SUPPLEMENTARY MATERIALS

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

Xiaotian Zhang[1], Li Zhou[2], Chan Zhou[2], Lin Shen[1]*

[1] Peking University Cancer Hospital & Institute, Beijing, China

[2] Eli Lilly and Company, Shanghai, China

*Corresponding author

Address for corresponding author: Department of Gastrointestinal Oncology, Peking University Cancer Hospital & Institute, No.52 Fucheng Road, Haidian District, Beijing 100142, China

Email addresses for all authors: Xiaotian Zhang (zhangxiaotianmed@163.com); Li Zhou (zhou_li7@lilly.com); Chan Zhou (zhou_chan@lilly.com); Lin Shen (linshenpku@163.com)

Table of contents

Appendix 1 PRISMA 2020 for Abstracts Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	No
Synthesis of results	6	Specify the methods used to present and synthesise results.	No
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	No
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	No
Registration	12	Provide the register name and registration number.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Appendix 2 PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 5-6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 5-6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 6

Section and Topic	Item #	Checklist item	Location where item is reported
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 6-7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 6-7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 6-7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 6-7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Not applicable
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not applicable
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applicable
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not applicable
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not applicable
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 8 and Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Not applicable
Study characteristics	17	Cite each included study and present its characteristics.	Page 8 and Table 1

Section and Topic	Item #	Checklist item	Location where item is reported
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 9
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 1 and Table 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Table 1
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 9-13, Figure 2, and Figure 3
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 10
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not applicable
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not applicable
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 14-17
	23b	Discuss any limitations of the evidence included in the review.	Page 16-17
	23c	Discuss any limitations of the review processes used.	Page 16-17
	23d	Discuss implications of the results for practice, policy, and future research.	Page 16-17
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 2 and 5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 2 and 5

Section and Topic	Item #	Checklist item	Location where item is reported
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not applicable
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 19
Competing interests	26	Declare any competing interests of review authors.	Page 19
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 20

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Appendix 3 Search strategies for English databases

PubMed

#1. "Stomach Neoplasms"[Mesh] OR "Stomach cancer*"[tw] OR "Stomach adenocarcinoma*"[tw] OR "gastric cancer*"[tw] OR "gastric adenocarcinoma*"[tw] OR "gastroesophageal junction adenocarcinoma*"[tw] OR "gastroesophageal junction cancer*"[tw] OR "gastro-oesophageal junction adenocarcinoma*"[tw] OR "gastro-oesophageal junction cancer*"[tw] OR GEJC[tw] OR "Stomach tumour*"[tw] OR "Stomach tumor*"[tw] OR "gastric tumour*"[tw] OR "gastric tumor*"[tw] OR "gastroesophageal junction tumour*"[tw] OR "gastroesophageal junction tumor*"[tw] OR "gastro-oesophageal junction tumour*"[tw] OR "gastro-oesophageal junction tumor*"[tw]

#2. Advanced[tw] OR metastatic[tw] OR unresectable[tw] OR Metastas*[tw]

#3. #1 AND #2

#4. "ramucirumab" [Supplementary Concept] OR ramucirumab OR LY3009806 OR Cyramza OR "IMC-1121B" OR IMC1121B

#5. #3 AND #4

#6. "Japan"[Mesh] OR "Korea"[Mesh] OR Japan OR Japanese OR Tokyo OR Hokkaido OR Osaka OR Kyoto OR Yokohama OR Nagoya OR Kobe OR Fukuoka OR Sapporo OR Sendai OR Hiroshima OR Korea OR Korean OR Seoul OR Sejong OR Jeju OR Suwon OR Busan OR Daegu OR Incheon OR Gwangju OR Daejeon OR ulsan

#7. "China"[Mesh] OR "Taiwan"[Mesh] OR China OR Chinese OR Taiwan OR Taiwanese OR "Hong kong" OR Hongkong OR Macau OR Macao OR Beijing OR Shanghai OR Tianjin OR Chongqing OR "Inner Mongolia" OR Tibet OR Guangxi OR Sinkiang OR Ningxia OR Xinjiang OR Hebei OR Shanxi OR Liaoning OR Jilin OR Heilongjiang OR Jiangsu OR Zhejiang OR Anhui OR Fujian OR Jiangxi OR Shandong OR Henan OR Hubei OR Hunan OR Guangdong OR Hainan OR Sichuan OR Guizhou OR Yunnan OR Shaanxi OR Gansu OR Qinghai

#8. #5 AND (#6 OR #7)

Embase

#1. 'stomach cancer'/exp OR (((Stomach OR gastric OR "gastroesophageal junction" OR "gastro-oesophageal junction") NEAR/3 (cancer* OR adenocarcinoma* OR tumour* OR tumor* OR carcinoma*)) OR GEJC):ab,ti,kw

#2. (Advanced OR metastatic OR unresectable OR Metastas*):ab,ti,kw

#3. #1 AND #2

#4. 'ramucirumab'/exp OR (ramucirumab OR LY3009806 OR Cyramza OR "IMC-1121B" OR

IMC1121B):ab,ti,kw

#5. #3 AND #4

#6. 'Japan'/exp OR 'Korea'/exp OR (Japan OR Japanese OR Tokyo OR Hokkaido OR Osaka OR Kyoto OR Yokohama OR Nagoya OR Kobe OR Fukuoka OR Sapporo OR Sendai OR Hiroshima OR Korea OR Korean OR Seoul OR Sejong OR Jeju OR Suwon OR Busan OR Daegu OR Incheon OR Gwangju OR Daejeon OR ulsan):ti,ab,ad,ff

#7. 'China'/exp OR (China OR Chinese OR Taiwan OR "Hong kong" OR Hongkong OR Macau OR Macao OR Beijing OR Shanghai OR Tianjin OR Chongqing OR "Inner Mongolia" OR Tibet OR Guangxi OR Sinkiang OR Ningxia OR Xinjiang OR Hebei OR Shanxi OR Liaoning OR Jilin OR Heilongjiang OR Jiangsu OR Zhejiang OR Anhui OR Fujian OR Jiangxi OR Shandong OR Henan OR Hubei OR Hunan OR Guangdong OR Hainan OR Sichuan OR Guizhou OR Yunnan OR Shaanxi OR Gansu OR Qinghai):ti,ab,ad,ff

#8. #5 AND (#6 OR #7)

Cochrane Library

#1. MeSH descriptor: [Stomach Neoplasms] explode all trees

#2. (((Stomach OR gastric OR "gastroesophageal junction" OR "gastro-oesophageal junction") NEAR/3 (cancer* OR adenocarcinoma* OR tumour* OR tumor* OR carcinoma*)) OR GEJC):ti,ab,kw

#3. #1 OR #2

#4. (Advanced OR metastatic OR unresectable OR Metastas*):ti,ab,kw

#5. #3 AND #4

#6. ramucirumab OR LY3009806 OR Cyramza OR "IMC-1121B" OR IMC1121B

#7. #5 AND #6

#8. MeSH descriptor: [Japan] explode all trees

#9. MeSH descriptor: [Korea] explode all trees

#10. Japan OR Japanese OR Tokyo OR Hokkaido OR Osaka OR Kyoto OR Yokohama OR Nagoya OR Kobe OR Fukuoka OR Sapporo OR Sendai OR Hiroshima OR Korea OR Korean OR Seoul OR Sejong OR Jeju OR Suwon OR Busan OR Daegu OR Incheon OR Gwangju OR Daejeon OR ulsan

#11. MeSH descriptor: [China] explode all trees

#12. China OR Chinese OR Taiwan OR "Hong kong" OR Hongkong OR Macau OR Macao OR Beijing OR Shanghai OR Tianjin OR Chongqing OR "Inner Mongolia" OR Tibet OR Guangxi OR Sinkiang OR Ningxia OR Xinjiang OR Hebei OR Shanxi OR Liaoning OR Jilin OR Heilongjiang OR Jiangsu OR Zhejiang OR Anhui OR Fujian OR Jiangxi OR Shandong OR Henan OR Hubei OR Hunan OR Guangdong OR Hainan OR Sichuan OR Guizhou OR Yunnan OR Shaanxi OR Gansu OR Qinghai

#13. #7 AND (#8 OR #9 OR #10 OR #11 OR #12)

Appendix 4 Search strategies for Chinese databases (*original Chinese version*)

Note: Pages 11-12 show the *original Chinese version* of search strategies for Chinese databases, including CNKI, Wanfang, and CBM. The search terms are the Chinese translation of the above terms presented in Appendix 3. Although corresponding search terms were used in Chinese databases as those in English databases, there are still some differences between different retrieval databases in retrieval principles and methods. In this view, the search strategies for Chinese databases will not be the same as those for English databases, just as those in PubMed and Embase are not the same. For *translated English version*, please refer to Appendix 5 on page 13-15.

中国知网（China national knowledge infrastructure, CNKI）（期刊、学位、会议，中英文扩展：否）

#1. (SU%=胃癌+胃腺癌+食管胃癌+食管胃腺癌+食管胃结合部癌+食管胃结合部腺癌+胃食管结合部癌+胃食管结合部腺癌+食管胃交界部癌+食管胃交界部腺癌+食管胃交界癌+食管胃交界腺癌+食管胃交界处癌+食管胃交界处腺癌+胃食管交界部癌+胃食管交界部腺癌+胃食管交界癌+胃食管交界腺癌+胃食管交界处癌+胃食管交界处腺癌 OR TKA=胃癌+胃腺癌+食管胃癌+食管胃腺癌+食管胃结合部癌+食管胃结合部腺癌+胃食管结合部癌+胃食管结合部腺癌+食管胃交界部癌+食管胃交界部腺癌+食管胃交界癌+食管胃交界腺癌+食管胃交界处癌+食管胃交界处腺癌+胃食管交界部癌+胃食管交界部腺癌+胃食管交界癌+胃食管交界腺癌+胃食管交界处癌+胃食管交界处腺癌) AND (SU%=转移+转移性+晚期+局部晚期+局晚期+扩散+中晚期+不可切除+无法切除+不可手术+无法手术 OR TKA=转移+转移性+晚期+局部晚期+局晚期+扩散+中晚期+不可切除+无法切除+不可手术+无法手术)

#2. #1 AND (SU%=雷莫芦单抗+雷莫卢单抗+雷莫西尤单抗+雷莫西尤+ramucirumab+ Cyramza OR TKA=雷莫芦单抗+雷莫卢单抗+雷莫西尤单抗+雷莫西尤+ramucirumab+ Cyramza)

万方（Wanfang data knowledge service platform, Wanfang）

#1. 主题:("胃癌" OR "胃腺癌" OR "食管胃癌" OR "食管胃腺癌" OR "食管胃结合部癌" OR "食管胃结合部腺癌" OR "胃食管结合部癌" OR "胃食管结合部腺癌" OR "食管胃交界部癌" OR "食管胃交界部腺癌" OR "食管胃交界癌" OR "食管胃交界腺癌" OR "食管胃交界处癌" OR "食管胃交界处腺癌" OR "胃食管交界部癌" OR "胃食管交界部腺癌" OR "胃食管交界癌" OR "胃食管交界腺癌" OR "胃食管交界处癌" OR "胃食管交界处腺癌") and 主题:(转移 OR 晚期 OR 局部晚期 OR 局晚期 OR 扩散 OR 中晚期 OR "不可切除" OR "无法切除" OR "不可手术" OR "无法手术")

#2. #1 and 主题:(雷莫芦单抗 OR 雷莫卢单抗 OR 雷莫西尤单抗 OR 雷莫西尤 OR ramucirumab OR Cyramza)

中国生物医学文献数据库（China Biology Medicine, CBM）

#1. ("胃癌"[常用字段:智能] OR "胃腺癌"[常用字段:智能] OR "食管胃癌"[常用字段:智能] OR "食管胃腺癌"[常用字段:智能] OR "食管胃结合部癌"[常用字段:智能] OR "食管胃结合部腺癌"[常用字段:智能] OR "胃食管结合部癌"[常用字段:智能] OR "胃食管结合部腺癌"[常用字段:智能] OR "食管胃交界部癌"[常用字段:智能] OR "食管胃交界部腺癌"[常用字段:智能] OR "食管胃交界癌"[常用字段:智能] OR "食管胃交界腺癌"[常用字段:智能] OR "食管胃交界处癌"[常用字段:智能] OR "食管胃交界处腺癌"[常用字段:智能] OR "胃食管交界部癌"[常用字段:智能] OR "胃食管交界部腺癌"[常用字段:智能] OR "胃食管交界癌"[常用字段:智能] OR "胃食管交界腺癌"[常用字段:智能] OR "胃食管交界处癌"[常用字段:智能] OR "胃食管交界处腺癌"[常用字段:智能]) AND ("转移"[常用字段:智能] OR "转移性"[常用字段:智能] OR "晚期"[常用字段:智能] OR "局部晚期"[常用字段:智能] OR "局晚期"[常用字段:智能] OR "扩散"[常用字段:智能] OR "中晚期"[常用字段:智能] OR "不可切除"[常用字段:智能] OR "无法切除"[常用字段:智能] OR "不可手术"[常用字段:智能] OR "无法手术"[常用字段:智能])
#2. #1 AND ("雷莫芦单抗"[常用字段:智能] OR "雷莫卢单抗"[常用字段:智能] OR "雷莫西尤单抗"[常用字段:智能] OR "雷莫西尤"[常用字段:智能] OR "ramucirumab"[常用字段:智能] OR "Cyramza"[常用字段:智能])

Appendix 5 Search strategies for Chinese databases (*translated English version*)

Note: Pages 13-15 show the *translated English version* of search strategies for Chinese databases, including CNKI, Wanfang, and CBM. This is a word-for-word translation. Some recurring terms are due to the situation that some Chinese terms with same or similar meaning but slightly different expressions are corresponding to the same English term. The *translated English version* is for reference purpose only. For the *original Chinese version*, please refer to Appendix 4 on pages 11-12.

China national knowledge infrastructure (CNKI) (Journals, degrees, conferences, English and Chinese extensions: No)

#1. (Topic=Stomach cancer + stomach adenocarcinoma + esophagogastric cancer + esophagogastric adenocarcinoma + esophagogastric junction cancer + esophagogastric junction adenocarcinoma + gastroesophageal junction cancer + gastroesophageal junction adenocarcinoma + esophagogastric junction cancer + esophagogastric junction adenocarcinoma + esophagogastric junction cancer + esophagogastric junction adenocarcinoma + esophagogastric junction cancer + esophagogastric junction adenocarcinoma + gastroesophageal junction cancer + gastroesophageal junction adenocarcinoma + gastroesophageal junction cancer + gastroesophageal junction adenocarcinoma + gastroesophageal junction cancer + gastroesophageal junction adenocarcinoma OR TKA *(abbreviation of "title or keyword or abstract")*=Stomach cancer + stomach adenocarcinoma + esophagogastric cancer + esophagogastric adenocarcinoma + esophagogastric junction cancer + esophagogastric junction adenocarcinoma + gastroesophageal junction cancer + gastroesophageal junction adenocarcinoma + esophagogastric junction cancer + esophagogastric junction adenocarcinoma + esophagogastric junction cancer + esophagogastric junction adenocarcinoma + esophagogastric junction cancer + esophagogastric junction adenocarcinoma + gastroesophageal junction cancer + gastroesophageal junction adenocarcinoma + gastroesophageal junction cancer + gastroesophageal junction adenocarcinoma + gastroesophageal junction cancer + gastroesophageal junction adenocarcinoma) AND (Topic=metastasis + metastatic + advanced + locoregional advanced + locoregional advanced + metastasis + advanced + unresectable + unresectable + unresectable + unresectable OR TKA=metastasis + metastatic + advanced + locoregional advanced + locoregional advanced + metastasis + advanced + unresectable + unresectable + unresectable + unresectable)

#2. #1 AND (Topic=ramucirumab + ramucirumab + ramucirumab + ramucirumab +ramucirumab+ Cyramza OR TKA=ramucirumab + ramucirumab + ramucirumab + ramucirumab +ramucirumab + Cyramza)

Wanfang data knowledge service platform (Wanfang)

#1. Topic: ("Stomach cancer" OR "stomach adenocarcinoma" OR "esophagogastric cancer" OR "esophagogastric adenocarcinoma" OR "esophagogastric junction cancer" OR "esophagogastric junction adenocarcinoma" OR "gastroesophageal junction cancer" OR "gastroesophageal junction adenocarcinoma" OR "esophagogastric junction cancer" OR "esophagogastric junction adenocarcinoma" OR "esophagogastric junction cancer" OR "esophagogastric junction adenocarcinoma" OR "esophagogastric junction cancer" OR "esophagogastric junction adenocarcinoma" OR "gastroesophageal junction cancer" OR "gastroesophageal junction adenocarcinoma" OR "gastroesophageal junction cancer" OR "gastroesophageal junction adenocarcinoma" OR "gastroesophageal junction cancer" OR "gastroesophageal junction adenocarcinoma") and topic: (metastasis OR advanced OR locoregional advanced OR locoregional advanced OR metastasis OR advanced OR "unresectable" OR "unresectable" OR "unresectable" OR "unresectable")
#2. #1 and topic: (ramucirumab OR ramucirumab OR ramucirumab OR ramucirumab OR ramucirumab OR Cyramza)

China Biology Medicine (CBM)

#1. ("Stomach cancer" [common fields: intelligent] OR "stomach adenocarcinoma" [common fields: intelligent] OR "esophagogastric cancer"[common fields: intelligent] OR "esophagogastric adenocarcinoma" [common fields: intelligent] OR "esophagogastric junction cancer" [common fields: intelligent] OR "esophagogastric junction adenocarcinoma" [common fields: intelligent] OR "gastroesophageal junction cancer" [common fields: intelligent] OR "gastroesophageal junction adenocarcinoma" [common fields: intelligent] OR "esophagogastric junction cancer" [common fields: intelligent] OR "esophagogastric junction adenocarcinoma" [common fields: intelligent] OR "esophagogastric junction cancer" [common fields: intelligent] OR "esophagogastric junction adenocarcinoma" [common fields: intelligent] OR "esophagogastric junction cancer" [common fields: intelligent] OR "esophagogastric junction adenocarcinoma" [common fields: intelligent] OR "gastroesophageal junction cancer" [common fields: intelligent] OR "gastroesophageal junction adenocarcinoma" [common fields: intelligent] OR "gastroesophageal junction cancer" [common fields: intelligent] OR "gastroesophageal junction adenocarcinoma" [common fields: intelligent]) AND ("metastasis" [common fields: intelligent] OR " metastatic" [common fields: intelligent] OR "advanced" [common fields: intelligent] OR "locoregional advanced" [common fields: intelligent] OR "locoregional advanced" [common fields: intelligent] OR " metastasis" [common fields: intelligent] OR "advanced" [common fields: intelligent] OR

"unresectable" [common fields: intelligent] OR "unresectable" [common fields: intelligent] OR "unresectable" [common fields: intelligent] OR "unresectable" [common fields: intelligent])

#2. #1 AND ("ramucirumab" [common fields: intelligent] OR "ramucirumab" [common fields: intelligent] OR "ramucirumab" [common fields: intelligent] OR "ramucirumab" [common fields: intelligent] OR "ramucirumab" [common fields: intelligent] OR "Cyramza" [common fields: intelligent])

Table S1 Risk of bias assessment of controlled studies (NOS assessment tool)

Study ID			Arai 2021	Ishikawa 2020	Okunaka 2020a	Jung 2018
Selection	Representativeness of the exposed cohort	a) truly representative of the average condition in the community* b) somewhat representative of the average condition in the community* c) selected group of users eg nurses, volunteers d) no description of the derivation of the cohort	b1	b1	b1	a1
	Selection of the non exposed cohort	a) drawn from the same community as the exposed cohort* b) drawn from a different source c) no description of the derivation of the non exposed cohort	a1	a1	a1	a1
	Ascertainment of exposure	a) secure record (eg surgical records)* b) structured interview* c) written self report d) no description	a1	a1	a1	a1
	Demonstration that outcome of interest was not present at start of study	a) yes* b) no	a1	a1	a1	a1
Comparability	Comparability of cases and controls on the basis of the design or analysis	a) study controls for age* b) study controls for any additional factor*	a0b0	a1b1	a0b0	a0b1
Outcome	Assessment of outcome	a) independent blind assessment* b) record linkage* c) self report d) no description	d0	b1	d0	b1
	Was follow-up long enough for outcomes to occur	a) yes* b) no	a1	a1	a1	a1
	Adequacy of follow up of cohorts	a) complete follow up - all subjects accounted for* b) subjects lost to follow up unlikely to introduce bias-small number lost ≤ 20 % follow up, or description provided of those lost)* c) follow up rate > 20% and no description of those lost d) no statement	a1	a1	a1	a1
			6	9	6	8

Table S1 Risks of bias assessment of controlled studies (NOS assessment tool) (Continued)

Study ID			Imazeki 2019	Masuishi 2018	Shoji 2018	Kusumoto 2017
Selection	Representativeness of the exposed cohort	a) truly representative of the average condition in the community* b) somewhat representative of the average condition in the community* c) selected group of users eg nurses, volunteers d) no description of the derivation of the cohort	b1	b1	b1	b1
	Selection of the non exposed cohort	a) drawn from the same community as the exposed cohort* b) drawn from a different source c) no description of the derivation of the non exposed cohort	a1	a1	a1	a1
	Ascertainment of exposure	a) secure record (eg surgical records)* b) structured interview* c) written self report d) no description	a1	a1	a1	a1
	Demonstration that outcome of interest was not present at start of study	a) yes* b) no	a1	a1	a1	a1
Comparability	Comparability of cases and controls on the basis of the design or analysis	a) study controls for age* b) study controls for any additional factor*	a0b0	a1b1	a0b0	a0b0
Outcome	Assessment of outcome	a) independent blind assessment* b) record linkage* c) self report d) no description	d0	b1	d0	d0
	Was follow-up long enough for outcomes to occur	a) yes* b) no	a1	a1	a1	a1
	Adequacy of follow up of cohorts	a) complete follow up - all subjects accounted for* b) subjects lost to follow up unlikely to introduce bias - small number lost ≤ 20 % follow up, or description provided of those lost)* c) follow up rate > 20% and no description of those lost d) no statement	a1	a1	a1	a1
			6	9	6	6

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Table S2 Risk of bias assessment of non-controlled studies (NIH assessment tool)

Study ID		Han 2021	Hashida 2021	Fukuda 2018	Kim 2020	Kashiwada 2019a	Kashiwada 2019b	Kusumoto 2018	Matsumoto 2017	Lim 2016
1. Was the study question or objective clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	No									
	Other (CD, NR, NA)*									
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Yes	Yes		Yes	Yes	Yes			
	No									
	Other (CD, NR, NA)*			NR				NR	NR	NR
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	No									
	Other (CD, NR, NA)*									
4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	Yes	Yes		Yes					
	No									
	Other (CD, NR, NA)*			NR		NR	NR	NR	NR	NR
5. Was the sample size sufficiently large to provide confidence in the findings?	Yes									
	No									
	Other (CD, NR, NA)*	NR	NR	NR	NR	NR	NR	NR	NR	NR
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	Yes	Yes		Yes					
	No									
	Other (CD, NR, NA)*			NR		NR	NR	NR	NR	NR
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Yes	Yes							
	No									
	Other (CD, NR, NA)*			NR	NR	NR	NR	NR	NR	NR
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	Yes									
	No									
	Other (CD, NR, NA)*	NR	NR		NR	NR	NR	NR	NR	NR
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes	Yes
	No									
	Other (CD, NR, NA)*									

10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Yes	Yes	Yes	Yes					
	No									
	Other (CD, NR, NA)*					NR	NR	NR	NR	NR
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Yes		Yes		Yes					
	No									
	Other (CD, NR, NA)*	NR		NR		NR	NR	NR	NR	NR
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	Yes									
	No									
	Other (CD, NR, NA)*	NA	NA	NA	NA	NA	NA	NA	NA	NA

Table S2 Risks of bias assessment of non-controlled studies (NIH assessment tool) (Continued)

Study ID		Sasaki 2020	Natsume 2019	Komatsu 2021	Tozawa 2016	Sakai 2017	Shinohara 2016
1. Was the study question or objective clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	No						
	Other (CD, NR, NA)*						
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Yes		Yes			
	No						
	Other (CD, NR, NA)*		NR		NR	NR	NR
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	No						
	Other (CD, NR, NA)*						
4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	Yes		Yes			
	No						
	Other (CD, NR, NA)*		NR		NR	NR	NR
5. Was the sample size sufficiently large to provide confidence in the findings?	Yes						
	No						
	Other (CD, NR, NA)*	NR	NR	NR	NR	NR	NR
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	Yes	Yes	Yes	Yes		
	No						
	Other (CD, NR, NA)*					NR	NR
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Yes	Yes	Yes			
	No						
	Other (CD, NR, NA)*				NR	NR	NR
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	Yes						
	No						
	Other (CD, NR, NA)*	NR	NR	NR	NR	NR	NR
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Yes	Yes	Yes			Yes
	No						
	Other (CD, NR, NA)*				NR	NR	

10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes	Yes	Yes	Yes			
	No						
	Other (CD, NR, NA)*				NR	NR	NR
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Yes			Yes			
	No						
	Other (CD, NR, NA)*	NR	NR		NR	NR	NR
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	Yes						
	No						
	Other (CD, NR, NA)*	NA	NA	NA	NA	NA	NA

***CD, cannot determine; NA, not applicable; NR, not reported**

Table S3 Relative dose intensity (RDI) and duration of treatment (DoT) of RAM or RAM-based therapy

Treatment Regimen	Study ID	RDI Median (%)	Dose adjustment			DoT Median (months)
			Event-original, n	Sample size	Proportion (%)	
RAM + PTX						
	Summary	**Range of median:** **PTX: 61.3-80.0** **RAM: 97.6-100.0**	**—**	**Range: 18-1,053**	**Initial:** **PTX: 29.7-29.9** **RAM: 0.0-10.2** **During treatment:** **PTX: 56.5-71.0** **RAM: 1.1** **RAM + PTX: 42.4**	**Range of median:** **3.2-4.6**
	Ishikawa 2020	PTX: 80.0 (range: 39.4-100.0)	PTX: due to hematological toxicities: 52	92	56.5	3.2 (range: 0.2-19.8)
		RAM: 100.0 (range: 23.5-100.0)	RAM: due to fatigue: 1	92	1.1	
	Okunaka 2020a	PTX: 61.3	PTX: during treatment, dose reduction or interruption: 98	138	71.0	—
			PTX: initial dose reductions: 41	138	29.7	—
		RAM: 97.6	RAM: initial dose reductions: 0	138	0.0	—
	Fukuda 2018	—	PTX: dose reductions or delays: 57	89	64.0	4.6 (range: 0.9-19.3)
	Kusumoto 2017	PTX: 72.4	—	18	—	4.6
	Han 2021	—	After the first dose of RAM + PTX: 443	1,044	42.4	—
			The first dose reduced of PTX: 315	1,053	29.9	—
			The first dose reduced of PTX (ECOG ≥2): 59	97	60.8	—
			The first dose reduced of PTX (ECOG 0 or 1): 245	924	26.5	—
			The first dose reduced of RAM: 107	1,053	10.2	—
			The first dose reduced of RAM (ECOG ≥2): 21	97	21.6	—

			The first dose reduced of RAM (ECOG 0 or 1): 84	924	9.1	—
RAM + nab-PTX						
	Summary	**Range of median: nab-PTX: 57.1-70.7 RAM: 80.2-100.0**	**—**	**Range: 35-113**	**Initial: nab-PTX: 47.8 RAM: — During treatment: nab-PTX: 60.0-82.3 RAM: 0.0**	**Range of median: 2.8-3.2**
	Hashida 2021	nab-PTX: 59.4 (range: 25.9-100.0) RAM: 80.2 (range: 14.3-100.0)	—	43	—	2.8 (range: 0.9-10.1)
	Ishikawa 2020	nab-PTX: 70.7 (range: 33.3-100.0) RAM: 100.0 (range: 10.5-100.0)	nab-PTX: hematological toxicities: 21 RAM: 0	35	nab-PTX: 60.0 RAM: 0.0	3.2 (range: 0.5-11.0)
	Okunaka 2020a	nab-PTX: 57.1	nab-PTX: during treatment, dose reduction or interruption: 93	113	82.3	—
			nab-PTX: initial dose reductions: 54	113	47.8	—
		RAM: 98.2	RAM: 0	113	0.0	—
RAM + taxane						
	Summary	**—**	**—**	**Range: 3,650**	**—**	**Range of median: 3.6**
	Komatsu 2021	—	—	3,650	—	3.6

Notes: The median value was recalculated as one month equals 30.4 days if the original unit was not month. ECOG=Eastern Cooperative Oncology Group; nab-PTX=albumin-bound paclitaxel; PTX=paclitaxel; RAM=ramucirumab.

Table S4 Treatment discontinuation of RAM or RAM-based therapy

Treatment Regimen	Study ID	Sample size	Proportion of patients with discontinuation (%)	Reason for discontinuation (%)		
				PD (%)	AEs (%)	Others (%)[a]
RAM						
	Summary	**Range: 37**	**—**	**Range: RAM: 76.7**	**Range: RAM: 3.3**	**Range: RAM: 20.1**
	Jung 2018	37	—	RAM: 76.7	RAM: 3.3	RAM: 20.1
RAM + PTX						
	Summary	**Range: 8-1,050**	**Range: PTX + PTX: 95.0**	**Range: RAM + PTX: 67.9-76.4**	**Range: RAM: 9.7 PTX: 11.8-25.0 RAM + PTX: 5.3-6.3**	**Range: RAM + PTX: 17.3-26.9**
	Ishikawa 2020	93	—	—	RAM: 9.7	—
			—	—	PTX: 11.8	—
	Shinohara 2016	8	—	—	PTX: 25.0	—
	Han 2021	1,050	RAM + PTX: 95.0	RAM + PTX: 67.9	RAM + PTX: 5.3	RAM + PTX: 26.9
	Jung 2018	228	—	RAM + PTX: 76.4	RAM + PTX: 6.3	RAM + PTX: 17.3
RAM + nab-PTX						
	Summary	**Range: 35-43**	**Range: RAM + nab-PTX: 90.7**	**Range: RAM + nab-PTX: 69.2**	**Range: RAM: 8.6 nab-PTX: 8.6 RAM + nab-PTX: 5.1**	**Range: RAM + nab-PTX: 25.6**
	Hashida 2021	43	RAM + nab-PTX: 90.7	RAM + nab-PTX: 69.2	RAM + nab-PTX: 5.1	RAM + nab-PTX: 25.6
	Ishikawa 2020	35	—	—	RAM: 8.6	—
			—	—	nab-PTX: 8.6	—

Notes: The percentages of PD, AEs and others are calculated as the number of events divided by the total number of people who discontinued treatment; and the sum of the percentages of PD, AE and Other may not equal 100% due to rounding. [a]: Other includes death, lost to follow-up, patient withdrawal, intervention treatment, general condition or articles categorized as other. AEs=adverse events; nab-PTX=albumin-bound paclitaxel; PD=progressive disease; PTX=paclitaxel; RAM=ramucirumab.

Table S5 Post-discontinuation treatment (PDT) distributions

Treatment Regimen	Study ID	Sample size	3L therapies	
			Treatment category	Number (%)
RAM + PTX				
	Summary	**Range: 83-1,055**	**Range:**	
			All	**47.1-57.8%**
			CT	**54.2-62.8%**
			ICI	**23.3-37.5%**
	Han 2021	1,055	All	497 (47.1)
			CT	312 (62.8)
			ICI	116 (23.3)
			Others	69 (13.9)
	Ishikawa 2020	83	All	48 (57.8)
			CT	26 (54.2)
			ICI	18 (37.5)
			Others	4 (8.4)
RAM + nab-PTX				
	Summary	**Range: 28-43**	**Range:**	
			All	**60.7-74.4%**
			CT	**6.9-29.4%**
			ICI	**69.0-70.6%**
	Hashida 2021	43	All	29 (74.4)
			CT	2 (6.9)
			ICI	20 (69.0)
			RAM	2 (6.9)
			Others	5 (17.2)
	Ishikawa 2020	28	All	17 (60.7)
			CT	5 (29.4)
			ICI	12 (70.6)

Notes: Others=Other include radiotherapy, conversion surgery, investigational agents in clinical trials, 5-FU and DDP + RT, or articles categorized as other. 3L therapies=third-line therapies; CT=chemotherapy therapy; ICI=immune checkpoint inhibitor; nab-PTX=albumin-bound paclitaxel; PTX=paclitaxel; RAM=ramucirumab.

Table S6 Overall survival (OS) of patients treated with different regimens

Treatment Regimen	Study ID	Total / Subgroup	Sample size	Median (months)	95% confidence interval
RAM					
	Summary	—	**Range: 37**	**Range: 6.4**	—
	Jung 2018	Total	37	6.4	4.4-8.5
RAM + PTX					
	Summary	—	**Range: 18-1,063**	**Range: 7.4-12.2**	—
	Okunaka 2020a	Total	138	10.3	8.5-12.0
	Ishikawa 2020	Total	93	8.9	7.47-12.00
		Patients with peritoneal metastasis	62	8.0	6.18-9.67
		Patients without peritoneal metastasis	31	13.9	6.97-NA
	Imazeki 2019	Total	91	9.3	—
	Kashiwada 2019a	Elderly groups (≥65 years old)	24	6.8	4.4-15.5
		Nonelderly groups (＜65 years old)	17	9.3	3.2-17.6
	Shoji 2018	Total	28	12.2	—
	Masuishi 2018	High ascites group	41	6.2	—
		Low ascites group	86	10.6	—
	Kusumoto 2018	Total	25	9.5	—
	Fukuda 2018	Total	89	10.4	8.3-13.3
	Kusumoto 2017	Total	18	9.5	—
	Matsumoto 2017	Total	37	7.4	5.1-14.1
	Han 2021	Total	1,063	10.03	9.33-10.73
	Kim 2020	Total	116	7.76	6.51-11.54
	Jung 2018	Total	228	8.6	7.7-10.0
RAM + nab-PTX					
	Summary	—	**Range: 35-113**	**Range: 9.8-11.4**	—
	Hashida 2021	Total	43	9.8	5.9-13.1
	Ishikawa 2020	Total	35	11.4	7.37-15.23
		Patients with peritoneal metastasis	31	10.5	5.76-15.23
		Patients without peritoneal metastasis	4	15.1	12.66-NA
	Okunaka 2020a	Total	113	10.9	9.3-12.7

Notes: Studies that reported only subgroup results were not included in the calculation of range value. The median value was recalculated as one month equals 30.4 days if the original unit was not month. NA=not assessable; nab-PTX=albumin-bound paclitaxel; PTX=paclitaxel; RAM=ramucirumab.

Table S7 Progression-free survival (PFS) of patients treated with different regimens

Treatment Regimen	Study ID	Total / Subgroup	Sample size	Median (months)	95% confidence interval
RAM					
	Summary	—	**Range: 37**	**Range: 1.8**	—
	Jung 2018	Total	37	1.8	1.7-1.9
RAM + PTX					
	Summary	—	**Range: 18-1,063**	**Range: 3.35-7.0**	—
	Ishikawa 2020	Total	93	4.1	3.29-4.61
		Patients with peritoneal metastasis	62	3.5[a]	2.80-4.31
		Patients without peritoneal metastasis	31	5.7[a]	4.11-9.21
	Okunaka 2020a	Total	138	3.9	3.1-4.7
	Imazeki 2019	Total	91	4.1	—
	Kashiwada 2019a	Elderly groups (≥65 years old)	24	4.9	3.5-10.2
		Nonelderly groups (＜65 years old)	17	6.3	1.4-NA
	Kusumoto 2018	Total	25	4.3	—
	Masuishi 2018	High ascites group	PTX + RAM: 41 PTX: 63	3.5	—
		Low ascites group	PTX + RAM: 86 PTX: 115	5.2	—
	Fukuda 2018	Total	89	5.4	4.1-5.9
	Shoji 2018	Total	28	5.1	—
	Kusumoto 2017	Total	18	4.3	—
	Sakai 2017	Total	20	7.0	—
	Matsumoto 2017	Total	37	4.6	3.4-6.7
	Tozawa 2016	High NLR group (NLR ≥ 2.5)	8	2.3	—
		Low NLR group (NLR <2.5)	12	5.1	—
	Han 2021	Total	1,063	4.0	3.80-4.27
	Kim 2020	Total	116	3.35	3.29-4.47
	Jung 2018	Total	228	3.8	3.4-4.4
	Lim 2016	Total	70	4.1	3.3-4.9
RAM + nab-PTX					
	Summary	—	**Range: 14-113**	**Range: 3.7-7.6**	—
	Hashida 2021	Total	43	3.7	2.8-6.2
	Ishikawa 2020	Total	35	4.6	3.45-7.99
		Patients with peritoneal metastasis	4	5.8[a]	3.45-9.21
		Patients without peritoneal metastasis	31	2.4[a]	1.15-NA

	Okunaka 2020a	Total	113	3.9	3.4-4.3
	Kashiwada 2019b	Total	14	7.6	2.1-17.5
RAM + taxane					
	Summary	—	—	—	—
	Sasaki 2020	Anti-PD-1-naive group in 1L	110	3.4[b]	2.9-3.9
		Anti-PD-1-exposed group in 1L	39	4.8[b]	4.2-5.4

Notes: Studies that reported only subgroup results were not included in the calculation of range value. The median value was recalculated as one month equals 30.4 days if the original unit was not month. [a]: RAM + nab-PTX showed longer PFS than RAM + PTX in patients with peritoneal metastasis (median 5.8 months [95% CI 3.45-9.21] vs. median 3.5 months [95% CI 2.80-4.31], univariate Cox proportional hazards model HR 0.66, 95% CI 0.40-1.10; p=0.109), whereas RAM + nab-PTX showed shorter PFS than RAM + PTX in patients without peritoneal metastasis (median 2.4 months [95% CI 1.15-NA] vs. median 5.7 months [95% CI 4.11-9.21], univariate Cox proportional hazards model HR 2.45, 95% CI 0.83 to 7.20; p=0.105). [b]: Median PFS was significantly longer in the anti- PD-1- exposed group than the anti- PD-1- naïve group (median 4.8 months [95% CI 4.2-5.4] vs. median 3.4 months [95% CI 2.9-3.9], univariate Cox proportional hazards model HR 0.56, 95% CI 0.37-0.84, p=0.004; multivariate Cox proportional hazards model HR 0.50, 95% CI 0.32-0.78, p=0.003). NA=not assessable; nab-PTX=albumin-bound paclitaxel; NLR=neutrophil to lymphocyte ratio; PD-1=programmed cell death-1; PTX=paclitaxel; RAM=ramucirumab.

Table S8 Objective response rate (ORR) of patients treated with different regimens

Treatment Regimen	Study ID	Total / Subgroup	Sample size	ORR (%)
RAM				
	Summary	—	**Range: 37**	**Range: 5.4**
	Jung 2018	Total	37	5.4
RAM + PTX				
	Summary	—	**Range: 4-1,048**	**Range: 14.5-48.0**
	Ishikawa 2020	Total	54	20.4
	Okunaka 2020a	Total	106	27.4
	Imazeki 2019	Total	55	35.0
	Kusumoto 2018	Total	25	48.0
		Elderly group (≥75 years old)	4	50.0
		Younger group (<75 years old)	21	32.0
	Fukuda 2018	Total	40	40.0
	Shoji 2018	Total	28	28.0
	Kusumoto 2017	Total	18	22.0
	Matsumoto 2017	Total	29	31.0
	Shinohara 2016	Total	4	25.0
	Han 2021	Total	1,048	15.1
	Kim 2020	Total	116	36.3
	Jung 2018	Total	228	16.6
	Lim 2016	Total	55	14.5
RAM + nab-PTX				
	Summary	—	**Range: 14-83**	**Range: 32.4-40.0**
	Hashida 2021	Total	43	32.4
		Patients with measurable tumors	29	32.0
		Patients without measurable tumors	14	33.3
	Ishikawa 2020	Total	16	37.5
	Okunaka 2020a	Total	83	33.7
	Kashiwada 2019b	Total	14	40.0
RAM + taxane				
	Summary	—	—	—
	Sasaki 2020	Total	118	31.4
		Anti-PD-1-naive group	85	20.0[a]
		Anti-PD-1-exposed group	33	60.6[a]

Notes: Studies that reported only subgroup results were not included in the calculation of range value. [a]: ORR was significantly higher in the anti- PD-1- exposed group than the anti- PD-1- naïve group (60.6% vs. 20.0%, p<0.001, Fisher's exact test or Chi-square test). Notes: nab-PTX=albumin-bound paclitaxel; ORR=objective response rate; PD-1=programmed cell death-1; PTX=paclitaxel; RAM=ramucirumab.

Table S9 Disease control rate (DCR) of patients treated with different regimens

Treatment Regimen	Study ID	Total / Subgroup	Sample size	DCR (%)
RAM				
	Summary	—	**Range: 37**	**Range: 37.8**
	Jung 2018	Total	37	37.8
RAM + PTX				
	Summary	—	**Range: 18-1,048**	**Range: 56.0-80.3**
	Okunaka 2020a	Total	106	67.0
	Imazeki 2019	Total	55	76.0
	Kusumoto 2018	Total	25	56.0
		Younger group (<75 years old)	21	78.0
		Elderly group (≥75 years old)	4	50.0
	Fukuda 2018	Total	40	63.0
	Kusumoto 2017	Total	18	78.0
	Han 2021	Total	1,048	57.7
	Jung 2018	Total	228	66.3
	Lim 2016	Total	55	74.5
	Kim 2020	Total	116	80.3
RAM + nab-PTX				
	Summary	—	**Range: 14-83**	**Range: 70.2-100.0**
	Hashida 2021	Total	43	70.2
		Patients with measurable tumors	29	64.0
		Patients without measurable tumors	14	83.3
	Okunaka 2020a	Total	83	81.9
	Kashiwada 2019b	Total	14	100.0
RAM + taxane				
	Summary	—	—	—
	Sasaki 2020	Total	118	72.9
		Anti-PD-1-naive group in 1L	85	67.1[a]
		Anti-PD-1-exposed group in 1L	33	87.9[a]

Notes: Studies that reported only subgroup results were not included in the calculation of range value. [a]: DCR was significantly higher in the anti- PD-1- exposed group than the anti- PD-1- naïve group (87.9% vs. 67.1%, p=0.023, Fisher's exact test or Chi-square test). DCR=disease control rate; nab-PTX=albumin-bound paclitaxel; PD-1=programmed cell death-1; PTX=paclitaxel; RAM=ramucirumab.

Table S10 Total adverse events

Grade	Treatment regimen	Study ID	Total / Subgroup	Type of AEs	Sample size	Proportion (%)
Any grade						
	RAM + PTX	**Summary**	—	—	**Range: 93-138**	**Range: 97.1-98.0**
		Ishikawa 2020	Total	AE	93	98.0
		Okunaka 2020a	Total	TRAE	138	97.1
	RAM + nab-PTX	**Summary**	—	—	**Range: 35-113**	**Range: 94.0-99.1**
		Ishikawa 2020	Total	AE	35	94.0
		Okunaka 2020a	Total	TRAE	113	99.1
Grade ≥3						
	RAM + PTX	**Summary**	—	—	**Range: 138**	**Range: 63.8**
		Okunaka 2020a	Total	TRAE	138	63.8
	RAM + nab-PTX	**Summary**	—	—	**Range: 113**	**Range: 67.3**
		Okunaka 2020a	Total	TRAE	113	67.3

Notes: Okunaka 2020a reported the incidence of grade ≥3 adverse events, and did not report the incidence of grade 5 AEs separately. AEs=adverse events; nab-PTX=albumin-bound paclitaxel; PTX=paclitaxel; RAM=ramucirumab; TRAEs=treatment-related adverse events.

Table S11 Five most common adverse events

Treatment regimen	Outcome	Study ID	Total / Subgroup	Type of AEs	Sample size	Proportion (%)
Any grade						
RAM + PTX						
	Leukocytopenia	**Summary**	—	—	**Range: 21-138**	**Range: 67.0-77.5**
		Arai 2021	Total	AE	21	67.0
		Okunaka 2020a	Total	TRAE	138	77.5
	Neutropenia	**Summary**	—	—	**Range: 21-138**	**Range: 67.0-78.3**
		Arai 2021	Total	AE	21	67.0
		Okunaka 2020a	Total	TRAE	138	78.3
		Fukuda 2018	Total	TRAE	89	70.0
	Anemia	**Summary**	—	—	**Range: 21-138**	**Range: 31.0-81.2**
		Arai 2021	Total	AE	21	52.0
		Okunaka 2020a	Total	TRAE	138	81.2
		Fukuda 2018	Total	TRAE	89	31.0
	Fatigue	**Summary**	—	—	**Range: 21-138**	**Range: 23.9-81.0**
		Arai 2021	Total	AE	21	81.0
		Okunaka 2020a	Total	TRAE	138	23.9
		Fukuda 2018	Total	TRAE	89	33.0
	Anorexia	**Summary**	—	—	**Range: 21-138**	**Range: 17.0-62.0**
		Arai 2021	Total	AE	21	62.0
		Okunaka 2020a	Total	TRAE	138	21.0
		Fukuda 2018	Total	TRAE	89	17.0
RAM + nab-PTX						
	Anemia	**Summary**	—	—	**Range: 113**	**Range: 92.9**
		Okunaka 2020a	Total	TRAE	113	92.9
	Neutropenia	**Summary**	—	—	**Range: 113**	**Range: 80.5**
		Okunaka 2020a	Total	TRAE	113	80.5
	Leukopenia	**Summary**	—	—	**Range: 113**	**Range: 75.2**
		Okunaka 2020a	Total	TRAE	113	75.2
	Sensory neuropathy	**Summary**	—	—	**Range: 113**	**Range: 63.7**
		Okunaka 2020a	Total	TRAE	113	63.7
	Thrombocytopenia	**Summary**	—	—	**Range: 113**	**Range: 38.1**
		Okunaka 2020a	Total	TRAE	113	38.1
RAM + taxane						
	Neutropenia	**Summary**	—	—	**Range: 149**	**Range: 83.9**

		Sasaki 2020	—	TRAE	149	83.9
	Leukocytopenia	**Summary**	**—**	**—**	**Range: 149**	**Range: 81.9**
		Sasaki 2020	—	TRAE	149	81.9
	Anemia	Summary	**—**	**—**	**Range: 149**	**Range: 67.1**
		Sasaki 2020	—	TRAE	149	67.1
	Peripheral sensory neuropathy	**Summary**	**—**	**—**	**Range: 149**	**Range: 56.4**
		Sasaki 2020	—	TRAE	149	56.4
	Decreased appetite	**Summary**	**—**	**—**	**Range: 149**	**Range: 30.2**
		Sasaki 2020	—	TRAE	149	30.2
Grade ≥3						
RAM + PTX						
	Neutropenia	**Summary**	**—**	**—**	**Range: 21-1,051**	**Range: 33.0-55.1**
		Arai 2021	Total	AE	21	33.0
		Han 2021	Total	TRAE	1,051	35.3
		Okunaka 2020a	Total	TRAE	138	55.1
		Ishikawa 2020	Total	AE	93	48.4
		Fukuda 2018	Total	TRAE	89	39.0
		Jung 2018	Total	TRAE	228	46.9
		Imazeki 2019	Total	AE	91	55.0
		Matsumoto 2017	Total	AE	37	46.0
	Leucopenia	**Summary**	**—**	**—**	**Range: 21-138**	**Range: 27.0-34.8**
		Arai 2021	Total	AE	21	29.0
		Okunaka 2020a	Total	TRAE	138	34.8
		Ishikawa 2020	Total	AE	93	30.1
		Imazeki 2019	Total	AE	91	31.0
		Matsumoto 2017	Total	AE	37	27.0
	Anemia	**Summary**	**—**	**—**	**Range: 21-1,051**	**Range: 0.0-22.0**
		Arai 2021	Total	AE	21	5.0
		Han 2021	Total	TRAE	1,051	10.5
		Okunaka 2020a	Total	TRAE	138	13.8
		Ishikawa 2020	Total	AE	93	2.2
		Fukuda 2018	Total	TRAE	89	0.0
		Jung 2018	Total	TRAE	228	13.6
		Matsumoto 2017	Total	AE	37	22.0
	Febrile neutropenia	**Summary**	**—**	**—**	**Range: 21-1,054**	**Range: 1.0-14.0**
		Arai 2021	Total	AE	21	14.0

		Han 2021	Total	TRAE	1,054	4.5
		Okunaka 2020a	Total	TRAE	138	9.4
		Ishikawa 2020	Total	AE	93	5.4
		Fukuda 2018	Total	TRAE	89	1.0
		Jung 2018	Total	TRAE	228	7.0
	Gastrointestinal perforation	**Summary**	—	—	**Range: 8-1,051**	**Range: 0.6-12.5**
		Arai 2021	Total	AE	21	10.0
		Han 2021	Total	TRAE	1,051	0.6
		Ishikawa 2020	Total	AE	93	1.1
		Fukuda 2018	Total	TRAE	89	1.0
		Jung 2018	Total	TRAE	228	3.1
		Shinohara 2016	Total	AE	8	12.5
RAM + nab-PTX						
	Neutropenia	**Summary**	—	—	**Range: 14-113**	**Range: 53.5-60.0**
		Hashida 2021	Total	AE	43	53.5
		Okunaka 2020a	Total	TRAE	113	56.6
		Ishikawa 2020	Total	AE	35	54.3
		Kashiwada 2019b	Total	TRAE	14	60.0
	Leucopenia	**Summary**	—	—	**Range: 35-113**	**Range: 25.7-30.2**
		Hashida 2021	Total	AE	43	30.2
		Okunaka 2020a	Total	TRAE	113	30.1
		Ishikawa 2020	Total	AE	35	25.7
	Hypertension	**Summary**	—	—	**Range: 14-113**	**Range: 0.0-26.0**
		Hashida 2021	Total	AE	43	0.0
		Okunaka 2020a	Total	TRAE	113	13.3
		Ishikawa 2020	Total	AE	35	5.7
		Kashiwada 2019b	Total	TRAE	14	26.0
	Appetite loss	**Summary**	—	—	**Range: 43**	**Range: 9.3**
		Hashida 2021	Total	AE	43	9.3
	Anemia	**Summary**	—	—	**Range: 35-113**	**Range: 0.0-7.1**
		Hashida 2021	Total	AE	43	4.7
		Okunaka 2020a	Total	TRAE	113	7.1
		Ishikawa 2020	Total	AE	35	0.0
RAM						
	Anemia	**Summary**	—	—	**Range: 37**	**Range: 13.5**
		Jung 2018	Total	TRAE	37	13.5

Neutropenia	**Summary**	—	—	**Range: 37**	**Range: 8.1**
	Jung 2018	Total	TRAE	37	8.1
Vomiting	**Summary**	—	—	**Range: 37**	**Range: 5.4**
	Jung 2018	Total	TRAE	37	5.4
Diarrhea	**Summary**	—	—	**Range: 37**	**Range: 5.4**
	Jung 2018	Total	TRAE	37	5.4
Febrile neutropenia	**Summary**	—	—	**Range: 37**	**Range: 2.7**
	Jung 2018	Total	TRAE	37	2.7

Notes: The wording of AEs and TRAEs used in the primary studies were not differentiate when summarizing the five most common AEs. Han 2021 reported that six patients experienced febrile neutropenias (Grade 5). No one experienced a Grade 5 adverse event in Hashida 2021, Kashiwada 2019b and Jung 2018. Okunaka 2020a, Fukuda 2018 and Ishikawa 2020 reported the incidence of grade ≥3 adverse events, and did not report the incidence of grade 5 AEs separately. AEs=adverse events; nab-PTX=albumin-bound paclitaxel; PTX=paclitaxel; RAM=ramucirumab; TRAEs=treatment-related adverse events.