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Gastrointestinal Cancer

Toward a Treatment Sequencing Strategy: A Systematic Review of Treatment Regimens in Advanced Gastric Cancer/ Gastroesophageal Junction Adenocarcinoma

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Gastroesophageal adenocarcinoma • Systemic therapy • Treatment sequencing • Randomized controlled trials

Abstract

Background. Platinum and fluoropyrimidine combinations typically comprise first-line (1L) therapy in advanced gastric cancer or gastroesophageal junction adenocarcinoma (G/GEA), although controversy exists regarding the use of 5doublet versus triplet cytotoxic regimens. Historically, second-line (2L) and third-line or later (3L+) therapy has been fragmented. Recent trials have increased the need for optimal treatment sequencing in advanced G/GEA.

Materials and Methods. We conducted a systematic search of peer-reviewed manuscripts of randomized clinical trials examining 1L, 2L, and 3L+ therapy for advanced G/GEA published from 2009 through November 19, 2019. When available, overall survival, progression-free survival, time to progression, overall response rate, and toxicity were extracted from each and compared descriptively.

Results. In 1L therapy, chemotherapy triplets demonstrated variable efficacy improvements with invariable increased toxicity compared with platinum/fluoropyrimidine doublets. Currently, the only published report of positive outcomes using biologics in 1L describes adding trastuzumab in HER2-overexpressing advanced G/GEA. In 2L, doublet chemotherapy regimens are not uniformly more efficacious than single-agent taxanes or irinotecan, and ramucirumab has demonstrated improved outcomes both as monotherapy and in combination.

Conclusion. For advanced G/GEA, review of trial results from 2009–2019 support 1L therapy with platinum and fluoropyrimidine and sequencing with taxanes or irinotecan in combination with biologics as effective 2L options. Escalating to a triplet may add some efficacy at the expense of added toxicity. ***The Oncologist*** 2021;26:1–26

Implications for Practice: The rapidly changing treatment landscape for advanced gastric cancer includes increasing options for refractory disease. With multiple first-line platinum-based regimens, identification of those with the best benefit-to-risk ratio may provide guidance on treatment sequencing strategies. This article presents findings from the published literature of randomized controlled trials that included a first-line platinum/fluoropyrimidine combination and, for second-line trials, patients with platinum/fluoropyrimidine-refractory disease. This guiding summary could be a tool for clinicians to identify the optimal first-line regimen(s) followed by a strategy for subsequent regimens.

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Introduction

Gastric cancer is the fifth most common cancer and third leading cause of cancer-related deaths worldwide [1]. Gastric cancer is a histologically and molecularly diverse disease encompassing the stomach and gastroesophageal junction. Adenocarcinoma is the most common histological type, and gastric cancer or gastroesophageal junction adenocarcinoma (G/GEA), with or without esophageal adenocarcinoma, are commonly studied within the same clinical trials [2]. Developments in treatment for locally advanced and unresectable/metastatic G/GEA lag behind other solid malignancies, with a median survival of less than 1 year [3–5].

Despite multiple options, there is no single standard of care for first-line (1L), second-line (2L), or third-line (3L) and beyond (3L+) treatment of G/GEA [6,7]. Current guidelines do not address optimizing sequence. The Cochrane reviews by Wagner evaluated the efficacy of chemotherapy versus best supportive care (BSC), combination versus single-agent chemotherapy, and different chemotherapy combinations [8,9]. However, the question of treatment sequencing was not addressed.

In the 1L setting, current options include platinum agents, fluoropyrimidines, taxanes, irinotecan, and anthracyclines in doublet or triplet regimens, whereas epirubicin has fallen out of favor [10,11]. The most commonly used 1L treatment combinations include fluoropyrimidine plus platinum, with or without a third agent [8,12], although addition of a third cytotoxic agent to established doublet regimens is likely to increase toxicities as reported in 2006 [13]. Unfortunately, the majority of patients who respond to 1L chemotherapy will relapse or experience disease progression [8]. It is unclear if there is a significant benefit with doublet therapies versus monotherapies, intravenous versus oral formulations of fluorouracil (5-FU), cisplatin versus oxaliplatin, or irinotecan versus docetaxel.

There is disagreement regarding the preferred treatment regimen in the 2L and 3L+ settings. The treatment landscape is fragmented, particularly in the U.S. [14]. Current recommended 2L therapies include the anti–vascular endothelial growth factor receptor-2 monoclonal antibody, ramucirumab, as monotherapy or combined with paclitaxel, or single chemotherapy agents (irinotecan, docetaxel, or paclitaxel) [12,15]. The diverse array of regimens is counterproductive to developing clear, standardized, evidence-based guidelines. Moreover, with the recent publication of several randomized controlled trials (RCTs) investigating novel therapies and chemotherapy combinations, a new evaluation of existing evidence is needed that might better inform physicians and guide treatment recommendations.

We conducted a systematic review from published RCTs to evaluate and synthesize evidence and provide insights into an evidence-based treatment sequencing strategy for advanced G/GEA. To this end, the review focused on RCTs in which the commonly recommended platinum/fluoropyrimidine-backbone was used in 1L and, for 2L, RCTs that included a prior platinum and/or fluoropyrimidine. Given the recent changes to the G/GEA landscape, we have discussed top-line data from seminal trials and approvals in this report.

Materials and Methods

Search Strategy

The systematic literature review (SLR) search, selection, and data extraction were conducted and reported using PRISMA guidelines [16]. The databases MEDLINE, MEDLINE In-Process, Embase, and the Cochrane Library were searched to identify English-language publications of RCTs, SLRs, and meta-analyses since the Cochrane review by Wagner et al. [9]. The search for RCTs was limited to 2009 through November 19, 2019, and the search for SLRs and meta-analyses was limited to 2015 through November 19, 2019. The review only included RCTs of larger populations: ≥200 and ≥ 40 patients in 1L and 2L or later settings, respectively. Although outside the original SLR parameters, recent phase III RCT data are also discussed in relevant sections.

The RCT search, SLR, and meta-analyses were structured as follows: study type search terms, disease search terms, treatment search terms, population search terms, and exclusionary search terms. Further details regarding inclusion and exclusion criteria, screening, and study quality assessment methodology from the SLR are available in the supplemental online data.

Synthesis Methods

Overall survival (OS), progression-free survival (PFS), time to progression (TTP), and overall response rate (ORR) were the primary efficacy endpoints considered. Overviews of adverse events (AEs) were summarized. Included studies were heterogeneous in terms of study design; therefore, results are presented descriptively.

Results

Literature Search Results

The screening process and number of identified articles are detailed in Figure 1. Literature searches identified a total of 920 nonduplicate records, of which 647 and 212 records were excluded during level 1 and 2 screenings, respectively. Seventy publications meeting eligibility criteria were included (Fig. 1). Of these, 27 articles assessed 1L, 34 assessed 2L, and 8 assessed 3L+.

Risk of Bias

The quality of each study was evaluated using the bias assessment tool detailed in supplemental online Table 4.

Description of Included Studies

An overview of the studies is provided in the supplemental online data. Patient demographics and disease characteristics are summarized in Figure 2 and supplemental online Table 1. A summary of treatment interventions for each line of therapy is provided in Figure 3 and supplemental online Table 3.

Efficacy and Safety of 1L Interventions

First-line studies varied with respect to trial design and patient populations (supplemental online Table 1). Of

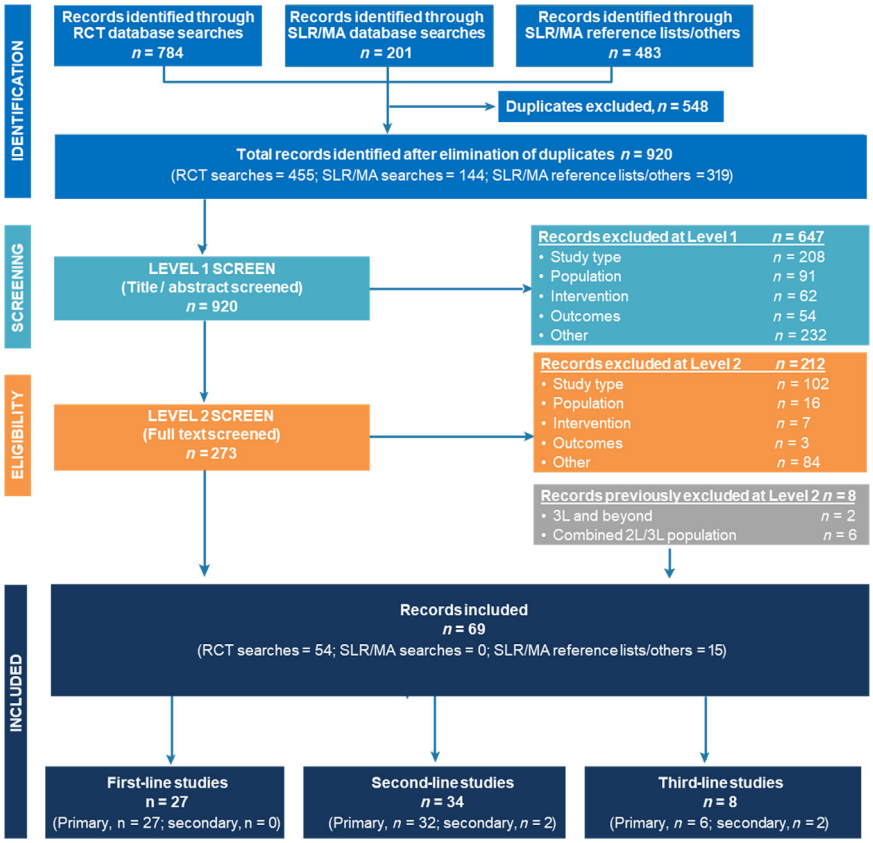

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram for study inclusion and exclusion. The PRISMA flow chart details the number of articles identified in the literature search and the number of articles included and excluded at each stage. Note that articles from the SLR-MA search that met the inclusion criteria for reference list review to identify potential primary RCT publications are listed in the PRISMA diagram as excluded at level 2 for reason "other" (as these articles are not primary RCTs).
Abbreviations: 2L, second line; 3L, third line; MA, meta-analysis; RCT, randomized controlled trial; SLR, systematic literature review.

27 RCTs, 22 reported OS and/or PFS data. Fourteen RCTs reported statistically significant findings for OS, 12-month survival, PFS, TTP, time to treatment failure (TTF), or ORR (Table 1; Table 2; supplemental online Table 2) [17–29]. An overview of AEs is summarized in supplemental online Table 3.

Chemotherapeutic Agents

The majority of studies assessed combination chemotherapy in both arms. Only one study included a monotherapy arm.

In this SLR, studies that excluded patients with HER2-overexpressing (HER2+) tumors generally evaluated regimens without biomarker targets, focusing on new combinations to optimize the benefit-to-risk ratio. Eleven RCTs compared the efficacy and/or safety of different doublet regimens. Cisplatin plus capecitabine versus cisplatin plus 5-FU showed noninferior OS and PFS and higher ORR while not significantly affecting toxicity [24].

Two studies compared the effect of S-1 plus cisplatin versus 5-FU plus cisplatin [26,27]. The FLAGS study found that median TTF was longer and the AE profile was more favorable with S-1 plus cisplatin than with 5-FU plus cisplatin [26]. The DIGEST study found no significant difference in OS between S-1 plus cisplatin and 5-FU plus cisplatin [27]. Although outside the inclusion parameters used in this review, the SC-101 and START studies established the benefits of frontline S-1–based combination therapies in Asian populations [30,31]. SC-101 demonstrated superior benefits for S-1 plus cisplatin compared with S-1 monotherapy or 5-FU plus cisplatin in Chinese patients, and the START study demonstrated significant clinical benefits (OS, 12.5 vs. 10.8 months; $p = .032$; PFS, 5.3 vs. 4.2 months; $p = .001$) in Korean and Japanese patients treated with docetaxel plus S-1 compared with S-1 monotherapy.

Shu et al. found that oxaliplatin plus S-1 was noninferior to oxaliplatin plus tegafur in terms of PFS and OS [32]. The G-SOX study evaluated S-1 plus oxaliplatin or S-1 plus cisplatin and showed noninferiority that was statistically significant [21]. These results may have been mediated by the observed better tolerability with oxaliplatin versus cisplatin in the elderly. In G-SOX, discontinuation rates due to AEs and serious AEs were higher in the S-1 plus cisplatin group than in the S-1 plus oxaliplatin group. Although outside the inclusion parameters of this review, Al-Batran et al. compared fluorouracil, leucovorin, and oxaliplatin (FLO) with fluorouracil, leucovorin, and cisplatin (FLP) in patients with advanced gastric cancer [33]. No significant OS or PFS benefits were observed between FLO and FLP arms, although in older adults FLO was associated with increased efficacy. Importantly, FLO was associated with significantly lower frequency of AEs (e.g., any grade vomiting 31% [FLO]

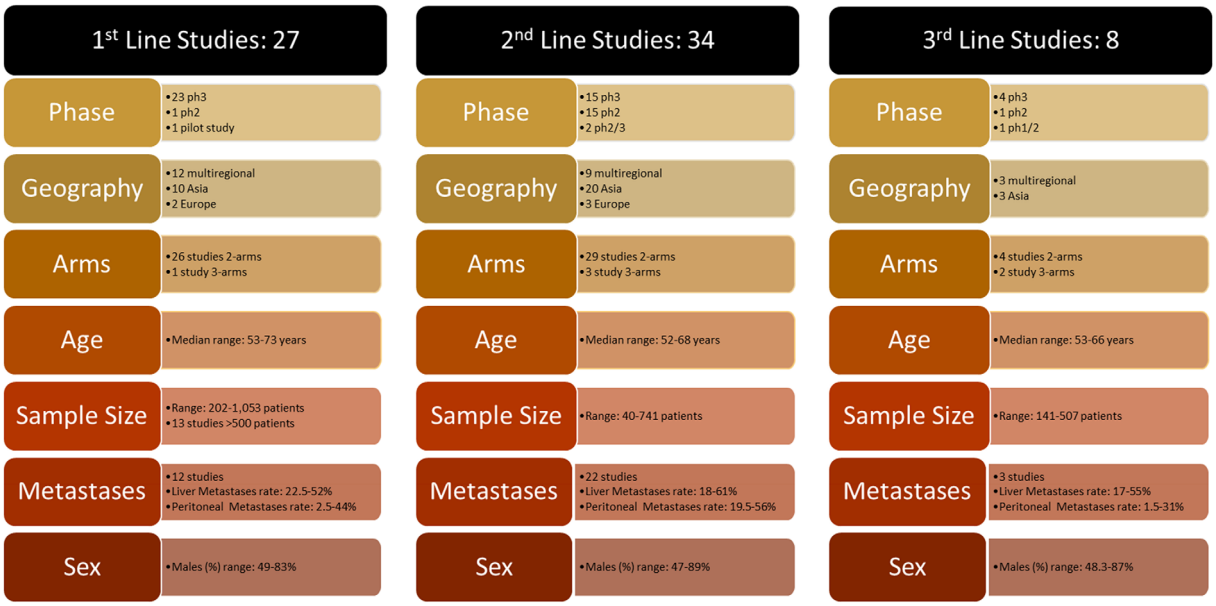

Figure 2. First-line, second-line, and third-line study overview.
Abbreviations: ph1, phase I; ph2, phase II; ph3, phase III.

vs. 52% [FLP]) and treatment-related serious AEs (9% [FLO] vs. 19% [FLP]). Along these lines, although the randomized phase II CALGB 80403 study of cetuximab with one of three chemotherapy regimens (epirubicin, cisplatin, and continuous-infusion fluorouracil; irinotecan plus cisplatin; or folinic acid plus 5-FU plus oxaliplatin [FOLFOX]) did not meet the inclusion criteria of 200 or more patients in 1L, its results indicated that FOLFOX was better tolerated and was the recommended backbone for 1L [34]. The FOLFOX arm reported fewer treatment modifications and discontinuations due to treatment-related AEs or deaths [34]. These data suggest better tolerability for oxaliplatin-based regimens versus cisplatin, with comparable efficacy.

One study compared the effect of cisplatin and docetaxel when paired with S-1 [35]. OS was numerically longer with S-1 plus docetaxel than with S-1 plus cisplatin (405 days vs. 378 days; $p = .5127$), although the difference was not significant. One study compared the effect of paclitaxel plus capecitabine with cisplatin plus capecitabine [29]. Lu et al. found no significant difference in OS between the two regimens [29]. These data suggest that a taxane-based doublet may be a suitable alternative to a platinum-based doublet.

Despite statistically significant longer OS (10.2 vs. 8.5 months; hazard ratio [HR], 0.71; $p = .0319$) and PFS (7.2 vs. 4.9 months; HR, 0.58; $p = .0008$) and improved ORR in patients treated with a modified combination of docetaxel plus cisplatin/5-FU (mDCF) relative to cisplatin/5-FU, toxicity was greater [19]. Incidence of grade 3/4 AEs (e.g., neutropenia) was higher in the mDCF arm [19]. A Japanese study showed no OS benefit (14.2 vs. 15.3 months; HR, 0.99) but higher grade 3 or worse AEs (neutropenia, leukopenia, and anorexia) when docetaxel was added to cisplatin plus S-1 [36].

A single three-arm RCT compared doublet with two triplet chemotherapy regimens: docetaxel plus oxaliplatin versus this doublet combined with 5-FU (TEF) or capecitabine [37]. With better safety, median PFS (mPFS) of 7.7 months, median OS of 14.6 months, and ORR of 46.6% in TEF-treated patients, TEF was deemed to have a significantly better therapeutic index. These studies demonstrate that although efficacy is better with triplet regimens, toxicities are increased compared with doublets.

Guimbaud et al. were the first to prospectively address therapy sequencing (1L and 2L) ECX (epirubicin, cisplatin, and capecitabine) followed by FOLFIRI (folinic acid plus 5-FU plus irinotecan) versus FOLFIRI followed by ECX [22]. Although PFS, OS, and ORR were similar, FOLFIRI administered prior to ECX as 2L led to a statistically significant increase in the primary endpoint of TTF relative to ECX given first (median 5.1 vs. 4.2 months, respectively). First-line FOLFIRI was also better tolerated with lower rates of grade 3/4 toxicities and hematologic AEs but similar rates of nonhematologic AEs [22].

Targeted Therapies

Findings from the current SLR in patients with HER2+ tumors support those of a previous Cochrane review (2010), which recommended trastuzumab plus cisplatin plus 5-FU or capecitabine [9]. In ToGA, addition of trastuzumab to chemotherapy improved OS (13.8 vs. 11.1 months), PFS (6.7 vs. 5.5 months), ORR (47% vs. 35%), TTP, and duration of response [17]. Similarly, in the TRIO-013/LOGiC study, mPFS was longer and ORR was higher with the addition of lapatinib to a combination of capecitabine plus oxaliplatin; however, lapatinib increased toxicity and OS was not significantly improved [23]. In the JACOB trial, addition of pertuzumab to trastuzumab plus chemotherapy did not significantly improve OS [38].

Two studies (RILOMET-1 and METGastric) assessed the impact of adding targeted therapy (rilotumumab or onartuzumab) to chemotherapy in patients with advanced mesenchymal-epithelial transition (MET)–positive G/GEA, a population with a poor prognosis [28,39]. However,

Figure 3. First-line, second-line, and third-line and beyond interventions. **(A):** First-line interventions. Targeted therapies include bevacizumab, cetuximab, lapatinib, onartuzumab, panitumumab, rilotumumab, trastuzumab, pertuzumab, and ramucirumab. Chemotherapy includes capecitabine, cisplatin, docetaxel, epirubicin, oxaliplatin, paclitaxel, S-1, tegafur, 5-fluorouracil, and leucovorin (folinic acid). Eleven studies compared the efficacy of chemotherapy doublets. **(B):** Second-line interventions. In the center of the diagram, "12 studies TT vs. CM/PB" include 12 studies with single-agent (SA) chemotherapy in both arms: six assessing the efficacy of SA versus SA and six assessing SA plus targeted therapy versus control. **(C):** Third-line interventions. Targeted therapies include avelumab, TAS-102, nivolumab (ICI), and ipilimumab (ICI). Chemotherapy includes irinotecan and paclitaxel.
Abbreviations: ↑, increased/higher dose; BSC, best supportive care; CM, chemotherapy; DB, doublet; ICI, immune checkpoint inhibitor; Pac, paclitaxel; PB, placebo; Pembro, pembrolizumab; TP, triplet; Traz, trastuzumab; TT, targeted therapy; TX, taxane; VP, valproic acid.

Table 1. Overview of efficacy results

Trial	Treatment arms	Efficacy variables								Analysis population	Statistical design
		OS	12-mo survival	PFS	TTP	TTF	ORR	DOR	DCR		
First-line studies											
SOS Ryu 2015 [109]	S-1 (D1–14) + Cis (D1) vs. S-1 (D1–21) + Cis (D1 or 8)									ITT (patients who met all eligibility criteria)	A hybrid design was used to test both noninferiority and superiority within the same trial
AVATAR Shen 2015 [110]	PBO + Cap + Cis vs. BEV + Cap + Cis									ITT (all randomized patients)	NR[a]
Van Cutsem 2015 [37]	Doc + Ox vs. Doc + Ox + FU/FOL									Full analysis set (all randomized and treated patients analyzed in the arm to which they were randomized); ITT (all randomized patients); per-protocol (patients who received study treatment and had at least one postbaseline tumor assessment without any major protocol violation)	NR[a]
REAL3 Waddell 2013 [18]	Epir + Ox + Cap vs. Epir + Ox + Cap + PAN	*								ITT (all eligible randomized participants)	NR[a]
Wang 2016 [19]	Doc + Cis + FU vs. Cis + FU	*		*		*	*			ITT	Superiority of Doc + Cis + FU compared with Cis + FU in terms of PFS
JapicCTI-101021 Yamada 2015 [20]	S-1 + Ox vs. S-1 + Cis			*						Per-protocol population (noninferiority analysis); ITT for some analyses (all randomized patients excluding patients who took no trial medication)	Noninferiority of S-1 + Ox compared with S-1 + Cis in terms of PFS Relative efficacy of S-1 + Ox and S-1 + Cis in terms of OS
G-SOX Bando 2016 [21]	S-1 + Ox (≥70 yr) vs. S-1 + Cis (≥70 yr) vs. S-1 + Ox (<70 yr)					*				Full analysis set (patients who met the main inclusion criteria and none of the exclusion criteria in the safety analysis set)	Noninferiority of S-1 + Ox compared with S-1 + Cis
ToGA Bang 2010 [17]	Tras + Chemo vs. Chemo	*		*	*		*	*		All randomized patients (whose tumors overexpressed HER2) who received study medication at least once	NR[a]
Curran 2009 [111]	IRI + folinic acid + FU vs. Cis + FU									Full analysis set (treated patients analyzed in the arm to which they were randomized); analyses were also conducted in the per-protocol population	Noninferiority of FOLFIRI compared with Cis + FU in terms of TTP
Guimbaud 2014 [22]	Epir + Cis + Cap vs. FOLFIRI					*				ITT	Superiority of FOLFIRI compared with Epir + Cis + Cap in terms of TTF
TRIO-013/LOGiC Hecht 2016 [23]	LAP + Cap + Ox vs. PBO + Cap + Ox			*			*			Primary efficacy population (patients with disease confirmed for HER2 overexpression)	NR[a]
Kang 2009 [24]	Cis + Cap vs. Cis + FU	*		*			*			Per-protocol population[b]	Noninferiority of Cis + Cap to Cis + FU in terms of PFS
Kim 2014 [112]	SIM + Cap + Cis vs. PBO + Cap + Cis									ITT (all recruited patients who received any study medication)	NR[a]
Li 2015 [113]	S-1 + Cis vs. FU + Cis									Full population	NR[a]
EXPAND Lordick 2013 [114]	CTX + Cap + Cis vs. Cap + Cis									ITT (all patients randomly allocated a study treatment)	NR[a]
AVAGAST Ohtsu 2011 [25]	BEV + Cis + Cap/FU vs. PBO + Cis + Cap/FU		*	*			*			ITT (all randomly assigned patients); measurable disease population (response rate only)	NR[a]
FLAGS Ajani 2010 [26]	S-1 + Cis vs. FU + Cis					*				Full analysis set (patients who received the assigned treatment)	Superiority of S-1 + Cis compared with FU + Cis in terms of overall survival
DIGEST Ajani 2017 [27]	S-1 + Cis vs. FU + Cis						*			ITT (all randomized patients)	NR[a]
RILOMET-1 Catenacci 2017 [28]	Rilotumumab + Epir + Cis + Cap vs. PBO + Epir + Cis + Cap	*	*	*			*		*	OS and PFS: ITT (all randomly assigned patients, according to randomly allocated treatment) ORR and DCR: all patients with at least one unidimensional measurable lesion at baseline per RECIST version 1.1	NR[a]

(continued)

Table 1. (continued)

Trial	Treatment arms	Efficacy variables: OS	12-mo survival	PFS	TTP	TTF	ORR	DOR	DCR	Analysis population	Statistical design
Lu 2018 [29]	Pac + Cap vs. Cis + Cap						*			ITT (all patients who intended to receive treatment)	NR[a]
METGastric Shah 2017 [39]	Onartuzumab + mFOLFOX6 vs. PBO + mFOLFOX6									ITT (all randomized patients)	NR[a]
Lu 2019 [35]	S-1 + Doc vs. S-1 + Cis									Full analysis set was analyzed according to ITT principle Per-protocol set[c]	Noninferiority of S-1 + Doc compared with S-1 + Cis in terms of PFS
Shu 2017 [32]	Ox + tegafur vs. Ox + Cis									NR	Noninferiority of Ox + tegafur compared with Ox + S-1 in terms of PFS and OS (co-primary endpoints)
HELOISE Shah 2017 [115]	SoC Tras + Cap + Cis vs. higher-dose Tras + Cap + Cis									Full analysis set (all randomized patients) Per-protocol set[d]	Superiority of higher-dose Tras compared with SoC Tras in terms of OS
RAINFALL Fuchs 2019 [40][e]	RAM + Cis + Cap/FU vs. PBO + Cis + Cap/FU			*	*			*		PFS was analyzed with data from the first 508 randomized patients[f] OS was analyzed in all randomized patients	NR[a]
JCOG1013 Yamada 2019 [36]	Doc + Cis/S-1 vs. Cis/S-1									ITT (all randomized patients)	Superiority of Doc + Cis and S-1 compared with Cis and S-1 in terms of OS
JACOB Tabernero 2018 [38]	Pertuzumab + Tras/Check vs. PBO + Tras/Chemo									ITT (all randomized patients)	NR[a]
Second-line studies											
JapicCTI-090849 Satoh 2015 [62]	Nimotuzumab + IRI vs. IRI									Full analysis set (randomized and received all study medications)	NR[a]
TyTAN Satoh 2014 [46]	LAP + Pac vs. Pac						*			ITT (patients randomized to treatment); mITT (randomized patients confirmed to be FISH positive; HER2:CEP17 ratio ≥ 2)	Superiority of LAP + Pac compared with Pac alone in terms of OS
Sym 2013 [55]	IRI vs. FOLFIRI									ITT (all enrolled patients)	NR[a]
JACCRO GC-05 Tanabe 2015 [56]	S-1 + IRI vs. IRI									Full analysis set	NR[a]
Thuss-Patience 2011 [47]	IRI + BSC vs. BSC	*								ITT	NR[a]
Yi 2012 [43]	Doc + sunitinib vs. Doc						*		*	ITT	NR[a]
Study 39 Bang 2015 [48]	Olaparib + Pac vs. PBO + Pac	*								Overall patient population (enriched for patients with ATM-low status) and the ATM-low population	NR[a]
COUGAR-02 Ford 2014 [49]	Doc vs. active symptom control	*								ITT	NR[a]
TCOG GI-0801/BIRIP Higuchi 2014 [44]	IRI + Cis vs. IRI			*					*	Full analysis set	Superiority of IRI + Cis compared with IRI in terms of PFS
REGARD Fuchs 2014 [42]	RAM vs. PBO	*		*					*	ITT (patients randomized to treatment)	NR[a]
RAINBOW Wilke 2014 [41]	RAM + Pac vs. PBO + Pac	*		*			*		*	ITT (patients randomized to treatment)	NR[a]
RAINBOW subgroup analysis (East Asia) Muro 2016 [63]	RAM + Pac vs. PBO + Pac			*			*		*	ITT (patients randomized to treatment)	NR[a]
RAINBOW subgroup analysis (Japan) Shitara 2016 [64]	RAM + Pac vs. PBO + Pac	*		*			*		*	ITT (patients randomized to treatment)	NR[a]
WJOG 4007 Hironaka 2013 [53]	Pac vs. IRI									Full analysis set (all randomly assigned patients who met the eligibility criteria)	NR[a]
Kim 2015 [45]	Doc vs. Doc + Ox			*					*	ITT	NR[a]
CCOG0701 Nakanishi 2016 [58]	Pac vs. Pac + S-1									Full analysis set	NR[a]
JCOG0407 Nishina 2016 [50]	Best available FU vs. Pac			*						ITT	NR[a]

(continued)

Table 1. (continued)

Trial	Treatment arms	Efficacy variables: OS	12-mo survival	PFS	TTP	TTF	ORR	DOR	DCR	Analysis population	Statistical design
Roy 2013 [54]	PEP02 vs. IRI vs. Doc									ITT (all recruited subjects who received any study medication); assessable population (patients who had received at least two cycles of treatment and were assessable for response)	NR[a]
TRICS Nishikawa 2015 [57]	IRI + Cis vs. IRI									ITT (all randomized patients)	Superiority of IRI + Cis compared with IRI in terms of OS
Bang 2017b [70][g]	Ipilimumab vs. BSC									ITT	NR[a]
GOLD Bang 2017a [69]	Olaparib + Pac vs. PBO + Pac									ITT	NR[a]
DREAM Kang 2018 [51]	DHP107 (oral Pac) vs. IV Pac									Per-protocol population (primary endpoint) Full analysis set (secondary endpoints; confirmatory analysis for primary endpoint)	Noninferiority of oral Pac compared with IV Pac in terms of PFS in the per-protocol population
KEYNOTE-061 Shitara 2018a [71][h]	Pembrolizumab vs. Pac									ITT	Superiority of pembrolizumab in terms of the primary endpoints (OS and PFS in patients with PD-L1 CPS ≥1)
GATSBY Thuss-Patience 2017 [66]	Taxane vs. Tras emtansine									ITT	Superiority of Tras emtansine compared with taxane in terms of OS
SHINE Van Cutsem 2017 [72]	AZD4547 vs. Pac									Full analysis set	NR[a]
Lee 2017 [116]	Doc vs. Doc + Cis vs. Doc + S-1	*								Modified ITT population, which excluded patients who were deemed ineligible or never started the study treatment from randomization	Superiority of the best treatment in terms of ORR
KCSG ST10-01 Lee 2019 [117]	Pac vs. IRI									ITT	Noninferiority of IRI vs. Pac in terms of PFS (i.e., median PFS of IRI would be at least longer than 2.65 mo)
ABSOLUTE Shitara 2017 [52]	Nab-Pac Q3W vs. nab-Pac QW vs. Pac									Full analysis set (all randomly assigned patients who received at least one dose of the allocated drug and who met the eligibility criteria)	Noninferiority of nab-Pac vs. Pac in terms of OS
Combined second- and third-line population											
Fushida 2016 [60]	Pac vs. Pac + valproic acid									NR (did not include patients that dropped out in the analysis)	NR[a]
Kang 2012 [61]	Doc or IRI + BSC vs. BSC	*								ITT (all randomized patients were included in the analysis)	NR[a]
Moehler 2016 [118]	Na-FOLFIRI + sunitinib vs. Na-FOLFIRI + placebo									PFS: ITT (set comprising all patients with at least one available postbaseline assessment of the primary analysis variable)	NR[a]
GRANITE-1 Ohtsu 2013 [73]	Everolimus + BSC vs. PBO + BSC			*						ITT (patients were analyzed per the treatment and stratum to which they were assigned on randomization)	NR[a]
INTEGRATE Pavlakis 2016 [74]	Regorafenib + BSC vs. PBO + BSC			*						Efficacy analysis set (comprised patients deemed eligible on blinded central clinical review)	NR[a]
Shitara 2014 [59]	Dose-escalated Pac vs. Pac			*					*	Full analysis set (all eligible patients who received at least one dose of paclitaxel)	Superiority of OS with a one-sided alpha error of 0.3 and a power of 0.8
Third-line and beyond studies											
Li 2013 [77]	Apatinib 850 mg once daily vs. apatinib 425 mg twice daily vs. PBO	*		*					*	Full analysis set (ITT patients, including those who were randomly assigned to a treatment group but who did not adhere to the full course of treatment)	NR[a]
Li 2016 [78]	Apatinib vs. PBO	*		*						Full analysis set (consisted of all randomly assigned patients who received at least one dose of study medication)	NR[a]

(continued)

Table 1. (continued)

Trial	Treatment arms	Efficacy variables: OS	12-mo survival	PFS	TTP	TTF	ORR	DOR	DCR	Analysis population	Statistical design
JAVELIN Gastric 300 Bang 2018 [82]	Avelumab + BSC vs. Chemo + BSC									ITT (all randomized patients)	Superiority of avelumab vs. Chemo in terms of OS
ATTRACTION-2 Kang 2017 [75]	Nivolumab vs. PBO	*		*						ITT for survival analyses (all randomized patients) Response evaluable population for tumor response (patients with measurable target lesion)	Superiority of nivolumab compared with placebo
ATTRACTION-2 subgroup analysis (Japanese patients) Kato 2019 [79]	Nivolumab vs. PBO	*		*			*		*	ITT for survival analyses (all randomized patients) Response assessment population for response rate (patients with measurable target lesion)	NR[a]
ATTRACTION-2 subgroup analysis (prior Tras use) Satoh 2020 [119]	Nivolumab vs. PBO	*		*						ITT (all randomized patients)	NR[a]
TAGS Shitara 2018b [76]	Trifluridine/tipiracil + BSC vs. PBO + BSC	*		*					*	ITT for OS and PFS (all randomized patients) ORR and DCR in tumor response assessable population (patients in the ITT population with measurable disease at baseline who underwent at least one tumor assessment while on treatment)	NR[a]
CheckMate-032 Janjigian 2018 [80]	Nivolumab 3 mg/kg vs. nivolumab 1 mg/kg + ipilimumab 3 mg/kg vs. nivolumab 3 mg/kg + ipilimumab 1 mg/kg									Tumor evaluable population	NR[a]

Shading key: dark green indicates primary endpoint; medium green indicates secondary endpoint; light green indicates additional endpoint (or endpoint not specified).

*Statistically significant results were found for this study for this endpoint.

[a]Because the publication did not specifically state whether this was a superiority or a noninferiority study, it can be inferred that it is a superiority study (where a statistically significant *p* value for the test statistic prompts rejection of the null hypothesis and leads to the conclusion that one treatment is superior to the other).

[b]In Kang et al. (2009) [24], the per-protocol population was defined as all randomized patients, except those who received <6 weeks of treatment for reasons other than progressive disease or death or < 50% of the anticipated treatment during the first 6 weeks of the trial and those who had major inclusion or exclusion criteria violations or inadequate information regarding tumor burden.

[c]In Lu et al. (2019) [35], the per-protocol set was defined as all patients who conformed to the test plan with good compliance, took at least one cycle of drugs without taking banned drugs during the study, and completed the case report form without filling in missing data resulting in imputation.

[d]In the HELOISE study [115], OS was assessed as a secondary endpoint in the per-protocol set, defined as patients with cycle 1 trastuzumab C_{trough} < 12 μg/mL after the initial loading dose of 8 mg/kg.

[e]In the RAINFALL study [40], investigator-assessed PFS survival was significantly longer in the ramucirumab group than the placebo group (hazard ratio [HR], 0.753; 95% confidence interval [CI], 0.607–0.935; $p = .0106$; median PFS 5.7 months [5.5–6.5] versus 5.4 months [4.5–5.7]). A sensitivity analysis based on central independent review of the radiological images did not corroborate the investigator-assessed difference in PFS (HR, 0.961; 95% CI, 0.768–1.203; $p = .74$).

[f]In the RAINFALL study [40], enrollment of the first 508 patients, with 346 progression events, was planned to achieve 90% power to detect a difference in investigator-assessed PFS between the two treatment groups (HR of 0.70, assuming an increase in median PFS from 5.6 months to 8.0 months), with a two-sided α level of 0.05.

[g]The primary endpoint in the study by Bang et al. (2017b) [70] was immune-related PFS, per assessment of a blinded independent review committee. Secondary endpoints were PFS by World Health Organization criteria, OS, and immune-related best overall response rate, and exploratory endpoints included DOR and immune-related TTP.

[h]The primary endpoints in the KEYNOTE-061 study (Shitara et al. [2018a] [71]) were OS and PFS in in patients with PD-L1 CPS of 1 or higher. Secondary endpoints included OS and PFS in the overall population.

Abbreviations: ATM, ataxia telangiectasia mutated; BEV, bevacizumab; BSC, best supportive care; Cap, capecitabine; CEP17, chromosome 17 centromere; Chemo, chemotherapy; Cis, cisplatin; CPS, combined positive score; CTX, cetuximab; D, day; DCR, disease control rate; Doc, docetaxel; DOR, duration of response; Epir, epirubicin; FISH, fluorescence in situ hybridization; FOL, folinic acid; FOLFIRI, irinotecan plus 5-fluorouracil plus folinic acid (also known as leucovorin); FU, fluorouracil; IRI, irinotecan; ITT, intent-to-treat; IV, intravenous; LAP, lapatinib; mFOLFOX6, modified FOLFOX6; mITT, modified intent-to-treat; Na-FOLFIRI, sodium folinate-FOLFIRI; nab-Pac, nab-paclitaxel; NR, not reported; ORR, overall response rate; OS, overall survival; Ox, oxaliplatin; Pac, paclitaxel; PAN, panitumumab; PBO, placebo; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q3W, once every 3 weeks; QW, once weekly; RAM, ramucirumab; SoC, standard of care; SIM, simvastatin; Tras, trastuzumab; TTF, time to treatment failure; TTP, time to progression.

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Table 2. Overall survival, progression-free survival, and overall response rate of included first-, second-, or third-line and beyond randomized controlled trials ordered by study publication year

Trial	Treatment	Patients, *n*	Overall survival[a–c]		Progression-free survival[a–c]		ORR[a–c]	
			Median (95% CI), mo	Effect size(95% CI)	Median (95% CI), mo	Effect size (95% CI)	%	Effect size
First-line studies								
Kang 2009 [24][d,e]	Cis + Cap	139	10.4 (9.1–11.0)	HR, 0.85 (0.65–1.11); $p = .005$ vs. noninferiority margin of 1.25	5.6 (4.8–6.9)	HR, 0.80 (0.63–1.03); $p < .001$ vs. noninferiority margin of 1.25		
	Cis + FU	137	8.9 (7.3–10.2)		5.0 (3.9–5.7)			
FLAGS Ajani 2010 [26][f,g]	S-1 + Cis	527	8.6	HR, 0.92 (0.80–1.05); $p = .1983$	4.8 (4.0–5.5)	HR, 0.99 (0.86–1.14); $p = .9158$	29.1	$p = .40$
	FU + Cis	526	7.9		5.5 (4.4–5.8)		31.9	
ToGA Bang 2010 [17][h,i]	Tras + Chemo[j]	294	13.8	HR, 0.74 (0.60–0.91); $p = .0046$	6.7	HR, 0.71 (0.59–0.85); $p = .0002$	47[k]	$p = .0017$
	Chemo	290	11.1		5.5		35[k]	
AVAGAST Ohtsu 2011 [25][d,l]	BEV + Cis + Cap/FU[m]	252	12.1 (11.1–13.8)	HR, 0.87 (0.73–1.03); $p = .1002$	6.7 (5.9–7.1)	HR, 0.80 (0.68–0.98); $p = .0037$		
	PBO + Cis + Cap/FU[m]	265	10.1 (9.0–11.3)		5.3 (4.4–5.6)			
REAL3 Waddell 2013 [18][d]	Epir + Ox + Cap	275	11.3 (9.6–13.0)	HR, 1.37 (1.07–1.76); $p = .013$	6.0 (5.5–6.5)	HR, 1.22 (0.98–1.52); $p = .068$	NR	NR
	Epir + Ox + Cap + PAN	278	8.8 (7.7–9.8)		7.4 (6.3–8.5)		NR	
EXPAND Lordick 2013 [114][d,n]	CTX + Cap + Cis	455	9.4 (8.3–10.6)	HR, 1.00 (0.87–1.17); $p = .95$	4.4 (4.2–5.5)	HR, 1.09 (0.92–1.29); $p = .32$		
	Cap + Cis	449	10.7 (9.4–11.3)		5.6 (5.1–5.7)			
Van Cutsem 2015 [37][i]	Doc + Ox	79	8.97 (7.79–10.87)	NR	4.5 (3.7–5.3)	NR	NR	NR
	Doc + Ox + FU/FOL	89	14.59 (11.70–21.78)		7.7 (7.0–9.4)			
	Doc + Ox + Cap	86	11.30 (8.08–14.03)		5.6 (4.3–6.4)		NR	
Guimbaud 2014 [22][d,o]	Epir + Cis + Cap	209	9.49	HR, 1.01 (0.82–1.24); $p = .95$	5.3	HR, 0.99 (0.81–1.21); $p = .96$	90.4	NS
	FOLFIRI	207	9.72		5.8		95.7	
Kim 2014 [112][d,p]	SIM + Cap + Cis	120	11.6 (9.2–13.9)	HR, 0.966 (0.722–1.293); $p = .818$	5.2 (4.3–6.1)	HR, 0.930 (0.684–1.264); $p = .664$		
	PBO + Cap + Cis	124	11.5 (9.9–13.1)		4.6 (3.5–5.7)			
SOS Ryu 2015 [109][h,q]	S-1 (D1–14) + Cis (D1)	306	14.1 (11.4–15.8)	HR, 0.99 (0.81–1.21); $p = .91$	5.5 (4.7–6.6)	HR, 0.82 (0.68–0.99); $p = .0418$	60	$p = .065$
	S-1 (D1–21) + Cis (D1 or 8)	309	13.9 (11.6–15.9)		4.9 (4.2–5.5)		50	
AVATAR Shen 2015 [110][d]	PBO + Cap + Cis	102	11.4 (8.6–16.0)	HR, 1.11 (0.79–1.56); $p = .56$	6.0 (4.9–7.4)	HR, 0.89 (0.66–1.21); $p = .47$	NR	NR
	BEV + Cap + Cis	100	10.5 (8.9–14.1)		6.3 (5.7–7.4)		NR	NR
JapicCTI-101021 Yamada 2015 [20][d,r]	S-1 + Ox	318	14.1 (13.0–15.8)	HR, 0.958 (0.803–1.142) (S-1 + Ox noninferior to S-1 + Cis)	5.5 (4.4–5.7)	HR, 1.004 (0.840–1.199); $p = .0044$ (noninferiority)	55.7	NR
	S-1 + Cis	324	13.1 (12.1–15.1)		5.4 (4.2–5.7)		52.2	

(continued)

Table 2. (continued)

Trial	Treatment	Patients, *n*	Overall survival[a–c]		Progression-free survival[a–c]		ORR[a–c]	
			Median (95% CI), mo	Effect size(95% CI)	Median (95% CI), mo	Effect size (95% CI)	%	Effect size
Li 2015 [113][e]	S-1 + Cis	120	10.0 (8.59–14.52)	$p = .82$				
	FU + Cis	116	10.46 (8.92–13.84)					
Wang 2016 [19][d,s]	Doc + Cis + FU	121	10.2 (8.6–11.9)	HR, 0.71 (0.52–0.97); $p = .0319$	7.2 (5.5–8.8)	HR, 0.58 (0.42–0.80); $p = .0008$ (log-rank test)	48.7	$p = .0244$
	Cis + FU	122	8.5 (7.1–9.5)		4.9 (4.5–6.0)		33.9	
G-SOX Bando 2016 [21][d]	S-1 + Ox (≥70 yr)	116	17.5	≥70 yr: HR, 0.857 (0.629–1.167); $p = .325$	5.7	HR, 0.805 (0.588–1.102); $p = .174$	NR	NR
	S-1 + Cis (≥70 yr)	104	13.5		5.5		NR	
	S-1 + Ox (<70 yr)	227	13.3	<70 yr: HR, 0.984 (0.800–1.209); $p = .877$	4.4	HR, 1.019 (0.827–1.256); $p = .862$	NR	
	S-1 + Cis (<70 yr)	238	13.1		5.3		NR	
TRIO-013/LOGiC Hecht 2016 [23][d,n]	LAP + Cap + Ox	249	12.2	HR, 0.91 (0.73–1.12); $p = .3492$	6.0	HR, 0.82 (0.68–1.00); $p = .0381$	NR	NR
	PBO + Cap + Ox	238	10.5		5.4		NR	
DIGEST Ajani 2017 [27]	S-1 + Cis	239	7.5 (6.7–9.3)	Unstratified: HR, 0.99 (0.76–1.28); $p = .9312$ Stratified: HR, 0.90 (0.68–1.19); $p = .4631$	4.4	HR, 0.86 (0.65–1.14); $p = .3039$	34.7	$p = .0122$
	FU + Cis	122	6.6 (5.7–8.1)		3.9		19.8	
RILOMET-1 Catenacci 2017 [28]	Rilotumumab + Epir + Cis + Cap	262	8.8 (7.7–10.2)	HR, 1.34 (1.10–1.63); $p = .003$	5.6 (5.3–5.9)	HR, 1.26 (1.04–1.51); $p = .016$	29.8	$p = .0005$
	PBO + Epir + Cis + Cap	267	10.7 (9.6–12.4)		6.0 (5.7–7.2)		44.6	
METGastric Shah 2017 [39]	Onartuzumab + mFOLFOX6	217	11.0	HR, 0.82 (0.59–1.15); $p = .24$	6.7	HR, 0.90 (0.71–1.16); $p = .43$	46.1	$p = .25$
	PBO + mFOLFOX6	207	11.3		6.8		40.6	
	MET 2+/3+ subgroup: onartuzumab + mFOLFOX6	78	11.0	HR, 0.64 (0.40–1.03); $p = .06$	6.9	HR, 0.79 (0.54–1.15); $p = .22$	53.8	$p = .23$
	MET 2+/3+ subgroup: PBO + mFOLFOX6	92	9.7		5.7		44.6	
Shu 2017 [32]	Ox + tegafur	164	13.4 (12.2–15.1)	HR, 0.96 (0.80–1.39)	5.5 (4.6–6.2)	HR, 1.02 (0.82–1.31)	44.5	$p = .702$
	Ox + Cis	168	14.2 (13.1–16.0)		6.1 (5.6–6.4)		48.8	
HELOISE Shah 2017 [115]	SoC Tras + Cap + Cis	124	12.5	HR, 1.24 (0.86–1.78); $p = .2401$	5.7	HR, 1.04 (0.76–1.40); $p = .8222$	58.9	$p = .76$
	Higher-dose Tras + Cap + Cis	124	10.6		5.6		56.9	
Lu 2018 [29]	Pac + Cap	160	12.5 (11.5–14.5)	HR, 0.878 (0.685–1.125); $p = .30$	4.994 (4.304–6.275)	HR, 0.906 (0.706–1.164); $p = .44$	43.1	$p = .01$
	Cis + Cap	160	11.8 (10.0–13.7)		5.257 (4.665–5.815)		28.8	
Lu 2019 [35]	S-1 + Doc	150	405 days	$p = .5127$	180 days	$p > .05$	NR	NR
	S-1 + Cis	150	378 days		171 days		NR	

(continued)

Table 2. (continued)

Trial	Treatment	Patients, *n*	Overall survival[a–c]		Progression-free survival[a–c]		ORR[a–c]	
			Median (95% CI), mo	Effect size(95% CI)	Median (95% CI), mo	Effect size (95% CI)	%	Effect size
RAINFALL Fuchs 2019 [40][t,u]	RAM + Cis + Cap/FU[v]	326	11.2 (9.9–11.9)	HR, 0.962 (0.801–1.156); $p = .68$	Investigator-assessed: 5.7 (5.5–6.5) Independent review: 5.5 (4.2–5.8)	Investigator-assessed: HR, 0.753 (0.607–0.935); $p = .011$ Independent review: HR, 0.961 (0.78–1.203); $p = .74$	41.1	$p = .17$
	PBO + Cis + Cap/FU[o]	319	10.7 (9.5–11.9)		Investigator-assessed: 5.4 (4.5–5.7) Independent review: 5.4 (4.4–5.7)		36.4	
JACOB Tabernero 2018 [38]	Pertuzumab + Tras/Chemo	388	17.5 (16.2–19.3)	HR,0.84 (0.71–1.00); $p = .057$	8.5 (8.2–9.7)	HR, 0.73 (0.62–0.86); $p = .0001$	56.7	$p = .026$
	PBO + Tras/Chemo	392	14.2 (12.9–15.5)		7.0 (6.4–8.2)		48.3	
JCOG1013 Yamada 2019 [36]	Doc + Cis/S-1	370	14.2 (12.9–15.9)	HR, 0.99 (0.85–1.16); $p = .47$	7.4 (6.7–7.8)	HR, 0.99 (0.86–1.15); $p = .92$	59	$p = .50$
	Cis/S-1	371	15.3 (14.2–16.2)		6.5 (5.9–7.4)		56	
Second-line studies								
Thuss-Patience 2011 [47][w–y,as]	IRI + BSC	21	4.0 (3.6–7.5)	All patients died: HR, 0.48 (0.25–0.92); $p = .012$	ITT population: 2.5 (1.6–3.9) Per-protocol population: 2.6 (1.7–4.3)	NR (results provided for IRI arm only)	0[z]	NR
	BSC	19	2.4 (1.7–4.9)		NR (results provided for IRI arm only)		NR	
Yi 2012 [43][x,as]	Doc + sunitinib	56	8.0 (5.4–10.6)	HR, 0.94 (0.60–1.49); $p = .802$	NR	NR	41.1	$p = .002$
	Doc	49	6.6 (3.6–9.7)		NR		14.3	
Sym 2013 [55][x,aa,as]	IRI	29	5.8 (3.0–8.7)	HR, 1.21 (0.69–2.11); $p = .514$	2.2 (0.2–4.3)	HR, 1.20 (0.72–2.02); $p = .481$	17.2	$p = .525$
	FOLFIRI	30	6.7 (5.3–8.2)		3.0 (2.0–3.7)		20.0	
WJOG 4007 Hironaka 2013 [53][aa,ab,as]	Pac	108	9.5 (8.4–10.7)	HR, 1.13 (0.86–1.49); $p = .38$	3.6 (3.3–3.8)	HR, 1.14 (0.88–1.49); $p = .33$	20.9	$p = .24$
	IRI	111	8.4 (7.6–9.8)		2.3 (2.2–3.1)		13.6	
Roy 2013 [54][x,aa,as]	PEP02[ac]	44	7.3 (3.84–9.17)	NR	2.7 (1.54–3.65)	NR	13.6	NR
	IRI	44	7.8 (4.90–9.20)		2.6 (1.48–4.34)		6.8	
	Doc	44	7.7 (5.32–12.32)		2.7 (1.41–5.45)		15.9	
TyTAN Satoh 2014 [46][x,aa,as]	LAP + Pac	132	11.0[ad]	HR, 0.84 (0.64–1.11); $p = .1044$	5.5[ad]	HR, 0.85 (0.63–1.13); $p = .2441$[ad]	27[ad]	Estimated OR, 3.85 (1.80–8.87); $p < .001$
	Pac	129	8.9[ad]		4.4[ad]		9[ad]	
COUGAR-02 Ford 2014 [49][at]	Doc	84	5.2 (4.1–5.9)	HR, 0.67 (0.49–0.92); $p = .01$	NR	NR	NR	NR
	Active symptom control	84	3.6 (3.3–4.4)		NR		NR	
TCOG GI-0801/BIRIP Higuchi 2014 [44][x,aa,as]	IRI + Cis	64	10.7	HR, 1.00 (0.69–1.44); $p = .9823$	3.8	HR, 0.68 (0.47–0.98); $p = .0398$	22	$p = .4975$
	IRI	63	10.1		2.8		16	

(continued)

Table 2. (continued)

Trial	Treatment	Patients, *n*	Overall survival[a–c]		Progression-free survival[a–c]		ORR[a–c]	
			Median (95% CI), mo	Effect size(95% CI)	Median (95% CI), mo	Effect size (95% CI)	%	Effect size
REGARD Fuchs 2014 [42][x,aa,av]	RAM	238	5.2 (IQR, 2.3–9.9)	HR, 0.776 (0.603–0.998); $p = .047$	2.1 (IQR, 1.3–4.2)	HR, 0.483 (0.376–0.620); $p < .0001$	3	$p = .76$
	PBO	117	3.8 (IQR, 1.7–7.1)		1.3 (IQR, 1.1–2.1)		3	
RAINBOW Wilke 2014 [41][ae,af,av]	RAM + Pac	330	9.6 (8.5–10.8)	HR, 0.807 (0.678–0.962); $p = .017$	4.4 (4.2–5.3)	HR, 0.635 (0.536–0.752); $p < .0001$	28	$p = .0001$
	PBO + Pac	335	7.4 (6.3–8.4)		2.9 (2.8–3.0)		16	
JACCRO GC-05 Tanabe 2015 [56][aa,ag,as]	S-1 + IRI	145	8.8 (IQR, 5.6–15.7)	$p = .92$ HR for death, 0.99 (0.78–1.25)	3.8 (IQR, 1.9–6.6)	HR for disease progression or death, 0.85 (0.67–1.07); $p = .16$	7.6	NS
	IRI	148	9.5 (IQR, 5.6–14.1)		3.4 (IQR, 1.6–5.3)		7.4	
JapicCTI-090849 Satoh 2015 [62][as]	Nimotuzumab + IRI	40	250.5 days[ah] (171.0–306.0)	HR, 0.994 (0.618–1.599)[ah]; $p = .9778$	73.0 days (55.0–112.0)	HR, 0.860 (0.516–1.435); $p = .5668$	18.4	$p = .3060$
	IRI	42	232.0 days[ah] (148.0–319.0)		85.0 days (37.0–93.0)		10.3	
Study 39 Bang 2015 [48][ae,ah,au,ax]	Olaparib + Pac	62	13.1	HR, 0.56 (0.35–0.87); $p = .010$	3.9	HR, 0.80 (80% CI, 0.62–1.03); $p = .131$	26.4	NS
	PBO + Pac	62	8.3		3.6		19.1	
TRICS Nishikawa 2015 [57][ai,as]	IRI + Cis	84	13.9 (10.8–17.6)	HR, 0.834 (0.596–1.167); $p = .288$	4.6 (3.4–5.9)	HR, 0.860 (0.610–1.203); $p = .376$	NR	NR
	IRI	84	12.7 (10.3–17.2)		4.1 (3.3–4.9)		NR	
Kim 2015 [45][x,ae]	Doc	27	7.2 (6.0–8.4)	$p = .353$	2.0 (1.2–2.9)	$p = .002$	14.8	$p = .40$
	Doc + Ox	25	8.1 (7.6–8.6)		4.9 (3.6–6.6)		24.0	
RAINBOW subgroup analysis (East Asia) Muro 2016 [63][ae,aj,as]	RAM + Pac	109	12.1	HR, 0.986 (0.727–1.337); $p = .929$	5.5	HR, 0.628 (0.473–0.834)	34	OR, 2.24 (1.18–4.24); $p = .0134$
	PBO + Pac	114	10.5		2.8		20	
RAINBOW subgroup analysis (Japan) Shitara 2016 [64][ae,ak,aw]	Japanese: RAM + Pac	68	11.4	HR, 0.880 (0.603–1.284); $p = .5113$	5.6	HR, 0.503 (0.348–0.728); $p = .0002$	41.2	$p = .0035$
	Japanese: PBO + Pac	72	11.5		2.8		19.4	
	Western: RAM + Pac	198	8.6	HR, 0.7326 (0.580–0.909); $p = .005$	4.2	HR, 0.631 (0.506–0.786); $p < .0001$	26.8	$p = .0004$
	Western: PBO + Pac	200	5.9		2.8		13.0	
CCOG0701 Nakanishi 2016 [58][aa,al,as]	Pac	40	10.0 (0.4–74.1)	HR, 0.834 (0.511–1.359)	4.6 (0.4–74.1)	HR, 0.862 (0.543–1.367); difference NS[b]	27	$p = .767$
	Pac + S-1	49	10.0 (1.3–72.0)		4.6 (0.4–59.6)		22	

(continued)

Table 2. (continued)

Trial	Treatment	Patients, *n*	Overall survival[a–c]		Progression-free survival[a–c]		ORR[a–c]	
			Median (95% CI), mo	Effect size(95% CI)	Median (95% CI), mo	Effect size (95% CI)	%	Effect size
JCOG0407 Nishina 2016 [50][w,as]	Best available FU	49	7.7 (6.7–9.0)	HR, 0.89 (0.57–1.38); $p = .298$	2.4 (1.7–3.6)	HR, 0.58 (0.38–0.88); $p = .005$	NR	NR
	Pac	51	7.7 (6.0–9.7)		3.7 (2.6–3.7)		NR	
Bang 2017b [70][w,ae]	Ipilimumab	57	12.7 (10.5–18.9)	NR	irPFS: 2.92 (1.61–5.16) PFS (mWHO criteria): 2.73 (1.45–2.96)	irPFS: HR, 1.44 80% CI, 1.09–1.91); $p = .097$ mWHO criteria: HR, 1.59 (80% CI, 1.20–2.10); $p = .034$ (“consistent with irPFS” [improvement was not observed])	1.8	NR
	BSC	57	12.1 (9.3–NE)		irPFS: 4.90 (3.45–6.54) PFS (mWHO criteria): 4.90 (3.45–6.08)		7.0	NR
GOLD Bang 2017a [69][x]	Olaparib + Pac	263	8.8 (7.4–9.6)	HR, 0.79 (97.5% CI, 0.63–1.00); $p = .026$ (NS)[an]	3.7 (3.7–4.2)	HR, 0.84 (97.5% CI, 0.67–1.04); $p = .065$	17 (adjusted, 24)[ae]	OR, 1.69 (97.5% CI, 0.92–3.17); $p = .055$
	PBO + Pac	262	6.9 (6.3–7.9)		3.2 (2.2–3.5)		11 (adjusted, 16)[ae]	
	ATM-negative tumors subgroup: Olaparib + Pac	48	12.0 (7.8–18.1)	HR, 0.73 (97.5% CI, 0.40–1.34); $p = .25$	5.3 (3.5–9.0)	HR, 0.74 (97.5% CI, 0.42–1.29); $p = .22$	25 (adjusted, 38)[ae]	OR, 4.24 (0.95–23.23); $p = .031$
	ATM-negative tumors subgroup: PBO + Pac	46	10.0 (6.4–13.3)		3.7 (1.9–5.3)		11 (adjusted, 16)[ae]	
GATSBY Thuss-Patience 2017 [66][x,ae]	Taxane	117	8.6 (7.1–11.2)	HR, 1.15 (0.87–1.51); $p = .86$	2.9 mo (2.8–4.0)	HR, 1.13 (0.89–1.43); $p = .31$	19.6	$p = .8406$
	Tras emtansine	228	7.9 (6.7–9.5)		2.7 (1.6–2.7)		20.6	
SHINE Van Cutsem 2017 [72][x,ae]	AZD4547	41	5.5 (95% CI, NR)	HR, 1.31 (80% CI, 0.89–1.95); $p = .8156$	1.8	HR, 1.57 (80% CI, 1.12–2.21); $p = .9581$	2.6	OR, 0.09 (80% CI, 0.02–0.35); $p = .9970$
	Pac	30	6.6 (95% CI, NR)		3.5		23.3	
Lee 2017 [116][aa]	Doc	23	10.0 (7.8–12.2)	All vs. Doc + S-1: $p = .023$ Doc + S-1 vs. Doc: $p = .421$ Doc + Cis vs. Doc: $p = .035$	1.3 (1.0–1.5)	All vs. Doc + S-1: $p = .072$ Doc + Cis vs. Doc: $p = .804$ Doc + S-1 vs. Doc: $p = .072$	4.3	$p > .990$ vs. Doc
	Doc + Cis	23	5.6 (4.4–6.7)		1.8 (0.8–2.9)		4.3	
	Doc + S-1	23	6.9 (2.1–11.7)		2.7 (1.0–4.4)		8.7	
ABSOLUTE Shitara 2017 [52]	Nab-Pac Q3W	243	10.3 (8.7–11.4)	Nab-Pac Q3W vs. Pac: HR, 1.06 (0.87–1.31); $p = .062$	3.8 (3.5–4.4)	Nab-Pac Q3W vs. Pac: HR, 1.03 (0.85–1.24); $p = .778$	25	(18.6–33.1); $p = .897$ vs. Pac
	Nab-Pac QW	240	11.1 (9.9–13.0)	Nab-Pac QW vs. Pac: HR, 0.97 (97.5% CI, 0.76–1.23); $p = .0085$	5.3 (4.0–5.6)	Nab-Pac Q3W vs. Pac: HR, 0.88 (0.73–1.06); $p = .176$	33	(25.2–40.8); $p = .106$ vs. Pac
	Pac	243	10.9 (9.4–11.8)		3.8 (3.7–3.9)		24	(18.0–31.4)
DREAM Kang 2018 [51][x,ae,ai]	DHP107 (oral Pac)	118	9.7 (7.1–11.5)	HR, 1.04 (0.76–1.41); $p = .824$	3.0 (1.7–4.0)	HR, 0.85 (0.64–1.13)	NR	NR
	IV Pac	118	8.9 (7.1–12.2)		2.6 (1.8–2.8)		NR	

(continued)

Table 2. (continued)

Trial	Treatment	Patients, *n*	Overall survival[a–c]		Progression-free survival[a–c]		ORR[a–c]	
			Median (95% CI), mo	Effect size(95% CI)	Median (95% CI), mo	Effect size (95% CI)	%	Effect size
KEYNOTE-061 Shitara 2018a [71][ae,ay]	Pembrolizumab	296	NR	NR	NR	NR	12.2	NR
	Pac	296	NR	NR	NR	NR	15.2	NR
	PD-L1 CPS ≥1 subgroup: Pembrolizumab	196	9.1 (6.2–10.7)	HR, 0.82 (0.66–1.03); $p = .0421$ (NS)[ao]	1.5 (1.4–2.0)	HR, 1.27 (1.03–1.57)	16	NR
	PD-L1 CPS ≥1 subgroup: Pac	199	8.3 (7.6–9.0)		4.1 (3.1–4.2)		14	NR
KCSG ST10-01 Lee 2019 [117][x,ae,am]	Pac	54	8.57 (7.1–10.0)	HR, 1.39 (0.91–2.11); $p = .126$	3.47 (2.2–4.7)	HR, 1.27 (0.86–1.88); $p = .234$	15.8	$p = .355$
	IRI	58	7.03 (5.6–8.4)		2.10 (1.4–2.8)		13.6	
Combined second- and third-line populations								
Kang 2012 [61][as]	Doc or IRI + BSC	133	5.3 (4.1–6.5)	HR, 0.657 (0.485–0.891); $p = .007$	NR	NR	NR	NR
	BSC	69	3.8 (3.1–4.5)		NR		NR	
GRANITE-1 Ohtsu 2013 [73][aa,ap,as]	Everolimus + BSC	439	5.4 (4.8–6.0)	HR, 0.90 (0.75–1.08); $p = .124$	1.7 (1.5–1.9)	HR, 0.66 (0.56–0.78); $p < .001$	4.5	(95% CI for the rate, 2.6–7.1)
	PBO + BSC	217	4.3 (3.8–5.5)		1.4 (1.4–1.5)		2.1	(95% CI for the rate, 0.6–5.3)
Shitara 2014 [59][ae,aq,as]	Dose-escalated Pac	44	11.8 (7.6–16.3)	HR, 0.75 (0.45–1.22); $p = .12$	4.3 (3.0–5.7)	HR, 0.55 (0.34–0.90); $p = .017$	30.3	(95% CI for the rate, 15.6–48.7)
	Pac	45	9.6 (7.4–11.7)		2.5 (1.8–3.7)		17.1	(95% CI for the rate, 6.6–33.7)
Fushida 2016 [60][ae,as]	Pac	33	9.8	HR, 1.19 (0.702–2.026); $p = .51$	4.5	HR, 1.29 (0.753–2.211); $p = .35$	NR	NR
	Pac + valproic acid	31	8.7		3.0		NR	
Moehler 2016 [118][x,as]	Na-FOLFIRI + sunitinib	45	10.4 (4.5–10.9)	HR, 0.82 (0.50–1.34); $p = .42$	3.5 (1.4–5.6)	HR, 1.11 (0.70–1.74); $p = .66$	20	NR
	Na-FOLFIRI + placebo	45	8.9 (5.9–11.8)		3.3 (1.5–5.2)		29	NR
INTEGRATE Pavlakis 2016 [74][ae,ar,as]	Regorafenib + BSC	97	5.8 (4.4–6.8)	HR, 0.74 (0.51–1.08); $p = .147$	2.6 (1.8–3.1)	HR, 0.40 (0.28–0.59); $p < .001$	3.0	(95% CI for the rate, 1–9)
	Placebo + BSC	50	4.5 (3.4–5.2)		0.9 (0.9–0.9)		2	(95% CI for the rate, 0–11)
Third-line and beyond studies								
Li 2013 [77]	Apatinib 850 mg once daily	47	4.83 (4.03–5.97)	HR, 0.37 (0.22–0.62); $p < .001$	3.67 (2.17–6.80)	HR, 0.18 (0.10–0.34); $p < .001$)	0	(95% CI for the rate, 1.3–17.5)
	Apatinib 425 mg twice daily	46	4.27 (3.83–4.77)	HR, 0.41 (0.24–0.72); $p = .0017$	3.20 (2.37–4.53)	HR, 0.21 (0.11–0.38); $p < .001$	6.38	(95% CI for the rate, 4.9–26.3)
	PBO	48	2.5 (1.87–3.70)		1.40 (1.20–1.83)		13.04	(95% CI for the rate, 0.0–7.4)
Li 2016 [78]	Apatinib	146	6.5 (4.8–7.6)	HR, 0.709 (0.537–0.937); $p = .0149$	2.6 (2.0–2.9)	HR, 0.444 (0.331–0.595); $p < .001$	2.84 (1.70)	$p = .1695$ ($p = .5532$)
	PBO	78	4.7 (3.6–5.4)		1.8 (1.4–1.9)		0	
ATTRACTION-2 Kang 2017 [75][ay]	Nivolumab	330	5.26 (4.60–6.37)	HR, 0.63 (0.51–0.78); $p < .0001$	1.61 (1.54–2.30)	HR, 0.60 (0.49–0.75); $p < .0001$	11.2	NR
	PBO	163	4.14 (3.42–4.86)		1.45 (1.45–1.54)		0	

(continued)

Table 2. (continued)

Trial	Treatment	Patients, *n*	Overall survival[a–c]		Progression-free survival[a–c]		ORR[a–c]	
			Median (95% CI), mo	Effect size(95% CI)	Median (95% CI), mo	Effect size (95% CI)	%	Effect size
JAVELIN Gastric 300 Bang 2018 [82][ay]	Avelumab + BSC	185	4.6 (3.6–5.7)	HR, 1.1 (0.9–1.4); $p = .81$	1.4 (1.4–1.5)	HR, 1.73 (1.4–2.2); $p > .99$	2.2	NR
	Chemo + BSC	185	5.0 (4.5–6.3)		2.7 (1.8–2.8)		4.3	
TAGS Shitara 2018b [76]	Trifluridine/tipiracil + BSC	337	5.7 (4.8–6.2)	HR, 0.69 (0.56–0.85); $p = .00029$	2.0 (1.9–2.3)	HR, 0.57 (0.47–0.70); $p < .0001$	4	$p = .28$
	PBO + BSC	170	3.6 (3.1–4.1)		1.8 (1.7–1.9)		2	
CheckMate-032 Janjigian 2018 [80][ay]	Nivolumab 3 mg/kg	59	6.2 (3.4–12.4)	NR	1.4 (1.2–1.5)	NR	7	NR
	Nivolumab 1 mg/kg + ipilimumab 3 mg/kg	49	6.9 (3.7–11.5)		1.4 (1.2–3.8)		20	NR
	Nivolumab 3 mg/kg + ipilimumab 1 mg/kg	52	4.8 (3.0–8.4)		1.6 (1.4–2.6)		4	NR
ATTRACTION-2 subgroup analysis (Japanese patients) Kato 2019 [79][ay]	Nivolumab	152	5.4 (4.6–7.4)	HR, 0.58 (0.42–0.78); $p = .0002$	1.7 (1.6–2.8)	HR, 0.53 (0.39–0.72); $p < .0001$	14.0	$p = .0023$
	Placebo	74	3.6 (2.8–5.0)		1.5 (1.5–1.6)		0	
ATTRACTION-2 subgroup analysis (prior Tras use) Satoh 2020 [119][ay]	History of Tras: nivolumab	59	8.3 (5.3–12.9)	HR, 0.38 (0.22–0.66); $p = .0006$	1.6 (1.5–4.0)	HR, 0.49 (0.29–0.85); $p = .0111$	16.9	NR
	History of Tras: PBO	22	3.1 (1.9–5.3)		1.5 (1.3–2.9)		0	
	No history of Tras: nivolumab	271	4.8 (4.1–6.0)	HR, 0.71 (0.57–0.88); $p = .0022$	1.6 (1.5–2.4)	HR, 0.64 (0.51–0.80); $p = .0001$	7.7	NR
	No history of Tras: PBO	141	4.2 (3.6–4.9)		1.5 (1.5–1.5)		0	

[a]In Ajani et al. (2010) [26], Ryu et al. (2015) [109], Waddell et al. (2013) [18], Wang et al. (2016) [19], Bando et al. (2016) [21], Bang et al. (2010) [17], Guimbaud et al. (2014) [22], Hecht et al. (2016) [23], Li et al. (2015) [113], and Lordick et al. (2013) [114], data were not reported as being either adjusted or unadjusted.
[b]In Shen et al. (2015) [110], Van Cutsem et al. (2015) [37], Yamada et al. (2015) [20], and Kang et al. (2009) [24], unadjusted data are presented for OS and PFS; for other endpoints, data were not reported as being either adjusted or unadjusted.
[c]In Kim et al. (2014) [112] and Ohtsu et al. (2011) [25], unadjusted data are presented for OS, PFS, and response; for other endpoints, data were not reported as being either adjusted or unadjusted.
[d]In Shen et al. (2015) [110], Waddell et al. (2013) [18], Wang et al. (2016) [19], Yamada et al. (2015) [20], Bando et al. (2016) [21], Guimbaud et al. (2014) [22], Hecht et al. (2016) [23], Kang et al. (2009) [24], Kim et al. (2014) [112], Lordick et al. (2013) [114], and Ohtsu et al. (2011) [25], RECIST version 1.0 criteria were used.
[e]In Kang et al. (2009) [24] and Li et al. (2015) [113], only patients with measurable disease were included.
[f]In Ajani et al. (2010) [26], RECIST criteria were used, but no version number was provided.
[g]In Ajani et al. (2010) [26], patients were stratified based on whether disease was measurable (95.6% of patients had measurable disease).
[h]In Bang et al. (2010) [17] and Van Cutsem et al. (2015) [37], there was no indication that RECIST criteria were used.
[i]In Bang et al. (2010) [17], patients were stratified based on whether disease was measurable (∼90% of patients had measurable disease).
[j]Cap plus Cis or FU plus Cis, chosen at the investigator's discretion.
[k]"Overall tumor response rate" (complete response plus partial response).
[l]In Ohtsu et al. (2011) [25], the measurable disease population was used to evaluate response rate (∼79% of patients had measurable disease).
[m]Patients unable to take oral medications received FU. Switching from Cap to FU during the study was not permitted.
[n]In Hecht et al. (2016) [23] and Lordick et al. (2013) [114], no information was provided regarding the handling of data from patients with measurable versus nonmeasurable disease.
[o]In Guimbaud et al. (2014) [22], patients were stratified based on whether disease was measurable (the proportion of patients with measurable disease was not provided).
[p]In Kim et al. (2014) [112], patients were stratified based on whether disease was measurable (∼64% of patients had measurable disease).
[q]In Ryu et al. (2015) [109], response rate was calculated only for patients with measurable disease (∼61% of patients).
[r]In Yamada et al. (2015) [20], those with no measurable disease were excluded from the per-protocol population (∼2.5% of patients).
[s]In Wang et al. (2016) [19], those with no measurable disease were excluded from the efficacy population (∼1.3% of patients).

[t]In Ryu et al. (2015) [109] and Fuchs et al. (2019) [40], RECIST version 1.1 criteria were used.
[u]In Fuchs et al. (2019) [40], adjusted data were presented for PFS; for other endpoints, data were not reported as being either adjusted or unadjusted.
[v]FU IV infusion was permitted in patients unable to take oral capecitabine.
[w]In Thuss-Patience et al. (2011) [47], Nishina et al. (2016) [50], and Bang et al. (2017b) [70], there was no indication that RECIST criteria were used.
[x]In Satoh et al. (2015) [62], Satoh et al. (2014) [46], Sym et al. (2013) [55], Thuss-Patience et al. (2011) [47], Yi et al. (2012) [43], Higuchi et al. (2014) [44], Fuchs et al. (2014) [42], Kim et al. (2015) [45], Roy et al. (2013) [54], Bang et al. (2017a) [69], Kang et al. (2018) [51], Thuss-Patience et al. (2017) [66], Van Cutsem et al. (2017) [72], Lee et al. (2019) [117], and Moehler et al. (2016) [118], no information was provided regarding the handling of data from patients with measurable versus nonmeasurable disease.
[y]In Thuss-Patience et al. (2011) [47], there was no indication that RECIST criteria were used.
[z]No objective remission according to World Health Organization criteria.
[aa]In Satoh et al. (2015) [62], Satoh et al. (2014) [46], Sym et al. (2013) [55], Tanabe et al. (2015) [56], Higuchi et al. (2014) [44], Fuchs et al. (2014) [42], Hironaka et al. (2013) [53], Nakanishi et al. (2016) [58], Roy et al. (2013) [54], Lee et al. (2017) [116], and Ohtsu et al. (2013) [73], RECIST version 1.0 criteria were used.
[ab]In Hironaka et al. (2013) [53], response rate was assessed in patients with measurable disease at baseline (∼80% of patients).
[ac]PEP02 is a highly stable liposomal nanocarrier formulation of irinotecan.
[ad]ITT population. Similar results were obtained for the modified ITT population (i.e., randomly assigned patients confirmed FISH positive by central laboratory).
[ae]In Bang et al. (2015) [48], Wilke et al. (2014) [41], Muro et al. (2016) [63], Shitara et al. (2016) [64], Bang et al. (2017a) [69], Kang et al. (2018) [51], Kim et al. (2015) [45], Shitara et al. (2018b) [76], Thuss-Patience et al. (2017) [66], Van Cutsem et al. (2017) [72], Lee et al. (2019) [117], Fushida et al. (2016) [60], Pavlakis et al. (2016) [74], and Shitara et al. (2014) [59], RECIST version 1.1 criteria were used.
[af]In Wilke et al. (2014) [41], patients were stratified based on whether disease was measurable (∼81% of patients had measurable disease).
[ag]In Tanabe et al. (2015) [56], response rate was calculated only for patients with measurable disease (∼82% of patients had measurable disease).
[ah]Eighteen-month OS.
[ai]In Nishikawa et al. (2015) [57] and Kang et al. (2012) [61], RECIST criteria were used, but no version number was provided.
[aj]In Muro et al. (2016) [63], patients were stratified based on whether disease was measurable (∼72% of East Asian patients and ∼ 81% of non–East Asian patients had measurable disease).
[ak]In Shitara et al. (2016) [64], patients were stratified based on whether disease was measurable (72.1% of Japanese patients and 83.4% of Western patients had measurable disease).
[al]In Nakanishi et al. (2016) [58], measurable disease was an adjustment factor during randomization (∼42% of patients had measurable disease).
[am]In Lee et al. (2019) [117], response evaluation was conducted on patients with at least one measurable lesion (38/54 in the paclitaxel group and 44/58 in the irinotecan group).
[an]In the GOLD study (Bang et al. [2017a] [69]), statistical significance was set at $p < .025$.
[ao]In the KEYNOTE-061 study (Shitara et al. [2018a] [71]), statistical significance was set at $p < .0215$.
[ap]In Ohtsu et al. (2013) [73], objective response of complete response or partial response, only assessed in the patients with measurable disease at baseline (approximately 86% in the everolimus plus BSC group and 88% in the placebo plus BSC group).
[aq]In Shitara et al. (2014) [59], objective response of complete response or partial response, only assessed in the patients with measurable disease at baseline (78% in the weekly paclitaxel group and 75% in the dose-escalated weekly paclitaxel group).
[ar]In Pavlakis et al. (2016) [74], only patients with measurable disease were included in the study.
[as]In Satoh et al. (2015) [62], Satoh et al. (2014) [46], Sym et al. (2013) [55], Tanabe et al. (2015) [56], Thuss-Patience et al. (2011) [47], Yi et al. (2012) [43], Higuchi et al. (2014) [44], Muro et al. (2016) [63], Hironaka et al. (2013) [53], Kim et al. (2015) [45], Nakanishi et al. (2016) [58], Nishina et al. (2016) [50], Roy et al. (2013) [54], Nishikawa et al. (2015) [50], Fushida et al. (2016) [60], Kang et al. (2012) [61], Moehler et al. (2016) [28], Ohtsu et al. (2013) [73], Pavlakis et al. (2016) [74], and Shitara et al. (2014) [59], data were not reported as being either adjusted or unadjusted.
[at]In Ford et al. (2014) [49], adjusted data are presented for OS; for other endpoints, data were not reported as being either adjusted or unadjusted.
[au]In Bang et al. (2015) [48], adjusted data are presented for OS and PFS; for other endpoints, data were not reported as being either adjusted or unadjusted.
[av]In Fuchs et al. (2014) [42] and Wilke et al. (2014) [41], unadjusted data are presented for OS and PFS; for other endpoints, data were not reported as being either adjusted or unadjusted.
[aw]In Shitara et al. (2016) [64], adjusted data are presented for ORR and disease control rate; for other endpoints, data were not reported as being either adjusted or unadjusted.
[ax]In Bang et al. (2015) [48], response rate was calculated only for patients with measurable disease (∼81% of patients).
[ay]In Bang et al. (2018) [82], Kang et al. (2017) [75], Kato et al. (2019) [79], Shitara et al. (2018a) [71], and Janjigian et al. (2018) [80], data were not reported as being either adjusted or unadjusted. In Satoh et al. (2020) [119], adjusted data are presented for ORR and disease control rate; for other endpoints, data were not reported as being either adjusted or unadjusted.

Abbreviations: ATM, ataxia telangiectasia mutated; BEV, bevacizumab; BSC, best supportive care; Cap, capecitabine; Chemo, chemotherapy; CI, confidence interval; Cis, cisplatin; CPS, combined positive score; CTX, cetuximab; D, day; Doc, docetaxel; Epir, epirubicin; FOL, folinic acid FOLFIRI, irinotecan plus 5-fluorouracil plus folinic acid (also known as leucovorin); FU, fluorouracil; HR, hazard ratio; IQR, interquartile range; IRI, irinotecan; irPFS, immune-related progression-free survival; ITT, intent-to-treat; IV, intravenous; LAP, lapatinib; MET, mesenchymal-epithelial transition; mWHO, modified World Health Organization; nab-Pac, nab-paclitaxel; NR, not reported; NS, not significant; OR, odds ratio; ORR, overall response rate; Ox, oxaliplatin; Pac, paclitaxel; PAN, panitumumab; PBO, placebo; PD-L1, programmed death-ligand 1; PFS, progression-free survival; QW, once weekly; Q3W, once every 3 weeks; RAM, ramucirumab; SIM, simvastatin; SoC, standard of care; Tras, trastuzumab.

neither improved clinical outcomes when combined with chemotherapy.

RAINFALL assessed the impact of adding ramucirumab to chemotherapy (cisplatin plus capecitabine or 5-FU) in patients with HER2-negative tumors. Investigator-assessed PFS was significantly longer for ramucirumab plus chemotherapy versus placebo plus chemotherapy; however, the benefit was not confirmed by an independent, central review, and there was no difference in OS between groups [40]. In the AVAGAST study, the addition of bevacizumab to chemotherapy did not improve OS [25].

The remaining 1L targeted therapy studies included in this review reported either no significant differences in PFS or OS or worsened clinical efficacy in the investigational versus comparator arm [18]. Despite several attempts, targeted therapies in 1L have not yielded significant benefits except for patients with HER2+ tumors.

Efficacy and Safety of 2L Interventions

Of the included studies, singlets and doublets with or without a targeted agent were the most commonly assessed interventions. Fifteen of the 34 included RCTs reported statistically significant findings for OS, PFS, TTF, ORR, and/or disease control rate (DCR) [26,41–50].

Chemotherapeutic Agents

Consistent with prior reviews [8,9], single-agent chemotherapy prolonged OS when compared with BSC or active symptom control measures in the post-1L setting [47,49]. RCTs that compared monotherapies included the JCOG0407 trial, where paclitaxel improved mPFS by 1.3 months compared with 5-FU [50]. This PFS benefit appeared to outweigh the toxicity profile. The DREAM study assessed the efficacy of DHP107, an oral paclitaxel, in patients with advanced gastric cancer after failure of first-line therapy [51]. DREAM demonstrated PFS noninferiority and a similar safety profile for DHP107. The ABSOLUTE study showed noninferior OS with weekly nab-paclitaxel compared with standard paclitaxel [52].

WJOG 4007 evaluated paclitaxel versus irinotecan and found similar OS and manageable toxicities for both [53]. Roy et al. showed the ORR of irinotecan was lower than that of either docetaxel or PEP02, a liposomal irinotecan (6.8% vs. 15.9% vs. 13.6%, respectively), although mPFS was similar [54].

Additional RCTs suggested that irinotecan combination regimens (e.g., FOLFIRI or irinotecan plus cisplatin) may be suitable post-1L chemotherapy. Sym et al. indicated the addition of 5-FU/leucovorin is as effective and tolerable as irinotecan monotherapy [55]. Thuss-Patience et al. found that OS (4.0 vs. 2.4 months, respectively) was longer when irinotecan was added to BSC [47]. In the TCOG GI-0801 study, irinotecan plus cisplatin improved PFS and DCR, but not OS or ORR, when compared with cisplatin alone [44]. JACCRO GC-05 [56] and TRICS [57] concluded that the addition of a second cytotoxic agent did not improve irinotecan efficacy. Taken together, these studies suggest the benefit-to-risk ratio for paclitaxel and irinotecan monotherapies in 2L is equivalent, whereas combination irinotecan-based chemotherapy, namely, modified FOLFIRI or irinotecan plus cisplatin, may be suitable although clinical benefit is debatable.

Taxane-containing doublets (docetaxel plus oxaliplatin) compared with taxane monotherapy (docetaxel) improved mPFS from 2 to 4.9 months in docetaxel alone, although OS and ORR were not different [45]. In contrast, the doublet of paclitaxel plus S-1 did not improve efficacy over paclitaxel alone [58]. Moreover, there were nearly twice as many discontinuations due to AEs in the combination, although grade 3/4 AE rates were similar between treatment arms. Lee et al. reported the addition of S-1, but not cisplatin, to docetaxel resulted in better PFS compared with docetaxel alone. These data indicate that careful consideration of efficacy and toxicities is necessary, especially of AEs observed in 1L, when planning taxane/platinum-based doublet therapies in 2L.

Several studies included in the SLR combined 2L and 3L. Shitara et al. reported that dose-escalated paclitaxel resulted in longer PFS compared with standard-dose paclitaxel [59]. Frequency of all grades of neutropenia was significantly higher with dose-escalated paclitaxel; however, no significant difference was observed in the proportion of patients experiencing grade 3 or higher AEs. Fushida et al. reported that the addition of paclitaxel to valproic acid did not significantly improve OS or PFS [60]. Kang et al. observed longer OS (5.3 vs. 3.8 months) and similar tolerability when docetaxel or irinotecan were added to BSC [61].

Targeted and Immunotherapies

Targeted therapies, either alone or in combination, were investigated in 13 2L studies [41–43,46,48,62–64]. Two trials examined ramucirumab as monotherapy (vs. BSC in REGARD) or combined with paclitaxel (RAINBOW) [41,42]. OS and PFS were significantly improved in the ramucirumab-containing arms in both studies. In REGARD, OS was 5.2 versus 3.8 months and PFS was 2.1 versus 1.3 months, respectively. In RAINBOW, OS was 9.6 versus 7.4 months and PFS was 4.4 versus 2.9 months, respectively. Although not powered to show significance, post hoc analyses supported clinical benefits for ramucirumab plus paclitaxel efficacy in both East Asian and non–East Asian patients [63,64]. Unlike PFS, significant OS benefits were not noted in either of these two subgroup analyses in Asian populations, and the authors suggested that post-discontinuation therapy may play a role in the observed modest OS differences [63,64]. Recently, the phase III RAINBOW-Asia study demonstrated significant PFS benefit for ramucirumab combined with paclitaxel compared with paclitaxel alone; however, no OS benefits were observed [65]. Taken together, these studies indicate that in Asian populations the OS benefit from a ramucirumab plus paclitaxel regimen may be limited. The pan-tyrosine kinase inhibitor, sunitinib, combined with docetaxel was compared with docetaxel alone for the primary endpoint of TTP in a phase II trial. Although TTP was not statistically different, higher ORR was observed and safety was reduced in the doublet combination arm [43].

In TyTAN, addition of lapatinib to paclitaxel failed to demonstrate significant survival benefits (PFS, OS) versus paclitaxel alone in patients with HER2+ tumors [46]. Of note, when compared with similar subgroups of patients

treated with paclitaxel, patients treated with the doublet combination who had higher HER2 expression or who were mainland Chinese patients had improved OS (11.0 vs. 8.9) and PFS (5.5 vs. 4.4) [46]. Safety was not affected by the addition of lapatinib to paclitaxel. In the GATSBY study, trastuzumab emtansine was not superior to a taxane in improving OS in patients with HER2+ tumors [66]. The COG phase III study analyzed gefitinib (epidermal growth factor receptor [EGFR] inhibitor) versus placebo in esophageal cancer demonstrating no statistical OS or PFS benefit, although palliative benefits in subgroups were observed [67,68]. More recently, the JAPICTI RCT compared irinotecan alone with adding irinotecan to nimotuzumab, an anti-EGFR targeting antibody [62]. The primary endpoint, PFS, was similar between treatment arms, although patients with high EGFR levels by immunohistochemistry had improved OS, PFS, and ORR without adversely affecting safety [62]. Despite these results, the phase III study of nimotuzumab with irinotecan was terminated (NCT01813253).

Other studies of targeted 2L therapies included olaparib, ipilimumab, pembrolizumab, and trastuzumab emtansine. Bang et al. (Study 39, 2015) showed that the addition of PARP inhibitor olaparib to paclitaxel improved OS in patients with low ataxia telangiectasia mutated levels in the intent-to-treat population, although these results are discordant with the GOLD trial in which OS benefit was not observed [48,69]. Bang et al. (2017b) reported that ipilimumab monotherapy did not improve PFS or OS compared with BSC [70]. In KEYNOTE-061, pembrolizumab did not significantly improve OS compared with paclitaxel in patients with programmed death-ligand 1 (PD-L1) combined positive score (CPS) of 1 or higher [71]. In the study by Van Cutsem et al., AZD4547 (a selective fibroblast growth factor receptor [FGFR] 1–3 tyrosine kinase inhibitor) did not significantly improve PFS compared with paclitaxel in patients with FGFR2 polysomy or gene amplification [72]. These negative results indicate that further studies are necessary to support the possibility for improving outcomes in biomarker enriched subgroups.

The GRANITE study failed to show statistically significant benefit for OS (primary), unlike for PFS, comparing everolimus plus BSC with placebo plus BSC [73]. The phase II INTEGRATE study, evaluating both 2L and 3L therapy, found that addition of regorafenib to BSC significantly improved PFS; the phase III study is ongoing [74].

Overall, these studies indicate that, in a 2L setting, single-agent chemotherapy (or combination with targeted therapy) is more efficacious than BSC, highlighting the need for careful consideration of control arms in future study designs.

Efficacy and Safety of 3L+ Interventions

Eight articles were identified that assessed 3L+ treatments: six primary RCTs and two secondary reports. Four of the six RCTs reported significant findings for OS, PFS, DCR, and/or TTP [75–78]. One secondary study reported significant findings for ORR [79].

ATTRACTION-2 showed statistically significantly longer OS (5.3 vs. 4.1 months) and PFS (1.61 vs. 1.45 months) and higher DCR with nivolumab (anti–PD-1 monoclonal antibody) than placebo in Asian patients with disease progression after at least two prior chemotherapies [75]. The safety profile was manageable, and survival benefit with nivolumab was sustained beyond 1 year, independent of PD-L1 expression (although this was evaluated with tumor positivity score (TPS), not combined positivity score (CPS)). Subgroup analyses of Japanese patients and patients with prior trastuzumab use from the ATTRACTION-2 study also demonstrated similar clinical and safety results.

Similarly, the phase I/II CheckMate-032 study demonstrated that nivolumab as monotherapy and combined with ipilimumab (dual PD-1/cytotoxic T-lymphocyte–associated antigen 4 blockade) produced some durable responses, long-term OS, and a manageable safety profile in Western patients who experienced disease progression following at least one prior chemotherapy regimen [80]. Nivolumab was approved for 3L treatment of metastatic gastric cancer in Japan, Taiwan, and Korea, supported by results from the ATTRACTION-2 study [80,81].

The JAVELIN Gastric 300 study found that avelumab did not statistically significantly improve OS, PFS, or ORR compared with chemotherapy, with a trend to worse OS [82]. The studies conducted in China by Li et al. found that apatinib significantly improved OS (6.5 vs. 4.7 months) and PFS (2.6 vs. 1.8 months) compared with placebo with an acceptable safety profile [77,78]; however, the global phase III ANGEL study, which included patients from Europe and North America in addition to Asia, failed to show significant OS benefit in the overall population (3L+) [83].

The TAGS study reported statistically significantly longer OS (5.7 vs. 3.6 months), PFS (2.0 vs. 1.8 months), and DFS with trifluridine/tipiracil (TAS-102) compared with placebo [76].

Discussion

Unlike previous SLRs, this SLR aimed to inform optimal treatment sequencing in advanced metastatic G/GEA. This study parallels earlier work by Wagner et al. that identified study types, disease, treatment, and population [9]. All 1L RCTs in the current study had a fluoropyrimidine/platinum combination in at least one treatment arm, and 1L, 2L, and 3L+ treatments were considered separately to address the treatment sequencing question. In previous reports, HER2 status was not considered, and comparisons of singlet or doublet regimens versus supportive care, and doublets compared with monotherapy, were a primary focus [9]. Despite our focus on larger RCTs in this population with advanced G/GEA, descriptive cross-trial comparisons that cannot account for confounding variables between differing study populations are limitations of this assessment. Treatment decisions are heavily reliant on clinician discernment of available evidence, and this report attempts to highlight important differences in the studies included within.

Despite considerable improvements in therapeutic options, the treatment of advanced G/GEA remains heterogeneous [3].

For those likely to tolerate chemotherapy, doublet regimens (i.e., platinum/fluoropyrimidine) are preferable over triplet chemotherapy. Doublets often exhibited lower toxicity rates, which may outweigh any incremental clinical benefits seen with triplet therapy. For example, the toxicity observed with addition of a third chemotherapy (docetaxel or epirubicin) to a platinum/fluoropyrimidine appears to outweigh a survival benefit, as was observed in the V325 study [13]. However, an mDCF regimen shows promise of extending survival with acceptable toxicity in two trials [19,84]. Controversy remains with taxane triplets. The phase III JCOG1013 trial ($n = 741$) was recently published comparing cisplatin plus S-1 (CS) versus CS plus docetaxel (DCS) in an exclusively Japanese patient population [36]; no significant difference was seen in OS between CS and DCS (median 15.3 vs. 14.2 months). In line with other trials examining taxane triplets, higher grade 3/4 neutropenia was seen with DCS (58.5%) versus CS (32.1%). Another emerging regimen is FOLFIRINOX (irinotecan plus platinum plus fluoropyrimidine), while not a randomized study, demonstrated similar clinical outcomes to platinum/fluropyrimidine/taxane but with better tolerabilty due to non-overlapping toxicity [85]. For 1L treatment of HER2+ advanced G/GEA, trastuzumab should be added to platinum/fluoropyrimidine, although recently, oxaliplatin-based regimens (capecitabine plus oxaliplatin [XELOX] or FOLFOX) have also been widely adopted instead of cisplatin/fluoropyrimidine for HER2+ tumors [86,87].

For patients with advanced HER2-negative G/GEA and a good performance status but who are not amenable to surgical resection, 1L recommended treatment options include FOLFOX or a combination of capecitabine plus oxaliplatin. The 2L RAINBOW study did not enroll patients with a prior docetaxel containing triplet therapy, and an exploratory analysis indicated increased toxicities with prior triplet compared with doublet therapies [88]. Given the improvements in OS in patients with favorable performance status using various 2L regimens, sequentially navigating patients to active 2L therapy as opposed to upfront triplets containing taxanes may provide survival benefits with less toxicity. Triplet 1L chemotherapy, however, may be a consideration for patients with heavy disease burden severe cancer-related symptoms at diagnosis but with minimal comorbidities.

With a greater emphasis of biologic, targeted agents in 1L trials, the lower toxicity of doublet versus triplet chemotherapy favors a backbone regimen such as FOLFOX. Indeed, the majority of recently published 1L clinical trial data with other targeted agents with or without a chemotherapy backbone has reported negative results. Theoretically, with taxane use increasing in 2L therapy, restricting taxanes in 1L could prevent drug resistance.

For G/GEA that progressed on a fluoropyrimidine/platinum 1L therapy (plus trastuzumab for HER2+ tumors), taxane-based therapy, or consideration of ramucirumab monotherapy if the patient is not a good candidate for cytotoxic chemotherapy, is indicated. Efficacy, safety, and treatment compliance are high-priority considerations when choosing a 2L therapy. Data also support use of irinotecan, either as monotherapy or in FOLFIRI. The addition of ramucirumab to an irinotecan backbone is a possibility, particularly in patients with neuropathy including oxaliplatin-induced neuropathy from 1L therapy. Evidence supports ramucirumab plus FOLFIRI or ramucirumab plus irinotecan as an alternative in 2L patients ineligible for ramucirumab/paclitaxel [89–91]. In a retrospective analysis by Klempner et al., patients receiving ramucirumab plus FOLFIRI (after 1L platinum plus fluoropyrimidine) had ORR of 23%, DCR of 79%, mPFS of 6.0, and median OS (mOS) of 13.4 months [89]. Lorenzen et al. reported that patients with prior taxane use receiving ramucirumab plus FOLFIRI had ORR of 24%, DCR of 67%, mPFS of 4.3, and mOS of 7.5 months [90], whereas Park et al. reported ORR of 25% for patients who advanced on 1L and were then treated with ramucirumab plus irinotecan [91]. The authors posit that a shorter time to initiation of 2L treatment following disease progression or development of unacceptable toxicity, but before patients experience performance status decline, is a key consideration. This in turn will benefit patients who are eligible to further receive 3L treatment options like TAS-102 that demonstrated statistically significant survival benefits (OS, PFS, DCR) in the TAGS study [76].

The Argument for Limiting Time on 1L/Maintenance 1L Therapy in Advanced G/GEA

Based on the success of maintenance therapy in colorectal cancer (OPTIMOX1 [92] and CAIRO3 [93]), many oncologists have adapted this approach to advanced G/GEA. Following a predetermined length of 1L therapy (typically 4–6 months), maintenance therapy may provide similar (or better) efficacy with less toxicity (particularly cumulative oxaliplatin-related neuropathy) compared with continuing 1L therapy until disease progression. Maintenance options include switch therapy or low-dose continuation of a 1L agent (i.e., 5-FU or capecitabine). In support of maintenance therapy, the 1L trial, ToGA, stopped chemotherapy after six cycles but continued trastuzumab [17]; AVAGAST and RAINFALL stopped cisplatin after six cycles but continued bevacizumab/placebo or ramucirumab/placebo with fluoropyrimidine, respectively [25,40]. OS rates were similar to other phase III studies without a maintenance approach, indicating that not all agents in 1L need to be continued indefinitely. The mPFS across major 1L trials ranged from 4.4 to 8.5 months. Park et al. compared continuous versus stop-and-go chemotherapy after disease stabilization with 1L induction chemotherapy [94]. After receiving six cycles of S-1 plus oxaliplatin (SOX), patients were randomized to receive continuous SOX until progression (continuous arm) or to have a chemotherapy-free interval followed by SOX reintroduction at progression (stop-and-go arm). Continued chemotherapy improved PFS but not duration of disease control or OS, had a negative impact on quality of life, and increased frequencies of adverse events, suggesting that the stop-and-go strategy may be an appropriate option compared with continuous 1L therapy. Indeed, for the use of oxaliplatin in 1L treatment regimens, the International Duration Evaluation of Adjuvant Therapy in therapy for colorectal cancer demonstrated more than doubling of grade 2 or higher neurotoxicity rates, 16.6% versus 47.7%, with 3 versus 6 months of FOLFOX exposure, respectively [95].

Potential for Integrating Immunotherapeutics

Beyond this review, we include a discussion of immunotherapeutics in the context of treatment sequencing in metastatic G/GEA. Immunotherapy has received significant attention in recent years, advancing therapy options in many tumor types. Recent large, phase III, randomized studies in the 2L and 3L settings of G/GEA compared monotherapy immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 signaling axis with standard monotherapy cytotoxic therapy (paclitaxel or irinotecan); however, reported results failed to meet primary endpoints for KEYNOTE-061 and JAVELIN Gastric 300, even for PD-L1–positive patients [71,82]. Pembrolizumab in the 3L setting was considered an option based on results from a single-arm phase II study (KEYNOTE-059) of PD-L1–positive patients, the incidence of which is ∼50%–60% of G/GEA when using a CPS cutoff of ≥1 (CPS of both PD-L1–expressing tumor and immune cells) [96], however the conditional approval has since been withdrawn. Nivolumab is also a 3L+ option in Asian patients based on improved OS versus placebo in the phase III ATTRACTION-2 study [75]. In the 2L setting or later, pembrolizumab was shown to be efficacious in tumors with high microsatellite instability (MSI) or mismatch repair deficiency, the incidence of which is ∼3% in metastatic G/GEA [97], as did a combined analysis of KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 [105]. Recently, pembrolizumab received tumor-agnostic U.S. Food and Drug Administration (FDA) approval for high tumor mutational burden (TMB) (≥10 mutations per megabase) based on the KEYNOTE-158 study [98]. It is important to note that KEYNOTE-158 did not include patients with G/GEA, although an exploratory analysis from the 2L KEYNOTE-061 study reported positive association with clinical outcomes in patients with TMB-high gastric cancer treated with pembrolizumab [99].

A Korean phase II trial of pembrolizumab also identified Epstein-Barr virus–positive tumors as a small molecular subset exhibiting a high proportion of durable responses [100]. Key 1L studies with ICIs have also been reported [101–104]. JAVELIN Gastric 100 failed to demonstrate avelumab switch maintenance therapy as superior to continuation of 1L FOLFOX/CAPOX (capecitabine plus oxaliplatin) chemotherapy [101]. A post hoc analysis using the CPS assay, as opposed to the trial's predefined analysis of tumor cell enumeration only (TPS), to determine PD-L1 expression demonstrated OS benefit of avelumab therapy, highlighting challenges to assay heterogeneity. KEYNOTE-062 failed to demonstrate significant benefit of 1L pembrolizumab monotherapy to chemotherapy, in patients preselected for PD-L1 CPS ≥1 [102]. ATTRACTION-4 analyzed the benefit of 1L nivolumab plus chemotherapy versus chemotherapy (SOX/CAPOX) in a non–PD-L1 selected Asian population; statistical PFS benefit was observed for ICI plus chemotherapy, whereas OS failed to demonstrate such benefits [103]; PD-L1 data were not reported to date to determine differential benefit in outcome as would be expected based on all studies to date. Meanwhile CheckMate-649, investigating 1L nivolumab plus FOLFOX/XELOX against FOLFOX/XELOX, demonstrated significant benefits for all endpoints of ICI plus chemotherapy in a global population with the analysis restricted to patients with PD-L1 CPS ≥5 [104] and recently received FDA approval in all comers as a 1L regimen while NCCN guidelines have provided a tiered recommendation based on PD-L1 score with category 1 for CPS ≥5, category 2B for CPS 1-4, and no recommendation for CPS 0. Overall, these recent studies demonstrate a combination regimen (ICI plus chemotherapy) to be efficacious compared with ICI monotherapy in 1L, particularly at higher PD-L1 cutoffs. Irrespective, the ICI plus chemotherapy regimen from Check Mate-649 is expected to become 1L therapy of choice for PD-L1 CPS ≥5, whereas 2L options are expected to remain unchanged. It is also important to highlight the role of significant benefits seen in patients with MSI-high tumors treated with ICIs, including within CheckMate-649 where overall survival was most pronounced in this group, with the median overall survival of 8.8 months versus not reached in the 1L chemotherapy versus 1L chemotherapy plus nivolumab arms, respectively (HR 0.33, 95% C.I. 0.12-0.87). Pembrolizumab is FDA approved for patients with MSI-high or mismatch repair–deficient tumors in 2L and beyond, and data from recent trials continue to demonstrate benefit in this patient subgroup [105]. Although outside the parameters of this review, it is important to note additional recent FDA approvals. KEYNOTE-590 analyzed pembrolizumab in combination with cisplatinum and fluoropyrimidine-based chemotherapy in 1L and demonstrated a statistically significant improvement in OS and PFS for patients receiving ICI plus chemotherapy irrespective of PD-L1 status, but again with improvements notably in tumors with PD-L1 CPS ≥10. This FDA approval provides another ICI regimen for patients with esophageal and gastroesophageal junction Siewert type I carcinoma, and similar to the tiered recommendation of the NCCN guidlines for nivolumab, a tiered recommendation for pembrolizumab includes category 1 for CPS ≥10, category 2B for CPS 1-9, and no recommendation for CPS 0. More recently, based on the KEYNOTE-811 study, the FDA granted accelerated approval for 1L pembrolizumab plus trastuzumab in combination with fluoropyrimidine- and platinum-containing chemotherapy for patients with locally advanced unresectable/metastatic HER2+ gastric or gastroesophageal adenocarcinoma based on interim analysis response rates. Coming shortly after the CheckMate-649 and KEYNOTE-590 approvals, the KEYNOTE-811 approval expands the frontline ICI availability to HER2+ patients, and the outcomes of the phase 3 study are awaited, as are the assessments to determine whether or not their is differential benefit by PD-L1 status in HER2+ tumors as their has repeatedly been shown in HER2- patients.

Overview of Studies Published After the Review Inclusion Period and Trials in Progress

Several large RCTs were either presented in abstract form or published in peer-reviewed journals after this literature search was performed or did not meet the inclusion criteria. Some are currently considered by oncologists when selecting regimens. For example, in the U.S., there is notable off-label use of trastuzumab continuation into 2L, despite the phase II randomized T-ACT trial (WJOG7112G) demonstrating that trastuzumab continued, with or without paclitaxel, does not provide additional benefit for patients

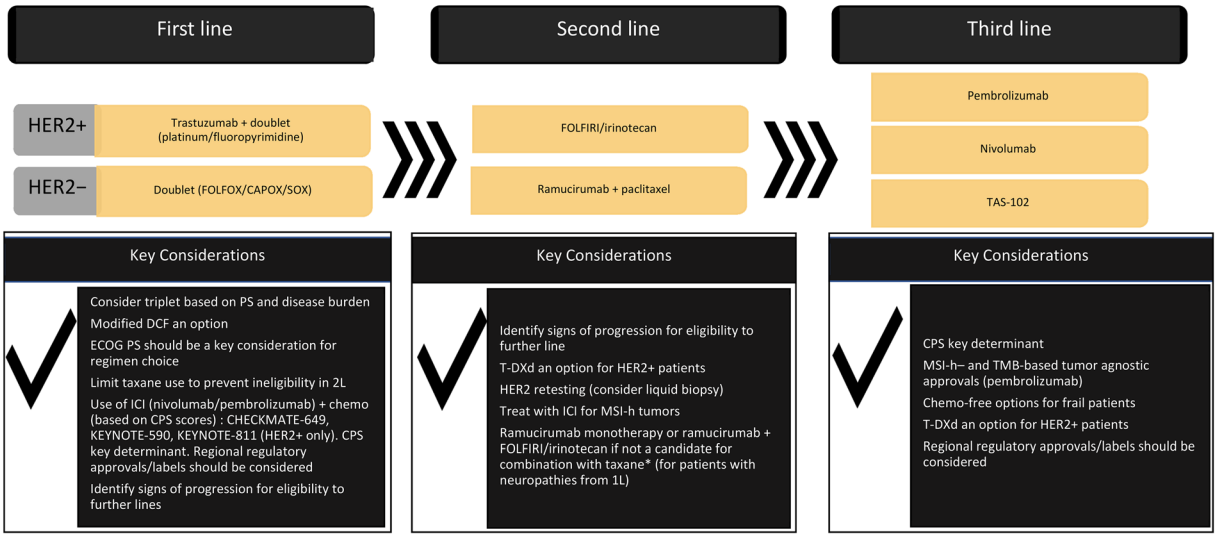

Figure 4. Potential treatment sequencing algorithm. The proposed sequential algorithm is based on the current analysis of randomized controlled trials as described in this systematic literature review. Recent approvals and key trial readouts are highlighted under "Key Considerations" and discussed in this article (see Discussion section). Checkmate-649, KEYNOTE-590, and KEYNOTE-811 are noted under 1L options that should be considered in treatment planning; HER2- tumors will be assessed and dichotimzed into PD-L1 CPS ≥5 or ≥10 and eligible for anti-PD1 therapy, or HER2-/PD-L1- and receive chemotherapy alone. These sequences were not tested in a clinical trial setting. 3L options also include irinotecan or taxane, whichever not yet used previously. Pembrolizumab in 3L had its approval recently voluntarily withdrawn; nivolumab approved for 3L only in Asia.
Abbreviations: 1L, first line; 2L, second line; CAPOX, capecitabine plus oxaliplatin; CPS, combined positive score; DCF, docetaxel plus cisplatin/5-fluorouracil; FOLFOX, folinic acid plus 5-FU plus oxaliplatin; FOLFIRI, folinic acid plus 5-fluorouracil plus irinotecan; HER2+, HER2 overexpressing; HER2−, HER2 negative; ICI, immune checkpoint inhibitor; MSI-h, high microsatellite instability; SOX, S-1 plus oxaliplatin; TAS-102, trifluridine/tipiracil; T-DXd, trastuzumab deruxtecan; TMB, tumor mutational burden.

with HER2+ advanced G/GEA refractory to 1L trastuzumab plus platinum/fluoropyrimidine [106]. However, the notion of loss of HER2 amplification in resistant disease in a large proportion of patients in that and other studies leads to the possibility of continued anti-HER2 therapy in those patients not having this conversion take place [108]. Recently, the DESTINY-Gastric01 study reported significant benefit of trastuzumab deruxtecan (T-DXd) versus paclitaxel or irinotecan in 3L and was approved in Japan and by the FDA. Importantly, patients had received a 1L trastuzumab-containing regimen, thereby making T-DXd a novel option for HER2+, trastuzumab-resistant, G/GEA tumors. Significant benefits favoring T-DXd were observed (mOS, 12.5 vs. 8.4 months; HR, 0.59; $p = .01$; ORR, 51.3% vs. 14.3%; $p < .0001$) with interstitial lung disease being a notable AE from T-DXd. [107]. Additional studies with T-DXd in 2L (NCT04014075, NCT04704934) and 1L (NCT03329690) are ongoing.

With similar conclusions to those of this report, the PANGEA phase 2 study highlights the importance of optimally sequenced therapies and endorses a combined personalized treatment strategy, starting from diagnosis and across all treatment lines, to enhance benefits compared with standard treatment approaches [108].

Considering all the evidence discussed in this SLR, we propose a treatment sequencing algorithm (Fig. 4). The regimen chosen at each line of therapy should balance the patient's performance status and comorbidities with the potential for serious AEs. It is important to consider that the proposed sequence or algorithm was not tested in clinical trial settings but was based on discussions of trial evidence in this review. In 1L, considering a doublet is recommended based on manageable toxicities compared with triplets; in addition, the recent approvals of CheckMate-649, KEYNOTE-590, and KEYNOTE-811 should be considered as 1L ICI plus chemotherapy options. In 2L (and 3L), T-DXd should be considered for HER2+ patients, although challenges to rebiopsy exist, and hence liquid biopsy to determine HER2 status should be considered where feasible. Beside a FOLFIRI/irinotecan-based regimen, combinations with biologics like ramucirumab plus taxane/irinotecan options should be considered for eligible patients, especially in patients who are ineligible to receive a taxane due to neuropathies in 1L. Furthermore, patients with MSI-high and TMB-high status should be considered for ICI-based treatment (pembrolizumab). In 3L, TAS-102 is a chemotherapy option along with chemotherapy-free options with the ICIs pembrolizumab (CPS >1) and nivolumab, which should be considered. Overall, screening patients for signs of progression across all lines of therapy is recommended so that eligible patients can be administered subsequent treatment options in a timely manner.

Conclusion

To our knowledge, this is the first systematic review that begins to address treatment sequencing in unresectable, advanced G/GEA, including recent evidence from larger RCTs. It builds upon currently available guidelines and provides a framework for planning effective disease

management, with the potential for further improvement in outcomes for patients and select patient subgroups.

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