INPLASY PROTOCOL

To cite: Zhang et al. Real-world effectiveness and safety of ramucirumab as a second-line treatment for patients with unresectable advanced or metastatic gastric or gastroesophageal junction adenocarcinoma in Eastern Asia: a systematic literature review. Inplasy protocol 2022120023. doi: 10.37766/inplasy2022.12.0023

Received: 05 December 2022

Published: 05 December 2022

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Support: **Eli Lilly and Company.**

Review Stage at time of this submission: **Data analysis.**

Conflicts of interest:
None declared.

Real-world effectiveness and safety of ramucirumab as a second-line treatment for patients with unresectable advanced or metastatic gastric or gastroesophageal junction adenocarcinoma in Eastern Asia: a systematic literature review

Zhang, XT[1]; Zhou, L[2]; Zhou, C[3]; Shen, L[4].

Review question / Objective: **Gastric cancer has the highest incidence and mortality in Eastern Asia. Ramucirumab plus paclitaxel has been established as a standard second-line therapy for advanced gastric cancer patients. A systematic literature review was conducted to evaluate ramucirumab effectiveness and safety in real-world clinical practice in Eastern Asia.**

Eligibility criteria: **We only included real-world study that contained cohort studies, post-marketing surveillance/safety studies, pragmatic clinical trials, and case series. Patients with unresectable advanced or metastatic G/GEA receiving ramucirumab or ramucirumab-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 ramucirumab or ramucirumab-based treatment as a second-line therapy. In this study, Eastern Asia comprised Japan, South Korea, and China, which includes mainland China, Hong Kong, Taiwan and Macau. Randomized controlled trials, 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.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 05 December 2022 and was last updated on 05 December 2022 (registration number INPLASY2022120023).

INTRODUCTION

Review question / Objective: **Gastric cancer has the highest incidence and mortality in Eastern Asia. Ramucirumab plus paclitaxel has been established as a standard second-line therapy for advanced gastric cancer patients. A systematic literature review was conducted to evaluate**

ramucirumab effectiveness and safety in real-world clinical practice in Eastern Asia.

Condition being studied: Globally, there were 19.3 million new cancer cases and 10.0 million cancer death in 2020. Among which, stomach cancer was the fifth most common incident cancer (one million new cases in 2020) and the fourth most common cause of cancer death.

As the 2020 WHO Cancer Today data showed Asia was the hardest-hit area of stomach cancer. One of the most important reasons was the specific dietary habits in Asia area, such as foods preserved by salting, grilled meat or fish. Among which, Eastern Asia ranked first in terms of new stomach cancer cases in 2020, whereas, the number of new cases was generally low in Northern America and Northern Europe. The age-standardized incidence rate (ASR/100,000) in Japan was 31.6, followed by Korea 27.9.

In China, Gastric cancer ranked the third most common cancer and the third leading cause of cancer-related deaths, which was responsible for approximately 478,508 new cases and 373,789 deaths in 2020.

In addition to incidence, the diagnostic criteria and clinicopathologic characteristics of stomach cancer also differed among regions, especially between Asia and the West. The recommended treatment regimens were similar across National Comprehensive Cancer Network (NCCN), Japanese gastric cancer treatment guidelines 2018 (5th edition) and Chinese Society of Clinical Oncology (CSCO) guidelines regarding first line treatment. However, for second line treatment, the recommendations were different in West, Eastern Asia and China. The preferred recommendations of NCCN guideline (Category 1 evidence) and Japanese gastric cancer treatment guideline (Evidence level A) were paclitaxel/ramucirumab combination, but CSCO recommended single-agent chemotherapy (paclitaxel/docetaxel/irinotecan) for human epidermal growth factor receptor 2 (HER2) positive or negative patients.

Ramucirumab is a human immunoglobulin G1 (IgG1) monoclonal antibody vascular endothelial growth factor receptor 2 (VEGFR-2) antagonist, prevents ligand binding and receptor-mediated pathway activation in endothelial cells. RAINBOW and REGARD showed that ramucirumab plus paclitaxel or ramucirumab monotherapy significantly improved overall survival and progression-free survival compared with paclitaxel or placebo, respectively. To date, ramucirumab is the first and only second-line anti-angiogenic targeted therapy approved for unresectable advanced or metastatic gastric or gastroesophageal junction adenocarcinoma (G/GEA) on global market, offering a new option for these patients.

The real-world studies and real-world evidence are becoming increasing important in recent years. Ramucirumab has been approved for a long time in Europe, the US and Asia, and was just approved in China in March, 2022. However, a systematic review of the effectiveness and safety of ramucirumab in real-world setting in Eastern Asia is lacking. Therefore, we plan to systematically review the real-world evidence on ramucirumab for unresectable advanced or metastatic G/GEA in Eastern Asia.

METHODS

Search strategy: 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)
#9. "second-line"[tw] OR "2nd-line"[tw] OR "2 line"[tw] OR "2L"[tw] OR "2-L"[tw] OR after[tiab] OR failure[tiab] OR fail[tiab] OR "first line progress*"[tw] OR "1st line progress*"[tw] OR "Recurrence"[Mesh] OR Relaps*[tw] OR Recurrenc*[tw] OR Recrudescenc*[tw] OR Refractor*[tw] OR "previously treated"[tw]
#10. ("Pragmatic Clinical Trials as Topic"[Mesh] OR "Real World"[tw] OR "Naturalistic Randomized Clinical Trial*"[tw] OR "Pragmatic randomized controlled trial*"[tw] OR "Practical Clinical Trial*"[tw] OR "Pragmatic Trial*"[tw] OR "Pragmatic Clinical Trial*"[tw] OR "Post marketing surveillance"[tw] OR "Post marketing safety"[tw] OR "Post market surveillance"[tw] OR "Post market safety"[tw] OR "Postmarketing surveillance"[tw] OR "Postmarketing safety"[tw] OR "Postmarket surveillance"[tw] OR "Postmarket safety"[tw] OR PMSS[tw] OR PMS[tw] OR PASS[tw] OR "Post-authorisation safety"[tw] OR PCT[tw] OR "Observational Study"[pt] OR "Observational Studies as Topic"[Mesh] OR "Cohort Studies"[Mesh] OR Observational Stud*[tiab] OR Cohort[tiab] OR "Follow-Up"[tiab] OR Longitudinal*[tiab] OR Prospectiv*[tiab] OR Retrospectiv*[tiab] OR "case series"[tiab] OR "single arm"[tiab]) NOT ("Animals"[Mesh] NOT ("Humans"[Mesh] AND "Animals"[Mesh]))
#11. #3 and #9 and #10
#12. #11 AND #7

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)
#3. #1 AND (SU%=二线+"second line"+2L+一线*进展+一线化疗后+一线治疗后+一线*失败+复发+难治+难治性+难治型 OR TKA=二线+"second line"+2L+一线*进展+一线化疗后+一线治疗后+一线*失败+复发+难治+难治性+难治型) AND (TKA=真实世界+观察性研究+病例

对照+队列+纵向+前瞻+回顾+追踪调查+调查追踪+跟踪调查+随访+(实效+实用)*(临床研究+临床试验)+上市后安全研究+上市后安全性研究 OR SU%=真实世界+观察性研究+病例对照+队列+纵向+前瞻+回顾+追踪调查+跟踪调查+随访+(实效+实用)*(临床研究+临床试验)+上市后安全研究+上市后安全性研究).

Participant or population: Unresectable advanced or metastatic G/GEA patients received second-line treatments in Eastern Asia area (China including mainland China, Hong Kong, Taiwan, and Macau; Japan; South Korea).

Intervention: 1) Ramucirumab; 2) Ramucirumab combination with other drugs. All of the above regimens were available, with no dose or treatment cycle limitation.

Comparator: No limitation.

Study designs to be included: Real world studies including non-interventional retrospective or prospective observational study, post marketing surveillance/safety study, pragmatic controlled trial.

Eligibility criteria: We only included real-world study that contained cohort studies, post-marketing surveillance/safety studies, pragmatic clinical trials, and case series. Patients with unresectable advanced or metastatic G/GEA receiving ramucirumab or ramucirumab-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 ramucirumab or ramucirumab-based treatment as a second-line therapy. In this study, Eastern Asia comprised Japan, South Korea, and China, which includes mainland China, Hong Kong, Taiwan and Macau. Randomized controlled trials, 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.

Information sources: Studies published between January, 2014 and December, 2021 were identified through computer-based searches in PubMed, EMBASE, The Cochrane Library, CNKI, CBM, Wanfang databases without limitations on language.

Main outcome(s): Effectiveness: ✓ Overall survival (OS), including number of events, median OS (95% confidence interval [CI]) and OS rate at certain time points; ✓ Profession free survival (PFS), including number of events and median PFS (95% CI) and PFS rate at certain time points.

Additional outcome(s):
Effectiveness:
✓ Time to progression (TTP);
✓ Objective response rate (ORR);
✓ Disease control rate (DCR);
✓ Duration of response (DOR).
Adverse events (AEs):
✓ Any grade AEs;
✓ Any grade treatment-related adverse events (TRAEs);
✓ Grade >=3 AEs;
✓ Grade >=3 TRAEs;
The definition of outcomes follows the original research report.

Data management: All data were extracted by two independent reviewers. Discrepancies were resolved by consensus or by involving a third team member. Before data extraction begins, a standardized data extraction form/database and data extraction guidelines were used following its review by the study statistician and upon achieving consensus by the study team on all included data fields.

Quality assessment / Risk of bias analysis: Two reviewers independently assessed the risk of bias in the included studies. We used the Newcastle-Ottawa Scale (NOS) for non-randomized studies of interventions. For single arm studies, we valuated every domain of risk of bias, basis on the standard criteria (Before-After (Pre-Post)) outlined by National Institutes of Health (NIH). Disagreements were resolved by discussion, with assistance from a third party if necessary.

Strategy of data synthesis: Study and patient characteristics, effectiveness outcomes, and safety outcomes will be summarized and presented by tables and bubble plots. Dichotomous outcome data were reported as proportions, and time to event outcome data as the median and 95% CI or hazard ratio (HR).

Subgroup analysis: Not applicable.

Sensitivity analysis: Not applicable.

Language restriction: No limitation.

Country(ies) involved: China.

Keywords: ramucirumab, advanced or metastatic gastric cancer, second-line treatment, Eastern Asia, real-world study.

Contributions of each author:
Author 1 - Xiaotian Zhang.
Author 2 - Li Zhou.
Author 3 - Chan Zhou.
Author 4 - Lin Shen.