ESMO Open
Cancer Horizons

Survival of patients with metastatic HER2 positive gastro-oesophageal cancer treated with second-line chemotherapy plus trastuzumab or ramucirumab after progression on front-line chemotherapy plus trastuzumab

Christopher Nevala-Plagemann,[1] Justin Moser,[2] Glynn Weldon Gilcrease,[2] Ignacio Garrido-Laguna[2]

To cite: Nevala-Plagemann C, Moser J, Gilcrease GW, *et al*. Survival of patients with metastatic HER2 positive gastro-oesophageal cancer treated with second-line chemotherapy plus trastuzumab or ramucirumab after progression on front-line chemotherapy plus trastuzumab. *ESMO Open* 2019;**4**:e000539. doi:10.1136/esmoopen-2019-000539

Received 3 May 2019
Revised 20 June 2019
Accepted 22 June 2019

[1]Internal Medicine, University of Utah, Salt Lake City, Utah, USA
[2]Oncology, Huntsman Cancer Institute, Salt Lake City, Utah, USA

Correspondence to
Dr Ignacio Garrido-Laguna; ignacio.garrido-laguna@hci.utah.edu

ABSTRACT

Background The role of continuing anti-HER2 therapy beyond progression on front-line therapy in patients with metastatic HER2 positive gastro-oesophageal cancer (GEC) is unclear. Continued chemotherapy plus trastuzumab (CT) has never been compared with the current standard second-line treatment, chemotherapy plus ramucirumab (CR).

Methods The Flatiron Health electronic health record derived database, a nationwide database comprising patient-level structured and unstructured data, curated via technology-enabled abstraction, was reviewed for patients with metastatic HER2 positive GEC who received first-line CT, followed by second-line CT or CR. Survival from second-line therapy (SST) and time to next therapy or death (TTNTD) were compared using Kaplan-Meier curves and logrank analysis.

Results 133 patients with metastatic HER2 positive GEC who received first-line CT were identified. 32 received second-line CR and 101 received CT. Median SST for patients treated with CT versus CR was 10.2 months (IQR 5.1–20.8) and 6.8 months (IQR 2.4–20.2), respectively (p=0.29). Median TTNTD for second-line CT versus CR was 4.9 months (IQR 2.8–9.8) and 5.1 months (IQR 2.3–7.5), respectively (p=0.65). Patients who received second-line CT were more likely to receive a multiagent chemotherapy backbone (76% vs 3%, p≤0.001).

Conclusions This analysis showed no significant difference in SST for patients treated with second-line CT versus CR. Further studies are needed to clarify the role of trastuzumab in the second line, especially in patients with confirmed retention of HER2 positivity following progression.

Key questions

What is already known about this subject?

- Studies are conflicting with regard to the continued use of trastuzumab after progression on first-line therapy in patients with metastatic HER2 positive gastro-oesophageal cancer.
- A recent retrospective analysis suggested that continuation of trastuzumab after progression on first-line therapy may improve outcomes when compared with chemotherapy alone while a prospective phase II trial in Japan showed no significant improvement in survival with the addition of trastuzumab to chemotherapy in the second line.
- Continuation of trastuzumab has never been directly compared with the current second-line standard of care of chemotherapy plus ramucirumab.

What does this study add?

- This retrospective analysis using real-world data showed no significant difference in survival outcomes between continuation of trastuzumab plus chemotherapy versus chemotherapy plus ramucirumab.

How might this impact on clinical practice?

- Optimal second-line treatment of patients with metastatic HER2 positive gastro-oesophageal cancer remains unclear, however, this study suggests that second-line chemotherapy plus trastuzumab may be a reasonable option for select patients.

INTRODUCTION

In 2019, there will be an estimated 17 650 new cases of oesophageal cancer and 27 510 cases of gastric cancer diagnosed in the USA with an estimated 27 220 deaths combined.[1] Although the overall prognosis for patients with metastatic gastro-oesophageal cancer (mGEC) remains poor, progress has been made in the management of this disease over the past decade.

For patients with HER2 positive gastric cancer, a randomised phase III study, the TOGA trial, showed a survival improvement with the addition of trastuzumab to a fluoropyrimidine doublet.[2] In the second-line

setting, results of the REGARD and RAINBOW trials, which included patients with GEC regardless of HER2 status, have led to approval of ramucirumab, a monoclonal antibody against vascular endothelial growth factor receptor 2, for use as either a single agent or in combination with chemotherapy in patients who progress on front-line chemotherapy.[3 4]

Optimal management of patients with metastatic HER2 positive GEC following progression on front-line chemotherapy plus trastuzumab (CT) remains unclear. Studies investigating the use of HER2-targeted therapies in the second line in GEC, including the TyTAN and GATSBY trials, which evaluated lapatinib and ado-trastuzumab, respectively, have thus far not demonstrated a significant survival benefit.[5 6] In patients with metastatic breast cancer, however, several trials have shown benefit from continuing trastuzumab beyond progression.[7 8] In the absence of randomised data in Western patients with GEC, treating physicians often use evidence from metastatic breast cancer to support continuing trastuzumab beyond progression.

A small retrospective study has suggested that continuation of trastuzumab after progression may lead to improved clinical outcomes when compared with chemotherapy alone in patients with HER2 positive gastric cancer.[9] More recently published prospective data from a phase II trial, however, showed no significant difference in survival between chemotherapy alone as compared with CT in 91 Japanese patients with advanced HER2 positive gastric or gastro-oesophageal junction cancer who progressed on front-line CT.[10] A small subset analysis in this study included 16 patients who underwent repeat biopsies prior to receiving second-line therapy and showed that 70% of them had lost HER2 amplification after progression on first line trastuzumab. To date there have been no studies comparing second-line chemotherapy with trastuzumab to the current standard of care of second-line ramucirumab with or without chemotherapy in HER2 positive GEC patients in the USA.

In this study, we use real-world data to retrospectively compare second-line CT to chemotherapy plus ramucirumab (CR) in patients with metastatic HER2 positive GEC who are initially treated with CT. Our hypothesis was that overall survival would be greater in patients who continued treatment with trastuzumab in the second line.

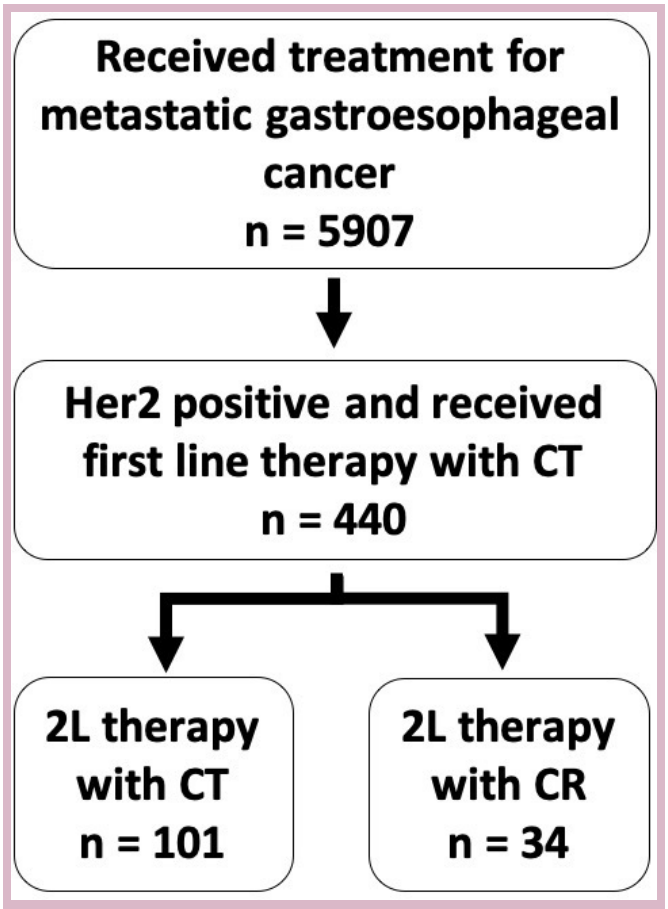

Figure 1 Study design. CR, chemotherapy plus ramucirumab; CT, chemotherapy plus trastuzumab.

METHODS

Data source

Data were obtained by retrospectively reviewing a longitudinal, demographically and geographically diverse database derived from electronic health record (EHR) data, which includes data from over 265 cancer clinics (~800 sites of care) representing more than 2 million US patients with cancer available for analysis. Patient-level data include structured and unstructured data. To extract data from unstructured sources such as clinic notes, a 'technology-enabled' chart abstraction methodology was used to collect data points from thousands of patient charts on a daily basis. This technology facilitates improved document classification and visual organisation, text search within documents, and selective surfacing of relevant documents to chart abstractors who manually review all data obtained from unstructured sources according to explicit abstraction protocols.[11] Quality control during the abstraction process consists of duplicate chart abstraction, logic checks and formal adjudication based on the complexity of select variables, as has been described in the previous analyses.[12–14]

Study cohort

Using the EHR-derived database, we identified all patients diagnosed with metastatic HER2 positive GEC between 2012 and 2018. Within this group, we then identified all patients who received first-line treatment with CT followed by second-line treatment with either CT or CR. Patients with insufficient follow-up data, defined as less than 1 month of follow-up after starting second-line therapy, were excluded from our analysis. Variables compared between groups included ages, sex, performance defined by Eastern Cooperative Oncology Group (ECOG) status within 30 days of the start of second-line therapy, disease site and duration of first-line therapy. Study design is shown in figure 1.

Table 1 Baseline patient characteristics

	CT (n=101)	CR (n=32)	P value
Mean age (IQR)	62.9 (54.0–73.0)	63.8 (56.8–71.3)	0.675
Sex (%)			<0.001
Male	79 (78.2)	28 (87.5)	
Female	22 (21.8)	4 (12.5)	
ECOG (%)			0.102
0–1	44 (43.6)	18 (56.3)	
>1	8 (7.9)	5 (15.6)	
Unknown	49 (48.5)	9 (28.1)	
Disease site (%)			0.224
Gastric	22 (21.8)	9 (28.1)	
GEJ	40 (39.6)	16 (50.0)	
Oesophageal	39 (38.6)	7 (21.9)	
Mean months on 1 L therapy (IQR)	7.8 (2.7–9.1)	9.1 (4.7–10.8)	0.375
Received multiagent 2 L chemotherapy backbone (%)	77 (76.2)	31 (3.0)	<0.001

CR, chemotherapy plus ramucirumab; CT, chemotherapy plus trastuzumab; ECOG, Eastern Cooperative Oncology Group; GEJ, gastro-oesophageal junction; 1L, first line; 2L, second line.

Statistical analysis

Standard t-test and X^2 analyses were used to compare demographics and other variables between treatment groups. The primary outcomes of interest were survival from initiation of second-line therapy and time to next therapy or death (TTNTD). TTNTD was used as a surrogate for progression-free survival as treatment response and disease progression data are not included in the Flatiron Health database. For TTNTD, events were defined as the start of third-line therapy or death that occurred prior to starting third line of therapy. Patient who were alive and who had not started on third line therapy at the time of our analysis were censored at last follow-up. Outcomes were compared using Kaplan-Meier curves and log-rank test analysis. Statistical analysis was carried out using JMP V.14.

RESULTS

Study cohort characteristics

A total of 5907 patients with mGEC who received treatment were identified in the Flatiron Health database. Of these patients, 440 were HER2 positive and received first-line therapy with CT. After excluding those without sufficient follow-up data, 133 patients were identified who received second-line therapy with either CT (n=101) or CR (n=32). Baseline characteristics are summarised in table 1. There was no significant difference between groups with regard to mean age (62.9 vs 63.8, p=0.68), mean duration of first-line therapy (7.8 m vs 9.1 m, p=0.38), ECOG status (p=0.102) or disease site (p=0.28). Patients who received second-line CR were more likely to be male (p<0.001) and those who received second-line CT were more likely to have received a multiagent chemotherapy backbone (76% vs 3%, p<0.001). A summary of the chemotherapy backbone regimens used in combination with trastuzumab in both the first-line and second-line setting is shown in table 2. In the first line, 74 out of 133 (55%) patients received chemotherapy with a fluoropyrimidine doublet plus trastuzumab and 15 out of 133 (11%) patients received a fluoropyrimidine triplet plus trastuzumab. In those who continued trastuzumab in the second line, 28 out of 101 (27%) received a fluoropyrimidine doublet plus trastuzumab and 6 out of 101 (5%) received a fluoropyrimidine triplet. All but one patient

Table 2 Chemotherapy backbones used in combination with trastuzumab

First line	No
FOLFOX	39
Fluoropyrimidine, platinum	31
Platinum, taxane	22
Fluoropyrimidine based triplet	15
Other	26
Total	**133**
Second line	**No**
Platinum, taxane	23
FOLFOX	17
FOLFIRI	15
Taxane	14
Fluoropyrimidine based triplet	6
Other	26
Total	**101**

FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX, folinic acid, fluorouracil, and oxaliplatin.

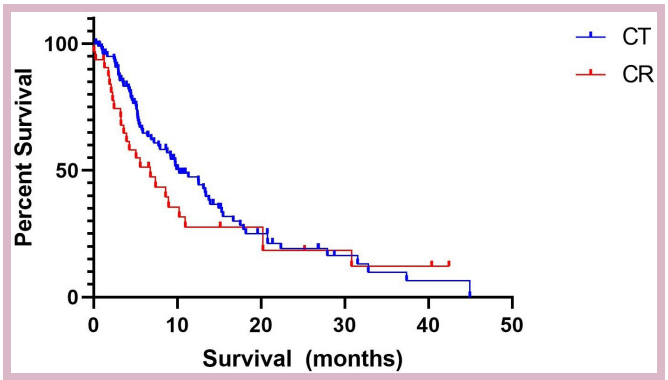

Figure 2 Survival from second-line therapy for patients treated with second-line chemotherapy plus trastuzumab (CT) versus chemotherapy plus ramucirumab (CR).

who received second-line ramucirumab was given single agent paclitaxel as the chemotherapy backbone. Six patients underwent repeat biopsy with testing for HER2, of these four remained positive for HER2.

Survival analysis

Median survival from second-line therapy (SST) for patients treated with CT was 10.2 months (IQR 5.1–20.8) and 6.8 months (IQR 2.4–20.2) for those treated with CR (p=0.29) (figure 2). Median TTNTD for patients treated with second-line CT versus CR was 4.9 months (IQR 2.8–9.8) and 5.1 months (IQR 2.3–7.53), respectively (p=0.65) (figure 3).

DISCUSSION

Our analysis of the Flatiron Health EHR-derived database did not demonstrate any significant difference between second-line CT compared with second-line CR with regard to SST or TTNTD. However, we did observe a trend towards increased SST in the second-line CT group (10.2 vs 6.8 months). This trend towards a clinical benefit with CT was not seen in the TTNTD analysis. It is possible that some aspect of second-line CT is allowing patients to continue on to receive additional therapies. However, given the increased number of patients who received a multiagent chemotherapy backbone in the 2L CT group (73% vs 3% in the 2L CR group), it is also possible that there was a bias towards more fit patients receiving second-line CT despite there not being a significant difference between groups with regard to ECOG status at the start of 2L therapy. While not shown, the types of therapies received by both groups in the third line and beyond were comparable so it is unlikely that this had any significant impact on our observations.

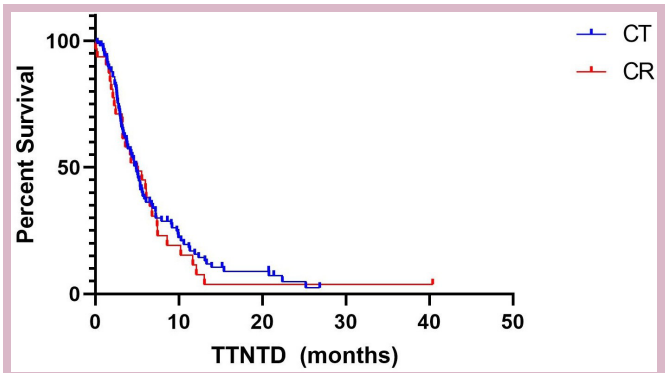

Figure 3 Time to next therapy or death for patients treated with second-line chemotherapy plus trastuzumab (CT) versus chemotherapy plus ramucirumab (CR). TTNTD, time to next therapy or death.

A recent phase II clinical trial from Japan also attempted to address the question of how to manage metastatic HER2 positive GEC patients after progression.[10] In this study, 91 patients who progressed on first-line CT were randomised to receive either paclitaxel alone or paclitaxel plus trastuzumab. Overall survival was 9.9 months in the paclitaxel alone group and 10.2 months in the paclitaxel plus trastuzumab group, a non-significant difference. While the results from this study appear to contradict the trend we observed, it should be noted that this was a different patient population, and thus, results may not apply to treatment of patients in the USA, as our study is focused.

Interestingly, 16 of the patients in the Makiyama *et al* study underwent a repeat biopsy prior to enrolment. Of these patients, a majority (69%) were found to have lost HER2 positivity. This finding of HER2 status change may certainly help explain why no significant benefit to continuing trastuzumab was observed in all comers in their study and could also help explain why prior studies investigating the use of HER2-targeted therapies in the second line have not shown significant benefit in GEC.[5 6] However, this may also suggest that a subpopulation of patients exists that could benefit from continuation of HER2 directed therapy after progression on front-line therapy and may help explain why we noticed a trend towards a survival benefit to continuing trastuzumab in our analysis.

While the limited number of patients who underwent repeat biopsy in this study restricts our ability to make any real conclusions regarding the effect of HER2 status on our results, of the six patients who underwent repeat biopsy, four (66%) were found to be HER2 positive. It should be noted that these biopsies were obtained at various points between the start of second-line therapy all the way up to the start of fifth-line therapy in one patient, thus, while the percentage of persistent HER2 positivity after progression on first-line CT in our study is greater than that seen in the Makiyama *et al*, these findings are not directly comparable. When taken together, however, our real-world data combined with data from Makiyama *et al* in Japanese patients suggest that repeating biopsies to confirm HER2 amplifications may be critical to identify, in the absence of randomised data, those patients more likely to benefit from continuing trastuzumab beyond progression.

Future clinical trials investigating the use of HER2 directed therapies in mGEC should consider including

repeat biopsy with repeat determination of HER2 status at the time of disease progression. It is possible that responses to novel agents targeting HER2, such as DS-8201 an antibody drug conjugate that has recently showed promising activity in HER2 positive mGEC with an objective response rate (ORR) of 40%,[15] could be improved if confirmation of HER2 amplification is required as an eligibility criteria. If studies confirm this phenomenon of variable HER2 positivity, one could argue for the implementation of repeat biopsies in all mGEC patients at the time of progression similar to the strategy currently used in metastatic breast cancer.

The main limitation of this study is the lack of randomisation, small sample size and retrospective nature of our analysis. The real-world data included in the Flatiron Health EHR-derived database are dependent on complete documentation by treating physicians, thus, the accuracy of line of therapy data cannot be confirmed and some variables, most notably ECOG status, have missing data. Three times as many patients were treated in the second-line setting with CT, this may suggest a selection bias in our study that we were unable to account for. There were also significant differences in the baseline characteristics between groups as well as significant variations in the chemotherapy regimens used in combination with trastuzumab (both first and second line). Future studies could consider performing a multivariable analysis or propensity score analysis to more fully explore the impact of different variables on survival in this patient population.

CONCLUSION

This retrospective analysis using real-world data showed no significant difference in survival outcomes for patients with HER2 positive GEC who continue trastuzumab beyond progression on first-line CT as compared with those who received second-line CR. Given the non-significant trend towards increased survival in the second-line CT group, it is possible that a subgroup of patients exists that would benefit from continuing trastuzumab. Repeat biopsies to confirm HER2 positivity after progression of disease may be critical to identify which patients may benefit. Further prospective studies are needed to clarify the optimal second-line management for this patient population.

Contributors CN-P: data analysis, writing—original draft, writing—review and editing. JM: study design, data curation, data analysis, writing—original draft, writing—review and editing. GWG: writing—review and editing. IG-L: supervision, writing—review and editing.

Funding This study was supported by National Cancer Institute (P30CA042014-23).

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Institutional review board approval of the study protocol was obtained prior to study conduct, and included a waiver of informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019;69:7–34.
2. Bang Y-J, Van Cutsem E, Feyereislova A, *et al*. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *The Lancet* 2010;376:687–97.
3. 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;15:1224–35.
4. 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. *The Lancet* 2014;383:31–9.
5. Satoh T, Xu R-H, Chung HC, *et al*. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of *HER2*-amplified advanced gastric cancer in Asian populations: TyTAN--a randomized, phase III study. *J Clin Oncol* 2014;32:2039–49.
6. Thuss-Patience PC, Shah MA, Ohtsu A, *et al*. Trastuzumab emtansine versus taxane use for previously treated HER2-positive locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma (GATSBY): an international randomised, open-label, adaptive, phase 2/3 study. *Lancet Oncol* 2017;18:640–53.
7. Bartsch R, Wenzel C, Altorjai G, *et al*. Capecitabine and trastuzumab in heavily pretreated metastatic breast cancer. *JCO* 2007;25:3853–8.
8. von Minckwitz G, du Bois A, Schmidt M, *et al*. Trastuzumab beyond progression in human epidermal growth factor receptor 2–Positive advanced breast cancer: a German breast group 26/Breast international group 03-05 study. *JCO* 2009;27:1999–2006.
9. Palle J, Tougeron D, Pozet A, *et al*. Trastuzumab beyond progression in patients with HER2-positive advanced gastric adenocarcinoma: a multicenter AGEO study. *Oncotarget* 2017;8:101383–93.
10. Makiyama A, Sagara K, Kawada J, *et al*. A randomized phase II study of weekly paclitaxel ± trastuzumab in patients with HER2-positive advanced gastric or gastro-esophageal junction cancer refractory to trastuzumab combined with fluoropyrimidine and platinum: WJOG7112G (T-ACT). *Journal of Clinical Oncology* 2018;36(15_suppl):4011.
11. Abernethy AP, Gippetti J, Parulkar R, *et al*. Use of electronic health record data for quality reporting. *J Oncol Pract* 2017;13:530–4.
12. Presley CJ, Tang D, Soulos PR, *et al*. Association of broad-based genomic sequencing with survival among patients with advanced non-small cell lung cancer in the community oncology setting. *JAMA* 2018;320:469–77.
13. Griffith SD, Tucker M, Bowser B, *et al*. Generating real-world tumor burden endpoints from electronic health record data: comparison of RECIST, Radiology-Anchored, and Clinician-Anchored approaches for Abstracting real-world progression in non-small cell lung cancer. *Adv Ther* 2019;151.
14. Singal G, Miller PG, Agarwala V, *et al*. Association of patient characteristics and tumor genomics with clinical outcomes among patients with non-small cell lung cancer using a Clinicogenomic database. *JAMA* 2019;321:1391–9.
15. Iwata H, Tamura K, Doi T, *et al*. Trastuzumab deruxtecan (DS-8201a) in subjects with HER2-expressing solid tumors: long-term results of a large phase 1 study with multiple expansion cohorts. *Journal of Clinical Oncology* 2018;36(15_suppl):2501.