Review Article

Targeting ERBB2/HER2 genetic alterations: an expanding therapeutic opportunity in gastrointestinal cancers

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Abstract: *HER2* amplification and/or activating variations of its protein, human epidermal growth factor receptor 2 (HER2), are associated with distinct clinical and pathological features in gastrointestinal tumors, including a worse overall prognosis and a higher incidence of metastatic lesions in the central nervous system. Notably, the role of HER2 as a therapeutic target continues to expand beyond the scope of breast and gastroesophageal tumors, now encompassing colorectal and biliary tract cancers (BTCs), among others. In parallel, there is a burgeoning array of therapeutic agents designed to inhibit the activity of the HER2 pathway, including monoclonal antibodies, orally available tyrosine kinase inhibitors, bispecific antibodies, and antibody-drug conjugate compounds. In this comprehensive review, we will explore the current body of evidence that supports the implementation of HER2-targeting strategies in the treatment of patients with gastric, esophageal, colorectal, and biliary tract tumors. We will also describe testing methods for HER2 status in clinical practice, including immunohistochemistry (IHC), and its correlation with next-generation sequencing-based techniques. Additionally, we will review the key treatment-related adverse events associated with specific anti-HER2 agents, emphasizing the need for early diagnosis and effective management. Furthermore, a critical aspect of this exploration is determining the optimal treatment sequencing among the available therapies, which will be pivotal in enhancing treatment outcomes

Keywords: HER2; gastroesophageal cancer (GEC); colorectal cancer (CRC); biliary tract cancer (BTC); targeted therapy

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Introduction

The *HER2* oncogene encodes the receptor tyrosine-protein kinase ERBB2, also known as human epidermal growth factor receptor 2 (HER2), which belongs to the epidermal growth factor receptor (EGFR) family of receptors. HER2 overexpression, mainly owing to gene amplification, leads to its constitutive activation with subsequent dysregulated cell proliferation, carcinogenesis, and metastasis (1). A myriad of anti-HER2 agents with distinct mechanisms of action is available, including monoclonal antibodies, oral tyrosine kinase inhibitors, antibody-drug conjugates, and bispecific antibodies. Beyond breast and gastroesophageal (GE) tumors, emerging evidence suggested the benefit of anti-HER2 therapy in refractory HER2-positive metastatic colorectal cancer (CRC) and cholangiocarcinoma. Herein, we aim to summarize the clinical implications of HER2-overexpression in gastrointestinal tumors.

Detection methodology

The standard detection method for *HER2* gene amplification consists of immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). These protocols were initially developed for breast cancer and later adapted for other tumors. Although this is a low-cost, fast, and widely available testing platform, it only assesses one single biomarker and requires knowledge and training for the scoring criteria. IHC is first applied to categorize tumor HER2 overexpression into four levels (0 to 3+) based on staining intensity. Although the scoring criteria vary based on primary tumor histology, the consensus is that an IHC of 0 and 1+ are considered negative, 2+ is equivocal, and 3+ represents a positive result. In tumors with an IHC of 2+, a reflex FISH is then performed. In gastric and gastroesophageal tumors, hybridization probes directed towards *HER2* and chromosome 17 enumeration probe (CEP17) are used, and a positive result is obtained if HER2/CEP17 ratio is ≥2 (2). In CRC, the FISH probe set and criteria are similar and a HER2/CEN17 ratio of ≥2.0 is considered positivity (3). Of clinical significance, breast tumors with HER2 IHC1+ or IHC2+/FISH negative have been recently re-designated as HER2-low tumors, given emerging data showing benefits associated with newer antibody drug-conjugates (4). However, this clinicopathological re-categorization has yet to be standardized in gastrointestinal tumors due to lack of clinical data, and a recognition that the IHC assays are not optimized to reproducibly accomplish this categorization.

With the advances in laboratory medicine, next-generation sequencing (NGS) is becoming routine in our practice and allows simultaneous detection for multiple genomic variations. Tissue-based NGS identifies *HER2* amplifications with high concordance with the combined IHC/FISH testing. However, discrepancies may occur in samples with low tumor content and/or intratumor HER2 heterogeneity (5). Liquid biopsy of circulating tumor DNA (ctDNA) represents a promising tool for diagnosing and monitoring of key genomic variations including *HER2* copy number variations. Although it is minimally invasive and highly specific, its performance depends on assay characteristics and the degree of ctDNA shedding from the primary or metastatic lesions (6,7). Using NGS-based tests in conjunction with IHC/FISH, based on specimen availability and clinical context may support effective clinical decision making.

Gastroesophageal cancer (GEC)

GEC encompasses a heterogeneous group of carcinomas with significant variation in epidemiology, histology, and molecular features, including the incidence of HER2 overexpression. Based on the primary location, gastroesophageal junction (GEJ) carcinomas overexpress HER2 in approximately 32% of cases, compared to 21% in primary gastric carcinomas (8-11). At a histological level, amplified HER2 occurs in 23% of intestinal-type gastric cancer, whereas it is a rare finding in diffuse-type gastric tumor samples (0–6%) (12). While overexpressed HER2 is a well-established adverse prognostic factor in breast cancer (13), its prognostic value in GECs remains controversial. In a metanalysis with over 11,000 patients with all stages of gastric cancer, HER2 overexpression was associated with worse 5-year overall survival (OS) of 42% compared to 52% in HER2-negative tumors. However, only one included study used the above interpretive criteria for HER2 IHC/FISH testing for GEC (14). Moreover, retrospective analysis of HER2 status in participants from seven prospective trials (not included in the metanalysis above) disclosed conflicting results: five studies found that HER2 status was not a statistically significant prognostic factor (15-19), one endorsed HER2-overexpression predicted better response and reduced risk for death (20), while another reported its negative predictive value (21).

The clinical activity of anti-HER therapy in GEC was first described in the ToGA trial with patients with untreated HER2-positive advanced gastric or GEJ adenocarcinoma. In this phase 3 study, adding trastuzumab to chemotherapy (cisplatin plus a fluoropyrimidine) was associated with a higher objective response rate (ORR) (47% *vs.* 35%; P=0.0017) and a modest but significant improvement in median OS [13.8 *vs.* 11.1 months; hazard ratio (HR) 0.74, 95% confidence interval (CI): 0.60–0.91, P=0.0046]. In subgroup analyses, trastuzumab yielded better survival in IHC3+ tumors (HR for death 0.66, 95% CI: 0.50–0.87), and was ineffective in IHC0 or 1+ tumors (22). When combined with trastuzumab in the first-line setting, no trials indicated superiority of a specific chemotherapy backbone (*Table 1*). A metanalysis compared the ToGA regimen to other cytotoxic therapies from 15 cohorts with 557 patients. Compared to a cisplatin-containing regimen, the study concluded that oxaliplatin plus a fluoropyrimidine plus trastuzumab was associated with longer median OS (20.7 *vs.* 16 months; pooled HR 0.75, 95% CI: 0.59–0.99,

Table 1 Summary of phase 2 and 3 trials using anti-HER2 therapy in metastatic gastric and/or gastroesophageal cancer

Authors (trial name)	Treatment setting	Tumor histology	Phase	Control arm	Experimental regimen	ORR, experimental arm *vs.* control arm	Median OS, experimental arm *vs.* control arm	Subgroup analysis based on IHC score
Bang *et al.* (ToGA) (22)	First line	Gastric or gastroesophageal adenocarcinoma	3	Cisplatin plus a fluoropyrimidine	Trastuzumab plus control	47% *vs.* 35%	13.8 *vs.* 11.1 months (HR 0.74, 95% CI: 0.60–0.91, P=0.0046)	Post-hoc analysis showed OS benefit only in the IHC2+/FISH+ and IHC3+ groups
Janjigian *et al.* (KEYNOTE-811) (23)	First line	Gastric adenocarcinoma	3	Trastuzumab, and chemotherapy (fluoropyrimidine plus cisplatin or oxaliplatin)	Pembrolizumab plus control	74.4% *vs.* 51.9%	Pending final analysis	Pending final analysis
Makiyama *et al.* (T-ACT) (24)	Second line	Gastric or gastroesophageal adenocarcinoma	2	Paclitaxel	Trastuzumab plus paclitaxel	32% *vs.* 33%	10 *vs.* 10 months (HR 1.2, 95% CI: 0.75–2, P=0.20)	Adding trastuzumab did not improve PFS regardless of IHC group
Satoh *et al.* (TyTAN) (25)	Second line	Gastric adenocarcinoma	3	Paclitaxel	Lapatinib plus paclitaxel	27% *vs.* 9% (OR 3.9, 95% CI: 1.8–8.9, P<0.001)	11 *vs.* 8.9 months (HR 0.84, 95% CI: 0.64–1.11, P=0.1044	In IHC3+ subgroup, adding lapatinib showed lower risk for death (HR 0.59, 95% CI: 0.37–0.93, P=0.0176)
Thuss-Patience *et al.* (GATSBY) (26)	Second line	Gastric adenocarcinoma	2/3	Docetaxel or paclitaxel	Trastuzumab emtansine	20.6% *vs.* 19.6%	8.6 *vs.* 7.9 months (HR 1.15, 95% CI: 0.87–1.51, P=0.86)	IHC3+ status was not associated improved survival
Shitara *et al.* (DESTINY-Gastric01) (27)	After two or more prior therapies	Gastric or gastroesophageal adenocarcinoma	2	Irinotecan or paclitaxel	Fam-trastuzumab deruxtecan	51% *vs.* 14%	12.5 *vs.* 8.4 months (HR 0.59, 95% CI: 0.39–0.88, P=0.01)	Only IHC3+ group had significantly improved ORR and median OS

ORR, objective response rate; OS, overall survival; IHC, immunohistochemistry; HR, hazard ratio; CI, confidence interval; FISH, fluorescence in situ hybridization; PFS, progression-free survival; OR, odds ratio.

P<0.05) and better treatment tolerability. Furthermore, this metanalysis did not observe additive benefits with a triple cytotoxic backbone or when trastuzumab is combined with bevacizumab plus a doublet regimen (28).

The first interim analysis of the phase 3 KEYNOTE-811 trial endorsed adding pembrolizumab, an anti-programmed death 1 (PD-1) antibody, to first line trastuzumab-containing regimen. In 264 patients with HER2-positive advanced gastric or GEJ adenocarcinoma, pembrolizumab was significantly associated with higher ORR (74%, 95% CI: 66–82% *vs.* 52%, 95% CI: 43–61%), higher complete response rate (11% *vs.* 3%), and higher ongoing response rate beyond six-months (70% *vs.* 61%) (23). Subgroup analysis revealed improvement of ORR was likely limited to tumors with a programmed cell death ligand 1 (PD-L1) combined positive score (CPS) ≥1 and those with IHC3+. The safety profile of combined pembrolizumab to trastuzumab and chemotherapy was manageable. Final analyses are pending and will inform the survival benefit of this combined therapy based on tumor PD-L1 expression.

Beyond first-line setting, therapy selection and sequencing are poorly defined in HER2-overexpressed GEC. In the phase 2 T-ACT trial with recurrent HER2-positive GE adenocarcinoma, continuing trastuzumab plus paclitaxel beyond progression failed to show benefit compared to paclitaxel alone (median OS in both arms were 10 months; HR 1.2, 95% CI: 0.75–2, P=0.20). Notably, 16 participants had available tissues after progression for HER2 status reassessment. Eleven (69%) showed loss of HER2 overexpression in the tumor, despite four of them had positive *HER2* amplification in ctDNA (24). Lapatinib is an orally available inhibitor of EGFR and HER2. In the TyTAN trial with recurrent gastric cancer, adding lapatinib to paclitaxel failed to improve progression-free survival (PFS) or OS. However, in the IHC3+ subgroup, lapatinib was associated with a significantly lower risk for death (HR 0.59, 95% CI: 0.37–0.93, P=0.0176) (25). In the phase 2/3 GATSBY trial, patients with advanced HER2-positive gastric cancer were randomized to the physician's choice of chemotherapy or trastuzumab emtansine (T-DM1), an antibody-drug conjugate of trastuzumab linked to a microtubule inhibitor. The study observed no difference in median OS, which were respectively 8.6 and 7.9 months (HR 1.15, 95% CI: 0.87–1.51, one-sided P=0.86) (26).

Fam-trastuzumab deruxtecan (T-DXd), a newer antibody-drug conjugate with an anti-HER antibody attached to a topoisomerase I inhibitor through a cleavable tetrapeptide-based linker, showed positive results in phase 2 DESTINY-Gastric01 trial. This randomized study enrolled 187 patients whose HER2-positive gastric cancer had progressed on two prior therapies including trastuzumab. Compared to the clinician's choice of chemotherapy, T-DXd demonstrated higher ORR (51% *vs.* 14%), and longer median OS (12.5 *vs.* 8.4 months; HR 0.59, 95% CI: 0.39–0.88, P=0.01). Subgroup analysis showed significant benefit was associated with the IHC3+ group and less likely with the IHC2+/FISH+ group. Notably, 10% of participants developed interstitial lung disease (ILD), which is a well-described adverse event more frequently associated with T-DXd than T-DM1 (27). In a recent systematic review of 14 studies with different types of advanced tumors treated with T-DXd, the overall incidence of ILD was 11.4%. Albeit most of these cases (78.7%) were grade 1 or 2 events, death was reported in 10.7% of all patients with ILDs (29). Therefore, careful monitoring with prompt treatment discontinuation and early steroid initiation are warranted with patients receiving T-DXd with respiratory symptoms.

Additional anti-HER2 agents are under examination. Zanidatamab, an anti-HER2 bispecific antibody, was safe when combined with chemotherapy in a phase 1 multicohort study with HER2-positive advanced tumors (30). In the subgroup with previously treated GE adenocarcinoma, zanidatamab alone and with chemotherapy achieved an ORR of 38% and 60%, respectively (31). A subsequent phase 2 study with first-line zanidatamab plus chemotherapy showed a promising 12-month survival rate of 88% (95% CI: 73–95%) and ORR of 79% (95% CI: 63–90%) in patients with HER2-positive metastatic GE adenocarcinoma (32). The ongoing phase 3 HERIZON-GEA-01 study (NCT05152147) with zanidatamab with chemotherapy with and without tislelizumab will further examine the efficacy and safety of this regimen (33). Disitamab vedotin is an antibody-drug conjugate that showed activity in heavily treated HER2-positive gastric cancer and received conditional approval in China as second-line therapy in these patients (34). The phase 3 RC48-C007 will further elucidate its clinical activity (NCT04714190).

CRC

HER2 overexpression occurs in 3–5% of CRC, with a predominance in *RAS* wild type left-sided and rectal tumors (35,36). As with breast and GE tumors, HER2-positive CRC has the propensity to metastasize to the central nervous system (37). At a molecular level, HER2-

positive CRC tumors often show microsatellite stability and enrichment of *BRAF* and *PIK3CA* mutations (38) and have been associated with poor response to anti-EGFR therapies (39,40). Notably, discordance in HER2 overexpression between the primary CRC tumor and metastatic lesions may be detected in up to 15% of cases (41).

As opposed to GEC where anti-HER2 therapy is integrated to the first-line therapy, chemotherapy alone remains the choice in HER2-overexpressing metastatic CRC. Various regimens with dual HER2 blockade agents have demonstrated activity in the relapsed setting. The MyPathway trial examined the activity of trastuzumab plus pertuzumab. In the CRC-specific cohort, the ORR was 40% in *KRAS* wild-type tumors compared to 8% in *KRAS*-mutant CRC, which indicated an underlying predictive association (42). In the TAPUR study, another basket trial with 28 patients with heavily pretreated metastatic CRC, trastuzumab plus pertuzumab showed a lower ORR of 14%, which was likely due to enrollment of patients with concomitant *KRAS* mutations (43). *Table 2* contains a key summary of clinical trials using anti-HER2 therapy in metastatic CRC.

In the open-label phase 2 HERACLES-A trial, trastuzumab plus lapatinib attained an objective response in 8 (30%) of 27 patients, which included one complete response (37,44). Respective median PFS and OS were 21 and 46 weeks. Grade 3 toxicity occurred in 6 (22%) participants and consisted of fatigue, skin rash, and hyperbilirubinemia.

Similarly, the phase II MOUNTAINEER trial examined tucatinib alone or combined with trastuzumab in patients with *HER2*-amplified and *RAS* wild-type metastatic CRC. The doublet regimen showed an ORR of 38.1%, while tucatinib arm had an ORR of 3.3%. In this latter group, 28 patients were allowed to cross over to tucatinib plus trastuzumab, which was associated with an improved ORR of 17.9%. The most common adverse events were diarrhea (64%), fatigue (44.2%), and nausea (34.9%) (45,46). A recent update of this trial included a retrospective central assessment of tumor HER2 status and found an inter-test agreement of 92.6% between IHC/FISH and tissue-based NGS, which was higher than 81% between blood NGS and tissue, and 79.5% between IHC/FISH and blood NGS testing. When stratified by HER2 positivity, IHC3+ group had the highest confirmed ORRs ranging 41.1% to 46.7% depending on the testing platform. The ORR in the IHC2+/FISH+ group (N=15) was lower at 20% (49). The phase 3 MOUNTAINEER-03 trial is underway and will compare standard chemotherapy with and without tucatinib plus trastuzumab in previously untreated HER2-positive metastatic CRC (NCT05253651) (50).

The phase 2 dose-finding, single-arm DESTINY-CRC01 trial showed the benefit of T-DXd in 78 patients with HER2-expressing *RAS* wild-type metastatic CRC (47). Patients were stratified based on an IHC of 3+ or 2+/FISH positive (cohort A), IHC2+/FISH negative (cohort B), or IHC1+ (cohort C). There were no responses in cohorts B or C. Cohort A yielded an overall ORR of 45.3%, and subgroup analysis showed various highlights. First, IHC3+ status was associated with the highest ORR of 57.5%, while IHC2+/FISH positive status had a low ORR of 7.7%. Secondly, the efficacy of T-DXd was similar in patients with and without prior HER2-targeted therapy (respective ORRs were 43.8% and 45.9%). This finding may justify reserving T-DXd upon disease progression after prior anti-HER2 therapy. Notably, the DESTINY-CRC01 trial also reported severe treatment-related adverse events occurring in 61% of patients, including myelosuppression and gastrointestinal toxicity. Eight (9%) patients had T-DXd-induced ILD and three passed away.

The primary results of multicenter phase 2 DESTINY-CRC02 trial (NCT04744831) also reported antitumor response of T-DXd in 122 heavily pre-treated patients with HER2-overexpressing metastatic CRC. Patients received T-DXd at 5.4 and 6.4 mg/kg dosages, which were associated with similar median PFS of 5.8 (95% CI: 4.6–7) and 5.5 (95% CI: 4.2–7) months, respectively. ORR was higher in HER2 IHC3+ group (46.9% at 5.4 mg/kg group, and 29.4% with 6.4 mg/kg group) compared to IHC2+/FISH+ group (5.6% and 16.7%, respectively) (48). ORRs were similar between patients who had received prior anti-HER2 therapy (40%) compared to those who did not (41.2%). Noteworthy, the incidence of ILD was 12.8% in the 6.4 mg/kg group and 8.4% in the 5.4 mg/kg group, which favored the use of the lower dosage regimen for clinical use.

The zanidatamab trial mentioned above also included patients with HER2-positive metastatic CRC and biliary tract cancer (BTC). An antitumor response was observed in 10 of 32 patients with CRC (ORR 38%, 95% CI: 20–59%) and 8 of 22 participants with cholangiocarcinoma (ORR 38%, 95% CI: 18–62%) (30).

BTC

Approximately 18–20% of BTC, particularly those of extrahepatic localization, harbor *HER2* amplification or

Table 2 Summary of relevant clinical trials using anti-HER2 therapy in metastatic colorectal cancer

Authors (trial name)	Treatment setting	Phase	Control arm	Experimental regimen	ORR, experimental arm (*vs.* control arm if applicable)	Median OS, experimental arm (*vs.* control arm if applicable)	Subgroup analysis based on IHC score
Meric-Bernstam *et al.* (MyPathway) (42)	Refractory to standard of care	2	NA	Trastuzumab plus pertuzumab	26.2%	Not reported	Not reported
Gupta *et al.* (TAPUR) (43)	Refractory to standard of care	2	NA	Trastuzumab plus pertuzumab	25%	60 weeks	Not reported
Sartore-Bianchi *et al.* (HERACLES-A) (44)	Refractory to standard of care	2	NA	Trastuzumab plus lapatinib	30%	46 weeks	Not reported
Strickler*et al.* (MOUNTAINEER) (45,46)	Refractory to standard of care	2	NA	Tucatinib with or without trastuzumab	Doublet arm: 38.1% Tucatinib alone: 3.3% Tucatinib cross-over to doublet arm: 17.9%	Not reported	Not reported
Siena *et al.* (DESTINY-CRC01) (47)	Two or more previous regimens, including prior HER2-targeted therapy	2	NA	Fam-trastuzumab deruxtecan	Cohort A (IHC3+ and 2+/FISH positive): 45.3%	Cohort A: 5.4 months	ORR in the IHC3+ group: 57.5% ORR in IHC2 +/FISH positive group: 7.7%
Raghav *et al.* (DESTINY-CRC02) (48)	Three or more previous regimens, including prior HER2-targeted therapy	2	NA	Fam-trastuzumab deruxtecan	5.4 mg/kg T-DXd group: 37.8% 6.4 mg/kg T-DXd group: 27.5%	NA	IHC3+ group that received 5.4 mg/kg T-DXd: 46.9% IHC2+/FISH+ group that received 5.4 mg/kg T-DXd: 5.6% IHC3+ group that received 6.4 mg/kg T-DXd: 29.4% IHC2+/FISH+ group that received 6.4 mg/kg T-DXd: 16.7%

ORR, objective response rate; OS, overall survival; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; T-DXd, trastuzumab deruxtecan; NA, not applicable.

HER2 overexpression (51-53). Amplified *HER2* correlated with lower tumor histology grade and a poorer prognosis in patients with nodal metastasis (53,54).

Although limited, emerging evidence suggests the benefit of anti-HER2 therapy in treating locally advanced or metastatic HER2-overexpressing BTC (*Table 3*). The results from the open-label phase 2 SUMMIT trial included 25 patients with refractory BTC treated with neratinib monotherapy. The overall ORR was 16%, and median PFS and OS were 2.8 and 5.4 months, respectively. When analyzed by primary tumor location, ten patients with gallbladder cancer had a better outcome, their median PFS and median OS were respectively 3.7 and 9.8 months (55). The TreeTopp examined combinations of capecitabine plus varlitinib or placebo in second-line settings. Adding varlitinib did not improve ORR (9.4% with varlitinib

Table 3 Summary of relevant clinical trials using anti-HER2 therapy in metastatic biliary tract cancer

Authors (trial name)	Treatment setting	Phase	Control arm	Experimental regimen	ORR, experimental arm (*vs.* control arm if applicable)	Median OS, experimental arm (*vs.* control arm if applicable)
Harding *et al.* (SUMMIT) (55)	Previously treated	2	NA	Neratinib	16%	5.4 months (9.8 months in gallbladder cancer)
Javle *et al.* (TreeTopp) (56)	Second line	2	Capecitabine	Capecitabine plus varlitinib	9.4% *vs.* 4.8%	7.8 *vs.* 7.5 months (HR 1.11, 95% CI: 0.69–1.79, P=0.66
Javle *et al.* (MyPathway) (57)	Previously treated	2	NA	Pertuzumab plus trastuzumab	23%	10.9 months
Ohba *et al.* (HERB) (58)	Refractory or intolerant to gemcitabine	2	NA	Fam-trastuzumab deruxtecan	HER2-positive cohort: 36.4%	HER2-positive cohort: 7.1 months
					HER2-low: 12.5%	HER2-low: 8.9 months
Nakamura *et al.* (SGNTUC-019) (59)	Previously treated	2	NA	Tucatinib plus trastuzumab	IHC2+/3+ group: 46.7%	12-months OS rate was 53.8%
Pant *et al.* (HERIZON-BTC-01) (60)	Previously treated	2	NA	Zanidatamab	IHC2+/3+ group: 41%	NA
					IHC0/1+: 0%	

ORR, objective response rate; OS, overall survival; HR, hazard ratio; CI, confidence interval; IHC, immunohistochemistry; NA, not applicable.

vs. 4.8% with placebo, P=0.42) or median OS (7.8 *vs.* 7.5 months; HR 1.11, 95% CI: 0.69–1.79, P=0.66) (56).

Targeting HER2 by combination therapies was also studied in this disease group. The MyPathway multiple basket study included a cohort of HER2-positive metastatic biliary tract tumors. Among 39 patients treated with pertuzumab plus trastuzumab, nine (23%) attained an antitumor response with a median duration of response of 10.8 months (57).

In another single-arm phase 2 HERB trial with advanced cholangiocarcinoma, T-DXd was administered to 24 participants with HER2-positive tumors and eight with HER2-low disease. In the HER2-positive cohort, ORR was 36.4%, while median PFS and OS were 4.4 and 7.1 months, respectively. Importantly, the HER2-low cohort achieved an ORR of 12.5% and median OS of 8.9 months (58).

In SGNTUC-019, a phase 2 basket study, 30 previously treated patients with BTC received tucatinib plus trastuzumab. The doublet was associated with an ORR of 46.7% which included one complete response and 13 partial responses. Median PFS was 5.5 (90% CI: 3.9–8.1) months and 12-month OS rate was 53.8% (90% CI: 35.2–69.1%). Common side effects included pyrexia (43.3%) and diarrhea (40%) (59).

In the phase 2b HERIZON-BTC-01 study, zanidatamab was administered to patients whose BTC had progressed on prior lines of treatment. In the HER2 IHC2+/3+ group, ORR was 41% with median DOR of 12.9 month. ORR was 0% in HER IHC0/1+ group. PFS and OS data are underway (60).

Trastuzumab plus modified FOLFOX is being explored in the second line setting for advanced and metastatic HER2-positive BTC (NCT04722133). Trials with newer antibody-drug conjugates are also underway (NCT04837508, NCT04450732).

Conclusions and future perspectives

HER2 is an effective actionable therapeutic target in patients with various advanced gastrointestinal tumors. Parallel to mounting evidence indicating activity of various anti-HER2 agents, many remaining questions warrant further investigation. It will be essential to determine the treatment sequence of available therapies. Additionally, mitigation strategies for treatment resistance (such as tumoral loss of HER2 expression and acquired activation of PI3K pathway) will be key to achieving a durable therapeutic response or better salvage options. Finally, generalized awareness regarding early diagnosis and management of treatment-related adverse events will be key

to allow safe and effective administration of the different agents in clinical use.

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Footnote

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