC, with limited tumor responses and disappointing results (116).

The phase II trial assessing the role of second-line MK-2206, an AKT selective inhibitor, was stopped prematurely, after the enrollment of 8 CCA patients (117). Median PFS was 1.7 months and median OS 3.5 months; two patients reported SD (25%) and 6 PD (75%) as best response.

The mTOR inhibitor everolimus was tested in a phase II study (EUDRACT 2008-007152-94) on 39 CCA patients refractory to first-line therapy (118). In this trial, ORR and DCR were 5.1% and 44% respectively, with a median PFS of 3.2 months and a median OS of 7.7 months.

Several ongoing trials are currently exploring the role of combination or sequential strategies using dual AKT-mTOR blockade or PI3K-mTOR inhibitors plus systemic chemotherapy in order to overcome resistance mechanisms related to the use of single targeted agents (NCT02465060,

Table II. *Current ongoing trials involving PARP inhibitors as second-line treatment in BTC registered on clinicaltrials.gov.*

NCT number	Cohort	Therapeutic regimen	Design	DDR defect screening	Primary endpoint
NCT03212274	Refractory and metastatic cholangiocarcinoma with *IDH1* or *IDH2* mutation	Olaparib	Phase 2	No	ORR
NCT03207347	Advanced or metastatic CCA after prior standard systemic treatment	Niraparib	Phase 2	Yes	ORR
NCT03991832	*IDH*-mutated BTC after no more than 2 previous treatment	Olaparib + durvalumab	Phase 2	No	ORR
NCT03878095	*IDH*-mutated CCA or other solid malignancy after prior standard treatment or with no available treatment	Olaparib + ceralasertib	Phase 2	No	ORR DCR
NCT03639935	BTC after prior standard systemic treatment	Rucaparib + nivolumab	Phase 2	No	Proportion of patients alive and without PD at 4 months
NCT04042831	BTC with somatic/germline mutations in DDR genes after exposure/completion of platinum-based chemotherapy	Olaparib	Phase 2	Yes	ORR

ORR: Overall response rate; DCR: disease control rate.

NCT02836847, NCT02631590) (119). Given the extensive crosstalk characterizing the PI3K/AKT/mTOR pathway and the connections with several other pathways and networks regulating cancer proliferation and progression, combination strategies based on resistance mechanisms and co-occurring drivers could be the keys for the successful development of agents targeting this pathway (120).

PARP

Poly adenosine diphosphate-ribose polymerase inhibitors (PARPis) represent an emerging therapeutic class for cancer patients harboring germline and somatic aberrations in DNA damage repair (DDR) genes (121). In BTCs, alterations in DDR genes have been identified in 28 up to 63% of patients, including mutations in *ATM, ATR, BAP1, BRCA1, BRCA2, BARD1, BRIP1, CHEK2, ARID1A, MLH1, MSH2, MSH6, PALB2, RAD50, FANCA* and *FANCD2* (122, 123). *BRCA1* and *BRCA2* are the most well-known DDR genes and BRCA 1/2 mutations occur in 1-7% of BTC patients (124, 125). In a retrospective analysis by Golan *et al*., 4 of 18 CCA patients with a confirmed *BRCA* mutation were treated with PARPis with a favorable response in first or further lines (125), and interestingly, 44% of patients (8 of 18) had a previous tumor or a family history of BRCA-associated malignancies (breast, ovarian, prostate and pancreatic cancer). Nevertheless, there is a lack of consensus regarding which BTC patients should be tested for *BRCA1/2* mutations and the optimal therapeutic strategy in BTC tumors harboring homologous repair deficiency (HRD) alterations is yet to be defined. With regard to second-line setting, few data are available supporting the efficacy of PARPis in second and further lines, given the absence of RCTs evaluating these agents.

Moreover, it would be important to understand the real prevalence of germline and somatic DDR mutations in BTCs across populations and further studies are needed to classify tumors as DNA-repair deficient, therefore screening groups with different genetic backgrounds is required. Ongoing clinical trials are aimed at identifying which genetic alterations are most likely to benefit from DNA-damaging therapies and are testing the combination of PARPis with various agents including chemotherapy, ICIs and small molecule inhibitors targeting various signaling pathways (126, 127). Table II summarizes ongoing trials on PARPis as second-line therapy in BTC registered on clinicaltrials.gov.

NTRK

Gene fusions involving *NTRK1*, *NTRK2* and *NTRK3* genes (encoding the neurotrophin receptors TRKA, TRKB and TRKC, respectively) occur in a broad range of adult and pediatric cancers (128, 129). Larotrectinib (LOXO-101) is a first-in-class potent and highly selective TRK inhibitor, which has shown promising clinical activity in patients with tumors harboring *NTRK* gene fusions (130, 131). The landmark study assessing the role of larotrectinib showed an ORR of 75% (95%CI=61-85%) with an acceptable safety profile in 55 NTRK-positive malignancies, including 2 cases of previously treated CCA (132). At the time of primary data cutoff, 7 patients (13%) achieved CR and 34 (62%) PR;

moreover, 71% of patients had ongoing response and 55% were progression-free at 1 year. The results of this study led to the approval of larotrectinib by the FDA (November 2018) and EMA (September 2019) for the treatment of pediatric and adult patients with NTRK-positive, locally advanced or metastatic solid tumors, which progressed after standard treatments and/or have no satisfactory alternative treatments (133). Larotrectinib is being assessed in the phase II NAVIGATE basket trial, which is enrolling NTRK-fusion positive solid malignancies, including patients affected by BTC (NCT02576431). Similarly, the TRK inhibitor entrectinib (RDX-101) is currently under investigation in an ongoing phase II basket trial on metastatic solid tumors, including CCA (STARTRK-2, NCT02568267). Additional data from these clinical trials will help to confirm the activity of TRK inhibitors in NTRK-positive malignancies and possibly to expand their use for tumor-agnostic treatments (134, 135). Since recent studies have reported a 4% frequency of NTRK fusion in iCCA and in light of the modest benefit of alternative treatment options, testing patients for NTRK aberration may be a reasonable strategy in this setting (136, 137).

Immunotherapy

The introduction of ICIs has revolutionized the treatment of several hematological and solid malignancies in the last decade (138-140). In this landscape, tumour mutational burden (TMB), programmed death ligand 1 (PD-L1) protein expression, mismatch repair deficiency (dMMR) and instable microsatellite (MSI) phenotype are currently considered important markers of response to immunotherapy (141). Higher TMB is associated with better response to ICIs in a number of solid tumours, and similarly, a wide range of studies have suggested a correlation between dMMR / MSI-high phenotype and ORR and PFS rates in patients receiving ICIs (142). Based on these findings, in 2017, the FDA approved pembrolizumab for the treatment of any MSI-high or dMMR malignancies, regardless of histology (143).

With regard to BTC, important differences in terms of aetiology, immune-microenvironment and genetic features exist among the anatomical subgroups, and these differences may be implicated in the clinical response to ICIs. Furthermore, recent studies have suggested that approximately 3% of BTCs presents a high TMB or dMMR phenotype (144, 145).

The anti-PD-1 agent pembrolizumab was firstly evaluated in the phase Ib KEYNOTE-028 trial (146). In this study, 24 pretreated patients with PD-L1 positive BTCs (20 CCAs and 4 GBCs) were enrolled and treated with pembrolizumab monotherapy; 4 (17%) patients achieved PR and 4 (17%) had SD. More recently, the KEYNOTE-158 trial (NCT02628067) tested the use of pembrolizumab in 104 CCA and GBC patients with disease progression after at least one prior treatment regimen. The trial included no MSI-high tumors while the 60% of patients were PD-L1 positive, considering the cutoff of 1% of PD-L1 expression. In this study, ORR for unselected patients was 5.8%, with a median OS and PFS of 7.4 and 2.0 months, respectively (147).

Pembrolizumab is also under investigation in several ongoing trials on second- and further-line settings (NCT02703714, NCT03695952, NCT04234113). A single-arm, phase II trial (NCT03110328) is testing the role of pembrolizumab in patients with metastatic BTC as second-line treatment after systemic chemotherapy, regardless of PD-L1 expression.

Another anti-PD-1 agent, nivolumab, has been studied in a recent phase II trial involving 54 BTC patients; in this trial, nivolumab obtained an ORR of 22% and a median OS of 14.24 months (148). The study enrolled patients after failure of at least one standard treatment regimen for BTC.

The anti-PD-L1 agent durvalumab was tested as monotherapy and in combination with tremelimumab in a phase I trial on pretreated, Asian BTC patients (149). Median duration of response for the durvalumab and the durvalumab plus tremelimumab cohorts were 9.7 and 8.5 months, respectively. Moreover, median OS was 8.1 months (95%CI=5.6-10.1) in patients receiving durvalumab and 10.1 months (95%CI=6.2-11.4) in the durvalumab plus tremelimumab combination.

Since combining ICIs to targeted therapies or systemic chemotherapy is an emerging approach in a spectrum of malignancies, this strategy is under evaluation also in BTC. More specifically, combination therapies may play a role in changing immune cell infiltrate, thus enhancing the efficacy of ICIs, as suggested in preclinical models.

The association between the VEGFR-2 inhibitor ramucirumab and pembrolizumab was analyzed in a phase I trial on 26 previously treated metastatic BTCs, where the combination yielded an ORR of 4% while median PFS and OS were 1.6 and 6.4 months, respectively (150).

Another recent phase II trial studied the association of lenvatinib plus pembrolizumab or nivolumab in 14 iCCA patients who had received at least two prior anticancer treatments. ORR and DCR were 21.4% and 92.9%, respectively, with a median PFS of 5.9 months (95%CI=4.2-6.2) (151).

The combination of pembrolizumab plus lenvatinib is also under evaluation in the phase II LEAP-005 trial, which is enrolling previously treated patients with solid malignancies, including BTC (NCT03797326). Similarly, the combination of pembrolizumab plus CAPOX (capecitabine plus oxaliplatin) regimen is being assessed in an ongoing phase II trial on previously treated BTC patients (NCT03111732). Table III summarizes ongoing trials on ICIs as second-line treatment in BTC registered on clinicaltrials.gov.

Table III. *Current ongoing trials involving ICIs as second-line treatment in BTC registered on clinicaltrials.gov.*

NCT number	Status	Therapeutic regimen	Checkpoint target	Setting	Phase
NCT03260712	Not yet recruiting	Pembrolizumab	PD-1	Second-line	2, single-arm
NCT03046862	Recruiting	Durvalumab + tremelimumab	PD-1, CTLA-4	Second-line	2, single-arm
NTC03101566	Recruiting	Nivolumab + ipilimumab	PD-1, CTLA-4	Second-line	2, open-label
NCT03668119	Recruiting	Nivolumab + ipilimumab	PD-1, CTLA-4	TMB high solid tumors	2, open-label
NCT02923934	Recruiting	Nivolumab + ipilimumab	PD-1, CTLA-4	Second-line or more	2, single-arm
NCT02834013	Recruiting	Nivolumab + ipilimumab	PD-1, CTLA-4	Second-line or more	2, single-arm
NCT02829918	Active, not recruiting	Nivolumab	PD-1	Second-line	2, single-arm
NCT03111732	Recruiting	Pembrolizumab + CAPOX	PD-1	Second-line or more	2, single-arm
NCT01174121	Recruiting	Pembrolizumab + autologous TILs	PD-1, TIL	Metastatic cancer including BTC	2, multi-arm

The Clinical Background: What we Should Remember

As previously stated, many BTC patients receiving first-line treatment fail to achieve a response and, even in responders, responses are short lived (1, 3). In this setting, medical oncologists are faced with the vexing decision to treat the "inevitable" tumor progression in patients with frequently declining performance status (4, 5). However, a non-negligible number of BTC patients are still medically fit to be offered second-line therapy and there is an increasing use of systemic treatments beyond first line setting (8, 9). Thus, understanding which BTC patients may benefit from second-line therapy is of growing interest and several prognostic factors have been recently suggested to influence clinical outcomes in second-line treatment (14). In an Italian, multicenter, retrospective study involving 811 patients with advanced BTC, 357 subjects (44%) received a second-line therapy (13), 25% of whom received fluoropyrimidine monotherapy and 32% a platinum-based schedule. In this study, patients who achieved a first line PFS ^{3} 6 months had better prognosis compared with those who did not. Moreover, Eastern Cooperative Oncology Group (ECOG) - performance status (PS), CA19.9 levels, and previous surgery were independently associated with longer OS. The association between previous surgery and good ECOG-PS (0-1) with better survival has been recently suggested also by a large international multicenter study with 797 patients (152). Peritoneal carcinomatosis was an independent prognostic factor for OS, according to the results of the study. However, prognostic factors in second-line treatment are currently subject to debate and remain unclear.

Evidently, the use of second-line treatment should be considered in suitably motivated patients with good PS, adequate organ function and longer expected survival (≥3 months). In this scenario, recent advances in genomic profiling have the potential to open a new era in BTC management, moving towards a personalized approach based on specific molecular aberrations (153). For the reasons mentioned above, in BTC patients whose disease has progressed after front-line treatment, careful consideration should be given to genomic testing and enrolment in biomarker-driven clinical trials assessing novel targeted agents and combinations.

Conclusion

Identification of effective and well-tolerated second-line treatment regimens for previously treated BTC patients is urgently needed. Despite notable advancements in the comprehension of the BTC molecular landscape, many questions are yet to be answered. To date, precision medicine in BTC is limited to iCCA and has mainly focused on agents targeting IDH and FGFR. The detection of the subset of patients which might benefit from second-line treatment, the choice of the optimal regimen and the effects of treatment on quality of life remain mandatory elements in choosing the best therapeutic strategy in this setting.

Conflicts of Interest

The Authors state that they have no conflicts of interest in regard to this study.

Authors' Contributions

AR, ADR: concept, design, review of literature and final review; NT, MCN, MM: concept, design, review of literature; AP, FA, GF, SDL: final review and approval; ST, GB: concept, design, final review and approval.

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