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REVIEW

Real-World Effectiveness and Safety of Ramucirumab as a Second-Line Treatment for Patients with Unresectable Advanced or Metastatic Gastric/Gastroesophageal Junction Adenocarcinoma in Japan and South Korea: A Systematic Literature Review

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ABSTRACT

Introduction: Gastric cancer has the highest incidence and mortality in Eastern Asia. The efficacy and safety of ramucirumab (RAM) monotherapy or in combination with paclitaxel (PTX) for patients with unresectable advanced or metastatic gastric/gastroesophageal junction adenocarcinoma (G/GEA) have been established in clinical trials. To assess the effectiveness and safety of RAM or RAM-based therapy as a second-line treatment in real-world clinical practice in Eastern Asia and to pave the way for future research, a systematic literature review (SLR) was conducted.

Methods: Studies published between January 2014 and December 2021 were identified in PubMed, Embase, Cochrane Library, CNKI, Wanfang, and CBM databases.

Results: This SLR included 23 studies from Japan and South Korea, of which 22 were retrospective and 11 were full-text articles. Most studies investigated RAM + PTX (range of median overall survival [mOS] 7.4–12.2 months; median progression-free survival [mPFS] 3.35–7.0 months). Data were limited for RAM, RAM + albumin-bound paclitaxel, and RAM + taxane. RAM + PTX was associated with longer survival (mOS 9.3–12.2 months vs. 5.2–9.7 months; mPFS 4.1–5.1 months vs. 3.0–4.1 months) than PTX. Patients with prior anti-programmed cell death 1 (anti-PD-1) exposure experienced longer mPFS (4.8 vs. 3.4 months) from RAM + taxane than those without prior anti-PD-1 exposure. Few patients (3.3–6.3%) discontinued RAM or RAM-based therapy because of adverse events (AEs). Hematological toxicities were most frequently occurring AEs and no new safety signals were identified compared to clinical trials.

Conclusion: RAM + PTX as a second-line treatment is effective and associated with an acceptable toxicity profile in patients with advanced or metastatic G/GEA in real-world settings of Japan and South Korea. More studies are recommended to further evaluate

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effectiveness and safety of RAM or RAM-based therapy, especially after anti-PD-1 therapy, in a wider Eastern Asian population.
Trial Registration: INPLASY registration number INPLASY2022120023.

Keywords: Ramucirumab; Advanced or metastatic gastric cancer; Second-line treatment; Systematic review; Real-world study

Key Summary Points

The efficacy and safety of ramucirumab (RAM) monotherapy or in combination with paclitaxel (PTX) have been established in the phase 3 clinical trials while the effectiveness and safety in real-world settings remain uncertain.

Therefore, a systematic literature review (SLR) of real-world studies (RWSs) is necessary, particularly in Eastern Asia where gastric cancer poses a significant burden.

Effectiveness and safety results of RAM monotherapy and RAM + PTX in RWSs were generally consistent with those reported in the phase 3 clinical trials.

With the increasing use of immunotherapy plus chemotherapy as a standard of care in first-line settings for patients with advanced or metastatic gastric cancer, more extensive research is needed to confirm whether prior anti-programmed cell death 1 (anti-PD-1) exposure would enhance the effectiveness of RAM-based therapy.

More RWSs are recommended in future, especially studies from China, which has a large population of patients with gastric cancer.

INTRODUCTION

Gastric cancer is the fifth most common malignancy and the fourth leading cause of cancer death worldwide, with 1.09 million new cases and 0.77 million deaths in 2020 [1]. There is a heavy burden of gastric cancer in Eastern Asia, which has the highest number of new cases (0.66 million, 60.6% of the total) and deaths (0.44 million, 57.1%) [1].

Platinum-based or fluoropyrimidine-based chemotherapies are globally accepted first-line treatments for patients with gastric cancer [2–6]. For patients with human epidermal growth factor receptor 2 (HER2)-positive gastric cancer, trastuzumab combined with a chemotherapeutic agent is recommended [2–6]. The recent introduction of immune checkpoint inhibitors (ICIs), such as nivolumab [7], in combination with chemotherapy has led to improved patient survival and expanded the options available of first-line treatment panels.

When patients progress while receiving first-line therapies, chemotherapeutic agents, including docetaxel (DTX), paclitaxel (PTX), albumin-bound paclitaxel (nab-PTX), irinotecan (IRI), and fluoropyrimidine, are commonly used as second-line treatments [8]. However, the median survival of patients receiving these chemotherapeutic agents is typically less than 6 months [9–11]. Ramucirumab (RAM, brand name Cyramza) is a humanized monoclonal antibody that specifically targets the extracellular domain of the vascular endothelial growth factor (VEGF) receptor 2 [12]. On the basis of the results of three phase 3 trials, REGARD [12], RAINBOW [13], and RAINBOW-Asia [14], RAM has been approved worldwide, as monotherapy or in combination with PTX, for use as a second-line treatment for advanced gastric/gastroesophageal junction adenocarcinoma (G/GEA). RAM and RAM + PTX therapies are preferred or recommended as grade I level in guidance and have been widely used in clinical practice [2–6].

Real-world studies (RWSs) have become an essential complement to randomized controlled trials (RCTs) for informing healthcare decision-making. Though the efficacy and safety of RAM

[12] and RAM + PTX [13] have been established in phase 3 trials, the effectiveness and safety in real-world settings remain uncertain as clinical practice involves a diverse patient population. Therefore, a systematic literature review (SLR) of RWSs is necessary, particularly in Eastern Asia where gastric cancer poses a significant burden. This SLR aims to summarize the effectiveness and safety of RAM or RAM-based therapy in real-world settings in Eastern Asia in an effort to help guide future research endeavors.

METHODS

This SLR followed the guidelines of the preferred reporting items for systematic review and meta-analyses (PRISMA) [15], and the PRISMA checklist was used for verification (Supplementary Material Appendix 1 and 2). The SLR was registered in the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) (ID INPLASY2022120023, available from https://inplasy.com/inplasy-2022-12-0023/). This review is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Eligibility Criteria

We only included RWSs that contained cohort studies, post-marketing surveillance/safety studies (PMSS), pragmatic clinical trials, and case series. Patients with unresectable advanced or metastatic G/GEA receiving RAM or RAM-based therapy as a second-line treatment in Eastern Asia were included. The selection criterium for second-line treatment was that at least 80% of patients received RAM or RAM-based therapy as a second-line treatment. In this study, Eastern Asia comprised Japan, Korea, and China, which includes Mainland China, Hong Kong, Taiwan, and Macau. RCTs, controlled clinical trials, and pre–post trials were not included. Studies that did not report outcomes of interest or those that were not in English or Chinese were also excluded.

Outcomes

The primary outcome of interest was effectiveness of treatment, including overall survival (OS) and progression-free survival (PFS). The secondary outcomes were drug utilization, objective response rate (ORR), disease control rate (DCR), and adverse events (AEs). Drug utilization included relative dose intensity (RDI), treatment discontinuation (TD), duration of treatment (DoT), and post-discontinuation treatment (PDT). AEs referred to the incidence rate of any grade AEs and grade $\geq$ 3 AEs.

Search Strategy

Studies published between January 2014 and December 2021 were identified through computer-based searches in PubMed, Embase, and Cochrane Library without limitations on language. The following keywords were used in combination: ("stomach cancer" OR "gastric cancer" OR "gastroesophageal junction cancer" OR "gastroesophageal junction adenocarcinoma") AND ("advanced" OR "metastatic" OR "unresectable") AND ("ramucirumab" OR "Cyramza" OR "LY3009806") AND ("Japan" OR "Korea" OR "China"). Complete search strategies are presented in Supplementary Material Appendix 3. We also searched the following three Chinese databases: CNKI, Wanfang, and CBM using the same search strategy as the one used in English databases except the keywords were translated into Chinese. Complete search strategies are presented in Supplementary Material Appendix 4 and 5.

Study Screening

Two reviewers screened studies on the basis of the titles and abstracts. All potentially relevant citations were requested and inspected in detail using the full-text version, where available. Disagreements were resolved by discussion with assistance from a third team member, if necessary. A PRISMA flow diagram was constructed to show the full-study selection process.

Data Extraction

All data were extracted by two independent reviewers using a pre-defined data extraction form that included study characteristics (i.e., country, study design, and sample size), participant characteristics (i.e., age, gender, and location of metastasis), interventions, and outcomes. Discrepancies were resolved by consensus or by involving a third team member. Multiple reports of the same study were collated and judged on the basis of the population and intervention. We always chose the most recently published study with more participants or more comprehensive outcomes.

Assessment of Bias

Two reviewers independently assessed the risk of bias in the included studies. Disagreements were resolved by discussion with assistance from a third team member, if necessary. We used the Newcastle–Ottawa Scale (NOS) for controlled studies in which there was more than one treatment group [16]. For non-controlled studies in which all patients received the same treatment, we used the "quality assessment tool for before–after (pre–post) studies with no control group" outlined by National Institutes of Health (NIH) to assess risk of bias [17].

Data Summary

The characteristics of the included studies and patients along with data on the effectiveness and safety outcomes were summarized and presented using tables and figures. Proportions were used to report dichotomous outcomes data, while time-to-event outcomes data were reported as the median and 95% confidence interval [CI] or hazard ratio [HR]. The range of median RDI, proportion of TD, proportion of PDT, median DoT, median OS, median PFS, ORR, and DCR were summarized by treatment in all included studies. The comparative effectiveness (OS, PFS, ORR, DCR) of different treatments or subgroup of patients were subsequently described in comparative studies. The range of the overall incidence of AEs (any grade, grade $\geq$ 3), top five most frequently occurring AEs (any grade, grade $\geq$ 3), and AEs of special interest (grade $\geq$ 3) were summarized by treatment in all included studies. The comparative safety of different treatments or subgroup of patients were subsequently described in comparative studies. In this review, no distinctions were made between the terminology used to describe AEs and treatment-related adverse events (TRAEs) used in the original studies.

RESULTS

Study Selection

In the database search, a total of 852 records were obtained. After removal of 302 duplicates, 550 studies were screened on the basis of their titles and abstracts. Out of these, 477 studies were excluded because of ineligible patients, treatments, and study designs. The remaining 73 studies underwent full-text examination. In cases where full-text format was not available, abstracts were further assessed for eligibility. Among these assessments, 49 studies were excluded. Ultimately, a total of 23 studies published in English were deemed eligible and included in the analysis (Fig. 1) [18–41].

Study and Patient Characteristics

The 23 included studies published between 2016 and 2021, 4 (17.4%) from South Korea [20, 25, 34, 41] and 19 (82.6%) from Japan [18, 19, 21–24, 26–33, 35–40]. Of the 23 studies, 8 (34.8%) were controlled studies [21, 23, 24, 26, 30–32, 34, 38], and 15 (65.2%) were non-controlled studies. With one prospective study [25], all studies (95.7%) were retrospective. Additionally, 6 studies (26.1%) were conducted in multiple centers [18, 20, 21, 30, 32, 34], 12 (52.2%) were conducted in a single center [19, 22–24, 26–29, 31, 33, 35–37], and the location of the remaining 5 (21.7%) was unknown [25, 38–41]. Of these included studies, 11 (47.8%) were available in full text

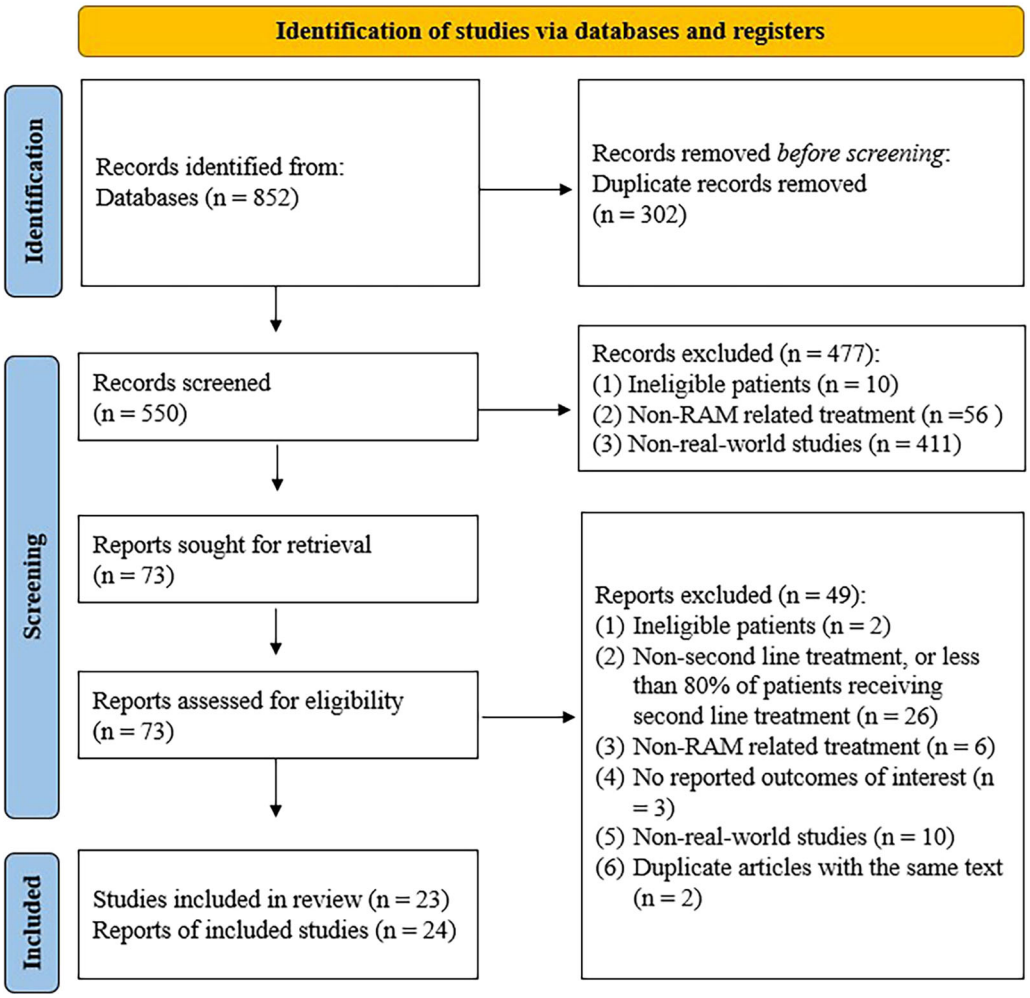

Fig. 1 PRISMA flowchart. *PRISMA* preferred reporting items for systematic review and meta-analyses, *RAM* ramucirumab

[18–27, 34, 35], and the other 12 (52.2%) were presented as conference abstracts (Table 1).

The sample size of included studies ranged from 8 to 3650, with 43.5% of studies having more than 100 patients [18, 20–26, 30, 32, 34]. The median age ranged from 57 to 75 years [19–21, 24–27, 30, 31, 34, 35], and male individuals accounted for more than half of the patients [18–21, 24–27, 30, 34, 35]. Eight (34.8%) studies reported the location of tumor metastases, including peritoneum, liver, lung, lymph nodes, bone, and others [18, 20–24, 26, 35, 40]. First-line treatments were described in 16 (69.6%) studies [18–24, 26, 27, 30–32, 34, 37–40], 14 of which were platinum and/or fluoropyrimidine-containing chemotherapy [18–21, 23, 24, 26, 27, 30–32, 37–40]. In this SLR, the RAM-containing treatments included RAM monotherapy (hereinafter referred to as RAM) and several combination therapies: RAM + PTX, RAM + nab-PTX, and RAM + taxane (PTX or nab-PTX). RAM + PTX accounted for the majority (18, 78.3%) of included studies. Effectiveness outcomes were reported in 20 (87.0%) studies, safety outcomes in 15 (65.2%), and data on drug utilization were available in only 5 (21.7%) studies (Table 1, Fig. 2).

Risk of Bias in Included Studies

The NOS and NIH quality assessment tool were used in eight and 15 studies, respectively.

Table 1 Characteristics of included studies

Study ID	Country	Study design	Center Multi/ single	Sample size	Age Median (range)	Gender Male *n* (%)	Interventions	Outcomes		Full text/ abstract[d]
								Effectiveness	Safety	
Controlled study										
Arai 2021 [21]	Japan	Retrospective observational study-cohort	Multi	108 RAM + PTX: 21 Taxane: 87	63 (25–83)	62 (57.4)	RAM + PTX; taxane	–	AEs	Full text
Ishikawa 2020 [26]	Japan	Retrospective observational study-cohort	Single	128 RAM + PTX: 93 RAM + nab-PTX: 35	RAM + PTX: 67.2 (30–84) RAM + nab-PTX: 66.6 (34–79)	89 (70)	RAM + nab-PTX; RAM + PTX	ORR, OS, PFS (RECIST 1.1)	AEs (CTCAE 4.0)	Full text
Okunaka 2020a [24]/ Okunaka 2020b [23][a]	Japan	Retrospective observational study-cohort	Single	251 RAM + nab-PTX: 113 RAM + PTX: 138	nab-PTX + RAM: 67 (25–84) PTX + RAM: 69 (40–85)	166 (66.1)	RAM + nab-PTX; RAM + PTX	ORR, DCR, OS, PFS (RECIST 1.1)	TRAEs (CTCAE 4.0)	Full text
Imazeki 2019 [30]	Japan	Retrospective observational study-cohort	Multi	154 PTX + RAM: 91 PTX: 63	PTX + RAM: 64 PTX: 64	110 (71.4)	RAM + PTX; PTX	ORR, DCR, OS, PFS	AEs	Abstract
Jung 2018 [34]	Korea	Retrospective observational study-cohort	Multi	265 RAM: 37 RAM + PTX: 228	RAM + PTX: 57 (23–81) RAM: 62 (35–80)	178 (67.2)	RAM + PTX; RAM	ORR, DCR, OS, PFS (RECIST 1.1)	TRAEs (CTCAE 4.0)	Full text

Table 1 continued

Study ID	Country	Study design	Center Multi/ single	Sample size	Age Median (range)	Gender Male *n* (%)	Interventions	Outcomes		Full text/ abstract[d]
								Effectiveness	Safety	
Masuishi 2018 [32]	Japan	Retrospective observational study-cohort	Multi	305 RAM + PTX: 127 PTX: 178	–	–	RAM + PTX; PTX	OS, PFS	AEs	Abstract
Shoji 2018 [31]	Japan	Retrospective observational study-cohort	Single	85 RAM + PTX: 28 PTX: 29 IRI: 28	75 (71–85)	–	RAM + PTX; PTX; IRI	ORR, OS, PFS	–	Abstract
Kusumoto 2017 [38]	Japan	Retrospective observational study-cohort	NR	RAM + PTX: 18 PTX: NR	–	–	RAM + PTX; PTX	ORR, DCR, OS, PFS	AEs	Abstract
Non-controlled study										
Sakai 2017 [36][b]	Japan	Retrospective observational study-cohort	Single	RAM + PTX: 20 RAM: 2	–	–	RAM + PTX; RAM	PFS	–	Abstract
Han 2021 [20]	Korea	Retrospective observational study-cohort	Multi	1063	60 (1–88)	724 (68.1)	RAM + PTX	ORR, DCR, OS, PFS (RECIST 1.1)	TRAEs (CTCAE 5.0)	Full text
Hashida 2021 [19]	Japan	Retrospective observational study-cohort	Single	43	70 (36–90)	28 (65.1)	RAM + nab-PTX	ORR, DCR, OS, PFS (RECIST 1.1)	AEs (CTCAE 4.0)	Full text
Komatsu 2021 [18]	Japan	Retrospective observational study-cohort	Multi	3650	–	2677 (73.3)	RAM + taxane (PTX or nab-PTX)	–	–	Full text

Table 1 continued

Study ID	Country	Study design	Center Multi/ single	Sample size	Age Median (range)	Gender Male *n* (%)	Interventions	Outcomes		Full text/ abstract[d]
								Effectiveness	Safety	
Kim 2020 [25]	Korea	Prospective observational study-cohort	NR	116	58 (47–63)	71 (61.2)	RAM + PTX	ORR, DCR, OS, PFS (RECIST 1.1)	–	Full text
Sasaki 2020 [22]	Japan	Retrospective observational study-cohort	Single	149	–	106 (71.1)	RAM + taxane (PTX or nab-PTX)	ORR, DCR, PFS (RECIST 1.1)	TRAEs (CTCAE 5.0)	Full text
Kashiwada 2019a [29]	Japan	Retrospective observational study-cohort	Single	41	–	–	RAM + PTX	OS, PFS	–	Abstract
Kashiwada 2019b [28]	Japan	Retrospective observational study-cohort	Single	14	–	–	RAM + nab-PTX	ORR, DCR, PFS	TRAEs	Abstract
Natsume 2019 [27]	Japan	Retrospective observational study-cohort	Single	26	67 (40–81)	8 (30.8)	RAM or RAM + PTX	ORR, OS, PFS (Subgroup-PlGF-low, PlGF-high)[c] (RECIST 1.1)	–	Full text
Fukuda 2018 [35]	Japan	Retrospective observational study-cohort	Single	89	67 (35–83)	47 (52.8)	RAM + PTX	ORR, DCR, OS, PFS (RECIST 1.1)	TRAEs (CTCAE 4.0)	Full text
Kusumoto 2018 [33]	Japan	Retrospective observational study-cohort	Single	25	–	–	RAM + PTX	ORR, DCR, OS, PFS	AEs	Abstract
Matsumoto 2017 [37]	Japan	Retrospective observational study-cohort	Single	37	–	–	RAM + PTX	ORR, OS, PFS	AEs	Abstract
Lim 2016 [41]	Korea	Retrospective observational study-cohort	NR	70	–	–	RAM + PTX	ORR, DCR, PFS	–	Abstract

Table 1 continued

Study ID	Country	Study design	Center Multi/ single	Sample size	Age Median (range)	Gender Male *n* (%)	Interventions	Outcomes		Full text/ abstract[d]
								Effectiveness	Safety	
Shinohara 2016 [40]	Japan	Retrospective observational study-case series	NR	8	–	–	RAM + PTX	ORR	AEs (CTCAE 4.0)	Abstract
Tozawa 2016 [39]	Japan	Retrospective observational study-cohort	NR	20	–	–	RAM + PTX	PFS	–	Abstract

AEs adverse events, *CTCAE* Common Terminology Criteria for Adverse Events version, *DCR* disease control rate, *IRI* irinotecan, *nab-PTX* albumin-bound paclitaxel, *NR* not reported, *ORR* objective response rate, *OS* overall survival, *PFS* profession-free survival, *PTX* paclitaxel, *RAM* ramucirumab, *RECIST* response evaluation criteria in solid tumors, *TRAEs* treatment-related adverse events

[a]Okunaka 2020a (full text) and Okunaka 2020b (conference abstract) were multiple reports of the same study, and only the outcome data from Okunaka 2020a were included in the data analysis

[b]Although patients in Sakai 2017 received RAM or RAM + PTX, no result was reported in the original study about patients receiving RAM, so in this SLR, we deemed it non-controlled study

[c]Data from Natsume 2019 were not included in the analysis because although patients were treated with RAM or RAM + PTX, no separate results were reported by intervention

[d]All abstract studies were conference abstracts derived from the Japanese Society of Medical Oncology (JSMO) Annual Meeting, the European Society for Medical Oncology (ESMO) Congress, the ESMO World Congress on Gastrointestinal (GI) Cancer, the American Society of Clinical Oncology (ASCO) Annual Meeting, the ASCO Symposium on GI Cancer, and the Asia Pacific Digestive Week (APDW) Innovative Approaches to Gastroenterology

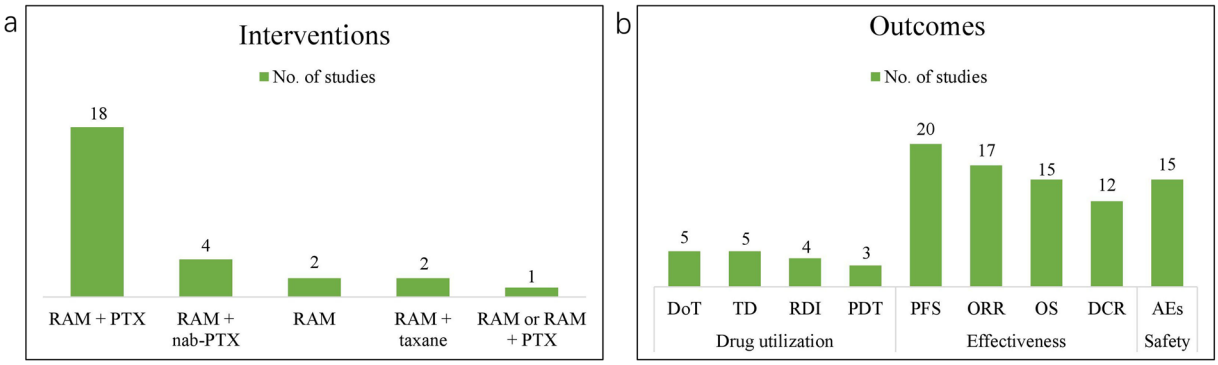

Fig. 2 Summary of the interventions (**a**), and outcomes (**b**). The RAM + taxane intervention shown in **a** corresponds to RAM + PTX/nab-PTX as reported in the original studies. The original studies did not present individual results for RAM + PTX or RAM + nab-PTX. Similarly, the original study did not provide separate results on RAM or RAM + PTX in the intervention named RAM or RAM + PTX. *AEs* adverse events, *DCR* disease control rate, *DoT* duration of treatment, *nab-PTX* albumin-bound paclitaxel, *ORR* objective response rate, *OS* overall survival, *PDT* post-discontinuation treatment, *PFS* profession-free survival, *PTX* paclitaxel, *RAM* ramucirumab, *RDI* relative dose intensity, *TD* treatment discontinuation

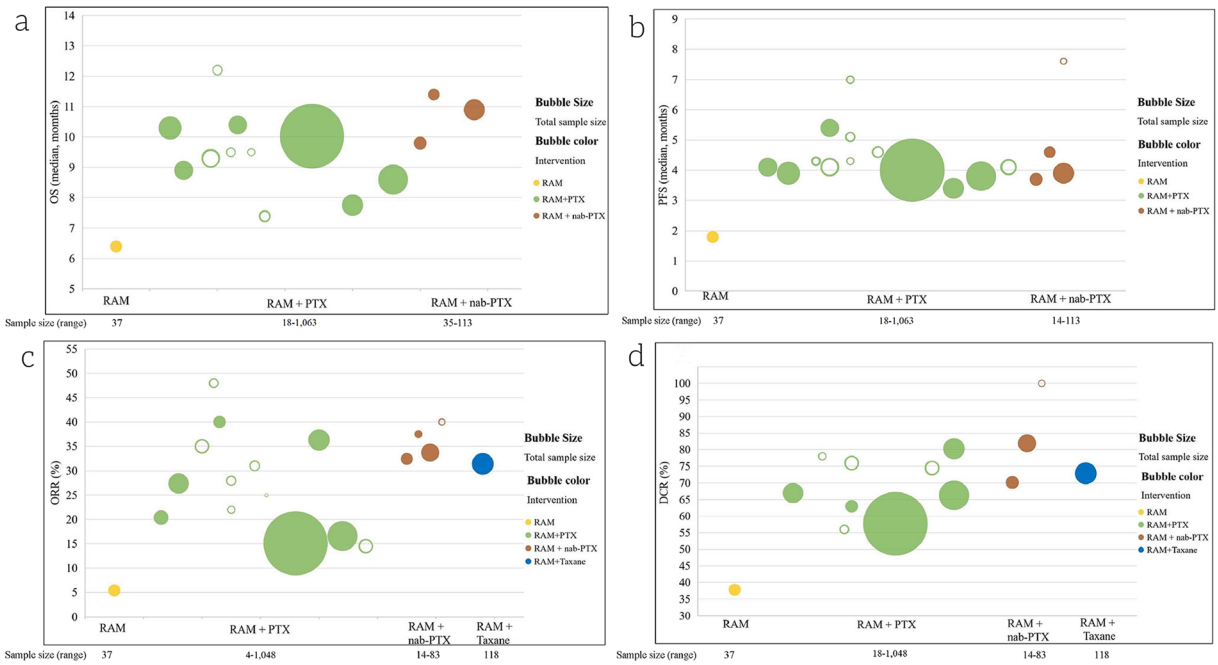

Fig. 3 Bubble plots for the median OS (**a**), PFS (**b**), ORR (**c**), and DCR (**d**). (In the bubble plot, the total sample size of each study is represented by the bubble size. Solid bubbles represent full-text studies and hollow bubbles represent studies presented as conference abstracts. Different types of treatments are presented in the *x*-axis. Median survival or response rate for each study is presented in the *y*-axis. Results on subgroup populations with specific characteristics are not presented here.). *OS* overall survival, *PFS* progression-free survival, *ORR* objective response rate, *DCR* disease-free survival, *RAM* ramucirumab, *PTX* paclitaxel, *nab-PTX* albumin-bound paclitaxel

Table 2 Data from comparative studies

Study ID	Interventions	Groups and sample size	OS			PFS			ORR		DCR	
			Median (month)	HR (95% CI) *p* value		Median (month)	HR (95% CI) *p* value		%	*p* value	%	*p* value
Total study population												
Imazeki 2019	RAM + PTX	RAM + PTX: 91	9.3	0.73[e]		4.1	0.66[e]		35.0	–	76.0	–
	PTX	PTX: 63	7.0	(0.52–1.04)		3.2	(0.47–0.93)		18.0		56.0	
				$p = 0.083$			$p = 0.016$					
Shoji 2018[f]	RAM + PTX	RAM + PTX: 28	12.2	–		5.1	–		28.0	–	–	–
	PTX	PTX: 29	9.7			4.1			17.2		–	
Kusumoto 2017	RAM + PTX	RAM + PTX: 18	9.5[h]	–		4.3[h]	–		22.0	–	78.0	–
	PTX	PTX: NR	5.2[h]			3.0[h]			21.0		48.0	
Ishikawa 2020[g]	RAM + nab-PTX	RAM + nab-PTX: 35	11.4	0.95[a]		4.6	0.90[a]		37.5	0.328[e]	–	–
				(0.56–1.62)			(0.58–1.41)					
	RAM + PTX	RAM + PTX: 93	8.9	$p = 0.847$		4.1	$p = 0.643$		20.4		–	
Okunaka 2020a	RAM + nab-PTX	RAM + nab-PTX: 113	10.9	0.82[a]		3.9	1.08[a]		33.7	0.385[d]	81.9	0.016[d]
				(0.61–1.10)			(0.83–1.40)					
	RAM + PTX	RAM + PTX: 138	10.3	$p = 0.188$[c]		3.9	$p = 0.573$[c]		27.4		67.0	
Shoji 2018[f]	RAM + PTX	RAM + PTX: 28	12.2	–		5.1	–		28.0	–	–	–
	IRI	IRI: 28	9.8			3.3			18.5		–	
Jung 2018	RAM + PTX	RAM + PTX: 228	8.6	$p = 0.399$[c]		3.8	$p = 0.405$[c]		16.6	$p = 0.127$[d]	66.3	$p = 0.008$[d]
	RAM	RAM: 37	6.4			1.8			5.4		37.8	
Subgroup population with specific characteristics												
Masuishi 2018	RAM + PTX	RAM + PTX (high ascites group): 41	6.2	0.57[a]	0.64[b]	3.5	0.61[a]	0.57[b]	–	–	–	–
	PTX	PTX (high ascites group): 63	4.8	(0.37–0.88)	(0.40–0.99)	2.2	(0.40–0.92)	(0.42–0.77)	–		–	
				$p = 0.01$	$p = 0.046$		$p = 0.02$	$p = 0.0003$				
	RAM + PTX	RAM + PTX (low ascites group): 86	10.6	0.67[a]	0.69[b]	5.2	0.56[a]	0.59[b]	–	–	–	–
	PTX	PTX (low ascites group): 115	6.9	(0.48–0.93)	(0.49–0.97)	3.0	(0.42–0.75)	(0.44–0.79)	–		–	
				$p = 0.02$	$p = 0.03$		$p < 0.0001$	$p = 0.0004$				

Table 2 continued

Study ID	Interventions	Groups and sample size	OS		PFS			ORR		DCR	
			Median (month)	HR (95% CI) *p* value	Median (month)	HR (95% CI) *p* value		%	*p* value	%	*p* value
Ishikawa 2020[g]	RAM + nab-PTX	RAM + nab-PTX (with peritoneal metastasis group): 31	10.5	0.83[a] (0.46–1.50)	5.8	0.66[a] (0.40–1.10)		–	–	–	–
	RAM + PTX	RAM + PTX (with peritoneal metastasis group): 62	8.0	$p = 0.535$	3.5	$p = 0.109$		–		–	
	RAM + nab-PTX	RAM + nab-PTX (without peritoneal metastasis group): 4	15.1	1.08[a] (0.30–3.84)	2.4	2.45[a] (0.83–7.20)		–	–	–	–
	RAM + PTX	RAM + PTX (without peritoneal metastasis group): 31	13.9	$p = 0.906$	5.7	$p = 0.105$		–		–	
Kashiwada 2019a	RAM + PTX	< 65 years group: 17	9.3	0.92[c]	6.3	0.66[c]		–	–	–	–
		≥ 65 years group: 24	6.8	(0.42–2.06)	4.9	(0.29–1.49)		–		–	
				$p = 0.8475$		$p = 0.8858$					
Sasaki 2020	RAM + taxane	Prior anti-PD-1-exposed group: 39	–	–	4.8	0.56[a]	0.50[b]	60.6	$p < 0.001$[d]	87.9	$p = 0.023$[d]
		Prior anti-PD-1-naive group: 110	–		3.4	(0.37–0.84)	(0.32–0.78)	20.0		67.1	
						$p = 0.004$	$p = 0.003$				

CI confidence interval, *DCR* disease control rate, *HR* hazard ratio, IRI irinotecan, *nab-PTX* albumin-bound paclitaxel, *NR* not reported, *ORR* objective response rate, *OS* overall survival, *PFS* profession-free survival, *PTX* paclitaxel, *RAM* ramucirumab

[a]Univariate Cox proportional hazards model

[b]Multivariate Cox proportional hazards model

[c]Log-rank test

[d]Fisher's exact test

[e]Statistical method not reported

[f]Shoji 2018 reported the comparative effectiveness between RAM + PTX vs. PTX and RAM + PTX vs. IRI

[g]Ishikawa 2020 reported effectiveness results for total and subgroup populations

[h]The original study presented the OS and PFS results in "days". To ensure consistency in reporting, this SLR transformed them into "months", with the understanding that 1 month equals 30.4 days

According to the NOS, five studies were assessed with a score of 6, one study was rated as 8, and two studies were rated with a maximum score of 9. Lack of descriptions on the comparability of cases and controls and assessment of outcomes were items that lost points (Supplementary Material Table S1). Regarding the NIH quality assessment, the included studies reported most of the items. Almost all studies had clearly stated objectives, selection criteria, and information representative of participants (Supplementary Material Table S2).

Effectiveness

All Included Studies

Summary of Drug Utilization Four studies presented information on RDI. In RAM + PTX studies, the median RDI ranged from 97.6% to 100.0% for RAM and from 61.3% to 80.0% for PTX [24, 26, 38]. In RAM + nab-PTX studies, the median RDI ranged from 80.2% to 100.0% for RAM and from 57%.1 to 70.7% for nab-PTX [19, 24, 26]. However, there were no data on RDI for RAM monotherapy or RAM + taxane. Data on DoT were available in five studies, with RAM + PTX and RAM + nab-PTX having a median range from 3.2 to 4.6 months [26, 35, 38] and from 2.8 to 3.2 months [19, 26], respectively. One study reported the median DoT of RAM + taxane was 3.6 months [18]. No data were available for DoT of RAM monotherapy (Supplementary Material Table S3).

Data on treatment discontinuation were available in five studies. Disease progression was the primary reason for discontinuation across different treatments, with the proportion of 76.7%, 67.9–76.4%, and 69.2% for RAM [34], RAM + PTX [20, 26, 34, 40], and RAM + nab-PTX [19, 26], respectively. In contrast, the proportion of treatment discontinuation due to AEs was much lower for RAM (3.3%), RAM + PTX (5.3–6.3%), and RAM + nab-PTX (5.1%). None of the studies reported treatment discontinuation for RAM + taxane (Supplementary Material Table S4). After treatment discontinuation, 47.1–57.8% of patients treated with RAM + PTX [20, 26] and 60.7–74.4% of patients treated with RAM + nab-PTX [19, 26] continued to receive third-line therapies (Supplementary Material Table S5).

Summary of OS, PFS, ORR, and DCR The effectiveness data mainly focused on RAM + PTX [20, 24–26, 30, 31, 33–38, 40, 41], with limited data for RAM + nab-PTX, RAM, and RAM + taxane. Across all studies that examined RAM + PTX, the median OS ranged from 7.4 to 12.2 months, median PFS ranged from 3.35 to 7.0 months, ORR ranged from 14.5% to 48.0%, and DCR ranged from 56.0% to 80.3%. The findings remained relatively consistent even after excluding data from conference abstracts. In full-text studies, the median OS ranged from 7.76 to 10.4 months, PFS ranged from 3.35 to 5.4 months, ORR ranged from 15.1% to 40.0%, and DCR ranged from 57.7% to 80.3%. However, there were few data on OS and PFS rates. One study reported the 6-month OS and 6-month PFS rates in patients who received RAM + PTX were 66.9% and 28.5%, respectively [34].

Four studies evaluated the effectiveness of RAM + nab-PTX [19, 24, 26, 28]. The median OS ranged from 9.8 to 11.4 months, median PFS from 3.7 to 7.6 months, ORR from 32.4% to 40.0%, and DCR from 70.2% to 100.0%. In full-text studies, the median OS ranged from 9.8 to 11.4 months, median PFS from 3.7 to 4.6 months, ORR from 32.4% to 37.5%, and DCR from 70.2% to 81.9%.

There were limited data available on the effectiveness outcomes for patients receiving RAM [34] or RAM + taxane [22], with only one study for each. The RAM study reported a median OS of 6.4 months, a median PFS of 1.8 months, an ORR of 5.4%, and a DCR of 37.8%. The 6-month OS and 6-month PFS rates were 53.2% and 27.7%, respectively [34]. The RAM + taxane study reported an ORR of 31.4% and a DCR of 72.9%. This study did not disclose OS and PFS results (Fig. 3, Supplementary Material Table S6, S7, S8, and S9).

Comparative Studies

Nine studies reported comparative effectiveness results in a crude and unadjusted form, four as full texts [22, 24, 26, 34] and five as conference abstracts [29–32, 38] (Table 2). Three of the

studies compared RAM + PTX with PTX and consistently demonstrated that patients who received RAM + PTX had longer OS, PFS, and higher ORR [30, 31, 38]. Specifically, median OS, median PFS, and ORR for RAM + PTX vs. PTX ranged from 9.3 to 12.2 months vs. 5.2 to 9.7 months, 4.1 to 5.1 months vs. 3.0 to 4.1 months, and 22.0% to 35.0% vs. 17.2% to 21.0%, respectively. Two studies also showed a higher DCR in patients receiving RAM + PTX, with values ranging from 76.0% to 78.0% vs. 48.0% to 56.0% for RAM + PTX vs. PTX [30, 38], respectively. However, a statistically significant difference was not reached in most of these studies. Only one study reported treatment with RAM + PTX was associated with significantly longer PFS than treatment with PTX (Table 2) [30].

Two studies compared the effectiveness of RAM + nab-PTX and RAM + PTX, with no significant differences found in OS (10.9–-11.4 months vs. 8.9–10.3 months), PFS (3.9–4.6 months vs. 3.9–4.1 months), and ORR (33.7–37.5% vs. 20.4–27.4%) [24, 26]. However, Okunaka et al. reported a significantly higher DCR with RAM + nab-PTX than with RAM + PTX [24]. When RAM + PTX was compared with IRI [31] or RAM [34], patients receiving RAM + PTX showed longer OS and PFS, as well as higher ORR, although a statistical significance was not reached. Nonetheless, a significantly higher DCR was observed in patients receiving RAM + PTX than RAM (Table 2) [34].

In terms of subgroup analysis, four studies compared the effectiveness of different treatments in specific patient groups. One study examined the effectiveness of RAM + PTX vs. PTX in patients with high (extended from the pelvic cavity to the upper abdomen) or low (no or limited to either the pelvic cavity or upper abdomen) levels of ascites and found that regardless of ascites level, patients receiving RAM + PTX had significantly longer OS and PFS than those receiving PTX [32]. Another study investigated the effectiveness of RAM + nab-PTX vs. RAM + PTX in patients with or without peritoneal metastasis and found the median PFS for RAM + nab-PTX was better in patients with peritoneal metastasis and worse in patients without peritoneal metastasis. Multivariate Cox proportional hazard model analysis revealed a significant interaction between PFS and RAM + nab-PTX vs. RAM + PTX in patients with or without peritoneal metastasis ($p = 0.039$), although no significant interaction with OS was observed (Table 2) [26].

One study compared the effectiveness of RAM + PTX in elderly patients (≥ 65 years old) and young patients (< 65 years old). Although young patients experienced longer OS and PFS, there was no statistically significant difference between the two groups [29]. Evidence regarding the effectiveness of RAM-based therapy in patients with prior anti-programmed cell death 1 (anti-PD-1) therapy exposure was very limited, with only one study evaluating the effectiveness of RAM + taxane in this population. This study demonstrated patients with prior anti-PD-1 exposure had significantly longer PFS and higher ORR and DCR than those without prior anti-PD-1 exposure (Table 2) [22].

Safety

Fifteen studies provided safety data on RAM or RAM-based therapy [19–24, 26, 28, 30, 32–35, 37, 38, 40]. The incidence of any grade AEs associated with RAM + PTX or RAM + nab-PTX ranged from 94.0% to 99.1% [24, 26], while the incidence of grade ≥ 3 AEs ranged from 63.8% to 67.3% [24]. No study reported the total incidence of any grade or grade ≥ 3 AEs for RAM or RAM + taxane (Supplementary Material Table S10). Hematological toxicities were the most frequently observed AEs associated with any grade or grade ≥ 3 for RAM or RAM-based therapy [19–22, 24, 26, 30, 34, 35, 37]. The most commonly observed AEs of any grade were leukocytopenia (67.0–77.5%), neutropenia (67.0–78.3%), anemia (31.0–81.2%), fatigue (23.9–81.0%), and anorexia (17.0–62.0%) for RAM + PTX [21, 24, 35]; anemia (92.9%), neutropenia (80.5%), leukopenia (75.2%), sensory neuropathy (63.7%), and thrombocytopenia (38.1%) for RAM + nab-PTX [24]; neutropenia (83.9%), leukocytopenia (81.9%), anemia (67.1%), peripheral sensory neuropathy (56.4%), and decreased appetite (30.2%) for RAM + taxane [22]. No data were available for

RAM (Supplementary Material Table S11). The most common grade ≥ 3 AEs included neutropenia (33.0–55.1%), leukopenia (27.0–34.8%), anemia (0.0–22.0%), febrile neutropenia (1.0–14.0%), and gastrointestinal perforation (0.6–12.5%) for RAM + PTX [20, 21, 24, 26, 30, 34, 35, 37, 40]; neutropenia (53.5–60.0%), leukopenia (25.7–30.2%), hypertension (0.0–26.0%), appetite loss (9.3%), and anemia (0.0–7.1%) for RAM + nab-PTX [19, 24, 26, 28]; anemia (13.5%), neutropenia (8.1%), vomiting (5.4%), diarrhea (5.4%), and febrile neutropenia (2.7%) for RAM [34]. No data were available for RAM + taxane (Supplementary Material Table S11). Gastrointestinal perforation, gastric or gastrointestinal hemorrhage, and thromboembolic events were AEs of special interest (AESI) associated with anti-angiogenesis therapy. The severity of AESI was mild to moderate across different treatments. For RAM + PTX, the incidence of grade ≥ 3 AEs of gastrointestinal perforation, gastric or gastrointestinal hemorrhage, and thromboembolic events ranged from 0.6% to 12.5% [20, 21, 26, 34, 35, 40], 0.0% to 2.2% [20, 21, 26, 34], and 0.2% to 1.0% [20, 35], respectively. For RAM + nab-PTX and RAM, data were only available for grade ≥ 3 AEs of gastrointestinal perforation and gastric or gastrointestinal hemorrhage, which were both 2.9% for RAM + nab-PTX [26] and 0.0% for RAM [34].

In comparative studies, the incidence of grade ≥ 3 neutropenia (55.0% vs. 21.0%) and leukopenia (31.0% vs. 19.0%) were higher with RAM + PTX than with PTX [30]. The incidence of febrile neutropenia was higher in patients treated with RAM + PTX vs. PTX in the high ascites group (12.0% vs. 3.0%) but the same in the low ascites group (3.0% vs. 3.0%) [32]. The safety profile of RAM + nab-PTX was comparable to that of RAM + PTX [24, 26]. Among patients treated with RAM + taxane, no severe or unexpected AEs were reported in the prior anti-PD-1-exposed group or the prior anti-PD-1-naive group [22]. The incidence of grade ≥ 3 neutropenia (exposure vs. naive, 51.3% vs. 51.8%), leukocytopenia (33.3% vs. 29.1%), anemia (7.7% vs. 4.5%), and thrombocytopenia (2.6% vs. 5.5%) was similar between the two groups [22].

DISCUSSION

To our knowledge, the present SLR, with a total of 23 studies that assess the effectiveness and safety of second-line RAM or RAM-based therapy in patients with unresectable advanced or metastatic G/GEA, provides the most comprehensive analysis of real-world evidence on RAM or RAM-based treatment in Japan and South Korea. This SLR indicates RAM + PTX is effective and associated with an acceptable toxicity profile. Compared to PTX, RAM + PTX appears to be associated with longer survival and a better response rate. Prior anti-PD-1 therapy exposure may enhance the effectiveness of RAM + taxane, but further research is needed.

In this SLR, the effectiveness data predominantly focused on RAM + PTX, presenting a range of values for median OS, median PFS, ORR, and DCR that aligned with the findings reported in both the RAINBOW trial [13] and RAINBOW-Asia trial [14], even after excluding data obtained from conference abstracts. Additionally, although there was limited data available for RAM, the range of values for median OS, median PFS, ORR, and DCR summarized in the SLR were also consistent with those reported in the REGARD trial [12]. In the RAINBOW trial, patients receiving RAM + PTX had significantly longer median OS (9.6 vs. 7.4 months, HR 0.807, 95% CI 0.678–0.962, $p = 0.017$) and median PFS (4.4 vs. 2.9 months, HR 0.635, 95% CI 0.536–0.752, $p < 0.0001$), along with significantly higher ORR (28% vs. 16%, $p = 0.0001$) and DCR (80% vs. 64%, $p < 0.0001$) than those receiving PTX [13]. These findings were further confirmed by the RAINBOW-Asia trial, a bridging study of RAINBOW, conducted predominantly on Chinese patients, demonstrating consistent efficacy of RAM + PTX [14]. The SLR also supported the superior effectiveness of RAM + PTX over PTX. However, it should be noted that some comparative results in the original studies did not reach statistical significance. This could be attributed to the smaller sample size in RWSs compared to RCTs. In addition, the comparative effectiveness data of RAM + PTX vs. PTX in this SLR were derived from three retrospective cohort studies

presented as conference abstracts. These studies lacked adequate descriptions of the statistical method employed and did not account for confounding factors, which are essential in analyzing comparative effectiveness. Consequently, caution should be exercised when interpreting the comparative results between RAM + PTX and PTX in this SLR. Peritoneal metastasis, malignant ascites, and old age are commonly associated with poor prognosis in patients with gastric cancer [42–45]. Patients with these characteristics often have poor tolerance for and low sensitivity to chemotherapy. Despite these challenges, RAM + PTX therapy was found to be effective as well [26, 29, 32].

The median RDI was 99% for RAM with a median DoT of 18.0 weeks in RAINBOW trial [13] and the median RDI was 98.4% for RAM with a median DoT of 14.0 weeks in RAINBOW-Asia trial [14]. This SLR found similar RDI and DoT ranges for patients treated with RAM + PTX. However, it is worth noting that the discontinuation rate due to AEs was slightly higher in both trials (12% for RAINBOW [13] and 7% for RAINBOW-Asia [14]) than in the SLR (5.3–6.3%). This difference may be attributed to the higher incidence of grade ≥ 3 AEs in the RAINBOW (81.7%) [13] and RAINBOW-Asia (79.5%) [14] trials than in the SLR (63.8%). Consistent with the results from these two trials, we found hematological toxicities were commonly observed AEs among patients treated with RAM + PTX. Gastrointestinal perforation, gastrointestinal hemorrhage, and thromboembolic events were AESI associated with anti-angiogenesis therapy. The RAINBOW trial reported grade ≥ 3 incidence rates of 1.2%, 3.7%, and 3.4% for these events, respectively [13]. Similarly, in the RAINBOW-Asia trial, the rates were 0.0%, 2.7%, and 0.7% [14]. These rates were generally lower in this SLR, except for two study with a small sample size ($n = 8$, $n = 21$), in which the incidence of gastrointestinal perforation was 12.5% [40] and 10.0% [21], respectively. This value should be interpreted with caution because of the potential bias inherent in the small sample size. Our findings regarding comparative safety are consistent with those of the RAINBOW trial and RAINBOW-Asia. In the RAINBOW trial, grade ≥ 3 neutropenia (40.7% vs. 18.8%) and leukopenia (17.4% vs. 6.7%) occurred more frequently with RAM + PTX than with PTX [13]. Similarly, in the RAINBOW-Asia trial, the rates were 54.3% vs. 38.6% for grade ≥ 3 neutropenia and 43.3% vs. 29.0% for leukopenia. These results collectively provide evidence supporting a favorable safety profile for RAM.

From the perspective of AEs, treatment with RAM + nab-PTX has been conditionally recommended by Japanese gastric cancer treatment guidelines (JGCG) when nab-PTX is preferred over PTX [3]. Our findings suggest RAM + nab-PTX and RAM + PTX are comparable in terms of effectiveness and safety and support the use of RAM + nab-PTX as a second-line treatment option for patients with gastric cancer [24, 26]. In this SLR, one study indicated RAM + nab-PTX was associated with longer PFS than RAM + PTX in patients with peritoneal metastasis [26]. Conversely, data from a recently disclosed phase 2 trial (P-SELECT) in Japan showed no significant difference between the two regimens in terms of OS, PFS, ORR, and DCR, irrespective of the presence or absence of peritoneal metastasis [46]. More evidence might be needed to further evaluate whether patients with peritoneal metastasis can benefit more from RAM + nab-PTX or RAM + PTX.

In this SLR, most patients were given fluoropyrimidine-containing and/or platinum-containing regimens in first-line treatment. Although three studies included a few patients who received prior fluoropyrimidine plus taxanes chemotherapy, no effectiveness or safety data were available for the subgroup of patients [19, 27, 34].

ICIs combined with chemotherapeutic agents as a first-line treatment have been shown to improve the survival of patients with advanced G/GEA in the phase 3 Checkmate-649 [7] and ATTRACTION-4 [47] trials. Following this initial treatment, RAM was administered as one of the subsequent therapies in these studies. Unlike the ATTRACTION-4, the Checkmate-649 also provided PFS2 results, which measured the time from randomization to progression after subsequent systemic therapy, initiation of second subsequent systemic therapy, or death, whichever occurred earlier. In the Checkmate-

649, the median PFS2 benefit was observed with nivolumab + chemotherapy vs. chemotherapy (12.2 vs. 10.4 months, HR 0.75, 95% CI 0.67–0.84) [48]. This suggests nivolumab + chemotherapy may improve the efficacy of second-line treatments, including RAM. However, data were not available for the subgroup of patients who received RAM as a second-line treatment in the Checkmate-649 trial. It is worth noting that there is another recently published subgroup analysis of a phase 3 clinical trial which analyzed the effect of RAM after pre-treatment with ICIs, with results suggesting that RAM plus irinotecan is an effective subsequent treatment after ICIs progression [49]. One study included in this SLR showed patients with prior anti-PD-1 exposure who subsequently received RAM + taxane had significantly improved PFS, ORR, and DCR with an acceptable toxicity profile when compared with patients without prior anti-PD-1 exposure [22]. In addition, a recent RWS by Kankeu Fonkoua et al. conducted in the USA demonstrated patients with prior ICIs receiving RAM + PTX as a second-line or later therapy had significantly improved OS (14.8 vs. 7.4 months, HR 0.33, 95% CI 0.15–0.72), PFS (8.9 vs. 4.9 months, HR 0.37, 95% CI 0.15–0.91), and ORR (57.9% vs. 17.7%, $p < 0.0001$) when compared with patients without prior ICIs [50]. Our findings support the notion that patients with prior anti-PD-1 therapy may benefit more from RAM treatment. Recent studies have illuminated the potential mechanisms underlying these findings. In addition to promoting tumor vessel growth, VEGF also suppresses the immune system by inhibiting the function and recruitment of T-cells, promoting the recruitment of regulatory T cells and myeloid-derived suppressor cells (MDSCs), as well as inhibiting the differentiation and activation of dendritic cells. As an anti-VEGF targeted agent, RAM may address these issues, thus overcoming anti-PD-1 resistance [51, 52]. However, more extensive research is needed to confirm these observations as result of the limited evidence currently available.

Strengths: This is the first SLR to summarize the real-world effectiveness and safety of RAM as a second-line therapy for the treatment of patients with unresectable advanced or metastatic G/GEA in Japan and South Korea since its first approval in 2014. These findings, as an essential complement to randomized controlled clinical trial data, will provide valuable insights for clinicians treating patients with advanced or metastatic G/GEA, especially in Eastern Asia.

Limitations: The first limitation is the literature search of this SLR was up to December 2021. The authors conducted an additional quick literature search using the same search strategy, with the publication date limited from January 1, 2022 to January 22, 2024. After screening, there were only two studies published in 2022 from Japan met the inclusion/exclusion criteria and the two studies did not provide additional data that would have a substantial impact on the key results and conclusion of the current manuscript. Secondly, only half of the included RWSs were full-text studies, and most were retrospective cohort studies with small sample size or limited information on statistical methods used. This somewhat diminishes the credibility of the comparative effectiveness results. As a result of these limitations, we relied on descriptive methods instead of meta-analysis to address research questions, which itself is a limitation. Thirdly, although the use of ICIs in first-line treatments are increasing these days, there were few RWSs evaluating the impact of ICIs on the effectiveness and safety of RAM or RAM-based therapy in the second-line setting. Lastly, we aimed to summarize the relevant real-world evidence in Eastern Asia; unfortunately, none of the included studies were conducted in China, which has a large population of patients with gastric cancer. This is possibly because RAM has only been approved in Mainland China for 1 year.

Recognizing these limitations can guide future research efforts to generate more evidence and address uncertainties in the management of advanced or metastatic G/GEA. It is encouraging to note that a prospective observational PMSS of RAM in Chinese patients with G/GEA is ongoing (EU PAS Register Number EUPAS47676) [53], and more real-world data are expected soon.

CONCLUSION

RAM + PTX as a second-line treatment is effective and associated with an acceptable toxicity profile in patients with advanced or metastatic G/GEA in the real-world settings of Japan and South Korea. This will provide a valuable reference for clinicians managing patients with gastric cancer. More studies, especially well-designed prospective RWSs, are recommended to evaluate the effectiveness and safety of RAM or RAM-based therapy, especially after anti-PD-1 therapy, in a wider Eastern Asian population.

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Data Availability. All data generated or analyzed during this study are included within this article and the supplementary material.

Declarations

Conflict of Interest. Li Zhou and Chan Zhou are employees of Eli Lilly and Company. Lin Shen has received grants or contracts from Beijing Xiantong Biomedical Technology, Qilu Pharmaceutical, ZaiLab Pharmaceutical (Shanghai), Beihai Kangcheng (Beijing) Medical Technology, Yaojie Ankang (Nanjing) Technology Co., Ltd, Baiji Shenzhou (Beijing) Biotechnology Co., Ltd, and Jacobio Pharmaceuticals; consulting fees from Mingji Biopharmaceutical, Haichuang Pharmaceutical, Herbour Biomed; payment for speakers bureaus from Hutchison Whampoa, Hengrui, ZaiLab, and CSTONE Pharmaceutical; and has participated as a data safety monitoring board or advisory board member for MSD, Merk, BMS, BI, Sanofi, Roche, SERVIER, and AZ. Xiaotian Zhang declares that she has no competing interests.

Ethical Approval. This review article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

REFERENCES

1. World Health Organization. GLOBOCAN 2020. Cancer fact sheets. Stomach. https://gco.iarc.fr/today/data/factsheets/cancers/7-Stomach-fact-sheet.pdf. Accessed 21 Nov 2022.

2. Ajani JA, D'amico TA, Bentrem DJ, et al. Gastric cancer, version 2.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw. 2022;20(2):167–92.

3. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). Gastric Cancer. 2021;24(1):1–21.

4. Guideline Committee of the Korean Gastric Cancer Association (KGCA), Development Working Group & Review Panel. Korean practice guideline for gastric cancer 2018: an evidence-based, multi-disciplinary approach. J Gastric Cancer. 2019;19(1):1–48.

5. Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Anna Oncol. 2016;27(-suppl 5):v38–49.

6. The Chinese Society of Clinical Oncology (CSCO). Clinical guidelines for the diagnosis and treatment of gastric cancer 2022. Chin J Digest Surg. 2022;21(09):1137–64.

7. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet. 2021;398(10294):27–40.

8. Mahipal A, Choi M, Kim R. Second-line treatment of advanced gastric cancer: where do we stand? J Natl Compr Cancer Netw. 2015;13(10):1281–91 (quiz 92).

9. Ford HE, Marshall A, Bridgewater JA, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. Lancet Oncol. 2014;15(1):78–86.

10. Kang JH, Lee SI, Lim DH, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. J Clin Oncol. 2012;30(13):1513–8.

11. Thuss-Patience PC, Kretzschmar A, Bichev D, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer–a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer. 2011;47(15):2306–14.

12. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2014;383(9911):31–9.

13. Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol. 2014;15(11):1224–35.

14. Xu RH, Zhang Y, Pan H, et al. Efficacy and safety of weekly paclitaxel with or without ramucirumab as second-line therapy for the treatment of advanced gastric or gastroesophageal junction adenocarcinoma (RAINBOW-Asia): a randomised, multicentre, double-blind, phase 3 trial. Lancet Gastroenterol Hepatol. 2021;6(12):1015–24.

15. Page MJ, Mckenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.

16. Wells G, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 21 Nov 2022.

17. NIH. Quality assessment tool for before-after (pre-post) studies with no control group 2014. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Accessed 21 Nov 2022.

18. Komatsu Y, Hironaka S, Tanizawa Y, et al. Treatment pattern for advanced gastric cancer in Japan and factors associated with sequential treatment: a retrospective administrative claims database study. Adv Ther. 2021;39(1):296–313.

19. Hashida S, Tanaka N, Takahashi Y, et al. Efficacy and safety of ramucirumab/nab-paclitaxel for previously treated advanced gastric cancer in community hospitals. Acta Med Okayama. 2021;75(2):133–8.

20. Han HS, Kim BJ, Jee HJ, et al. Ramucirumab plus paclitaxel as second-line treatment in patients with advanced gastric or gastroesophageal junction adenocarcinoma: a nationwide real-world outcomes in Korea study (KCSG-ST19-16). Ther Adv Med Oncol. 2021;13:17588359211042812.

21. Arai H, Kawahira M, Yasui H, et al. Second-line chemotherapy using taxane in patients with

advanced gastric cancer who presented with severe peritoneal metastasis: a multicenter retrospective study. Int J Clin Oncol. 2021;26(2):355–63.

22. Sasaki A, Kawazoe A, Eto T, et al. Improved efficacy of taxanes and ramucirumab combination chemotherapy after exposure to anti-PD-1 therapy in advanced gastric cancer. ESMO Open. 2020;4(Suppl 2):e000775.

23. Okunaka M, Kotani D, Demachi K, et al. Efficacy and safety of nabpaclitaxel plus ramucirumab versus paclitaxel plus ramucirumab as second-line treatment for patients with advanced gastric cancer: a single institutional experience. J Clin Oncol. 2020;38(4):322.

24. Okunaka M, Kotani D, Demachi K, et al. Retrospective cohort study of nanoparticle albumin-bound paclitaxel plus ramucirumab versus paclitaxel plus ramucirumab as second-line treatment in patients with advanced gastric cancer. BMC Cancer. 2020;20(1):1111.

25. Kim HD, Ryu MH, Yoon S, et al. Clinical implications of neutrophil-to-lymphocyte ratio and MDSC kinetics in gastric cancer patients treated with ramucirumab plus paclitaxel. Chin J Cancer Res. 2020;32(5):621–30.

26. Ishikawa M, Iwasa S, Nagashima K, et al. Retrospective comparison of nab-paclitaxel plus ramucirumab and paclitaxel plus ramucirumab as second-line treatment for advanced gastric cancer focusing on peritoneal metastasis. Investig New Drugs. 2020;38(2):533–40.

27. Natsume M, Shimura T, Iwasaki H, et al. Placental growth factor is a predictive biomarker for ramucirumab treatment in advanced gastric cancer. Cancer Chemother Pharmacol. 2019;83(6): 1037–46.

28. Kashiwada T, Nishioka A, Komiya K, Aragane N, Kimura S. Nab-paclitaxel plus ramucirumab combination therapy as second-line with advanced gastric cancer: retrospective study. Ann Oncol. 2019;30:vi140.

29. Kashiwada T, Nishioka A, Aragane N, Kimura S. Paclitaxel plus ramucirumab combination therapy as second-line therapy in elderly patients with metastatic advanced gastric cancer: a single-center retrospective study. Ann Oncol. 2019;30:iv91.

30. Imazeki H, Sakamoto T, Nakano M, et al. A multicenter retrospective study of paclitaxel vs. paclitaxel plus ramucirumab for advanced gastric cancer patients. Ann Oncol. 2019;30:vi85.

31. Shoji A, Hasegawa H, Kato S, et al. Efficacy and prognostic factor analysis in second-linechemotherapy for elderly patients with metastatic gastric cancer. J Clin Oncol. 2018;36(4):143.

32. Masuishi T, Kadowaki S, Hirano H, et al. Impact of adding ramucirumab to paclitaxel in patients with advanced gastric cancer according to the level of ascites: a multicenter retrospective study. Ann Oncol. 2018;29:viii229.

33. Kusumoto T, Uehara H, Hashimoto K, et al. Paclitaxel combined with ramucirumab as the second-line chemotherapy for elderly patients with advanced gastric cancer. J Clin Oncol. 2018;36(15): e16088.

34. Jung M, Ryu MH, Oh DY, et al. Efficacy and tolerability of ramucirumab monotherapy or in combination with paclitaxel in gastric cancer patients from the Expanded Access Program Cohort by the Korean Cancer Study Group (KCSG). Gastric Cancer. 2018;21(5):819–30.

35. Fukuda N, Takahari D, Wakatsuki T, et al. Early hypertension is associated with better clinical outcomes in gastric cancer patients treated with ramucirumab plus paclitaxel. Oncotarget. 2018;9(20):15219–27.

36. Sakai D, Kudo T, Kato A, et al. Retrospective study of ramucirumab in patients with advanced gastric cancer. J Clin Oncol. 2017;35(4):199.

37. Matsumoto T. Retrospective analysis of paclitaxel and ramucirumab for unresectable gastric cancer. Hypertension during 1st cycle has possibility of predictive factor. Ann Oncol. 2017;28:x65.

38. Kusumoto T, Egashira A, Sonoda H, et al. Efficacy and safety of paclitaxel/ramucirumab as the second-line chemotherapy in Japanese patients with advanced gastric cancer. J Clin Oncol. 2017;35(15): e15540.

39. Tozawa K, Hara K, Tomita T, et al. The baseline ratio of neutrophils to lymphocytes is associated with outcome of paclitaxel plus ramucirumab treated metastatic or unresectable locally advanced gastric adenocarcinoma. J Gastroenterol Hepatol (Australia). 2016;31:96.

40. Shinohara Y, Kuwayama M, Kajitani T, Oda H, Esaki T. Our experience of chemotherapy with ramucirumab in combination with paclitaxel. Ann Oncol. 2016;27:vii94.

41. Lim S, Heo SJ, Kim TS, et al. Predictive biomarkers to ramucirumab in Asian metastatic gastric cancer patients: circulating angiogenic factors of VEGFR2 and neurophilin are predictive to ramucirumab efficacy in Asian recurrent/metastatic gastric cancer patients. Ann Oncol. 2016;27:vi225.

42. Wei J, Wu ND, Liu BR. Regional but fatal: intraperitoneal metastasis in gastric cancer. World J Gastroenterol. 2016;22(33):7478–85.

43. Shirao K, Boku N, Yamada Y, et al. Randomized phase III study of 5-fluorouracil continuous infusion vs. sequential methotrexate and 5-fluorouracil therapy in far advanced gastric cancer with peritoneal metastasis (JCOG0106). Jpn J Clin Oncol. 2013;43(10):972–80.

44. Saif MW, Makrilia N, Zalonis A, Merikas M, Syrigos K. Gastric cancer in the elderly: an overview. Eur J Surg Oncol. 2010;36(8):709–17.

45. Kamiya H, Komatsu S, Ohashi T, et al. Postoperative complications and open gastrectomy affect non-cancer-related death and shorten life expectancy in elderly patients with gastric cancer. Am J Cancer Res. 2021;11(10):5038–44.

46. Hirata K, Hamamoto Y, Shoji H, et al. A randomized phase II trial of paclitaxel plus ramucirumab versus nab-paclitaxel plus ramucirumab for gastric cancer with peritoneal dissemination refractory to first-line therapy (WJOG10617G/P-SELECT). J Clin Oncol. 2022;40(4_suppl):280–380.

47. Kang YK, Chen LT, Ryu MH, et al. Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2022;23(2):234–47.

48. Shitara K, Janjigian YY, Moehler MH, et al. Nivolumab (NIVO) plus chemotherapy (chemo) versus chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): expanded efficacy, safety, and subgroup analyses from CheckMate 649. J Clin Oncol. 2022;40(suppl):240.

49. Kawabata R, Sakai D, Kadowaki S, et al. Subgroup analyses of the effect of ramucirumab in pretreatment with immune checkpoint inhibitor in RINDBeRG: a randomized clinical trial in third- or further-line treatment of gastric cancer. J Clin Oncol. 2024;42(3_suppl):339.

50. Kankeu Fonkoua LA, Chakrabarti S, Sonbol MB, et al. Outcomes on anti-VEGFR-2/paclitaxel treatment after progression on immune checkpoint inhibition in patients with metastatic gastroesophageal adenocarcinoma. Int J Cancer. 2021;149(2):378–86.

51. Baxter MA, Middleton F, Cagney HP, Petty RD. Resistance to immune checkpoint inhibitors in advanced gastro-oesophageal cancers. Br J Cancer. 2021;125(8):1068–79.

52. Yang J, Yan J, Liu B. Targeting VEGF/VEGFR to modulate antitumor immunity. Front Immunol. 2018;9:978.

53. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. https://www.encepp.eu/encepp/viewResource.htm?id=47677. Accessed 21 Nov 2022.