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Anti-tumour Treatment

HER-2 directed therapies across gastrointestinal tract cancers – A new frontier

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ABSTRACT

Gastrointestinal (GI) cancers are common and in the metastatic setting they have a poor prognosis. The current mainstay of treatment of GI cancers is chemotherapy; however, the biomarker-directed treatment landscape is evolving. HER-2 is overexpressed in a portion of GI cancers and is an emerging target for therapy, with recent FDA tumor agnostic approval for trastuzumab deruxtecan. Testing for HER-2 expression is not standardized across GI cancers, methodology requires further optimization and standardization as HER-2 targeted therapy emerges into the treatment landscape. There is established rationale for use of HER-2 targeted therapy in first line treatment of metastatic gastric cancer, and emerging evidence with variable benefit in bile duct, pancreatic and colorectal cancers.

Background

Gastrointestinal (GI) cancers including esophageal, gastric, bile duct, pancreatic, colorectal, and anal cancers accounted for 5.1 million new diagnoses, and 3.6 million cancer-related deaths worldwide in 2020 [1].

Cytotoxic chemotherapy, in the neoadjuvant, adjuvant and palliative disease stages has been the mainstay of systemic treatment of GI cancers. Recent advances in several GI cancer treatments, apart from microsatellite-stable colorectal cancer and pancreatic cancer, have led to the use of immunotherapy to stimulate the innate immune system to target cancer cells [2]. Precision Medicine approaches have also advanced the treatment of GI cancers with targeted therapies for genotypically-defined sub-groups of patients, one of the most topical being human epidermal growth factor receptor 2 (HER-2). This is increasingly being viewed as a tumour agnostic target.

HER-2 is a receptor tyrosine kinase (RTK) transmembrane protein encoded by the HER-2 oncogene on chromosome 17. HER-2 belongs to a group of four proteins, the others including HER-1 (also known as epidermal growth factor receptor (EFGR)), HER-3 and HER-4. HER-2 is activated by either homodimerization or heterodimerization with HER3. Once activated, it initiates a cascade of intracellular signaling that promotes oncogenesis [3].

The expression of HER-2 is assessed initially with immunohistochemistry (IHC), then reported as a score from 0-3 +.

Possible results include not amplified (IHC 0), HER-2 low (IHC 1 +), HER-2 indeterminate (IHC 2 +), HER-2 positive (IHC 3 +) [4]. Low and indeterminate HER-2 on IHC requires further assessment of HER-2 gene amplification with in-situ hybridization (ISH) which can be performed using fluorescence in situ hybridization (FISH), dual in situ hybridization (DISH), chromogenic in situ hybridization (CISH) or silver in situ hybridization (SISH). Next generation sequencing using tissue samples and liquid biopsy to detect cell free DNA, has also been incorporated into the diagnostic pathway for assessing HER-2 amplification in ongoing studies [5]. There is no universal scoring system across all cancers, including GI cancers, for HER-2 due to variable expression of HER-2 in different primary cancers [4,6].

Since the discovery of HER-2 and its overexpression in patients with breast cancer in 1984 there has been investigation into its role in cancer pathogenesis and prognosis [7–10]. Reports on the prognostic impact of HER-2 amplification or overexpression show conflicting evidence with a trend toward poor prognosis across all GI tumour types, this may be related to intratumoral heterogeneity, discrepancy in testing method across studies and small sample sizes due to relative rarity of HER-2 alterations among GI cancers [11–19]. The first HER-2 targeted therapy, trastuzumab – a monoclonal antibody (MAb), when used as monotherapy was found to achieve durable response in patients with metastatic HER-2 positive breast cancer [20]. Trastuzumab was subsequently introduced as standard of care into earlier lines of treatment of HER-2 positive breast cancer, in combination with chemotherapy, in the first line metastatic, adjuvant and neoadjuvant settings [21–23]. Across

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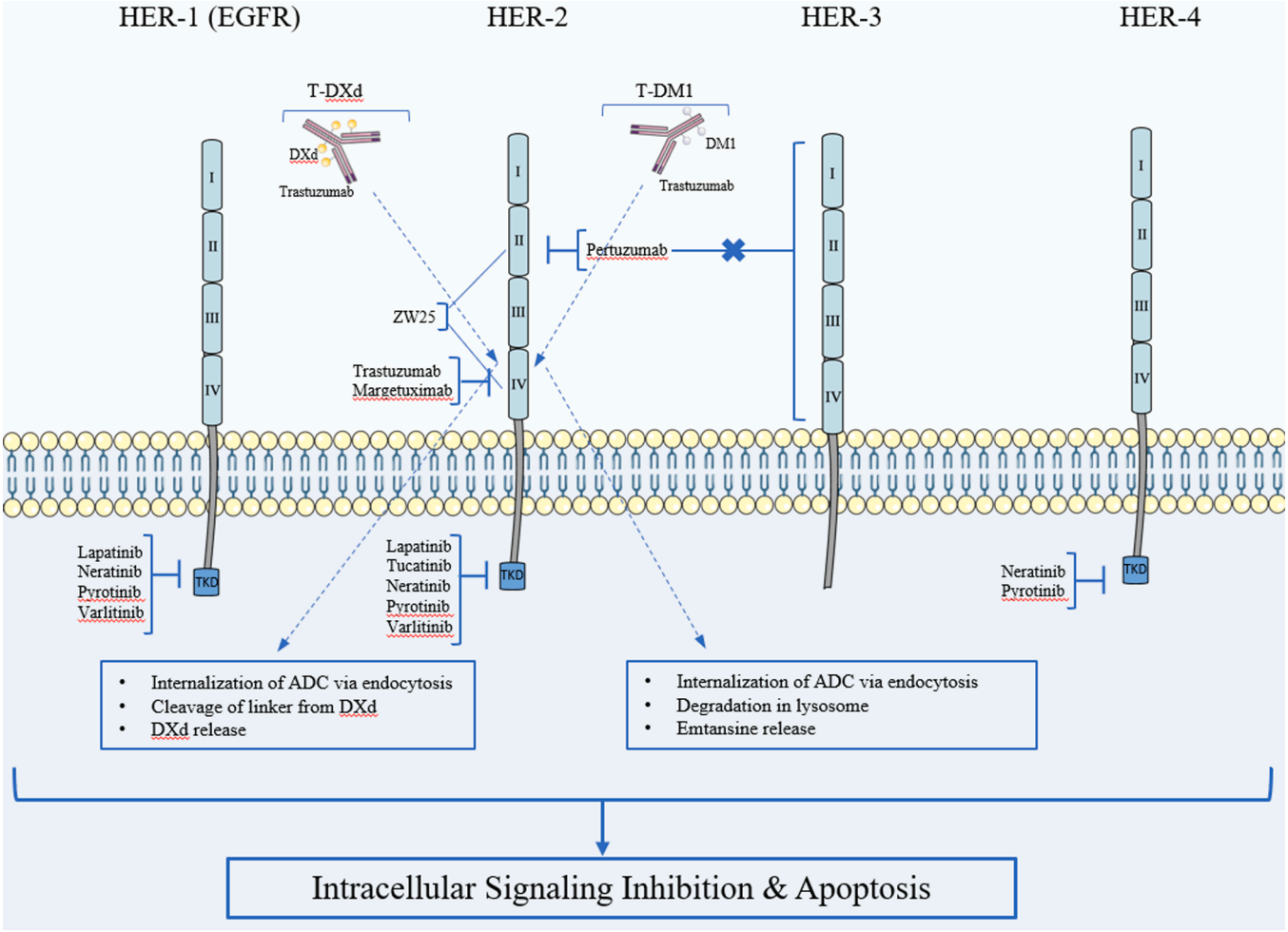

Fig. 1. Site of action of HER directed therapies Abbreviations: HER – human epidermal growth factor receptor; EGFR – epidermal growth factor receptor; ADC – antibody-drug conjugate; T-DXd – trastuzumab deruxtecan; DXd – deruxtecan; T-DM1 – trastuzumab emtansine; DM1 – emtansine; TKD – tyrosine kinase domain; ZW25 – zanidatamab This Figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license [134].

all solid tumours, breast has been an exemplar for development of additional HER-2 targeted therapies including tyrosine kinase inhibitors (TKI), antibody-drug conjugates (ADC) and bispecific antibodies which have also become standard of care in the treatment of advanced breast cancer with HER-2 overexpression [24]. In 2010 the ToGa trial demonstrated improved overall survival (OS) in patients with metastatic gastroesophageal cancer with the addition of trastuzumab to first-line chemotherapy, introducing the first HER-2 directed therapy as standard of care in a GI cancer [25].

Given such a favorable response to HER-2 targeted therapies in breast and gastric cancer, HER-2 has been investigated as a target for treatment in many other cancers including hepatobiliary, pancreatic, colorectal, lung and genitourinary cancers and as a tumour agnostic target across solid cancers in general [26]. Overexpression and/or amplification of HER-2 is widely variable across the different types of GI cancers and is a target of interest for potential treatment strategies. This article will review HER-2 directed therapy for GI cancers.

HER-2 directed therapy

Current drug classes that target HER-2 include monoclonal antibodies (MAb), tyrosine kinase inhibitors (TKI), antibody-drug conjugates (ADC) and bispecific antibodies (Fig. 1). HER-2 can be targeted intracellularly by TKIs and extracellularly by MAbs, ADCs and bispecific antibodies.

Tyrosine kinase inhibitors

TKIs are small molecule oral agents that bind to the intracellular tyrosine kinase domain (TKD) of receptor tyrosine kinase (RTK) proteins, blocking the ATP binding site and thereby preventing activation. In cancer cells with overexpression of RTKs there is increased signalling for replication of abnormal cells [27]. RTK proteins require binding of ATP to promote intracellular signalling and cell proliferation, by blocking this site the cell signalling is diminished thus halting the replication of cancer cells [27,28]. TKDs are present on the HER-1, HER-2, and HER-4 proteins. HER-2 targeting TKIs include tucatinib, which targets HER-2 specifically, lapatinib and varlitinib which target HER-1, HER-2 and HER-4, and neratinib and pyrotinib which target HER-1 and HER-2 [29–33].

Monoclonal antibodies

MAbs are targeted therapies that impair intracellular signalling by binding to an antigen expressed by cancer cells and engaging the innate immune system to kill those cancer cells [34]. Trastuzumab was the first humanized MAb proven to be effective in treating HER-2 positive cancers [35,36]. It binds to HER-2 extracellularly and inhibits downstream

Table 1
Current evidence for HER-2 directed therapy in gastroesophageal cancer.

Line of therapy	Trial	Year	Phase	Therapy	n	Primary Endpoint	Result
Neoadjuvant	INNOVATION [83]	2023	II	Perioperative chemotherapy (CT)+/- trastuzumab (T) or trastuzumab + pertuzumab (P)	161	Major pathological response rate	MpRR 23.3 % (CT) vs 37.0 % (CT + T) vs 26.4 % (CT + T + P)
	NRG Oncology/ RTOG-1010 [78]	2022	III	Trastuzumab +/- paclitaxel + carboplatin + radiation	606	DFS	19.6 months (95 % CI 13.5–26.2) vs 14.2 months (95 % CI 10.5–23.0), p = 0.97
	TRAP [79]	2020	II	Trastuzumab + pertuzumab + carboplatin + paclitaxel + radiation	40	Feasibility	83 % completed treatment
	ST03 [80]	2019	II	Epirubicin + cisplatin + capecitabine +/- lapatinib	46	Safety (Grade 3–4 diarrhea)	21 % vs 0 %
Perioperative	PETRARCA [82]	2022	II	Trastuzumab + pertuzumab + FLOT vs FLOT	81	pCR	12 % vs 35 % p = 0.02
	HER-FLOT [81]	2021	II	Trastuzumab + FLOT	56	pCR	21.4 % (95 % CI 11.6–34.4)
First Line, Metastatic	HERIZON-GEA-01 [72]	2023	II	Zanidatamab + chemotherapy (FOLFOX, CAPOX or 5-FU + cisplatin)	46	ORR	79 % (95 % CI 63–90)
	INTEGA [71]	2022	II	Trastuzumab + nivolumab + FOLFOX vs. trastuzumab + nivolumab + ipilimumab	88	12-month OS	70 % (95 % CI 54–81) FOLFOX vs 57 % (95 % CI 41–71) ipilimumab
	KEYNOTE 811 [69]	2023	III	Trastuzumab, chemotherapy +/- Pembrolizumab	698	PFS and OS	PFS 10.0 months (95 % CI 8.6–11.7) vs 8.1 months (95 % CI 7.0–8.5), HR 0.72, p = 0.0002 OS pending final analysis
	JACOB [66]	2018	III	Trastuzumab + capecitabine or 5-FU + cisplatin +/− pertuzumab	780	OS	17.5 vs. 14.2 months (HR 0.84, 95 % CI 0.71–1.00, $p = 0.057$)
	HELOISE [65]	2017	IIIb	Cisplatin, capecitabine + trastuzumab (8 mg/kg IV day 1 then 6 mg/kg q3weeks) OR trastuzumab (8 mg/kg then 10 mg/kg q3weeks)	248	OS	12.5 vs. 10.6 months (HR 1.24, 95 % CI 0.86–1.78, $p = 0.2401$]
	TRIO-013/LOGiC [86]	2016	III	Capecitabine, oxaliplatin +/− lapatinib	545	OS	12.2 vs. 10.5 months (HR 0.91, 95 % CI 0.73–1.12, $p = 0.32$)
	ToGA [25]	2010	III	Capecitabine or 5-FU, cisplatin +/− trastuzumab	594	OS	13.8 vs. 11.1 months (HR 0.74, 95 % CI 0.60–0.91, $p = 0.0046$)
Later line, Metastatic	DESTINY-Gastric02 [77]	2022	II	Trastuzumab deruxtecan	79	ORR	ORR of 38 % (95 % CI, 27.3–49.6)
	CP-MGAH22-05 [84]	2020	Ib/II	Margetuximab + pembrolizumab	95	ORR	18.5 % (95 % CI 11.15–27.93)
	T-ACT [88]	2020	II	Paclitaxel +/− trastuzumab	91	PFS	3.2 vs. 3.7 months (HR 0.91, 80 % CI 0.67–1.22, $p = 0.33$)
	GATSBY [74]	2017	II/III	Trastuzumab emtansine vs. taxane	302	OS	7.9 vs. 8.6 months (HR 1.15, 95 % CI 0.87–1.51, $p = 0.86$)
	TyTan [87]	2014	III	Paclitaxel +/− lapatinib	261	OS	11.0 vs. 8.9 months (HR 0.84, 95 % CI 0.64–1.11, $p = 0.10$)
	DESTINY-Gastric01 [75]	2020	II	Trastuzumab deruxtecan vs. physician's choice chemotherapy (irinotecan or paclitaxel)	187	ORR	51 % (95 % CI 42–61) vs. 14 % (95 % CI 6–26), p < 0.001
	SUMMIT [85]	2018	II	Neratinib	5 (GE)	8-week ORR	0 % (95 % CI 0–52.2)

Abbreviations: DFS – disease free survival, OS – overall survival, ORR – objective response rate, PFS – progression free survival, pCR – pathologic complete response, FLOT – fluorouracil, leucovorin, oxaliplatin, docetaxel, 5-FU – 5-fluorouracil, CI – confidence interval, HR – hazard ratio.

cell signalling of the TKD thereby halting progression and development of further cancer cells that have overexpression of HER-2. It is also thought to inhibit dimerization and cause endocytosis of the HER-2 receptor and impact the immune response of antibody-dependent cell-mediated cytotoxicity (ADCC) [37,38]. Pertuzumab, a humanized MAb, binds to the extracellular domain of HER-2 at a site that inhibits dimerization of HER-2 and HER-3 which is a required mechanism for cell signalling [39]. When given together in patients with breast cancer trastuzumab and pertuzumab demonstrate synergistic activity [40]. Margetuximab is a chimeric MAb, it binds to HER-2 to inhibit downstream cell signalling in a similar mechanism as trastuzumab, it has altered Fc region properties which increase binding to the activating Fc receptor on natural killer cells promoting an increased immune response via ADCC [41,42]. Further progression in MAb development includes the subcutaneous formulation of trastuzumab and pertuzumab that has been proven non-inferior to intravenous trastuzumab in breast cancer, leading to FDA and EMA approval [43,44]. There is no current approval for subcutaneous trastuzumab in GI cancers, but this represents a potential next step in delivering HER-2 targeted therapy.

Antibody-drug conjugates

ADCs are complex therapies that link MAbs to a cytotoxic chemotherapy payload to deliver chemotherapy directly to targeted cancer cells while potentially reducing systemic chemotherapy-related toxicity. Trastuzumab emtansine (T-DM1) combines a MAb (trastuzumab) with an anti-microtubule chemotherapy (emtansine/DM1), these drugs are connected by a stable linker that is degraded in the lysosome after internalization [45,46]. After cleavage from the linker, DM1 is released intracellularly where it inhibits proliferation of cancer cells by disrupting microtubule formation in mitosis, with a greater effect than trastuzumab monotherapy [46,47]. Trastuzumab deruxtecan (T-DXd) combines a MAb (trastuzumab) with a topoisomerase I inhibitor (deruxtecan) via an enzyme linker that is cleaved intracellularly. Upon cleavage cytotoxic chemotherapy is released directly into the cell resulting in DNA damage via double-stranded breaks and ultimately apoptosis of the targeted HER-2 over-expressing cancer cell and trastuzumab exerts effect via ADCC [48,49]. Linker technology is crucial in ADC development, the linker must remain stable in the blood to ensure that toxic drug is not released before delivery to the target cancer cell thereby limiting efficacy and increasing risk of off-target toxicity; cleavability is important to consider as cleavable linkers may be less

stable but have the benefit of ADCC and drug diffusion to nearby cancer cells that may not express the target receptors, non-cleavable linkers have a more narrow targeted effect but may remain more stable in the blood [50]. ADCs represent an exciting treatment option across many cancer types and are an important area of ongoing research and drug development, future directions are exploring ADCs that use bispecific antibodies, dual-payloads, immune-stimulating payloads and radionucleotides [51].

As ADCs become more commonly used agents with more antibody tares and different payloads, it is crucial to acknowledge a different side effect profile compared to traditionally used cytotoxic chemotherapy. For example, T-DXd has emerged as a promising HER-2 targeted therapy across many GI and non-GI cancers. It has unique, potentially severe or fatal side effects that require vigilant monitoring including pneumonitis and cardiotoxicity which occurred in 10.9 % and 1.2 % of patients, respectively, in a *meta*-analysis of 8 clinical trials [52]. Early detection and investigation of suspected pneumonitis following new respiratory symptoms including cough, exertional dyspnea or changes noted on surveillance CT scans requires urgent investigation which may include high resolution CT, pulse oximetry, pulmonary function testing. Management of grade ≥ 1 pneumonitis requires interruption of T-DXd until complete resolution to grade 0 along with consideration of use of corticosteroids and consultation with a respiratory specialist, which is earlier than typical intervention for grade 1 toxicity from standard chemotherapy drugs. Grade 1 pneumonitis persisting beyond 49 days of last infusion or grade ≥ 2 mandates permanent discontinuation of T-DXd [53].

Bispecific antibody

Zanidatamab (ZW25) is a bispecific antibody which binds to HER-2 on the second and fourth extracellular domains, in *trans*, resulting in crosslinking and formation of HER-2 clusters which trigger cellular-dependent cytotoxicity. There is increased antibody binding and HER-2 receptor internalization when compared to MAbs, trastuzumab and pertuzumab, when given separately and in combination, and activation of innate complement-dependent cytotoxicity to inhibit intracellular signalling and growth of cancer cells [54–56].The unique binding of ZW25 represents a novel mechanism further contributing to the diversity of available targeted therapies in the HER-2 space with potential for even greater clinical efficacy compared to previously developed therapies. Looking ahead it may represent an option for further studies investigating use of ZW25 as first- or later-line targeted therapy in sequential HER-2 targeted treatment.

HER-2 directed therapy by primary tumor type

Gastroesophageal cancer

In GI cancers, HER-2 targeted approaches were first trialled in gastric and gastroesophageal (GE) cancer, there is relatively high level of HER-2 overexpression, approximately 22.1 %, when assessed using a scoring system that has been validated in GE cancers [57]. The relationship of HER-2 overexpression and response to targeted therapy with trastuzumab has been prospectively investigated and found to be predictive of response in metastatic gastric cancer. Gomez-Martin et al found that patients with HER2/CEP17 ratio greater than 4.7 were more sensitive to therapy [58]. The VARIANZ study noted significant discrepancies between local and central HER-2 scoring, when assessing centrally confirmed HER-2 positive patients they found that HER-2 expression level was predictive of response, patients with HER2/CEP17 ratio greater than 3.0 or more than 40 % HER-2 positive cells had improved OS [59]. Gastric cancer has been found to have significant intratumoral heterogeneity when tested for HER-2 overexpression and amplification [13]. A modified scoring system was created, and validated, for use in gastric cancers which accounts for discrepancies in HER-2 assessment using tools that were initially developed for breast cancer, in gastric cancer HER-2 expression is more heterogeneous, and basolateral membrane staining is less complete when compared to breast cancer [60]. First-line HER-2 directed therapy is approved for patients with metastatic GE and gastric cancer and is undergoing further assessment in both the neoadjuvant and perioperative settings (Table 1). Current ESMO and NCCN guidelines recommend testing HER-2 status with initial molecular tests for workup of all gastric and GE cancers [61–64].

MAbs have been introduced into treatment regimens for patients with metastatic GE cancers as standard of care in the first line setting. The ToGA phase 3 trial was the first to support the use of HER-2 directed therapy in a GI cancer after demonstrating a 13.8-month OS in patients with gastric and GE cancer treated with chemotherapy (5-fluorouracil (5-FU) or capecitabine plus cisplatin) and trastuzumab compared to 11.1 month OS in patients treated with chemotherapy alone, $p = 0.0046$; A pre-planned exploratory analysis of HER-2 high patients (HER-2 IHC 3 + and IHC 2 + with FISH +) demonstrated median OS 16.0 vs 11.8 months, HR 0.65 (95 % CI 0.51–0.83), $p = 0.036$ when compared to HER-2 negative and low [25]. The HELOISE trial assessed trastuzumab standard dosing (8 mg/kg IV day 1 then 6 mg/kg q3weeks) in comparison with high dose trastuzumab (8 mg/kg then 10 mg/kg q3weeks) and found no significant difference between dose levels, supporting ongoing use of the lower, standard of care, dose [65]. The JACOB phase 3 trial investigated the addition of pertuzumab to patients treated with trastuzumab and chemotherapy (capecitabine or 5-FU plus cisplatin), OS was improved in the pertuzumab arm by 3.3 months but was not statistically significant, $p = 0.057$ [66].Interestingly, this outcome was not consistent with findings in breast cancer when the addition of pertuzumab was investigated in HER-2 positive patients; the CLEOPATRA trial added pertuzumab to trastuzumab and chemotherapy, patients had a median OS to 57.1 months compared to 40.8 months for those treated with trastuzumab and chemotherapy, HR 0.69; these results led to adoption of using both MAbs in combination with chemotherapy as standard of care in HER-2 positive breast cancer [67].

Combination treatment of anti PD-1 antibodies and HER-2 targeted therapy in metastatic GE cancer has been studied in the KEYNOTE-811 and INTEGA clinical trials. The phase 3 KEYNOTE-811 trial demonstrated a significant overall response rate (ORR) of 74.4 % in patients treated with trastuzumab, pembrolizumab and standard of care chemotherapy, where standard of care was dependent on local guidelines, compared to 51.9 % in those treated with trastuzumab and standard of care chemotherapy [68]. Co-primary endpoints for the KEYNOTE-811 trial are PFS and OS; data from the PFS interim analysis showed significant benefit of the addition of pembrolizumab with PFS 10.0 months vs 8.1 months, $p = 0.0002$ in all patients, final OS data is still pending [69]. This regimen received approval for first line treatment in patients with metastatic gastric cancer and HER-2 overexpression in May 2021 representing a major shift in the treatment paradigm for these patients, the approval was updated in November 2023 limiting use to patients with PD-L1 CPS ≥ 1 based on subgroup analysis in the interim analysis showing lack of benefit in patients with CPS < 1 who had a PFS HR 1.41 (95 % CI 0.90–2.20 [70]. The INTEGA phase 2 trial investigated HER-2 directed treatment in combination with immunotherapy as a possible chemotherapy-sparing approach for patients with HER-2 amplification, patients received trastuzumab and nivolumab and were randomized to also receive either chemotherapy with 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX) or ipilimumab. They demonstrated a 70 % 12-month OS in patients who received chemotherapy compared to 57 % in patients who received ipilimumab, suggesting that chemotherapy remains a crucial component of treatment in this setting [71]. Zanidatamab was added to standard first-line chemotherapy in a study of 46 patients with metastatic HER-2 positive gastroesophageal adenocarcinomas, it was found to be well tolerated and demonstrated an ORR of 79 % (95 % CI: 63–90 %), prompting development of a phase 3 trial, HERIZON-GEA-01, that is investigating the addition of a PD-1 inhibitor [72].

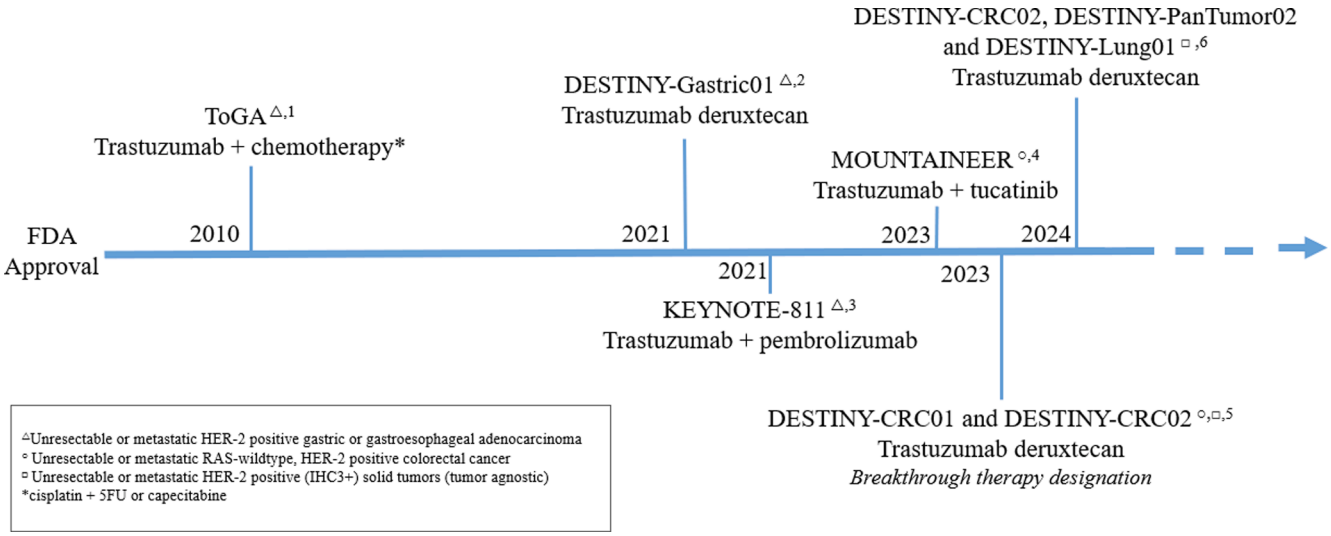

Fig. 2. FDA approval timeline for HER-2 directed therapies.

The earliest use of ADCs in advanced gastric cancer did not yield positive results but progress has been advancing in recent years and now represent a promising treatment strategy for HER-2 positive metastatic gastric cancers. TDM-1 was initially investigated in the EMILIA trial for HER-2 positive metastatic breast cancer, where it showed efficacy when used in patients with 2 prior lines of therapy when compared to capecitabine and lapatinib combination therapy (median OS 30.9 months vs 25.1 months, 95 % CI 0.55–0.85, HR = 0.68, $p < 0.001$) [73]. Interestingly, when used in gastric cancer treatment with TDM-1 did not show the same efficacy; Patients in the GATSBY phase 2/3 clinical trial were randomized to taxane chemotherapy or T-DM1, there was no OS benefit shown in patients who received T-DM1 (7.9 vs. 8.6 months, $p = 0.86$) [74]. Subsequent trials of ADC therapy in gastric cancers investigated the benefit of T-DXd, in patients with previously treated metastatic GE cancer with HER-2 overexpression there is promising activity in the DESTINY-Gastric clinical trials of T-DXd. In DESTINY-Gastric01 patients who had at least 2 prior lines of therapy were treated with T-DXd and had a 51 % ORR compared to 14 % who were treated with physicians' choice chemotherapy (irinotecan or paclitaxel), $p < 0.001$ [75]. The results of DESTINY-Gastric01 represented a pivotal development in the treatment paradigm of metastatic GE cancer and led to the first ADC with approval in GE cancer by the FDA and Japan Pharmaceuticals and Medical Devices Agency (Fig. 2). An exploratory cohort of HER-2 low patients in DESTINY-Gastric01 included HER-2 IHC 2 + and ISH negative or HER-2 IHC 1+, overall response rates were 26.3 % and 9.5 %, respectively, suggesting that there is potential for benefit with HER-2 targeted therapy in this subset of patients [76]. DESTINY-Gastric01 enrolled primarily Asian patients, DESTINY-Gastric02 assessed the generalizability of the same regimen in Western patients in an earlier setting, patients enrolled had only one prior HER-2 directed line of therapy, they demonstrated an ORR of 38 % (95 % CI, 27.3–49.6) [77]. Further development is ongoing to bring ADC therapy into earlier lines of treatment and assess efficacy of use in combination with other immunotherapies including anti PD-L1 and anti CTLA-4 agents.

In the neoadjuvant setting, MAbs have been added to a standard chemotherapy backbone of paclitaxel and carboplatin along with radiation in the phase 3 RTOG-1010 and phase 2 TRAP clinical trials for patients with HER-2 positive gastric cancer. RTOG-1010 did not show significant improvement in DFS; patients treated with trastuzumab, chemotherapy and radiation had a disease-free survival (DFS) of 19.6 months (95 % CI 13.5–26.2) vs 14.2 months (95 % CI 10.5–23.0) for those who were treated with only chemotherapy and radiation ($p = 0.97$) [78]. However, the TRAP trial assessed a combination of two MAbs, trastuzumab and pertuzumab, when added to chemotherapy and radiation to assess feasibility in a cohort of 40 patients. They showed that 83 % of patients completed treatment, and 34 % had a pathologic complete response, indicating that this is a tolerable regimen worthy of further investigation in a phase 3 setting [79]. The ST03 trial assessed the addition of lapatinib to a neoadjuvant regimen of epirubicin, cisplatin and capecitabine in a cohort of 46 patients to determine safety of adding HER-2 directed therapy to neoadjuvant treatment, they demonstrated that 21 % of patients treated with lapatinib had grade 3–4 diarrhea which exceeded the predefined safety parameters set at 20 %, however there was no significant difference in post-operative complications [80].

In the perioperative setting, exploration of benefit of HER-2 directed therapy is underway. The HER-FLOT phase 2 trial assessed patients who were treated pre-operatively with 4 cycles of fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) with trastuzumab, then an additional 4 cycles of FLOT and 9 cycles of trastuzumab post-operatively, the trial met its primary endpoint which was set at pathologic complete response (pCR) > 20 % (21.4 %), secondary endpoints of DFS and 3-year OS were 42.5 months and 82.1 %, respectively [81]. The PETRARCA phase 2 trial assessed the addition of both pertuzumab and trastuzumab to perioperative FLOT chemotherapy and demonstrated a pCR rate of 35 % in patients treated with the addition of pertuzumab and trastuzumab, compared to 12 % in patients treated with FLOT alone [82]. The INNOVATION trial also investigated the addition of trastuzumab or combined trastuzumab and pertuzumab to standard of care perioperative chemotherapy, there was a 3.1 % increase in major pathological response rate when comparing chemotherapy alone to chemotherapy with trastuzumab and pertuzumab (23.3 % vs 26.4 %, $p = 0.378$) as the first test, subsequent analysis of chemotherapy with trastuzumab was not carried out given that the first test did not meet pre-defined criteria to proceed. Notably, there was a 37.0 % major pathological response rate among patients treated with chemotherapy and trastuzumab [83]. Ongoing follow up is needed to assess whether the pCR improvement translates into an OS benefit in this population.

Trials of later line HER-2 directed treatments for metastatic GE cancers are ongoing with a variety of agents, to date treatments studied include use of MAbs, ADCs, and TKIs. An early phase 1b/2 trial, CP-MGAH22-05, demonstrated an 18.5 % ORR for patients treated with margetuximab and pembrolizumab [84]. The SUMMIT basket trial recruited patients with HER-2 and HER-3 mutated, not amplified, cancers to investigate response rate to HER-2 targeted therapy, there was no demonstrated ORR in a subgroup analysis of patients with GE cancers who were treated with neratinib [85]. The LOGiC phase 3 trial did not show improvement in OS with the addition of lapatinib to capecitabine

Table 2
Current evidence for HER-2 directed therapy in biliary tract cancer.

Line of therapy	Trial	Year	Phase	Therapy	n	Primary Endpoint	Result
Later-Line, Metastatic	Destiny-PanTumor-02 [95]	2023	II	Trastuzumab deruxtecan	41 (BTC)	ORR	22 %
	HERIZON-BTC-01 [98]	2023	IIb	Zanidatamab	80	ORR	41.3 % (95 % CI 30.4–52.8)
	SGNTUC-019 [97]	2023	II	Trastuzumab + tucatinib	30	ORR	46.7 % (90 % CI 30.8–63.0)
	KCSG-HB19-14 [83]	2023	II	Trastuzumab + FOLFOX	34	ORR	29.4 % (95 % CI 16.7–46.3)
	HERB [94]	2022	II	Trastuzumab deruxtecan	22	ORR	36.4 % (90 % CI 19.6–56.1)
	TreeTopp [31]	2021	II	Capecitabine +/- Varlitinib	127	ORR PFS	ORR: 9.4 % vs. 4.8 % (p = 0.42) PFS: 2.83 vs. 2.79 months (95 % CI 0.60–1.37, p = 0.63)
	MyPathway [100]	2021	IIa	Pertuzumab + trastuzumab	39	ORR	23 % (95 % CI 11–39)
	Tan et a [l100]	2019	Pooled analysis of 3 phase I trials	Varlitinib + platinum-based doublet chemotherapy	43	ORR	33.3 %
	SUMMIT [85]	2018	II	Neratinib	9 (BTC)	8-week ORR	22.2 % (95 % CI 2.8–60.0)
	Li et al [101]	2018	II	Trastuzumab exemestane	6	ORR	17 %

Abbreviations: ORR – objective response rate, PFS – progression free survival, CI – confidence interval.

and oxaliplatin chemotherapy, OS in the lapatinib arm was improved by only 1.7 months, p = 0.32 [86].The TyTAN phase 3 trial investigated the addition of lapatinib to paclitaxel but did not demonstrate improvement in OS (11.0 vs. 8.9 months, $p = 0.10$) [87]. In the phase 2 T-ACT trial patients were treated with paclitaxel and randomized to receive trastuzumab or placebo, there was no significant improvement in progression free survival (PFS) (3.2 vs. 3.7 months, $p = 0.33$) [88].

The introduction of HER-2 targeted therapy has significantly changed the treatment paradigm of gastric and gastroesophageal cancers in the metastatic setting. Thus far, perioperative trials have not delivered practice-changing results, further follow up of studies in the perioperative setting may demonstrate a role for HER-2 targeted agents if the demonstrated improved pCRs are found to be reflective of improved OS. There is further opportunity in this space to investigate benefit of new strategies with combination of immunotherapies, ADCs or novel agents.

Biliary tract cancer

HER-2 is amplified and/or overexpressed in 26.5 % of biliary tract cancers (BTC), the highest expression found in extrahepatic and gallbladder cancers, in a *meta*-analysis there was no correlation between IHC positivity (2 + or 3 +) with positive ISH [89]. BTCs represent a range of cancer subtypes including intrahepatic, extrahepatic, gallbladder and ampullary carcinomas. HER-2 overexpression and heterogeneity were assessed prospectively in 454 patients, overexpression was found to range from 3.0-31.3 % among primary BTC sites, the highest expression being in gallbladder cancers, heterogeneity of HER-2 expression within tumor samples was found in 83 % of BTC [90]. The current available evidence for HER-2 directed therapy for patients with BTC is limited to later-line treatment in the metastatic setting (Table 2). Current NCCN guidelines recommend testing HER-2 status with initial molecular tests for workup of locally advanced/metastatic BTC to allow for targeted therapy in the second line and beyond, or for consideration for first-line targeted therapy clinical trial enrolment [91,92].

In treatment of metastatic or locally advanced unresectable HER-2 positive BTCs there have been trials of chemotherapy in combination with MAb and T-DXd. A cohort of 34 patients were treated with the addition of trastuzumab to FOLFOX (a standard second line chemotherapy backbone in BTC), the ORR was 29·4% (95 % CI 16·7–46·3) [93]. T-DXd has been assessed in the HERB and DESTINY-PanTumor-02 clinical trials. The HERB trial enrolled HER-2 positive and HER-2 low patients who were treated with T-DXd. HER-2 positive patients had an ORR of 36.4 % (90 % CI, 19.6–56.1), p = 0.01; 8 patients classified as HER-2 low were assessed as a secondary endpoint, ORR was 12.5 % (95 % CI: 0.3–52.7), mOS was 8.9 months (95 % CI: 3.0–12.8) [94]. Interim results of DESTINY-Pantumor-02 showed an ORR of 56.3 % among 16 patients with HER-2 IHC 3+, and ORR of 0 % among 14 patients with HER-2 IHC 2 + who were treated with T-DXd [95]. The results of this cleverly designed basket trial which allowed for demonstration of efficacy across tumor groups within one trial, taken into consideration with results of DESTINY-CRC02 and DESTINY-Lung01, informed a pivotal shift in the treatment of HER-2 positive cancers with FDA approval for use of T-DXd with a tumor agnostic approach for HER-2 IHC 3 + tumours in 2024 [96].

Chemotherapy-sparing treatments are appealing, those assessed in metastatic BTCs include combination treatment with tucatinib and trastuzumab or zanidatamab monotherapy. The combination of tucatinib and trastuzumab was assessed in the second line and beyond in a cohort of 30 patients, demonstrating a promising ORR of 46.7 % (90 % CI, 30.8–63.0), the most common adverse event demonstrated was different compared to standard chemotherapy side effects, 43.3 % of patients experienced pyrexia [97]. In a phase 2b trial of zanidatamab monotherapy in a cohort of 80 patients who had HER2 IHC 2 + or 3 + and prior treatment with a gemicitabine-based regime there was an ORR of 41.3 % (95 % CI 30.4–52.8), adverse events were manageable and only 2 patients (2.3 %) required treatment discontinuation demonstrating that it is well tolerated, these results prompted ongoing assessment of zanidatamab in the first line setting [98].

Varlitinib, a pan-HER TKI has been studied in metastatic BTC after prior lines of treatment. It was initially assessed in a pooled analysis from 3 phase I studies when given in combination with chemotherapy doublet in pre-treated patients, ORR was 33.3 % of patients, they found that 81.5 % of patients had a disease control rate (DCR) > 6 weeks [99]. The TreeTopp trial investigated the addition of varlitinib to capecitabine second line chemotherapy for metastatic BTC and did not show benefit, in those who received varlitinib ORR was 9.4 % compared to 4.8 % with capecitabine monotherapy (p = 0.42); median PFS for those treated with capecitabine and varlitinib was 2.83 months compared to 2.79 months with capecitabine monotherapy (95 % CI: 0.60–1.37, p = 0.63) [31]. Following these results, varlitinib and capecitabine combination therapy is no longer being investigated in BTC.

Basket trials are an effective way to screen patients in a tumour agnostic fashion and have investigated HER-2 directed therapies in pre-treated BTC including pertuzumab and trastuzumab, neratinib and T-DM1. The MyPathway basket trial included 29 patients with HER-2 overexpressing BTCs who were treated with pertuzumab and trastuzumab, in the absence of standard cytotoxic chemotherapy, the ORR was 23 % [100]. The SUMMIT trial included 9 patients with BTC that were treated with neratinib, the preliminary 8-week ORR was 22.2 %, this

Table 3
Current evidence for HER-2 directed therapy in pancreatic cancer.

Line of therapy	Trial	Year	Phase	Therapy	n	Primary Endpoint	Result
First Line, Metastatic	GATE 1 [109]	2020	II	Trastuzumab + gemcitabine + erlotinib	59	DCR	74.6 % (95 % CI 61.8–85.0)
	Harder et al [107]	2012	II	Trastuzumab + capecitabine	17	PFS (12 week)	28.6 % (95 % CI 8.4–58.1)
	Safran et al [106]	2004	II	Trastuzumab + gemcitabine	32	ORR	6 %
Second Line, Metastatic	DESTINY-PanTumor-02 [95]	2023	II	Trastuzumab deruxtecan	25 pancreatic	ORR	4 %
	THERAPY [108]	2015	I/II	Trastuzumab + cetuximab	33	ORR	0 %

Abbreviations: DCR – disease control rate, OS – overall survival, ORR – objective response rate, PFS – progression free survival, CI – confidence interval, RR – response rate.

trial is still undergoing accrual prior to final efficacy analysis [85]. Treatment with T-DM1 is undergoing evaluation in a basket trial, an initial analysis of 6 patients with BTC showed an ORR of 17 % [101].

Targeted therapies are an important treatment strategy in BTC which are molecularly diverse cancers. Data for treatment with T-DXd and zanidatamab represent promising, chemotherapy-sparing, novel treatment options for biliary tract cancers with HER-2 overexpression or amplification. Current standard of care treatment in BTC is limited to cytotoxic chemotherapy in combination with immunotherapy in the first line, followed by second line chemotherapy options with marginal benefit. Optimizing targeted therapy for patients with HER-2 positive disease may offer meaningful survival improvement for this subgroup of patients with very few treatment options available.

Pancreatic cancer

HER-2 overexpression and/or amplification in pancreatic cancer ranges between 2.1–10.3 %][102–104]. The variability of scoring may reflect the use of multiple scoring systems; HER-2 overexpression and amplification has been evaluated in pancreatic cancer using scoring systems that are standard for breast cancer and gastric cancer. The HER-2 scoring system used in gastric cancer has been validated, and recommended, to assess HER-2 overexpression in pancreatic cancer [60,103]. Current trials of HER-2 directed therapy for patients with pancreatic cancer are in the metastatic setting (Table 3), there is currently no evidence for HER-2 directed therapy in neoadjuvant or adjuvant treatment of pancreatic cancer. NCCN guidelines recommend testing HER-2 status with initial molecular tests for workup of locally advanced/metastatic pancreatic cancer is suspected, there are no specific ESMO recommendations for timing of HER-2 testing [105]. While there are no standard of care HER-2 targeted therapies in pancreatic cancer, knowledge of HER-2 status would highlight patients that may benefit from clinical trial enrolment.

Trastuzumab has been added to standard chemotherapy regimens in studies with patients who have metastatic pancreatic cancer and HER-2 overexpression. A phase 2 study of 32 patients with HER-2 overexpression who were treated with trastuzumab and gemcitabine, 6 % had a confirmed partial response; FISH was performed in 13 of these patients and only 2 were found to have HER-2 gene amplification [106]. A trial of HER-2 overexpressing patients treated with first line trastuzumab and capecitabine showed a 12-week PFS of 23.5 % (n = 17, 95 % CI: 6.8–49.9). This trial was closed early due to low recruitment, in a post-hoc analysis they found that the concordance rate of HER-2 IHC 3 + and gene amplification on FISH was 64 % [107]. An interim analysis of DESTINY-PanTumor-02 revealed a lower response rate compared to other cohorts among the 25 patients with HER-2 positive pancreatic cancer treated with T-DXd, only 12 % after central review, prompting early closure of this treatment arm [95].

Some trials in pancreatic cancer, THERAPY and GATE 1, have investigated treatment with HER-2 directed therapy in allcomers then subsequently performed HER-2 testing. THERAPY, a phase I/II trial for patients with metastatic pancreatic cancer who had previous gemcitabine-based treatment, assessed treatment with trastuzumab and cetuximab and found that of the 33 patients evaluable for efficacy, there was no objective response. Secondary endpoints of PFS and OS were 1.8 months (95 % CI: 1.7–2.0) and 4.6 months (95 % CI: 2.7–6.6), respectively; HER-2 was found to be positive in 8 patients of the 64 % of the study population with samples amenable to testing [108]. The GATE 1 trial assessed DCR in patients with metastatic pancreatic cancer after treatment with trastuzumab, gemcitabine and erlotinib. The primary endpoint, DCR, was 74 %; secondary endpoints included PFS (3.5 months, 95 % CI 2.4–3.8), OS (7.9 months, 95 % CI: 5.1–10.2) and tolerance (12.9 % premature discontinuation). They did not require HER-2 overexpression for participation, 66 % of patients had available samples to assess, HER-2 was overexpressed in 21 patients and found to be correlated with poorer prognosis for PFS (HR 2.66, 95 % CI: 1.22–5.81, p = 0.01) and OS (HR 2.98, 95 % CI: 1.28–6.97, p = 0.008) in a univariate analysis [109].

In pancreatic cancer, HER-2 targeted therapy has not demonstrated the promising results that have been shown in other GI cancers, which warrants further review and research for better understanding of how to optimize therapy in this setting. The pancreatic tumor microenvironment has been associated with poor response to most systemic therapies, rarity of HER-2 positive pancreatic cancer and poor prognosis for patients diagnosed with this aggressive cancer is likely contributing to small sample sizes and poor recruitment in trials to date.

Colorectal cancer

HER-2 is overexpressed or amplified in 1.3–5 % of colorectal cancers (CRC) when assessed by IHC and ISH, overexpression is associated with absence of KRAS or BRAF mutations and left sided primary tumors [15,110]. In a *meta*-analysis of RAS wildtype metastatic CRC (mCRC) treated with chemotherapy and anti-EGFR agents, HER-2 overexpression or amplification was associated with worse PFS and ORR when compared to HER-2 negative patients leading to its application as a negative selection biomarker for use of anti-EGFR in first-line treatment of mCRC [107]. 4–5.8 % of patients with CRC were found to have HER-2 amplification on exome sequencing using next generation sequencing (NGS) [111,112]. The use of NGS panel to assess for HER-2 copy number variation has been found to be concordant with positive HER-2 on IHC/ISH in CRC [113]. Tissue based HER-2 scoring using IHC is nuanced in colorectal cancer; The HERACLES Diagnostic Criteria was established in 2016 and draws upon scoring criteria in gastric and breast cancers and has been used to assess HER-2 positivity in CRC in the absence of a universal scoring system specific to CRC [114]. HER-2 status in the HERACLES trial was assessed using the VENTANA 4B5 IHC assay, positivity is defined as IHC 3 + in ≥ 50 % of cells, or if IHC 3 + in > 10 and < 50 % or 2+ (>10 % but < 50 % of cells) with confirmatory FISH HER2/CEP17 ratio is ≥ 2 or in ≥ 50 % of cells [115]. These criteria for HER-2 positivity are more stringent than criteria for gastric cancer, where IHC 3 + only requires ≥ 10 % to be confirmatory of HER-2

Table 4
Current evidence for HER-2 directed therapy in colorectal cancer.

Line of therapy	Trial	Year	Phase	Therapy	n	Primary Endpoint	Result
Later-line Metastatic	DESTINY-CRC02 [128]	2023	II	Trastuzumab deruxtecan	80	ORR	5.4 mg/kg 37.8 % (95 % CI, 27.3–49.2), 6.4 mg/kg 27.5 % (95 % CI, 14.6–43.9)
	HER2-FUSCC-G [119]	2022	II	Trastuzumab + pyrotinib	16	ORR	50 %
	TAPUR [123]	2022	II	Pertuzumab + trastuzumab	38		
	MOUNTAINEER [120]	2022	II	Trastuzumab + tucatinib vs tucatinib	116	ORR	Trastuzumab + tucatinib: 38.1 % Tucatinib: 3.3 %
	TRIUMPH [122]	2021	II	Pertuzumab + trastuzumab	30 (27 tissue, 25 ctDNA)	ORR	tissue+: 30 % (95 % CI, 14–50 %), ctDNA+: 28 % (95 % CI, 12–49 %)
	DESTINY-CRC01 [126]	2021	II	Trastuzumab deruxtecan	53	ORR	45.3 % (95 %CI 31.6–59.6)
	HERACLES-B [125]	2020	II	Pertuzumab + trastuzumab-exemestane	31	ORR	9.7 % (95 % CI 0–28)
	MyPathway [124]	2019	IIa	Pertuzumab + trastuzumab	57	ORR	32 % (95 % CI 20–45)
	SUMMIT [85]	2018	II	Neratinib	12 (CRC)	8-week ORR	0 %(95 % CI 0–26.5)
	HERACLES [114]	2016	II	Trastuzumab + lapatinib	27	ORR	30 % (95 % CI 14–50)

Abbreviations: ORR – objective response rate, CI – confidence interval, DC – disease control.

positivity not requiring reflex ISH testing. Both breast and gastric cancer HER-2 scoring guidelines have been assessed in the CRC patients enrolled in the MOUNTAINEER trial and had high concordance, supporting either criterion to score HER-2 status in CRC patients [116]. There is no current standard of care recommendation for first-line HER-2 directed treatment of CRC, preliminary trials to date include patients with metastatic disease who have been pre-treated with at least one line of cytotoxic chemotherapy (Table 4). ESMO and NCCN guidelines recommend testing HER-2 status with initial workup of mCRC, even though there is no current first-line HER-2 targeted therapy in standard of care it is a likely future direction for treatment of mCRC [117,118].

HER-2 targeted TKIs have been studied in patients with colorectal cancer, initially with negative results when used as monotherapy. Treatment with neratinib did not show any response in a small study of 12 patients with HER-2 or HER-3 mutations identified on NGS [85]. Trastuzumab has been combined with a TKI in 3 studies to assess dual HER-2 targeted therapy. Trastuzumab and pyrotinib was used to treat 16 HER-2 positive patients, the ORR was 50 %, in a subgroup analysis of RAS wild-type patients, the ORR increased to 57.1 % [119]. The combination of trastuzumab and lapatinib in 27 HER-2 positive patients with metastatic CRC demonstrated an ORR of 30 % (95 % CI 14–50) [114]. In the MOUNTAINEER trial tucatinib was studied as monotherapy and in combination with trastuzumab in HER-2 positive, RAS wildtype patients; the combination of tucatinib with trastuzumab had an ORR of 38.1 % with disease control rate of 71.4 %, tucatinib monotherapy had a much lower ORR of 3.3 % but notably the disease control rate was 80.0 % [120]. It is thought that the increased efficacy of combined MAb (trastuzumab) and TKI (tucatinib) is a result of dual targeting of HER-2, extracellularly with trastuzumab and intracellularly with TKI. The results of this study led to FDA approval of tucatinib and trastuzumab in January 2023 as standard of care for patients with RAS wildtype metastatic CRC with HER-2 positivity after progression on standard chemotherapy [121].

Combination treatment with MAbs, trastuzumab and pertuzumab, has been investigated in metastatic CRC. The TRIUMPH trial treated patients with HER-2 overexpression or ctDNA amplification; HER-2 overexpression and ctDNA amplification were concordant in 22 of 30 patients who were assessed by both means. The ORR was 28 % and 30 % in ctDNA positive and tissue positive patients, respectively. These results were compared to a database of patients that were not enrolled on study but had known metastatic CRC with HER-2 overexpression/amplification; the comparison cohort was treated with standard of care regimens reflective of real-world practice and found an ORR of 0 % with non-HER-2 directed treatment [122]. The TAPUR basket trial investigated the use of trastuzumab and pertuzumab in patients with HER-2 amplification or HER-2/3 gene mutation with the primary objective of DCR, which included stable disease and objective response; of the 28 patients with HER-2 amplification 54 % had disease control and 25 % had objective response, of the 10 patients with ERBB2/3 mutation, 10 % had disease control and 0 % had objective response [123]. These results suggest that patients with HER-2 overexpression and amplification respond differently to targeted therapy than those with genomic mutations. The MyPathway basket trial treated 57 HER-2 positive patients with pertuzumab and trastuzumab, ORR was 32 % (95 % CI 20–45); KRAS mutational status was also included in a subgroup analysis which demonstrated that ORR in KRAS wild type was 40 % compared to 8 % in KRAS mutated patients highlighting the importance of RAS status when considering HER-2 targeted therapy [124].

The role for ADCs has been assessed in HER-2 positive colorectal cancer in the HERACLES-B and DESTINY-CRC01 phase 2 clinical trials. HERACLES-B assessed treatment with pertuzumab in combination with T-DM1 in 31 HER-2 positive, RAS/BRAF wild type patients with metastatic CRC, the ORR was 9.7 %, in an exploratory analysis of disease stability the overall disease control rate was 77.4 % [125]. DESTINY-CRC01 enrolled patients with varying HER-2 expression levels for treatment with T-DXd; Of the 53 patients that were HER-2 positive (IHC 3 + or IHC 2 + and positive FISH) the ORR was 45.3 % (95 % CI 31.6–59.6), HER-2 low (IHC 2 + and negative FISH) and HER-2 negative patients did not demonstrate objective response to treatment [126]; In the HER-2 positive cohort median PFS was 6.9 months (95 % CI 4.1–8.7) and median OS was 15.5 months (95 % CI 8.8–20.8) [127]. The subsequent phase 2 trial, DESTINY-CRC02, assessed optimal dosing of T-DXd comparing 6.4 mg/kg to 5.4 mg/kg every three weeks, they enrolled patients with RAS mutated disease which has previously been an exclusion criteria for HER-2 targeted therapy in CRC; the 5.4 mg/kg dose was found to be effective in patients with RAS wild type and mutated disease with ORR 37.8 % (95 % CI 27.3–49.2 %) compared to 27.5 % (95 % CI 14.6–43.9 %) in the 6.4 mg/kg arm, it also demonstrated an improved safety profile on preliminary analysis supporting the use of lower dose [128]. The results of DESTINY-CRC-01 and DESTINY-CRC02 led to FDA breakthrough therapy designation for use of T-DXd in patients with mCRC who have been treated with two prior regimens in August 2023 [129].

HER-2 targeting in CRC is emerging as a promising treatment option in later-lines of disease in the metastatic setting, going forward it will be important to continue assessment of HER-2 targeted therapy in earlier lines of treatment to define the optimal timing of HER-2 targeted treatment in the pathway. It is possible that in the future sequential

Table 5
Ongoing phase 1/2 to phase 3 clinical trials that are active and/or recruiting for HER-2 directed therapy in GI cancers as of 18 April 2024.

ClinicalTrials.gov Identifier	Official title	Phase	Intervention	n	Primary endpoint	HER-2 Status	Trial status
GASTROESOPHAGEAL							
PHASE 3:							
NCT06123494	SHR-A1811 for Subjects With Her2-positive Gastric Cancer and Gastroesophageal Junction Adenocarcinoma After Progression on or After First-line Anti-HER2 Therapy-containing Regimen	3	SHR-A1811 vs ramucirumab/ paclitaxel/docetaxel/ irinotecan (cnvestigators choice)	360	OS	IHC 3 + or IHC 2 + and evidence of HER2 amplification by ISH	Recruiting
NCT05188313	The Efficacy of the Addition of TRAstuzumab and Pertuzumab to Neoadjuvant Chemoradiation: a Randomized Multi-center Study in Resectable HER2 Overexpressing Adenocarcinoma of the Esophagus or Gastroesophageal Junction. The TRAP-2 Study	3	CROSS chemoradiation +/- trastuzumab + pertuzumab	376	OS	IHC3 + or IHC 2 + and ISH+	Recruiting
NCT05152147	A Randomized, Multicenter, Phase 3 Study of Zanidatamab in Combination With Chemotherapy With or Without Tislelizumab in Subjects With HER2-positive Unresectable Locally Advanced or Metastatic Gastroesophageal Adenocarcinoma (GEA)	3	Zanidatamab + chemotherapy +/- tislelizumab vs chemotherapy + trastuzumab	714	PFS, OS	IHC3 + or IHC 2 + and ISH+	Recruiting
NCT04704934	A Phase 3, Multicenter, 2-Arm Randomized, Open-Label Study of Trastuzumab Deruxtecan in Subjects With HER2-Positive Metastatic and/or Unresectable Gastric or Gastro-Esophageal Junction (GEJ) Adenocarcinoma Subjects Who Have Progressed on or After a Trastuzumab-Containing Regimen (DESTINY-Gastric04)	3	T-DXd vs ramucirumab + paclitaxel	490	OS	IHC3 + or IHC 2 + and ISH+	Recruiting
NCT04499924	A Randomized, Double-blind, Placebo-controlled, Active Comparator Phase 2/3 Study of Tucatinib in Combination With Trastuzumab, Ramucirumab, and Paclitaxel in Subjects With Previously Treated, Locally-advanced Unresectable or Metastatic HER2 + Gastric or Gastroesophageal Junction Adenocarcinoma (GEC)	2/3	Tucatinib + trastuzumab + ramucirumab + paclitaxel vs Ramucirumab + paclitaxel + tucatinib + placebo vs Ramucirumab + paclitaxel + tucatinib placebo + trastuzumab placebo	17	Phase 2: DLTs, Aes, Dose modification, Lab abnormalities Phase 3: OS, PFS	Phase 2: HER2 amplification in a blood-based NGS assay performed at a central laboratory OR No HER2 amplification by blood-based NGS assay, but HER2 overexpression/ amplification by IHC and ISH (IHC3 + or IHC2+/ISH +) assay of a tumor tissue sample. Phase 3: HER2 amplification in a blood-based NGS assay performed at a central laboratory	Active, not recruiting
NCT04082364	A Phase 2/3 Trial to Evaluate Margetuximab in Combination With INCMGA00012 and Chemotherapy or MGD013 and Chemotherapy in Patients With Metastatic or Locally Advanced, Treatment-naïve, HER2-Positive Gastric or Gastroesophageal Junction Cancer	2/3	A: Single arm	40–110	A: Safety of margetuximab + retifanlimab, ORR	A: HER2 IHC 3 + and PD-L1-positive (CPS $\geq$ 1 %) B: HER2 IHC 3 + or IHC 2 + with FISH+	Active, not recruiting
			B1 – margetuximab plus retifanlimab plus chemotherapy, margetuximab plus tebotelimab, plus chemotherapy, margetuximab plus chemotherapy, or trastuzumab plus chemotherapy. B2 – most effective combination from B1 – randomized to margetuximab plus retifanlimab or tebotelimab plus chemotherapy, or to trastuzumab plus chemotherapy.	50/ arm 250/ arm			

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Table 5 (*continued*)

ClinicalTrials.gov Identifier	Official title	Phase	Intervention	n	Primary endpoint	HER-2 Status	Trial status
NCT05427383	A Randomized, Multicenter, Double-Blind, Phase II/III Study of KN026 in Combination With Chemotherapy Versus Chemotherapy Alone in the Second Line Treatment of HER-2 Positive Advanced or Metastatic Gastric Cancer	2/3	Stage 1 − open-label, multicenter, phase II study of KN026 and paclitaxel or irinotecan when given in combination Stage 2 − randomized, multicenter, phase III study designed to evaluate the OS and PFS in patients receiving KN026 and chemotherapy compared to patients receiving placebo and chemotherapy.		safety/efficacy	IHC3 + or IHC 2 + and ISH+	Recruiting
NCT05002127	A Phase 2/3 Study of Evorpacept (ALX148) in Patients With Advanced HER2-Overexpressing Gastric/Gastroesophageal Junction Adenocarcinoma (ASPEN-06)	2/3	Phase 2: Trastuzumab + ramucirumab + paclitaxel +/- evorpacept. Phase 3: Ramucirumab + paclitaxel +/- evorpacept + trastuzumab	450	Phase 2: ORR Phase 3: OS	HER2 overexpression	Recruiting
PHASE 2:							
NCT06253650	Adjuvant TRastuzumab Deruxtecan for HER2-positive Gastroesophageal Cancer With Persistence of miNImal Residual Disease (TRINITY)	2	T-DXd + 5-FU x 6 cycles vs FLOT x 4 cycles	46	ctDNA clearance rate at 1 year	IHC 3 + or 2+/ISH amplified	Active, not recruiting
NCT05975749	A Study of Compared Adjuvant Serplulimab and Trastuzuma and Chemotherapy vs Chemotherapy Only in HER-2 Positive Gastric Cancer With II-III Stage Following Curative Resection	2	Serplulimab + Trastuzuma + Chemotherapy	114	DFS	HER2 + by IHC or FISH	Recruiting
NCT04661150	A Phase II, Randomized Study of Atezolizumab (Anti-PD-L1 Antibody) and Trastuzumab in Combination With Capecitabine and Oxaliplatin (Xelox) in Patients With HER2 Positive Locally Advanced Resectable Gastric Cancer of Adenocarcinoma of Gastroesophageal Junction (GEJ)	2	Capecitabine + oxaliplatin (XELOX) + trastuzumab +/- atezolizumab	41	pCR	IHC3 + or IHC 2 + and ISH+	Active, not recruiting
NCT05141747	An Open-label, Multi-center, Phase II Clinical Study to Evaluate the Safety, Efficacy and Pharmacokinetics of MRG002 in Patients With HER2-positive/HER2-low Locally Advanced or Metastatic Gastric/ Gastroesophageal Junction Cancer	2	MRG002	60	ORR, Aes	Cohort 1: HER2 IHC 3 + or IHC 2 + and ISH positive. Cohort 2: HER2 IHC 1 + or 2 + and ISH negative	Recruiting
NCT05070598	A Prospective, Single-arm, Phase II Study of Camrelizumab Combined With Pyrotinib Maleate, Nab-paclitaxel and Tegafur Chemotherapy in First-line Treatment of HER2-positive Gastric Cancer	2	Camrelizumab + pyrotinib + Nab-paclitaxel + Tegafur	35	ORR	Not mentioned	Recruiting
NCT05190445	A Phase 2, Multi-Center, Open-Label Study of Cinrebafusp Alfa (PRS-343) in Combination With Ramucirumab and Paclitaxel in Patients With HER2-Positive Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma and in Combination With Tucatinib in Patients With HER2 Low Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma	2	A: Cinrebafusp alfa + ramucirumab + paclitaxel B: Cinrebafusp alfa + tucatinib	80	ORR	A: Demonstration of HER2 positivity assessed by a test with appropriate regulatory validation in a current tissue specimen and following guidelines for assessment in gastric or GEJ adenocarcinoma B: Demonstration of HER2 IHC 1 + or IHC 2 + without HER2/ neu amplification assessed by a test with appropriate regulatory validation in a current tissue specimen and following guidelines for assessment in	Active, not recruiting

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Table 5 (*continued*)

ClinicalTrials.gov Identifier	Official title	Phase	Intervention	n	Primary endpoint	HER-2 Status	Trial status
						gastric or GEJ adenocarcinoma	
NCT05311176	nextHERIZON: An Open-Label, Signal Generating, Phase 2 Study of HER-Vaxx in Combination With Chemotherapy or Pembrolizumab in Patients With Metastatic HER2/Neu Over-Expressing Gastric or Gastroesophageal Junction (GEJ) Adenocarcinomas Who Have Previously Received Trastuzumab and Progressed on This Treatment	2	IMU-131 + ramucirumab + paclitaxel vs IMU-131 + pembrolizumab	30	Aes, ORR	HER2/neu overexpression assessed using post-progression fresh or archival tissue, or post-progression pathology report	Recruiting
NCT05034887	Phase 2 Study of Trastuzumab Deruxtecan (T-DXd) in the Neoadjuvant Treatment for Patients With HER2 Positive Gastric and GastroesophagealJunction Adenocarcinoma	2	Trastuzumab deruxtecan	37	Major pathological response (MPR)	HER2 overexpression: IHC3+, or IHC2 + and ISH positive HER2 Low expression: IHC1+, or IHC2 + and ISH-negative [FISH or DISH] with HER2-ECD > 11.6 ng/mL in the exploratory cohort	Recruiting
NCT04309578	A Phase II Clinical Study of Trastuzumab in Combination With Capecitabine and Cisplatin (XP) in Patients With Tissue HER2-negative But Serum HER2-positive Advanced Gastric Cancer: XP + Samfenet	2	Trastuzumab + capecitabine + cisplatin	28	ORR	Tissue HER2-negative tumors (primary or metastatic tumors) defined as IHC2 + and FISH- or IHC 0 or 1 + according to gastric cancer assessment system for HER2	Recruiting
NCT02205047	INtegratioN of Trastuzumab, With or Without Pertuzumab, Into periOperatiVe chemotherApy of HER-2 posiTIve stOmach caNcer: the INNOVATION-TRIAL	2	Chemotherapy (cisplatin + capecitabine or cisplatin + 5FU) +/- trastuzumab +/- pertuzumab	171	Near complete pathological response rate	HER2 overexpression	Active, not recruiting
PHASE 1/2:							
NCT04379596	A Phase 1b/2 Multicenter, Open-label, Dose-escalation and Dose-expansion Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Immunogenicity, and Antitumor Activity of Trastuzumab Deruxtecan (T-DXd) Monotherapy and Combinations in Adult Participants With HER2-expressing Gastric Cancer (DESTINY-Gastric-03)	1b/2	T-DXd monotherapy or T-DXd in combination with 5-FU, capecitabine, durvalumab, CAPOX, 5-FU + durvalumab, capecitabine + durvalumab, pembrolizumab, pembrolizumab + 5FU or capecitabine, volrustomig + 5-FU or capecitabine, rilvegostomig + 5-FU or capecitabine	413	Part 1: AEs, DLTs, Change in baseline labs, vital signs or ECGs. Part 2,3 and 4: ORR	HER-2 Positive: IHC 3 + or IHC 2+/ISH+; HER-2 Low: IHC 2+/ ISH-negative or IHC 1+	Recruiting
NCT05982834	Disitamab Vedotin Combined With Fruquintinib and Tislelizumab in Second-line Treatment for HER2-positive Metastatic Gastric Cancer. A Prospective Phase Ib/II Study	1b/2	Disitamab vedotin + furquintinib + tislelizumab	43	ORR	IHC 2 + or 3 + and ISH+	Active, recruiting
NCT02901301	A Phase Ib/II Study of First Line Pembrolizumab in Combination With Trastuzumab, Capecitabine, and Cisplatin in HER2 Positive Gastric Cancer	1b/2	Pembrolizumab + trastuzumab + capecitabine + cisplatin	41	ORR, recommended dose	HER2 positive advanced gastric cancer	Active, not recruiting
NCT05671822	A Phase Ib/II Study of SHR-A1811 Combinations in Patients With Advanced/ Metastatic HER2 + Gastric /Gastroesophageal Junction Adenocarcinoma	1b/2	SHR-A1811 +/- SHR-1701 alone or in combination with capecitabine +/- oxaliplatin	156	DLTs, ORR	HER2 positive	Recruiting
NCT04492488	An Open-Label, Multi-center Phase I/II Dose Escalation and Expansion Study to Assess the Safety, Efficacy and Pharmacokinetics of MRG002 in Patients With HER2-Positive Advanced Solid Tumors and Locally Advanced or Metastatic Gastric/ Gastroesophageal Junction (GEJ) Cancer	1/2	MRG002	129	MTD, RP2D, ORR, Aes	HER2 positive	Recruiting

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Table 5 (*continued*)

ClinicalTrials.gov Identifier	Official title	Phase	Intervention	n	Primary endpoint	HER-2 Status	Trial status
NCT04467515	A Multi-Center Open Label Dose Escalation and Dose Expansion Study to Evaluate Safety, Tolerability, Dosimetry, and Preliminary Efficacy of the HER2Directed Radioligand CAM-H2 in Patients With Advanced/ Metastatic HER2-Positive Breast, Gastric, and GEJ Cancer	1/2	CAM-H2	70	ORR, clinical benefit rate	HER2 positive	Recruiting
NCT05207722	A Phase I/IIa Open Label, Non-Randomized, Multicenter Study of CYNK-101 in Combination With Trastuzumab and Pembrolizumab in Patients With Locally Advanced Unresectable or Metastatic HER2-Positive Gastric or Gastroesophageal Junction (G/GEJ) Aenocarcinoma	1/2	CYNK-101 + rhIL2 + pembrolizumab + trastuzumab + cyclophosphamide + fludarabine + mesna		Phase 1: DLT, MTD. Phase 2: ORR	IHC 3 + or IHC 2 + with ISH + or ISH + alone	Active, not recruiting
NCT04276493	Phase 1b/2 Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activity of Anti-HER2 Bispecific Antibody ZW25 in Combination With Chemotherapy With/ Without Tislelizumab in Patients With Advanced HER2-positive Breast Cancer or Gastric/GastroesophagealJunction Adenocarcinoma	1b/2	ZW25 + docetaxel vs ZW25 + tiselizumab + chemotherapy	71	Aes, ORR	IHC 3 + or IHC 2 + with ISH+	Active, not recruiting
NCT02795988	A Phase 1b/2 Open-Label Study With Randomization in Phase 2 of IMU-131 HER2/ Neu Peptide Vaccine Plus Standard of Care Chemotherapy in Patients With HER2/Neu Overexpressing Metastatic or Advanced Adenocarcinoma of the Stomach or Gastroesophageal Junction	1b/2	Chemotherapy (cisplatin + capecitabine or cisplatin + 5FU) +/- IMU 131	36	Safety, recommended phase 2 dose, clinical efficacy (OS)	IHC 3 + or IHC 2 + with or without ISH + based on trial discretion	Active, not recruiting
BILIARY TRACT							
PHASE 3:							
NCT06282575	Efficacy and Safety of Zanidatamab With Standard-of-care Therapy Against Standard-of-care Therapy for Advanced HER2-positive Biliary Tract Cancer	3	Standard of care chemotherapy + PD-1/ L1 (investigators choice) +/- Zanidatamab	286	PFS in IHC 3+	IHC 3+; or IHC 2+/ ISH+	Recruiting
PHASE 2:							
NCT06178445	Efficacy and Safety of GemCis Plus Trastuzumab Plus Pembrolizumab in Previously Untreated HER2-positive Biliary Tract Cancer (TRAP-BTC)	2	Gemcitabine + Cisplatin + Trastuzumab + Pembrolizumab	24	ORR	IHC 3 + or IHC 2+/ ISH + or NGS	Active, not recruiting
NCT04466891	A Phase 2b, Open-label, Single-arm Study of ZW25 Monotherapy in Subjects With Advanced or Metastatic HER2-amplified Biliary Tract Cancers	2b	Zanidatamab	87	ORR	HER2 amplification by ISH-assay at a central laboratory on a new biopsy or archival tissue	Active, not recruiting
NCT04837508	An Open-label, Single-arm, Multi-center, Phase II Clinical Study of MRG002 in the Treatment of Patients With HER2-positive Unresectable, Locally Advanced or Metastatic Biliary Tract Cancer	2	MRG002	86	ORR	IHC 3 + or IHC 2 +	Recruiting
NCT05417230	RC48-ADC in Combination With Envolizumab for the First-line Treatment of Locally Advanced or Metastatic Biliary Tract Cancer With PositiveHER-2: A Prospective, Single-arm Phase II Trial.	2	RC48-ADC + envafolimab	29	ORR	IHC 3 + or 2+	Not yet recruiting
COLORECTAL							
PHASE 3:							
NCT05673512	To Evaluate IAH0968 in Combination With CAPEOX in HER2-positive Metastatic Colorectal Cancer	2/3	CAPEOX +/- IAH0968	279	PFS	IHC3 + or IHC 2 + and ISH+	Recruiting
NCT05253651	An Open-label Randomized Phase 3 Study of Tucatinib in Combination With Trastuzumab and mFOLFOX6 Versus mFOLFOX6 Given With or Without Either Cetuximab or Bevacizumab as First-line Treatment for Subjects With HER2 + Metastatic Colorectal Cancer	3	Tucatinib + trastuzumab + mFOLFOX vs SOC chemotherapy (mFOLFOX + bevacizumab or cetuximab)	400	PFS	HER2 + as determined by a tissue based assay performed at a central laboratory	Recruiting
PHASE 2:							
NCT04744831	A Phase 2, Multicenter, Randomized, Study of Trastuzumab Deruxtecan in Participants With HER2-overexpressing Locally Advanced, Unresectable or Metastatic Colorectal Cancer (DESTINY-CRC02)	2	Trastuzumab deruxtecan	122	ORR	IHC3 + or IHC 2 + and ISH+	Active, not recruiting

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Table 5 (*continued*)

ClinicalTrials.gov Identifier	Official title	Phase	Intervention	n	Primary endpoint	HER-2 Status	Trial status
NCT03457896	Study of Neratinib + Trastuzumab or Neratinib + Cetuximab in Patients With KRAS/NRAS/BRAF/PIK3CA Wild-Type Metastatic Colorectal Cancer by HER2 Status	2	Neratinib + trastuzumab OR neratinib + cetuximab	35	PFS	HER2 amplification or mutation by CLIA testing	Active, not recruiting
NCT05493683	A Single Arm, Open Label, Multiple Center, Prospective Study of Disitamab Vedotin Combined With Tislelizumab in HER2 Positive Advanced Colorectal Cancer Failed at Least Two Lines of Systemic Treatment.	2	Disitamab Vedotin + tislelizumab	29	ORR	IHC 3 + or IHC 2+	Recruiting
NCT03365882	S1613, A Randomized Phase II Study of Trastuzumab and Pertuzumab (TP) Compared to Cetuximab and Irinotecan (CETIRI) in Advanced/Metastatic Colorectal Cancer (mCRC) With HER-2 Amplification	2	Trastuzumab + pertuzumab vs cetuximab + irinotecan	240	PFS	IHC 3 + or 2 + and ISH+	Active, not recruiting
NCT05845450	Window-of-opportunity Umbrella Platform Trial of Short-course Pre-operative Targeted Treatments in Patients With Molecularly Selected and Resectable Primary Colorectal Cancer: the UNICORN Study	2	Cohort 1 (HER2 positive) − trastuzumab deruxtecan	98	Pathological response rate	IHC 3 + or IHC 2 + and ISH+	Active, not recruiting
PHASE 1/2:							
NCT04278144	Phase 1/2 Study of BDC-1001 as a Single Agent and in Combination With Nivolumab in Patients With Advanced HER2-Expressing Solid Tumors	1/2	BDC-1001	390	AEs, DLTs, MTD, ORR	Documented HER2-protein expression or gene amplification for which approved therapies have been exhausted or are not clinically indicated.	Recruiting
BASKET TRIALS PHASE 2:							
NCT03929666	Phase 2 Study of ZW25 Plus First-line Combination Chemotherapy in HER2-Expressing Gastrointestinal (GI) Cancers, Including Gastroesophageal Adenocarcinoma (GEA), Biliary Tract Cancer (BTC), and Colorectal Cancer (CRC)	2	Zanidatamab	362	DLTs, AEs, ORR	IHC 3 + with or without gene amplification; or IHC 0, 1 + or 2 + with gene amplification	Recruiting *does not include pancreatic cancers
NCT04579380	A Phase 2 Basket Study of Tucatinib in Combination With Trastuzumab in Subjects With Previously Treated, Locally Advanced Unresectable or Metastatic Solid Tumors Driven by HER2 Alterations	2	Tucatinib + trastuzumab	217	ORR	HER2 overexpression/amplification from fresh or archival tumor tissue or blood or known activating HER2 mutations detected in fresh or archival tumor tissue or blood	Active, not recruiting
NCT04482309	A Phase 2, Multicenter, Open-label Study to Evaluate the Efficacy and Safety of Trastuzumab Deruxtecan (T-DXd, DS-8201a) for the Treatment of Selected HER2 Expressing Tumors (DESTINY-PanTumor02)	2	Trastuzumab deruxtecan	268	ORR	HER2 expression by local or central assessment, excluding ERBB2 somatic mutation without HER2 tumoral protein expression	Active, not recruiting
NCT04639219	A Phase II, Multicenter, Open-label Study to Evaluate the Efficacy and Safety of Trastuzumab Deruxtecan (T-DXd) for the Treatment of Unresectable and/or Metastatic Solid Tumors Harboring HER2 Activating Mutations Regardless of Tumor Histology	2	Trastuzumab deruxtecan	102	ORR	Pre-specified HER2 mutations locally determined by NGS	Active, not recruiting
NCT04430738	A Phase 1b/2 Dose Escalation and Expansion Study of Tucatinib in Combination With Trastuzumab and Oxaliplatin-based Chemotherapy or Pembrolizumab-containing Combinations for HER2 + Gastrointestinal Cancers	1b/2	Multiple combinations (dose finding)	120	Aes, DLTs	HER2 + disease, as determined by historic or local laboratory testing	Recruiting
NCT03602079	A Phase I-II, FIH Study of A166 in Locally Advanced/Metastatic Solid Tumors Expressing Human Epidermal Growth Factor Receptor 2 (HER2) or Are HER2 Amplified That Did Not Respond or Stopped Responding to Approved Therapies	1/2	A166 (ADC)	49	Phase 1: max tolerated dose (no outcome measures listed for phase 2…)	HER2 positive (by ISH or NGS) disease or HER2 expressing disease. HER2 expression of IHC ≥ 1+	Active, not recruiting
NCT05150691	A Phase 1/2a, Multicenter, Open-Label, Non-Randomized First in Human Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Antitumor Activity of DB-1303 in	1/2a	DB-1303	360	Phase 1: AEs, DLTs, SAEs, MTD, Recommended phase 2 dose. Phase 2a: %	Provide pre-existing diagnosis of HER2 status or resected tumor samples or undergo fresh tumor	Recruiting

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Table 5 (*continued*)

ClinicalTrials.gov Identifier	Official title	Phase	Intervention	n	Primary endpoint	HER-2 Status	Trial status
	Patients With Advanced/Metastatic Solid Tumors				TEAEs, SAEs, ORR	biopsy for HER2 testin	

HER-2 targeting in CRC will be an option, like the treatment paradigm in HER-2 overexpressing breast and gastric cancers.

Discussion

The treatment landscape for GI cancers that exhibit HER2 overexpression or amplification is evolving rapidly, offering improved outcomes for this biomarker-defined group of patients across many GI cancers.

A standardized method for scoring HER-2 based on tissue analysis in GI cancers would be highly useful, one current limitation in this space is that there is significant variability among scoring and testing practices making the prevalence of HER-2 amplification/overexpression unclear and will impact ease of uptake of more universal testing. Currently there is only standardized tumor specific HER-2 testing in breast and gastric cancer. Strategies such as a pan-cancer HER-2 index would be valuable to introduce a standard testing approach for future clinical trial design and ultimately, if successful, implementation into clinical practice [130].

It is important to consider alternative options for investigating for the presence of HER-2 amplification, there is a potential role for circulating tumor DNA (ctDNA) in this space. For example, HER-2 gene copy number when assessed by ctDNA has been found to be concordant with standard of care ISH/IHC testing at rates of 61–91 % [131,132]. ctDNA is an attractive option for testing as it offers a less invasive approach for obtaining samples from patients. Methods to improve concordance with known markers of HER-2 amplification require further investigation before this can become a standard of care test, and it may still require reflex tissue testing if ctDNA is not detected in the blood.

Optimal and timely testing with any methodology will be important to transition HER-2 targeted therapies into routine care as they become available in standard of care and until then, available on clinical trial. As with MMR/MSI testing, there may be an argument for HER-2 to be a reflexively tested biomarker at diagnosis across all GI cancers. The line of sight for cancer treatment incorporates biomarker directed therapies, in this era of establishing routine biomarker testing it is critical to consider methods in line with companion diagnostics for each treatment option. Challenges for implementation in routine pathways include methodology which may be tissue/tissue NGS/blood-based NGS, depending on levels of validation. Implementation needs to be routine across different healthcare systems in a way that is fair, equitable and strategic.

Response to HER-2 directed therapy has not been uniform across GI tumor types, this is demonstrated by a great, practice changing, response following the ToGA trial in gastric cancer, but the same benefit has not been demonstrated by the same treatment regimen in other tumor sites. Advancement in the HER-2 targeting space using T-DXd opened a new FDA-approved tumour agnostic indication in all solid tumours for patients who have no further standard of care treatment options and HER-2 IHC3+ [96]. Current HER-2 directed therapy that has become standard of care in GE cancers has been used in addition to PD-1 inhibition, the synergistic effects warrant further investigation in other GI tumor types [68]. It has been demonstrated that HER-2 directed therapy with MAbs requires an adaptive immune response to improve tumor control [133]. Further investigation into immune system activation in combination with HER-2 targeted therapies is warranted.

There are several ongoing clinical trials assessing HER-2 targeted treatments in GI cancers including novel MAbs, ADCs, bispecific T cell engagers, vaccines, and CAR-T (Table 5). Findings from these trials could offer meaningful treatment opportunities for patients with previously poor prognosis.

Declaration of interest

LJ – none. DC – Clovis, Eli Lilly, 4SC, Bayer, Celgene, NIHR EME, Leap, Roche, Ovibio. NS – Guardant, AstraZeneca, BMS, Eli Lilly, Merck, Roche, MSD Oncology, Servier, GSK, Novartis, Amgen, Pierre Fabre, Seagen, Pfizer, Gilead, Janssen.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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