Personalised Oncology in Biliary Tract Cancer: Are We Entering a New Era? Interviews with Three Key Opinion Leaders

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Interview Summary

Biliary tract cancer (BTC) comprises a heterogeneous group of malignancies arising from the epithelial lining of the bile ducts and gallbladder. BTCs are rare, accounting for around 1% of all human cancers, and are aggressive and challenging to treat. Between 60–70% of patients present with advanced, unresectable disease, limiting curative treatment options and resulting in poor prognosis. Among patients eligible for surgical resection, recurrence rates can be extremely high, highlighting a significant unmet need and demand for novel, effective therapies.

Historically, treatment has focused on the use of chemotherapy in advanced, metastatic BTC not suitable for surgical resection. Combination approaches, including chemotherapy plus immunotherapy, have marginally improved survival outcomes. Such approaches, however, do not directly address the underlying genetically driven biology that characterises many BTC subtypes. Further recognition of BTCs as separate anatomical and morphological entities is essential for effective management, as each provides distinct clinical, molecular, and, therefore, treatment profiles. Comprehensive molecular profiling reveals recurrent, targetable mutations, particularly in cases of intrahepatic cholangiocarcinoma (iCCA), moving beyond the standard of care to a more personalised, biomarker-driven treatment approach. While targeted therapies and combination approaches have the potential to usher in a new era of BTC management, further Phase III RCTs are needed to optimise the treatment strategies.

For this article, EMJ conducted interviews in February 2026 with three key opinion leaders: James Harding, Memorial Sloan Kettering Cancer Center, New York, USA; Arndt Vogel, Toronto General Hospital and UHN-Princess Margaret Cancer Centre, Canada; and Teresa Macarulla, Hospital Clínic de Barcelona, Spain, all of whom have a wealth of experience and expertise in the diagnosis and management of patients with BTC, having contributed to many research studies in this area. The experts shared their valuable insights on the rising global incidence of BTC, current BTC treatment pathways, updated clinical guidelines, specific biomarker approaches, and testing considerations. The impact of targeted therapies and combination approaches on the management of BTC was discussed, including significant results from the most recent clinical trials, and the experts shared their personal outlook on the future of BTC management, considering both first and second-line treatment strategies, both in silo and in combination.

INTRODUCTION

BTC refers to a spectrum of invasive tumours, arising from the gallbladder, cystic duct, and the intrahepatic and extrahepatic biliary tree. BTC is being increasingly characterised by anatomical and biological distinctions, including large duct and small duct subtypes. Although rare, accounting for around 1% of all human cancers,[1] BTCs are aggressive and challenging to treat. Between 60–70% of patients with BTC present with advanced, unresectable disease, limiting treatment options and resulting in poor prognosis.[2] This is often driven by non-specific symptoms during early-stage disease, specifically in iCCA, and patients presenting with no known risk factors.[3,4] The 5-year survival rate of BTC is less than 5% for unresectable disease and up to approximately 40% for resectable tumours.[1,5] Resectable survival rate can be differentiated based on anatomical location, stage, and surgical margin, with the 5-year survival for resectable tumours falling to around 20% in cases with nodal and vascular involvement.[1] The current standard of care for unresectable disease is chemotherapy plus immunotherapy, followed by second-line chemotherapy and targeted therapies, with modest survival benefits. BTCs exhibit high levels of inter- and intratumour heterogeneity, driven by a diverse and complex interplay of risk factors

and cells of origin, complicating the efficacy of available therapeutic interventions.[6] Patients frequently experience a significantly reduced health-related quality of life at baseline diagnosis, further exacerbated by tumour and treatment-related symptoms.[1,7] A high symptom burden is common, and within the context of a poor prognosis, is regularly associated with a rapid decline in mental wellbeing and increased psychological distress.[8] While surgical resection remains the only curative treatment modality, most patients are not candidates for surgery due to distant metastasis or local progression, and those who are typically experience a 3-year recurrence rate of approximately 80%. The significant unmet need for this patient population highlights the importance of continued research and development focus.

RISING INCIDENCE AND REGIONAL PREVALENCE

While BTC currently accounts for only 1% of all human cancers worldwide, prevalence is increasing. The global incidence of cholangiocarcinoma (CCA) is relatively low in Western countries, less than two per 100,000, but rates exceed six per 100,000 in Thailand and other Eastern countries.[9] The global mortality rate for CCA has increased, according to the WHO and Pan American Health Organization (PAHO) databases.[10,11] Vogel explains that while the data suggest an increase in rates of iCCA, rates of extrahepatic CCA (eCCA) have remained more or less stable.[12] Harding rationalises that improvements in initial diagnosis classification could be one explanation for this rising incidence, noting that iCCA is now recognised as the second most common primary liver tumour,[13] when historically many cases were likely classified as carcinoma of unknown primary.[14] Harding explains that an increasing awareness, both academically and clinically, of systematic workups and appropriate immunohistochemical stains has improved the accuracy of identification and correct attribution of the disease. Macarulla agrees with this rationale, but also agrees with Vogel's suggestion that, beyond early misclassification, the rising incidence of BTC may also reflect the growing burden of chronic liver disease. Around 25% of patients with CCA have chronic liver diseases, and one in 10 have cirrhosis,[15] associated more commonly with iCCA. Vogel explains that hepatitis B or C, fatty liver disease, alcohol related liver disease, and obesity are well-established risk factors for hepatocellular carcinoma,[16,17] and are becoming increasingly prevalent in CCA.[18] Vogel also points to rare risk factors such as primary sclerosing cholangitis with high tumour incidence,[19] and liver fluke-associated CCA seen in parts of Asia.[20] These factors could specifically explain the high incidence rates in countries such as Thailand.[21] Macarulla adds that increasing global mobility may also be influencing incidence patterns, stating that there is a great deal more movement today, with people relocating from one part of the world to another. As a result, individuals from endemic areas may move to Western countries, which could contribute to rising incidence.[2] While incidences of gallbladder cancer are relatively low in Western Europe and the USA (1.6–2.0 cases per 100,000 population) and decreasing, this could be explained by an increase in incidental gallbladder cancer findings following routine cholecystectomy.[22]

UNMET NEEDS ALONG THE BTC TREATMENT PATHWAY

Stage at Diagnosis

Sixty to seventy percent of patients with BTC present with advanced, unresectable disease and have poor prognosis, defined as metastatic or unresectable tumours that are not amenable to local therapy with curative intent.[5] Macarulla explains that clinically meaningful symptoms often only present during the later stages of disease, which means that many patients who are diagnosed with BTC are not candidates for curative treatment, only palliative. While surgical resection remains the only curative treatment modality, most patients are not candidates for surgery due to distant metastasis or local progression; typically, only 20–30% of patients are resectable at diagnosis.[23] Even among those who do undergo curative-intent resection, outcomes remain a challenge, with around 60–70% of patients expected to have disease recurrence.[24] Adjuvant chemotherapy

with capecitabine, established following the BILCAP trial, has improved outcomes in this setting, with a reported median survival of 53 months.[23] Harding, however, considers this to be a key area for improvement, highlighting the need to do a better job of bringing treatments that we now know to be efficacious in later-stage disease into the earlier stages of treatment. According to all of the experts, patients presenting with locally advanced or metastatic disease is a key driver of poor outcomes, as while there have been advances in treatment options for patients over the last decade, there are still relatively few active and efficacious treatments in advanced and later stage disease.

Standard of Care Versus Combination Therapy

The established first-line standard of care for patients with metastatic BTC not suitable for surgical resection has long been systemic chemotherapy, namely gemcitabine plus cisplatin (GemCis), leading to a modest median overall survival of 11.7 months compared with 8.1 months for gemcitabine alone (ABC-02-trial: NCT00262769).[25] The addition of immune checkpoint inhibitors to GemCis has led to modest but statistically significant improvements in overall survival in the first-line setting.[26] According to all of the key opinion leaders, two Phase III trials have demonstrated that the combination of GemCis with immune checkpoint inhibitors, durvalumab (TOPAZ-1: NCT03875235)[27] or pembrolizumab (KEYNOTE-966: NCT04003636),[28] improved survival compared to GemCis alone. TOPAZ-1 results showed an estimated 24-month overall survival rate of 23.6% in the durvalumab plus gemcitabine-cisplatin group, and 11.5% in the placebo plus gemcitabine-cisplatin group.[27] KEYNOTE-966 results indicated a median overall survival of 12.7 months in the pembrolizumab group versus 10.9 months in the placebo group.[28] These data have led to chemotherapy-based regimens with or without immunotherapy becoming the standard of care. Harding explains the rationale behind combination therapies: "In preclinical models, combinatorial therapy outperforms precision medicine alone. Given the heterogeneity of BTC, with initiating driver events alongside subclonal populations and both intra- and intertumoural variability, targeting multiple pathways early in the disease may improve outcomes." While combination therapy offers additional therapy options for a patient population with significant unmet need, its effects vary based on tumour biology and underlying molecular alterations.

Second-Line Chemotherapy Considerations

In the absence of molecular markers, the second-line standard of care is FOLFOX chemotherapy (5-fluorouracil, leucovorin, and oxaliplatin). Previous iterations of the European Society for Medical Oncology (ESMO) BTC management guidelines did not consider second-line chemotherapy as a standard treatment option, and patients were often offered supportive care only after progression to first-line chemotherapy. However, the ABC-06 trial (NCT01926236) demonstrated a modest survival benefit with FOLFOX compared with active symptom control alone, with a median overall survival of 6.2 months versus 5.3 months, respectively.[29] Although some modest survival benefits have been identified through combination approaches, such approaches do not directly address the underlying genetically driven biology that characterises many BTC subtypes, and the overall survival with first and second-line chemotherapy has not seen any significant improvements over the last 20 years,[30] highlighting a critical need for novel targeted therapies.[31] Traditionally, only around 15–25% of patients with BTC progressed onto second-line chemotherapy, reflecting the aggressive nature of BTC, rapid deterioration, and limited treatment options following first-line therapy; more recent data, however, suggest that around 40–50% proceed to second line.[32]

THE IMPORTANCE OF SUB-CLASSIFICATION

Previously grouped together as a single entity, these cancers are now recognised by their anatomical location, as well as distinct molecular, morphological, and management profiles.[33] BTCs are sub-classified by their primary, anatomical location: iCCA, arising from the bile ductules proximal to the second-order bile ducts, encompassing both small duct and large duct subtypes; perihilar CCA, arising in the right and/or left hepatic duct and/or at their junction; and distal CCA, arising from the epithelium distal to the insertion of the cystic duct.[34] Although perihilar CCA and distal CCA have traditionally been collectively referred to as eCCA, according to ESMO Clinical Practice Guidelines, this classification has been discouraged due to insufficient anatomical specificity.[10] While close in proximity, each BTC subtype often has distinct molecular characteristics.

Harding explains that while each of the BTC subtypes is unique clinically in its presentation and natural history, they also differ genetically. Macarulla explains that while the anatomical subtypes in BTC help physicians and investigators to understand the biology and heterogeneity of the disease, along with the feasibility of surgical resection, this information is not used to guide ongoing treatment decisions as systemic therapy is uniformly applied.[31] She explains that instead, clinicians decide the most appropriate second-line treatment option for patients with BTC based on the results of molecular testing. Vogel explains that we know certain molecular alterations are enriched in certain subtypes, specifically between the small duct type and large duct type, and it is this enrichment that must be considered when ordering molecular testing, as these results can change the treatment pathway. He highlights the importance of this understanding by saying: "If I could decide, everyone would perform comprehensive molecular testing immediately after first diagnosis, regardless of whether the disease is resectable or unresectable." It is important to note, however, that current clinical guidelines recommend molecular profiling at initiation of first-line systemic therapy.

MOLECULAR PROFILING FOR PERSONALISED ONCOLOGY

Around 40% of patients with BTC have molecular alterations that are eligible for targeted therapy, the most common being *FGFR2* fusions and *IDH1* mutations, present in around 15% of iCCAs.[2] Updated ESMO 2025 guidelines[35] recommend molecular profiling when first-line systemic treatment is initiated in patients with locally advanced, advanced, or metastatic disease. The guidelines specify that clinically relevant markers for BTC include human epidermal growth factor receptor 2 (HER2), *IDH1*, *NTRK*, *FGFR2*, *BRAF*, *KRAS*, *MET*, MMR, *PIK3CA*, *RNF43*, and *PRKAC A/B*, including amplification, mutation, fusion, and protein overexpression.[35-37] Several targeted therapies have shown improved response rates in patients with BTC, including isocitrate dehydrogenase 1 (IDH1)-directed, fibroblast growth factor receptor (FGFR)-directed, *NTRK*-directed, and HER2-directed therapies.[38]

Harding elaborates on the different molecular variations underpinning each subtype. He explains that in small duct iCCA, we see enrichment for *IDH1* and *IDH2* point mutations and *FGFR2* fusions or rearrangements, which are among the most well-characterised and targetable alterations in this subgroup. In contrast, he explains that gallbladder cancers more frequently harbour *HER2* amplification or overexpression, and occasionally *HER2* mutations. eCCA tends to have a molecular profile that is more similar to pancreatic ductal adenocarcinoma, with *KRAS* mutations acting as a common oncogenic driver.[39] The recognition that there are multiple, potentially actionable genomic alterations within each subtype of BTC reinforces the need for comprehensive molecular profiling in all patients with advanced disease. Over the last decade, this enhanced understanding of the underlying biology of BTC subtypes has translated into the development of targeted therapies, redefining BTC management beyond systemic chemotherapy and immunotherapy combination towards a more personalised treatment approach.

HER2 PREVALENCE AND IMPACT

Overexpression or amplification of HER2 are promising therapeutic targets in patients with BTC.[40] HER2 alterations, including gene amplifications, mutations, and protein overexpression, are reported in around 5–10% of BTC cases.[35] Prevalence and type vary significantly based on anatomical subtype. While *HER2* amplification is considered rare in small duct iCCA, this alteration can be found in 20% of gallbladder cancer cases, and 15% of eCCA cases, typically representing the best option for targeted treatments in these particular subtypes.[37] Vogel considers HER2 to be an established molecular target within the realm of oncology, noting the overwhelming evidence for targeting HER2 across gastric, colon, and breast cancers,[41] with many data specific to CCA ongoing. He explains that HER2 testing there should be a reflex testing for all solid tumours, stating: "I don't recall any tumour in which HER2-targeted therapies should not be considered."

Molecular Testing Modalities

A range of testing methods can be used to confirm HER2 status, including next-generation sequencing (NGS), immunohistochemistry (IHC), and *in situ* hybridisation. Differentiating the benefits and individual use for each testing modality has a significant impact on treatment decisions, particularly in the much-needed second-line setting. While NGS is considered the gold standard for comprehensive genomic profiling in a broad range of tumour types, it does not directly assess protein overexpression, and for this reason, all of the experts agreed that IHC remains an essential tool for the identification of HER2 protein overexpression. HER2 status IHC 3+ tumours refer to cancers that show strong protein overexpression on IHC testing, which, according to the experts, is the current indication for HER2-targeted therapy. Macarulla explains that clinical trials have shown that the activity of anti-HER2 therapies is really only observed in patients with IHC 3+ tumours, and while NGS can identify *HER2* amplification, we currently do not know how the number of copies correlates with HER2 protein overexpression. Therefore, to guide treatment decisions, IHC is required. Real-world data suggest that clinical implementation of molecular profiling remains inconsistent, lacking harmonisation across platforms and centres.[42] Harding states that applying a purely gene-based analysis for patients with BTC is hazardous, and clinicians "need to be vigilant about trying to detect all of the genetic abnormalities in a reasonable panel at the time of diagnosis." He suggests that molecular testing should be almost immediate at all stages of the disease to help clinicians optimise treatment strategy, recommending HER2 IHC with reflex *in situ* hybridisation to determine HER2 overexpression, both at a protein and gene-based level. Harding highlights an additional challenge, noting that tumour-specific HER2 scoring criteria for BTC have not yet been fully standardised, with many clinicians applying the gastric HER2 scoring system as a pragmatic, yet widely accepted strategy. With HER2-directed therapies becoming more widely accepted in the landscape of BTC, a validated scoring system is essential.

The Practicalities of Tissue Biopsy

Pathologic diagnosis is essential prior to initiating non-surgical treatment to confirm the diagnosis and to identify targetable aberrations. BTC biopsies, however, can be technically challenging, with >10% of metastatic tumour biopsies yielding insufficient tumour content or DNA quality for analysis by NGS.[43] Vogel highlights how this translates into clinical practice, underscoring the need for sufficient tissue and validated assays. He estimates that for 90% of patients, he can obtain enough tissue for sequencing, but in challenging cases where repeat biopsy fails to provide adequate testing material, liquid biopsy may be considered (circulating tumour DNA).[44] Harding agrees that in the event of a small tissue sample, he would re-biopsy or use liquid biopsy, arguing that while some health insurers may disagree with this decision in early-stage disease, the clinician must understand the molecular characteristics of the disease sooner

rather than later, especially given the high chance of recurrence. Macarulla suggests that the time it takes to do molecular profiling could be the difference between receiving second-line targeted treatment and not. She acknowledges that clinicians are often working under the constraints of local testing availability and that limited access to comprehensive molecular testing can restrict the identification of actionable alterations. Harding, who practices in the USA, considers his own practice in the context of reimbursement considerations. Vogel and Macarulla, who work in Canada and Spain, also explain that liquid biopsy is not reimbursed within their healthcare system, and so for patients without tissue, they are left with limited options. That being said, Vogel highlights that in instances of insufficient tissue for NGS testing, there may still be sufficient tissue for HER2 IHC testing. All three of the experts consider the importance of molecular testing during all stages of disease, as without a comprehensive understanding of the molecular profile of the tumour, targeted treatment cannot be applied.

HER2-TARGETED TREATMENTS

There are currently two HER2-targeted therapies with clinical relevance in BTC, zanidatamab and trastuzumab deruxtecan (T-DXd), each with distinct mechanisms of action. Zanidatamab is approved in the USA, EU, UK, and China for the treatment of adults with previously treated, unresectable, locally advanced or metastatic HER2-positive BTC, with a documented HER2-positive tumour status classified as IHC3+. T-DXd is approved in the USA under a tumour-agnostic accelerated approval for adult patients with unresectable or metastatic HER2-positive solid tumours (IHC3+), who have received prior systemic therapy and have no satisfactory alternative treatment options. Harding explains how they differ in mechanism of action. T-DXd is an antibody–drug conjugate comprising an anti-HER2 antibody linked to a topoisomerase I inhibitor payload (deruxtecan). Zanidatamab is a bispecific HER2-targeted antibody, binding two distinct epitopes of the HER2 receptor via extracellular domain (ECD)2 and ECD4 binding regions to enhance immune-mediated tumour cell killing through multiple mechanisms. This includes inhibition of HER2 signalling, reduced tumour cell proliferation, and activation of complement-dependent and cell-dependent immunity.[45]

Zanidatamab in HER2-Positive BTC

All of the experts were extremely familiar with the data points for both treatments, Harding being lead author on the Herizon-BTC-01 trial (NCT04466891),[46] a pivotal global Phase II study of zanidatamab in HER2-positive BTC. In a cohort of 97 patients, zanidatamab demonstrated meaningful clinical benefit with a manageable safety profile in patients with treatment-refractory, HER2-positive BTC. Macarulla highlights that the greatest outcome was observed in patients identified as IHC3+, noting that the drug's tolerability and toxicity profile was excellent, with some infusion reactions and diarrhoea, but no Grade 4 treatment-related adverse events and no treatment-related deaths. "We saw probably for the first time that you could achieve a higher objective response rate," explains Harding, "being 41.3% in the total population, and in excess of 50% in tumours scoring IHC3+." Responses were observed, with a median duration of response close to 15 months in the overall population. However, as Vogel notes, responses were not always durable, with many experiencing less than 1 year of benefit before secondary resistance emerges. According to Harding, the accelerated regulatory approvals confirm that there is anti-tumour activity, making it even more critical to apply HER2 IHC testing to all patients with BTC, to identify those with HER2 IHC3+ who would then be candidates for treatment with zanidatamab after progression on a gemcitabine-based regimen. Macarulla and Vogel both agree, with Macarulla arguing that with targeted therapy, patients with an otherwise poor prognosis have a realistic opportunity to respond to oncological treatment.

Tumour-Agnostic HER2-Directed Therapy

T-DXd gained regulatory approval in the USA following data from the DESTINY-

Breast-01 trial (NCT03248492),[47] initially approved for use in heavily pretreated patients with HER2-positive breast cancer. Subsequent data from DESTINY-Breast03 and the DESTINY-PanTumor trials have supported the expansion of use to additional tumour types and populations. While the primary readout for the BTC cohort has been published, further trial expansion across tumour types is ongoing. During the DESTINY-PanTumor01 trial (NCT04639219), T-DXd was administered to 102 patients with unresectable or metastatic solid tumours with specific activating *HER2* mutations, with an objective response rate of 29.4%.[48] Fifty-two patients had a treatment-emergent adverse event of Grade 3 or worse, including anaemia and decreased neutrophil count, and adjudicated drug-related interstitial lung disease or pneumonitis of any grade occurred in 11 patients.[48] Further safety and efficacy were evaluated via the DESTINY-PanTumor02 Phase II trial,[49] which showed an objective response rate (ORR) of 37.1%, median progression-free survival (PFS) of 6.9 months, and median overall survival of 13.4 months. However, in patients with central HER2 IHC3+ expression, ORR increased to 61.3%, median PFS increased to 11.9 months, and the median OS reached 21.1 months. Macarulla explains that data from this DESTINY trial include a much broader range of tumour types, with data specific to BTC much lower than in Herizon-BTC-01. While there is a subset of patients with BTC who could benefit from this treatment, it is a tumour-agnostic HER2-directed therapy indicated for adult patients with unresectable or metastatic HER2-positive solid tumours, defined by strong HER2 expression (IHC 3+), who have received prior systemic therapy and have no satisfactory alternative treatment options. Vogel considers that there may be a role for sequential treatment and sequential targeting of HER2 and having more than one option is beneficial for this patient population, particularly in the context of advanced, metastatic disease.

Further Investigation Needed

Accelerated approval pathways have enabled the regulatory approval of these two targeted agents, zanidatamab and T-DXd. However, BTC relevant findings are currently being confirmed in ongoing Phase III studies, including Herizon-BTC-302 (NCT06282575),[50] and DESTINY-BTC-01 (NCT06467357).[51] Further studies are needed to establish continued approval and potential integration into first-line therapy. Vogel explains that while we know there has been an improved response rate from these therapies, and in a subset of cancer that is difficult to treat it is good to have options, we need the ongoing data from controlled trials in order to definitively prove that these treatments translate to improved survival.

Vogel also considers specific areas of research that need further investigation, including primary and acquired resistance. He explains that some tumours do not respond to targeted therapy from the start, known as primary resistance, and we do not yet fully understand why. Even in patients who initially respond, secondary or acquired resistance often develops,[52] limiting the duration of response and PFS. While targeted therapies still perform better than chemotherapy alone, these resistance mechanisms highlight the need for further research and combination treatment strategies to improve outcomes.

THE FUTURE OF BTC MANAGEMENT

Although prognosis remains poor, marked improvements in molecular characterisation and the accelerated approvals of novel targeted therapies are changing the therapeutic landscape for advanced BTC. Harding considers the future of BTC management promising, provided research and drug development continue at the same pace as in recent years. He explains that when he first started treating BTCs 10 or 11 years ago, chemotherapy was the only treatment option. Over the last decade, a number of targeted therapies have been approved in this setting, alongside combination immunotherapies, and there has been strong interest in drug development. Harding hopes that this progress will continue over the next 10 years, explaining that the readouts from Phase III studies may ultimately change practice.

Updated Guidelines and Practice

Macarulla argues that it is very clear how patients should be treated, as management is very well standardised according to updated clinical guidelines, including those from ESMO and the American Society of Clinical Oncology (ASCO).[35] Vogel, who recently co-authored the latest ESMO BTC clinical practice guideline update, highlights the need to promote and enhance global access and global standards. He states that while it is globally accepted from an academic point of view that we need to perform molecular testing as early as possible, ideally before starting systemic therapy, many countries are still lagging behind, and there is an urgent need for better alignment and implementation into clinical practice. While many drugs have been approved, access to drugs is not homogeneous within Europe, and differences in access between healthcare systems could lead to significant disparities.[53] Macarulla explains that disease awareness may also be having an impact on diagnosis and treatment, and she would like to see more opportunities for patients to participate in clinical trials.

Are We Entering a New Era?

Harding, Vogel, and Macarulla were aligned on their opinion that targeted therapies should be, and will likely be, moved into first-line treatment. "All targeted therapies will likely move into first-line management alone or in combination with systemic therapy," explains Vogel. While targeted agents are currently used primarily in later lines of therapy, there is a growing interest in incorporating them earlier into the treatment pathway, considering even quadruple regimens. Evidence supporting such strategies is ongoing; Macarulla considers it promising. A meta-analysis of trials combining chemotherapy with targeted therapy examined nine RCTs, with overall analysis showing a significant improvement in ORR in patients treated with chemotherapy plus targeted therapy compared to those treated with chemotherapy alone.[54] The HERIZON-BTC-302 (NCT06282575) Phase III study considers zanidatamab with standard-of-care therapy versus standard of care alone, to demonstrate that administering HER2-targeted therapy in combination with first-line can improve overall survival and PFS.[50] The DESTINY-BTC-01 (NCT06467357)[51] Phase III trial considers T-DXd and rilvegostomig versus standard-of-care gemcitabine, cisplatin, and durvalumab in a combination first-line setting in advanced HER2-expressing BTC. Macarulla considers that combining zanidatamab with an immune checkpoint inhibitor may have synergistic antitumour effects in patients with HER2-positive cancers, and, therefore, results from these Phase III studies could represent a new era in BTC clinical management. Macarulla notes that moving targeted therapies into first-line combination treatment would ensure that 100% of patients have the opportunity to receive targeted treatment, as otherwise, patients often deteriorate to the point of not receiving it at all. Considering the context of late-stage, advanced, or metastatic disease with limited treatment options, the experts all acknowledge that this could be an efficacious treatment paradigm.

CONCLUSION

BTC is a rare, aggressive group of malignancies characterised by poor outcomes and a substantial unmet clinical need. The high heterogeneity of disease, both anatomically and molecularly, has long since complicated treatment efficacy and drug development. According to the three key opinion leaders, who are considered experts in the field of BTC management, the last decade has seen advances in systemic therapy, alongside the development of combination immunotherapy and novel targeted therapies. Early and comprehensive molecular profiling facilitates insight into the underlying disease biology, which can be used to optimise treatment sequencing and improve clinical outcomes. HER2 overexpression or amplification of *HER2* are promising therapeutic targets in patients with BTC, particularly in cases of gallbladder cancer and eCCA. HER2-targeted therapies, guided by IHC3+, have demonstrated meaningful clinical activity in a traditionally difficult-to-treat subset of cancer, facilitating a more personalised, therapeutic approach.

Despite such advances and clear clinical guidelines, global disparities in access to molecular testing and targeted treatments remain a challenge, and there is a clear need to intensify first-line strategies to improve outcomes for patients with BTC.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Jazz Pharmaceuticals on +44 8081890387 or via email at AEReporting@jazzpharma.com.

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