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Immunotherapy for Gastrointestinal Malignancies

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Abstract

Gastrointestinal (GI) malignancies (esophageal, gastric, pancreatic, intra- and extra-biliary ductal, hepatocellular, and colorectal cancers) are an important cause of cancer incidence and mortality in the US and globally. GI cancers account for 15.4% and 23.8% of incident cancers and cancer-related deaths respectively in the US alone. Although earlier diagnosis and treatment advances have improved outcomes for some GI malignancies, the need for improved therapies in all disease phases (adjuvant, neoadjuvant and advanced) is paramount. Utilization of monoclonal antibodies targeting against vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) has shown the success in selected colorectal carcinoma patients. More investigations of immunotherapy are on going in the treatment of GI malignances with different mechanisms and methods. In this article, we review data for established and evolving immunotherapy-related treatment options in GI malignancies.

Keywords

Colorectal Carcinoma, Gastric Carcinoma, Pancreatic Carcinoma, Hepatocellular Carcinoma, Gallbladder and Biliary Duct Carcinoma, Advanced, Metastatic, Immunotherapy, Vaccine, Monoclonal Antibody

1. Introduction

Gastrointestinal (GI) malignancies refer to malignant neoplasms of the GI tract and accessory organs of digestion system: esophagus, stomach, liver and biliary system, pancreas, small intestine, colon and rectum, appendix and anus. Overall, GI malignancies account for more incident cases and deaths than any other organ system. However, these cancers are highly disparate: involving tumors of various histological types (e.g. adenocarcino-

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ma vs. squamous carcinoma and others) and subtypes with vastly different incidences, lifetime risks and outcomes as outlined in **Table 1**.

The primary intently curative treatment option for most GI malignancies is still surgical resection though combined modality therapy (concurrent chemotherapy and radiotherapy) has equivalent outcomes in anal cancer. Adjuvant and/or neoadjuvant chemotherapy or chemoradiotherapy has been shown to improve overall survival in select populations. However, given the absence of a proven screening modality in malignancies other than colonoscopy in colorectal cancer, most patients with cancers from GI system are diagnosed at an advanced stage. Effective screening modalities for cancers and discovering active chemotherapeutic, biologic agents in advanced disease are both areas of active investigational efforts in GI malignancies.

Unlike melanoma and renal cell cancer in which immunotherapeutic options were a focus of early efforts, similar approaches in GI malignancies have only recently been exploited likely secondary to early successes with cytotoxic chemotherapy. However, observations support exploring immunotherapeutic modalities in GI malignancies: tumor associated antigens (TAA) associated with tumor-specific immune responses in esophageal (MAGE-A3/4 and NYESO-1), gastric (Her-2/neu), pancreatic (MUC1 and mesothelin), hepatocellular (AFP, GPC3, NY-ESO-1, SSX-2, MAGE-A and TERT) and colorectal (CEA) malignancies [1]-[12]; tumor-specific cytotoxic T-cells higher levels of which correlate with improved prognosis [13] [14]; and T-cell inhibitory factors [CD4+ Foxp3+ regulatory T-cells (Tregs) and myeloid-derived suppressor cells (MDSCs)] higher levels of which correlate with poorer prognosis [15] [16]. In this article, we broadly delineate the various immunotherapeutic options that have been or are explored in GI malignancies.

2. Monoclonal Antibody Mediated Targeted Therapy

2.1. EGFR Inhibition: Cetuximab (Erbitux®) and Panitumumab (Vectibix®)

Epidermal growth factor receptor (EGFR) mediated signaling plays important roles in colorectal cancer (CRC) initiation and progression making EGFR inhibition an attractive target. There have been extensive studies in CRC regarding the efficacy, appropriate subpopulation and toxicity. However, limited studies have been pursued in esophageal, gastric, pancreatico-biliary and/or hepatocellular carcinomas.

EGFR engages several downstream signaling cascades including PI3K (PI3K/AKT/mTOR) and MAP kinase (RAS/RAF/MEK/ERK) pathways which mediate cell differentiation, proliferation, and survival. RAS is a membrane bound protein which exchanges bound GDP for GTP and has intrinsic GTPase activity which ensures self-inactivation by GTP hydrolysis. RAS couples growth factor receptors to intracellular signaling pathways by activating downstream targets such as RAF, ERK1, ERK2 and PI3K that promote cell proliferation [17]. Three human RAS genes have been identified: HRAS, KRAS, and NRAS. Oncogenic KRAS typically contain single amino acid substitutions (most frequently, in codons 12/13/61) that produce KRAS proteins with strongly reduced intrinsic GTPase activity resulting in constitutively activated GTP-bound state. Activating KRAS mutations are instrumental in the growth and proliferation of a wide variety of tumor types including melanoma, lung, CRC, thyroid and pancreatic carcinomas with a prevalence ranking from 11% (melanoma) to 95% (pancreatic adenocarcinoma) [18]. Uniquely in CRC, the chronological sequence of mutations during the tumorigenic pro-

Table 1. Incidence and survival in GI malignancies.

	Cases in 2013 (% of New Cancer Cases)	Incidence of New Cases (per 100,000 population, 2006-2010)	Deaths in 2013 (% of Cancer Deaths)	Death Incidence (per 100,000 population, 2006-2010)	5-Year Survival (%, 2003-2009)	Lifetime Risk
Colo-Rectal Cancer	142,820 (8.6%)	45.0	50,830 (8.8%)	16.4	64.9%	4.8%
Pancreatic	45,220 (2.7%)	12.2	38,460 (6.6%)	10.9	6.0%	1.5%
Liver and Bile Duct (intra-hepatic)	30,640 (1.8%)	7.7	21,670 (3.7%)	5.6	16.1%	0.9%
Esophageal	17,990 (1.1%)	4.4	15,210 (2.6%)	4.3	17.3%	0.5%
Small Intestine	8810 (0.5%)	2.1	1170 (0.2%)	0.4	64.5%	0.2%
Anal	7060 (0.4%)	1.7	880 (0.2%)	0.2	65.6%	0.2%

Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Mortality—All COD, Aggregated with State, Total US (1969-2010), National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013, accessed March 30, 2014. Underlying mortality data provided by NCHS (www.cdc.gov/nchs).

cess determines the eventual phenotype [19].

Cetuximab (a mouse/human chimeric, IgG1) and panitumumab (a full human, IgG2) are anti-EGFR monoclonal antibodies (MoAb) that competitively inhibit ligand-receptor binding and GTP phosphorylating, effectively disrupting downstream signaling. Additionally, given IgG1 isotype, cetuximab may activate complement pathway and mediate antibody-dependent cellular cytotoxicity (ADCC). Early phase studies of EGFR inhibition in CRC yielded positive results and prompted phase III studies [20]-[40]. Given KRAS' role in mediating EGFR signaling, it was postulated that gain of function mutations would result in constitutively activated KRAS and consequent loss of sensitivity to EGFR inhibition in colorectal carcinoma. Proof of concept was initially provided by retrospective analysis of the NCIC CTG/AGITG CO17 phase III trial. KRAS mutation status was determined in 68.9% of the original cohort, and was fortuitously well-balanced in both arms. Authors reported KRAS mutant patients did not benefit from cetuximab, while KRAS wild type (WT) patients had significantly improved PFS/OS [20] [21]. This observation was buttressed by analyses of the CRYSTAL and OPUS studies [26]. Other published data supports a lower rate of response to EGFR inhibition in patients with BRAF/NRAS/HRAS mutations or activating mutations of PIK3CA pathway [41]. The FDA and EMA recommend that EGFR inhibitors be utilized only in KRAS WT patients, and NCCN guideline recommends further that EGFR inhibitorsshould only be considered in mCRC patients with KRAS and NRAS WT [42].

Cetuximab was the first EGFR inhibitor to be approved by the Food and Drug Administration (FDA) and European Medicine Agency (EMA) both as a single agent in relapsed/refractory colorectal carcinomaand together with combination chemotherapy in the 1st line setting on the basis of several randomized phase III studies. Similar results have been observed with panitumumab subsequently. These results are discussed below and depicted in **Table 2**.

Since agents targeting both EGFR (cetuximab and panitumumab) and vascular endothelial growth factor (VEGF) (bevacizumab, ziv-aflibercept) have gained regulatory approval for KRAS/NRAS WT mCRCpatients, the sequence of application of either agent has been in debate. FIRE-3, a phase III randomizedstudy, compared FOLFIRI/cetuximab to FOLFIRI/bevacizumab in 592 KRAS WT patients as the first line therapy. Overall response rate (ORR) and median progression-free survival (mPFS) were similar in both arms, however, the median overall-all survival (mOS) was significantly prolonged with the arm with cetuximabfirst compared to the arm with bevacizumabfirst (28.7 vs. 25.0 months respectively) despite greater treatment intensity in the bevacizumab arm [31]. Whether the improved mOS observed was related to cetuximab itself or post-progression therapy remains unclear as final results have yet to be published. CALGB/SWOG C80405 is a randomized phase III study of standard chemotherapy regimens (FOLFOX or FOLFIRI) in combination with either bevacizumab or cetuximab in KRAS WT patients as the first line therapy that completed accrual in 2012, the results of which may clarify this issue.

Depending on whether patients were initially treated with a regimen with an oxaliplatin-backbone (FOLFOX/XELOX) or an irinotecan-backbone (FOLFIRI/XELIRI), 2nd line therapy typically involves a switch between backbones. In KRAS/NRAS WT patients who did not received 1st line EGFR inhibition, adding either cetuximab or panitumumab is advised. There is no data to guide decision making between cetuximab and panitumumab though the higher rate of cetuximab-related infusion reactions in certain geographical regions (in tandem with increased rates of atopy) is a practical consideration [43]. In KRAS/NRAS WT patients who received 1st line EGFR inhibition (either cetuximab or panitumumab), this is typically not continued at the time of progression as cross-resistance is assumed given the similar mechanisms of action. Minimal data is available to address this issue: two clinical trials of panitumumab use in KRAS WT patients who progressed on cetuximab containing regimens arrived at divergent conclusions [44] [45].

Somatic mutations in KRAS (<5% - 10%) and BRAF (2%) are unusual events in esophageal and gastric cancers [46]. Non-randomized studies suggested added RFS/OS/RR benefit when cetuximab was added to conventional chemotherapy in advanced esophagogastric cancer. However, this was not borne out in 2 phase III randomized trials of gastric cancer (EXPAND) and esophagogastric cancer (REAL-3) (see **Table 2**) [34] [40]. The role of adjuvant EGFR inhibition in advanced esophagogastric cancer is being evaluated in a NCI non-randomized phase II study (NCT01360086, perioperative cisplatin/5-FU with cetuximab).

Although phase II studies in unselected populations were promising, the S0205 phase III study of cetuximab in advanced pancreatic cancer was negative [35]. However, both cetuximab and panitumumabin combination with cytotoxic agents have demonstrated benefit in several phase II studies in advancedcholangiocarcinoma [47]-[50].

Initial phase II studies demonstrated tolerability of cetuximab when added to chemotherapy in HCC [51] [52].

Table 2. Published phase III trials of monoclonal antibodies in GI malignancies.

Agent (Trade name, Sponsors)	Study Reference	Disease Type (No. of Evaluable Patients)	Study Design and Endpoints	Dose and Schedule	Response Rate (%)	PFS and OS
Cetuximab (Erbitux®, ImClone LLC and Eli Lilly)	NCIC CTG/ AGITG CO.17 (CA225025) [20] [21]	2nd line relapsed/ refractorymCRCagainst BSC (572 evaluable) Initial enrollment (572): • cetuximab+BSC (287) vs. BSC (285) Repeat analysis: By KRAS mutation status (394): • KRAS mutant (164, 41.6%): Cetuximab + BSC 40.9% vs. BSC 42.3% • KRAS WT (230, 58.4%): Cetuximab+BSC 59.1% vs. BSC 57.7% By arm: • Cetuximab+BSC (198): WT 58.4% vs. mutant 41.6% • BSC (196): WT 58.4% vs. mutant 41.6%	Randomized open-label phase III trial of BSC +/− weekly cetuximab Primary: OS Secondary: PFS, RR	Cetuximab: IV cetuximab 400 mg/m^2 induction followed by maintenance IV cetuximab 250 mg/m^2 qweekly	Initial analysis (C vs. BSC, all analyses significant): • RR: 8% (all PR) vs. 0% • Disease stabilization: 39.4% (PR/SD) vs. 10.9% (SD) Repeat analysis by KRAS mutation status (C vs. BSC): • Not reported	Initial analysis (C vs. BSC): • OS: 4.6 mths vs. 6.1 mths • PFS: unreported Repeat analysis by KRAS mutation status (C vs. BSC): KRAS mutant: • OS: 4.6 mths vs. 4.5 mths • PFS: 1.8 mths vs. 1.8 mths KRAS WT • OS: 4.8 mths vs. 9.5 mths • PFS: 1.9 mths vs. 3.7 mths
	CRYSTAL [22] [23] [26]	1st line mCRC treated with FOLFIRI (1198 evaluable) Initial enrollment (1198): • FOLFIRI/C (599) vs. FOLFIRI (599) Subgroupanalysis: By KRAS mutation status (540): • KRAS WT 64.4% vs. mutant 35.6% By arm: • FOLFIRI+C: 66.9% WT vs. mutant 33.1% • FOLFIRI: 62.1% WT vs. mutant 37.9%	Randomized open-label phase III trial of 2 weekly FOLFIRI +/− weekly cetuximab Primary: PFS Secondary: OS, RR	FOLFIRI: IV irinotecan 180 mg/m^2 D1, IV leucovorin, IV 5-FU bolus 400 mg/m^2 D1 with 2400 mg/m^2 46 hr infusion FOLFIRI +/− cetuximab: Cetuximab as above + FOLFIRI	Initial analysis (FOLFIRI vs. FOLFIRI/C): • RR 38.7% vs. 46.9% Subgroup analysis by KRAS mutation status (FOLFIRI vs. FOLFIRI/C): • KRAS mutant: 40.2% vs. 36.2% • KRAS WT: 53.2% vs. 59.3%	Initial analysis (FOLFIRI vs. FOLFIRI/C): • OS: 18.6 mths vs. 19.9 mths • PFS: 8.0 mths vs 8.9 mths Subgroup analysis by KRAS mutation status: KRAS mutant (FOLFIRI vs. FOLFIRI/C): • OS: 17.7 mths vs. 17.5 mths • PFS: 8.1 mths vs. 7.6 mths KRAS WT (FOLFIRI vs. FOLFIRI/C) • OS: 21.0 mths vs. 24.9 mths • PFS: 8.7 mths vs. 9.9 mths
	OPUS (EMR 62 202-047) [24]-[26]	1st line mCRC treated with FOLFOX-4 (337 evaluable) Initial enrollment (337): • FOLFOX-4 (168) vs. FOLFOX-4/C (169) Subgroupanalysis: By KRAS mutation status (315): • KRAS WT 56.8% vs. mutant 43.2% By arm: • FOLFOX-4 (156): 62.2% WT vs. 37.8% mutant • FOLFOX-4/C (159): 51.6% WT vs. 48.4% mutant	Randomized open-label phase II trial of 2 weekly FOLFOX-4 +/− weekly cetuximab Primary: RR Secondary: rate of curative metastatic surgery, DCR, OS, PFS	FOLFOX-4: IV oxaliplatin 85 mg/m^2 D1, IV leucovorin, IV 5-FU bolus 400 mg/m^2 D1 with 600 mg/m^2 22 hr infusion FOLFOX-4 +/− cetuximab: Cetuximab as above + FOLFOX-4	Initial analysis of RR (FOLFOX-4 vs. FOLFOX-4/C: • 36% vs. 46% Initial analysis of DCR (FOLFOX-4 vs. FOLFOX-4/C): • 81% vs. 85% Subgroup analysis of RR by KRAS mutation status (FOLFOX-4 vs. FOLFOX-4/C): • KRAS mutant: 49% vs. 33% • KRAS WT: 37% vs. 61% Subgroup analysis of DCR by KRAS mutation status (FOLFOX-4 vs. FOLFOX-4/C): • KRAS mutant: 85% vs. 85% • KRAS WT: 78% vs. 92%	Initial analysis (FOLFOX-4 vs. FOLFOX-4/C): • Median PFS: 7.2 mths vs. 7.2 mths Subgroup analysis by KRAS mutation status: KRAS mutant (FOLFOX-4 vs. FOLFOX-4/C): • Median PFS: 8.6 mths vs. 5.5 mths • Median OS: 17.5 mths vs. 13.4 mths KRAS WT (FOLFOX-4 vs. FOLFOX-4/C) • Median PFS: 7.2 mths vs. 8.3 mths • Median OS: 18.5 mths vs. 22.8 mths

Continued

Cetuximab (Erbitux®, ImClone LLC and Eli Lilly)	MRC COIN [27]	1st line mCRC treated with FOLFOX-6/XELOX (OPTIMOX-2 regimenevaluated in arm C reportedseparately) (1630 evaluable) Initial enrollment (1630): • FOLFOX-6/XELOX (815) vs. FOLFOX-6+C/XELOX+C (815) Subgroupanalysis: By KRAS mutation status (1316): • KRAS/NRAS WT 55.4% vs. mutant 44.6% By arm: • FOLFOX-6/XELOX (648): 56.6% WT vs. 41.4% mutant (2.0% BRAF) • FOLFOX-6+C/XELOX+C (668): 54.2% WT vs. 44.5% mutant (1.3% BRAF)	Randomized open-label phase III trial of FOLFOX-6/ XELOX (FOLFOX-6 2 weekly, XELOX 3 weekly) +/− weekly cetuximab Primary: OS Secondary: PFS	FOLFOX-6: IV oxaliplatin 85 mg/m^2 D1, IV leucovorin, IV 5-FU bolus 400 mg/m^2 D1 with 2400 mg/m^2 46 hr infusion XELOX: IV oxaliplatin 85 mg/m^2 D1 + capecitabine 850 mg/m^2 twice daily FOLFOX-6/ XELOX +/− cetuximab: Cetuximab as above + FOLFOX-4/ XELOX	Analysis of ORR by KRAS mutation status (FOLFOX-6/XELOX vs. FOLFOX-6+ C/XELOX+C) • KRAS WT: 57% vs. 64%	Analysis by KRAS mutation status: KRAS mutant (FOLFOX-6/ XELOX vs. FOLFOX-6+ C/XELOX+C) • Median PFS: not reported • Median OS: 14.8 mths vs. 13.6 mths KRAS WT (FOLFOX-6/XELOX vs. FOLFOX-6+ C/XELOX+C) • Median PFS: 8.6 mths vs. 8.6 mths • Median OS: 17.9 mths vs. 17.0 mths
	NORDIC-VII [28]	1st line mCRC treated with continuous/intermittent FLOX (566 evaluable) Initial enrollment (566): • FLOX (A-185) vs. FLOX+C (B-194) vs. intermittent FLOX+C (C-187) Subgroupanalysis: By KRAS mutation status (498): • KRAS WT 61% vs. mutant 39% By BRAF mutation status (457): • BRAF WT 88% vs. mutant 12% By arm: • KRAS mutant: FLOX (37% mutant) vs. FLOX+C (43% mutant) vs. intermittent FLOX+C (37% mutant) • BRAF mutant: FLOX (13% mutant) vs. FLOX+C (13% mutant) vs. intermittent FLOX+C (10% mutant)	Randomized open-label phase III trial of continuous/ intermittent FLOX +/− weekly cetuximab Primary: PFS Secondary: OS, ORR	Continuous FLOX: IV oxaliplatin 85 mg/m^2 D1, IV leucovorin, IV 5-FU bolus 500 mg/m^2 D1 Cetuximab as above	Overall analysis of ORR (FLOX vs. FLOX+C vs. intermittent FLOX+C): • 41% vs. 49% vs. 47%	Overall analysis (FLOX vs. FLOX+C vs. intermittent FLOX+C) • Median PFS: 7.9 mths vs. 8.3 mths vs. 7.3 mths • Median OS: 20.4 mths vs. 19.7 mths vs. 20.3 mths Analysis by KRAS mutation status: KRAS WT • PFS/OS: No difference KRAS mutant • PFS: Trend towards improved PFS with cetuximab, no significant difference. • OS: No significant difference
	EPIC [29]	2nd line mCRCafterfailing FOLFOX in combinationwithirinotecan (1298 evaluable) Initial enrollment (1298): • I (650) vs. I/C (648) Subgroup analysis by KRAS mutation status: • Not reported	Randomized multi-center open-label phase III trial of 3 weekly irinotecan +/− cetuximab Primary: OS Secondary: PFS, RR	I +/− cetuximab: IV irinotecan 350 mg/m^2 q3 weekly Cetuximab as above	Initial analysis of RR (I vs. I/C): • 4.2% vs. 16.4% Subgroup analysis by KRAS mutation status: • Not reported	Initial analysis (I vs. I/C): • OS: 10.0 mths vs. 10.7 mths • PFS: 2.6 mths vs. 4.0 mths Subgroup analysis by KRAS mutation status: • Not reported

Continued

Cetuximab (Erbitux®, ImClone LLC and Eli Lilly)	ASPECCT [30]	Relapsed/refractory KRAS WT mCRC (1010 evaluable)	Randomized non-inferiority multi-center open-label phase III trial of 2-weekly panitumumab vs. weekly cetuximab Primary: OS (non-inferiority) Secondary: PFS, RR	Panitumumab: IV panitumumab 6 mg/m^2 q2 weekly Cetuximab as above	Not reported	Initial analysis: • OS: HR 0.966 (95% CI 0.839 - 1.113, non-inferiority boundary met) • PFS/RR not reported
	FIRE-3 [31]	1st line KRAS exon 2 WT mCRC in combinationwith FOLFIRI (735 evaluable)	Randomized multi-center open-label phase III trial of FOLFIRI/cetuximab (arm A) vs. FOLFIRI/bevacizumab (arm B) Primary: ORR	FOLFIRI as above Cetuximab as above Bevacizumab: IV bevacizumab 5 mg/kg q2 weekly	Initial analysis of RR (FOLFIRI/C vs. FOLFIRI/B): • 62% vs. 57% (non-significant)	Initial analysis of PFS/OS (FOLFIRI/C vs. FOLFIRI/B): • Median PFS: 10.3 mths vs. 10.4 mths (non-significant) • Median OS: 28.8 mths vs. 25.0 mths (significant)
	NCCTG N0147 [32]	Adjuvant CRC in combinationwith FOLFOX-6 in resected stage III CRC (2686 enrolled/randomized, treatmenthalted and trial closedafter 2580 treated) Initial enrollment (2686): • FOLFOX-6 (1337) vs. FOLFOX-6/C (1349) Subgroupanalysis: By KRAS mutation status (2580): • KRAS WT 72.2% vs. mutant 27.8% By arm: • FOLFOX-6: KRAS WT 70.8% vs. mutant 29.2% • FOLFOX-6/C: KRAS WT 73.6% vs. mutant 26.4%	Randomized multi-center open-label phase III trial of adjuvant FOLFOX-6 +/− cetuximab in stage III CRC following resection Primary: DFS Secondary: OS, TTR	FOLFOX-6 as above Cetuximab as above	Not applicable	Analysis by mutation status (FOLFOX-6 vs. FOLFOX-6/C) KRAS mutant • 3-year DFS: 67.1% vs. 65.0% • OS: 87.9% vs. 82.7% • TTR: 67.9% vs. 67.0% KRAS WT • 3-year DFS: 74.6% vs. 71.5% • OS: 87.3% vs. 85.6% • TTR: 76.9% vs. 74.4% BRAF mutant • 3-year DFS: 67.3% vs. 68.9% • OS: 74.8% vs. 73.7% • TTR: 71.2% vs. 71.9%
	PETACC-8 [33]	Adjuvant CRC in combination with FOLFOX-4 in resected stage III CRC (2344 randomized) Subgroupanalysis: By KRAS mutation status (2344): • KRAS WT 68.3% vs. mutant 31.7% By arm: • FOLFOX-6: Not reported • FOLFOX-6/C: Not reported	Randomized multi-center open-label phase III trial of FOLFOX-4 +/− cetuximab Primary: DFS Secondary: Not reported	FOLFOX-4 as above Cetuximab as above	Not applicable	Analysis by mutation status (FOLFOX-4 vs. FOLFOX-4/C) KRAS mutant • DFS/OS: No significant difference KRAS WT • DFS: HR 1.05 • OS: HR 1.09

Continued

	EXPAND [34]	1st line advancedgastric cancer in combination with cisplatin/capecitabine (882 evaluable)	Randomized multi-center open-label phase III trial of cisplatin/capecitabine (CX) +/− cetuximab Primary: PFS Secondary: OS, RR	Cisplatin/ capecitabine (CX): IV cisplatin 80 mg/m^2 D1 only + oral capecitabine 1000 mg/m^2 twice daily D1-D15 q3 weekly Cetuximab as above	Analysis of RR (CX vs. CX/C): • RR (CR/PR): 29% vs. 30% • DCR (CR/PR/SD): 71% vs. 73%	Analysis of PFS/OS (CX vs. CX/C): • Median PFS: 5.6 mths vs. 4.4 mths • Median OS: 10.7 mths vs. 9.4 mths
	S0205 [35]	1st line advancedpancreatic cancer in combination with gemcitabine (743 evaluable)	Randomized multi-center open-label phase III trial of gemcitabine (G) +/− cetuximab Primary: OS Secondary: OR, PFS	Gemcitabine: IV gemcitabine 1000 mg/m^2 weekly 7-on, 1-off Cetuximab as above	Initial analysis of RR (G vs. G/C): • RR (CR/PR): 14% vs. 12% • DCR (CR/PR/SD): 30% vs. 37%	Initial analysis of PFS/OS (G vs. G/C): • Median PFS: 3.0 mths vs. 3.4 mths • Median OS: 5.9 mths vs. 6.3 mths
Panitumumab (Vectibix®, Illumina and Amgen)	Van Cutsem E, *et al*. [36]	2nd line relapsed/refractorymCRC against BSC (463evaluable) Initial enrollment (463): • panitumumab+BSC (231) vs. BSC (232)	Randomized open-label phase III trial of BSC +/− 2-weekly panitumumab Primary: PFS Secondary: RR, OS	Panitumumab: IV panitumumab 6 mg/m^2 q2 weekly	Initial analysis (BSC vs. P): • RR: 0% vs. 10% (all PR) • DCR: 10% (SD) vs. 27% (PR/SD)	Initial analysis (BSC vs. P): • OS: HR 1.00 • PFS: 8 weeks vs. 7.3 weeks
	PRIME [37]	1st line mCRC in combination with FOLFOX-4 (1183) Initial enrollment (1183 evaluable): • FOLFOX-4 (590) • FOLFOX-4/P (593) By KRAS mutation status (1096): • FOLFOX-4 (550) • FOLFOX-4/P (546) By arm: • FOLFOX-4: KRAS WT (60.2%) vs. KRAS mutant (39.8%) • FOLFOX-4/P: KRAS WT (59.5%) vs. KRAS mutant (40.5%)	Randomized multi-center open-label phase III trial of 1st line FOLFOX-4 vs. FOLFOX-4/P Primary: PFS Secondary: OS, ORR	FOLFOX-4 +/− P: FOLFOX-4 as above Panitumumab as above	Analysis by KRAS mutation status (FOLFOX-4 vs. FOLFOX-4/P): • KRAS mutant: 48% vs. 55% • KRAS WT: 40% vs. 40%	Analysis by KRAS mutation status (FOLFOX-4 vs. FOLFOX-4/P): KRAS mutant: • Median OS: 19.3 mths vs. 15.5 mths • Median PFS: 8.8 mths vs. 7.3 mths KRAS WT: • Median OS: 19.7 mths vs. 23.9 mths • Median PFS: 8.0 mths vs. 9.6 mths
	181 [38]	2nd line relapsed/refractory mCRC after failing priorchemotherapy (1186 evaluable) Initial enrollment (1186): • FOLFIRI (595) • FOLFIRI/P (591) By KRAS mutation status (1083): • FOLFIRI (542) • FOLFIRI/P (541) By arm: • FOLFIRI: KRAS WT (54.2%) vs. KRAS mutant (45.8%) • FOLFIRI/P: KRAS WT (56.0%) vs. KRAS mutant (44.0%)	Randomized multi-center open-label phase III trial of 2nd line FOLFIRI vs. FOLFIRI/P Primary: PFS and OS Secondary: ORR	FOLFIRI +/− P: FOLFIRI as above Panitumumab as above	Analysis by KRAS mutation status (FOLFIRI vs. FOLFIRI/P): • KRAS mutant: 35% vs. 10% • KRAS WT: 13% vs. 14%	Analysis by KRAS mutation status (FOLFIRI vs. FOLFIRI/P): KRAS mutant: • Median OS: 11.1 mths vs. 11.8 mths • Median PFS: 4.9 mths vs. 5.0 mths KRAS WT: • Median OS: 12.5 mths vs. 14.5 mths • Median PFS: 3.9 mths vs. 5.9 mths

Continued

Panitumumab (Vectibix®, Illumina and Amgen)	PICCOLO [39]	2nd line mCRCafterfailing 5-FU and/oroxaliplatin in combination with irinotecan in KRAS WT patients (460 evaluable) Initial enrollment (460): • I (230) vs. I/P (230)	Randomized multi-center open-label phase III trial of 2nd line irinotecan +/− panitumumab in KRAS WT patients Primary: OS Secondary: PFS, RR	I:IV irinotecan 350 mg/m^2 q3 weekly Panitumumab: IV panitumumab 9 mg/m^2 q3 weekly	Analysis (I vs. I/P): • RR: OR of response 4.12	Analysis (I vs. I/P): • Primary OS analysis after 246 deaths: 10.5 mths vs. 10.4 mths • Final OS analysis: 10.9 mths vs. 10.4 mths • PFS: HR 0.78
	REAL3 [40]	1st line advance desophagealadenoCA in combination with EOC (553 evaluable) Initial enrollment (553): • EOC (275) vs. EOC/P (278)	Randomized multi-center open-label phase III trial of 1st line EOC +/− panitumumab Primary: OS Secondary: PFS, RR	EOC: IV epirubicin 50 mg/m^2 D1, IV oxaliplatin 100 mg/m^2 D1, oral capecitabine 1000 mg/m^2 twice daily D1-D21 Panitumumab: IV panitumumab 9 mg/m^2 q3 weekly	Analysis (EOC vs. EOC/P): • RR: 42% vs. 46%	Analysis (EOC vs. EOC/P): • PFS: 7.4 mths vs. 6.0mths • 1-year PFS: 21% vs. 20% • OS analysis after 251 deaths: 11.3 mths vs. 8.8 mths • 1-year OS: 46% vs. 33%
	ASPECCT [30]			Seeabove		
Bevacizumab (Avastin®, Genentech)	Hurwitz *et al*. [56] [57]	1st line mCRC in combination with IFL (813 evaluable) Initial enrollment (813): • IFL/placebo (402) vs. IFL/B (411)	Randomized multi-center placebo-controlled phase III trial of 1st line IFL +/− bevacizumab Primary: OS Secondary: PFS, RR	IFL (given weekly for 4 weeks, cycles repeat q6weekly: IV irinotecan 125 mg/m^2 qweekly, IV 5-FU 500 mg/m^2 qweekly, IV leucovorin 20 mg/m^2 qweekly Bevacizumab: IV bevacizumab 5 mg/m^2 q2 weekly	Analysis (IFL vs. IFL/B): • RR: 34.8% vs. 44.8%	Analysis (IFL vs. IFL/B): • PFS: 6.2 mths vs. 10.6 mths • OS: 15.6 mths vs. 20.3 mths
	E3200 [58]	2nd line mCRCafterfailing 5-FU and/or irinotecan in combination with FOLFOX-4 (820 evaluable) Initial enrollment (820): • FOLFOX-4 (291) vs. FOLFOX-4/B (286) vs. B (243)	Randomized multi-center open-label phase III trial of 2nd line FOLFOX +/− bevacizumab Primary: OS Secondary: PFS, RR	FOLFOX-4 as above Bevacizumab: IV bevacizumab 10 mg/m^2 q2 weekly	Analysis (FOLFOX-4 vs. FOLFOX-4/B vs. B): • RR: 8.6% vs. 22.7% vs. 3.3%	Analysis (FOLFOX-4 vs. FOLFOX-4/B vs. B): • PFS: 4.7 mths vs. 7.3 mths vs. 2.7 mths • OS: 10.8 mths vs. 12.9 mths vs. 10.2 mths

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	NO16966 [59]	1st line mCRC 2 × 2 factorial combination with FOLFOX-4 or XELOX (1401 randomized, 1400 evaluable) Initial enrollment (1401): • FOLFOX-4 (351) vs. FOLFOX-4/B (349) vs. XELOX (350) vs. XELOX/B (350)	Randomized multi-center placebo-controlled 2 × 2 factorial phase III trial of 1st line FOLFOX/XELOX +/− bevacizumab Primary: PFS Secondary: on-treatment PFS, OS, RR	FOLFOX-4 as above XELOX: IV oxaliplatin 130 mg/m^2 D1 + oral capecitabine 1000 mg/m^2 twice daily D1-D15 q3 weekly Bevacizumab: IV bevacizumab 5 mg/m^2 q2 weekly (with FOLFOX-4) or 7.5 mg/m^2 q3 weekly (with XELOX)	Analysis (FOLFOX-4/XELOX vs. FOLFOX-4/ XELOX + B): • Investigator-assessed RR: 49% vs. 47% • Independent response review committee RR: 38% vs. 38%	Analysis (FOLFOX-4/ XELOX vs. FOLFOX-4/ XELOX + B): • PFS: 8.0 mths vs 9.4 mths • On-treatment PFS: 7.9 mths vs 10.4 mths • OS: 19.9 mths vs. 21.3 mths
	TML/ ML18147 [60]	Continuation bevacizumab in mCRC with switch chemotherapy in 1st progression (819 evaluable) Initial enrollment (819): • Switch chemotherapy (410) vs. switch chemotherapy + B (409)	Randomized multi-center open-label phase III trial of switch chemotherapy +/− bevacizumab maintenance Primary: OS Secondary: PFS, on-treatment PFS, RR	FOLFOX-4, XELOX, FOLFIRI, XELIRI as above Bevacizumab: IV bevacizumab 5 mg/m^2 q2 weekly (with FOLFOX-4/ FOLFIRI) or 7.5 mg/m^2 q3 weekly (with XELOX/ XELIRI)	Analysis (switch chemotherapy vs. switch chemotherapy+B): • RR (PR/CR): 3.9% vs. 5.4% • DCR (SD/PR/CD): 54.2% vs. 68.1%	Analysis (switch chemotherapy vs. switch chemotherapy+B): • On-treatment PFS: 4.0 vs. 5.7 mths • OS: 9.8 mths vs. 11.2 mths • Median OS from start of 1st line therapy: 22·5 mths vs. 23.9 mths
	TRIBE [61]	1st line mCRC combination bevacizumab with FOLFIRI vs. FOLFOXIRI (508 evaluable) Initial enrollment (508): • FOLFIRI/B vs. FOLFOXIRI/B	Randomized multi-center open-label phase III trial of FOLFIRI/B vs. FOLFOXIRI/B Primary: PFS Secondary: OS, RR, R0 resection rate	FOLFIRI/B as above. FOLFOXIRI/ B: IV oxaliplatin 85 mg/m^2 D1, IV irinotecan 165 mg/m^2 D1, IV leucovorin, IV 5-FU 3200 mg/m^2 48 hr infusion Bevacizumab: IV bevacizumab 5 mg/m^2 q2 weekly	Analysis (FOLFIRI/B vs. FOLFOXIRI/B): • RR (PR/CR): 53% vs. 65%	Analysis (FOLFIRI/B vs. FOLFOXIRI/B): • Median PFS: 9.7 mths vs. 12.2 mths • Median OS: 25.8 mths vs. 31.0 mths • R0 resection rate: 12% vs. 15%
	NSABP C-08 [62]	Adjuvant bevacizumab in stage II/III resected CRC in combination with FOLFOX-6 (2672 evaluable) Initial enrollment (2672): • FOLFOX-6 (1338) vs. FOLFOX-6/B (1334)	Randomized multi-center open-label phase III trial of FOLFOX-6 vs. FOLFOX-6/B in resected stage II/III CRC Primary: DFS Secondary: OS	FOLFOX-6 as above for 6 months Bevacizumab as above for 1 year	Not applicable	Analysis (FOLFOX-6 vs. FOLFOX-6/B): • Median DFS: HR 0.89 (non-significant) • 3-year DFS: 75.5% vs. 77.4% • 3-year DFS (stage II): 84.7% vs. 87.4% • 3-year DFS (stage III): 72.4% vs. 74.2%

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AVANT [63]	Adjuvant bevacizumab in stage II/III resected CRC in combination with FOLFOX-6 [3451 evaluable, 2861 (83%) stage III] Initial enrollment (3451): • FOLFOX-4 (1151/955 stage III) vs. FOLFOX-4/B (1155/960 stage III) vs. XELOX/B (1145/952 stage III)	Randomized multi-center open-label phase III trial of FOLFOX-4 vs. FOLFOX-4/B vs. XELOX/B in resected stage II/III CRC Primary: DFS (stage III patients)	FOLFOX-4, FOLFOX-4/B and XELOX/B as above	Not applicable	Analysis: • DFS: HR 1.17 (FOLFOX-4 vs. FOLFOX-4/B) (non-significant) • DFS: HR 1.07 (FOLFOX-4 vs. XELOX/B) (non-significant) • OS: HR 1.27 (FOLFOX-4 vs. FOLFOX-4/B) (significant) • OS: HR 1.15 (FOLFOX-4 vs. XELOX/B) (non-significant)
FIRE-3 [31]	Seeabove				
AVAGAST [64]	1st line metastaticgastriccarcinoma in combination with cisplatin/capecitabine (774 evaluable) Initial enrollment (774): • CX (387) vs. CX/B (387)	Randomized international multi-center placebo-controlled phase III trial of cisplatin/ capecitabine (CX) +/− bevacizumab Primary: OS Secondary: PFS, RR	Cisplatin/ capecitabine (CX) as above Bevacizumab: IV bevacizumab 7.5 mg/m^2 q3 weekly	Analysis (CX vs. CX/B): • RR: 37.4% vs. 46.0% (significant)	Analysis (CX vs. CX/B): • Median PFS: 5.3 mths vs 6.7 mths (significant) • Median OS: 10.1 mths vs. 12.1 mths (non-significant)
AVATAR [65]	1st line metastaticgastriccarcinoma in combination with cisplatin/capecitabine in Asian patients (202 evaluable) Initial enrollment (202): • CX (102) vs. CX/B (100)	Randomized multi-center placebo-controlled phase III trial of cisplatin/ capecitabine (CX) +/− bevacizumab Primary: OS Secondary: PFS, RR	Cisplatin/ capecitabine as above Bevacizumab as above	Analysis (CX vs. CX/B): • RR (PR/CR): 33.7% vs. 40.7% • DCR (PR/CR/SD): 72.1% vs. 75.3%	Analysis (CX vs. CX/B): • Median PFS: 6.0 mths vs 6.3 mths • Median OS: 11.4 mths vs. 10.5 mths
CALGB 80303 [66]	1st line metastaticpancreaticcarcinoma in combination with gemcitabine (535 evaluable) Initial enrollment (535): • G (256) vs. G/B (279)	Randomized multi-center placebo-controlled phase III trial of gemcitabine (G) +/− bevacizumab Primary: OS Secondary: PFS, RR	Gemcitabine (G vs. CX/B): IV gemcitabine 1000 mg/m^2 D1, 8 and 15 q4weekly Bevacizumab: IV bevacizumab 10 mg/m^2 D1 and 15 q4weekly	Analysis (G vs. G/B): • RR (PR/CR): 10% vs. 13%	Analysis (G vs. G/B): • Median PFS: 3.8 mths vs 2.9 mths • Median OS: 5.9 mths vs. 5.8 mths

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Ramucirumab (Cyramza®, Eli Lilly)	REGARD (I4T-IE-JVBD) [67]	2nd line relapsed/ refractorymetastaticesophagogastriccarcinoma against BSC (355 evaluable) Initial enrollment (535): • BSC (117) vs. BSC/R (238)	Randomized international placebo-controlled phase III trial of BSC +/ ramucirumab Primary: OS Secondary: PFS, 12-week, RR	Ramucirumab: IV ramucirumab 8 mg/kg q2 weekly	Analysis (BSC vs. BSC/R): • RR (PR/CR): 3% vs 3% • DCR (PR/CR/SD): 23% vs. 49%	Analysis (BSC vs. BSC/R): • Median OS: 3.8 mths vs. 5.2 mths • 6 month OS 31.6% vs. 41.8% • 12 month OS 11.8% vs. 17.6% • Median PFS 1.3 mths vs. 2.1 mths • Median 12-week PFS 15.8% vs. 40.1%
	RAINBOW (I4T-IE-JVBE) [68]	2nd line metastaticesophagogastriccarcinoma in combination with paclitaxel following progression on 1st line platinum- and fluoropyrimidine-containingchemotherapy (665 evaluable) Initial enrollment (665): • Paclitaxel (335) vs. paclitaxel/R (330)	Randomized international placebo-controlled phase III trial of paclitaxel +/− ramucirumab Primary: OS Secondary: PFS, 12-week, RR	Paclitaxel: IV paclitaxel 80 mg/m^2 D1, 8, 15 q4 weekly Ramucirumab as above	Analysis (P vs. P/R): • RR: 16% vs. 28%	Analysis (P vs. P/R): • Median OS: 7.4 mths vs. 9.6 mths • Median PFS: 2.9 mths vs. 4.4 mths
Ziv-aflibercept (Zaltrap®, Regeneron and Bayer)	VELOUR [69]	2nd line mCRC in combinationwith FOLFIRI following priortreatment with oxaliplatin-basedregimens (1226 evaluable) Initial enrollment (1226): FOLFIRI/placebo (614) vs. FOLFIRI/Z (612)	Randomized multi-center placebo-controlled phase III trial of FOLFIRI/ placebo vs. FOLFIRI/Z Primary: OS Secondary: RR	FOLFIRI as above q2 weekly Aflibercept: IV aflibercept 4 mg/kg q2 weekly	Analysis (FOLFIRI/placebo vs. FOLFIRI/Z): • RR (PR/CR): 11.1% vs 19.8%	Analysis (FOLFIRI/placebo vs. FOLFIRI/Z): • Median OS: 12.1 mths vs. 13.5 mths • 2 year survival: 18.7% vs. 28.0% • Median PFS: 4.7 mths vs. 6.9 mths
	VANILLA [70]	1st line metastaticpancreaticcarcinoma in combination with gemcitabine (546 evaluable) Initial enrollment (546): • G/placebo (275) vs. G/Z (271)	Randomized multi-center placebo-controlled phase III trial of G/placebo vs. G/Z Primary: OS Secondary: PFS, RR	Gemcitabine: IV gemcitabine 1000 mg/m^2 qweekly for 7 weeks out of 8 then qweekly for 3 weeks out of 4 Aflibercept as above	Analysis (G/placebo vs. G/Z): • RR (PR/CR): Not reported	Analysis (G/placebo vs. G/Z): • Median OS: 7.8 mths vs. 6.5 mths • 6 mth survival: 63% vs 54% • 12 mth survival: 25% vs. 21% • Median PFS: 3.7 mths vs. 3.7 mths • 6 mth PFS: 30% vs. 27% • 12 mth PFS: 4% vs. 3%

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Trastuzumab (Herceptin®, Roche)	TOGA [78]	1st line metastatic HER2+ GEJ/gastriccarcinoma in combination with cisplatin and 5-FU/capecitabine (CF or CX) (584 evaluable) Initial enrollment (584): • Chemotherapy (290) vs. chemotherapy/T (294)	Randomized international multi-center open-label phase III trial of chemotherapy vs. chemotherapy/T Primary: OS Secondary: PFS, RR	Chemotherapy (CF/CX): Cisplatin/5-FU (CF): IV cisplatin 80 mg/m^2 D1 + IV 5-FU 800 mg/m^2 daily D1-5 Cisplatin/ capecitabine (CX) as above Trastuzumab: IV trastuzumab 8 mg/kg induction followed by maintenance IV trastuzumab 6 mg/kg q3 weekly	Analysis (chemotherapy vs. chemotherapy/T): • RR (PR/CR): 35% vs 47% • DCR (PR/CR/SD): 70% vs. 79%	Analysis (chemotherapy vs. chemotherapy/T): • Median OS: 11.1 mths vs. 13.8 mths • Median PFS: 5.5 mths vs. 6.7 mths

PFS—progression-free survival; OS—overall survival; mCRC—metastatic colorectal carcinoma; BSC—best supportive care; RR—response rate; DCR—disease control rate.

However, a recent phase II study reported OS results that would be inferior when compared to sorafenib [53]. No further phase III evaluation of EGFR inhibition is planned in this disease.

2.2. VEGF Inhibition: Bevacizumab (Avastin®), Ramucirumab (Cyramza®) and Ziv-Aflibercept (Zaltrap®)

The ability of tumors to induce angiogenesis is a central concept in cancer proliferation [54]. Our understanding of tumor angiogenesis and its inhibition has evolved considerably: rather than directly inhibit tumor growth, VEGF-inhibition may mainly normalize abnormal tumor vasculature and improve delivery of cytotoxic agents [55].

Bevacizumab is a humanized monoclonal antibody that binds circulating VEGF-A, preventing its engagement with downstream VEGF receptors (VEGFR-1/2/3) with multifarious effects including inhibition of angiogenic signaling. Bevacizumab was the first biologic agent approved by the FDA to treat any malignancy in 2004 and EMA approval followed in 2005. Approval centered on the results of a front-line randomized phase III study in metastatic CRC with the combination of cytotoxic IFL (irinotecan/5-FU/leucovorin) chemotherapy plus bevacizumab vs. placebo, in which bevacizumab conferred an OS benefit of 4.7 months over IFL alone (20.3 vs. 15.6 months) [56]. A flurry of trials followed, evaluating bevacizumab's role in 1st and 2nd line settings with alternative chemotherapy combinations and in other diseases (non-small cell lung cancer, renal cell carcinoma, ovarian carcinoma, and glioblastomamultiforme). These results are summarized in **Table 2** [56]-[69].

The aggregate data demonstrated that bevacizumab is preferred in KRAS mutant mCRCpatients population since they do not benefit from EGFR inhibition. Mounting evidence supports prolonged duration of anti-VEGF therapy in metastatic CRC. NO16966 data suggested further improvement when bevacizumab was continued till overt progression and ML18147 confirmed that bevacizumab continuation past progression improved PFS and OS [59] [60]. Based on the negative results of AVANT and NSABP C-08, bevacizumabdid not show obvious benefit in either overall survival (OS) or disease-free survival(DFS) at the adjuvant setting for resected CRC [62] [63].

The role of bevacizumab in gastroesophageal cancer treatment has not been approved based on the 2 published large randomized phase III studies (AVAGAST, AVATAR). The AVAGAST study compared chemotherapy versus chemotherapy plus bevacizumab as the first line in patients with metastatic gastric cancer. Although, the study did not show obvious survival benefit by adding bevacizumab, patients with high baseline plasma VEGF-A levels, and low baseline expression of neuropilin-1 showed a trend toward improved overall survival [64] [106]. The other study, AVATAR, did not show benefit of bevacizumabadding to the combination of capecitabine and cisplatin in Chinese patients with metastatic gastric cancer [65]. A randomized phase III

study (ST03) is evaluating the role of adjuvant VEGF inhibition in EGJ/proximal gastric adenocarcinomas.

Ramucirumab is a fully human monoclonal antibody (IgG1) asVEGFR2 receptor antagonist that prevents the binding of VEGF to VEGFR2—the interaction thought to mediate the bulk of VEGF downstream effects. Ramucirumabmonotherapy modestly improved OS (5.2 months vs. 3.8 months) in 2nd line advanced EGJ/gastric carcinoma compared to placebo after prior platinum-containing or fluoropyrimidine-containing chemotherapy [67]. Ramucirumab has demonstrated benefit in the 2nd line setting when combined with paclitaxel chemotherapy in patients who progressed on prior 1st line platinum- and 5-FU-based combinations (RAINBOW) [68]. The median overall survival was 9.6 months for the ramucirumab and paclitaxel combination compared to 7.4 months for paclitaxel alone ($p = 0.0169$) with 19% reduction in the risk of death. Prior front-line studies utilizing bevacizumab (AVAGAST, AVATAR) were negative, and it is possible that the benefit seen with ramucirumab is secondary to the greater interruption of VEGF signaling with ramucirumabcompared to bevacizumab [64] [65].

For unclear reason, VEGF inhibition has not proved beneficial in pancreatic carcinoma (CALGB 80303-bevacizumab, VANILLA-aflibercept) [66] [70].

In contrast to bevacizumab and ramucirumab, ziv-aflibercept (Zaltrap®) is a fusion protein that acts as a decoy receptor for VEGF-A, VEGF-B, and placental growth factor (PlGF). *In vitro* studies demonstrated that ziv-aflibercept bound VEGF-A with 100-fold greater affinity and more potent blockade of VEGFR-1/VEGFR-2 than bevacizumab. The phase III VELOUR trial evaluated the combination of ziv-aflibercept and FOLFIRI in the second line metastatic CRC after progression on prior oxaliplatin-based therapy and reported modest benefit [69]. Data to support the use of ziv-aflibercept in the 1st line setting is lacking—the AFFIRM trial which reported similar PFS between both arms was a non-comparative study that was not powered to evaluate the addition of ziv-aflibercept to FOLFOX-6 compared to FOLFOX-6; hence the trial is better considered as an evaluation of alternative 1st line VEGF inhibition together with FOLFOX-6 [71] [72]. A phase II trial is evaluating the OPTIMOX strategy (FOLFOX-7) in the 1st line setting in combination with aflibercept (NCT01802684, VELVET).

In HCC, bevacizumab has shownimproved survival singly and in combination in multiple phase II studies. VEGF inhibition is considered to have a role in the systemic treatment of advanced HCC in addition tosorafenib [73] [74]. However, further randomized phase III trials are needed to confirm this result.

2.3. Monoclonal Antibodies: Her-2/neu Inhibition: Trastuzumab (Herceptin®), Pertuzumab (Perjeta®) and Trastuzumab-Emtansine (T-DM1, Kadcyla®)

HER2/neu encodes the ERBB2 protein, a member of the EGFR family of receptor tyrosine kinases—all of which comprise an extracellular ligand binding domain, a transmembrane domain, and an intracellular domain. HER2 ligand binding activates multiple downstream signals including via the MAPK (RAS/RAF/MEK/ERK), PI3K/AKT, STAT, phospholipase C γ and protein kinase C pathways. HER2/neu over expression has been observed in approximately 15% - 25% of breast cancers and is associated with poorer responses to therapy and a clinically aggressive course. HER2/neu over expression occurs at a slightly lower frequency (12% - 22%) in esophagogastric malignancies compared to breast cancers although the prognostic implication is unclear [75]-[77]. Incidence between esophageal and gastric malignancies is similar; though among gastric cancer sub-types, HER2/neu positivity is seen more often with intestinal-type than diffuse-type cancers [78]. For the 7% - 22% of patients whose tumors overexpress HER2 by FISH or IHC, the phase III TOGA study was unequivocally positive and resulted in regulatory approval for 1st line use (see **Table 2**) [79]. TOGA's chemotherapy arm consisted of cisplatin with 5-FU or capecitabine, and the addition of trastuzumab to regimens.

Diminished efficacy to trastuzumab may develop secondary to primary or secondary resistance—with primary resistance rates as high as 66% - 88% in HER2-overexpressing metastatic breast cancer. Although several mechanisms of resistance in breast cancer have been proposed, no data is available in EGJ/gastric carcinomas. Pharmacokinetic data from phase I/II breast cancer trials suggests that failure to achieve steady-state levels secondary to rapid clearance may contribute to primary resistance [80]. HELOISE (NCT01450696) is an international phase III study (NCT01450696) evaluating standard (8 mg/kg loading, then 6 mg/kg q3 weekly) versus high (8 mg/kg loading, then 10 mg/kg q^3 weekly) in advanced HER2+ EGJ/gastric carcinomas.

Trastuzumabemtansine (T-DM1) is an antibody-drug conjugate consisting of trastuzumab linked to the antitubulin agent mertansine (DM1). T-DM1 improved survival by 5.8 months compared to lapatinib/capecitabine in trastuzumab resistant metastatic breast cancer [81]. In advanced HER2+ EGJ/gastric carcinomas, T-DM1 is

being evaluated in combination with physician choice taxane (docetaxel or paclitaxel). The phase II/III study (NCT01641939) utilizes a novel adaptive design that will evaluate two schedules of T-DM1 (2.4 or 3.6 mg/kg q3 weekly) and pick the phase III dose of T-DM1 depending on the tolerability at 12 weeks. Pertuzumab is a humanized monoclonal antibody that inhibits HER2 dimerization, as distinct from trastuzumab. Combined HER2 blockade with trastuzumab/pertuzumab was evaluated in both the neoadjuvant (TRYPHAENA) and metastatic settings (CLEOPATRA) in breast cancer with high pathologic complete response (pCR) rates and significant improvements in OS respectively [82] [83]. Combined HER2 blockade in HER2+ EGJ/gastric carcinomas with trastuzumab/pertuzumab is under evaluation in a phase III trial (BO25114, NCT01774786).

HER2 inhibition is not being evaluated in other GI malignancies.

2.4. Checkpoint Inhibitors: Cytotoxic T Lymphocyte Antigen-4 (CTLA-4) and Programmed Death-1 (PD-1)

Peptide antigens presented in association with major histocompatibility proteins (MHC) by antigen-presenting cells (APC) to T-cell receptors (TCR) triggers antigen-specific T-cell activation. T-cells have evolved a two-step mechanism that requires a second signal to mediate whether the antigen-TCR interaction results in proliferation, cytokine secretion, and differentiation or development of tolerance and anergy. T-cell co-stimulatory and co-inhibitory signals are thus potent homeostatic mechanisms that maintain a balance between effective immune responses and peripheral tolerance. T-cell CD28 is the primary co-stimulatory signal modulator while CTLA-4 (CD152) is the primary co-inhibitory signal regulator for CD4+ T-helper, CD8+ T-effector and CD25+ Foxp3+ regulatory T cells. The functional outcome of the ligand-APC-T-cell interaction depends on the relative engagement between APC B7-1/B7-2 (CD80/86) and T-cell CD28 versus CTLA-4.

In addition to CTLA-4, several T-cell surface molecules participate in negative and positive regulation of T-cell activation. The exact role of these molecules in T-cell priming, growth and survival and more specifically in T-effector function, T-helper differentiation, and memory T-cell sustenance are reviewed elsewhere [84]. While CTLA-4 initiates the negative feedback loop in T-cell activation, PD-1 is part of the effector phase of this loop. PD-L1 is ubiquitously expressed on tumors and the PD-1/PD-L1 interaction downregulates T-effector responses possibly through suppression of PI3K/AKT activation [85].

CTLA-4 blockade and PD-1 inhibition were thus attractive targets to augment anti-tumor T-cell immunity in cancer. Two CTLA-4 inhibitors [ipilimumab (Yervoy, BMS) and tremelimumab (CP-675206)] and several PD-1/PD-L1 inhibitors have been developed [nivolumab (BMS-936558, BMS), lambrolizumab (MK-3475, Merck) and MPDL3280A (Roche/Genentech/Chugai)] and are in various phases of clinical testing. Of these, ipilimumab has been approved for the treatment of metastatic melanoma in both the 1st line and relapsed settings following successful phase III trials against chemotherapy (dacarbazine) and vaccine (GP-100) comparators respectively [86] [87]. Despite promising phase II results, a phase III study of tremelimumab in advanced melanoma was negative and further interest has stalled [88].

Initial evaluation of PD-1 and CTLA-4 inhibition in GI malignancies centered on pancreatic carcinoma but was subsequently extended to advanced CRC and HCC [89]. Microsatellite stability is an important prognostic marker in CRC: tumors with high-degree microsatellite instability (MSI-H) have a better prognosis than tumors with low-degree instability (MSI-L) or stable microsatellite (MSS) status. This may be related, in part, to greater immunogenicity associated with MSI-H tumors [90] [91]. Investigational approaches in advanced MSI-H CRC include PD-1 (NCT01876511) or PD-1/CTLA-4 combination (NCT01928394, CheckMate 142). Early phase studies are evaluating this approach in combination with chemotherapy in advanced pancreatic cancer (NCT-01473940-gemcitabine/ipilimumab and NCT01896869-FOLFIRINOX/GM-CSF vaccine) and singly in advanced HCC (NCT01658878). A summary of the ongoing trials is provided in **Table 3**.

2.5. Vaccines

Cancer vaccines aim to produce persistent anti-tumor immunity that result in prolonged durable responses. Vaccines are classified based on the antigen(s) incorporated—whole cell, protein, peptide, recombinant virus, dendritic cell, and naked DNA. Cancer vaccines have been studied in various settings (adjuvant, neo-adjuvant and metastatic) across a gamut of malignancies. It is beyond the scope of the article to discuss these studies in detail; however the NCI experience with cancer vaccination between 1995 and 2010 was reviewed in 2 separate publi-

Table 3. Phase I/II trials of co-stimulatory agents in GI malignancies in accrual.

Disease Type	Agent(s)	Description	Tumor Type	Study Design/ Endpoints	Dose and Schedule
Pancreatic	Ipilimumab + Gemcitabine	Ipilimumab – CTLA-4 inhibitor	Recurrent/metastatic pancreatic carcinoma (NCT01473940)	Non-randomized open-label phase I study Primary: Safety (MTD), toxicity Secondary: RR, irRC, TTP, PFS, OS	Ipilimumab • IV ipilimumab q3 weeks for 4 doses (induction) then q12 weeks till progression (maintenance) Gemcitabine • IV gemcitabine qweekly (weeks 1 - 7, 9 - 11), then weekly
	FOLFIRINOX + ipilimumab vs. FOLFIRINOX + vaccine	FOLFIRINOX – standard of care chemotherapy for pancreatic carcinoma Ipilimumab – CTLA-4 inhibitor Vaccine-allogenic GM-CSF transfected pancreatic tumor vaccine	Recurrent/metastatic pancreatic carcinoma (NCT01896869)	Randomized open-label phase II study Primary: OS Secondary: PFS, irPFS	Ipilimumab • IV ipilimumab 10 mg/kg q3 weeks for 4 doses FOLFIRINOX q2 weeks: • IV oxaliplatin 85 mg/m^2 D1 • IV irinotecan 180 mg/m^2 D1 • IV leucovorin 400 mg/m^2 D1 • IV 5-FU 400 mg/m^2 bolus then 2400 mg/m^2 over 46 hrs D1-2 Allogenic GM-CSF transfected pancreatic tumor vaccine • 6 intra-dermal immunizations of 300 million immunotherapy cells days 1, 8, 15, 29, 43 and 57 • Additional 12 intra-dermal immunizations on days 1 and 15 (of 4 week cycles) in patients with distant disease for up to 18 total doses
Hepatocellular	Nivolumab	Nivolumab – PD-1 inhibitor	Advanced hepatocellular carcinoma (NCT01658878)	Non-randomized open-label phase I study in 3 cohorts (non-infected, HCV-infected, HBV-infected) Primary: Safety/toxicity Secondary: ORR, DCR, PK	IV nivolumab (0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg) q2 weeks till progression
Colorectal	Ipilimumab + Nivolumab	Ipilimumab – CTLA-4 inhibitor Nivolumab – PD-1 inhibitor	Recurrent/metastatic microsatellite high (MSI-H) colorectal carcinoma (NCT01928394, CheckMate 142)	Non-randomized open-label phase I/II study Primary: OS Secondary: DFS	Dose level -1 • IV nivolumab 0.3 mg/kg + IV ipilimumab 1 mg/kg q3 weeks for 4 doses then IV nivolumab 0.3 mg/kg q2 weeks till progression Dose level 1 • IV nivolumab 1 mg/kg + IV ipilimumab 1 mg/kg q3 weeks for 4 doses then IV nivolumab 1 mg/kg q2 weeks till progression Dose level 2a • IV nivolumab 1 mg/kg +IV ipilimumab 3 mg/kg q3 weeks for 4 doses then IV nivolumab 1 mg/kg q2 weeks till progression Dose level 2b • IV nivolumab 3 mg/kg + IV ipilimumab 1 mg/kg q3 weeks for 4 doses then IV nivolumab 3 mg/kg q2 weeks till progression

Continued

	MK-3475	MK-3475 – PD-1 inhibitor	Recurrent/metastatic colorectal carcinoma (MSI and MSS) and non-colorectal MSI tumors(NCT01876511)	Non-randomized open-label phase II study Primary: 20-week irPFS, 20-week irOR Secondary: OS, RR, DCR	MK-3475 • MK-345 10 mg/kg q2 weeks till progression

MTD—maximal tolerated dose; RR—response rate; irOR—immune-related objective response; irRC—immune-related response criteria; TTP—time to progression; PFS—progression-free survival; irPFS—immune-related progression-free survival; OS—overall survival.

cations and reported low response rates of 3% - 4% with only infrequent CRs in select malignancies [92] [93].

As TAA have been identified in esophageal (MAGE-A3/4 and NYESO-1), gastric (Her-2/neu), pancreatic (MUC1 and mesothelin), hepatocellular (AFP, GPC3, NY-ESO-1, SSX-2, MAGE-A and TERT) and colorectal (CEA) malignancies, cancer vaccination is an attractive strategy in GI malignancies. Given the lack of proven benefit in the phase III setting, no cancer vaccine is approved in the adjuvant, neo-adjuvant and/or advanced disease settings so far. The panoply of ongoing vaccine trials in GI malignancies is summarized in **Table 4**.

Several early phase vaccine studies in CRC and esophagogastric cancers are in accrual.

- Adjuvant CRC: phase I study of engineered alphavirus vaccine expressing CEA in stage III disease (NCT-01890213).
- Advanced CRC: colorectal GVAX (in combination with Cy + DNA methyltransferase inhibitor SGI-110, NCT01309126); DC vaccination (NCT01348256); and polysaccharide beta 1,3/1,6 glucan(Imprime PGG) with cetuximab compared to cetuximab alone in KRAS WT patients at 1st progression (PRIMUS, NCT-01309126).
- Adjuvant esophagogastric cancers following definitive surgery and combined modality therapy: NY-ESO-1 expressing tumors (NCT01522820); cancer testis antigen expressing tumors (NCT01143545 and NCT-02054104).
- Advanced gastric cancer: HER2 positive (AVX901-NCT01526473); and FOXM1/DEPDC1/KIF20A/URLC10/VEGFR1 positive in patients withwith HLA-2402 haplotype (OTSGC-A24-NCT01227772).

In advanced pancreatic cancer, several adjuvant vaccines have been developed including whole cell vaccines (Algenpantucel-L, GM-CSF vaccine); peptide and DNA vaccines [Ras, telomerase peptide, survivin, oncofetal peptides CEA/MUC1]; DC vaccines (utilizing CEA/MUC1 antigen pulsed DC cells) and heat-shock protein (HSP). Aside from Algenpantucel-L (HyperAcute®, NewLink Genetics Corporation) and GVAX, these approaches have largely been unsuccessful and are reviewed elsewhere [94].

Algenpantucel-L is an allogeneic whole pancreatic cell vaccine engineered to express α-galactosyl (αGal) epitopes that elicit complement-mediated lysis and antibody-dependent cell-mediated toxicity. GVAX is a tumor cell vaccine created by harvesting allogenic cancer cells with subsequent transfection of the granulocyte macrophage-colony stimulating factor (GM-CSF) gene. The algenpantucel-L phase II study involved 70 patients with resected pancreatic adenocarcinoma who received algenpantucel-L vaccination in addition to 5-FU/gemcitabine based chemoradiotherapy (investigational arm of RTOG-9704) post-operatively. Allowing for inherent biases in cross-trial comparisons, 12-month DFS and OS were improved with the addition of algenpantucel-L compared to 5-FU/gemcitabine chemoradiotherapy arm in RTOG-9704 [95] [96]. Algenpantucel-L is pending evaluation in a phase III study comparing 5-FU/gemcitabine chemoradiotherapy with or without algenpantucel-L immunization in resected high-risk pancreatic carcinoma (NCT01072981).

Early studies of GVAX immunotherapy in renal cell cancer and melanoma produced middling results but the approach gained traction when an early study reported durable long-term responses in patients with advanced non-small cell lung cancer [97]. Both ipilimumab and GVAX have previously been evaluated in advanced pancreatic adenocarcinoma with negative results previously [98] [99]. Recent work has shed light on the extensive immunosuppressive microenvironment encircling the primary tumor in pancreatic adenocarcinoma, and explains the poor results observed with conventional immunotherapeutic approaches in prior studies [100]. Paradoxically, given the limited access to host immune cells, pancreatic cells may actually be more sensitive to immune attack; and suggests that strategies that combine vaccination with immune checkpoint blockade may be more successful than unselected vaccination. Results of a recent phase Ib study combining GVAX vaccination and ipilimumab in advanced pancreatic adenocarcinoma patients in the 2nd line setting were promising [101]. This has prompted

Table 4. Trials of cancer vaccines in GI malignancies in accrual.

Disease Type	Agent (Trade name, Sponsors)	Description	Tumor Type	Study Design/ Endpoints
NY-ESO-1 expressing tumors (esophageal, gastric, HCC, colorectal)	DEC-205-NY-ESO-1 fusion protein vaccine	mTOR inhibition with rapamycin for enhancing intranodal dendritic cell vaccine induced anti-tumor immunity in patients with NY-ESO-1 expressing solid tumors	NY-ESO-1 expressing tumors following resection including esophageal, gastric, HCC and colorectal carcinomas (NCT01522820)	Non-randomized phase I study of DEC-205-NY-ESO-1 fusion protein vaccine in combination with mTOR inhibitor sirolimus in NY-ESO-1 expressing tumors following resection Primary: Safety Secondary: NY-ESO-1 specific cellular and humoral immunity
Esophageal	K562-GM tumor cell vaccine	Allogeneic K562-GM tumor cell vaccine expressing cancer testis antigens	Resected high-risk thoracic malignancies (including esophageal) expressing cancer testis antigens (NCT01143545)	Non-randomized phase I/II study of K562-GM tumor cell vaccine in combination with metronomic oral cyclophosphamide and celecoxib Primary: Safety Secondary: Induction of immunity; reduction of T-regulatory cells in peripheral blood
	H1299 cell lysate/Iscomatrix vaccine	Allogeneic H1299 cell lysate/Iscomatrix vaccine expressing cancer testis antigens	Resected high-risk thoracic malignancies (including esophageal) expressing cancer testis antigens (NCT02054104)	Randomized phase I/II study of H1299 cell lysate/Iscomatrix vaccine with or without the combination with metronomic oral cyclophosphamide and celecoxib Primary: Immune response rates Secondary: Immune response rates
Gastric	AVX901	Recombinant Venezuelan equine encephalitis (VEE) alphavirus packaged in virus-like replicon particles (VRP) expressing HER2	Metastatic HER2 positive cancers including gastric adenocarcinoma (NCT01227772)	Non-randomized phase I study of AVX901 vaccine Primary: Safety Secondary: Induction of HER2 specific immunity
	OTSGC-A24	Allogeneic cell vaccine expressing tumor specific antigensand VEGFR1 HLA-A24 epitopes	Metastatic gastric adenocarcinoma (NCT01526473)	Non-randomized phase I/IIa study of OTSGC-A24 vaccine Primary: Safety Secondary: Induction of T-effector specific immunity
Pancreatic Cancer	Algenpantucel-L (HyperAcute®, NewLink Genetics Corporation)	Allogeneic whole pancreatic cells expressing α-galactosyl (αGal) epitopes that elicit complement-mediated lysis and antibody-dependent cell-mediated toxicity	Resected high-risk pancreatic carcinoma (NCT01072981)	Randomized open-label phase III trial of algenpantucel-L gemcitabine with or without 5-flurouracil (5FU) chemoradiation vs. gemcitabine with or without 5FU chemoradiation alone Primary: OS Secondary: DFS
			Borderline resectable or locally advanced unresectable pancreatic carcinoma (NCT01836432)	Randomized open-label phase III trial of algenpantucel-L with FOLFIRINOX vs. FOLFIRINOX alone Primary: OS Secondary: PFS, immune response

Continued

Pancreatic Cancer	GVAX + CRS-207	CRS-207-attenuated Listeria monocytogenes genetically engineered to elicit immune responses against tumor-associated mesothelin GVAX – tumor cell vaccine created by harvesting allogenic cancer cells with subsequent transfection of the granulocyte macrophage-colony stimulating factor (GM-CSF) gene. Cyclophosphamide (Cy) – low-dose metronomic cyclophosphamide	Relapsed/refractory pancreatic carcinoma (ECLIPSE) (NCT02004262)	Randomized open-label phase IIB trial of vs GVAX + CRS-207 vaccination. CRS-207 vaccination alone vs. chemotherapy Primary: OS Secondary: toxicity
Colorectal carcinoma	GVAX + Cy + SGI-110	SGI-110 – DNA methyltransferase inhibitor GVAX – tumor cell vaccine created by harvesting allogenic cancer cells with subsequent transfection of the granulocyte macrophage-colony stimulating factor (GM-CSF) gene. Cyclophosphamide (Cy) – low-dose metronomic cyclophosphamide	mCRC maintenance therapy (NCT01309126)	Open-label phase I trial of SGI-110 in combination with GVAX/Cy as maintenance therapy Primary: Safety/toxicity Secondary: OS, PFS, TTP
	CEA(6D)-VRP (AVX701)	Recombinant Venezuelan equine encephalitis (VEE) alphavirus packaged in virus-like replicon particles (VRP) expressing CEA (6D) (to enhance binding to HLA-A2, and enhanced recognition by TCR)	Stage III colorectal carcinoma following completion of adjuvant 5-FU based chemotherapy (NCT01890213)	Open-label phase I trial of AVX701 Primary: Safety/toxicity Secondary: None
	DC vaccine	DC vaccination with autologous tumor antigen	mCRC with hepatic metastasis following resection and standard adjuvant chemotherapy (NCT01348256)	Open-label phase II trial of DC vaccination
	Imprime PGG and cetuximab or cetuximab alone	Imprime PGG-polysaccharide beta 1.3/1.6 glucan derived from *Saccharomyces cerevi siae* cell wall	Recurrent/metastatic KRAS WT CRC (PRIMUS) (NCT01309126)	Randomized open-label phase III trial of cetuximab vs. cetuximab/Imprimg PGG Primary: OS Secondary: RR, PFS
Hepatocellular Cancer	COMBIG-DC	Intra-tumoral DC vaccine	Advanced HCC (NCT01974661)	Open-label phase I trial of DC vaccination Primary: Safety/tolerability Secondary: RR, tumor marker (AFP)
	Cytokine-induced killer (CIK) cells	Ex-vivo expanded T-cells which present a mixed T/NK phenotype and have MHC-unrestricted antitumor activity	Hepatocellular carcinoma post-resection (NCT01749865)	Randomized open-label phase III trial of standard care vs. CIK Primary: Time to recurrence Secondary: DFS

PFS—progression-free survival; DFS—disease-free survival; OS—overall survival; TTP—time to progression; RR—response rate.

further investigation in the adjuvant setting with GVAX alone in combination with FOLFIRINOX, RT and low-dose cyclophosphamide (NCT01595321) and in advanced disease—GVAX/ipilimumab with FOLFIRINOX (NCT01896869), and GVAX with CRS-207 (ECLIPSE, NCT02004262).

Vaccination is also an exciting option in HCC especially considering the presence of HCC-specific TAA (AFP, GPC3, NY-ESO-1, SSX-2, MAGE-A and TERT). Although the tolerogenic tumor micro-environment and HCC-specific tumor suppressive mechanisms are considerations underlying successful vaccination, several studies have demonstrated the validity of this approach. A Japanese study of 150 patients randomized following curative resection to either observation or vaccination with autologous lymphocytes activated *in vitro* by IL-2 and anti-CD3 reported improved RFS and disease specific survival [102]. More recently, an autologous pulsed dendritic cell (DC) approach demonstrated clinical benefit in advanced disease [103]. Ongoing vaccine study strategies include intra-tumoral DC vaccination (NCT01974661), NY-ESO-1 vaccination in combination with sirolimus (NCT01522820) and adjuvant treatment following hepatectomy with cytokine-induced T-cells (NCT-01749865).

3. Conclusions

With the advent of efficacious cytotoxic options in GI malignancies, immunotherapeutic approaches were not pursued aggressively. However, the development and subsequent success of VEGF, EGFR and HER2 inhibition in several GI malignancies have rekindled interest in MoAbs targeting these axes in several settings.

VEGF inhibition (bevacizumab, ziv-aflibercept and regorafenib) and EGFR inhibition (in KRAS/NRAS WT patients) have well defined roles in the management of metastatic CRC. In advanced KRAS/NRAS WT mCRC, both VEGF (bevacizumab) and EGFR (cetuximab/panitumumab) inhibition should be pursued.

EGFR inhibition has no approved role in advanced HCC, esophagogastric, and pancreatic malignancies. Phase II studies of cetuximab-chemotherapy combinations in advanced cholangiocarcinoma appear promising but randomized phase III data are lacking. Aside from CRC, VEGF inhibition may have use in HCC though it appears unhelpful in pancreatic malignancies. The data in esophagogastric cancers are mixed. Although bevacizumab did not show the improvement in outcomes, ramucirumab demonstrated the survival benefit in a heavily pre-treated patient population with advanced gastric cancer (REGARD) [67], which suggests that alternative (and possibly more intense) VEGF pathway inhibition can improve outcomes, especially when combined with chemotherapy [68]. HER2 inhibition has a defined role in HER2+ esophagogastric malignancies. Continued HER2 inhibition post-progression and combined HER2 blockade are areas of ongoing interest.

MSI-H CRC represents a distinct CRC subtype characterized by TAA expression that elicit a strong local (CD8+ T-cell infiltrates and peritumoral lymphoid nodules) host immune response [104] [105]. Immune checkpoints (PD-1 and CTLA-4) inhibitors may circumvent immune evasion that contributes to distant spread and the results of NCT01876511 (PD-1 in MSI-H CRC) and CheckMate 142/NCT01928394 (PD-1/CTLA-4 combination in MSI-H CRC) are eagerly awaited. These observations also provide a strong mechanistic rationale for using a peri-operative neoadjuvant approach in stage II/III MSI-H CRC.

Although many GI malignancies have defined TAA, prior vaccine trials were largely negative. Current vaccine studies are utilizing novel delivery systems [CEA expressing virus-like replicon particles (VRP)]; immunomodulatory strategies (low-dose metronomic cyclophosphamide); and are focusing on more immunogenic subtypes of GI malignancies (MSI-H CRC).

Recent trials have validated diverse immunotherapeutic approaches in GI malignancies beyond MoAbs inhibiting EGFR/VEGF. Existing MoAbs are being exploited in alternative settings and novel vaccine strategies are being developed. Immunotherapy is poised at the forefront of adjuvant, neoadjuvant and advanced approaches for the treatment and eradication of GI malignancies.

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