Cochrane
Library

Cochrane Database of Systematic Reviews

Palliative chemotherapy and targeted therapies for esophageal and gastroesophageal junction cancer (Review)

Janmaat VT, Steyerberg EW, van der Gaast A, Mathijssen RHJ, Bruno MJ, Peppelenbosch MP, Kuipers EJ, Spaander MCW

Janmaat VT, Steyerberg EW, van der Gaast A, Mathijssen RHJ, Bruno MJ, Peppelenbosch MP, Kuipers EJ, Spaander MCW.
Palliative chemotherapy and targeted therapies for esophageal and gastroesophageal junction cancer.
Cochrane Database of Systematic Reviews 2017, Issue 11. Art. No.: CD004063.
DOI: [10.1002/14651858.CD004063.pub4](https://doi.org/10.1002/14651858.CD004063.pub4).

www.cochranelibrary.com

Palliative chemotherapy and targeted therapies for esophageal and gastroesophageal junction cancer (Review)

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	15
OBJECTIVES	15
METHODS	15
RESULTS	18
Figure 1.	19
Figure 2.	23
Figure 3.	26
Figure 4.	26
Figure 5.	27
Figure 6.	29
Figure 7.	29
DISCUSSION	32
AUTHORS' CONCLUSIONS	34
ACKNOWLEDGEMENTS	35
REFERENCES	36
CHARACTERISTICS OF STUDIES	51
DATA AND ANALYSES	140
Analysis 1.1. Comparison 1 Main analysis: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone, Outcome 1 Overall survival.	141
Analysis 1.2. Comparison 1 Main analysis: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone, Outcome 2 Progression-free survival.	141
Analysis 2.1. Comparison 2 Sensitivity analysis: studies that also included participants with gastric cancer, Outcome 1 Overall survival.	142
Analysis 3.1. Comparison 3 Sensitivity analysis: effect of intervention on participants with GE-junction cancer versus effect of intervention on participants with gastric cancer, Outcome 1 Overall survival, GE-junction cancer outcomes.	142
Analysis 3.2. Comparison 3 Sensitivity analysis: effect of intervention on participants with GE-junction cancer versus effect of intervention on participants with gastric cancer, Outcome 2 Overall survival, gastric cancer outcomes.	143
Analysis 4.1. Comparison 4 Subcomparison 1: chemotherapy or targeted therapy plus BSC versus BSC, Outcome 1 Overall survival.	143
Analysis 4.2. Comparison 4 Subcomparison 1: chemotherapy or targeted therapy plus BSC versus BSC, Outcome 2 Progression-free survival.	144
Analysis 5.1. Comparison 5 Subcomparison 2: studies with participants receiving second-line therapy, Outcome 1 Overall survival.	144
Analysis 5.2. Comparison 5 Subcomparison 2: studies with participants receiving second-line therapy, Outcome 2 Progression-free survival.	145
Analysis 6.1. Comparison 6 Subgroup analysis 4a: EGFR-targeting agent plus control intervention versus control intervention alone, Outcome 1 Overall survival.	145
Analysis 6.2. Comparison 6 Subgroup analysis 4a: EGFR-targeting agent plus control intervention versus control intervention alone, Outcome 2 Progression-free survival.	146
Analysis 7.1. Comparison 7 Subgroup analysis 4b: cetuximab plus control intervention versus control intervention alone, Outcome 1 Overall survival.	146
Analysis 7.2. Comparison 7 Subgroup analysis 4b: cetuximab plus control intervention versus control intervention alone, Outcome 2 Progression-free survival.	146
Analysis 8.1. Comparison 8 Subgroup analysis 4c: ramucirumab plus control intervention versus control intervention alone, Outcome 1 Overall survival.	147
Analysis 8.2. Comparison 8 Subgroup analysis 4c: ramucirumab plus control intervention versus control intervention alone, Outcome 2 Progression-free survival.	147
Analysis 9.1. Comparison 9 Subcomparison 5: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone in participants with AC of the esophagus, Outcome 1 Overall survival.	148

Analysis 9.2. Comparison 9 Subcomparison 5: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone in participants with AC of the esophagus, Outcome 2 Progression-free survival.	148
Analysis 10.1. Comparison 10 Subcomparison 6: chemotherapy or targeted therapy agent(s) plus control arm versus control arm in participants with SCC of the esophagus, Outcome 1 Overall survival.	149
Analysis 10.2. Comparison 10 Subcomparison 6: chemotherapy or targeted therapy agent(s) plus control arm versus control arm in participants with SCC of the esophagus, Outcome 2 Progression-free survival.	149
APPENDICES	149
WHAT'S NEW	151
HISTORY	151
CONTRIBUTIONS OF AUTHORS	151
DECLARATIONS OF INTEREST	152
SOURCES OF SUPPORT	152
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	152
INDEX TERMS	153

[Intervention Review]

Palliative chemotherapy and targeted therapies for esophageal and gastroesophageal junction cancer

Vincent T Janmaat¹, Ewout W Steyerberg², Ate van der Gaast³, Ron HJ Mathijssen³, Marco J Bruno¹, Maikel P Peppelenbosch¹, Ernst J Kuipers¹, Manon CW Spaander¹

¹Department of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, Netherlands. ²Department of Public Health, Erasmus University Medical Center, Rotterdam, Netherlands. ³Department of Medical Oncology, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, Netherlands

Contact address: Ernst J Kuipers, Department of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, Netherlands. e.j.kuipers@erasmusmc.nl.

Editorial group: Cochrane Upper GI and Pancreatic Diseases Group.

Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 11, 2017.

Citation: Janmaat VT, Steyerberg EW, van der Gaast A, Mathijssen RHJ, Bruno MJ, Peppelenbosch MP, Kuipers EJ, Spaander MCW. Palliative chemotherapy and targeted therapies for esophageal and gastroesophageal junction cancer. *Cochrane Database of Systematic Reviews* 2017, Issue 11. Art. No.: CD004063. DOI: [10.1002/14651858.CD004063.pub4](https://doi.org/10.1002/14651858.CD004063.pub4).

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Almost half of people with esophageal or gastroesophageal junction cancer have metastatic disease at the time of diagnosis. Chemotherapy and targeted therapies are increasingly used with a palliative intent to control tumor growth, improve quality of life, and prolong survival. To date, and with the exception of ramucirumab, evidence for the efficacy of palliative treatments for esophageal and gastroesophageal cancer is lacking.

Objectives

To assess the effects of cytostatic or targeted therapy for treating esophageal or gastroesophageal junction cancer with palliative intent.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, the Web of Science, PubMed Publisher, Google Scholar, and trial registries up to 13 May 2015, and we handsearched the reference lists of studies. We did not restrict the search to publications in English. Additional searches were run in September 2017 prior to publication, and they are listed in the 'Studies awaiting assessment' section.

Selection criteria

We included randomized controlled trials (RCTs) on palliative chemotherapy and/or targeted therapy versus best supportive care or control in people with esophageal or gastroesophageal junction cancer.

Data collection and analysis

Two authors independently extracted data. We assessed the quality and risk of bias of eligible studies according to the *Cochrane Handbook for Systematic Reviews of Interventions*. We calculated pooled estimates of effect using an inverse variance random-effects model for meta-analysis.

Main results

We identified 41 RCTs with 11,853 participants for inclusion in the review as well as 49 ongoing studies. For the main comparison of adding a cytostatic and/or targeted agent to a control arm, we included 11 studies with 1347 participants. This analysis demonstrated an

increase in overall survival in favor of the arm with an additional cytostatic or targeted therapeutic agent with a hazard ratio (HR) of 0.75 (95% confidence interval (CI) 0.68 to 0.84, high-quality evidence). The median increased survival time was one month. Five studies in 750 participants contributed data to the comparison of palliative therapy versus best supportive care. We found a benefit in overall survival in favor of the group receiving palliative chemotherapy and/or targeted therapy compared to best supportive care (HR 0.81, 95% CI 0.71 to 0.92, high-quality evidence). Subcomparisons including only people receiving second-line therapies, chemotherapies, targeted therapies, adenocarcinomas, and squamous cell carcinomas all showed a similar benefit. The only individual agent that more than one study found to improve both overall survival and progression-free survival was ramucirumab. Palliative chemotherapy and/or targeted therapy increased the frequency of grade 3 or higher treatment-related toxicity. However, treatment-related deaths did not occur more frequently. Quality of life often improved in the arm with an additional agent.

Authors' conclusions

People who receive more chemotherapeutic or targeted therapeutic agents have an increased overall survival compared to people who receive less. These agents, administered as both first-line or second-line treatments, also led to better overall survival than best supportive care. With the exception of ramucirumab, it remains unclear which other individual agents cause the survival benefit. Although treatment-associated toxicities of grade 3 or more occurred more frequently in arms with an additional chemotherapy or targeted therapy agent, there is no evidence that palliative chemotherapy and/or targeted therapy decrease quality of life. Based on this meta-analysis, palliative chemotherapy and/or targeted therapy can be considered standard care for esophageal and gastroesophageal junction carcinoma.

PLAIN LANGUAGE SUMMARY

Palliative (without intention to cure) chemotherapy and targeted therapies for cancer in the esophagus or gastroesophageal junction

Review question

This review aimed to investigate the effectiveness of adding cytostatic or targeted therapy to supportive care in people with esophageal or gastroesophageal junction cancer.

Background

Esophageal cancer is the eighth most common cancer in the world. Many people are diagnosed only after the disease has spread to other parts of the body, when cure is rarely possible. These people can be treated with palliative chemotherapy or targeted therapy (a drug directed against a specific component of the tumor). The aim of this treatment is to control tumor growth and increase survival, without a significant decrease in quality of life.

Study characteristics

We searched reference lists, biomedical databases (Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, the Web of Science, PubMed Publiher, and Google Scholar), and trial registries up to 13 May 2015. Additional searches were run in September 2017 prior to publication, and they are listed in the 'Studies awaiting assessment' section.

Key results

We identified 41 randomized controlled trials (RCTs) that met our inclusion criteria for inclusion in the review, as well as 49 ongoing studies. This review and meta-analysis shows that people who receive more chemotherapeutic or targeted therapeutic agents live longer and with less disease progression than people who receive best supportive care or less therapy. The only individual agent that more than one study found to improve survival was ramucirumab. We found severe treatment-associated toxicities (grade 3 or above) more frequently in the arms with an additional chemotherapy or targeted therapy agent. However, there is no evidence that palliative chemotherapy and/or targeted therapy decreases quality of life. Our meta-analysis indicates that chemotherapy and targeted therapy are effective palliative treatments for people with esophageal and gastroesophageal junction cancer.

Quality of the evidence

The evidence that more chemotherapeutic or targeted therapeutic agents increase survival is of high quality, as is the evidence for improved survival compared to best supportive care. The evidence for the increased occurrence of severe treatment-related toxicities is of very low quality, while the evidence showing no decrease in quality of life is also low quality.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings table: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone for palliative treatment of esophageal and GE-junction carcinoma

Chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone for palliative treatment of esophageal and GE-junction carcinoma

Patient or population: palliative participants with esophageal and GE-junction carcinoma

Setting: hospital

Intervention: chemotherapy or targeted therapy agent(s) plus control intervention

Comparison: control intervention

Outcome	Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
Overall survival	HR 0.75 (0.68 to 0.84) Median OS 6.7 months in the chemotherapy or targeted therapy agent(s) + control arm versus 5.7 months in the control arm	1347 participants (11 RCTs)	⊕⊕⊕⊕ High	Quality not downgraded. Although participant populations and agents used differ between studies, there is low imprecision and low inconsistency. Cochrane's Q test for heterogeneity showed almost no heterogeneity ($I^2 = 5\%$, $P = 0.50$)
Progression-free survival	HR 0.64 (0.45 to 0.92)	883 participants (5 RCTs)	⊕⊕⊕⊖ Moderate ^a	Cochrane's Q test for heterogeneity showed considerable heterogeneity ($I^2 = 79\%$, $P < 0.001$)
Toxicity	Palliative chemotherapy and/or targeted therapy appear to increase the frequency of treatment-related toxicity of at least grade 3. However, treatment-related deaths did not occur more frequently.	For 3296 participants with esophageal, GE-junction, and gastric cancer (9 RCTs) information was provided on toxicity according to WHO or NCI-CTC guidelines. For at least 1189 participants with esophageal and GE-junction cancer from these trials, toxicity was reported.	⊕⊖⊖⊖ Very low ^b	Small sample size of studies reporting toxicity for the esophageal and GE-junction cancer subgroup separately, for both arms, and with validated methods. Heterogeneity in the relative frequency of toxicities due to palliative chemotherapy and/or targeted therapy.
Quality of life	Quality of life was measured with validated methods in 5 studies included in this analysis. Although the 5 studies were not representative of	For 1870 participants with esophageal, GE-junction, and gastric cancer (5 RCTs), information was provided on quality of	⊕⊖⊖⊖ Very low ^c	Small sample size of studies reporting data for the esophageal and GE-junction cancer subgroup separately whilst using validated methods

all the studies in this analysis, as 4 tested a targeted agent, the quality of life reported improved in the arms with the additional agent.

life. For at least 823 participants with esophageal and GE-junction cancer, quality of life was reported.

CI: confidence interval; **GE:** gastroesophageal; **HR:** hazard ratio; **NCI-CTC:** National Cancer Institute Common Toxicity Criteria; **OS:** overall survival; **RCT:** randomized controlled trial; **WHO:** World Health Organization.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^aDowngraded by one level due to inconsistency.

^bDowngraded by three levels due to small sample size of studies reporting toxicity for the esophageal and GE-junction cancer subgroup separately, for both arms, and with validated methods. Additionally, some studies in general, or for specific toxicities, reported no difference in toxicity, which indicates possible inconsistency.

^cDowngraded by three levels due to lack of studies reporting data for the esophageal and GE-junction cancer subgroup separately whilst using validated methods.

Summary of findings 2. Summary of findings table (sensitivity analysis): interventions esophageal and GE-junction carcinoma versus gastric carcinoma

Sensitivity analysis: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone for palliating esophageal and GE-junction carcinoma versus gastric carcinoma

Patient or population: palliative participants with esophageal and GE-junction carcinoma or gastric carcinoma

Setting: hospital

Intervention: chemotherapy or targeted therapy agent(s) plus control arm

Comparison: control arm

Comparison	Outcome	Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
Studies with gastric cancer participants in addition to eligible participants	Overall survival	HR 0.94 (0.83 to 1.05)	1755 participants (8 RCTs)	It should not be judged independently as it is not meant to be an exhaustive summary of either esophageal, GE-junction, or gastric cancer participant data.	Cochrane's Q test for heterogeneity showed considerable heterogeneity ($I^2 = 54\%$, $P = 0.03$).

Sensitivity analysis, meta-regression analysis, first part	Overall survival	HR 0.75 (0.68 to 0.84) versus HR 0.94 (0.83 to 1.05), P = 0.004 (treatment has a significantly different effect)	1347 participants (11 RCTs) versus 1755 participants (8 RCTs)	⊕⊕⊕⊕ Very low ^a	Cochrane's Q test for heterogeneity showed almost no heterogeneity ($I^2 = 5\%$, $P = 0.50$) in the arm with esophageal and GE-junction cancer participants. Cochrane's Q test for heterogeneity showed considerable heterogeneity ($I^2 = 54\%$, $P = 0.03$) in the arm that included also gastric cancer participants.
Sensitivity analysis, only esophageal and GE-junction cancer participants	Overall survival	HR 0.66 (0.54 to 0.81)	538 participants (5 RCTs)	It should not be judged independently as it is not meant to be an exhaustive summary of either esophageal and GE-junction participant data.	Cochrane's Q test for heterogeneity showed no heterogeneity ($I^2 = 0\%$, $P = 0.56$). This meta-analysis was not meant to be exhaustive with regard to the effect of chemotherapy or targeted therapy in people with esophageal and GE-junction cancer.
Sensitivity analysis, only gastric cancer participants	Overall survival	HR 0.89 (0.76 to 1.04)	2093 participants (5 RCTs)	It should not be judged independently as it is not meant to be an exhaustive summary of gastric cancer participant data.	Cochrane's Q test for heterogeneity showed heterogeneity ($I^2 = 52\%$, $P = 0.08$). This meta-analysis was not meant to be exhaustive with regard to the effect of chemotherapy or targeted therapy in people with gastric cancer.
Sensitivity analysis, meta-regression analysis, second part	Overall survival	HR 0.66 (0.54 to 0.81) versus HR 0.89 (0.76 to 1.04), P = 0.03 (treatment has a significantly different effect)	538 participants (5 RCTs) versus 2093 participants (5 RCTs)	⊕⊕⊕⊕ Moderate ^b	Cochrane's Q test for heterogeneity showed no heterogeneity ($I^2 = 0\%$, $P = 0.56$) in the arm with only GE-junction cancer participants and heterogeneity ($I^2 = 52\%$, $P = 0.08$) in the arm with only gastric cancer participants. This result applies only to GE-junction versus gastric cancer.

CI: confidence interval; **GE:** gastroesophageal; **HR:** hazard ratio; **OS:** overall survival; **RCT:** randomized controlled trial.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^aDowngraded by three levels due to inconsistency in the group of studies with gastric cancer participants besides eligible participants. Additionally, quality was downgraded because the interventions in both groups of studies were not similar, making the comparison indirect.

^bDowngraded by one level due to small sample size (for a meta-regression analysis) and inconsistency of the arm of the meta-regression analysis that contains gastric cancer participants.

Summary of findings 3. Summary of findings table (subcomparison 1): chemotherapy or targeted therapy plus best supportive care (BSC) versus BSC for palliative treatment of esophageal and GE-junction carcinoma

Subcomparison 1: chemotherapy or targeted therapy plus best supportive care (BSC) versus BSC for palliative treatment of esophageal and GE-junction carcinoma

Patient or population: palliative participants with esophageal and GE-junction carcinoma

Setting: hospital

Intervention: chemotherapy or targeted therapy plus BSC

Comparison: BSC

Outcomes	Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
Overall survival	HR 0.81 (0.71 to 0.92) Median OS 4.7 months in the chemotherapy or targeted therapy arm versus 4.2 months in the BSC arm	750 (5 RCTs)	⊕⊕⊕⊕ High	Quality not downgraded. Participant populations and agents used differ between studies. However, there is low imprecision and low inconsistency. Cochrane's Q test for heterogeneity showed almost no heterogeneity ($I^2 = 0\%$, $P = 0.57$), indicating that results of the studies were consistent.
Progression-free survival	HR 0.58 (0.28 to 1.18)	540 (2 RCTs)	⊕⊕⊕⊕ Very low ^a	95% CI includes benefit and harm. Cochrane's Q test for heterogeneity showed considerable heterogeneity ($I^2 = 85\%$, $P = 0.01$).
Toxicity	Palliative chemotherapy and/or targeted therapy appear to increase the frequency of treatment-related toxicity of at least grade 3. However, treatment-related deaths did not occur more frequently.	For 972 participants with esophageal, GE-junction, and gastric cancer (3 RCTs) information was provided on toxicity according to WHO or NCI-CTC guidelines. For at least 632 participants with esophageal and GE-junction cancer from these trials, toxicity was reported.	⊕⊕⊕⊕ Very low ^b	3/5 studies reported on toxicities with validated methods. 1/3 studies reporting on toxicity, reported it for the esophageal and GE-junction cancer subgroup separately, for both arms and with validated methods.
Quality of life	On average, the quality of life reported improved in the arms with the additional agent.	For 1129 participants with esophageal, GE-junction, and gastric cancer (4 RCTs) information was provided on quality of life. For at least 789 participants with	⊕⊕⊕⊕ Very low ^c	4/5 studies reported on quality of life. 2/4 studies reported quality of life separately for the esophageal and GE-junction cancer subgroup.

esophageal and GE-junction cancer, quality of life was reported.

BSC: best supportive care; **CI:** confidence interval; **GE:** gastroesophageal; **HR:** hazard ratio; **NCI-CTC:** National Cancer Institute Common Toxicity Criteria; **OS:** overall survival; **RCT:** randomized controlled trial; **WHO:** World Health Organization.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^aDowngraded by three levels due to very serious imprecision (small sample size, 95% CI includes appreciable benefit and harm) and serious inconsistency.

^bDowngraded by three levels due to non-validated methods used and failure to report toxicities specifically for esophageal and GE-junction cancer patient group.

^cDowngraded by three levels because not all studies reported on quality of life, and not all studies reported quality of life specifically for esophageal and GE-junction cancer patients.

Summary of findings 4. Summary of findings table (subcomparison 2): second-line chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone for palliative treatment of esophageal and GE-junction carcinoma

Subcomparison 2: second-line chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone for palliative treatment of esophageal and GE-junction carcinoma

Patient or population: palliative participants with esophageal and GE-junction carcinoma previously treated with chemotherapy

Setting: hospital

Intervention: chemotherapy or targeted therapy agent(s) plus control arm

Comparison: control arm

Outcomes	Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
Overall survival	HR 0.71 (0.54 to 0.94) Median OS 5.1 months in the chemotherapy or targeted therapy arm versus 4.4 months in the BSC arm	769 participants (4 RCTs)	⊕⊕⊕⊖ Moderate ^a	2 studies investigated the same agent. Cochrane's Q test for heterogeneity showed considerable heterogeneity ($I^2 = 57\%$, $P = 0.07$)
Progression-free survival	HR 0.51 (0.29 to 0.90)	677 participants	⊕⊕⊖⊖ Low ^b	2 studies investigated the same agent. Cochrane's Q test for hetero-

	(3 RCTs)			geneity showed considerable heterogeneity ($I^2 = 86\%$, $P < 0.001$)
Toxicity	Palliative chemotherapy and/or targeted therapy appear to increase the frequency of treatment-related toxicity of at least grade 3. However, treatment-related deaths did not occur more frequently.	For 1638 participants with esophageal, GE-junction, and gastric cancer (4 RCTs) information was provided on toxicity according to WHO or NCI-CTC guidelines. For at least 769 participants with esophageal and GE-junction cancer from these trials toxicity was reported.	⊕⊕⊕⊕ Very low ^c	1/4 studies reported toxicity for the esophageal and GE-junction cancer subgroup separately, for both arms, and with validated methods.
Quality of life	On average, the quality of life reported improved in the arms with the additional agent.	For 1638 participants with esophageal, GE-junction, and gastric cancer (4 RCTs) information was provided on quality of life. For at least 769 participants with esophageal and GE-junction cancer, quality of life was reported.	⊕⊕⊕⊕ Very low ^d	1/4 studies reported quality of life separately for the esophageal and GE-junction cancer subgroup.

CI: confidence interval; **GE:** gastroesophageal; **HR:** hazard ratio; **NCI-CTC:** National Cancer Institute Common Toxicity Criteria; **OS:** overall survival; **RCT:** randomized controlled trial; **WHO:** World Health Organization.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^aDowngraded by one level due to small sample size and inconsistency.

^bDowngraded by two levels due to small sample size and inconsistency.

^cDowngraded by three levels due to the use of non-validated methods and failure to report toxicities specifically for esophageal and GE-junction cancer patient group.

^dDowngraded by three levels because not all studies reported on quality of life, and not all studies reported quality of life specifically for esophageal and GE-junction cancer patients.

Summary of findings 5. Summary of findings table (subcomparison 3): chemotherapy agent(s) plus control intervention versus control intervention alone for palliative treatment of esophageal and GE-junction carcinoma

Subcomparison 3: chemotherapy agent(s) plus control intervention versus control intervention alone for palliative treatment of esophageal and GE-junction carcinoma

Patient or population: palliative participants with esophageal and GE-junction carcinoma

Setting: hospital

Intervention: chemotherapy agent(s) plus control arm

Comparison: control arm

Outcome	Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
Overall survival	HR 0.73 (0.63 to 0.85) Median OS 6.9 months in the chemotherapy + control arm versus 5.8 months in the control arm.	358 participants (5 RCTs)	⊕⊕⊕⊖ Moderate ^a	There is low imprecision and low inconsistency. Cochrane's Q test for heterogeneity showed low heterogeneity ($I^2 = 0\%$, $P = 0.50$).
Progression-free survival	No data on progression-free survival was available for this comparison.			
Toxicity	Palliative chemotherapy and/or targeted therapy appear to increase the frequency of treatment-related toxicity of at least grade 3. However, treatment-related deaths did not occur more frequently.	For 1638 participants with esophageal, GE-junction, and gastric cancer (4 RCTs) information was provided on toxicity according to WHO or NCI-CTC guidelines. For at least 769 participants with esophageal and GE-junction cancer from these trials toxicity was reported.	⊕⊖⊖⊖ Very low ^b	1/4 studies reported toxicity for the esophageal and GE-junction cancer subgroup separately, for both arms, and with validated methods.
Quality of life	On average, the quality of life reported improved in the arms with the additional agent.	For 450 participants with esophageal and GE-junction cancer, quality of life was reported.	⊕⊖⊖⊖ Very low ^c	4/5 studies reported on quality of life. 1/4 studies reported quality of life separately for the esophageal and GE-junction cancer subgroup.

CI: confidence interval; **GE:** gastroesophageal; **HR:** hazard ratio; **NCI-CTC:** National Cancer Institute Common Toxicity Criteria; **OS:** overall survival; **RCT:** randomized controlled trial; **WHO:** World Health Organization.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^aDowngraded by one level due to small sample size.

^bDowngraded by three levels due to the use of non-validated methods and failure to report toxicities specifically for esophageal and GE-junction cancer patient group.

^cDowngraded by three levels because not all studies reported on quality of life, and not all studies reported quality of life specifically for esophageal and GE-junction cancer patients.

Summary of findings 6. Summary of findings table (subcomparison 4): targeted therapy agent plus control intervention versus control intervention alone for palliative treatment of esophageal and GE-junction carcinoma

Subcomparison 4: targeted therapy agent plus control intervention versus control intervention alone for palliative treatment of esophageal and GE-junction carcinoma

Patient or population: palliative participants with esophageal and GE-junction carcinoma

Setting: hospital

Intervention: targeted therapy agent plus control arm

Comparison: control arm

Outcome	Comparison	Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
Overall survival	Subcomparison 4, targeted therapy	HR 0.75 (0.63 to 0.90) Median OS 6.7 months in the targeted therapy agent(s) + control arm versus 5.7 months in the control arm	989 participants (6 RCTs)	⊕⊕⊕⊕ High	Quality not downgraded. Participant populations and agents used differ between studies. However, there is low imprecision and low inconsistency. Cochrane's Q test for heterogeneity showed low heterogeneity ($I^2 = 24\%$, $P = 0.25$).
	Subcomparison 4a, EGFR-targeting agents	HR 0.86 (95% CI 0.73 to 1.01)	655 participants (3 RCTs)	⊕⊕⊕⊖ Moderate ^a	Cochrane's Q test for heterogeneity showed low heterogeneity ($I^2 = 0\%$, $P = 0.56$).
	Subcomparison 4b, cetuximab	HR 0.76 (95% CI 0.55 to 1.04)	206 participants (2 RCTs)	⊕⊕⊖⊖ Low ^b	95% CI includes benefit and harm. Cochrane's Q test for heterogeneity showed low heterogeneity ($I^2 = 0\%$, $P = 0.58$).
	Subcomparison 4c, ramucirumab	HR 0.62 (0.43 to 0.88)	228 participants (2 RCTs)	⊕⊕⊕⊖ Moderate ^a	Cochrane's Q test for heterogeneity showed low heterogeneity ($I^2 = 28\%$, $P = 0.24$).
Progression-free survival	Subcomparison 4, targeted therapy	HR 0.64 (0.45 to 0.92)	883 participants (5 RCTs)	⊕⊕⊕⊖ Moderate ^c	Cochrane's Q test for heterogeneity showed low heterogeneity ($I^2 = 79\%$, $P < 0.001$).
	Subcomparison 4a, EGFR-targeting agents	HR 0.85 (0.73 to 1.00)	655 participants (3 RCTs)	⊕⊕⊖⊖ Low ^b	95% CI includes benefit and lack of effect. Cochrane's Q test for heterogeneity showed low heterogeneity ($I^2 = 2\%$, $P = 0.36$).
	Subcomparison 4b, cetuximab	HR 0.90 (0.59 to 1.37)	206 participants (2 RCTs)	⊕⊖⊖⊖ Very low ^d	95% CI includes benefit and harm. Cochrane's Q test for heterogeneity showed

					a moderate amount of heterogeneity ($I^2 = 53\%$, $P = 0.14$). One of the two studies was not blinded and did not use an independent review board.
	Subcomparison 4c, ramucirumab	HR 0.39 (0.28 to 0.54)	228 participants (2 RCTs)	⊕⊕⊕⊖ Moderate ^a	Cochrane's Q test for heterogeneity showed low heterogeneity ($I^2 = 0\%$, $P = 0.99$).
Toxicity	Subcomparison 4, targeted therapy	Palliative chemotherapy and/or targeted therapy appear to increase the frequency of treatment-related toxicity of at least grade 3. However, treatment-related deaths did not occur more frequently.	For 3020 participants with esophageal, GE-junction, and gastric cancer (6 RCTs) information was provided on toxicity according to WHO or NCI-CTC guidelines. For at least 990 participants with esophageal and GE-junction cancer from these trials toxicity was reported.	⊕⊖⊖⊖ Very low ^e	2/6 studies reported toxicity for the esophageal and GE-junction cancer subgroup separately, for both arms and with validated methods.
Quality of life	Subcomparison 4, targeted therapy	On average, the quality of life reported improved in the arms with the additional agent.	For 2054 participants with esophageal, GE-junction, and gastric cancer (4 RCTs) information was provided on quality of life. For at least 784 participants with esophageal and GE-junction cancer, quality of life was reported.	⊕⊖⊖⊖ Very low ^f	4/6 studies reported on quality of life. 1/4 studies reported quality of life separately for the esophageal and GE-junction cancer subgroup.

CI: confidence interval; **EGFR:** epidermal growth factor receptor; **GE:** gastroesophageal; **HR:** hazard ratio; **NCI-CTC:** National Cancer Institute Common Toxicity Criteria; **OS:** overall survival; **RCT:** randomized controlled trial; **WHO:** World Health Organization.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^aDowngraded by one level due to small sample size.

^bDowngraded by two levels due to small sample size and imprecision.

^cDowngraded by one level due to inconsistency.

^dDowngraded by three levels due to small sample size and imprecision.

^eDowngraded by three levels due to use of non-validated methods and failure to report toxicities specifically for esophageal and GE-junction cancer patient group.

^fDowngraded by three levels because not all studies reported on quality of life, and not all studies reported quality of life specifically for esophageal and GE-junction cancer patients.

Summary of findings 7. Summary of findings table (subcomparison 5): chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone in participants with AC of the esophagus

Subcomparison 5: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone in participants with AC of the esophagus

Patient or population: palliative participants with AC of the esophagus

Setting: hospital

Intervention: chemotherapy or targeted therapy plus BSC

Comparison: BSC

Outcomes	Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
Overall survival	HR 0.66 (0.54 to 0.81) Median OS 7.1 months in the chemotherapy or targeted therapy arm versus 6.0 months in the BSC arm	538 (5 RCTs)	⊕⊕⊕⊕ High	Quality not downgraded. Participant populations and agents used differ between studies. However, there is low imprecision and low inconsistency. Cochrane's Q test for heterogeneity showed almost no heterogeneity ($I^2 = 0\%$, $P = 0.55$), indicating that results of the studies were consistent.
Progression-free survival	HR 0.62 (0.38 to 1.00)	713 (4 RCTs)	⊕⊕⊕⊕ Very low ^a	95% CI includes benefit and no effect. Cochrane's Q test for heterogeneity showed considerable heterogeneity ($I^2 = 84\%$, $P < 0.001$).
Toxicity	Palliative chemotherapy and/or targeted therapy appear to increase the frequency of treatment-related toxicity of at least grade 3. However, treatment-related deaths did not occur more frequently.	For 2676 participants with esophageal, GE-junction, and gastric cancer (5 RCTs) information was provided on toxicity according to WHO or NCI-CTC guidelines. For at least 570 participants with esophageal and GE-junction cancer from these trials, toxicity was reported.	⊕⊕⊕⊕ Very low ^b	0/5 studies reported toxicity for the esophageal and GE-junction cancer subgroup separately, for both arms, and with validated methods.

Quality of life	On average, the quality of life reported improved in the arms with the additional agent.	For 1772 participants with esophageal, GE-junction, and gastric cancer (4 RCTs) information was provided on quality of life. For at least 426 participants with esophageal and GE-junction cancer, quality of life was reported.	⊕⊕⊕⊕ Very low ^c	4/5 studies reported on quality of life. 0/4 studies reported quality of life separately for the esophageal and GE-junction cancer subgroup.
------------------------	--	--	--------------------------------------	--

AC: adenocarcinoma; **BSC:** best supportive care; **CI:** confidence interval; **HR:** hazard ratio; **NCI-CTC:** National Cancer Institute Common Toxicity Criteria; **OS:** overall survival; **RCT:** randomized controlled trial; **WHO:** World Health Organization.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^a Downgraded three levels due to very serious imprecision (95% CI includes appreciable benefit and no effect) and serious inconsistency.

^b Downgraded by three levels due to use of non validated methods and failure to report toxicities, specifically for esophageal and GE-junction cancer patient group.

^c Downgraded by three levels because not all studies reported on quality of life, and not all studies reported quality of life specifically for esophageal and GE-junction cancer patients.

Summary of findings 8. Summary of findings table (subcomparison 6): chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone in participants with SCC of the esophagus

Subcomparison 6: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone in participants with SCC of the esophagus

Patient or population: palliative participants with SCC of the esophagus

Setting: hospital

Intervention: chemotherapy or targeted therapy plus BSC

Comparison: BSC

Outcomes	Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
Overall survival	HR 0.76 (95% CI 0.65 to 0.90) Median OS 8.0 months in the chemotherapy or targeted thera-	268 (4 RCTs)	⊕⊕⊕⊕ High	Quality not downgraded. Participant populations and agents used differ between studies. However, there is low imprecision and low inconsistency. Cochrane's Q test for heterogeneity showed almost no hetero-

	py arm versus 6.5 months in the BSC arm.			geneity ($I^2 = 0\%$, $P = 0.95$), indicating that results of the studies were consistent.
Progression-free survival	HR 0.72 (95% CI 0.55 to 0.96)	168 (2 RCTs)	⊕⊕⊕⊕ Very low ^a	Cochrane's Q test for heterogeneity showed significant heterogeneity ($I^2 = 0\%$, $P = 0.97$), indicating that results of the 2 studies were not consistent. One of the 2 studies was not blinded and did not use an independent review board.
Toxicity	Palliative chemotherapy and/or targeted therapy appear to increase the frequency of treatment-related toxicity of at least grade 3. However, treatment-related deaths did not occur more frequently.	For 150 participants with esophageal and GE-junction cancer (2 RCTs) information was provided on toxicity according to WHO or NCI-CTC guidelines.	⊕⊕⊕⊕ Very low ^b	2/4 studies reported on toxicities with validated methods. 2/2 studies reporting toxicity for the esophageal and GE-junction cancer subgroup separately, for both arms, and with validated methods.
Quality of life	On average, the quality of life reported improved in the arms with the additional agent.	For 156 participants with esophageal and GE-junction cancer (1 RCT) information was provided on quality of life.	⊕⊕⊕⊕ Very low ^c	1/4 studies reported on quality of life.

BSC: best supportive care; **CI:** confidence interval; **GE:** gastro-esophageal; **HR:** hazard ratio; **NCI-CTC:** National Cancer Institute Common Toxicity Criteria; **OS:** overall survival; **RCT:** randomized controlled trial; **SCC:** squamous cell carcinoma; **WHO:** World Health Organization.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^aDowngraded by two levels due to small sample size, and one level due lack of blinding or use of an independent review board.

^bDowngraded by three levels due to use of non-validated methods and failure to report toxicities specifically for esophageal and GE-junction cancer patient group.

^cDowngraded by three levels because not all studies reported on quality of life, and not all studies reported quality of life specifically for esophageal and GE-junction cancer patients.

BACKGROUND

See [Appendix 1](#) for a glossary of key terms.

Description of the condition

Epidemiology

Esophageal cancer is the eighth most common cancer worldwide ([Arnold 2015](#)), with approximately 398,000 people diagnosed with squamous cell carcinoma (SCC) and 52,000 with adenocarcinoma in 2012. This corresponds with incidence rates of 5.2 and 0.7 per 100,000 population, respectively. Adenocarcinomas develop from metaplastic Barrett mucosa located in the lower esophagus, while SCC develops from the squamous epithelium ([Enzinger 2003](#)). Both histological types have dysplasia as their precursor. Recent epidemiological data indicate that 79% of SCCs worldwide occur in Southeastern and Central Asia, whereas 46% of people with adenocarcinomas are diagnosed in Northern and Western Europe, North America, and Oceania. In general, incidence of esophageal cancer is higher in men than in women, especially in adenocarcinoma, for which the male to female ratio is 4.4:1, compared to 2.7:1 for SCC ([Arnold 2015](#)). In the past few decades, developed countries have seen an increase in the incidence of adenocarcinoma ([Edgren 2013](#)), attributed to the higher prevalence of obesity. On the other hand, the decreasing incidence of SCC in these contexts correlates with the decline in smoking ([Cook 2009](#)). SCC remains most common in low- and middle-income countries, including in Africa and Eastern Asia ([Lin 2013](#); [Ocamo 2008](#); [Somdya 2010](#); [White 2009](#)). Almost half of people with esophageal carcinoma have distant disease at the time of diagnosis ([Howlader 2014](#)).

Prognosis and management options

Endoscopic therapy may be an option for early oesophageal cancers, but a Cochrane Review found no randomized controlled trials (RCTs) comparing management options for this early stage ([Bennett 2012](#)). Surgical resection is the potentially curative treatment for esophageal cancer, but it is only feasible in people who are fit for surgery, have locally resectable disease, and show no signs of distant metastases. Unfortunately, most people develop recurrent tumor growth within the first few years after surgery. Palliative care is the only option for metastatic disease, with a five-year survival rate of less than three per cent ([Hur 2013](#)). Palliative therapy aims to control tumor growth and increase survival without significantly decreasing quality of life.

Description of the intervention

In daily practice, clinicians often offer palliative chemotherapy to control tumor growth, increase quality of life, and increase life expectancy. Clinicians have the option to choose from cytostatic therapy, which is directed at fast dividing cells in general, or from targeted therapies directed against specific molecules needed for carcinogenesis and tumor growth. The most extensively used agents for this disease are 5-fluorouracil (5-FU) and cisplatin, which are included in most combination chemotherapy regimens. However, the chemotherapy agents used in RCTs are very heterogeneous. Researchers have examined targeted therapies as palliative treatment for a decade ([Lorenzen 2009](#)). People treated with these anti-neoplastic agents experience fewer side effects compared to people treated with classic cytotoxic chemotherapies. The most common targets studied are the epidermal growth factor

receptor (EGFR) and the vascular endothelial growth factor receptor two (VEGFR2). Most targeted therapies studied are monoclonal antibodies, except for the tyrosine kinase inhibitor, gefitinib ([Dutton 2014](#)).

Why it is important to do this review

Palliative chemotherapy and/or targeted therapies are widely accepted treatment options. However, except for ramucirumab, evidence for the efficacy of palliative treatment for esophageal and gastroesophageal cancer is lacking. To assess whether a benefit exists, there is a need for large randomized studies assessing the effects of chemotherapy or targeted therapy for treating people with esophageal and GE-junction cancer with palliative intent. In a randomized gastric cancer study, [Thuss-Patience 2011](#) reported that accrual for first-line studies is very difficult because most people refuse randomization, so new data from large randomized studies investigating first-line chemotherapy or targeted therapy versus best supportive care (BSC) will probably not become available. On the other hand, interesting new data have become available regarding targeted therapies and second-line therapies. Due to the limited availability of relevant data, summarizing the available evidence could increase insight into whether chemotherapy and targeted therapies are justifiably being prescribed to people with advanced or metastatic esophageal or gastroesophageal (GE)-junction cancer.

We have chosen to construct the main meta-analysis in a way that summarizes the largest number of studies. The downside of this approach is the heterogeneity of the included studies in terms of intervention and participant groups. Because this approach complicates the straightforward translation of results to individuals, we performed subgroup analyses wherever possible to investigate whether the overall result was consistent across subsets of treatments and participants.

OBJECTIVES

To assess the effects of cytostatic or targeted therapy for treating esophageal or gastroesophageal junction cancer with palliative intent.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs with or without blinding. We included abstracts that met the inclusion criteria and that reported data on review outcomes as studies awaiting classification. If the abstract was a study protocol, we included it as an ongoing study.

We excluded all non-randomized and quasi-randomized studies, as we considered they did not provide sufficiently high-quality evidence.

Types of participants

People with advanced (T3-T4NxM0 non-resectable; and all TxNxM1), recurrent, or metastatic carcinoma of the esophagus and GE-junction. We included only studies involving participants with advanced or non-resectable disease who received chemotherapy with palliative intent. We did not consider studies including participants receiving chemotherapy for locally advanced cancer

in order to assess resectability. We included people with both SCC and adenocarcinoma, as well as people who had received prior chemotherapy.

We included in the qualitative synthesis studies involving only a subset of eligible participants, for instance studies including participants with both GE-junction cancer and gastric cancer, if they described the results for GE-junction cancer separately and included at least 15 eligible participants. We evaluated these studies for inclusion in the quantitative synthesis under certain circumstances (see [Sensitivity analysis](#)).

Types of interventions

We included treatments with systemic intravenous and single oral chemotherapy or targeted therapy, as well as combination regimens in all doses and schedules. We defined 'control arm' as BSC or treatment with at least one chemotherapy agent whose composition, dose, and schedule were equal in both arms. Dose-defining RCTs were not eligible for this review. Chemotherapy encompassed all cytotoxic and anti-neoplastic drug treatment, and targeted therapy encompasses all anti-neoplastic drug treatment targeting a specific protein or small group of proteins. We did not consider combined radiochemotherapy or radio-targeted therapy interventions for this review.

Our main comparison was chemotherapy or targeted therapy agent(s) plus any control intervention versus control intervention alone. We also performed a sensitivity analysis to assess the effect of the intervention in people with esophageal and GE-junction cancer versus gastric cancer.

Finally, we performed several subgroup analyses.

- a. Chemotherapy or targeted therapy plus BSC versus BSC.
- b. Effect of intervention in participants who had received previous chemotherapy (versus control intervention alone).
- c. Chemotherapeutic agent plus control intervention versus control intervention alone.
- d. Targeted therapeutic agent plus control intervention versus control intervention alone.
 - i. Epidermal growth factor receptor (EGFR)-targeting agent plus control intervention versus control intervention alone.
 - ii. Cetuximab plus control intervention versus control intervention alone.
 - iii. Ramucirumab plus control intervention versus control intervention alone.
- e. Chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone in people with adenocarcinoma of the esophagus.
- f. Chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone in people with SCC of the esophagus.

Types of outcome measures

We did not use the outcome measures mentioned below as inclusion criteria but as a list of outcome measures of interest to this review.

Primary outcomes

Median overall survival (OS) (time to death) and hazard ratio (HR) with 95% confidence interval (CI).

Secondary outcomes

- Median progression-free survival (PFS) (time to disease progression and/or death) and HR with 95% CI.
- Toxicity (type, severity, and percentage of acute and chronic toxic effect, including toxic death), classified according to World Health Organization (WHO) or National Cancer Institute Common Toxicity Criteria (NCI-CTC). The focus was on toxicities of grade 3 or higher. Grade 3 toxicities are described in the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 as "severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living" ([Common Toxicity Criteria 4.0](#)).
- Quality of life (including all validated outcome measures).

Search methods for identification of studies

Electronic searches

We identified records by searching the following electronic databases using the search strategies detailed in the appendices.

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 9) in the Cochrane Library (searched 19 September 2017; [Appendix 2](#)).
2. MEDLINE (1950 to 19 September 2017; [Appendix 3](#)).
3. Embase (1980 to 19 September 2017; [Appendix 4](#)).
4. Web of Science (1900 to 19 September 2017; [Appendix 5](#)).
5. Pubmed Publisher (1950 to 19 September 2017; [Appendix 6](#)).
6. Google Scholar (1592 to 19 September 2017; [Appendix 7](#)).
7. [Clinicaltrials.gov](#) (searched 19 September 2017; [Appendix 8](#)).
8. WHO International Clinical Trials Registry Platform (ICTRP) (searched 19 September 2017; [Appendix 9](#)).

We constructed the search strategy by applying a sensitivity maximizing approach, using a combination of MeSH subject headings and text words related to chemotherapy or targeted therapy with a palliative intent for cancer of the esophagus and GE-junction. We adapted the MEDLINE search strategy for use in the other databases. We did not confine the search to English-language publications. We placed studies identified after the search of 13 May 2015 in 'Studies awaiting classification' or 'Ongoing studies'. In the next version of the review, we will screen these and incorporate them as appropriate.

Searching other resources

We handsearched reference lists from studies included in the qualitative assessment to identify further relevant studies. Additionally, within the retrieved records, we identified and selected reviews based on title and abstract, extracting relevant references and including them as retrieved records.

Data collection and analysis

Selection of studies

Two review authors (VJ, MS) independently scanned the title and abstract of every record retrieved during the search. If the information given suggested that the RCT included participants with advanced (T3-T4NxM0 non-resectable; and all TxNxM1), recurrent, or metastatic carcinoma of the esophagus or GE-junction and used random allocation to generate the comparison groups, or if there was any doubt regarding these criteria, we retrieved the full text for detailed assessment. We resolved differences in data extraction through discussion.

Data extraction and management

Two review authors (VJ, MS) independently extracted details on study population, interventions, and outcomes by using a standardized data extraction form, which included the following items.

- General information: title, authors, source, contact address, country, publication status, full paper/abstract, language, and year of publication.
- Study characteristics: design, allocation concealment, blinding, number of arms, phase, and duration of follow-up.
- Participants: inclusion and exclusion criteria, sample size, baseline characteristics, similarity of groups at baseline, dropouts described, and ITT performed.
- Intervention: which comparison was performed, type, dose, route, and schedule of drug administration.
- Outcomes: as specified above: median OS and PFS, HRs and their 95% CIs, toxicity, and quality of life.

We contacted authors of all eligible studies to provide us with individual participant data.

Assessment of risk of bias in included studies

Two review authors (VJ, MS) independently assessed the risk of bias and the quality of the eligible studies according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). In case of disagreements, they consulted a third review author to reach consensus. We extracted data using the assessment form designed for this review.

We assessed each study taking into account the following points (Higgins 2011; Jadad 1996).

- Was the allocation random?
- Was the concealment of treatment allocation adequate?
- Was the study blinded?
- Was there selective reporting?
- Were the groups similar at baseline?
- Were the number of withdrawals, dropouts, and losses to follow-up described?
- Was intention-to-treat analysis performed?

We rated each study as being at low, high, or unclear risk of bias for these domains.

We defined baseline comparability as follows: we considered the most important prognostic factors to be tumor stage

(advanced versus metastatic disease), performance index (Eastern Cooperative Oncology Group (ECOG) status 0 to 1 versus 2 to 3), and the number of organs involved in metastatic disease (one versus more than one). We considered a difference of more than 15% between study arms to be clinically relevant. For the median age of participants in treatment arms, we considered baseline differences of five years to be clinically relevant.

We defined intention-to-treat analysis as either randomized analysis restricted to participants who received at least one cycle of chemotherapy or targeted therapy and for which survival data were available, or methodologies that included all participants at randomization in the analysis.

Measures of treatment effect

We extracted or directly or indirectly estimated HRs and 95% CIs from the given data in each included study (Altman 2001). If we could not extract the data directly from the text, we determined them indirectly. For example, we estimated HRs from ratios of median survival times, from observed to expected event ratios and from time point survival ratios (Machin 1997; Parmar 1998). Sometimes, we had to read these ratios from a Kaplan-Meier graph provided in the paper. We extracted median overall and progression-free survival times if available.

Dealing with missing data

Where studies did not report outcomes directly, we calculated them if possible (see [Measures of treatment effect](#)) and reported them narratively if not.

Assessment of heterogeneity

For each data synthesis, we calculated pooled estimates of effect and investigated results for statistical heterogeneity. We assessed forest plots for heterogeneity by visual inspection. To quantify inconsistency across studies, we calculated the I^2 statistic as $[(Q - df) / Q] \times 100\%$, where Q is the χ^2 statistic and df its degrees of freedom. See also [Sensitivity analysis](#).

Assessment of reporting biases

We assessed small study effects such as publication bias in a qualitative manner using a funnel plot if enough studies were present (i.e. at least 10).

Data synthesis

In the meta-analyses, we aimed to combine data from different RCTs reporting similar comparisons. Therefore, only RCTs in which treatments were added to BSC or a control arm were included. Given the amount of variation in the interventions studied in the included studies, we calculated pooled estimates of effect using an inverse variance random-effects model for the meta-analyses. We did not include all studies in the quantitative synthesis. Under [Included studies](#), subheading 'Interventions', we give a summary of which agents are included in the analyses.

We synthesized data on OS and PFS in meta-analyses, and we summarized data on toxicity and quality of life. We present the results on toxicity and quality of life narratively for the main comparison but not for the subcomparisons.

Subgroup analysis and investigation of heterogeneity

For the main objective, we identified six subcomparisons. In subcomparison 1, we investigated chemotherapy or targeted therapy plus BSC versus BSC alone. In subcomparison 2, we investigated the effect of the intervention for second-line chemotherapy or targeted therapy. For subcomparison 3, we included only interventions with a chemotherapy drug. For subcomparison 4, we included only interventions with a targeted therapy agent. For subcomparison four, we identified three further subgroups. The first subgroup, 4a, consisted of studies that investigated regimens containing EGFR-targeting agents versus those containing a non-EGFR-targeting agent. The second subgroup, 4b, consisted of studies that investigated cetuximab versus non-cetuximab containing regimens. The third subgroup, 4c, consisted of studies that investigated regimens that contained ramucirumab versus those that did not. In subcomparison 5, we investigated chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone in people with adenocarcinoma of the esophagus. In subcomparison 6, we assessed the same comparison for people with SCC of the esophagus.

Sensitivity analysis

A potential effect modifier in the meta-analyses was the inclusion of studies that included participants with gastric cancer. If the effect of the interventions investigated in the included studies were similar for both participants with esophageal or GE-junction cancer versus participants with gastric cancer, it would have been reasonable to include studies involving participants with any of these cancers and which did not report results separately for these groups. Thereto, we investigated eligibility for inclusion into the quantitative synthesis by assessing the effect of the interventions on both the esophageal and GE-junction versus the gastric cancer subgroups. We compared all studies included in the meta-analysis of the main comparison for OS (including only esophageal and GE-junction) to a group of studies that had included participants with esophageal, GE-junction, and gastric cancer, through a random-effects meta-

regression analysis using the R statistical computing software ([R 2014](#)). In this meta-regression analysis, the interventions in both groups of studies were not similar. Therefore, we performed a second meta-regression analysis that focused on studies reporting the effect of the intervention on OS for esophageal and GE-junction cancer groups and gastric cancer groups separately. If non-significant heterogeneity existed between the two groups of participants, we included studies containing a subset of eligible participants for the main analysis.

Summary of findings tables

We used the GRADE system to assess the quality of evidence for each analysis ([Guyatt 2008](#)), presenting our assessments in 'Summary of findings' tables using Review Manager 5 ([RevMan 2014](#)). The GRADE system describes the quality of evidence based on how confident the authors are that an estimate of effect reflects the comparison being assessed. The quality of evidence considers study limitations, inconsistent results, indirectness of evidence, imprecision, and publication bias. We present the synthesized data and these assessments in 'Summary of findings' tables, using Review Manager 5 ([RevMan 2014](#)).

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#); [Characteristics of ongoing studies](#).

Results of the search

We retrieved 5786 unique records and excluded 5571 after screening title and abstract. We excluded 69 (see [Excluded studies](#) and [Figure 1](#)). The quantitative synthesis includes 41 studies. We added a total of 46 and 49 potential new studies of interest to a list of 'Studies awaiting classifications' and 'Ongoing studies', respectively. We will assess these and incorporate as appropriate in the next version of this review.

Figure 1. Study flow diagram: review update

Figure 1. (Continued)

Included studies

Eleven studies in 1347 participants contributed data to the meta-analysis of the main comparison: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone. For more details about the included studies, see [Characteristics of included studies](#). We performed six subcomparisons, described below.

Participants

The median age of participants in the population included in the meta-analyses was 60 years (range 53 to 72 years). The proportion of participants reported as having metastatic disease ranged from 69% in [Al-Batran 2013](#) to 100% in [Nicolaou 1982](#). We could not extract the percentage of people with metastasis in 5 out of 19 studies included in the meta-regression analyses. For information on individual studies, see [Characteristics of included studies](#).

With regard to baseline differences, we saw a five-year difference in median age between the study arms in one trial ([Rao 2010](#)). In another, the proportion of the metastatic sites involved per participant was not similar at baseline: 29% of participants in the intervention group had one site involved, compared to 58% in the BSC group ([Thuss-Patience 2011](#)). Performance status was well balanced in all studies, with no differences greater than 15% between study arms. The percentage of participants with ECOG-2 or -3 was in the range of 0% to 35%.

Seven studies included in the meta-analyses took place completely or partially in Asia ([Bang 2010](#); [Fuchs 2014](#); [Huang 2009](#); [Lordick 2013](#); [Ohtsu 2011](#); [Shen 2014](#); [Wilke 2014](#); [Xu 2013a](#)). One study was translated from Chinese ([Huang 2009](#)).

Two studies selected participants based on biomarker expression. The effect of a targeted therapeutic can be expected to depend on the presence of the target in the tumor. The first included only EGFR-positive participants ([Lorenzen 2009](#)). The second included only participants that were eligible if their tumor samples, stained with HER2, were scored as 3 or more on immunohistochemistry or if they tested positive using fluorescent in situ hybridization (FISH) analysis (HER2:CEP17 ratio ≥ 2) ([Bang 2010](#)). The results of

these studies cannot be extrapolated to people that do not have biomarker expression as defined by these studies.

Comparisons

Main comparison

Eleven studies contributed data to the meta-analysis for the main comparison: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone in people with esophageal and GE-junction cancer. Trials used the following agents: 5-FU ([Bleiberg 1997](#)), 5-FU and cisplatin ([Levard 1998](#)), cetuximab ([Lordick 2013](#); [Lorenzen 2009](#)), cyclophosphamide and doxorubicin ([Nicolaou 1982](#)), docetaxel ([Ford 2014](#)), gefitinib ([Dutton 2014](#)), ramucirumab ([Fuchs 2014](#); [Wilke 2014](#)), Shenyi Capsule ([Huang 2009](#)), and trastuzumab ([Bang 2010](#)). Six studies were first-line therapy regimens ([Bang 2010](#); [Bleiberg 1997](#); [Levard 1998](#); [Lordick 2013](#); [Lorenzen 2009](#); [Nicolaou 1982](#)), one was a mixed therapy ([Huang 2009](#)), and the others were second-line treatments. Three studies were included in the main comparison but did not provide enough detail for inclusion in the meta-analysis ([Eatock 2013](#); [Wilkes 2011](#); [Xu 2013a](#)).

Sensitivity analysis

We compared the effect of the intervention in the studies of the main comparison to the effect of intervention in the studies that also included gastric cancer participants. These studies investigated: bevacizumab ([Ohtsu 2011](#); [Shen 2014](#)), cetuximab ([Richards 2013](#)), docetaxel ([Al-Batran 2013](#)), irinotecan ([Thuss-Patience 2011](#)), matuzumab ([Rao 2010](#)), mitomycin ([Tebbutt 2002](#)), and rilotumumab ([Iveson 2014](#)). Six studies were first-line therapies ([Al-Batran 2013](#); [Iveson 2014](#); [Ohtsu 2011](#); [Rao 2010](#); [Shen 2014](#); [Tebbutt 2002](#)), and two were mixed or unclear ([Richards 2013](#); [Thuss-Patience 2011](#)). The subsequent meta-regression analysis focused on studies that reported the effectiveness of the intervention for GE-junction and gastric cancer participants separately. We made a direct comparison with regard to the effectiveness of treatment on these two subgroups in five studies: [Bang 2010](#) (trastuzumab), [Ford 2014](#) (docetaxel), [Fuchs 2014](#) (ramucirumab), [Lordick 2013](#) (cetuximab), and [Wilke 2014](#) (ramucirumab). Two studies focused on first-line therapy regimens ([Bang 2010](#); [Lordick 2013](#)), and three used second-line therapies

(Ford 2014; Fuchs 2014; Wilke 2014). SCCs were not included in any of these studies.

Subcomparison 1

Five studies investigated chemotherapy or targeted therapy plus BSC versus BSC, using the following agents: cyclophosphamide plus doxorubicin (Nicolaou 1982), 5-FU plus cisplatin (Levard 1998), docetaxel (Ford 2014), ramucirumab (Fuchs 2014), and gefitinib (Dutton 2014). Two studies were first-line therapy regimens (Nicolaou 1982; Levard 1998), and the others were second-line regimens.

Subcomparison 2

Four studies investigated second-line therapy regimens. Dutton 2014 investigated gefitinib in participants with progression after chemotherapy and excluded participants receiving either cytotoxic chemotherapy, immunotherapy, hormonal therapy, or radiotherapy to the site of measurable or evaluable disease within the four weeks prior to inclusion. Ford 2014 investigated docetaxel in a participant population with documented disease progression during or within six months of treatment with platinum and fluoropyrimidine-based treatment. These participants were not allowed to have had previous chemotherapy with a taxane. Fuchs 2014 investigated ramucirumab in a participant population with disease progression either within four months of the last dose of first-line platinum-containing or fluoropyrimidine-containing chemotherapy for metastatic disease, or within six months of the last dose of platinum-containing or fluoropyrimidine-containing adjuvant treatment. Wilke 2014 investigated ramucirumab with participants that had disease progression during or within four months of the last dose of first-line platinum and fluoropyrimidine doublet.

Subcomparison 3

Five studies compared a chemotherapy agent(s) plus control intervention versus control intervention, using the following agents: 5-FU (Bleiberg 1997), 5-FU plus cisplatin (Levard 1998), docetaxel (Ford 2014), cyclophosphamide plus doxorubicin (Nicolaou 1982), and Shenyi Capsule (Huang 2009). Three studies were first-line therapy regimens (Bleiberg 1997; Levard 1998; Nicolaou 1982), one used mixed therapies (Huang 2009), and one a second-line regimen (Ford 2014). One study included in the subcomparison did not provide enough detail for inclusion in the meta-analysis (Wilkes 2011).

Subcomparison 4

Six studies compared a targeted therapeutic agent plus control intervention versus control intervention alone, testing the following agents: cetuximab (EGFR) (Lordick 2013; Lorenzen 2009), gefitinib (tyrosine kinase inhibitor for EGFR) (Dutton 2014), ramucirumab (VEGFR2) (Fuchs 2014; Wilke 2014), and trastuzumab (HER2) (Bang 2010). Three studies focused on first-line regimens (Bang 2010; Lordick 2013; Lorenzen 2009), and the others used second-line therapies. One study was included in the subcomparison but did not provide enough detail for inclusion in the meta-analysis (Xu 2013a).

Subgroup 4a. Three studies investigated EGFR-targeting agents plus control intervention versus control intervention alone (Dutton 2014; Lordick 2013; Lorenzen 2009). Two studies were first-line therapies (Lordick 2013; Lorenzen 2009), and one was a second-line

regimen (Dutton 2014). One study was included in the subgroup but did not provide enough detail for inclusion in the meta-analysis (Xu 2013a).

Subgroup 4b. Two studies investigated the EGFR-targeting agent cetuximab plus control intervention versus control intervention alone, both with first-line therapy regimens (Lordick 2013; Lorenzen 2009).

Subgroup 4c. Two studies compared VEGFR2-targeting agent ramucirumab plus control intervention versus control intervention alone, both with second-line therapies (Fuchs 2014; Wilke 2014).

Subcomparison 5

Five studies investigated chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone in participants with adenocarcinoma of the esophagus, using the following agents: trastuzumab (Bang 2010), docetaxel (Ford 2014), ramucirumab (Fuchs 2014), cetuximab (Lordick 2013), and ramucirumab (Wilke 2014). Two studies were first-line therapy regimens (Bang 2010; Lordick 2013), and three were second-line therapies (Ford 2014; Fuchs 2014; Wilke 2014). One study was included in the subcomparison but did not provide enough detail for inclusion in the meta-analysis (Eatock 2013).

Subcomparison 6

Five studies investigated chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone in participants with SCC of the esophagus, using 5-FU (Bleiberg 1997), 5-FU and cisplatin (Levard 1998), cetuximab (Lorenzen 2009), doxorubicin (Nicolaou 1982), and gefitinib (Dutton 2014). Four studies were first-line therapy regimens (Bleiberg 1997; Levard 1998; Lorenzen 2009; Nicolaou 1982), and one was a second-line therapy (Dutton 2014). One study was included in the subcomparison but did not provide enough detail for inclusion in the meta-analysis (Xu 2013a).

We describe all interventions in detail, along with the type and location of the tumors, in the [Characteristics of included studies](#). We defined second-line therapy studies as including only participants that had received previous chemotherapy or targeted therapy within six months of starting the study regimen, including adjuvant therapy.

Studies excluded from the comparisons

Five studies included only eligible participants, however, these studies were not eligible for inclusion in any of our comparisons. Waddell 2013 studied panitumumab and adjusted the control regimen of epirubicin, oxaliplatin, and capecitabine in the experimental arm. One study was not eligible because it compared leucovorin and 5-FU versus S-1 on a background of cisplatin (Pang 2014). Three studies used an equal number of agents in each arm. These studies compared: atofludung versus ftorafur on a background of either mitomycin C plus etoposide, cisplatin plus hydroxycamptothecin, cisplatin plus vindesine, or mitomycin C plus adriamycin (Li 2002), epirubicin versus mitomycin on a background of cisplatin plus 5-FU (Ross 2002), and adriamycin versus methotrexate or 5-FU (Ezdinli 1980).

There were 15 studies that also included participants with gastric cancer that we excluded from the comparisons because they did not compare the addition of an agent to an unaltered

control regimen. These studies compared: S1 versus 5-FU on a background of cisplatin ([Ajani 2010](#)); oxaliplatin versus cisplatin on a background of 5-FU plus leucovorin ([Al-Batran 2008](#)); cisplatin versus oxaliplatin on a background of epirubicin plus 5-FU or capecitabine, and 5-FU versus capecitabine on a background of epirubicin plus cisplatin or oxaliplatin ([Cunningham 2008](#)); irinotecan plus folinic acid versus cisplatin on a background of 5-FU ([Dank 2008](#)); continuous 5-FU plus cisplatin versus bolus 5-FU plus leucovorin ([Duffour 2006](#)); irinotecan versus cisplatin on a background of capecitabine ([Moehler 2010](#)); 5-FU versus cisplatin on a background of irinotecan ([Pozzo 2004](#)); irinotecan versus 5-FU on a background of docetaxel ([Roy 2012](#)); and epirubicin plus cisplatin versus doxorubicin plus methotrexate on a background of 5-FU ([Waters 1999](#)). Five studies did add an agent to a control regimen but adjusted their control regimens in the experimental arm. They investigated docetaxel plus cisplatin ([Ajani 2005](#)); docetaxel plus oxaliplatin, either with or without 5-FU ([Van Cutsem 2015](#)); lapatinib ([Lorenzen 2015](#)); docetaxel plus oxaliplatin with or without capecitabine ([Van Cutsem 2015](#)); or cisplatin and 5-FU with or without docetaxel ([Van Cutsem 2006](#)). One study was not eligible for inclusion because it tested two agents (cisplatin, 5-FU) versus one agent (capecitabine) ([Tebbutt 2010](#)).

In order to analyze the data from studies with a mixed participant population, including both eligible and ineligible participants, we requested individual participant data from authors of studies that we included after the search round of 3 October 2013. Only one author responded and provided individual participant data. Subsequently, we decided to investigate the information from the studies that included both esophageal and/or GE-junction, mixed with gastric cancer participants, in a sensitivity analysis to assess the influence of gastric cancer participants on the outcome of the individual studies.

Outcomes

OS and toxicity were the most commonly described outcomes, followed by PFS, time to progression (TTP), and objective response rate. Studies did not always classify toxicity according to NCI-CTC or WHO. Studies published before 2010 did not report quality of life with validated methods, and where reported, authors did not always report this outcome separately for esophageal and GE-junction cancer subgroups.

Excluded studies

See [Characteristics of excluded studies](#). We updated and revised the search for this version of the review. We excluded 5571 records based on their title and abstract as well as another 69 articles after reading the full text. The most frequent reason for exclusion was because the study turned out not to involve esophageal or GE-junction cancer participants. The reasons for exclusion are further specified in [Figure 1](#) according to the recommendations of the PRISMA statement ([Moher 2009](#)). We included studies that contained non-eligible participants as well as eligible participants. However, we excluded two studies that contained only nine and four eligible participants ([Cascinu 2011](#) and [Li 2011](#), respectively), as they did not provide sufficient data. We also excluded [Koizumi 2010](#) because authors did not specify the number of participants with GE-junction cancer. Additionally, we excluded several studies currently published as abstracts only, because full information on risk of bias and/or data on the esophageal and GE-junction cancer subgroup were unavailable. We classified these as 'Studies awaiting classification'.

Risk of bias in included studies

For details on the included studies see [Characteristics of included studies](#) and the summary figure of the quality assessment ([Figure 2](#)). Investigators performed and described blinding in 8 out of 41 studies. This poses a certain risk of bias in many of the included studies.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Selective reporting (reporting bias)	Similar at baseline for most prognostic factors (selection bias)	Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Intention-to-treat analysis performed (selection bias)
Ajani 2005	+	?	-	+	+	+	+
Ajani 2010	+	?	?	+	+	+	+
Al-Batran 2008	+	?	?	+	+	+	+
Al-Batran 2013	+	?	?	+	+	+	+
Bang 2010	+	+	-	+	+	+	+
Bleiberg 1997	+	?	?	+	+	+	+
Cunningham 2008	+	+	-	+	+	+	+
Dank 2008	+	?	+	+	+	+	+
Duffour 2006	+	?	?	+	+	+	+

Figure 2. (Continued)

Duffour 2006	+	?	?	+	+	+	+
Dutton 2014	+	+	+	+	+	+	+
Eatock 2013	+	+	+	+	+	+	+
Ezdinli 1980	+	?	?	+	-	+	+
Ford 2014	+	+	-	+	+	+	+
Fuchs 2014	+	+	+	+	+	+	+
Huang 2009	+	?	?	+	+	+	+
Iveson 2014	+	+	+	+	+	+	+
Levard 1998	+	+	?	+	+	+	+
Li 2002	?	?	-	+	+	-	-
Lordick 2013	+	+	-	+	+	+	+
Lorenzen 2009	+	?	-	+	+	+	+
Lorenzen 2015	+	+	-	+	?	+	+
Moehler 2010	+	?	-	+	+	+	-
Nicolaou 1982	?	?	?	+	+	+	+
Ohtsu 2011	+	+	+	+	+	+	+
Pang 2014	?	?	?	+	+	+	-
Pozzo 2004	+	?	?	+	+	+	-
Rao 2010	+	+	-	+	-	+	+
Richards 2013	+	?	-	+	+	+	+
Ross 2002	+	+	?	?	+	+	+
Roy 2012	?	?	?	+	+	+	+
Shen 2014	+	+	+	+	+	-	+
Tebbutt 2002	+	?	?	+	+	+	+
Tebbutt 2010	?	?	-	+	+	+	+
Thuss-Patience 2011	+	?	-	+	-	+	+
Van Cutsem 2006	+	?	?	+	+	+	+
Van Cutsem 2015	+	+	?	+	+	+	+
Waddell 2013	+	?	-	+	+	+	+
Waters 1999	+	+	?	+	+	+	+
Wilke 2014	+	+	+	+	+	+	+

Figure 2. (Continued)

Wilke 2014	+	+	+	+	+	+	+
Wilkes 2011	+	+	?	+	+	+	+
Xu 2013a	?	?	?	+	+	-	-

Allocation

Studies frequently failed to describe allocation concealment, and six studies did not describe the method of random sequence generation.

Blinding

Two studies evaluated progression using a blinded independent review board (Lordick 2013; Rao 2010). We did not downgrade the GRADE level of evidence for the primary outcome, OS, due to lack of binding or mentioning of blinding in the study report. This because we assume knowledge of allocation has limited effect on survival and the detection of survival and would, thus, not induce performance or detection bias. Seven studies described use of an external review board but did not describe blinding (Ajani 2005; Ajani 2010; Duffour 2006; Pozzo 2004; Roy 2012; Tebbutt 2010; Van Cutsem 2006).

Incomplete outcome data

Incomplete outcome data with risk of attrition bias was present in a few included studies, either because there was no intention-to-treat analysis (Li 2002; Moehler 2010; Pang 2014; Pozzo 2004; Van Cutsem 2006; Xu 2013a), or because authors did not describe dropouts (Li 2002; Xu 2013a).

Selective reporting

Risk of reporting bias was present in one study (Ross 2002), where authors reported the data in esophageal participants separately for overall response rate but not for other outcomes. We did not consider studies that reported overall survival for esophageal participants separately and did not report on other outcome measures to be at high risk of reporting bias, as overall survival was the primary endpoint of analysis in this review.

Other potential sources of bias

We considered that four studies had groups that were not similar at baseline. This was due to age difference (Rao 2010), number of organs involved in metastatic disease (Lorenzen 2015; Thuss-Patience 2011), or both (Ezdinli 1980). We assessed small study effects, such as publication bias, in a qualitative manner using a funnel plot for the main analysis, but we found no evidence that these effects were present.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings table: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone for palliative treatment of esophageal and GE-junction carcinoma;

Summary of findings 2 Summary of findings table (sensitivity analysis): interventions esophageal and GE-junction carcinoma versus gastric carcinoma; **Summary of findings 3** Summary of findings table (subcomparison 1): chemotherapy or targeted therapy plus best supportive care (BSC) versus BSC for palliative treatment of esophageal and GE-junction carcinoma; **Summary of findings 4** Summary of findings table (subcomparison 2): second-line chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone for palliative treatment of esophageal and GE-junction carcinoma; **Summary of findings 5** Summary of findings table (subcomparison 3): chemotherapy agent(s) plus control intervention versus control intervention alone for palliative treatment of esophageal and GE-junction carcinoma; **Summary of findings 6** Summary of findings table (subcomparison 4): targeted therapy agent plus control intervention versus control intervention alone for palliative treatment of esophageal and GE-junction carcinoma; **Summary of findings 7** Summary of findings table (subcomparison 5): chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone in participants with AC of the esophagus; **Summary of findings 8** Summary of findings table (subcomparison 6): chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone in participants with SCC of the esophagus

Main analysis: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone

Overall survival

Eleven studies in 1347 participants contributed data to this meta-analysis (Bang 2010; Bleiberg 1997; Dutton 2014; Ford 2014; Fuchs 2014; Huang 2009; Levard 1998; Lordick 2013; Lorenzen 2009; Nicolaou 1982; Wilke 2014). These studies included only people with esophageal and/or GE-junction cancer, or they reported the results separately for this group. The overall HR in favor of the arm with the additional agent was 0.75 (95% CI 0.68 to 0.84, high-quality evidence), showing an OS benefit (Analysis 1.1; Figure 3). On average, participants in the arm with the additional chemotherapy or targeted therapy agent received 2.1 chemotherapy or targeted therapy agents, versus an average of 1.0 agents in the control arms. Median OS, weighted for study size, in the arm with the additional agent was 6.7 months versus 5.7 months in the control arm. We could not include two studies because they did not report median overall survival data (Bang 2010; Huang 2009). Cochrane's Q test for heterogeneity showed a non-significant amount of heterogeneity ($I^2 = 5\%$, $P = 0.40$), which indicated that results of the different studies were consistent in their findings. We did not note any small study effects such as publication bias (Figure 4).

Figure 3. Forest plot of the main analysis: chemotherapy or targeted therapy agent(s) plus control arm versus control arm, outcome: 1.1 Overall survival. **Figure 4. Funnel plot of the main comparison: chemotherapy or targeted therapy agent(s) plus control arm versus control arm, outcome: 1.1 Overall survival.**

Two studies included in the meta-analysis selected participants based on biomarker expression (Bang 2010; Lorenzen 2009). We could not include three studies under this comparison in the meta-analysis because of insufficient information. Eatock 2013 investigated trebananib. Median OS times at the time of analysis were 9.1 months, 9.4 months, and 12.8 months for the 10.0 mg/kg, 3.0 mg/kg, and control arms, respectively. Wilkes 2011 studied thalidomide and reported that survival was not affected by group allocation. Xu 2013a found higher, statistically significant ($P < 0.05$) OS in the nimotuzumab group relative to the control group.

Progression-free survival

Of all studies included in this comparison, only studies that investigated a targeted therapy agent reported PFS. Therefore,

we describe the results of this analysis in more detail under subcomparison 4, 'Progression-free survival'. The analysis contained five studies in 883 participants. The addition of a targeted therapeutic agent probably leads to an HR of 0.64 (95% CI 0.45 to 0.92, moderate-quality evidence; Analysis 1.2; Figure 5). Eatock 2013 investigated trebananib in esophageal adenocarcinoma participants but did not provide enough detail for inclusion in the meta-analysis. Median PFS times at the time of analysis were 4.2 months, 4.9 months, and 5.2 months for the 10.0 mg/kg, 3.0 mg/kg, and control arms, respectively.

Figure 5. Forest plot of the main analysis: chemotherapy or targeted therapy agent(s) plus control arm versus control arm, outcome: 1.2 Progression free survival.

Toxicity

All 11 studies included in the main analysis reported on toxicity. All studies reported the frequency of toxic effects, although not all used WHO or NCI-CTC guidelines. Five studies did not report toxicity for the esophageal and GE-junction cancer subgroup separately (Bang 2010; Ford 2014; Fuchs 2014; Lordick 2013; Wilke 2014). Therefore, in this review, we only compared toxicity between study arms, not between studies. Nicolaou 1982 and Levard 1998 did not use WHO or NCI-CTC guidelines. All other studies used NCI-CTC, except for two that used WHO guidelines (Bleiberg 1997; Huang 2009).

In Bang 2010, the most common grade 3 and 4 adverse events reported with trastuzumab plus chemotherapy versus chemotherapy alone were neutropenia (27% versus 30%), anemia (12% versus 10%), and diarrhea (9% versus 4%). Treatment-related mortality was 3% in the trastuzumab plus chemotherapy arm, versus 1% in the chemotherapy alone arm. Bleiberg 1997 reported that grade 3 and 4 adverse events occurred most frequently in the 5-FU cisplatin arm versus the cisplatin alone arm. These were nausea or vomiting (27% versus 11%) and leukocytopenia and thrombocytopenia (both 12% versus 0%). Seven (16%) treatment-related deaths occurred in the treatment arm. Dutton 2014 reported that any grade 3, 4, or 5 toxicities occurred in 45% of participants in the gefitinib plus control arm versus 39% of

participants in the control arm. Two treatment-related deaths occurred in the placebo group and one in the gefitinib group. Ford 2014 found that grade 4 toxicities occurred more frequently in participants treated with docetaxel compared to participants in the control arm (21% versus 4%). Neutropenia, infections, and febrile neutropenia were the toxicities that differed most between the study arms. None of the deaths were attributed to the treatment. In both arms of Fuchs 2014, 2% of the participants died due to drug-related toxicity. Ramucirumab was not associated with increased rates of fatigue, decreased appetite, vomiting, anemia, or other notable toxic effects. Huang 2009 used WHO guideline classifications but did not specify the grade of the side effects that occurred. In Lordick 2013, any grade 3 or 4 adverse events occurred in 83% of participants in the cetuximab plus control arm versus 77% in the control arm. Nine per cent of participants in the chemotherapy plus cetuximab arm and eight per cent of participants in the control arm had an adverse event leading to death. Lorenzen 2009 reported that grade 3 and 4 adverse events, which occurred more frequently in the cetuximab group, were diarrhea (16% versus 0%), neutropenia (22% versus 13%), and rash (6% versus 0%). Additionally, they reported one (3%) treatment-related death in the control arm and none in the experimental arm. Wilke 2014 found that the most frequently occurring grade 3, 4, and 5 adverse events in the ramucirumab arm versus the control arm were neutropenia (41% versus 19%), leukopenia (18% versus 7%),

and hypertension (15% versus 3%). In both arms, 2% of participants had adverse events leading to death with a causal relation to the study drugs.

Overall, palliative chemotherapy and/or targeted therapy appears to increase the frequency of treatment-related toxicity of at least grade 3. Treatment-related deaths were rare in most studies, and there is no clear evidence that treatment-related deaths occur more frequently in the study arms with an additional chemotherapy or targeted therapy agent.

Quality of life

Five studies included in the main analysis did not report on quality of life (Bleiberg 1997; Lordick 2013; Lorenzen 2009; Nicolaou 1982; Wilkes 2011). Four studies did not report quality of life separately for the esophageal and GE-junction cancer subgroup (Bang 2010; Ford 2014; Fuchs 2014; Wilke 2014). Two studies reported on quality of life but did not use validated methods (Huang 2009; Levard 1998). Huang 2009 used improvement after treatment in the treatment arm versus the control arm for the Karnofsky score (33% versus 10%) and body weight (27% versus 6.7%). Levard 1998 studied dysphagia in order to judge the quality of life during the survival of their participants. Bang 2010 (see Satoh 2014) reported that trastuzumab plus chemotherapy versus chemotherapy alone prolonged time to 10% definitive deterioration in all QLQ-C30 and QLQ-STO22 scores (Aaronson 1993; Blazeby 2004), including QLQ-C30 global quality of life score, from 6.4 months to 10.2 months. Dutton 2014 reported no differences between the gefitinib and placebo groups in global quality of life measured with QLQ-C30. However, odynophagia worsened for participants on placebo and improved significantly for participants on gefitinib. Ford 2014 reported that the mean quality-adjusted life weeks (QLQ-C30) were 12.1 weeks (standard deviation (SD) 0.84) for the docetaxel group and 9.3 weeks (SD 0.73) for the control group. Fuchs 2014 reported a trend toward better quality of life (QLQ-C30) at six weeks for participants in the ramucirumab group compared to those in the placebo group ($P = 0.23$). Median time of deterioration to a score of 2 or worse in ECOG performance status was 2.4 months (95% CI 1.3 to not reached) in the placebo group and 5.1 months (95% CI 1.9 to 16.8) in the ramucirumab group. Wilke 2014 reported that baseline and end-of-treatment results for global quality of life from the QLQ-C30 and index scores from the EQ-5D-3L were similar in the treatment groups (EuroQol 1990). Overall, the studies reporting quality of life did so in different ways. Although recent studies often use the QLQ-C30, the outcomes were reported in the form of either mean values with SD, change from the baseline, proportions improved, or mean area under the curve. This prohibited a meta-analysis of quality of life outcomes. The five studies were not representative for all the studies in this analysis, as four of them tested a targeted agent, and four did not report data separately for the esophageal and GE-junction cancer subgroup. However, the quality of life improved in the arms with the additional agent.

Sensitivity analysis: effect of the intervention in participants with esophageal and GE-junction cancer versus gastric cancer

We conducted this sensitivity analysis to investigate whether there was a significant difference in the effect of the intervention between both the participants with esophageal and GE-junction cancer and the participants with gastric cancer. The sensitivity analysis consisted of two parts, both regarding OS. Firstly, we compared the group of studies that included participants with both

esophageal/GE-junction and gastric cancer to the group of studies that included only participants with esophageal and GE-junction cancer through a meta-regression analysis. In this meta-regression analysis, the interventions between groups of studies were not similar, making the comparison indirect. Therefore, we performed a second sensitivity analysis, also by meta-regression, that focused on five studies that reported the effect of the intervention on OS for participant groups with both GE-junction and gastric cancer separately.

For the first part of the sensitivity analysis, we meta-analyzed the group of studies that included participants with both esophageal/GE-junction and gastric cancer. This group contained eight studies and 1755 participants, 459 of whom had esophageal or GE-junction cancer (Al-Batran 2013; Iveson 2014; Ohtsu 2011; Rao 2010; Richards 2013; Shen 2014; Tebbutt 2002; Thuss-Patience 2011). Iveson 2014 investigated rilotumumab at two concentrations, 7.5 mg/kg and 15 mg/kg. The HR that we used in the meta-analysis was derived from both groups versus the control arm. In this analysis, the overall HR, in favor of the arm with the additional agent was 0.94 (95% CI 0.83 to 1.05), showing a trend toward a survival benefit in the arm with the additional agent versus the control arm (Analysis 2.1). Cochrane's Q test for heterogeneity showed a considerable amount of heterogeneity ($I^2 = 54\%$, $P = 0.03$), which indicated that results of the different studies were somewhat inconsistent in their findings.

We performed a meta-regression analysis to compare the effect of the intervention in studies involving participants with esophageal and GE-junction cancer (main analysis group, HR 0.75, 95% CI 0.68 to 0.84, high-quality evidence), versus studies in participants with both gastric and esophageal/GE-junction cancer (HR 0.94, 95% CI 0.83 to 1.05). This meta-regression analysis showed that there was a difference in the effect of intervention between the two groups of studies ($P = 0.004$).

For the second part of the sensitivity analysis, we assessed the group of studies reporting the effect of the intervention on OS for participants with both GE-junction and gastric cancer separately in two meta-analyses, each containing five studies (Bang 2010; Ford 2014; Fuchs 2014; Lordick 2013; Wilke 2014). The meta-analysis of the participant subgroups with GE-junction cancer contained 538 participants. The meta-analysis of the participant subgroups with gastric cancer contained 2093 participants. The effect of adding a chemotherapeutic or targeted therapeutic agent in the participant subgroups with GE-junction cancer on OS in these studies was HR 0.66 (95% CI 0.54 to 0.81; Analysis 3.1). The effect of adding a chemotherapeutic or targeted therapeutic agent to the participant subgroups with gastric cancer in these studies was HR 0.89 (95% CI 0.76 to 1.04; Analysis 3.2). That said, this was a selected group of participants with gastric cancer, so this meta-analysis might not accurately reflect the effect of adding a chemotherapeutic or targeted agent to the control regimen of participants with gastric cancer in general. This meta-analysis was not meant to be exhaustive with regard to the effect of chemotherapy or targeted therapy in people with gastric cancer. For more information, see Wagner 2010. We performed a meta-regression analysis between these groups, which indicated that both participant subgroups responded significantly differently to the investigated interventions ($P = 0.03$), in line with the first part of the sensitivity analysis. This meta-regression analysis indicated that the studied interventions appeared to result in an

increased beneficial effect on OS in participants with GE-junction cancer compared to participants with gastric cancer. Therefore, we excluded the studies that also included participants with gastric cancer and did not report outcomes separately from the meta-analyses of this review.

Subcomparison 1: chemotherapy or targeted therapy plus BSC versus BSC

Overall survival

Five studies in 750 participants contributed data to this meta-analysis (Dutton 2014; Ford 2014; Fuchs 2014; Levard 1998;

Nicolaou 1982). For overall survival, we found an HR of 0.81 (95% CI 0.71 to 0.92, high-quality evidence; Analysis 4.1; Figure 6) in favor of the chemotherapy or targeted therapy arm. Median OS, weighted for study size, in the chemotherapy arm was 4.7 months versus 4.2 months in the BSC arm. Only two studies used first-line therapies (Levard 1998; Nicolaou 1982), while the others used second-line. Cochrane's Q test for heterogeneity was non-significant ($I^2 = 0\%$, $P = 0.56$), which indicated that results of the five studies were consistent in their findings.

Figure 6. Forest plot of subcomparison 1: chemotherapy or targeted therapy agent(s) plus BSC versus BSC, outcome 4.1: overall survival.

Progression-free survival

Two studies in 540 participants contributed data to this meta-analysis (Dutton 2014; Fuchs 2014). Both studies assessed a targeted therapeutic agent. The other three studies did not report on PFS. The overall HR of 0.58 (95% CI 0.28 to 1.18, very low-quality evidence; Analysis 4.2; Figure 7) in favor of targeted therapy demonstrated that there was a larger, non-significant effect

estimate toward a PFS benefit when participants received targeted therapy; however, we are uncertain of these findings due to the very low quality of evidence. Median progression-free survival was only available from Dutton 2014 and was 1.6 months in the targeted therapy arm versus 1.2 months in the BSC arm. Cochrane's Q test for heterogeneity showed significant heterogeneity ($I^2 = 85\%$, $P = 0.01$), which indicated that results of the two studies were not consistent.

Figure 7. Forest plot of subcomparison 1: chemotherapy or targeted therapy agent(s) plus BSC versus BSC, outcome 4.1: progression free survival.

Subcomparison 2: participants who had received previous chemotherapy

We intended for this subcomparison to investigate whether chemotherapy or targeted therapy for participants that had previously received chemotherapy resulted in a benefit for overall

survival, progression-free survival, or both. We did not include studies if only some of the participants had received previous chemotherapy. For a description of criteria used for including studies with regard to previous chemotherapy, see Characteristics of included studies, 'Participants' section.

Overall survival

This meta-analysis included four studies in 769 participants (Dutton 2014; Ford 2014; Fuchs 2014; Wilke 2014). Three studies included participants with GE-junction cancer only. In Dutton 2014, 24% of the esophageal cancers were SCC. Two studies investigated ramucirumab (Fuchs 2014; Wilke 2014), which we analyzed separately in subgroup analysis 4b. The overall HR of 0.71 (95% CI 0.54 to 0.94, moderate-quality evidence; Analysis 5.1) in favor of the arm with the additional agent demonstrated that an additional chemotherapeutic or targeted agent leads to a survival benefit. Median OS, weighted for study size, was 5.1 months in the chemotherapy arm versus 4.4 months in the BSC arm. Cochrane's Q test for heterogeneity showed significant heterogeneity ($I^2 = 57\%$, $P = 0.07$), indicating that results of the three included studies were quite inconsistent in their findings.

Progression-free survival

Three studies in 677 participants contributed data to this meta-analysis (Dutton 2014; Fuchs 2014; Wilke 2014). All three studies investigated targeted agents. Two studies (both of ramucirumab) included participants with GE-junction cancer only. In the third study, 24% of the esophageal cancers were SCC. The overall HR of 0.51 (95% CI 0.29 to 0.90, low-quality evidence; Analysis 5.2) in favor of the targeted therapy arms demonstrated that there may be a PFS benefit for people receiving targeted therapy agents. Cochrane's Q test for heterogeneity showed substantial heterogeneity ($I^2 = 83\%$, $P < 0.001$), which indicated that results of the three studies were inconsistent in their findings.

Subcomparison 3: chemotherapy agent(s) plus control intervention versus control intervention alone

Overall survival

Five studies in 358 participants contributed data to this meta-analysis (Bleiberg 1997; Ford 2014; Huang 2009; Levard 1998; Nicolaou 1982). The overall HR of 0.73 (95% CI 0.63 to 0.85, moderate-quality evidence; Analysis 1.1; Figure 3, subcomparison 3) in favor of the arm with the additional chemotherapy agent demonstrates that there is probably a significant survival benefit in people receiving an additional chemotherapy agent. Median survival time, weighted for study size, was 6.9 months in the chemotherapy arm versus 5.8 months in the control arm. We could not include Huang 2009 in the median OS analysis because it did not report this outcome. Cochrane's Q test for heterogeneity showed non-significant heterogeneity ($I^2 = 0\%$, $P = 0.50$), which indicated that results of the five studies were consistent in their findings. Considering the limited number of studies and the low heterogeneity in the model, we consider that the quality of evidence is moderate.

One study included in the comparison did not contribute to the meta-analysis for subcomparison 3 for OS because the publication did not provide enough information. Wilkes 2011 only reported that survival was not affected by group allocation or whether the participant was able to complete the protocol.

Progression-free survival

None of the four studies reported on PFS.

Subcomparison 4: targeted agent plus control intervention versus control intervention alone.

Overall survival

Six studies with 989 participants contributed to this meta-analysis (Bang 2010; Dutton 2014; Fuchs 2014; Lordick 2013; Lorenzen 2009; Wilke 2014). The overall HR in favor of the arm containing a targeted agent was 0.75 (95% CI 0.63 to 0.90, high-quality evidence). This analysis demonstrated a survival benefit for participants randomized to the arm with the additional targeted agents (Analysis 1.1; Figure 3, subcomparison 4). Median OS in the arm with the additional targeted agent, weighted for study size, was 6.7 months versus 5.7 months in the control arm. We could not include Bang 2010 because it did not report median OS data. Cochrane's Q test for heterogeneity showed low heterogeneity ($I^2 = 24\%$, $P = 0.25$), indicating that results of the different studies were quite consistent in their findings.

Two studies included in the meta-analysis selected participants based on biomarker expression (Bang 2010; Lorenzen 2009). Xu 2013a found higher PFS and OS in the nimotuzumab group. However, the study did not provide enough information to extract HRs, so we could not include it in the analyses.

Subgroup analysis 4a: EGFR-targeting agent plus control intervention versus control intervention alone

Three studies in 655 participants contributed data to this meta-analysis (Dutton 2014; Lordick 2013; Lorenzen 2009). The overall HR of 0.86 (95% CI 0.73 to 1.01, moderate-quality evidence; Analysis 6.1) in favor of the arms that contained an EGFR-targeting agent showed that there is probably a survival benefit in the arm with the additional EGFR-targeting agent. Cochrane's Q test for heterogeneity showed no significant heterogeneity ($I^2 = 0\%$, $P = 0.56$), which indicated that results of the four studies were very consistent in their findings. Median OS, weighted for study size, was 6.4 months in the treatment arm containing an EGFR-targeting agent versus 5.5 months in the control arm.

One study included in the meta-analysis selected participants based on biomarker expression (Lorenzen 2009). Xu 2013a found higher PFS and the OS in the nimotuzumab group. However, the study did not provide enough information to extract HRs, so we could not include it in the meta-analysis.

Waddell 2013 investigated panitumumab. We could not formally include this study in the comparison because the control regimen was adjusted in the arm with the additional EGFR-targeting agent. This study found that the addition of panitumumab resulted in an HR for OS of 1.37 (95% CI 1.07 to 1.76), but readers should interpret these results with caution.

Subgroup analysis 4b: cetuximab plus control intervention versus control intervention alone

Two studies in 206 participants contributed data to this meta-analysis (Lordick 2013; Lorenzen 2009). Lordick 2013 investigated the addition of cetuximab to a control arm of capecitabine plus cisplatin; Lorenzen 2009 used cisplatin plus 5-FU as a control regimen. The overall HR of 0.76 (95% CI 0.55 to 1.04, low-quality evidence; Analysis 7.1) in favor of the cetuximab arm showed that there may be a non-significant survival benefit for participants randomized to receive cetuximab. Median OS, weighted for study size, was 12.2 months in the cetuximab arm versus 9.4 months in

the control arm. Cochrane's Q test for heterogeneity showed non-significant heterogeneity ($I^2 = 0\%$, $P = 0.58$), which indicated that results of the two studies were consistent in their findings. One study included in the meta-analysis selected participants based on biomarker expression (Lorenzen 2009).

Subgroup analysis 4c: ramucirumab plus control intervention versus control intervention alone

Two studies in 228 participants contributed data to this meta-analysis (Fuchs 2014; Wilke 2014). Fuchs 2014 investigated ramucirumab versus BSC, while Wilke 2014 added ramucirumab to paclitaxel. The two studies included only people with GE-junction cancer who had previously received chemotherapy, so the results of this meta-analysis are not generalizable to other patient populations. The overall HR of 0.62 (95% CI 0.43 to 0.88, moderate-quality evidence; Analysis 8.1) in favor of the ramucirumab arm showed that there is probably an overall survival benefit. Median OS, weighted for study size, was 7.5 months in the ramucirumab arm versus 6.3 months in the control arm. Cochrane's Q test for heterogeneity showed non-significant heterogeneity ($I^2 = 28\%$, $P = 0.24$), which indicated that results of the two studies were consistent in their findings.

Progression-free survival

Five studies in 883 participants contributed data to this meta-analysis (Dutton 2014; Fuchs 2014; Lordick 2013; Lorenzen 2009; Wilke 2014). The five studies investigated targeted therapies. In this analysis, the overall HR, in favor of the treatment arm that contained a targeted therapy agent, was 0.64 (95% CI 0.45 to 0.92, moderate-quality evidence). This showed that there is probably a PFS benefit for people treated with the targeted therapy agent (Analysis 1.2; Figure 5). Median progression-free survival, weighted for study size, was 2.9 months in the arm with the additional targeted therapy agent versus 2.4 months in the control arm. We could not include two studies in the analysis because they did not report median PFS data (Fuchs 2014; Wilke 2014). Cochrane's Q test for heterogeneity showed substantial heterogeneity ($I^2 = 79\%$, $P < 0.001$), which indicated that results of the individual studies were quite inconsistent in their findings. One study included in the meta-analysis selected participants based on biomarker expression (Lorenzen 2009).

Subgroup analysis 4a: EGFR-targeting agent plus control intervention versus control intervention alone

Three studies in 655 participants contributed data to this meta-analysis (Dutton 2014; Lordick 2013; Lorenzen 2009). The overall HR of 0.85 (95% CI 0.73 to 1.00, low-quality evidence; Analysis 6.2) in favor of the arm with the EGFR-targeting agent demonstrated that there may be a non-significant PFS benefit in the arms with the EGFR-targeting agents. Cochrane's Q test for heterogeneity showed non-significant results ($I^2 = 2\%$, $P = 0.36$), which indicated that results of the three studies were consistent in their findings. Median progression-free survival, weighted for study size, was 2.9 months in the treatment arm that contained an EGFR-targeting agent versus 2.4 months in the control arm.

One study included in the meta-analysis selected participants based on biomarker expression (Lorenzen 2009). Waddell 2013 investigated panitumumab, but we could not formally include it in the comparison because the control regimen was adjusted in the panitumumab arm. The addition of panitumumab resulted in an HR

for PFS of 1.22 (95% CI 0.98 to 1.52), but readers should interpret these results with caution.

Subgroup analysis 4b: cetuximab plus control intervention versus control intervention alone

Two studies in 206 participants contributed data to this meta-analysis (Lordick 2013; Lorenzen 2009). The overall HR of 0.90 (95% CI 0.59 to 1.37, very low-quality evidence; Analysis 7.2) shows a small and very uncertain PFS benefit in favor of the cetuximab arm. Median progression-free survival, weighted for study size, was 5.7 months in the cetuximab arms versus 5.0 months in the control arms. Cochrane's Q test for heterogeneity showed a considerable amount of heterogeneity ($I^2 = 53\%$, $P = 0.14$), which indicated that results of the two studies were not very consistent in their findings. One study included in the meta-analysis selected participants based on biomarker expression (Lorenzen 2009).

Subgroup analysis 4c: ramucirumab plus control intervention versus control intervention alone

Two studies in 228 participants contributed data to this meta-analysis (Fuchs 2014; Wilke 2014). This meta-analysis only applies to GE-junction participants, the only participants included. The overall HR of 0.39 (95% CI 0.28 to 0.54, moderate-quality evidence; Analysis 8.2) in favor of the ramucirumab arm demonstrated that there was probably a PFS benefit in the ramucirumab group. We could not determine median PFS, as neither study reported this outcome. Cochrane's Q test for heterogeneity showed non-significant heterogeneity ($I^2 = 0\%$, $P = 0.99$), which indicated that results of the two studies were very consistent in their findings.

Subcomparison 5: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone in participants with adenocarcinoma of the esophagus

Overall survival

Five studies in 538 participants contributed data to this meta-analysis (Bang 2010; Ford 2014; Fuchs 2014; Lordick 2013; Wilke 2014). For overall survival, we found an HR of 0.66 (95% CI 0.54 to 0.81, high-quality evidence; Analysis 9.1) in favor of the experimental arm. Median OS, weighted for study size, was 7.1 months in the added agent arm versus 6.0 months in the control arm. We could not include Bang 2010 because it did not report median overall survival data. Two studies were first-line therapy regimens (Bang 2010; Lordick 2013), and three were second-line therapies (Ford 2014; Fuchs 2014; Wilke 2014). Cochrane's Q test for heterogeneity was non-significant ($I^2 = 0\%$, $P = 0.55$), which indicated that results from the five studies were consistent in their findings. Eatock 2013 investigated trebananib in participants with esophageal adenocarcinoma but did not provide enough detail for inclusion in the meta-analysis. Median OS at the time of analysis were 9.1 months, 9.4 months, and 12.8 months for the 10.0 mg/kg, 3.0 mg/kg, and control arms, respectively.

Progression-free survival

Four studies in 713 participants contributed data to this meta-analysis (Dutton 2014; Fuchs 2014; Lordick 2013; Wilke 2014). For progression-free survival, we found an HR of 0.62 (95% CI 0.38 to 1.00, very low-quality evidence; Analysis 9.2) in favor of the experimental arm; however, we are uncertain of these results due to the low-quality evidence. Median OS, weighted for study size, was 1.8 months in the added agent arm versus 1.7 months in the control

arm. We could not include two studies in the analysis because they did not report median PFS data (Fuchs 2014; Wilke 2014). One study was on first-line therapy regimens (Lordick 2013), and three were second-line therapies (Dutton 2014; Fuchs 2014; Wilke 2014). Cochrane's Q test for heterogeneity was non-significant ($I^2 = 84\%$, $P < 0.001$), which indicated that results of the four studies were very inconsistent in their findings. Eatock 2013 investigated trebananib in participants with esophageal adenocarcinoma but did not provide enough detail for inclusion in the meta-analysis. Median PFS times at the time of analysis were 4.2 months, 4.9 months, and 5.2 months for the 10.0 mg/kg, 3.0 mg/kg, and control arms, respectively.

Subcomparison 6: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone in participants with SCC of the esophagus

Overall survival

Four studies in 268 participants contributed data to this meta-analysis (Bleiberg 1997; Levard 1998; Lorenzen 2009; Nicolaou 1982). For overall survival, we found an HR of 0.76 (95% CI 0.65 to 0.90, high-quality evidence; Analysis 10.1) in favor of the experimental arm. Median OS, weighted for study size, was 8.0 months in the added agent arm versus 6.5 months in the control arm. All studies were first-line therapy regimens. Cochrane's Q test for heterogeneity was non-significant ($I^2 = 0\%$, $P = 0.95$), which indicated that results of the four studies were consistent in their findings. Xu 2013a found that the OS of the nimotuzumab group was increased relative to the control group.

Progression-free survival

Two studies in 168 participants contributed data to this meta-analysis (Dutton 2014; Lorenzen 2009). For overall survival, an HR of 0.72 (95% CI 0.55 to 0.96, low-quality evidence; Analysis 10.2) showed that there may be a benefit in favor of the experimental arm. Median OS, weighted for study size, was 1.7 months in the added agent arm versus 1.2 months in the control arm. All studies were first-line therapy regimens. Cochrane's Q test for heterogeneity was non-significant ($I^2 = 0\%$, $P = 0.97$), which indicated that results of the four studies were consistent in their findings. Xu 2013a found that the PFS of the nimotuzumab group was higher than in the control group.

Studies excluded from the meta-analysis

Li 2002 did not detect a difference between the response rates of participants with esophageal cancer who received atofludung (20.0%) versus ftorafur (24.6%). Ross 2002 reported that the overall response rate with epirubicin, cisplatin, and 5-FU was 37.5% for participants with esophageal cancer and 54.8% for participants with GE-junction cancer versus an overall response rate with mitomycin, cisplatin, and 5-FU of 49.5% for participants with esophageal cancer and 41.5% for participants with GE-junction cancer. Ezdinli 1980 reported median overall survival of 8.1 months for the adriamycin arm, 13.7 months for the methotrexate arm, and 15.4 months for the 5-FU arm. Pang 2014 reported that the median OS of the intervention (leucovorin, 5-FU, and cisplatin) was 12 months versus 9 months in the control group (cisplatin and S-1) ($P = 0.045$). Waddell 2013 found that the addition of panitumumab resulted in an HR for OS of 1.37 (95% CI 1.07 to 1.76) and an HR for PFS of 1.22 (95% CI 0.98 to 1.52). This study adjusted the dose of the control regimen in the experimental arm. Our analysis did

not include the information from studies that contain participants with esophageal and/or GE-junction cancer alongside that from participants with gastric cancer. A meaningful sensitivity analysis was not possible, and we could not quantify the influence of the participants with gastric cancer on the outcome of the individual studies.

DISCUSSION

Summary of main results

This review and meta-analysis included only RCTs. Eight of the included studies reported details on adequate blinding. Apart from blinding, the most common methodological weakness in the included studies was the lack of description regarding allocation concealment. Palliative chemotherapy and/or targeted therapy significantly increased OS compared to BSC in participants with esophageal or GE-junction carcinoma. Additionally, participants who received multiple chemotherapeutic or targeted therapeutic agents had an increased OS and PFS. Although treatment-associated toxicities of at least grade 3 occurred more frequently in the arms with an additional chemotherapy or targeted therapy agent, there was no evidence that palliative chemotherapy and/or targeted therapy decreased quality of life.

Main comparison: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone

The meta-analysis focused on the addition of a chemotherapeutic or targeted agent to the regimen or BSC treatment provided in the control arm. This meta-analysis provided evidence of an OS benefit for participants treated with an additional chemotherapy or targeted therapy agent (Analysis 1.1; Figure 3). Results of the different studies were consistent in their findings. Median OS, weighted for study size, was longer in the arm with the additional agent versus the control arm, and we did not find small study effects.

The meta-analysis for PFS provided evidence of a benefit for participants who had received an additional targeted agent (Analysis 1.2; Figure 5). Median progression-free survival, weighted for study size, was longer in the arm with the additional agent versus in the control arm. Palliative chemotherapy and/or targeted therapy appears to increase the frequency of treatment-related toxicity of at least grade 3. However, treatment-related deaths did not appear to occur more frequently. Five studies included in this analysis measured quality of life with validated methods. Although the five studies were not representative of all the studies in this analysis, as four out of five tested a targeted agent and four did not report data separately for the esophageal and GE-junction cancer subgroup, the quality of life improved in the arms with the additional agent.

Sensitivity analysis: effect of the intervention in participants with esophageal and GE-junction cancer versus gastric cancer

We included the group of studies that also included gastric cancer participants in a separate meta-analysis. Subsequently, we performed a meta-regression analysis between these studies and those including only esophageal and GE-junction cancer participants. This analysis showed significant heterogeneity between groups of studies. Studies that included participants with esophageal or GE-junction cancer only showed a larger OS risk reduction compared to studies that also included participants

with gastric cancer. In this sensitivity analysis, the interventions between the groups of studies were not similar, complicating a straightforward comparison. Therefore, we performed a second sensitivity analysis that focused on five studies reporting the effect of the intervention on OS for participants with GE-junction and gastric cancer separately. This meta-regression analysis indicated that the studied interventions appeared to result in an increased beneficial effect on OS in participants with GE-junction cancer compared to participants with gastric cancer. Therefore, we excluded the studies involving participants with gastric cancer from the meta-analyses of this review. We did not perform any further meta-regression analyses because a comparison between participant groups exposed to the same intervention was not possible. Additionally, the sample size was too small for meta-regression analyses of responses in different participant groups across interventions.

Subcomparison 1: chemotherapy or targeted therapy plus BSC versus BSC

This analysis showed that palliative chemotherapy or targeted therapy for participants with esophageal or GE-junction cancer in the palliative setting increased OS ([Analysis 4.1](#); [Figure 6](#)). We are uncertain whether PFS increased when participants with esophageal or GE-junction cancer received chemotherapy or targeted therapy in the palliative setting ([Analysis 4.2](#); [Figure 7](#)). Considering the data available, toxicity levels were similar in both arms of the studies, except for in [Levard 1998](#). Only [Dutton 2014](#) described quality of life, showing a trend toward improvement for the chemotherapy arm for one domain.

Subcomparison 2: participants who had received previous chemotherapy

In the main analysis, we analyzed first- and second-line palliative chemotherapy together. In subcomparison 2, we investigated the effect of the intervention in participants who had received previous chemotherapy, i.e. second-line palliative therapy studies. This subanalysis showed a probable OS benefit even in participants with prior chemotherapy who received additional chemotherapy or targeted therapy (i.e. second-line therapy). Regarding PFS, there may be a benefit for participants treated with an additional targeted therapy agent.

Subcomparison 3: chemotherapy agent(s) plus control intervention versus control intervention alone

The meta-analyses of subcomparison 3 on OS demonstrated that there is probably an effect with regard to OS in favor of the arm with the additional chemotherapy agent, ([Analysis 1.1](#); [Figure 3](#), subcomparison 3). Median OS in the arm with the additional chemotherapy agent, weighted for study size, was longer than in the control arm.

Subcomparison 4: targeted therapy agent plus control intervention versus control intervention alone

The meta-analyses of subcomparison 4 regarding OS demonstrated the presence of an effect with regard to OS in favor of the arm with the additional targeted agent ([Analysis 1.1](#); [Figure 3](#), subcomparison 4). Median overall survival in the arm with the additional targeted agent, weighted for study size, was longer than in the control arm. We performed a subgroup analysis with three studies investigating agents targeting EGFR signaling,

finding that these agents probably prolong OS. Subsequently, cetuximab, an EGFR-targeting agent, may decrease the hazard of death. We performed another subgroup analysis that focused on studies investigating ramucirumab and found that this agent also probably decreases the hazard of death. The two studies included only GE-junction participants. The meta-analyses of subcomparison 4 regarding PFS was identical to the meta-analysis of comparison one for PFS as described above. We performed a subgroup analysis investigating EGFR-targeting agents plus control intervention versus control intervention alone, finding a possible reduction of the HR of PFS. Subsequently, we analyzed cetuximab plus control intervention versus control intervention alone; results showed uncertainty with regard to whether this agent reduces the HR for PFS. We performed a third subgroup analysis that focused on studies investigating ramucirumab plus control intervention versus control intervention alone. This resulted in a probable reduction of the HR in favor of the ramucirumab arm, indicating a probable PFS benefit in the ramucirumab group. This meta-analysis only applied to participants with GE-junction cancer. Regarding quality of life, [Wilke 2014](#) and [Dutton 2014](#) reported no differences between groups. Furthermore, [Fuchs 2014](#) reported a trend toward better quality of life for the arm with the addition of the targeted therapy, ramucirumab in this case.

Subcomparison 5: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone in participants with adenocarcinoma of the esophagus

The meta-analyses of subcomparison 5 regarding OS demonstrated the presence of an effect in favor of the arm with the additional chemotherapy or targeted therapy agent ([Analysis 9.1](#)). Median OS in the arm with the additional chemotherapy agent, weighted for study size, was longer than in the control arm.

Subcomparison 6: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone in participants with SCC of the esophagus

The meta-analyses of subcomparison 6 regarding OS demonstrated the presence of an effect with regard to OS in favor of the arm with the additional chemotherapy or targeted therapy agent ([Analysis 10.1](#)). Median OS in the arm with the additional chemotherapy agent, weighted for study size, was longer than in the control arm.

Overall completeness and applicability of evidence

In most of the included studies, the participants were only partially representative of all people with esophageal and GE-junction cancer. For instance, they were generally younger, with a median age of 60 years, compared to the overall population of people with esophageal and GE-junction cancer. The proportion of participants with metastatic disease was 69% to 100%, which is roughly comparable to the population normally seen in the clinic. The percentage of participants with ECOG-2 or -3 was in the range of 0% to 35% in the included studies. Two studies selected participants based on tumor biomarker expression, and their results cannot be extrapolated to people that do not have biomarker expression as defined by these studies. The effect of a targeted therapeutic can be expected to depend on the presence of the target in the tumor. [Lorenzen 2009](#) included only people with EGFR-positive cancer, and [Bang 2010](#) included only people with HER2-positive cancer. It is therefore not possible to apply these studies' findings to all people, and it is unclear whether they are equally generalizable to everyone with both esophageal and GE-junction cancer. Furthermore, it was

not feasible to differentiate between participants with esophageal SCC and adenocarcinoma or investigate their response to various treatments individually because of insufficient availability of data.

Palliative therapy that shows increased survival but without evidence of its effect on quality of life has unclear applicability. Therefore, the preservation of quality of life is an important goal and should be an outcome measure in clinical studies of palliative treatment modalities (Blazeby 2001). Because not all included studies reported on quality of life in a validated manner, we can only conclude that there is no evidence that palliative chemotherapy and/or targeted therapy decreases quality of life. Various validated measures are available to assess generic as well as disease-specific quality of life. The most commonly used measure for esophageal cancer is the EORTC QLQ-C30 (Aaronson 1993). This measure is specifically designed to measure quality of life in people diagnosed with cancer. A worthwhile addition to this questionnaire is the EORTC QLQ-OES18, a measure specifically designed for people with esophageal cancer that contains more specific questions on dysphagia, chest pain, and reflux symptoms (Blazeby 2003). Only Rao 2010 used this last measure. More recent studies often use the QLQ-C30 to measure quality of life.

The median absolute survival gain found in the above described analyses, weighted for study size, is limited. For the main analysis, this survival gain applies to the addition of 1.1 agents on average. Adding three agents to BSC, for instance, will likely increase the absolute survival gain. In addition, this analysis also included second-line studies for which the potential survival gain is likely less in absolute terms when compared to first-line palliative care regimens. Except for these limitations, readers may consider the evidence cited above as complete and applicable.

Quality of the evidence

We generally considered the analyzed RCTs to be at low risk of bias in most domains. However, studies were frequently at unclear or high risk of bias with regard to blinding and allocation concealment. More recent RCTs often contained more useful information for determining risk of bias in their descriptions of methodology when compared to older RCTs. For more details about risk of bias, see [Risk of bias in included studies](#).

Various chemotherapy and targeted therapy regimens have been applied for esophageal and GE-junction cancer in a palliative setting. As the regimens in the included RCTs of this review are very heterogeneous, it was often not feasible to make a direct comparison between the various chemotherapeutic agents. The only agents that more than one trial investigated by adding them individually to a control regimen were cetuximab and ramucirumab. Because of the heterogeneity of the agents used, most information can be extracted from an analysis in the form of the main comparison. However, it remains largely unclear which agents lead to a survival benefit. Moderate-quality evidence supports the effectiveness of ramucirumab, and targeting EGFR signalling appears promising. The same heterogeneity is present in the agents that make up the control arms of the studies. Today, some of these agents are no longer or rarely used. Studies testing agents on a background of more popular regimens, for instance containing platinum-based agents and 5-FU, could influence the added effect of the tested agent on survival.

Potential biases in the review process

One significant threat to the validity of the review was the possibility of publication bias, that is, studies that did not find the treatments to have been effective may not have been published. We investigated small study effects such as publication bias in a qualitative manner using a funnel plot (Figure 4) but found no evidence of its presence.

Agreements and disagreements with other studies or reviews

Mohammad 2015 investigated whether a triplet regimen was superior to a doublet regimen in terms of overall survival, progression-free survival, and objective response rate in participants receiving first-line chemotherapy for advanced or metastatic esophagogastric carcinoma. They found a significant improvement in OS in favor of a triplet regimen (HR 0.90, 95% CI 0.83 to 0.97). Additionally, they found that toxicity grades 3 and 4 were significantly higher in the triplet regimens. Both of these conclusions are in line with our findings.

Amdal 2013 investigated the effect of palliative radiotherapy and/or chemotherapy on symptoms and quality of life, as assessed by person-reported outcomes and measurement of toxicity for people with esophageal cancer. They had included mixed populations, including those with gastric, GE-junction, or esophageal cancer. They found no clear association between quality of life and treatment toxicity. Interestingly, two of the RCTs included in our review, which investigated chemotherapy, reported better quality of life despite more treatment toxicity in the experimental arm versus the standard arm (Van Cutsem 2006; Waters 1999).

Differences in risk factors, gene expression, and tumor biology exist between adenocarcinoma of the stomach, GE-junction, and esophagus (Marsman 2005; Shah 2011). In this review, we found a difference in chemotherapy and targeted therapy efficacy between GE-junction adenocarcinoma and gastric adenocarcinoma. We found a similar trend in a study by Chau 2009 using individual participant data from four studies (Cunningham 2008; Ross 2002; Tebbutt 2002; Waters 1999). They concluded that response rates in participants were 44.1% in esophageal, 41.1% in GE-junction, and 35.6% in gastric cancer. Regarding chemotherapeutic treatment of advanced gastric carcinoma, a Cochrane Review has been published (Wagner 2010).

AUTHORS' CONCLUSIONS

Implications for practice

Palliative chemotherapy and targeted therapy increase overall survival in people with esophageal or GE-junction carcinoma compared to BSC. With regard to PFS, we saw a probable trend in the same direction. Additionally, adding chemotherapeutic or targeted agents increases OS, and adding a targeted agent lengthens PFS. However, the median survival benefit is limited. Of all the individual chemotherapeutic and targeted agents studied, only cetuximab and ramucirumab were investigated more than once. Only ramucirumab significantly prolonged OS and PFS in people with GE-junction cancer that had previously been treated with chemotherapy. Palliative chemotherapy and/or targeted therapy appear to increase the frequency of treatment-related toxicity of at least grade 3. However, treatment-related deaths did not occur more frequently. Five studies measured quality of life

with validated methods in this analysis. Although they were not perfectly representative of all the studies in this analysis, they did show that quality of life improved in the arms with the additional agent. Overall, palliative chemotherapy and/or targeted therapy can be considered as standard care for esophageal and GE-junction carcinoma.

Implications for research

There is a need for well-designed, adequately powered, phase III studies on chemotherapy and targeted therapy for metastatic esophageal and GE-junction carcinoma. The main objective should be increased survival, with an additional emphasis on quality of life. These future studies comparing palliative treatment modalities should assess quality of life with validated measures. Studies should be designed in such a way that they enable the comparison of different individual agents on a meta-analysis level. Our results suggest that the participants with GE-junction cancer respond differently to chemotherapy and targeted therapy when compared to the participants with gastric cancer. We do not suggest excluding

either group from studies. However, it is advisable to report outcomes separately for these and other subgroups of participants. Additionally, studies pooling these plausibly differently reacting populations might underestimate the number of participants necessary to reach definitive conclusions for each subgroup. Separate reporting for SCC, adenocarcinoma of the esophagus, and adenocarcinoma of the GE-junction would further increase the understanding of the effectiveness of chemotherapies and targeted therapies in these groups.

ACKNOWLEDGEMENTS

The authors would like to thank the Cochrane Upper Gastrointestinal and Pancreatic Group for their critical review, support and advice. Additionally, the authors would like to thank the biomedical information specialists of the medical library of the Erasmus MC, University Medical Center Rotterdam, the Netherlands for their support with building the search. Finally, we thank the previous authors of this review who paved the way for this updated version.

REFERENCES

References to studies included in this review

Ajani 2005 {published data only}

Ajani JA, Fodor MB, Tjulandin SA, Moiseyenko VM, Chao Y, Cabral Filho S, et al. Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. *Journal of Clinical Oncology* 2005;**23**(24):5660-7.

Ajani 2010 {published data only}

Ajani JA, Buyse M, Lichinitser M, Gorbunova V, Bodoky G, Douillard JY, et al. Combination of cisplatin/S-1 in the treatment of patients with advanced gastric or gastroesophageal adenocarcinoma: results of noninferiority and safety analyses compared with cisplatin/5-fluorouracil in the First-Line Advanced Gastric Cancer Study. *European Journal of Cancer* 2013;**49**(17):3616-24.

* Ajani JA, Rodriguez W, Bodoky G, Moiseyenko V, Lichinitser M, Gorbunova V, et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. *Journal of Clinical Oncology* 2010;**28**(9):1547-53.

Bodoky G, Scheulen ME, Rivera F, Jassem J, Carrato A, Moiseyenko V, et al. Clinical benefit and health-related quality of life assessment in patients treated with cisplatin/S-1 versus Cisplatin/5-FU: secondary end point results from the first-line advanced gastric cancer study (FLAGS). *Journal of Gastrointestinal Cancer* 2015;**46**(2):109-17.

Al-Batran 2008 {published data only}

Al-Batran SE, Hartmann JT, Probst S, Schmalenberg H, Hollerbach S, Hofheinz R, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. *Journal of Clinical Oncology* 2008;**26**(9):1435-42.

Al-Batran 2013 {published data only}

Al-Batran SE, Pauligk C, Homann N, Hartmann JT, Moehler M, Probst S, et al. The feasibility of triple-drug chemotherapy combination in older adult patients with oesophagogastric cancer: a randomised trial of the Arbeitsgemeinschaft Internistische Onkologie (FLOT65+). *European Journal of Cancer* 2013;**49**(4):835-42.

Bang 2010 {published data only}

* Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki 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. *Lancet* 2010;**376**(9742):687-97.

Satoh T, Bang YJ, Gotovkin EA, Hamamoto Y, Kang YK, Moiseyenko VM, et al. Quality of life in the trastuzumab for gastric cancer trial. *Oncologist* 2014;**19**(7):712-9.

Sawaki A, Ohashi Y, Omuro Y, Satoh T, Hamamoto Y, Boku N, et al. Efficacy of trastuzumab in Japanese patients with HER2-positive advanced gastric or gastroesophageal junction cancer: a subgroup analysis of the Trastuzumab for Gastric Cancer (ToGA) study. *Gastric Cancer* 2012;**15**(3):313-22.

Shiomiwa T, Fukuda T, Shimoizuma K. Cost-effectiveness analysis of trastuzumab to treat HER2-positive advanced gastric cancer based on the randomised ToGA trial. *British Journal of Cancer* 2011;**105**(9):1273-8.

Bleiberg 1997 {published data only}

Bleiberg H, Conroy T, Paillot B, Lacave AJ, Blijham G, Jacob JH, et al. Randomised phase II study of cisplatin and 5-fluorouracil (5-Fu) versus cisplatin alone in advanced squamous cell oesophageal cancer. *European Journal of Cancer* 1997;**33**(8):1216-20.

Cunningham 2008 {published data only}

* Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *New England Journal of Medicine* 2008;**358**(1):36-46.

Sumpter K, Harper-Wynne C, Cunningham D, Rao S, Tebbutt N, Norman AR, et al. Report of two protocol planned interim analyses in a randomised multicentre phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophagogastric cancer receiving ECF. *British Journal of Cancer* 2005;**92**(11):1976-83.

Dank 2008 {published data only}

Curran D, Pozzo C, Zaluski J, Dank M, Barone C, Valvere V, et al. Quality of life of palliative chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction treated with irinotecan combined with 5-fluorouracil and folinic acid: results of a randomised phase III trial. *Quality of Life Research* 2009;**18**(7):853-61.

* Dank M, Zaluski J, Barone C, Valvere V, Yalcin S, Peschel C, et al. Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction. *Annals of Oncology* 2008;**19**(8):1450-7.

Duffour 2006 {published data only}

Duffour J, Bouche O, Rougier P, Milan C, Bedenne L, Seitz JF, et al. Safety of cisplatin combined with continuous 5-FU versus bolus 5-FU and leucovorin, in metastatic gastrointestinal cancer (FFCD 9404 randomised trial). *Anticancer Research* 2006;**26**(5 B):3877-83.

Dutton 2014 {published data only}

Dutton SJ, Ferry DR, Blazeby JM, Abbas H, Dahle-Smith A, Mansoor W, et al. Gefitinib for oesophageal cancer progressing after chemotherapy (COG): a phase 3, multicentre, double-blind, placebo-controlled randomised trial. *Lancet Oncology* 2014;**15**(8):894-904.

Eatock 2013 {published data only}

Eatock MM, Tebbutt NC, Bampton CL, Strickland AH, Valladares-Ayerbes M, Swieboda-Sadlej A, et al. Phase II randomized, double-blind, placebo-controlled study of AMG 386 (trebananib) in combination with cisplatin and capecitabine in patients with metastatic gastro-oesophageal cancer. *Annals of Oncology* 2013;**24**(3):710-8.

Ezdinli 1980 {published data only}

Ezdinli EZ, Gelber R, Desai DV, Falkson G, Moertel CG, Hahn RG. Chemotherapy of advanced esophageal carcinoma. *Cancer* 1980;**46**(10):2149-53.

Ford 2014 {published data only}

Ford HER, Marshall A, Bridgewater JA, Janowitz T, Coxon FY, Wadsley J, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. *Lancet Oncology* 2014;**15**(1):78-86.

Fuchs 2014 {published data only}

* Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, 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.

Muro K, Cho JY, Bodoky G, Goswami C, Chao Y, Dos Santos LV, et al. Efficacy and safety of ramucirumab (RAM) for metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma across age subgroups in two global phase 3 trials. *Journal of Clinical Oncology* 2017 Feb [Epub ahead of print]; Vol. 35, issue 4 Suppl 3. [DOI: [10.1200/JCO.2017.35.4_suppl.3](https://doi.org/10.1200/JCO.2017.35.4_suppl.3)]

Huang 2009 {published data only}

Huang JY, Sun Y, Fan QX, Zhang YQ. Efficacy of Shenyi Capsule combined with gemcitabine plus cisplatin in treatment of advanced esophageal cancer: A randomized controlled trial. *Chinese Journal of Integrative Medicine* 2009;**7**(11):1047-51.

Iveson 2014 {published data only}

Iveson T, Donehower RC, Davidenko I, Tjulandin S, Deptala A, Harrison M, et al. Rilotumumab in combination with epirubicin, cisplatin, and capecitabine as first-line treatment for gastric or oesophagogastric junction adenocarcinoma: an open-label, dose de-escalation phase 1b study and a double-blind, randomised phase 2 study. *Lancet Oncology* 2014;**15**(9):1007-18.

Levard 1998 {published data only}

* Levard H, Pouliquen X, Hay J-M, Fingerhut A, Langlois-Zantain O, Huguier M, et al. 5-Fluorouracil and cisplatin as palliative treatment of advanced oesophageal squamous cell carcinoma. *European Journal of Surgery* 1998;**164**(11):849-57.

Pouliquen X, Levard H, Hay J-M, McGee K, Fingerhut A, Langlois-Zantain O. 5-Fluorouracil and cisplatin therapy after palliative surgical resection of squamous cell carcinoma of the esophagus. A multicenter randomized trial. French Associations for Surgical Research. *Annals of Surgery* 1996;**223**(2):127.

Li 2002 {published data only}

Li Q, Feng FY, Han J, Sui GJ, Zhu YG, Zhang Y, et al. Phase III clinical study of a new anticancer drug atofluding. *Ai Zheng* 2002;**21**(12):1350-3.

Lordick 2013 {published data only}

Lordick F, Kang YK, Chung HC, Salman P, Oh SC, Bodoky G, et al. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. *Lancet Oncology* 2013;**14**(6):490-9.

Lorenzen 2009 {published data only}

Lorenzen S, Schuster T, Porschen R, Al-Batran SE, Hofheinz R, Thuss-Patience P, et al. Cetuximab plus cisplatin-5-fluorouracil versus cisplatin-5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized phase II study of the Arbeitsgemeinschaft Internistische Onkologie. *Annals of Oncology* 2009;**20**(10):1667-73.

Lorenzen 2015 {published data only}

Lorenzen S, Riera Knorrenschild J, Haag GM, Pohl M, Thuss-Patience P, Bassermann F, et al. Lapatinib versus lapatinib plus capecitabine as second-line treatment in human epidermal growth factor receptor 2-amplified metastatic gastro-oesophageal cancer: a randomised phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. *European Journal of Cancer* 2015;**51**(5):569-76.

Moehler 2010 {published data only}

Moehler M, Kanzler S, Geissler M, Raedle J, Ebert MP, Daum S, et al. A randomized multicenter phase II study comparing capecitabine with irinotecan or cisplatin in metastatic adenocarcinoma of the stomach or esophagogastric junction. *Annals of Oncology* 2010;**21**(1):71-7.

Nicolaou 1982 {published data only}

Nicolaou N, Conlan AA. Cyclophosphamide, doxorubicin and celetin intubation for inoperable oesophageal carcinoma. *South African Medical Journal* 1982;**61**(12):428-31.

Ohtsu 2011 {published data only}

Ohtsu A, Shah MA, Van Cutsem E, Rha SY, Sawaki A, Park SR, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. *Journal of Clinical Oncology* 2011;**29**(30):3968-76.

Pang 2014 {published data only}

Pang LN, Wang F, He W, Zhou R, Cao L, Fan QX. Efficacy and safety of S-1 or fluorouracil combined with cisplatin in treatment of advanced esophagus cancer. *World Chinese Journal of Digestology* 2014;**22**(3):383-8.

Pozzo 2004 {published data only}

Pozzo C, Barone C, Szanto J, Padi E, Peschel C, Bukki J, et al. Irinotecan in combination with 5-fluorouracil and folinic acid or with cisplatin in patients with advanced gastric or esophageal-gastric junction adenocarcinoma: results of a randomized phase II study. *Annals of Oncology* 2004;**15**(12):1773-81.

Rao 2010 {published data only}

Rao S, Starling N, Cunningham D, Sumpter K, Gilligan D, Ruhstaller T, et al. Matuzumab plus epirubicin, cisplatin and capecitabine (ECX) compared with epirubicin, cisplatin and capecitabine alone as first-line treatment in patients with advanced oesophago-gastric cancer: a randomised, multicentre open-label phase II study. *Annals of Oncology* 2010;**21**(11):2213-9.

Richards 2013 {published data only}

Richards D, Kocs DM, Spira AI, David McCollum A, Diab S, Hecker LI, et al. Results of docetaxel plus oxaliplatin (DOCOX) (plus or minus) cetuximab in patients with metastatic gastric and/or gastroesophageal junction adenocarcinoma: results of a randomised phase 2 study. *European Journal of Cancer* 2013;**49**(13):2823-31.

Ross 2002 {published data only}

Ross P, Nicolson M, Cunningham D, Valle J, Seymour M, Harper P, et al. Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. *Journal of Clinical Oncology* 2002;**20**(8):1996-2004.

Roy 2012 {published data only}

Roy A, Cunningham D, Hawkins R, Sorbye H, Adenis A, Barcelo JR, et al. Docetaxel combined with irinotecan or 5-fluorouracil in patients with advanced oesophago-gastric cancer: a randomised phase II study. *British Journal of Cancer* 2012;**107**(3):435-41.

Shen 2014 {published data only}

Shen L, Li J, Xu J, Pan H, Dai G, Qin S, et al. Bevacizumab plus capecitabine and cisplatin in Chinese patients with inoperable locally advanced or metastatic gastric or gastroesophageal junction cancer: randomized, double-blind, phase III study (AVATAR study). *Gastric Cancer* 2014;**18**(1):168-76.

Tebbutt 2002 {published data only}

Tebbutt NC, Norman A, Cunningham D, Iveson T, Seymour M, Hickish T, et al. A multicentre, randomised phase III trial comparing protracted venous infusion (PVI) 5-fluorouracil (5-FU) with PVI 5-FU plus mitomycin C in patients with inoperable oesophago-gastric cancer. *Annals of Oncology* 2002;**13**(10):1568-75.

Tebbutt 2010 {published data only}

Tebbutt NC, Cummins MM, Sourjina T, Strickland A, Van Hazel G, Ganju V, et al. Randomised, non-comparative phase II study of weekly docetaxel with cisplatin and 5-fluorouracil or with capecitabine in oesophagogastric cancer: the AGITG ATTAX trial. *British Journal of Cancer* 2010;**102**(3):475-81.

Thuss-Patience 2011 {published data only}

Thuss-Patience PC, Kretzschmar A, Dogan Y, Rothmann F, Blau I, Schwaner I, et al. Docetaxel and capecitabine for advanced gastric cancer: investigating dose-dependent efficacy in two patient cohorts. *British Journal of Cancer* 2011;**105**(4):505-12.

Van Cutsem 2006 {published data only}

Ajani JA, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, et al. Clinical benefit with docetaxel plus fluorouracil and cisplatin compared with cisplatin and fluorouracil in a phase III trial of advanced gastric or gastroesophageal cancer adenocarcinoma: the V-325 study group. *Journal of Clinical Oncology* 2007;**25**(22):3205-9.

Ajani JA, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, et al. Quality of life with docetaxel plus cisplatin and fluorouracil compared with cisplatin and fluorouracil from a phase III trial for advanced gastric or gastroesophageal adenocarcinoma: the V-325 study group. *Journal of Clinical Oncology* 2007;**25**(22):3210-6.

* Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 study group. *Journal of Clinical Oncology* 2006 Nov;**24**(31):4991-7.

Van Cutsem 2015 {published data only}

Van Cutsem E, Boni C, Tabernero J, Massuti B, Middleton G, Dane F, et al. Docetaxel plus oxaliplatin with or without fluorouracil or capecitabine in metastatic or locally recurrent gastric cancer: a randomized phase II study. *Annals of Oncology* 2015;**26**(1):149-56.

Waddell 2013 {published data only}

* Waddell T, Chau I, Cunningham D, Gonzalez D. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. *Lancet Oncology* 2013;**14**(6):481-9.

Waddell TS, Chau I, Barbachano Y, De Castro DG, Wotherspoon A, Saffery C, et al. A randomized multicenter trial of epirubicin, oxaliplatin, and capecitabine (EOC) plus panitumumab in advanced esophagogastric cancer (REAL3). *Journal of Clinical Oncology* 2012;**30**(6):18.

Waddell TS, Chau I, Peckitt C, Gonzalez D, Wotherspoon A, Patel B, et al. Quality of life (QoL) analysis from the randomized phase III REAL3 trial of epirubicin, oxaliplatin, and capecitabine (EOC) with or without panitumumab (P) in advanced esophagogastric adenocarcinoma. *Journal of Clinical Oncology* 2014;**32**(15):4067.

Waters 1999 {published data only}

* Waters JS, Norman A, Cunningham D, Scarffe JH, Webb A, Harper P, et al. Long-term survival after epirubicin, cisplatin and fluorouracil for gastric cancer: results of a randomized trial. *British Journal of Cancer* 1999;**80**(1-2):269-72.

Webb A, Cunningham D, Scarffe JH, Harper P, Norman A, Joffe JK, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *Journal of Clinical Oncology* 1997;**15**(1):261-7.

Wilke 2014 {published data only}

Al-Batran SE, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, Hironaka S, et al. Quality-of-life and performance status results from the phase III RAINBOW study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated gastric or gastroesophageal junction adenocarcinoma. *Annals of Oncology* 2016;**27**(4):673-9.

Muro K, Cho JY, Bodoky G, Goswami C, Chao Y, Dos Santos LV, et al. Efficacy and safety of ramucirumab (RAM) for metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma across age subgroups in two global phase 3 trials. *Journal of Clinical Oncology* 2017 Feb [Epub ahead of print]; Vol. 35, issue 4 Suppl 3. [DOI: [10.1200/JCO.2017.35.4_suppl.3](https://doi.org/10.1200/JCO.2017.35.4_suppl.3)]

Muro K, Oh SC, Shimada Y, Lee KW, Yen CJ, Chao Y, et al. Subgroup analysis of East Asians in RAINBOW: A phase 3 trial of ramucirumab plus paclitaxel for advanced gastric cancer. *Journal of Gastroenterology and Hepatology* 2016;**31**(3):581-9.

Shitara K, Muro K, Shimada Y, Hironaka S, Sugimoto N, Komatsu Y, et al. Subgroup analyses of the safety and efficacy of ramucirumab in Japanese and Western patients in RAINBOW: a randomized clinical trial in second-line treatment of gastric cancer. *Gastric Cancer* 2016;**19**(3):927-38.

* Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, 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 Oncology* 2014;**15**(11):1224-35.

Wilkes 2011 {published data only}

Wilkes EA, Selby AL, Cole AT, Freeman JG, Rennie MJ, Khan ZH. Poor tolerability of thalidomide in end-stage oesophageal cancer. *European Journal of Cancer Care* 2011;**20**(5):593-600.

Xu 2013a {published data only}

Xu Z, Chen J, Tao M. Nimotuzumab combined with cisplatin and 5-FU in treatment of patients with advanced esophageal squamous cell carcinoma. *Journal of Practical Oncology* 2013;**28**(6):650-3.

References to studies excluded from this review
Adenis 2010 {published data only}

Adenis A, Penel N, Horn S, Dominguez S, Vanhuyse M, Mirabel X. Palliative chemotherapy does not improve survival in metastatic esophageal cancer. *Oncology* 2010;**79**(1-2):46-54.

Al-Batran 2010 {published data only}

Al-Batran SE, Ajani JA. Impact of chemotherapy on quality of life in patients with metastatic esophagogastric cancer. *Cancer* 2010;**116**(11):2511-8.

Albertsson 2007 {published data only}

Albertsson M, Johansson B, Friesland S, Kadar L, Letocha H, Frykholm G, et al. Phase II studies on docetaxel alone every third week, or weekly in combination with gemcitabine in patients with primary locally advanced, metastatic, or recurrent

esophageal cancer. *Medical Oncology (Northwood, London, England)* 2007;**24**(4):407-12.

Boku 2009 {published data only}

Boku N, Yamamoto S, Fukuda H, Shirao K, Doi T, Sawaki A, et al. Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. *Lancet Oncology* 2009;**10**(11):1063-9.

Brell 2009 {published data only}

Brell JM, Krishnamurthi SS, Javle M, Saltzman J, Wollner I, Pelley R, et al. A multi-center phase II study of oxaliplatin, irinotecan, and capecitabine in advanced gastric/gastroesophageal junction carcinoma. *Cancer Chemotherapy and Pharmacology* 2009;**63**(5):851-7.

Burris 2017 {published data only}

Burris HA, Kurkjian CD, Hart L, Pant S, Murphy PB, Jones SF, et al. TAK-228 (formerly MLN0128), an investigational dual TORC1/2 inhibitor plus paclitaxel, with/without trastuzumab, in patients with advanced solid malignancies. *Cancer Chemotherapy and Pharmacology* 2017;**80**(2):261-73.

Cascinu 2011 {published data only}

Cascinu S, Galizia E, Labianca R, Ferraro F, Pucci F, Silva RR, et al. Pegylated liposomal doxorubicin, 5-fluorouracil and cisplatin versus mitomycin-C, 5-fluorouracil and cisplatin for advanced gastric cancer: a randomized phase II trial. *Cancer Chemotherapy and Pharmacology* 2011;**68**(1):37-43.

Du 2015 {published data only}

Du F, Zheng Z, Shi S, Jiang Z, Qu T, Yuan X, et al. S-1 and cisplatin with or without nimotuzumab for patients with untreated unresectable or metastatic gastric cancer: a randomized, open-label phase 2 trial. *Medicine (Baltimore)* 2015;**94**(23):e958. [10.1097/MD.0000000000000958]

Eichhorst 2016 {published data only}

Eichhorst B, Fink AM, Bahlo J, Busch R, Kovacs G, Maurer C, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. *Lancet Oncology* 2016;**17**(7):928-42.

Font 2008 {published data only}

Font A, Salazar R, Maurel J, Taron M, Ramirez JL, Tabernero J, et al. Cisplatin plus weekly CPT-11/docetaxel in advanced esophagogastric cancer: a phase I study with pharmacogenetic assessment of XPD, XRCC3 and UGT1A1 polymorphisms. *Cancer Chemotherapy and Pharmacology* 2008;**62**(6):1075-83.

Grunberger 2007 {published data only}

Grunberger B, Raderer M, Schmidinger M, Hejna M. Palliative chemotherapy for recurrent and metastatic esophageal cancer. *Anticancer Research* 2007;**27**(4 C):2705-14.

Gubanski 2010 {published data only}

Gubanski M, Johnsson A, Fernebro E, Kadar L, Karlberg I, Flygare P, et al. Randomized phase II study of sequential

docetaxel and irinotecan with 5-fluorouracil/folinic acid (leucovorin) in patients with advanced gastric cancer: the GATAC trial. *Gastric Cancer* 2010;**13**(3):155-61.

Gubanski 2014 {published data only}

Gubanski M, Glimelius B, Lind PA. Quality of life in patients with advanced gastric cancer sequentially treated with docetaxel and irinotecan with 5-fluorouracil and folinic acid (leucovorin). *Medical Oncology (Northwood, London)* 2014;**31**(4):906.

Hironaka 2013 {published data only}

Hironaka S, Ueda S, Yasui H, Nishina T. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. *Journal of Clinical Oncology* 2013;**31**(35):4438-44.

Horgan 2011 {published data only}

Horgan AM, Knox JJ, Liu G, Sahi C, Bradbury PA, Leighl NB. Capecitabine or infusional 5-fluorouracil for gastroesophageal cancer: a cost-consequence analysis. *Current Oncology (Toronto)* 2011;**18**(2):e64-e70.

Ilhan-Mutlu 2013 {published data only}

Ilhan-Mutlu A, Preusser M, Schoppmann SF, Asari R, Ba-Ssalamah A, Schwameis K, et al. Comparison between DCF (Docetaxel, Cisplatin and 5-Fluorouracil) and modified EOX (Epirubicin, Oxaliplatin and Capecitabine) as palliative first-line chemotherapy for adenocarcinoma of the upper gastrointestinal tract. *Anticancer Research* 2013;**33**(8):3455-9.

Imazawa 2009 {published data only}

Imazawa M, Kojima T, Boku N, Onozawa Y, Hironaka S, Fukutomi A, et al. Efficacy of sequential methotrexate and 5-fluorouracil (MTX/5FU) in improving oral intake in patients with advanced gastric cancer with severe peritoneal dissemination. *Gastric Cancer* 2009;**12**(3):153-7.

Jeung 2011 {published data only}

Jeung HC, Rha SY, Im CK, Shin SJ, Ahn JB, Yang WI, et al. A randomized phase 2 study of docetaxel and S-1 versus docetaxel and cisplatin in advanced gastric cancer with an evaluation of SPARC expression for personalized therapy. *Cancer* 2011 May 15;**117**(10):2050-7.

Kang 2009 {published data only}

Kang YK, Kang WK, Shin DB, Chen J, Xiong J, Wang J, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. *Annals of Oncology* 2009;**20**(4):666-73.

Kerkar 2009 {published data only}

Kerkar SP, Kemp CD, Duffy A, Kammula US, Schrupp DS, Kwong KF, et al. The GYMSSA trial: a prospective randomized trial comparing gastrectomy, metastasectomy plus systemic therapy versus systemic therapy alone. *Trials* 2009;**10**:121.

Kim 2014 {published data only}

Kim YS, Sym SJ, Park SH, Park I, Hong J, Ahn HK, et al. A randomized phase II study of weekly docetaxel/cisplatin versus weekly docetaxel/oxaliplatin as first-line therapy for patients with advanced gastric cancer. *Cancer Chemotherapy and Pharmacology* 2014;**73**(1):163-9.

Koizumi 2010 {published data only}

Koizumi W, Tanabe S, Azuma M, Ishido K, Nishimura K, Sasaki T, et al. Impacts of fluorouracil-metabolizing enzymes on the outcomes of patients treated with S-1 alone or S-1 plus cisplatin for first-line treatment of advanced gastric cancer. *International Journal of Cancer [Journal International du Cancer]* 2010;**126**(1):162-70.

Koizumi 2014 {published data only}

Koizumi W, Kim YH, Fujii M, Kim HK, Imamura H, Lee KH, et al. Addition of docetaxel to S-1 without platinum prolongs survival of patients with advanced gastric cancer: a randomized study (START). *Journal of Cancer Research and Clinical Oncology* 2014;**140**(2):319-28.

Komatsu 2011 {published data only}

Komatsu Y, Takahashi Y, Kimura Y, Oda H, Tajima Y, Tamura S, et al. Randomized phase II trial of first-line treatment with tailored irinotecan and S-1 therapy versus S-1 monotherapy for advanced or recurrent gastric carcinoma (JFMC31-0301). *Anticancer Drugs* 2011;**22**(6):576-83.

Konings 2010 {published data only}

Konings IR, van der Gaast A, van der Wijk LJ, de Jongh FE, Eskens FA, Sleijfer S. The addition of pravastatin to chemotherapy in advanced gastric carcinoma: a randomised phase II trial. *European Journal of Cancer* 2010;**46**(18):3200-4.

Le Tourneau 2015 {published data only}

Le Tourneau C, Delord JP, Gonçalves A, Gavoille C, Dubot C, Isambert N, et al. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): A multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. *Lancet Oncology* 2015;**16**(13):1324-34.

Li 2011 {published data only}

Li XD, Shen H, Jiang JT, Zhang HZ, Zheng X, Shu YQ, et al. Paclitaxel based vs oxaliplatin based regimens for advanced gastric cancer. *World Journal of Gastroenterology* 2011;**17**(8):1082-7.

Lim 2010 {published data only}

Lim do H, Park SH, Park KW, Kang JH, Oh SY, Hwang IG, et al. Retrospective analyses of cisplatin-based doublet combination chemotherapy in patients with advanced gastric cancer. *BMC Cancer* 2010;**10**:583.

Lim 2017 {published data only}

Lim SH, Shim YM, Park SH, Kim HK, Choi YS, Ahn MJ, et al. A randomized phase II study of leucovorin/5-fluorouracil with or without oxaliplatin (LV5FU2 vs. FOLFOX) for curatively-resected, node-positive esophageal squamous cell carcinoma. *Cancer Research and Treatment* 2017;**49**(3):816-23.

Lissoni 2009 {published data only}

Lissoni P, Rovelli F, Brivio F, Zago R, Colciago M, Messina G, et al. A randomized study of chemotherapy versus biochemotherapy with chemotherapy plus *Aloe arborescens* in patients with metastatic cancer. *In Vivo* 2009;**23**(1):171-5.

Lu 2014 {published data only}

Lu YM, Liu ZC, Zhang J. S-1 plus oxaliplatin vs. S-1 as first-line treatment in patients with previously untreated advanced gastric cancer: a randomized phase II study. *Journal of Chemotherapy (Florence)* 2014;**26**(3):159-64.

Lundholm 2010 {published data only}

Lundholm K, Gunnebo L, Korner U, Iresjo BM, Engstrom C, Hylander A, et al. Effects by daily long term provision of ghrelin to unselected weight-losing cancer patients: a randomized double-blind study. *Cancer* 2010;**116**(8):2044-52.

Lustberg 2010 {published data only}

Lustberg MB, Bekaii-Saab T, Young D, Otterson G, Burak W, Abbas A, et al. Phase II randomized study of two regimens of sequentially administered mitomycin C and irinotecan in patients with unresectable esophageal and gastroesophageal adenocarcinoma. *Journal of Thoracic Oncology* 2010;**5**(5):713-8.

Macedo 2009 {published data only}

Macedo A, Pereira C, Goncalves J, Sousa C. Economic evaluation of capecitabine use as first line treatment in patients with advanced gastric carcinoma in Portugal. *Acta Medica Portuguesa* 2009;**22**(6):827-32.

Mizota 2011 {published data only}

Mizota A, Shitara K, Kondo C, Nomura M, Yokota T, Takahara D, et al. A retrospective comparison of docetaxel and paclitaxel for patients with advanced or recurrent esophageal cancer who previously received platinum-based chemotherapy. *Oncology (Switzerland)* 2011;**81**(3-4):237-42.

Moehler 2016b {published data only}

Moehler M, Gefner-Tuma I, Maderer A, Thuss-Patience PC, Ruessel J, Hegewisch-Becker S, et al. Sunitinib added to FOLFIRI versus FOLFIRI in patients with chemorefractory advanced adenocarcinoma of the stomach or lower esophagus: A randomized, placebo-controlled phase II AIO trial with serum biomarker program. *BMC Cancer* 2016;**16**(1):699. [DOI: [10.1186/s12885-016-2736-9](https://doi.org/10.1186/s12885-016-2736-9)]

Moon 2010 {published data only}

Moon YW, Rha SY, Jeung HC, Kim C, Hong MH, Chang H, et al. Outcomes of multiple salvage chemotherapy for advanced gastric cancer: implications for clinical practice and trial design. *Cancer Chemotherapy and Pharmacology* 2010;**66**(4):797-805.

Nakashima 2008 {published data only}

Nakashima K, Hironaka S, Boku N, Onozawa Y, Fukutomi A, Yamazaki K, et al. Irinotecan plus cisplatin therapy and S-1 plus cisplatin therapy for advanced or recurrent gastric cancer in a single institution. *Japanese Journal of Clinical Oncology* 2008;**38**(12):810-5.

Narahara 2011 {published data only}

Narahara H, Iishi H, Imamura H, Tsuburaya A, Chin K, Imamoto H, et al. Randomized phase III study comparing the efficacy and safety of irinotecan plus S-1 with S-1 alone as first-line treatment for advanced gastric cancer (study GC0301/TOP-002). *Gastric Cancer* 2011;**14**(1):72-80.

Ochendusko 2015 {published data only}

Ochendusko S, Konopka K, Puskulluoglu M, Urbanczyk K, Budzynski A, Matlok M, et al. Comparison of efficacy and tolerance of first-line palliative chemotherapy EOX and mDCF regimens in patients with locally advanced inoperable or metastatic gastric or gastroesophageal junction adenocarcinoma without overexpression of HER2 receptors. *Journal of Clinical Oncology* 2015;**33**(3 Suppl):135.

Ohtsu 2013 {published data only}

Ohtsu A, Ajani JA, Bai YX, Bang YJ, Chung HC, Pan HM, et al. Everolimus for previously treated advanced gastric cancer: Results of the randomized, double-blind, phase III GRANITE-1 study. *Journal of Clinical Oncology* 2013;**31**(31):3935-43.

Ojima 2016 {published data only}

Ojima T, Nakamori M, Nakamura M, Katsuda M, Hayata K, Kato T, et al. Neoadjuvant chemotherapy with divided-dose docetaxel, cisplatin and fluorouracil for patients with squamous cell carcinoma of the esophagus. *Anticancer Research* 2016;**36**(2):829-34.

Okines 2008 {published data only}

Okines AFC, Norman AR, McCloud PI, Kang Y, Cunningham D. Meta-analysis of the real 2 and ML17032 trials comparing capecitabine with 5-fluorouracil (5-Fu) in advanced oesophago-gastric cancer. *Annals of Oncology* 2008;**19**(S8):viii169.

Okines 2010a {published data only}

Okines AFC, Ashley SE, Cunningham D, Oates J, Turner A, Webb J, et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for advanced esophagogastric cancer: Dose-finding study for the prospective multicenter, randomized, phase II/III REAL-3 trial. *Journal of Clinical Oncology* 2010;**28**(25):3945-50.

Okines 2010b {published data only}

Okines AFC, Asghar U, Cunningham D, Ashley S, Ashton J, Jackson K, et al. Rechallenge with platinum plus fluoropyrimidine +/- Epirubicin in patients with oesophagogastric cancer. *Oncology (Switzerland)* 2010;**79**(1-2):150-8.

Park 2006 {published data only}

Park SH, Lee WK, Chung M, Lee Y, Han SH, Bang SM, et al. Paclitaxel versus docetaxel for advanced gastric cancer: a randomized phase II trial in combination with infusional 5-fluorouracil. *Anti-cancer Drugs* 2006;**17**(2):225-9.

Park 2014 {published data only}

Park JW, Yoon J, Cho CK, Lee YW, Yoo HS. Survival analysis of stage IV metastatic gastric cancer patients treated with HangAm-Plus. *Chinese Journal of Integrative Medicine* 2014;**20**(1):49-55.

Roth 2007 {published data only}

Roth AD, Fazio N, Stupp R, Falk S, Bernhard J, Saletti P, et al. Docetaxel, cisplatin, and fluorouracil; Docetaxel and cisplatin; and epirubicin, cisplatin, and fluorouracil as systemic treatment for advanced gastric carcinoma: A randomized phase II trial of the Swiss Group for Clinical Cancer Research. *Journal of Clinical Oncology* 2007;**25**(22):3217-23.

Sadighi 2006 {published data only}

Sadighi S, Mohagheghi MA, Montazeri A, Sadighi Z. Quality of life in patients with advanced gastric cancer: a randomized trial comparing docetaxel, cisplatin, 5-FU (TCF) with epirubicin, cisplatin, 5-FU (ECF). *BMC Cancer* 2006;**6**:274.

Sakamoto 2010 {published data only}

Sakamoto T, Yasui H, Boku N, Onozawa Y, Hironaka S, Fukutomi A, et al. Comparison of combination chemotherapy with irinotecan and cisplatin regimen administered every 2 or 4 weeks in pretreated patients with unresectable or recurrent gastric cancer: retrospective analysis. *International Journal of Clinical Oncology* 2010;**15**(3):287-93.

Satoh 2014 {published data only}

Satoh T, Xu RH, Chung HC, Sun GP, Doi T. 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. *Journal of Clinical Oncology* 2014;**32**(19):2039-49.

Satoh 2015 {published data only}

Satoh T, Lee KH, Rha SY, Sasaki Y, Park SH, Komatsu Y, et al. Randomized phase II trial of nimotuzumab plus irinotecan versus irinotecan alone as second-line therapy for patients with advanced gastric cancer. *Gastric Cancer* 2015;**18**(4):824-32.

Seol 2009 {published data only}

Seol YM, Song MK, Choi YJ, Kim GH, Shin HJ, Song GA, et al. Oral fluoropyrimidines (capecitabine or S-1) and cisplatin as first line treatment in elderly patients with advanced gastric cancer: a retrospective study. *Japanese Journal of Clinical Oncology* 2009;**39**(1):43-8.

Sgourakis 2012 {published data only}

Sgourakis G, Gockel I, Karaliotas C, Moehler M, Schimanski CC, Schmidberger H, et al. Survival after chemotherapy and/or radiotherapy versus self-expanding metal stent insertion in the setting of inoperable esophageal cancer: a case-control study. *BMC Cancer* 2012;**12**:70.

Shenfine 2009 {published data only}

Shenfine J, McNamee P, Steen N, Bond J, Griffin SM. A randomized controlled clinical trial of palliative therapies for patients with inoperable esophageal cancer. *American Journal of Gastroenterology* 2009;**104**(7):1674-85.

Shirao 2013 {published data only}

Shirao K, Boku N, Yamada Y, Yamaguchi K, Doi T, Goto M, 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). *Japanese Journal of Clinical Oncology* 2013;**43**(10):972-80.

Shitara 2011 {published data only}

Shitara K, Matsuo K, Mizota A, Kondo C, Nomura M, Takahari D, et al. Association of fluoropyrimidines, platinum agents, taxanes, and irinotecan in any line of chemotherapy with survival in patients with advanced gastric cancer. *Gastric Cancer* 2011;**14**(2):155-60.

Shu 2017 {published data only}

Shu ZB, Ding DY, Li YC. Adjuvant chemotherapy for chemotherapy-naïve advanced gastric cancer patients with oxaliplatin plus tegafur versus oxaliplatin plus S-1. *International Journal of Clinical and Experimental Medicine* 2017;**10**(6):9322-9.

Sun 2013 {published data only}

Sun J, Sheng ZJ. Clinical study on efficacy of Aidi injection combined with PT chemotherapy protocol in advanced esophageal cancer patients. *Cancer Research and Clinic* 2013;**25**(8):547-9.

Takashima 2010 {published data only}

Takashima A, Yamada Y, Nakajima TE, Kato K, Hamaguchi T, Shimada Y. Standard first-line chemotherapy for metastatic gastric cancer in Japan has met the global standard: evidence from recent phase III trials. *Gastrointestinal Cancer Research* 2010;**3**(6):33-8.

Tanaka 2010 {published data only}

Tanaka T, Fujita H, Matono S, Nagano T, Nishimura K, Murata K, et al. Outcomes of multimodality therapy for stage IVB esophageal cancer with distant organ metastasis (M1-Org). *Diseases of the Esophagus* 2010;**23**(8):646-51.

Thuss-Patience 2005 {published data only}

Thuss-Patience PC, Kretzschmar A, Repp M, Kingreen D, Henneser D, Micheel S, et al. Docetaxel and continuous-infusion fluorouracil versus epirubicin, cisplatin, and fluorouracil for advanced gastric adenocarcinoma: a randomized phase II study. *Journal of Clinical Oncology* 2005;**23**(3):494-501.

Whistance 2011 {published data only}

Whistance RN, Blazeby JM. Systematic review: quality of life after treatment for upper gastrointestinal cancer. *Current Opinion in Supportive and Palliative Care* 2011;**5**(1):37-46.

Xu 2013b {published data only}

Xu Y, Zhao AG, Li ZY, Zhao G, Cai Y, Zhu XH, et al. Survival benefit of traditional Chinese herbal medicine (a herbal formula for invigorating spleen) for patients with advanced gastric cancer. *Integrative Cancer Therapies* 2013;**12**(5):414-22.

Yamada 2015 {published data only}

Yamada Y, Higuchi K, Nishikawa K, Gotoh M, Fuse N, Sugimoto N, et al. Phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naïve patients with advanced gastric cancer. *Annals of Oncology* 2015;**26**(1):141-8.

Yamazaki 2008 {published data only}

Yamazaki K, Hironaka S, Boku N, Yasui H, Fukutomi A, Yoshino T, et al. A retrospective study of second-line chemotherapy for unresectable or recurrent squamous cell carcinoma of the esophagus refractory to chemotherapy with 5-fluorouracil plus platinum. *International Journal of Clinical Oncology* 2008;**13**(2):150-5.

Yu 2010 {published data only}

Yu J, Wang BH, Zhang XZ. Clinical study of paclitaxel plus nedaplatin versus paclitaxel plus cisplatin in treatment of patients with advanced esophageal carcinoma. *Chinese Journal of Cancer Prevention and Treatment* 2010;**17**(9):693-5.

Yun 2010 {published data only}

Yun J, Lee J, Park SH, Park JO, Park YS, Lim HY, et al. A randomised phase II study of combination chemotherapy with epirubicin, cisplatin and capecitabine (ECX) or cisplatin and capecitabine (CX) in advanced gastric cancer. *European Journal of Cancer* 2010;**46**(5):885-91.

Zhang 2006 {published data only}

Zhang P, Feng FY, Wu LY, Hu Y, Liu JW, Gao YJ, et al. Phase II multicenter clinical trial of nedaplatin in the treatment of malignant tumors. *Zhonghua Zhong Liu Za Zhi* 2006;**28**(3):230-4.

References to studies awaiting assessment
Ajani 2017 {published data only}

Ajani JA, Abramov M, Bondarenko I, Shparyk Y, Gorbunova V, Hontsa A, et al. A phase III trial comparing oral S-1/cisplatin and intravenous 5-fluorouracil/cisplatin in patients with untreated diffuse gastric cancer. *Annals of Oncology* 2017;**28**(9):2142-8.

Al-Batran 2017 {published data only}

Al-Batran SE, Riera-Knorrenschild J, Pauligk C, Goetze TO, Hegewisch-Becker S, Seraphin J, et al. A randomized, double-blind, multicenter phase III study evaluating paclitaxel with and without RAD001 in patients with gastric cancer who have progressed after therapy with a fluoropyrimidine/platinum-containing regimen (RADPAC). *Journal of Clinical Oncology* 2017;**35**(4 Suppl):4. [DOI: [10.1200/JCO.2017.35.4_suppl.4](https://doi.org/10.1200/JCO.2017.35.4_suppl.4)]

Bang 2017 {published data only}

Bang YJ, Cho JY, Kim YH, Kim JW, Di Bartolomeo M, Ajani JA, et al. Efficacy of sequential ipilimumab monotherapy versus best supportive care for unresectable locally advanced/metastatic gastric or gastroesophageal junction cancer. *Clinical Cancer Research* 2017;**23**(19):5671-8.

Bi 2011 {published data only}

Bi F, Li Q, Zhou C, Yu J, Cai X, Qiu M, et al. Preliminary results of a randomized phase II study: Treatment of Chinese patients with advanced gastric cancer with FOLFIRI followed by FOLFOX7 or the reverse sequence. *Journal of Clinical Oncology* 2011;**29**(15):Supplement.

Cohen 2013 {published data only}

Cohen DJ, Christos PJ, Kindler HL, Catenacci DVT, Bekaii-Saab TB, Tahiri S, et al. Vismodegib (V), a hedgehog (HH)

pathway inhibitor, combined with FOLFOX for first-line therapy of patients (pts) with advanced gastric and gastroesophageal junction (GEJ) carcinoma: a New York Cancer Consortium led phase II randomized study. *Journal of Clinical Oncology* 2013;**31**(15):4011.

Denlinger 2016 {published data only}

Denlinger CS, Maqueda MA, Watkins DJ, Sym SJ, Bendell JC, Park SH, et al. Randomized phase 2 study of paclitaxel (PTX), trastuzumab (T) with or without MM-111 in HER2 expressing gastroesophageal cancers (GEC). *Journal of Clinical Oncology* 2016;**34**(15 Suppl):4043.

Enzinger 2016 {published data only}

Enzinger PC, Burtneess BA, Niedzwiecki D, Ye X, Douglas K, Ilson DH, et al. CALGB 80403 (Alliance)/E1206: a randomized phase II study of three chemotherapy regimens plus cetuximab in metastatic esophageal and gastroesophageal junction cancers. *Journal of Clinical Oncology* 2016;**34**(23):2736-42.

Hall 2017 {published data only}

Hall PS, Lord SR, Collinson M, Marshall H, Jones M, Lowe C, et al. A randomised phase II trial and feasibility study of palliative chemotherapy in frail or elderly patients with advanced gastroesophageal cancer (321GO). *British Journal of Cancer* 2017;**116**(4):472-8.

Hecht 2016 {published data only}

Hecht JR, Bang YJ, Qin SK, Chung HC, Xu JM, Park JO, et al. Lapatinib in combination with capecitabine plus oxaliplatin in human epidermal growth factor receptor 2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma: TRIO-013/LOGIC - A randomized phase III trial. *Journal of Clinical Oncology* 2016;**34**(5):443-51.

Huang 2016 {published data only}

Huang J, Liu Y, Dai S, Lu P, Ba Y, Wu L, et al. Randomized, open-label, phase III study comparing irinotecan plus S-1 with S-1 alone in patients with advanced esophageal squamous cell carcinoma after failure of prior platinum- or taxane-based chemotherapy: Results of an interim analysis. *Annals of Oncology* 2016;**27**(6 Suppl):LBA27. [DOI: [10.1093/annonc/mdw435.18](https://doi.org/10.1093/annonc/mdw435.18)]

Iqbal 2017 {published data only}

Iqbal S, McDonough S, Lenz HJ, Ilson DH, Burtneess B, Nangia CS, et al. A randomized phase II pilot study prospectively evaluating treatment for patients based on ERCC1 for advanced/metastatic esophageal, gastric, or gastroesophageal junction cancer: SWOG S1201. *Journal of Clinical Oncology* 2017;**35**(15 Suppl):4009.

Janjigian 2017 {published data only}

Janjigian YY, Bendell JC, Calvo E, Kim JW, Ascierto PA, Sharma P, et al. CheckMate-032: Phase I/II, open-label study of safety and activity of nivolumab (nivo) alone or with ipilimumab (ipi) in advanced and metastatic (A/M) gastric cancer (GC). *Journal of Clinical Oncology* 2016;**34**(14 Suppl):4010.

Kang 2017 {published data only}

Kang YK, Satoh T, Ryu MH, Chao Y, Kato K, Chung HC, et al. Nivolumab (ONO-4538/BMS-936558) as salvage treatment after second or later-line chemotherapy for advanced gastric or gastro-esophageal junction cancer (AGC): A double-blinded, randomized, phase III trial. *Journal of Clinical Oncology* 2017;**35**(4 Suppl):2.

Lee 2013 {published data only}

Lee KH, Baba E, Ryu MH, Boku N, Park YI, Hyodo I, et al. Phase III trial of a 3-weekly vs. 5-weekly schedule of S-1 plus cisplatin (SP) combination chemotherapy for first-line treatment of advanced gastric cancer (AGC): SOS study. *European Journal of Cancer* 2013;**49**(14):S614-5.

Lee 2015 {published data only}

Lee SJ, Kim S, Kim M, Lee J, Park YH, Im Y-H, et al. Capecitabine in combination with either cisplatin or weekly paclitaxel as a first-line treatment for metastatic esophageal squamous cell carcinoma: A randomized phase II study. *BMC Cancer* 2015;**15**(1):693.

Li 2015 {published data only}

Li YH, Qiu MZ, Xu JM, Sun GP, Lu HS, Liu YP, et al. S-1 plus Cisplatin versus fluorouracil plus cisplatin in advanced gastric or gastro-esophageal junction adenocarcinoma patients: A pilot study. *Oncotarget* 2015;**6**(33):35107-15.

Li 2016a {published data only}

Li J, Qin S, Xu J, Xiong J, Wu C, Bai Y, et al. Randomized, double-blind, placebo-controlled phase III trial of apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction. *Journal of Clinical Oncology* 2016;**34**(13):1448-54.

Li 2016b {published data only}

Li K, Liu J. Clinical efficacy and safety of nedaplatin combined with paclitaxel liposome in treatment of advanced esophageal cancer. *Cancer Research and Clinic* 2016;**28**(11):748-51. [10.3760/cma.j.issn.1006-9801.2016.11.007]

Liu 2016 {published data only}

Liu Y, Ren R, Yuan L, Xu S, Yao Z, Qiao L, et al. Paclitaxel plus cisplatin vs. 5-fluorouracil plus cisplatin as first-line treatment for patients with advanced squamous cell esophageal cancer. *American Journal of Cancer Research* 2016;**6**(10):2345-50.

Luelmo 2008 {published data only}

Luelmo S, Polee M, Van Bochove A, Pruijt H, Ouwerkerk J, Sleeboom H, et al. Randomized phase II study of cisplatin and high dose 5-fluorouracil/leucovorin or paclitaxel and high-dose 5-fluorouracil/leucovorin in locally advanced or metastatic gastric cancer and adenocarcinomas of the gastroesophageal junction. *Annals of Oncology* 2008;**19**(S8):viii173-viii174.

Moehler 2013 {published data only}

Moehler MH, Thuss-Patience PC, Schmoll HJ, Hegewisch-Becker S, Wilke H, Al-Batran SE, et al. FOLFIRI plus sunitinib versus FOLFIRI alone in advanced chemorefractory esophagogastric cancer patients: A randomized placebo-

controlled multicentric AIO phase II trial. *Journal of Clinical Oncology* 2013;**31**(15 Suppl):4086.

Moehler 2016a {published data only}

Moehler MH, Cho JY, Kim YH, Kim JW, Di Bartolomeo M, Ajani JA, et al. A randomized, open-label, two-arm phase II trial comparing the efficacy of sequential ipilimumab (ipi) versus best supportive care (BSC) following first-line (1L) chemotherapy in patients with unresectable, locally advanced/metastatic (A/M) gastric or gastro-esophageal junction (G/GEJ) cancer. *Journal of Clinical Oncology* 2016;**34**(Suppl):4011.

Moehler 2017 {published data only}

Moehler MH, Thuss-Patience PC, Brenner B, Longo F, Meiler J, Ettrich TJ, et al. Cisplatin/5-FU (CF) +/- panitumumab (P) for patients (pts) with non-resectable, advanced, or metastatic esophageal squamous cell cancer (ESCC): An open-label, randomized AIO/TTD/BDGO/EORTC phase III trial (POWER). *Journal of Clinical Oncology* 2017;**35**(15 Suppl):4011.

Pavakis 2015 {published data only}

Pavakis N, Sjoquist KM, Tsoanis E, Martin AJ, Kang YK, Bang YJ, et al. INTEGRATE: A randomized, phase II, double-blind, placebo-controlled study of regorafenib in refractory advanced oesophagogastric cancer (AOGC): A study by the Australasian Gastrointestinal Trials Group (AGITG)-Final overall and subgroup results. *Journal of Clinical Oncology* 2015;**33**(15 Suppl):4003.

Ryu 2016 {published data only}

Ryu MH, Park YI, Chung IJ, Lee KW, Oh HS, Lee KH, et al. Phase III trial of s-1 plus oxaliplatin (SOX) vs s-1 plus cisplatin (SP) combination chemotherapy for first-line treatment of advanced gastric cancer (AGC): SOPP study. *Journal of Clinical Oncology* 2016;**34**(15 Suppl):4015.

Sahin 2015 {published data only}

Sahin U, Al-Batran SE, Hozaeel W, Zvirbule Z, Freiberg-Richter J, Lordick F, et al. IMAB362 plus zoledronic acid (ZA) and interleukin2 (IL2) in patients (pts) with advanced gastroesophageal cancer (GEC): Clinical activity and safety data from the PILOT phase I trial. *Journal of Clinical Oncology* 2015 [Epub ahead of print]; Vol. 33, issue 15 Suppl. [DOI: [10.1200/jco.2015.33.15_suppl.e15079](https://doi.org/10.1200/jco.2015.33.15_suppl.e15079)]

Schuler 2016 {published data only}

Schuler M, Al-Batran SE, Zvirbule Z, Manikhas G, Lordick F, Rusyn A, et al. Final results of the FAST study, an international, multicenter, randomized, phase II trial of epirubicin, oxaliplatin, and capecitabine (EOX) with or without the anti-CLDN18.2 antibody IMAB362 as first-line therapy in patients with advanced CLDN18.2+ gastric and gastroesophageal junction (GEJ) adenocarcinoma. *Annals of Oncology* 2016 Oct 11 [Epub ahead of print]; Vol. 27, issue 6 Suppl. [DOI: [10.1093/annonc/mdw371.06](https://doi.org/10.1093/annonc/mdw371.06)]

Shah 2015 {published data only}

Shah MA, Janjigian YY, Stoller R, Shibata S, Kemeny M, Krishnamurthi S, et al. Randomized multicenter phase II study of modified docetaxel, cisplatin, and fluorouracil (DCF) versus DCF plus growth factor support in patients with metastatic

gastric adenocarcinoma: A study of the US gastric cancer consortium. *Journal of Clinical Oncology* 2015;**33**(33):3874-9.

Shah 2016 {published data only}

Shah MA, Cho JY, Tan IB, Tebbutt NC, Yen CJ, Kang A, et al. A randomized phase II study of FOLFOX with or without the MET inhibitor onartuzumab in advanced Adenocarcinoma of the stomach and Gastroesophageal junction. *Oncologist* 2016;**21**(9):1085-90.

Shah 2017a {published data only}

Shah MA, Bang YJ, Lordick F, Alsina M, Chen M, Hack SP, et al. Effect of fluorouracil, leucovorin, and oxaliplatin with or without onartuzumab in HER2-negative, MET-positive gastroesophageal adenocarcinoma: The METGastric Randomized Clinical Trial. *JAMA Oncology* 2017;**3**(5):620-7.

Smyth 2011 {published data only}

Smyth EC, Enzinger PC, Li J, Vincitore M, Lacy J, El-Rayes BF, et al. Bevacizumab (Bev) plus chemotherapy for advanced gastroesophageal adenocarcinoma (GC): combined U.S. experience. *Journal of Clinical Oncology* 2011;**29**(15 Suppl):4056.

Song 2016 {published data only}

Song L. Effect of S-1 maintenance chemotherapy following first-line regimen in patients with advanced esophageal cancer. *Diseases of the Esophagus* 2016;**29**:130A-131A.

Tebbutt 2013 {published data only}

Tebbutt NC, Price TJ, Sjoquist KM, Veillard AS, Hall M, Ferraro DA, et al. Final results of AGITG ATTAX 3 study: Randomized phase II study of weekly docetaxel (T), cisplatin, and fluoropyrimidine (F) with or without panitumumab (P) in advanced esophagogastric (OG) cancer. *Journal of Clinical Oncology* 2013;**31**(15 Suppl):4081.

Tebutt 2016 {published data only}

Tebbutt NC, Price TJ, Ferraro DA, Wong N, Veillard AS, Hall M, et al. Panitumumab added to docetaxel, cisplatin and fluoropyrimidine in oesophagogastric cancer: ATTAX3 phase II trial. *British Journal of Cancer* 2016;**114**(5):505-9.

Thuss-Patience 2015 {published data only}

Thuss-Patience PC, Al-Batran SE, Siveke JT, Homann N, Malfertheiner P, Glaeser D, et al. Pazopanib and 5-FU/oxaliplatin as first-line treatment in advanced gastric cancer: PaFLO, a randomized phase II study from the AIO (Arbeitsgemeinschaft Internistische Onkologie). *Journal of Clinical Oncology* 2015;**33**(15 Suppl):4033.

Thuss-Patience 2017 {published data only}

Thuss-Patience PC, Shah MA, Ohtsu A, Van Cutsem E, Ajani JA, Castro H, 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 Oncology* 2017;**18**(5):640-53.

Wang 2010 {published data only}

Wang X-Q, Yang F. Clinical effects of Zhisheng capsule combined with chemotherapy on patients with middle or advanced stage oesophageal cancer. *Drugs & Clinic* 2010;**25**(4):297-9.

Wang 2016 {published data only}

Wang JW, Xu RH, Li J, Bai YX, Liu TS, Jiao SC, et al. Randomized multicenter phase III study of a modified docetaxel and cisplatin plus fluorouracil regimen compared with cisplatin and fluorouracil as first-line therapy for advanced or locally recurrent gastric cancer. *Gastric Cancer* 2016;**19**(1):234-44.

Wang 2017 {published data only}

Wang F, Fan QX, Wang HH, Han DM, Song NS, Lu H. Efficacy and safety of Xiaoaiping combined with chemotherapy in the treatment of advanced esophageal cancer. *Zhonghua Zhong Liu za Zhi [Chinese Journal of Oncology]* 2017;**39**(6):453-7.

Wu 2013 {published data only}

Wu J, Long GX. Clinical observation on Aidi injection supplemental to chemotherapy in treatment of advanced oesophageal carcinoma. *Journal of Internal Intensive Medicine* 2013;**19**(2):100-15.

Xie 2016 {published data only}

Xie C, Shi Y, Zhu Z, Li Z, Yu X. The efficacy and adverse reaction of docetaxel combined with oxaliplatin in the treatment of advanced esophageal cancer. *Anti-Tumor Pharma* 2016;**6**(5):361-5.

Yeh 2012 {published data only}

Yeh KH, Chen JS, Sobrero A, Singhal N, De Dosso S, Kang YK, et al. Safety and tolerability data from a phase II study of AUY922 compared with chemotherapy in patients with advanced gastric cancer. *Annals of Oncology* 2012;**23**(4):118.

Yoon 2016 {published data only}

Yoon HH, Bendell JC, Braiteh FS, Firdaus I, Philip PA, Cohn AL, et al. Ramucirumab combined with FOLFOX as front-line therapy for advanced esophageal, gastroesophageal junction, or gastric adenocarcinoma: a randomized, double-blind, multicenter Phase II trial. *Annals of Oncology* 2016;**27**(12):2196-203.

Zaanan 2015 {published data only}

Zaanan A, Bennouna J, Hiret S, Douillard JY, Bouche O, Tougeron D, et al. Masitinib plus irinotecan for second line treatment of esophagogastric adenocarcinoma: An open label phase Ib/II trial. *Journal of Clinical Oncology* 2015;**33**(15 Suppl):4027.

Zhang 2015 {published data only}

Zhang X, Shen L, Lu Z, Liu W, Liu T, Hu B, et al. Comparison of efficacy and safety of paclitaxel and capecitabine followed by capecitabine as maintenance therapy versus cisplatin and capecitabine therapy for advanced gastric cancer: A multicentre, randomised, active-controlled phase III study. *Annals of Oncology* 2015;**26**(9 Suppl):ix44. [DOI: [10.1093/annonc/mdv523.05](https://doi.org/10.1093/annonc/mdv523.05)]

Zhou 2016 {published data only}

Zhou Y, Liu C, Tang Y, Wang S. Clinical observation of S-I in the maintenance treatment of advanced esophageal cancer. *Cancer Research and Clinic* 2016;**28**(7):452-4.

References to ongoing studies
Aanur 2017 {published data only}

Aanur P, Gutierrez M, Kelly RJ, Ajani JA, Ku GY, Denlinger CS, et al. FRACTION (Fast Real-time Assessment of Combination Therapies in Immuno-ONcology)-gastric cancer (GC): A randomized, open-label, adaptive, phase 2 study of nivolumab in combination with other immuno-oncology (IO) agents in patients with advanced GC. *Journal of Clinical Oncology* 2017 [Epub ahead of print]; Vol. 35, issue 15 Suppl. [DOI: [10.1200/JCO.2017.35.15_suppl.TPS4137](https://doi.org/10.1200/JCO.2017.35.15_suppl.TPS4137)]

Bang 2014 {published data only}

Bang YJ, Kang YK, Alsina M, Wainberg ZA, Chau I, Zhu J, et al. JAGUAR: a randomized phase II study of the AKT inhibitor ipatasertib (GDC-0068) versus placebo in combination with mFOLFOX6 chemotherapy in patients (pts) with locally advanced or metastatic HER2-negative gastric (G) or gastroesophageal junction (GEJ) adenocarcinoma. *Journal of Clinical Oncology* 2014;**32**(15 Suppl):TPS4147.

Bendell 2017 {published data only}

Bendell JC, Starodub A, Huang X, Maltzman JD, Wainberg ZA, Shah MA. A phase 3 randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of GS-5745 combined with mFOLFOX6 as first-line treatment in patients with advanced gastric or gastroesophageal junction adenocarcinoma. *Journal of Clinical Oncology* 2017 [Epub ahead of print]; Vol. 35, issue 15 Suppl. [DOI: [10.1200/JCO.2017.35.15_suppl.TPS4139](https://doi.org/10.1200/JCO.2017.35.15_suppl.TPS4139)]

Cafferkey 2016 {published data only}

Cafferkey C, Chau I, Thistlethwaite F, Petty RD, Starling N, Watkins D, et al. PLATFORM: Planning treatment of oesophago-gastric (OG) cancer randomised maintenance therapy trial. *Journal of Clinical Oncology* 2016 [Epub ahead of print]; Vol. 34, issue 4 Suppl. [DOI: [10.1200/jco.2016.34.4_suppl.tps187](https://doi.org/10.1200/jco.2016.34.4_suppl.tps187); NCT02678182]

CTRI/2016/01/006474 {published data only}

CTRI/2016/01/006474. Palliative chemotherapy in esophageal cancer for survival [A randomized clinical trial of best supportive care compared with best supportive care with chemotherapy in advanced unresectable or metastatic esophageal cancer]. ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=13694 (first received 1 January 2016).

Doi 2016 {published data only}

Doi T, Bennouna J, Shen L, Enzinger PC, Wang R, Csiki I, et al. KEYNOTE-181: Phase 3, open-label study of second-line pembrolizumab vs single-agent chemotherapy in patients with advanced/metastatic esophageal adenocarcinoma. *Journal of Clinical Oncology* 2016 [Epub ahead of print]; Vol. 34, issue 15 Suppl. [DOI: [10.1200/JCO.2016.34.15_suppl.TPS4140](https://doi.org/10.1200/JCO.2016.34.15_suppl.TPS4140)]

Esaki 2017 {published data only}

Esaki T, Makiyama A, Kashiwada T, Hosokawa A, Kawada J, Moriwaki T, et al. ACT (WJOG7112G): 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. *Journal of Clinical Oncology* 2017 [Epub ahead of print]; Vol. 35, issue 4 Suppl. [DOI: [10.1200/JCO.2017.35.4_suppl.TPS218](https://doi.org/10.1200/JCO.2017.35.4_suppl.TPS218)]

EUCTR 2016-001514-20 {published data only}

EUCTR 2016-001514-20. A randomized phase 3 study of nivolumab plus ipilimumab or nivolumab combined with fluorouracil plus cisplatin versus fluorouracil plus cisplatin in subjects with unresectable advanced, recurrent or metastatic previously untreated esophageal squamous cell carcinoma. clinicaltrialsregister.eu/ctr-search/trial/2016-001514-20 (first received 17 October 2016).

Haag 2017 {published data only}

Haag GM, Stocker G, Quidde J, Jaeger D, Lordick F. Randomized controlled trial of S-1 maintenance therapy in metastatic esophagogastric cancer - the multinational MATEO study. *BMC Cancer* 2017;**17**(1):509.

Malka 2011 {published data only}

Malka D, Gourgou-Bourgade S, Emile J, Laurent-Puig P, Taieb J. Met or EGFR Inhibition in Gastroesophageal Adenocarcinoma (MEGA): FOLFOX alone or in combination with AMG 102 or panitumumab as first-line treatment in patients with advanced gastroesophageal adenocarcinoma: FNCLCC-FFCD-AGEO-GERCOR PRODIGE 17-ACCORD 20 randomized phase II trial. *Journal of Clinical Oncology* 2011;**29**(15 Suppl):TPS178.

NCT00515411 {published data only}

NCT00515411. Study of modified docetaxel, cisplatin, and fluorouracil (mDCF) in unresectable or metastatic gastric and gastroesophageal junction adenocarcinoma [A phase II study of modified docetaxel, cisplatin, and fluorouracil (mDCF) in patients with unresectable or metastatic gastric and gastroesophageal junction adenocarcinoma]. clinicaltrials.gov/ct2/show/NCT00515411 (first received 10 August 2007).

NCT00680901 {published data only}

NCT00680901. LOGiC - lapatinib optimization study in ErbB2 (HER2) positive gastric cancer: a phase III global, blinded study designed to evaluate clinical endpoints and safety of chemotherapy plus lapatinib [A phase III study for ErbB2 positive advanced or metastatic gastric, esophageal, or gastroesophageal junction adenocarcinoma treated with capecitabine plus oxaliplatin with or without lapatinib]. clinicaltrials.gov/ct2/show/NCT00680901 (first received 15 May 2008).

NCT00816634 {published data only}

NCT00816634. Efficacy comparison study of combination regimens to treat advanced esophageal squamous cell carcinoma (XP versus XT) [A randomized phase II trial of capecitabine plus cisplatin (XP) versus capecitabine plus paclitaxel (XT) as a first-line treatment for advanced or recurrent

esophageal squamous cell carcinoma]. clinicaltrials.gov/ct2/show/NCT00816634 (first received 30 December 2008).

NCT00824785 {published data only}

NCT00824785. REAL3 trial of efficacy of EOX with/without panitumumab in previously untreated adv OG cancer (REAL3) [REAL 3: a randomised open-labelled multicentre trial of the efficacy of epirubicin, oxaliplatin and capecitabine (EOX) with or without panitumumab in previously untreated advanced oesophago-gastric cancer]. clinicaltrials.gov/ct2/show/NCT00824785 (first received 16 January 2009).

NCT00982592 {published data only}

NCT00982592. Combination chemotherapy with or without vismodegib in treating patients with advanced stomach cancer or gastroesophageal junction cancer [A randomized, double blind placebo controlled phase 2 study of FOLFOX plus or minus GDC-0449 in patients with advanced gastric and gastroesophageal junction (GEJ) carcinoma]. clinicaltrials.gov/ct2/show/NCT00982592 (first received 22 September 2009).

NCT00991952 {published data only}

* NCT00991952. Irinotecan hydrochloride with or without alvocidib in treating patients with advanced stomach or gastroesophageal junction cancer that cannot be removed by surgery [A multicenter random assignment phase II study of irinotecan and alvocidib (flavopiridol) versus irinotecan alone for patients with p53 wild type gastric adenocarcinoma]. clinicaltrials.gov/ct2/show/NCT00991952 (first received 7 October 2009).

NCT01020630 {published data only}

NCT01020630. Sunitinib in patients with advanced gastric cancer and treated with FOLFIRI (SUN-CASE) [A randomized, placebo-controlled phase II trial investigating SUNTINIB versus placebo in patients with chemorefractory advanced adenocarcinoma of the stomach or lower esophagus treated with chemotherapy FOLFIRI]. clinicaltrials.gov/ct2/show/NCT01020630 (first received 23 November 2009).

NCT01246960 {published data only}

NCT01246960. A study of ramucirumab in participants with gastric, esophageal, and gastroesophageal cancer [Randomized, placebo-controlled, double-blind phase 2 study of mFOLFOX6 chemotherapy plus ramucirumab drug product (IMC-1121B) versus mFOLFOX6 plus placebo for advanced adenocarcinoma of the esophagus, gastroesophageal junction or stomach]. clinicaltrials.gov/ct2/show/NCT01246960 (first received 8 November 2010).

NCT01474642 {published data only}

NCT01474642. Phase II trial of XP versus XG in advanced esophageal squamous cell carcinoma [A randomized phase II trial of capecitabine plus cisplatin (XP) versus capecitabine plus genexol (XG) as a first-line treatment for advanced or recurrent esophageal squamous cell carcinoma]. clinicaltrials.gov/ct2/show/NCT01474642 (first received 18 November 2011).

NCT01498289 {published data only}

NCT01498289. S1201: combination chemo for patients w/advanced or metastatic esophageal, gastric, or

gastroesophageal junction cancer [A randomized phase II pilot study prospectively evaluating treatment for patients based on ERCC1(excision repair cross-complementing 1) for advanced/metastatic esophageal, gastric or gastroesophageal junction (GEJ) cancer]. clinicaltrials.gov/ct2/show/NCT01498289 (first received 22 December 2011).

NCT01503372 {published data only}

NCT01503372. FLO +/- pazopanib as first-line treatment in advanced gastric cancer (PaFLO) [Pazopanib with 5-fluorouracil, leucovorin and oxaliplatin (FLO) as 1st-line treatment in advanced gastric cancer; a randomized phase-ii-study of the arbeitsgemeinschaft internistische onkologie]. clinicaltrials.gov/ct2/show/NCT01503372 (first received 22 December 2011).

NCT01627379 {published data only}

NCT01627379. Cisplatin and 5-FU +/- panitumumab for patients with nonresectable, advanced or metastatic esophageal squamous cell cancer (POWER) [An open-label, randomized phase III trial of cisplatin and 5-fluorouracil with or without panitumumab for patients with nonresectable, advanced or metastatic esophageal squamous cell cancer]. clinicaltrials.gov/ct2/show/NCT01627379 (first received 13 June 2012).

NCT01704690 {published data only}

NCT01704690. Combination treatment of S-1 with paclitaxel in advanced esophageal cancer [Combination treatment of S-1 with paclitaxel versus paclitaxel+cisplatin and 5-Fu +cisplatin as first-line treatment in advanced esophageal cancer]. clinicaltrials.gov/ct2/show/NCT01704690 (first received 4 October 2012).

NCT01747551 {published data only}

NCT01747551. FOLFOX +/- ziv-aflibercept for esophageal and gastric cancer [Randomized, double-blind, placebo controlled phase II study of FOLFOX +/- ziv-aflibercept in patients with advanced esophageal and gastric cancer]. clinicaltrials.gov/ct2/show/NCT01747551 (first received 5 December 2012).

NCT01896531 {published data only}

NCT01896531. A study of GDC-0068 in combination with fluoropyrimidine plus oxaliplatin in participants with advanced or metastatic gastric or gastroesophageal junction cancer [A randomized, phase II, placebo controlled study of GDC-0068, an inhibitor to Akt, in combination with fluoropyrimidine plus oxaliplatin in patients with locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma]. clinicaltrials.gov/ct2/show/NCT01896531 (first received 8 July 2013).

NCT02137343 {published data only}

NCT02137343. A phase 3 study of rilotumumab (AMG 102) with cisplatin and capecitabine (CX) as first-line therapy in gastric cancer (RILOMET-2) [A phase 3, multicenter, randomized, double-blind, placebo controlled study of rilotumumab (AMG 102) with cisplatin and capecitabine (CX) as first-line therapy in advanced MET-positive gastric or gastroesophageal junction adenocarcinoma]. [Clinicaltrials.gov/ct2/show/NCT02137343](https://clinicaltrials.gov/ct2/show/NCT02137343) (first received 28 April 2014).

NCT02177552 {published data only}

NCT02177552. Study assessing the effects of chemotherapy in advanced esophagogastric adenocarcinoma (SEED) [Study assessing the effects of chemotherapy in advanced esophagogastric adenocarcinoma - carboplatin, docetaxel and capecitabine (CTX) or epirubicin, oxaliplatin and capecitabine: a randomised phase 2 trial]. clinicaltrials.gov/ct2/show/NCT02177552 (first received 18 June 2014).

NCT02178956 {published data only}

NCT02178956. A study of BBI608 plus weekly paclitaxel to treat gastric and gastro-esophageal junction cancer (BRIGHTER) [A phase III clinical trial of BBI608 plus weekly paclitaxel vs. placebo plus weekly paclitaxel in adult patients with advanced, previously treated gastric and gastro-esophageal junction adenocarcinoma]. clinicaltrials.gov/ct2/show/NCT02178956 (first received 27 June 2014).

NCT02344810 {published data only}

NCT02344810. C-Met inhibitor AMG 337, oxaliplatin, leucovorin calcium, and fluorouracil in treating patients with advanced stomach or esophageal cancer [A phase I and randomized phase II double blinded placebo controlled study of mFOLFOX6 +/- AMG 337 in the first line treatment of patients with Her2/ Neu negative and high MET expressing advanced gastric and esophageal adenocarcinoma]. clinicaltrials.gov/ct2/show/NCT02344810 (first received 16 January 2015).

NCT02409849 {published data only}

NCT02409849. Octreotide LAR as maintenance treatment for patients with NEC [Randomized phase II study of octreotide LAR as maintenance treatment after first-line chemotherapy for patients with unresectable or metastatic gastro-entero-pancreatic or esophageal neuroendocrine carcinomas]. clinicaltrials.gov/ct2/show/NCT02409849 (first received 1 April 2015).

NCT02569242 {published data only}

NCT02569242. Study of nivolumab in unresectable advanced or recurrent esophageal cancer [ONO-4538 phase III study a multicenter, randomized, open-label study in patients with unresectable advanced or recurrent esophageal cancer]. clinicaltrials.gov/show/NCT02569242 (first received 6 October 2015).

NCT02625610 {published data only}

Julien T, Maria DB, Antonio C, Jayne G, Deborah W, Huiling X, et al. Avelumab in first-line maintenance gastric cancer (JAVELIN Gastric 100). *Annals of Oncology* 2015;**27**:ii81-ii82.

NCT02625610. Avelumab in first-line maintenance gastric cancer (JAVELIN Gastric 100) [A phase III open-label, multicenter trial of maintenance therapy with avelumab (MSB0010718C) versus continuation of first-line chemotherapy in subjects with unresectable, locally advanced or metastatic, adenocarcinoma of the stomach, or of the gastro-esophageal junction]. clinicaltrials.gov/show/NCT02625610 (first received 9 December 2015).

NCT02625623 {published data only}

Eric VC, Lucjan W, Keun-Wook L, Fortunato C, Rosine G, Julien T, et al. JAVELIN gastric 300: phase 3 trial of avelumab (anti-PD-L1 antibody) + best supportive care (BSC) vs BSC ± chemotherapy as third-line treatment for advanced gastric or gastroesophageal junction cancer. *Annals of Oncology* 2015;**27**:ii82.

NCT02743494 {published data only}

NCT02743494. An investigational immuno-therapy study of nivolumab or placebo in patients with resected esophageal or gastroesophageal junction cancer (CheckMate 577) [A randomized, multicenter, double blind, phase iii study of adjuvant nivolumab or placebo in subjects with resected esophageal, or gastroesophageal junction cancer]. clinicaltrials.gov/show/NCT02743494 (first received 19 April 2016).

NCT02773524 {published data only}

Sjoquist KM, Pavlakis N, Martin AJ, Tsobanis E, Yip S, Bang YJ, et al. Integrate II: A randomised phase 3 double-blind placebo-controlled study of regorafenib in refractory advanced gastro-oesophageal cancer (AGOC) An international study organized by the Australasian Gastrointestinal Trials Group (AGITG). *Journal of Clinical Oncology* 2016 [Epub ahead of print]; Vol. 35, issue 15. [DOI: [10.1200/JCO.2017.35.15_suppl.TPS4136](https://doi.org/10.1200/JCO.2017.35.15_suppl.TPS4136)]

NCT02872116 {published data only}

Moehler MH, Janjigian YY, Adenis A, Aucoin JS, Boku N, Chau I, et al. CheckMate 649: A randomized, multicenter, open-label, phase 3 study of nivolumab (nivo) + ipilimumab (ipi) or nivo + chemotherapy (CTX) vs CTX alone in pts with previously untreated advanced (adv) gastric (G) or gastroesophageal junction (GEJ) cancer. *Journal of Clinical Oncology* 19 Aug 2016 [Epub ahead of print]; Vol. 35, issue 15. [DOI: [10.1200/JCO.2017.35.4_suppl.TPS213](https://doi.org/10.1200/JCO.2017.35.4_suppl.TPS213)]

NCT03002064 {published data only}

NCT03002064. Docetaxol plus cisplatin versus 5-Fu plus cisplatin as 1st-line chemotherapy in advanced ESCC patients [Docetaxel plus cisplatin versus 5-fluorouracil plus cisplatin as first-line treatment for metastatic esophageal squamous patients: a prospective multicenter, randomized controlled clinical study]. clinicaltrials.gov/show/NCT03002064 (first received 23 December 2016).

NCT03006432 {published data only}

NCT03006432. Phase III randomised trial to evaluate folfox with or without docetaxel (TFOX) as 1st line chemotherapy for locally advanced or metastatic oesophago-gastric carcinoma (GASTFOX) [Essai de phase iii randomise evaluant le folfox avec ou sans docetaxel (tfox) en 1ère ligne de chimiothérapie des adenocarcinomes oeso-gastriques localement avances ou metastatiques]. clinicaltrials.gov/show/NCT03006432 (first received 30 December 2016).

NCT03019588 {published data only}

NCT03019588. Efficacy and safety study of pembrolizumab (MK-3475) versus paclitaxel in Asian participants with advanced gastric or gastroesophageal junction adenocarcinoma who progressed after first-line therapy with platinum and

fluoropyrimidine (MK-3475-063/KEYNOTE-063) [A phase III, randomized, open-label clinical trial of pembrolizumab (MK-3475) versus paclitaxel in Asian subjects with advanced gastric or gastroesophageal junction adenocarcinoma who progressed after first-line therapy with platinum and fluoropyrimidine]. clinicaltrials.gov/show/NCT03019588 (first received 12 January 2017).

NCT03042611 {published data only}

Kang YK, Boku N, Kang WK, Yoon HH, Cascinu S, Al-Batran SE, et al. A prospective, randomized, double-blinded, placebo-controlled, phase III study to evaluate the efficacy and safety of apatinib plus best supportive care (BSC) compared to placebo plus BSC in patients with advanced or metastatic gastric cancer: The ANGEL study. *Journal of Clinical Oncology* 3 Feb 2017 [Epub ahead of print]; Vol. 35, issue 15. [DOI: [10.1200/JCO.2017.35.15_suppl.TPS4138](https://doi.org/10.1200/JCO.2017.35.15_suppl.TPS4138)]

NCT03168594 {published data only}

NCT03168594. Study to compare irinotecan combined with cisplatin (IP) versus etoposide combined with cisplatin (EP) in advanced and metastatic gastrointestinal pancreatic and esophageal neuroendocrine carcinoma [A randomized, controlled phase II study to compare irinotecan combined with cisplatin (IP) versus etoposide combined with cisplatin (EP) in advanced and metastatic gastrointestinal pancreatic and esophageal neuroendocrine carcinoma]. clinicaltrials.gov/show/NCT03168594 (first received 30 May 2017).

NCT03189719 {published data only}

NCT03189719. First-line esophageal carcinoma study with chemo vs. chemo plus pembrolizumab (MK-3475-590/KEYNOTE-590) [A randomized, double-blind, placebo-controlled phase III clinical trial of pembrolizumab (MK-3475) in combination with cisplatin and 5-fluorouracil versus placebo in combination with cisplatin and 5-fluorouracil as first-line treatment in subjects with advanced/metastatic esophageal carcinoma (KEYNOTE-590)]. clinicaltrials.gov/show/NCT03189719 (first received 16 June 2017).

NCT03279601 {published data only}

NCT03279601. Study to compare capecitabine combined with dacarbazine (CAPDTIC) versus capecitabine combined temozolomide (CAPTEM) in advanced and metastatic gastrointestinal pancreatic and esophageal neuroendocrine tumor [A randomized, controlled phase II study to compare capecitabine combined with dacarbazine (CAPDTIC) versus capecitabine combined temozolomide (CAPTEM) in advanced and metastatic gastrointestinal pancreatic and esophageal neuroendocrine tumor]. clinicaltrials.gov/show/NCT03279601 (first received 12 September 2017).

NCT03281369 {published data only}

NCT03281369. A study of multiple immunotherapy-based treatment combinations in patients with locally advanced unresectable or metastatic gastric or gastroesophageal junction cancer (G/GEJ) (UMBRELLA) [A phase Ib/II, open-label, multicenter, randomized, umbrella study evaluating the efficacy and safety of multiple immunotherapy-based treatment combinations in patients with locally advanced unresectable or metastatic gastric or gastroesophageal junction

cancer (morpheus-gastric cancer)]. clinicaltrials.gov/show/NCT03281369 (first received 13 September 2017).

Ohtsu 2015 {published data only}

Ohtsu A, Tabernero J, Bang YJ, Fuchs CS, Sun L, Wang Z, et al. KEYNOTE-061: pembrolizumab (MK-3475) versus paclitaxel as second-line therapy for advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma. *Annals of Oncology* 2015;**26**(9 Suppl):ix69.

Shah 2017b {published data only}

Shah MA, Metges JP, Chun PY, Smith V, Maltzman JD, Wainberg ZA. A phase II, open-label, randomized study to evaluate the efficacy and safety of GS-5745 combined with nivolumab versus nivolumab alone in subjects with unresectable or recurrent gastric or gastroesophageal junction adenocarcinoma. *Journal of Clinical Oncology* 2017;**35**(15 Suppl):TPS4141.

Tabernero 2013 {published data only}

Tabernero J, Hoff PM, Shen L, Ohtsu A, Yu R, Eng-Wong J, Kang YK. Pertuzumab (P) with trastuzumab (T) and chemotherapy (CTX) in patients (pts) with HER2-positive metastatic gastric or gastroesophageal junction (GEJ) cancer: an international phase III study (JACOB). *Journal of Clinical Oncology* 2013;**31**(15 Suppl):TPS4150.

Tabernero 2016 {published data only}

Tabernero J, Bang YJ, Fuchs CS, Ohtsu A, Kher U, Lam B, et al. KEYNOTE-062: Phase III study of pembrolizumab (MK-3475) alone or in combination with chemotherapy versus chemotherapy alone as first-line therapy for advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma. *Journal of Clinical Oncology* 2016;**34**(4):TPS185.

Toshihiko 2016 {published data only}

Toshihiko D, Jaafar B, Lin S, Peter E, Ruixue W, Ildiko C, et al. Pembrolizumab versus physician-choice chemotherapy for previously treated patients with advanced/metastatic squamous or adenocarcinoma of the esophagus or Siewert I adenocarcinoma of the esophagogastric junction (EGJ): randomized, phase 3 KEYNOTE-18. *Annals of Oncology* 2016;**27**(2 Suppl):i81.

Additional references

Aaronson 1993

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute* 1993;**85**(5):365-76.

Altman 2001

Altman DG. Systematic reviews of evaluations of prognostic variables. *BMJ* 2001;**323**(7306):224-8.

Amdal 2013

Amdal CD, Jacobsen A, Guren MGN, Bjordal K. Patient-reported outcomes evaluating palliative radiotherapy and chemotherapy

in patients with oesophageal cancer: a systematic review. *Acta Oncologica* 2013;**52**(4):679–90.

Arnold 2015

Arnold M, Soerjomataram I, Ferlay J, Forman D. Global incidence of oesophageal cancer by histological subtype in 2012. *Gut* 2015;**64**(3):381–7.

Bennett 2012

Bennett C, Green S, DeCaestecker J, Almond M, Barr H, Bhandari P, et al. Surgery versus radical endotherapies for early cancer and high-grade dysplasia in Barrett's oesophagus. *Cochrane Database of Systematic Reviews* 2012, Issue 11. [DOI: [10.1002/14651858.CD007334.pub4](https://doi.org/10.1002/14651858.CD007334.pub4)]

Blazeby 2001

Blazeby JM. Measurement of outcome. *Surgical Oncology* 2001;**10**(3):127–33.

Blazeby 2003

Blazeby JM, Conroy T, Hammerlid E, Fayers P, Sezer O, Koller M, et al. Clinical and psychometric validation of an EORTC questionnaire module, the EORTC QLQ-OES18, to assess quality of life in patients with oesophageal cancer. *European Journal of Cancer* 2003;**39**(10):1384–94.

Blazeby 2004

Blazeby JM, Conroy T, Bottomley A, Vickery C, Arraras J, Sezer O, et al. Clinical and psychometric validation of a questionnaire module, the EORTC QLQ-STO 22, to assess quality of life in patients with gastric cancer. *European Journal of Cancer* 2004;**40**(15):2260–8.

Chau 2009

Chau I, Norman AR, Cunningham D, Oates J, Hawkins R, Iveson T, et al. The impact of primary tumour origins in patients with advanced oesophageal, oesophago-gastric junction and gastric adenocarcinoma - 025EF individual patient data from 1775 patients in four randomised controlled trials. *Annals of Oncology* 2009;**20**(5):885–91.

Common Toxicity Criteria 4.0

National Cancer Institute. Common Terminology Criteria for Adverse Events v 4.0. Bethesda, MD: National Institutes of Health, National Cancer Institute; 2009 May. NIH publication #09-7473.

Cook 2009

Cook MB, Chow WH, Devesa SS. Oesophageal cancer incidence in the United States by race, sex, and histologic type, 1977–2005. *British Journal of Cancer* 2009;**101**(5):855–9.

Edgren 2013

Edgren G, Adami HO, Vainio EW, Nyren O. A global assessment of the oesophageal adenocarcinoma epidemic. *Gut* 2013;**62**(10):1406–14.

Enzinger 2003

Enzinger PC, Mayer RJ. Medical progress - Esophageal cancer. *New England Journal of Medicine* 2003;**349**(23):2241–52.

EuroQol 1990

EuroQol group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy* 1990;**16**(3):199–208.

Guyatt 2008

Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians. *BMJ* 2008;**336**(7651):995–8.

Higgins 2011

Higgins JP, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org. Chichester, UK: John Wiley & Sons, Ltd.

Howlader 2014

Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, et al. editors. SEER Cancer Statistics Review 1975–2011. Bethesda, MD: National Institutes of Health, National Cancer Institute; 2014 April. [http://seer.cancer.gov/csr/1975_2011/]

Hur 2013

Hur C, Miller M, Kong CY, Dowling EC, Nattinger KJ, Dunn M, et al. Trends in esophageal adenocarcinoma incidence and mortality. *Cancer* 2013;**119**(6):1149–58.

Jadad 1996

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary?. *Controlled Clinical Trials* 1996;**17**(1):1–12.

Lin 2013

Lin YS, Totsuka Y, He YT, Kikuchi S, Qiao YL, Ueda JK, et al. Epidemiology of esophageal cancer in Japan and China. *Journal of Epidemiology/Japan Epidemiological Association* 2013;**23**(4):233–42.

Machin 1997

Machin D, Stenning SP, Parmar MKP. Thirty years of Medical Research Council randomised trials in solid tumors. *Journal of Clinical Oncology* 1997;**9**(2):100–14.

Marsman 2005

Marsman WA, Tytgat GNJ, Ten Kate FJW, Van Lanschot JJB. Differences and similarities of adenocarcinomas of the esophagus and esophagogastric junction. *Journal of Surgical Oncology* 2005;**92**(3):160–8.

Mohammad 2015

Mohammad NH, ter Veer E, Ngai L, Mali R, van Oijen MG, van Laarhoven HW. Optimal first-line chemotherapeutic treatment in patients with locally advanced or metastatic esophagogastric carcinoma: triplet versus doublet chemotherapy: a systematic literature review and meta-analysis. *Cancer Metastasis Reviews* 2015;**34**(3):429–41.

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-

analyses: the PRISMA statement. *PLOS Medicine* 2009;**6**(7):1-7. [DOI: [10.1371/journal.pmed.1000097](https://doi.org/10.1371/journal.pmed.1000097)]

Ocama 2008

Ocama P, Kagimu MM, Odida M, Wabinga H, Opio CK, Colebunders B, et al. Factors associated with carcinoma of the oesophagus at Mulago Hospital, Uganda. *African Health Sciences* 2008;**8**(2):80-4.

Parmar 1998

Parmar MKB, Torri V, Steward L. Extracting summary statistics to perform meta-analysis of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(28):15-34.

R 2014 [Computer program]

R Core Team. R: A Language and Environment for Statistical Computing. Version 3.1.2. Vienna, Austria: R Foundation for Statistical Computing, 2014.

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Shah 2011

Shah MA, Khanin R, Tang L, Janjigian YY, Klimstra DS, Gerdes H, et al. Molecular classification of gastric cancer: a new paradigm. *Clinical Cancer Research* 2011;**17**(9):2693-701.

Somdyala 2010

Somdyala NIM, Bradshaw D, Gelderblom WCA, Parkin DM. Cancer incidence in a rural population of South Africa, 1998-2002. *International Journal of Cancer* 2010;**127**(10):2420-9.

Wagner 2010

Wagner AD, Unverzagt S, Grothe W, Kleber G, Grothey A, Haerting J, Fleig WE. Chemotherapy for advanced gastric

cancer. *Cochrane Database of Systematic Reviews* 2010, Issue 3. [DOI: [10.1002/14651858.CD004064.pub3](https://doi.org/10.1002/14651858.CD004064.pub3)]

White 2009

White RE, Parker RK, Fitzwater JW, Kasepoi Z, Topazian M. Stents as sole therapy for oesophageal cancer: a prospective analysis of outcomes after placement. *Lancet Oncology* 2009;**10**(3):240-6.

References to other published versions of this review

Homs 2003

Homs MYV, van der Gaast A, Siersema PD, Steyerberg EW, Kuipers EJ. Chemotherapy for metastatic carcinoma of the esophagus and gastric cardia. *Cochrane Database of Systematic Reviews* 2003, Issue 1. [DOI: [10.1002/14651858.CD004063](https://doi.org/10.1002/14651858.CD004063)]

Homs 2006

Homs MYV, van der Gaast A, Siersema PD, Steyerberg EW, Kuipers EJ. Chemotherapy for metastatic carcinoma of the esophagus and gastro-esophageal junction. *Cochrane Database of Systematic Reviews* 2006, Issue 4. [DOI: [10.1002/14651858.CD004063.pub2](https://doi.org/10.1002/14651858.CD004063.pub2)]

Homs 2010

Homs MYV, van der Gaast A, Siersema PD, Steyerberg EW, Kuipers EJ. Chemotherapy for metastatic carcinoma of the esophagus and gastro-esophageal junction. *Cochrane Database of Systematic Reviews* 2010, Issue 5. [DOI: [10.1002/14651858.CD004063.pub3](https://doi.org/10.1002/14651858.CD004063.pub3)]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ajani 2005

Methods	Multicenter, open-label, 2-arm RCT
Participants	155 participants with esophageal or gastric AC received chemotherapy and were included in the analyses. 49 participants had esophageal cancer, and 147 had metastasis. "No prior palliative chemotherapy was permitted in patients with advanced disease. Adjuvant and/or preoperative chemotherapy was allowed if more than 12 months had elapsed between end of therapy and registration." Participants had a median age of 57 years, 74% were males, study duration was 1 year and 2 months, median follow-up was 17.5 months. Participants came from Asia, Europe, North America, and South America. Setting of the trial, i.e. the type of hospitals, was not mentioned.
Interventions	Arm 1 (N = 76): docetaxel 75 mg/m ² , cisplatin 75 mg/m ² on day 1, and fluorouracil 750 mg/m ² /d as continuous infusion on days 1-5 Arm 2 (N = 79): docetaxel 85 mg/m ² and cisplatin 75 mg/m ² on day 1, every 3 weeks

Ajani 2005 (Continued)

Outcomes	ORR, safety, time to progression (TTP), and OS	
Notes	Translated from Chinese	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was centralized (Aventis, Antony, France) and was stratified for centre, liver and/or peritoneal metastases, prior gastrectomy, and measurable versus assessable disease."
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	"The randomized, open-label, phase II study was conducted at 34 institutions in Asia, Europe, North America, and South America between June 1998 and September 1999."
Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	"At least one dose reduction was required in 13% of DCF cycles and in 6% of DC cycles. Stomatitis, impaired renal function, lethargy, and neuropathy were the most frequent reasons for dose reductions or delays. Hematologic toxicity alone required dose reduction in only one cycle (1%) of DC and six cycles (1%) of DCF."
Intention-to-treat analysis performed (selection bias)	Low risk	"The primary end point of ORR was evaluated in both the modified intent-to-treat (ITT; all participants who were randomly assigned and treated) ..."

Ajani 2010

Methods	Multicenter, 2-arm, open-label RCT
Participants	<p>1053 participants with AC of the gastroesophageal junction or stomach were randomly assigned; 1029 were in the full analysis set (arm 1, N = 521; arm 2, N = 508). 170/1053 participants had esophageal cancer and 985 had metastasis. "Chemotherapy-naïve patients"</p> <p>Participants had a median age of 59 years, 71% were males, study duration was 1 year and 10 months, median follow-up was not mentioned. Participants came from 24 countries and 146 centers in the USA, Eastern and Western Europe, South America, Australia, and ex-Soviet Union block of nations. The setting of the trial, i.e. the type of hospitals, was not mentioned.</p>
Interventions	<p>Arm 1 (N = 527 randomized): S-1 at 50 mg/m² divided in 2 daily doses for 21 days and cisplatin at 75 mg/m² intravenously on day 1, repeated every 28 days</p> <p>Arm 2 (N = 526 randomized): fluorouracil infusion at 1000 mg/m²/24 h for 120 h and cisplatin at 100 mg/m² intravenously on day 1, repeated every 28 days</p>

Ajani 2010 (Continued)

Outcomes	OS, response rate, PFS, time-to-treatment failure, and safety	
Notes	—	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"By using 1:1 randomization, patients were randomly assigned to one of the two treatment arms and stratified by the extent of disease (locally advanced, one metastatic site or 2 metastatic sites), prior adjuvant therapy, measurable versus non measurable disease, and centre."
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Low risk	All outcome measures are reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	From figure 1 in the trial report: arm 1: not treated (n = 6), withdrew consent (n = 1; 0.2%), Ddisease progression (n = 1; 0.2%), adverse event (n = 2; 0.4%), death (n = 1; 0.2%), other (n = 1; 0.2%). Arm 2: not treated (n = 18), withdrew consent (n = 5; 1.0%), disease progression (n = 1; 0.2%), adverse event (n = 2; 0.4%), intercurrent illness (n = 1; 0.2%), investigator judgment (n = 1; 0.2%), death (n = 2; 0.4%), other (n = 6; 1.1%).
Intention-to-treat analysis performed (selection bias)	Low risk	ITT not mentioned; however, in figure 1 treated participant numbers are mentioned which correspond to the numbers of participants that are reported on for the primary outcome.

Al-Batran 2008

Methods	Multicenter, 2-arm RCT
Participants	<p>220 participants with locally advanced or metastatic gastric or esophagogastric junction AC. Median age was 64 years old, ECOG 2-3: 9%, and metastatic disease: 94% (n = 207). 44/220 participants had esophageal cancer</p> <p>"Further criteria were as follows: no prior palliative chemotherapy ..."</p> <p>Participants had a median age of 64 years, 66% were males, study duration was 2 years and 7 months, median follow-up was 14 months for surviving participants. Participants "were recruited from 31 centres in Germany and one centre in Switzerland". Setting of the trial, i.e. the type of hospitals, were both university and non-university clinics.</p>

Al-Batran 2008 (Continued)

Interventions	Arm 1: oxaliplatin 85 mg/m ² ; leucovorin 200 mg/m ² and 5-FU 2600 mg/m ² as 24-h continuous infusion every 14 days Arm 2: cisplatin 50 mg/m ² ; leucovorin 200 mg/m ² ; 5-FU 2000 mg/m ² weekly for 6 weeks followed by a 2-week rest
Outcomes	Median OS, tumor response and toxicity
Notes	A preplanned interim analysis of toxicity and response was conducted after 80 participants were included in the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were stratified by centre and randomly assigned to either FLO or FLP."
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Low risk	Report includes all expected outcomes (OS, RR and toxicity)
Similar at baseline for most prognostic factors (selection bias)	Low risk	Differences in baseline distribution of sex (42.9% versus 25% female) and metastatic disease (97.3% versus 90.7%) were mentioned by the authors. However, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	"Six patients, all in the FLP arm, never received the study treatment because of death (1), rapid disease progression with deterioration of general health status (3), or renal failure (1) before treatment was initiated, or receiving a non-protocol-based treatment (1)."
Intention-to-treat analysis performed (selection bias)	Low risk	"Therefore, 218 patients (FLO, 112 patients; FLP, 106 patients) were eligible for the efficacy analysis on an ITT basis ..." All participants from the efficacy population came from this population.

Al-Batran 2013

Methods	Multicenter, 2-arm RCT
Participants	143 participants with advanced and metastatic gastric or esophagogastric junction cancer were eligible for the efficacy analysis on an intention-to-treat basis. 51/139 participants (36.7%) had esophageal cancer, and 99 participants had metastasis. "Patients must have had no prior chemotherapy ..."

Al-Batran 2013 (Continued)

Participants had a median age of 69 years, 67% were males, study duration was 1 year and 1 month, median follow-up was not mentioned. Participants were recruited from "28 centres in Germany". Setting of the trial, i.e. the type of hospitals, were both university and non-university clinics.

Interventions	Arm 1 (N = 72): oxaliplatin 85 mg/m ² , leucovorin 200 mg/m ² and docetaxel 50 mg/m ² , each as an intravenous infusion followed by 5-FU 2600 mg/m ² as a 24-h continuous infusion Arm 2 (N = 71): the same regimen without docetaxel 50 mg/m ²
Outcomes	Toxicity, quality of life, OS, and PFS
Notes	Participants in the locally advanced stratum (N = 44) were reevaluated for operability after 4 cycles (8 weeks)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned ..."
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Low risk	All outcome measures were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	"One patient was excluded from the safety analysis because of consent withdrawal before study treatment."
Intention-to-treat analysis performed (selection bias)	Low risk	"In the ITT population, there was a..."

Bang 2010

Methods	International, open-label, phase III RCT
Participants	In total 584 participants of which 106 participants with advanced and metastatic esophageal and GE-junction cancer. 583 of the total 584 participants had metastasis. "Patients were eligible if their tumour samples were scored as 3+ on immunohistochemistry or if they were FISH positive (HER2:CEP17 ratio ≥2)." "Major exclusion criteria included previous chemotherapy for metastatic disease ..."

Bang 2010 (Continued)

Participants had a median age of 59 years, 76% were males, study duration was 3 years and 2 months, median follow-up was 18.6 months in arm 1 and 17.1 months in arm 2. Participants were recruited from "24 centres in Asia, Central and South America, and Europe". Setting of the trial, i.e. the type of hospitals, was not mentioned.

Interventions	<p>All participants received chemotherapy every 3 weeks for 6 cycles: capecitabine 1000 mg/m² orally twice a day for 14 days followed by 1 week rest + 5-FU 800 mg/m² per day by continuous intravenous infusion on days 1/5 of each cycle + cisplatin, 80 mg/m² on day 1 by intravenous infusion</p> <p>Arm 1 (N = 58): trastuzumab by intravenous infusion at a dose of 8 mg/kg on day 1 of the first cycle, followed by 6 mg/kg every 3 weeks until disease progression, unacceptable toxicity, or withdrawal of consent</p> <p>Arm 2 (N = 48): no trastuzumab</p>
Outcomes	The primary outcome was OS. Secondary outcomes included PFS, TTP, overall tumor response rate, duration of response, and safety.
Notes	PFS is not given for the esophageal and GE-junction cancer separately (N = 106). The outcome HR for OS is the only one given for the GE-junction cancer subgroup.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients who satisfied all eligibility criteria (including defined HER2 status and stratification factors) were randomly assigned in a 1:1 ratio to receive ..."
Allocation concealment (selection bias)	Low risk	"Treatment was assigned by use of a randomized block design with block sizes of four patients, via a central interactive voice recognition system (by telephone)."
Blinding (performance bias and detection bias) All outcomes	High risk	"Neither patients nor investigators were masked to treatment assignment in this open-label trial."
Selective reporting (reporting bias)	Low risk	All outcome measures were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 2 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	From figure 1 in the trial report: arm 1: 4 did not receive study treatment, 2 violated selection criteria, 2 withdrew consent; arm 2: 6 did not receive study treatment, 1 refused treatment, 3 withdrew consent, 1 administration error, 1 other violation
Intention-to-treat analysis performed (selection bias)	Low risk	As figure 1 from the trial report describes, only participants that received treatment were analyzed; we regarded this as ITT performed.

Bleiberg 1997

Methods	Multicenter, phase II RCT
Participants	88 participants with advanced or metastatic SCC. Prior surgery 15% "Patients had to have ... no prior chemotherapy" Participants had a median age of 58 years, 95% were males, study duration was 3 years and 6 months, median follow-up was not mentioned. Participants were recruited from Europe. Setting of the trial, i.e. the type of hospitals, was not mentioned.
Interventions	Arm 1 (N = 44): 100 mg/m ² every 3 weeks, 5-FU 1000 mg continuously on day 1-5 Arm 2 (N = 44): cisplatin 100 mg/m ² every 3 weeks
Outcomes	Median survival, 1- and 2-year survival, PFS, and toxicity
Notes	Only SCC. No definition of advanced esophageal cancer is given.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomized to CDDP/5-FU (Arm A) or CDDP alone (Arm B)."
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Low risk	Participant characteristics, toxicities, time to progression, treatment discontinuation and response to treatment are all described.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	"Three patients were ineligible. One had hypercalcaemia, 1 had no histology and 1 had an adenocarcinoma. Another patient who did not start the treatment due to a mediastinal fistula was excluded from the study."
Intention-to-treat analysis performed (selection bias)	Low risk	"Another patient who did not start the treatment due to a mediastinal fistula was excluded from the study. The total number of patients in the study was, therefore, 88." This number corresponds to the analyzed number of participants.

Cunningham 2008

Methods	Multicenter, open-label, 4-arm RCT
---------	------------------------------------

Cunningham 2008 (Continued)

Participants	<p>Between June 2000 and May 2005, a total of 1002 participants with advanced or metastatic (n = 745) esophagogastric junction cancer in the intention-to-treat population underwent randomization. 10.2% of included participants had SCC, 34.6% (n = 333) had esophageal cancer, and 25.7% had GE-junction tumors.</p> <p>"Major exclusion criteria were previous chemotherapy ..."</p> <p>Participants had a median age of 63 years, 81% were males, study duration was 4 years and 10 months, median follow-up was 17.1 months. Participants were recruited from 59 centers in the UK and 2 in Australia. Setting of the trial, i.e. the type of hospitals, was not mentioned.</p>	
Interventions	<p>On day 1 of every 3-week cycle, participants in all study groups received an intravenous bolus of epirubicin (at a dose of 50 mg/m²), in addition to:</p> <p>Arm 1 (ECF, N = 263 randomized): cisplatin 60 mg/m² IV with hydration + 5-FU 200 mg/m² daily</p> <p>Arm 2 (ECX, N = 250 randomized): cisplatin 60 mg/m² IV with hydration + capecitabine 625 mg/m²</p> <p>Arm 3 (EOF, N = 245 randomized): oxaliplatin 130 mg/m² IV during a 2-h period + 5-FU 200 mg/m² daily</p> <p>Arm 4 (EOX, N = 244 randomized): oxaliplatin 130 mg/m² IV during a 2-h period + capecitabine 625 mg/m² twice daily</p>	
Outcomes	Response rate, toxic effect, quality of life, OS, and PFS	
Notes	—	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"[W]e randomly assigned patients to one of four triplet therapies"
Allocation concealment (selection bias)	Low risk	"Study group assignments were made by means of a telephone call to an independent randomization service at the Clinical Trials and Statistics Unit of the Institute of Cancer Research, United Kingdom."
Blinding (performance bias and detection bias) All outcomes	High risk	"Both investigators and patients were aware of study-group assignments."
Selective reporting (reporting bias)	Low risk	All outcome measures were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	From figure 1 in the trial report: arm 1: 9 were not treated, 1 died, 2 had progressive disease, 3 had physical deterioration, 2 withdrew consent, 1 had unstable coexisting condition, 5 were ineligible, 3 had a delay (> 28 days) in commencing treatment, 2 had inadequate organ function; arm 2: 8 were not treated, 1 died, 2 had physical deterioration, 2 withdrew consent, 1 had unstable coexisting condition, 2 had clinical or laboratory abnormalities, 1 was ineligible because of a concurrent cancer; arm 3: 7 were not treated, 1 died, 1 had

Cunningham 2008 (Continued)

physical deterioration, 2 withdrew consent, 1 had unstable coexisting condition, 2 had CVAD-related complications, 3 were ineligible, 2 had a concurrent cancer, 1 had inadequate organ function, arm 4: 3 were not treated, 2 died, 1 had physical deterioration, 2 were ineligible because of inadequate organ function.

Intention-to-treat analysis performed (selection bias)	Low risk	"...assess overall survival in the intention-to-treat population..."
--	----------	--

Dank 2008

Methods	Multicenter, 2-arm, phase III RCT
Participants	333 participants with advanced and metastatic gastric and esophageal AC were randomized and treated. 65/333 participants had esophageal or GE-junction cancer, and 318/333 had metastasis. "Patients were excluded in the case of ... prior palliative chemotherapy or treatment with camptothecin; cumulative dose of prior cisplatin >300 mg/m ² ..." Participants had a median age of 63 years, 69% were males, study duration was 1 year and 8 months, median follow-up was not mentioned. Participants were recruited from Europe. Setting of the trial, i.e. the type of hospitals, was not mentioned.
Interventions	Arm 1 (N = 170: intravenously irinotecan 80 mg/m ² 30 min, folinic acid 500 mg/m ² 2 h, 5-FU 2000 mg/m ² 22 h, for 6-7 weeks Arm 2 (N = 163): cisplatin 100 mg/m ² 1-3 h, with 5-FU 1000 mg/m ² /d, days 1-5, every 4 weeks
Outcomes	OS, response rate, TTP, TTF, toxicities, quality of life, and clinical benefit
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was carried out using a biased coin method, applying stratification according to measurable versus evaluable disease, liver involvement (yes versus no), baseline weight loss 5% (yes versus no), prior surgery (yes versus no) and treatment centre."
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"An External Radiological Review Committee (ERRC), blinded to treatment arm, reviewed all disease assessments and determined evaluability for response and date of progression."
Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 2 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant.

Dank 2008 (Continued)

		The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	"Two patients in each arm were never treated (one due to fatal disease progression, three due to grades 3–4 AEs)."
Intention-to-treat analysis performed (selection bias)	Low risk	"Thus, the full-analysis population, defined as treated patients ..."

Duffour 2006

Methods	Multicenter, 2-arm, open-label, phase III RCT
Participants	<p>232 participants with metastatic esophageal (8.4% AC, 8.4% SCC), gastric or pancreatic carcinoma from 28 institutions (classified into 3 classes according to their size) were randomized. 6 participants were ineligible. 38/226 participants had esophageal cancer, and all participants had metastatic disease.</p> <p>"The eligibility criteria were as follows: ... no prior chemotherapy for metastatic disease and, in case of adjuvant chemotherapy, no regimen containing cisplatin ..."</p> <p>Participants had a median age of 60 years, 77% were males, study duration was 3 years, median follow-up was not mentioned. Participants were recruited from France. Setting of the trial, i.e. the type of hospitals, was not mentioned.</p>
Interventions	<p>Arm 1 (N = 113): 5-FU 800 mg/m²/d in continuous infusion 5 days and cisplatin 100 mg/m² on day 1 or 2</p> <p>Arm 2 (N = 113): leucovorin, 100 mg/m²/d in bolus 5 days, followed by 5-FU 350 mg/m²/d in 1 h infusion 5 days and cisplatin 100 mg/m² on day 1 or 2</p>
Outcomes	Toxicity, quality of life, ORR, OS, and PFS
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"They were then randomly assigned to receive either an FP (arm A) or an FLP regimen (arm B) by the FFCD data centre Dijon, France, using the minimization technique."
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15%

Duffour 2006 (Continued)

		between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	"Six patients were ineligible (3%), four because of incorrect histology, one was not metastatic (liver angioma) and one had previously been treated with cis-platin."
Intention-to-treat analysis performed (selection bias)	Low risk	"The overall responses to treatment for all 226 eligible patients (after expert review)..."

Dutton 2014

Methods	Multicenter, double-blind, placebo-controlled, phase III RCT
Participants	<p>450 participants with advanced esophageal cancer or type I/II Siewert GE-junction tumors, histologically confirmed SCC (24%) or AC (76%), who had progressed after chemotherapy. N participants with metastatic disease not reported</p> <p>"Eligible patients ... had up to two previous chemotherapy and one chemoradiotherapy regimens ... Participants with brain metastases were deemed eligible if they were stable after cranial irradiation at study entry. Participants receiving cytotoxic chemotherapy, immunotherapy or hormonal therapy, radiotherapy to site of measurable or evaluable disease within the previous 4 weeks, or ... were excluded."</p> <p>Participants had a median age of 65 years, 83% were males, study duration was 2 years and 9 months, median follow-up was not mentioned. Participants were recruited from 48 UK centers. Setting of the trial, i.e. the type of hospitals, was not mentioned.</p>
Interventions	<p>Arm 1 (N = 225): gefitinib 500 mg</p> <p>Arm 2 (N = 225): matching placebo</p>
Outcomes	The primary outcome was OS, secondary outcomes were PFS, safety, disease control, participant reported outcomes, HR-QoL
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned ..."
Allocation concealment (selection bias)	Low risk	"Patients were allocated to the two treatment arms by central computer allocation using simple randomization with permuted blocks with variable block sizes and no stratification factors."
Blinding (performance bias and detection bias) All outcomes	Low risk	"Patients, clinicians, and local site and trial office staff were masked to treatment allocation. Six months after completion of recruitment the masking was broken for patients remaining on trial treatment and patients on gefitinib were allowed to continue on gefitinib."

Dutton 2014 (Continued)

Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, performance index (ECOG status 0-1 versus 2-3) differed less than 15% between study arms and was thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant. Tumor stage and the number of organs involved in metastatic disease were not mentioned.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	"One patient in the gefitinib group withdrew consent shortly after randomisation and was excluded from all analyses."
Intention-to-treat analysis performed (selection bias)	Low risk	"All analyses were done in the intention-to-treat population."

Eatock 2013

Methods	Multicenter, 3-arm, blinded RCT
Participants	<p>Between 14 December 2007 and 18 July 2009, 171 participants with esophageal, GE-junction or gastric AC were enrolled. 40/161 participants had esophageal cancer and 158 participants had metastasis</p> <p>"Key exclusion criteria were prior therapy for metastatic disease; adjuvant or neoadjuvant chemotherapy, or chemoradiation within 12 months; radiation therapy less or equal to 14 days before randomization ..."</p> <p>Participants had (respectively for arms 1, 2, and 3) a median age of 61, 57, and 62 years; 73%, 75%, and 80% were males, study duration was 1 year and 6 months, median follow-up was 32 weeks. Participants were recruited from 40 centers in 10 unnamed countries. Setting of the trial, i.e. the type of hospitals, was not mentioned.</p>
Interventions	<p>Arm 1 (N = 56): CX (cisplatin 80 mg/m² IV 3 times weekly; capecitabine 1000 mg/m² orally twice daily, 3 times weekly for 2 weeks + intravenous trebananib 10 mg/kg once weekly)</p> <p>Arm 2 (N = 59): CX + intravenous trebananib 3 mg/kg once weekly</p> <p>Arm 3 (N = 56): CX + placebo once weekly</p>
Outcomes	The primary outcome was PFS. Secondary outcomes were ORR, duration of response, OS, time to response, TTP, incidence of adverse events and anti-trebananib antibodies, and assessment of trebananib pharmacokinetics
Notes	No OS data available due to few deaths in both groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Were randomly assigned 1:1:1 using a computerized interactive voice response system."

Eatock 2013 (Continued)

Allocation concealment (selection bias)	Low risk	"Were randomly assigned 1:1:1 using a computerized interactive voice response system."
Blinding (performance bias and detection bias) All outcomes	Low risk	"Investigators, the study sponsor, and patients were blinded to treatment assignments."
Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	<p>"The most common reasons for discontinuation of AMG 386/placebo were disease progression (Arm A/B/C, 39%/46%/57%) and AEs (34%/20%/7%)."</p> <p>From figure 1 in the trial report: arm 1: disease progression 22, adverse event 19, protocol deviation 1, noncompliance 1, lost to follow-up 1, death 1, consent withdrawn, other 3; arm 2: disease progression 27, adverse event 12, noncompliance 2, death 5, consent withdrawn 3, ineligibility determined 1, administrative decision, 1; arm 3: disease progression 32, adverse event 4, protocol deviation 1, death 2, consent withdrawn 4, other 3, administrative decision 1</p>
Intention-to-treat analysis performed (selection bias)	Low risk	All randomized participants were included in efficacy analysis.

Ezdinli 1980

Methods	Multicenter, phase II RCT
Participants	<p>88 participants randomized, 63 treated. Participants had non-resectable or metastatic ($\geq 51\%$) SCC esophageal cancer.</p> <p>"No prior chemotherapy or radiotherapy within the previous month and no major surgical procedures within the previous three weeks. Participants with prior chemotherapy with any of the study agents were ineligible." Prior treatment (surgery or radiation): 87%</p> <p>Participants had a median age of 62 years, 81% were males, study duration was 4 years, median follow-up was 14 weeks. Participants were recruited from the USA. Setting of the trial, i.e. the type of hospitals, was not mentioned.</p>
Interventions	<p>Arm 1 (N = 16): adriamycin 60 mg/m² every 3 weeks</p> <p>Arm 2 (N = 24): methotrexate 40 mg/m² every week</p> <p>Arm 3 (N = 23): 5-FU 500 mg/m²/d for 5 days every 5 weeks. Treatment was continued until evidence of relapse or progression was noted.</p>
Outcomes	Median survival, survival curves, toxicity
Notes	Adriamycin arm discontinued because of zero responders, 14% cross-over. 28% of participants were excluded after randomization for unknown reasons, the groups were not completely comparable at baseline.

Ezdinli 1980 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Treatment assignments to Adriamycin, methotrexate, or 5-FU were made from the Central Randomization Desk at ECOG Operations Office. A stratified randomisation scheme was used with the following stratification criteria: (1) Previous Treatment (1 -no prior therapy vs. 2-prior therapy), (2) ECOG Performance Status (1-ECOG 0 or 1 vs. 2-ECOG 2 or 3), (3) Heart Disease (1-absent vs. 2-present). Dynamic treatment allocation based on the participant's institution was utilized to insure a reasonably balanced assignment within each institution."
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Low risk	Survival and toxicity are reported.
Similar at baseline for most prognostic factors (selection bias)	High risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease) and performance index (ECOG status 0-1 versus 2-3) differed less than 15% between study arms and were thus not considered to be clinically relevant. Age difference more than 5 years between groups. Metastasis in liver and lung differ more than 15%
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	"Five entries were cancelled before any protocol treatment was given. Two patients refused treatment, two patients were treated with programs other than those in the protocol, and one patient did not start treatment because his initial blood counts were below specific levels."
Intention-to-treat analysis performed (selection bias)	Low risk	"Eighty-eight patients in all were randomized. Five entries were cancelled before any protocol treatment was given. Two patients refused treatment, two patients were treated with programs other than those in the protocol, and one patient did not start treatment because his initial blood counts were below specific levels."

Ford 2014

Methods	Multicenter, open-label, 2-arm, phase III RCT
Participants	<p>168 participants (n = 147 with metastasis) who had histologically confirmed advanced AC of the esophagus, GE-junction, or stomach. Of the 92 esophageal cancer participants 45 were randomized to the docetaxel group and 47 to the control group.</p> <p>"(Patients had) documented disease progression during or within 6 months of treatment with platinum and fluoropyrimidine-based treatment (which could have been given as adjuvant or neoadjuvant therapy, or for advanced disease)" "Important exclusion criteria were previous chemotherapy with a taxane ..."</p>

Ford 2014 (Continued)

Participants had a median age of 66 years, 81% were males, study duration was 4 years, median follow-up was 12 months. Participants were recruited from 30 UK sites. Setting of the trial, i.e. the type of hospitals, was not mentioned.

Interventions	Arm 1 (N = 45): docetaxel, a dose of 75 mg/m ² IV every 3 weeks for up to six cycles + BSC Arm 2 (N = 47): BSC alone
Outcomes	The primary outcome was OS. Secondary outcomes were best response to docetaxel, TTP, toxicity, and HR-QoL. Important HR-QoL outcomes identified before we started the study were physical and social function and fatigue (QLQ-C30) and eating restrictions and dysphagia (QLQ-STO22).
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"We randomly allocated patients ..."
Allocation concealment (selection bias)	Low risk	"... using a central computerised minimisation procedure generated at the Warwick Clinical Trials Unit." "To conceal the sequence the investigator or research nurse, who recruited the patients, contacted the Warwick Clinical Trials Unit for each participant's random allocation sequence."
Blinding (performance bias and detection bias) All outcomes	High risk	"Because this was an open-label study, participants, investigators, and trials staff were aware of treatment allocations."
Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease) and performance index (ECOG status 0-1 versus 2-3) and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant. The number of organs involved in metastatic disease was not mentioned.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	Figure 1, arm 1: 7 did not receive allocated intervention 3 died, 1 refused treatment, 1 withdrew, 1 delay > 21 days, 1 participant admitted for another disorder; arm 2: 6 did not receive allocated intervention, 4 withdrew, 1 entered another trial, 1 had progressive disease.
Intention-to-treat analysis performed (selection bias)	Low risk	"We did all analyses on an intention-to-treat basis."

Fuchs 2014

Methods	International, double-blind, placebo-controlled, 2-arm, phase III RCT
Participants	355 participants with metastatic or unresectable, locally recurrent gastric or GE-junction AC were randomly assigned to either the ramucirumab group (N = 238) or the placebo group (N = 117). 90/355 participants had esophageal cancer; at least 121 participants had metastasis.

Fuchs 2014 (Continued)

"[Participants] had disease progression within 4 months of the last dose of first-line platinum-containing or fluoropyrimidine-containing chemotherapy for metastatic disease, or within 6 months of the last dose of platinum-containing or fluoropyrimidine-containing adjuvant treatment"

Participants had a median age of 60 years, 70% were males, study duration was 2 years and 3 months, median follow-up was not mentioned. Participants were recruited from North America, Europe, Australia, New Zealand, South and Central America, India, South Africa, Middle East, and Asia. Setting of the trial, i.e. the type of hospitals, was not mentioned.

Interventions	Arm 1 (N = 60): BSC + either ramucirumab 8 mg/kg Arm 2 (N = 30): BSC + placebo, IV once every 2 weeks
Outcomes	The primary outcome was OS. Secondary outcomes were PFS, 12 week PFS, ORR, duration of response, quality of life, safety, and ramucirumab immunogenicity
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned ..."
Allocation concealment (selection bias)	Low risk	"... via a centralised interactive voice-response system"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Patients, medical and ancillary staff, the study investigators, and the sponsor were masked to group assignment. Unmasking could be done for individual patients in emergencies only; serious adverse events did not necessarily precipitate immediate unmasking."
Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	Figure 1, arm 1: 2 did not receive study drug, 7 withdrew consent, 3 other; arm 2: 2 did not receive study drug, 3 withdrew consent, 2 other.
Intention-to-treat analysis performed (selection bias)	Low risk	"We used a stratified log-rank test to assess OS and progression-free survival in the intention-to-treat population ..."

Huang 2009

Methods	Single-center, open RCT
Participants	60 participants with advanced, non-resectable and/or metastatic esophageal cancer

Huang 2009 (Continued)

Participants' last chemotherapy or radiotherapy had to be at least 1 month prior to inclusion.

Participants had a median age of 53 years, 58% were males, study duration was not mentioned, median follow-up was not mentioned. Participants were recruited from China. Setting of the trial was the Henan Tumor Hospital and the First Affiliated Hospital of Zhengzhou University.

Interventions	Arm 1 (N = 30): Shenyi Capsule + gemcitabine and cisplatin Arm 2 (N = 30): gemcitabine and cisplatin
Outcomes	OS, side effects, VEGF level, and quality of life
Notes	Translated from Chinese

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Translation: "By using random number table, research methods for parallel, controlled, and open clinical trials, patients were divided into treatment group and control group (30 cases for each group)."
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	"Patients had 3 to 12 months follow-up, and the follow-up rate was 100%."
Intention-to-treat analysis performed (selection bias)	Low risk	Since no dropouts or losses to follow-up occurred, intention-to-treat analysis had to be performed, even though it was not described.

Iveson 2014

Methods	Multicenter, double-blind, 3-arm, phase II RCT
Participants	121 participants with pathologically confirmed, unresectable locally advanced or metastatic gastric or GE-junction AC. 24/121 participants (19.8%) had esophageal cancer and 107 participants had metastasis.

Iveson 2014 (Continued)

"Major exclusion criteria were previous systemic therapy for locally advanced or metastatic disease, previous neo adjuvant or adjuvant chemotherapy or chemo-radio therapy less than 6 months before enrolment ..."

Participants had a median age of 60 years, 73% were males, study duration was 2 years and 3 months, median follow-up was 1 year and 10 months. Participants were recruited from 43 hospitals and academic institutions in Australia, Belgium, Canada, Greece, Hong Kong, Hungary, India, Poland, Russia, Singapore, Spain, the UK, and the USA. Setting of the trial included hospitals and academic institutions

Interventions	<p>Arm 1 (N = 40): rilotumumab 15 mg/kg</p> <p>Arm 2 (N = 42): rilotumumab 7.5 mg/kg</p> <p>Arm 3 (N = 39): placebo</p>
Outcomes	The primary outcome was PFS. Secondary outcomes were: OS, proportion of participants who achieved an objective response, proportion of participants who achieved disease control, time to response, duration of response, pharmacokinetics, the incidence of adverse events, laboratory value changes from baseline, and the presence of anti-rilotumumab antibodies
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomisation list was generated using permuted blocks with a block size of six and prepared by an individual independent of the study team ..."
Allocation concealment (selection bias)	Low risk	"[T]reatment allocation was assigned using an interactive voice response system."
Blinding (performance bias and detection bias) All outcomes	Low risk	"Patients, investigators, and the study team were masked to treatment allocation, which was straightforward because rilotumumab is a colourless liquid."
Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	Figure 1, arm 1: 0 still on study treatment, 39 discontinued study treatment, 21 disease progression, 5 partial consent withdrawn, 3 adverse event, 3 death, 2 administrative decision, 2 full consent withdrawn, 2 protocol-specified criteria, 1 protocol deviation; arm 2: 1 still on study treatment, 41 discontinued study treatment, 12 adverse event, 9 protocol-specified criteria, 8 disease progression, 4 administrative decision, 2 death, 2 full consent withdrawn, 2 partial consent withdrawn, 2 other; arm 3: 2 still on study treatment, 37 discontinued study treatment, 10 adverse event, 10 disease progression, 4 death, 4 full consent withdrawn, 4 partial consent withdrawn, 4 protocol-specified criteria, 1 other
Intention-to-treat analysis performed (selection bias)	Low risk	"We analysed PFS and OS in the intention to treat population ..."

Levard 1998

Methods	Multicenter, phase III RCT
Participants	<p>156 participants with SCC; at least 14 participants had distant metastasis. Possible previous chemotherapy is not mentioned. 24% of participants got additional treatment.</p> <p>Participants had a mean age of 58 years, 96% were males, study duration was 4 years and 6 months, median follow-up was 1 year. Participants were recruited from France. Setting of the trial, i.e. the type of hospitals, was not mentioned.</p>
Interventions	<p>Arm 1 (N = 72): chemotherapy: 5-FU 1000 mg/m²/d for 5 days, cisplatin 1000 mg/m² on day 1 or 20 mg/m² for 5 days, every 4 weeks, max 6-8 cycles</p> <p>Arm 2 (N = 84): no treatment</p>
Outcomes	Median survival, actuarial curves, toxicity, dysphagia
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"[R]andom allocation was accomplished by unfolding the previously stapled upper right hand corner of a questionnaire under which the nature of the treatment to be given was hidden, a method used in preference to the envelope method in which the envelopes can become mixed up."
Allocation concealment (selection bias)	Low risk	"[R]andom allocation was accomplished by unfolding the previously stapled upper right hand corner of a questionnaire under which the nature of the treatment to be given was hidden, a method used in preference to the envelope method in which the envelopes can become mixed up."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Low risk	"The main end point was the duration of survival based on median survival and actuarial curves. The subsidiary end point was the quality of survival as judged by the development of complications or mortality from chemotherapy, the course of swallowing disorders (improved, unchanged, or worsened), and the duration of ability to feed orally without mechanical treatment."
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	"Of 161 eligible patients initially included, five were withdrawn from analysis, two in the control group and three in the treated group. Three patients had ENT carcinoma which were initially unrecognised, one patient had hepatic metastases that occupied more than 30% of the liver, and one further patient was lost to follow-up."

Levard 1998 (Continued)

Intention-to-treat analysis performed (selection bias)	Low risk	The number of participants treated was also the number reported on.
--	----------	---

Li 2002

Methods	Multicenter, open-label, phase III RCT
Participants	<p>Out of a total of 320 participants, 62 had esophageal cancer. An unknown number of participants had metastases. The participants' last chemotherapy or radiotherapy had to be at least 1 month prior to inclusion.</p> <p>Participants had a median age of 56 years, 73% were males, study duration was not mentioned, median follow-up was not mentioned. Participants were recruited from China. Setting of the trial, i.e. the type of hospitals, was not mentioned.</p>
Interventions	<p>All participants received a background of either mitomycin C + etoposide, cisplatin + hydroxycarbopothecin, cisplatin + vindesine, or adriamycin + mitomycin C, in addition to:</p> <p>Arm 1 (N = 40 randomized, n = 30 treated): atofluding</p> <p>Arm 2 (N = 22 randomized, n = 14 treated): ftorafur</p>
Outcomes	Response rates were reported separately per tumor type
Notes	Translated from Chinese

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	High risk	"A multicenter, open randomised controlled trial was carried out."
Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	High risk	Dropouts not described

Li 2002 (Continued)

Intention-to-treat analysis performed (selection bias)	High risk	Intention-to-treat analysis not described
--	-----------	---

Lordick 2013

Methods	Multicenter, open-label, phase III RCT
Participants	<p>904 esophageal and gastric AC participants randomized to capecitabine/cisplatin/cetuximab (N = 455) or no cetuximab (N = 449). 875/904 participants had metastasis; 144 had GE-junction cancer.</p> <p>"Other inclusion criteria were ... no previous chemotherapy for metastatic or locally advanced unresectable gastric or GE-junction cancer; adjuvant chemotherapy completed at least one year before randomization and not more than 300 mg/m² cisplatin administered; no previous treatment with drugs targeting EGFR-related or VEGFR-related signaling pathways"</p> <p>Participants had a median age of 60 years for arm 1 and 59 age for 59 years, 74% were males, study duration was 2 years and 6 months, median follow-up was 22.4 months for arm 1 and 21.0 months for arm 2. Participants were recruited from 164 sites in 21 countries worldwide, including Argentina, Australia, Austria, Belgium, Bulgaria, China, Czech Republic, France, Greece, Germany, Israel, Italy, Japan, Poland, Portugal, Romania, Russia, South Korea, Spain, Taiwan, and the United Kingdom. Setting of the trial included teaching hospitals and clinics.</p>
Interventions	<p>3-week cycles of chemotherapy consisting of oral capecitabine 1000 mg/m² twice daily from the evening of day 1 until the morning of day 15 + intravenous cisplatin 80 mg/m² on day 1, in addition to:</p> <p>Arm 1 (N = 73): once-weekly cetuximab, 400 mg/m² at the first infusion then 250 mg/m² every week</p> <p>Arm 2 (N = 71): no cetuximab</p>
Outcomes	OS, PFS, overall response, treatment exposure, baseline characteristics, study profile, and adverse events are mentioned for the studied group as a whole; OS and PFS reported for a number of subgroups
Notes	The outcome HR for overall and PFS is the only one given for the esophageal cancer subgroup.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was done centrally with an interactive voice response system. We used a stratified, permuted, block randomisation procedure ..."
Allocation concealment (selection bias)	Low risk	"Randomisation was done centrally with an interactive voice response system. We used a stratified, permuted, block randomisation procedure ..."
Blinding (performance bias and detection bias) All outcomes	High risk	"In this open-label, randomised, controlled, phase III study ..."
Selective reporting (reporting bias)	Low risk	OS, PFS, overall response, treatment exposure, baseline characteristics, study profile, and adverse events are mentioned for the studied group as a whole; OS and PFS reported for a number of subgroups
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant.

Lordick 2013 (Continued)

The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.		
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	Figure 1, arm 1: 447 discontinued treatment, 247 disease progression, 74 adverse events, 24 deaths, 41 withdrawal of consent, 31 symptomatic deterioration, 4 non-compliance, 2 lost to follow-up, 24 other; arm 2: 444 discontinued treatment, 223 disease progression, 75 adverse events, 24 deaths, 51 withdrawal of consent, 22 symptomatic deterioration, 10 non-compliance, 1 lost to follow-up, 38 other
Intention-to-treat analysis performed (selection bias)	Low risk	"...did not receive ≥ 1 dose and were excluded from the safety analysis"

Lorenzen 2009

Methods	Multicenter, open-label, phase II RCT	
Participants	<p>62 participants with unresectable EGFR expressing advanced SCC. EGFR expression was defined as positive immunohistochemical staining of the membrane above background level in 1% or more of cancer cells. All participants had esophageal cancer; 54/62 participants had metastasis.</p> <p>"Patients ... who had not received (neo)adjuvant chemotherapy within 6 months of study entry or prior chemotherapy for recurrent or metastatic disease were eligible."</p> <p>Participants had a median age of 61 years for arm 1 and 62 years for arm 2, 84% were males, study duration was 2 years, median follow-up was 21.5 months. Participants were recruited from 12 institutions in Germany. Setting of the trial was not mentioned.</p>	
Interventions	<p>All participants received up to 6, 29-day cycles of chemotherapy (cisplatin 100 mg/m² over 60 min on day 1, with standard antiemetic prophylaxis and pre- and post cisplatin hydration, followed by 5-FU 1000 mg/m²/d as a continuous 24 h intravenous infusion from days 1–5), in addition to:</p> <p>Arm 1 (N = 32): cetuximab, administered as an initial dose of 400 mg/m² on day 1 over 120 min, followed by weekly doses of 250 mg/m² over 60 min</p> <p>Arm 2 (N = 30): no cetuximab</p>	
Outcomes	The primary outcome of the study was the confirmed ORR. Secondary outcomes included OS, PFS, duration of response, time to treatment failure, and safety	
Notes	—	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomised centrally 1 : 1, without stratification..."
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	High risk	"[O]pen label"

Lorenzen 2009 (Continued)

Selective reporting (reporting bias)	Low risk	The primary outcome of the study was the confirmed ORR. Secondary outcomes included OS, PFS, duration of response, time to treatment failure and safety.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	Figure 1, arm 1: one participant never received treatment; arm 2: three participants never received treatment.
Intention-to-treat analysis performed (selection bias)	Low risk	See definition and beginning of the Results section of the study.

Lorenzen 2015

Methods	Multicenter, open-label, 2-arm, phase II RCT	
Participants	<p>37 randomized participants. Participants had histologically confirmed HER2-positive metastatic AC of the esophagus, GE-junction, or stomach and were eligible for inclusion if they had documented disease progression during or within 6 months after treatment with at least one cytotoxic regimen for metastatic disease including a platinum agent. 22/37 participants had esophageal cancer; at least 26 participants had metastasis.</p> <p>"Patients ... were eligible for inclusion if they had documented disease progression during or within 6 months after treatment with at least one cytotoxic regimen for metastatic disease including a platinum agent."</p> <p>Participants had a median age of 56 years for arm 1 and 62 years for arm 2, 84% were males, study duration was 2 years and 2 months, median follow-up was not mentioned. Participants were recruited from 11 German institutions. Setting of the trial, i.e. the type of hospitals, was not mentioned.</p>	
Interventions	<p>Arm 1 (N = 18): LAP 1250 mg per day 1-21 + capecitabine 2000 mg/m² on days 1-14 of a 21-day cycle</p> <p>Arm 2 (N = 19): LAP 1500 mg monotherapy day 1-21</p>	
Outcomes	The primary outcome was the ORR defined as complete or partial response according to RECIST. Secondary outcomes were TTP, PFS, OS, and safety	
Notes	—	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was done via a centralised internet-based system."
Allocation concealment (selection bias)	Low risk	"Randomisation was done via a centralised internet-based system."

Lorenzen 2015 (Continued)

Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	Unclear risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease) and performance index (ECOG status 0-1 versus 2-3) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant. Concerning the number of metastatic sites, the 0-2 metastasis group was 39% in the LAP + CAP group and 21% in the LAP group.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	Figure 1, arm 1: 3 withdrew informed consent, 3 died, 2 adverse events, 3 by investigator decision, 1 lost to follow-up, 1 other reason ; arm 2: 1 withdrew informed consent, 5 died, 1 adverse events, 2 by investigator decision, 1 lost to follow-up, 5 other reason.
Intention-to-treat analysis performed (selection bias)	Low risk	All randomized participants were analyzed.

Moehler 2010

Methods	Open-label, randomized, multicenter, 2-arm study conducted at 16 centers in Germany	
Participants	<p>118 participants with metastatic esophageal, GE-junction and gastric AC were entered into a randomized study from October 2003 to December 2006. 24/112 participants had esophageal cancer; all participants had metastasis.</p> <p>"Patients who had received previous, adjuvant or neoadjuvant chemotherapy and/or radiotherapy were excluded."</p> <p>Participants had a median age of 61 years for arm 1 and 64 years for arm 2, 70% were males, study duration was 3 years and 2 months, median follow-up was 5.5 and 6.1 months for arms 1 and 2. Participants were recruited from Germany. Setting of the trial, i.e. the type of hospitals, was not mentioned.</p>	
Interventions	<p>All participants received 3-week cycles of capecitabine 1000 mg/m², twice daily for 14 days, in addition to:</p> <p>Arm 1 (N = 60): irinotecan 250 mg/m² on day 1</p> <p>Arm 2 (N = 58): cisplatin 80 mg/m² on day 1</p>	
Outcomes	The primary outcome was overall response rate; secondary outcomes included PFS, OS, and safety	
Notes	—	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were centrally randomly assigned 1:1 to receive ..."

Moehler 2010 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	High risk	"This was an open-label, randomised, multicenter, twin-arm trial conducted at 16 centers in Germany."
Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	"Six patients, three in each arm, received no study treatment and were consequently excluded from the study. Two patients had shown tumor progression before the start of treatment and the reasons for not participating in the other four patients could not be ascertained."
Intention-to-treat analysis performed (selection bias)	High risk	ITT is not described and not performed.

Nicolaou 1982

Methods	RCT, pilot study
Participants	24 participants with unresectable esophageal cancer, 92% had SCC. None of the participants had had previous chemotherapy. 2 participants had metastases found during laparoscopy.
Interventions	Arm 1 (N = 12): chemotherapy – doxorubicin 40 mg/m ² , cyclophosphamide 700 mg/m ² , every 2 weeks, 2-4 cycles, + Celestin tube Arm 2 (N = 12): Celestin tube only Participants had a median age of 57 years, 100% were males, study duration was 2 years, median follow-up was not mentioned. Participants were recruited from Leratong Hospital, Johannesburg
Outcomes	Median survival, 6 months and 1-year survival, toxicity
Notes	140 participants eligible, only 24 included

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"... randomised into two subgroups of 12 patients each." Not described how
Allocation concealment (selection bias)	Unclear risk	Not mentioned

Nicolaou 1982 (Continued)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Low risk	Median survival, 6 months and 1-year survival, toxicity
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	"Nine patients died because of progression of the tumour; 1 (patient 2) died from aspiration pneumonia, 1 (patient 3) from haematemesis and 1 (patient 9) from staphylococcal enterocolitis which was not related to the chemotherapy."
Intention-to-treat analysis performed (selection bias)	Low risk	All participants received treatment according to their treatment arm, therefore. ITT analysis had to be performed.

Ohtsu 2011

Methods	Multinational, placebo controlled, 2-arm RCT
Participants	<p>774 AC participants (387 in each group). 103/774 participants (13.3%) had GE-junction AC, 745 participants had metastasis.</p> <p>"(Neo)adjuvant chemotherapy was permitted if completed 6 months before random assignment. Surgery or radiotherapy was permitted if completed 28 days before random assignment."</p> <p>Participants had a median age of 58 years in arm 1 and 59 years in arm 2, 67% were males, study duration was 1 year and 3 months, median follow-up was 11.4 and 9.4 months in arms one and two. "Almost half (49%; n 376) the patients were enrolled from the Asia-Pacific region (90% from Japan and Korea); the remainder were enrolled in Europe (32%; n249) and Pan-America (19%; n 149), mainly Eastern Europe and Latin America, respectively." Setting of the trial, i.e. the type of hospitals, was not mentioned.</p>
Interventions	<p>Arm 1: bevacizumab 7.5 mg/kg</p> <p>Arm 2: matching placebo</p> <p>Following these interventions, all participants received cisplatin 80 mg/m² on day 1 + capecitabine 1000 mg/m² twice daily for 14 days every 3 weeks</p>
Outcomes	The primary study outcome was OS, defined as time between random assignment and death irrespective of cause. Secondary outcomes were PFS, overall response rate, and safety.
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
------	--------------------	-----------------------

Ohtsu 2011 (Continued)

Random sequence generation (selection bias)	Low risk	"Patients were assigned (1:1 ratio) to treatment by using permuted-block randomisation ..."
Allocation concealment (selection bias)	Low risk	"Allocation concealment was performed by an interactive voice recognition system supplied by a clinical research organization responsible for appropriate and independent treatment allocation."
Blinding (performance bias and detection bias) All outcomes	Low risk	"AVAGAST was a prospective, random-assignment, double-blind, placebo-controlled phase III clinical trial."
Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	"Adverse events or laboratory abnormalities led to withdrawal from a component of study treatment in 81 patients (21%) in the bevacizumab group versus 71 patients (19%) in the placebo group."
Intention-to-treat analysis performed (selection bias)	Low risk	"The intention-to-treat patient population, the primary population for efficacy analysis, included all randomly assigned patients."

Pang 2014

Methods	Single-center, 2-arm RCT
Participants	57 participants with advanced SCC. All participants had esophageal cancer. "[I]nterval between current treatment and last treatment is longer than 4 weeks."
Interventions	<p>Arm 1 (N = 28): leucovorin 200 mg/m², 5-FU 600 mg/m² from days 1-5 and cisplatin IV 75 mg/m² for days 1-3</p> <p>Arm 2 (N = 29): S-1 capsule 100 mg/d if the body surface area was < 15 m², otherwise 120 mg/d twice daily for 14 days and cisplatin IV 75 mg/m². Cycles were 21 days.</p> <p>Participants had a mean age of 59 years, 75% were males, study duration was not mentioned, median follow-up was more than 1 year. Participants were recruited from the first affiliated hospital of Zhengzhou University.</p>
Outcomes	Response rate, adverse reactions, TTP, and OS
Notes	Translated from Chinese

Risk of bias

Bias	Authors' judgement	Support for judgement
------	--------------------	-----------------------

Pang 2014 (Continued)

Random sequence generation (selection bias)	Unclear risk	"[R]andomly grouping into observed group and control"
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	Quoted from the translated manuscript: "One patient in arm 1 had a digestive tract reaction in the first period, diarrhea, this symptom disappeared after treatment. However, the patient refused any further treatment and died due to disease progression after 5 months. Another patient in arm 1 suffered from grade IV Myelosuppression (Blood platelet < 13X10 ⁹ /L) within the 4 th period, after treatment and a dose decrease of S-1 this patient proceeded for 6 more periods of chemotherapy."
Intention-to-treat analysis performed (selection bias)	High risk	"[T]erm effect current patients available for term effect evaluation was 56 (SP 27 patients, FP was 29 patients) due to one patient stopped treatment." ITT not performed

Pozzo 2004

Methods	Multicenter, 2-arm, phase II RCT
Participants	148 participants with advanced or metastatic AC of the GE-junction or stomach were randomly allocated. 35/146 participants had esophageal cancer and 137 participants had metastasis. "... [N]o previous palliative chemotherapy (previous adjuvant and/or neo-adjuvant chemotherapy were allowed provided a 12-month interval had elapsed since the end of therapy) ..." Participants had a median age of 57 years for arm 1 and 59 years for arm 2, 71% were males, study duration was 1 year and 2 months, median follow-up was not mentioned. Participants were recruited from 41 centers in 13 European countries and Israel, Lebanon, Turkey and South Africa. Setting of the trial, i.e. the type of hospitals, was not mentioned.
Interventions	Arm 1 (N = 75): irinotecan 80 mg/m ² IV, folinic acid 500 mg/m ² IV, and a 22-h infusion of 5-FU 2000 mg/m ² IV, weekly for 6 weeks with a 1-week rest Arm 2 (N = 73): irinotecan 200 mg/m ² IV and cisplatin 60 mg/m ² IV on day 1 for 3 weeks
Outcomes	The primary outcome was complete response rate, secondary outcomes included safety, TTP, and OS
Notes	—

Pozzo 2004 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"In this study, a minimization method was used to stratify randomisation according to: centre, liver and/or peritoneal metastases (yes versus no), prior gastrectomy (yes versus no) and disease type (measurable versus evaluable only lesions)."
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	"Twenty-three patients were not evaluable for response, 11 receiving irinotecan/cisplatin and 12 receiving irinotecan/5-FU/FA, either because of early treatment discontinuation [n = 5 (two deaths unrelated to treatment, two treatment-related adverse events and one major protocol violation) and n = 4 (one death unrelated to treatment, one non-treatment-related adverse event and two treatment-related adverse events), respectively], nonevaluable target (n = 2 and 6, respectively), or because the response was not properly assessed (n = 4 and 2, respectively)."
Intention-to-treat analysis performed (selection bias)	High risk	No ITT performed

Rao 2010

Methods	Multicenter, open-label, phase II RCT
Participants	<p>72 participants with metastatic gastric and esophageal cancer. 41/71 participants (57.7%) had esophageal cancer and 70 had metastasis.</p> <p>"Other eligibility requirements included ... a minimum 12-month interval from completion of any neoadjuvant or adjuvant chemotherapy, a minimum 4-week interval from completion of radiotherapy..." "Only patients with EGFR-positive tumors were enrolled into the study." 36 were randomized to ECX/matuzumab and 36 to ECX.</p> <p>Participants had a median age of 59 years for arm 1 and 64 years for arm 2, 72% were males, study duration was 1 year and 2 months, median follow-up was 28.5 and 23.0 months for arm 1 and arm 2. Participants were recruited from 22 centers in the UK and Europe. Setting of the trial, i.e. the type of hospitals, was not mentioned.</p>
Interventions	Arm 1 (N = 36): 800 mg matuzumab weekly + epirubicin 50 mg/m ² , cisplatin 60 mg/m ² on day 1 and capecitabine 1250 mg/m ² daily in a 21-day cycle (ECX)

Rao 2010 (Continued)

Arm 2 (N = 36): the same ECX regimen alone

Outcomes	Primary outcome was radiologically confirmed tumor response, as assessed by the IRC. Secondary outcomes included tumor response as assessed by the investigator, OS, PFS and quality of life.
----------	---

Notes	—
-------	---

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was carried out centrally in a blinded manner by telephone using an interactive voice response system with the random sequence previously generated by a computer programme ..."
Allocation concealment (selection bias)	Low risk	"Randomisation was carried out centrally in a blinded manner by telephone using an interactive voice response system with the random sequence previously generated by a computer programme ..."
Blinding (performance bias and detection bias) All outcomes	High risk	Open label
Selective reporting (reporting bias)	Low risk	All outcomes are reported on.
Similar at baseline for most prognostic factors (selection bias)	High risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. A 5-year difference in age was present.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	"One patient was withdrawn from the study directly after randomisation due to a poor GFR <60 ml/min."
Intention-to-treat analysis performed (selection bias)	Low risk	"The primary end point of response, as assessed by the IRC in the ITT population ..." "Furthermore, no notable difference in the median OS for the ITT population was observed ..."

Richards 2013

Methods	Multicenter, phase 2, open-label RCT
Participants	150 eligible participants with advanced or metastatic GE-junction and gastric AC. 79/150 participants (52.7%) had esophageal cancer; 117, metastasis "Patients were allowed to have had adjuvant radiation + treatment with 5-FU and leucovorin." Participants had a median age of 62 years and 64 years for arms one and two, 79% were males, study duration was 2 years and 3 months, median follow-up was not mentioned. Participants were recruited from the USA. Setting of the trial, i.e. the type of hospitals, was not mentioned.
Interventions	During each 21-day period:

Richards 2013 (Continued)

Arm 1 (N = 75): docetaxel 60 mg/m² IV followed by oxaliplatin 130 mg/m² IV and rested on days 8 and 15

Arm 2 (N = 75): docetaxel 60 mg/m² IV, followed by oxaliplatin 130 mg/m² IV, followed by a cetuximab loading dose of 400 mg/m² IV over 120 min on day 1 of cycle 1. Doses after day 1 of cycle 1 of cetuximab were 250 mg/m², and participants received cetuximab 250 mg/m² on days 8 and 15.

Outcomes	The primary objective was PFS. Secondary objectives were response rate, time to response, duration of response and safety.
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"... and thus randomisation was 1:1 centrally conducted within each of the two strata."
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	High risk	"This was a Phase 2, open-label, randomised, non comparative study ..."
Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	Figure 1, arm 1: 4 participants decided not to take the study drug, 1 investigator request due to declining condition, 1 AE/unrelated complication (GI bleeding), 1 insurance issue; arm 2: 1 participant decided not to take the study drug, 1 early disease progression, 1 insurance issue
Intention-to-treat analysis performed (selection bias)	Low risk	"Based on all intention-to-treat patients within each arm, the Kaplan–Meier method was used for the analysis of PFS and overall survival (OS) ..."

Ross 2002

Methods	2-arm RCT
Participants	<p>574 participants; 188 with esophageal and 125 with GE-junction cancer; 40 participants had SCC. In total 574 participants were randomized and eligible for analysis to epirubicin, cisplatin and 5-FU N = 313 or mitomycin, cisplatin and 5-FU N = 328. 328/574 participants had metastasis. Potential previous chemotherapy is not mentioned.</p> <p>"Potentially curative surgery was performed in 10 of these patients after chemotherapy (three ECF and seven MCF patients)."</p>

Ross 2002 (Continued)

Participants had a median age of 58 and 59 years for arm 1 and 2, 77% were males, study duration was 3 years, median follow-up of surviving participants was 13.8 months. Participants were recruited from 13 oncology centers in the United Kingdom. Setting of the trial, i.e. the type of hospitals, was not mentioned.

Interventions	Arm 1: epirubicin 50 mg/m ² every 3 weeks, cisplatin 60 mg/m ² every 3 weeks and PVI 5-FU 200 mg/m ² /d Arm 2: mitomycin 7 mg/m ² every 6 weeks, cisplatin 60 mg/m ² every 3 weeks, and PVI 5-FU 300 mg/m ² /d
Outcomes	OS, TTP, ORR, toxicity and quality of life. Only ORR is given for the esophageal cancer subgroup.
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A stratified (by centre) randomisation list was generated independently by the Clinical Trials Office, Institute of Cancer Research, using random permuted blocks. Randomization was allocated by telephone."
Allocation concealment (selection bias)	Low risk	"A stratified (by centre) randomisation list was generated independently by the Clinical Trials Office, Institute of Cancer Research, using random permuted blocks. Randomization was allocated by telephone."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Unclear risk	Since only objective response rate is available for the esophageal cancer participant group, this parameter can be inconsistent with the other outcome parameters.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	"Six patients (three ECF and three MCF) were ineligible because of inadequate renal function (n 3), abnormal ECG (n 1), and nonesophagogastric primary cancer (n 2; one breast and one uterus)."
Intention-to-treat analysis performed (selection bias)	Low risk	"...eligible for analysis on an intent-to-treat basis (Fig 1)."

Roy 2012

Methods	RCT
Participants	85 participants with advanced GE-junction and gastric AC. 39/85 participants had esophageal cancer and 80 participants had metastasis.

Palliative chemotherapy and targeted therapies for esophageal and gastroesophageal junction cancer (Review)

Roy 2012 (Continued)

"Previous adjuvant (and/or neoadjuvant) chemotherapy was allowed, provided a period of 12 months had elapsed since the end of therapy and first relapse. No prior palliative chemotherapy was permitted."

Participants had a median age of 62, 60 and 61 years for arms 1, 2 and 3, 82% were males, study duration was 8 months, median follow-up was not mentioned. Participants were recruited from 19 centers in 6 countries: Belgium, France, Germany, Norway, Spain, and the UK. Setting of the trial, i.e. the type of hospitals, was not mentioned.

Interventions	<p>Arm 1 (N = 42): 3 weekly docetaxel 60 mg/m² + irinotecan 250 mg/m² (day 1)</p> <p>Arm 2 (N = 43): 3 weekly docetaxel 85 mg/m² (day 1) followed by 5-FU 750 mg/m² per day as a continuous infusion (days 1–5)</p>
Outcomes	The primary outcome was a radiological response rate. Secondary outcomes included TTP, time to treatment failure, duration of response, OS, toxicities and clinical benefit.
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomised ..."
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	"One patient in the DI group was not treated and discontinued the study because of jaundice..."
Intention-to-treat analysis performed (selection bias)	Low risk	"The median OS (ITT) was ..."

Shen 2014

Methods	Multicenter, double-blind, 2-arm, phase III RCT
---------	---

Shen 2014 (Continued)

Participants	<p>202 participants with histologically confirmed, inoperable, locally advanced or recurrent, and/or metastatic AC of the stomach or GE-junction. 25/202 participants (12.3%) had GE-junction cancer and 189 participants had metastasis.</p> <p>"Patients with no prior treatment for advanced/metastatic disease ... were included in the study."</p> <p>Participants had a median age of 55 years, 80% were males, study duration was not mentioned, median follow-up was not mentioned. Participants were recruited from 15 Chinese centers. Setting of the trial, i.e. the type of hospitals, was not mentioned.</p>
Interventions	<p>All participants received capecitabine 1000 mg/m² orally twice daily for 14 days, followed by a 1-week rest, + cisplatin 80 mg/m² IV on day 1 every 3 weeks for 6 cycles, in addition to:</p> <p>Arm 1 (N = 100): bevacizumab 7.5 mg/kg IV on day 1 every 3 weeks</p> <p>Arm 2 (N = 102): matching placebo (bevacizumab vehicle)</p>
Outcomes	The primary outcome was OS; secondary outcomes were PFS and response rate.
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients who were eligible for study entry were randomly assigned (1:1) to one of the two treatment groups via an interactive voice response system using the dynamic least squares minimization randomisation method."
Allocation concealment (selection bias)	Low risk	"Patients who were eligible for study entry were randomly assigned (1:1) to one of the two treatment groups via an interactive voice response system using the dynamic least squares minimization randomisation method."
Blinding (performance bias and detection bias) All outcomes	Low risk	"This was a double-blind study in which neither patients nor investigators knew which treatment patients were receiving."
Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	High risk	Not described.
Intention-to-treat analysis performed (selection bias)	Low risk	All randomized participants were analyzed.

Tebbutt 2002

Methods	Multicenter, 2-arm RCT
Participants	<p>254 participants with inoperable esophageal (4% SCC), GE-junction or gastric cancer. 119/254 participants (46.9%) had esophageal cancer and 144 had metastasis. Potential previous chemotherapy is not mentioned.</p> <p>Participants had a median age of 72 years, 60% were males, study duration was 6 years and 6 months, median follow-up was 8.8 months. Participants were recruited from the UK. Setting of the trial, i.e. the type of hospitals, was not mentioned.</p>
Interventions	<p>Arm 1 (N = 125): PVI 5-FU commenced at a dose of 300 mg/m²/d, via an ambulatory pump</p> <p>Arm 2 (N = 127): PVI 5-FU (same regimen) + MMC, started on the same day at a dose of 10 mg/m² IV bolus every 6 weeks for 4 courses</p>
Outcomes	Primary outcomes were tumor response, survival, toxicity, and quality of life.
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"[P]atients were randomly assigned to treatment with PVI 5-FU or PVI 5-FU + MMC on a 1:1 basis according to a computer generated randomisation code."
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Low risk	All outcome measures were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	"Five patients withdrew from treatment after randomisation due to patient choice (two patients) or decline in clinical condition (three patients)."
Intention-to-treat analysis performed (selection bias)	Low risk	"Analysis of survival and failure-free survival (FFS) was performed using all randomised patients on an intention-to-treat basis."

Tebbutt 2010

Methods	Multicenter, open-label, 2-arm, phase II RCT
---------	--

Tebbutt 2010 (Continued)

Participants	<p>106 participants with metastatic esophageal (11% SCC), GE-junction or gastric cancer. 31/106 participants had esophageal cancer and 99 had metastasis.</p> <p>"Patients were not allowed to have had previous anticancer treatment, except for adjuvant radiotherapy or chemotherapy completed at least 12 months before."</p> <p>Participants had a median age of 60.5 years for arm 1 and 59.1 for arm 2, 79% were males, study duration was 1 year and 10 months, median follow-up was 40.7 months. Participants were recruited from 19 institutions in Australia and 1 in New Zealand. Setting of the trial, i.e. the type of hospitals, was not mentioned.</p>
Interventions	<p>Arm 1: wTCF (N = 50): docetaxel, 30 mg/m², on days 1 and 8, cisplatin, 60 mg/m², on day 1, and 5-FU, 200 mg/m², per day continuously, every 3 weeks</p> <p>Arm 2: wTX (N = 56): docetaxel, 30 mg/m², on days 1 and 8 and capecitabine, 1600 mg/m², per day on days 1–14, every 3 weeks</p>
Outcomes	The primary clinical outcome of the study was response rate. Secondary outcomes were OS, PFS, treatment-related toxicity, disease-associated symptoms, and quality of life.
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomisation was carried out centrally at the coordinating centre ..."
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	High risk	"The ATTAX study was a randomised, phase II, open-label, multicenter study of wTCF or wTX."
Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	Figure 1, of the treated participants, arm 1: one had no measurable disease, in one response was not properly assessed, one underwent a non-protocol treatment, and one withdrew consent for scans; arm 2: one had no measurable disease, one had no properly assessed response, and one died without progression.
Intention-to-treat analysis performed (selection bias)	Low risk	ITT not mentioned but it was performed as all randomized participants were reported on.

Thuss-Patience 2011

Methods	Multicenter, open-label, phase III RCT
Participants	<p>40 participants with advanced or metastatic GE-junction or gastric AC. 17/40 participants (42.5%) had esophageal cancer, and all participants had metastasis.</p> <p>"Eligible patients had to have ... no pretreatment with more than one prior palliative regimen of chemotherapy (neoadjuvant or adjuvant chemotherapy or radiation was permitted)".</p> <p>Participants had a median age of 58 years for arm 1 and 55 years for arm 2, 73% were males, study duration was 4 years and 1 month, median follow-up was not mentioned. Participants were recruited from 6 German hospitals. Setting of the trial, i.e. the type of hospitals, was not mentioned.</p>
Interventions	<p>Arm 1 (N = 21): irinotecan 250 mg/m² every 3 weeks (first cycle) to be increased to 350 mg/m², depending on toxicity</p> <p>Arm 2 (N = 19): BSC</p>
Outcomes	Toxicity, quality of life, objective response, response of tumor related symptoms, PFS and OS. Staging was optional in the BSC arm, therefore objective response and PFS could not be calculated for the BSC arm.
Notes	Study was closed due to poor accrual.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was done centrally. Randomisation blocks of four for each stratification arm were determined by using a coin."
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	High risk	"This randomised multicentre open label investigator initiated phase III study..."
Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	High risk	Not similar at baseline for the number of sites involved, 29% had one site involved in the irinotecan group and 58% in the BSC group.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	Figure 1, arm 1: two participants did not receive irinotecan due to clinical deterioration; arm 2: two participants received chemo on their own request.
Intention-to-treat analysis performed (selection bias)	Low risk	"These 2 patients are included in the intention to treat (ITT) population for overall-survival."

Van Cutsem 2006

Methods	Multicenter, open-label, 2-arm RCT
---------	------------------------------------

Van Cutsem 2006 (Continued)

Participants	<p>A total of 457 with advanced or metastatic gastric and GE-junction cancer participants. 98/445 participants had esophageal cancer and 430 participants had metastasis.</p> <p>"Major inclusion criteria were: ... no prior palliative chemotherapy; 6 weeks or longer from prior radiotherapy and 3 weeks or longer from surgery".</p> <p>Participants had a median age of 55 years, 71% were males, study duration was 2 years and 3 months, median follow-up was 3 years and 9 months. Participants were recruited from 72 centers in 16 countries. Setting of the trial, i.e. the type of hospitals, was not mentioned.</p>	
Interventions	<p>Arm 1 (N = 227): docetaxel 75 mg/m² and cisplatin 75 mg/m² (day 1) + fluorouracil 750 mg/m²/d (days 1-5) every 3 weeks</p> <p>Arm 2 (N = 230): cisplatin 100 mg/m² (day 1) + fluorouracil 1000 mg/m²/d (days 1-5) every 4 weeks</p>	
Outcomes	The primary objectives were TTP, toxicity, quality of life; the secondary objective was OS.	
Notes	—	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random assignment was centralized..." "Patients were randomly assigned (1:1)..."
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	Figure 2, after randomization, arm 1: ineligible (n = 30), inadequate organ function (n = 5), no measurable and no assessable metastatic disease (n = 21), no measurable and no assessable metastatic disease and inadequate organ function (n = 1), tumor type other than adenocarcinoma (n = 1), previous or recurrent other cancer (n = 1), unstable/serious comorbid condition (n = 1); arm 2: inadequate organ function (n = 2), no measurable and no assessable metastatic disease (n = 15), tumor type other than adenocarcinoma (n = 1)
Intention-to-treat analysis performed (selection bias)	Low risk	Figure 2 in the trial report shows all treated participants are analyzed.

Van Cutsem 2015

Methods	Prospective, multinational, 3-arm, phase II RCT
Participants	<p>A total of 254 participants with histologically proven metastatic or locally recurrent GE-junction or gastric AC. 91/254 participants had GE-junction cancer; the number of participants with metastasis was not mentioned.</p> <p>"Prior palliative chemotherapy was not permitted. Prior adjuvant (and/or neoadjuvant) 5-FU, cisplatin, and epirubicin were allowed if relapse occurred > 12 months after the end of chemotherapy. A period of 4 weeks had to have elapsed since the last round of palliative radiotherapy and of 3 weeks since last surgery."</p> <p>Participants had a median age of 59 years, 69% were males, study duration was 11 months, median follow-up was not mentioned. Participants were recruited from 52 sites in the USA and 11 countries in Europe. Setting of the trial, i.e. the type of hospitals, was not mentioned.</p>
Interventions	<p>Arm 1 (N = 79): docetaxel 75 mg/m² on day 1 + oxaliplatin 130 mg/m² on day 1</p> <p>Arm 2 (N = 89): docetaxel 50 mg/m² on day 1 + oxaliplatin 85 mg/m² on day 1 + 5-FU 2400 mg/m² via continuous IV for 46 h, and folinic acid 400 mg/m² on day 1</p> <p>Arm 3 (N = 86): docetaxel 65 mg/m² on day 1 + oxaliplatin 100 mg/m² on day 1 + capecitabine 625 mg/m² twice daily</p>
Outcomes	The primary efficacy parameter was PFS, secondary parameters were OS, tumor response, overall response rate, best overall response, and safety.
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomised centrally using an interactive voice response system ..."
Allocation concealment (selection bias)	Low risk	"Patients were randomised centrally using an interactive voice response system ..."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	Figure 1, arm 1: 1 participant was not treated; arm 2: 1 participant was not treated; arm 3: 4 participants were not treated.

Van Cutsem 2015 (Continued)

Intention-to-treat analysis performed (selection bias)	Low risk	"The primary efficacy population was the full analysis population ... with supportive analyses conducted using the intent-to-treat (ITT: all randomised patients)"
--	----------	--

Waddell 2013

Methods	Multicenter, open-label, phase III RCT
Participants	<p>553 participants with untreated, metastatic, or locally advanced GE-junction AC. 386 participants had esophageal or GE-junction carcinoma. 494/542 participants had metastasis.</p> <p>"Exclusion criteria included previous chemotherapy (including adjuvant chemotherapy), previous anti-EGFR therapy ..."</p> <p>Participants had a median age of 62 years for arm 1 and 63 years for arm 2, 83% were males, study duration was 3 years and 3 months, median follow-up of participants who were alive at the time of analysis was 4.6 months in arm 1 and 5.3 months in arm 2. Participants were recruited from 63 participating centers in the UK. Setting of the trial, i.e. the type of hospitals, was tertiary referral centers, teaching hospitals, and district general hospitals.</p>
Interventions	<p>Arm 1 (N = 275, n = 186 with esophageal or GE-junction carcinoma): epirubicin 50 mg/m² IV on day 1, oxaliplatin 130 mg/m² IV on day 1, and oral capecitabine 1250 mg/m² per day on days 1–21</p> <p>Arm 2 (N = 278; n = 200 with esophageal or GE-junction carcinoma): epirubicin 50 mg/m² IV on day 1, oxaliplatin 100 mg/m² IV on day 1, and oral capecitabine 1000 mg/m² per day on days 1–21, and intravenous panitumumab 9 mg/kg on day 1) every 21 days</p>
Outcomes	The primary outcome was OS, defined as the time from randomization until death from any cause. Secondary outcomes were PFS, response rate graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0; participant-reported outcomes; and KRAS mutation status.
Notes	The outcome HR for OS is the only one given for the esophageal cancer subgroup.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was done independently at the Institute for Cancer Research Clinical Trials and Statistics Unit (ICR-CTS) by random permuted blocks (block sizes of 6 and 8) and stratified by center region (locations were divided into 11 regions), extent of disease (locally advanced vs metastatic disease), and performance status (0 vs 1 vs 2).
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	High risk	"[O]pen label"
Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15%

Palliative chemotherapy and targeted therapies for esophageal and gastroesophageal junction cancer (Review)

90

Waddell 2013 (Continued)

		between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	Figure 1, arm 1: 4 withdrew after randomisation, 5 deteriorated before treatment; arm 2: 1 deteriorated before treatment, 1 had not started cycle 1 by trial closure
Intention-to-treat analysis performed (selection bias)	Low risk	In figure 1 of the trial report the numbers of participants randomized, these numbers correspond to those included in the analyses.

Waters 1999

Methods	Randomized, open-label, 2-arm RCT
Participants	274 participants with advanced esophagus GE-junction or gastric AC. 111/256 participants had esophageal cancer, and 158 had metastasis. Potential previous chemotherapy is not mentioned. Participants had a median age of 59 years for arm 1 and 60 years for arm 2, 82% were males, study duration was 2 years and 10 months, median follow-up was not mentioned. Participants were recruited from eight oncology centers in the UK. Setting of the trial, i.e. the type of hospitals, were oncology centers.
Interventions	Arm 1 (N = 137): 5-FU continuous IV at a dose of 200 mg/m ² day 1 for up to 6 months, epirubicin, 50 mg/m ² , and cisplatin, 60 mg/m ² , were given every 3 weeks to a maximum of 8 cycles Arm 2 (N = 137): methotrexate 1500 mg/m ² , 5-FU 1500 mg/m ² on day 1, and doxorubicin 30 mg/m ² on day 15 Cycles were repeated every 28 days to a maximum of 24 weeks.
Outcomes	Response, survival, and histology of surgical specimen
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A non stratified randomisation list was generated and held centrally in sealed envelopes. Randomization was allocated by telephone."
Allocation concealment (selection bias)	Low risk	"A non stratified randomisation list was generated and held centrally in sealed envelopes. Randomization was allocated by telephone."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15%

Waters 1999 (Continued)

between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.		
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	Webb 1997: "Eighteen patients (11 ECF and seven FAMTX) were ineligible due to squamous histology (n = 4), no histology (n = 1), colonic primary tumor (n = 2), laboratory tests (n = 5), patient refusal (n = 2), prior radiotherapy (n = 1), and no residual disease (n = 3)."
Intention-to-treat analysis performed (selection bias)	Low risk	"Therefore, 256 patients (126 ECF and 130 FAMTX) were assessable on a intention-to-treat basis."

Wilke 2014

Methods	Multinational, placebo-controlled, double-blind, phase III RCT	
Participants	665 participants with metastatic or non-resectable, locally advanced gastric or GE-junction AC. 137/665 participants had esophageal cancer and at least 224 participants had metastasis. "Eligibility criteria included ... documented objective radiological or clinical disease progression during or within 4 months of the last dose of first-line platinum and fluoropyrimidine doublet with or without anthracycline ..." Participants had a median age of 61 years, 71% were males, study duration was 1 years and 9 months, median follow-up was 7.9 months. Participants were recruited from 170 centers in 27 countries in North and South America, Europe, Asia, and Australia. Setting of the trial, i.e. the type of hospitals, was not mentioned.	
Interventions	Arm 1 (N = 330; n = 66 with GE-junction AC): ramucirumab 8 mg/kg IV on days 1 and 15 Arm 2 (N = 335; n = 71 with GE-junction AC): matching placebo All participants also received paclitaxel 80 mg/me IV on days 1, 8, and 15 of a 28-day cycle.	
Outcomes	The primary outcome was OS, and secondary outcomes were PFS, objective tumor response, disease control, participant-reported outcomes, immunogenicity of ramucirumab, and safety.	
Notes	—	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned..."
Allocation concealment (selection bias)	Low risk	"This sequence was programmed into a centralised interactive voice or web response system. Study sites enrolled patients by accessing the centralised interactive voice or web response system. The interactive voice or web-response system then assigned a unique identification number to each patient, and randomly assigned patients to one of the two treatment groups."
Blinding (performance bias and detection bias) All outcomes	Low risk	"Patients, medical staff, study investigators, individuals who handled and analysed the data, and the founder were masked to treatment assignment. Ramucirumab and placebo for infusion were identical in appearance to preserve masking."

Wilke 2014 (Continued)

Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	Figure 1, arm 1: 4 did not receive treatment, 313 (95%) discontinued study drug, 236 (72%) progressive disease, 39 (12%) adverse events, 12 (4%) deaths, 23 (7%) withdrew consent, 3 (<1%) other; arm 2: 5 did not receive treatment, 323 (96%) discontinued study drug, 255 (76%) progressive disease, 38 (11%) adverse events, 13 (4%) deaths, 13 (4%) withdrew consent, 3 (<1%) other, 1 (<1%) lost to follow-up.
Intention-to-treat analysis performed (selection bias)	Low risk	"Efficacy analyses were based on the intention-to-treat population and predefined subgroups."

Wilkes 2011

Methods	Single-center RCT
Participants	<p>34 participants with incurable esophageal cancer (18% SCC). All participants had esophageal cancer, possible metastatic carcinoma participants were not mentioned.</p> <p>"Patients were excluded ... although patients who had previously received chemo- or radiotherapy were eligible to enrol after a 4-week washout period."</p> <p>Participants had a mean age of 67 years, 82% were males, study duration was not mentioned, median follow-up was not mentioned. Participants were recruited from the Derby hospitals in the UK.</p>
Interventions	<p>Arm 1: thalidomide 200 mg daily</p> <p>Arm 2: matching placebo</p>
Outcomes	The primary outcomes, change in total body weight and lean body weight, were measured at baseline and 6 weeks.
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Treatment allocation was governed using a computer generated randomisation protocol held by the dispensing pharmacy. The protocol was generated by an independent statistician using block randomisation (block of four). Treatment allocation was disclosed to the investigators after the last participant had completed the protocol."
Allocation concealment (selection bias)	Low risk	"Treatment allocation was governed using a computer generated randomisation protocol held by the dispensing pharmacy. The protocol was generated by an independent statistician using block randomisation (block of four)."

Wilkes 2011 (Continued)

		Treatment allocation was disclosed to the investigators after the last participant had completed the protocol."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant. Although the placebo group had a significantly lower body mass, this was not described in the protocol as a violation of baseline comparability.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	Low risk	"Only eight patients in the thalidomide arm were able to attend for repeat studies at week 6, two of whom had discontinued treatment due to toxicity but all had taken at least 50% of their trial medication; a further two patients were able to tolerate treatment but were too unwell to attend for repeat studies. The remaining patients withdrew participation due to drug toxicity, disease progression or elective withdrawal. Sixteen patients who received placebo were able to complete the protocol; one patient on placebo died unexpectedly in his sleep after 7 days of participation."
Intention-to-treat analysis performed (selection bias)	Low risk	"An intention-to-treat analysis was performed ..."

Xu 2013a

Methods	Multicenter, 2-arm RCT
Participants	46 participants (23 in each group) with advanced esophageal SCC not suitable for operation. All participants had esophageal cancer, at least 24 participants had metastasis. 31/46 participants had previously received treatment. Participants had a median age of 62 years for arm 1 and 63 years for arm 2, 65% and 74% were males in arms one and two, study duration was 3 years and 10 months, median follow-up was not mentioned. Participants were recruited from the Suzhou University affiliated Changzhou tumor Hospital, the Jiangsu Provincial Tumor Hospital, and the Suzhou University first affiliated hospital.
Interventions	Arm 1: 80 mg/m ² of cisplatin IV once every 4 weeks, 750 mg/m ² of 5-FU for 24 h every 5 days Arm 2: 400 mg nimotuzumab IV once a week.
Outcomes	Response rate, adverse reactions, TTP, median survival time, and 1-year PFS
Notes	Translated from Chinese

Risk of bias

Bias	Authors' judgement	Support for judgement
------	--------------------	-----------------------

Xu 2013a (Continued)

Random sequence generation (selection bias)	Unclear risk	"[R]andomly dividing into PF group and union group"
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned
Selective reporting (reporting bias)	Low risk	All outcomes were reported on.
Similar at baseline for most prognostic factors (selection bias)	Low risk	According to table 1 of the trial report, tumor stage (advanced versus metastatic disease), performance index (ECOG status 0-1 versus 2-3), and the number of organs involved in metastatic disease (1 versus > 1) differed less than 15% between study arms and were thus not considered to be clinically relevant. The median age of participants in treatment arms differed less than 5 years and was thus not considered to be clinically relevant.
Complete description of the number of withdrawals, dropouts and losses to follow-up in each group. (selection bias)	High risk	Not mentioned
Intention-to-treat analysis performed (selection bias)	High risk	Not mentioned

5-FU: fluorouracil; **AC:** adenocarcinoma; **AE:** adverse event; **BSC:** best supportive care; **CVAD:** cyclophosphamide, vincristine, doxorubicin, and dexamethasone; **ECOG:** Eastern Cooperative Oncology Group; **EGFR:** epidermal growth factor receptor; **GE:** gastroesophageal; **GI:** gastrointestinal; **HR:** hazard ratio; **HR-QoL:** health-related quality of life; **IV:** intravenous; **LAP:** lapatinib; **ORR:** overall response rate; **OS:** overall survival; **PFS:** progression-free survival; **PVI:** protracted venous-infusion; **RCT:** randomized controlled trial; **RECIST:** response evaluation criteria in solid tumors; **SCC:** squamous cell carcinoma; **TTF:** time to failure; **TTP:** time to progression; **VEGF:** vascular endothelial growth factor; **VEGFR:** vascular endothelial growth factor receptor.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Adenis 2010	Non-randomized design
Al-Batran 2010	Review article
Albertsson 2007	Single-arm study
Boku 2009	Article does not mention the study group containing participants with esophageal cancer
Brell 2009	Single-arm study
Burris 2017	Study does not involve more than 15 eligible participants
Cascinu 2011	Study does not involve more than 15 eligible participants
Du 2015	Study does not involve more than 15 eligible participants

Study	Reason for exclusion
Eichhorst 2016	Article does not mention the study group containing participants with esophageal cancer
Font 2008	Single-arm study
Grunberger 2007	Review article
Gubanski 2010	Article does not mention the study group containing participants with esophageal cancer
Gubanski 2014	Article does not mention the study group containing participants with esophageal cancer
Hironaka 2013	Article does not mention the study group containing participants with esophageal cancer
Horgan 2011	Economic analysis
Ilhan-Mutlu 2013	Non-randomized design
Imazawa 2009	Article does not mention the study group containing participants with esophageal cancer
Jeung 2011	Article does not mention the study group containing participants with esophageal cancer
Kang 2009	Article does not mention the study group containing participants with esophageal cancer
Kerkar 2009	Trial protocol does not mention the study group containing participants with esophageal cancer
Kim 2014	Article does not mention the study group containing participants with esophageal cancer
Koizumi 2010	Article does not mention the study group containing participants with esophageal cancer
Koizumi 2014	Article does mention how many participants had esophageal junction cancer
Komatsu 2011	Article does not mention the study group containing participants with esophageal cancer
Konings 2010	Article does not mention the study group containing participants with esophageal cancer
Le Tourneau 2015	Study does not involve more than 15 eligible participants
Li 2011	Study does not involve more than 15 eligible participants
Lim 2010	Article does not mention the study group containing participants with esophageal cancer
Lim 2017	Not all included patients were treated with palliative intent
Lissoni 2009	Article does not mention the study group containing participants with esophageal cancer
Lu 2014	Article does not mention the study group containing participants with esophageal cancer
Lundholm 2010	No chemotherapy
Lustberg 2010	Dose-finding study. Participants not randomized to different chemotherapy regimens but to different doses of the same compound
Macedo 2009	Economic analysis
Mizota 2011	Non-randomized design

Study	Reason for exclusion
Moehler 2016b	Study does not involve more than 15 eligible participants
Moon 2010	Article does not mention the study group containing participants with esophageal cancer
Nakashima 2008	Article does not mention the study group containing participants with esophageal cancer
Narahara 2011	Article does not mention the study group containing participants with esophageal cancer
Ochendusko 2015	Study does not involve more than 15 eligible participants
Ohtsu 2013	Study includes gastric cancer patients with esophagogastric junction involvement but does not describe the inclusion of esophagogastric junction cancer patients.
Ojima 2016	Not all included patients were treated with palliative intent
Okines 2008	Review article
Okines 2010a	Dose-finding study
Okines 2010b	Non-randomized design
Park 2006	Article does not mention the study group containing participants with esophageal cancer
Park 2014	Article does not mention the study group containing participants with esophageal cancer
Roth 2007	Article does not mention the study group containing participants with esophageal cancer
Sadighi 2006	Article does not mention the study group containing participants with esophageal cancer
Sakamoto 2010	Article does not mention the study group containing participants with esophageal cancer
Satoh 2014	Article does not mention the study group containing participants with esophageal cancer
Satoh 2015	Study does not involve more than 15 eligible participants
Seol 2009	Non-randomized design
Sgourakis 2012	Non-randomized design
Shenfine 2009	No chemotherapy
Shirao 2013	Article does not mention the study group containing participants with esophageal cancer
Shitara 2011	Non-randomized design
Shu 2017	Article does not mention the study group containing participants with esophageal cancer
Sun 2013	Not all patients are in the palliative stage
Takashima 2010	Review article
Tanaka 2010	Non-randomized design
Thuss-Patience 2005	Article does not mention the study group containing participants with esophageal cancer

Study	Reason for exclusion
Whistance 2011	Review article
Xu 2013b	Article does not mention the study group containing participants with esophageal cancer
Yamada 2015	Article does not mention the study group containing participants with esophageal cancer
Yamazaki 2008	Non-randomized design
Yu 2010	Non-randomized design
Yun 2010	Article does not mention the study group containing participants with esophageal cancer
Zhang 2006	Non-randomized design

Characteristics of studies awaiting assessment *[ordered by study ID]*

[Ajani 2017](#)

Methods	International, 2-arm, multicenter, open-label, phase III RCT
Participants	361 participants with gastric or GE-junction AC were randomized and included in the analyses. 21 participants had GE-junction cancer, and all participants had metastasis. "[W]ho were chemotherapy naive" Participants had a median age of 56 years, 51% were males, study duration was 3 years and 4 months, median follow-up was 18.4 months. Participants came from the USA, Russia, Ukraine, Spain, Estonia, Brazil, and Italy. Setting of the trial, i.e. the type of hospitals, was not mentioned.
Interventions	Arm 1 (N = 239): S-1 (25 mg/m ²) was administered orally twice daily on days 1 through 21 followed by a 7-day rest period (days 22-28). One dose of cisplatin (75 mg/m ²) was administered IV over 1-3 h on day 1 of every 28-day cycle. Arm 2 (N = 122): 5-FU (800 mg/m ² /24 h) was administered as a continuous infusion over 5 days every 21 days. One dose of cisplatin (80 mg/m ²) was administered IV over 1-3 h on day 1 of every 21-day cycle before starting the 5-FU infusion. Cisplatin treatment in both groups was limited to 8 cycles.
Outcomes	OS, PFS, time to treatment failure, and ORR
Notes	—

[Al-Batran 2017](#)

Methods	Multicenter, double-blind, phase III study
Participants	Participants with gastric carcinoma or adenocarcinoma of the esophagogastric junction which has progressed after treatment with a fluoropyrimidine/platinum-containing regimen
Interventions	Arm 1: paclitaxel (80 mg/m ²) on day 1, 8 and 15 + placebo

Al-Batran 2017 (Continued)

	Arm 2: paclitaxel (80 mg/m ²) on day 1, 8 and 15 and RAD001 (10 mg daily, arm 2) days 1-28, repeated every 28 days as 2nd, 3rd or 4th line therapy
Outcomes	Primary end point was OS, secondary endpoints were best overall response, disease control rate, PFS, and toxicity
Notes	Preliminary results: the addition of RAD001 to paclitaxel/RAD001 did not significantly improve outcomes in pretreated metastatic gastric or esophagogastric junction adenocarcinoma

Bang 2017

Methods	Multinational, 2-arm, open-label, phase II RCT
Participants	114 participants with advanced or metastatic gastric or gastroesophageal junction cancer. Median age was 64 years old, 88% had metastatic disease. 19/114 participants had GE-junction cancer. "patients ... had received a platinum and fluoropyrimidine-based chemotherapy regimen as lead-in chemotherapy in the first-line setting consisting of either oxaliplatin + 5-fluorouracil every 14 days; oxaliplatin + capecitabine every 21 days; cisplatin + capecitabine every 21 days; cisplatin + 5-fluorouracil every 21 days; or cisplatin + S1 every 5 weeks." Participants were recruited from Korea, Italy, the USA, and Germany. The setting of the trial, i.e. the type of hospitals, was not mentioned.
Interventions	Arm 1 (N = 57): either IV ipilimumab 10 mg/kg, every 3 weeks for 4 doses during the induction phase and then 10 mg/kg every 12 weeks for up to 3 years during the maintenance phase Arm 2 (N = 51): BSC, which could have included the same fluoropyrimidine the participant received during first-line chemotherapy as maintenance but no other systemic anticancer therapy.
Outcomes	Immune-related (ir)PFS through assessment of a blinded independent review committee, PFS, OS, immune-related best overall RR (irBORR), safety, duration of response, and immune-related time to progression.
Notes	—

Bi 2011

Methods	Phase II RCT
Participants	Previously untreated participants with gastric or GE-junction AC
Interventions	Participants were randomized to arm 1: folinic acid, 5-FU, and irinotecan (mFOLFIRI) followed by folinic acid, 5-FU, and oxaliplatin (mFOLFOX7), or to arm 2: mFOLFOX7 followed by mFOLFIRI
Outcomes	Toxicity and anti-tumor effects
Notes	Preliminary results: both regimens were well-tolerated with acceptable and manageable toxicities

Cohen 2013

Methods	Phase II RCT
Participants	Participants with untreated metastatic or locally advanced gastric or GE-junction AC

Cohen 2013 (Continued)

Interventions	Participants were randomized 1:1, stratified by institution and disease status (with or without distant metastasis) to FOLFOX (oxilaplatin 85 mg/m ² , leucovorin 200 mg/m ² , 5-FU bolus 400 mg/m ² , 5-FU infusion 2400 mg/m ² over 48 h) every 14 days + vismodegib or placebo (150 mg oral daily). Cycle defined as 2 weeks and no cross-over allowed at progression
Outcomes	Primary outcome was PFS, secondary objectives were OS, RR, and toxicity
Notes	Preliminary results: addition of vismodegib to FOLFOX did not improve PFS in an unselected advanced GE carcinoma population

Denlinger 2016

Methods	Multicenter, open-label, phase II RCT
Participants	Participants with HER2 expressing advanced carcinomas of the distal esophagus, GE-junction, and stomach.
Interventions	Participants receive paclitaxel at 80 mg/m ² on days 1, 8, and 15 of a 28-day cycle; trastuzumab at 4 mg/kg loading dose then 2 mg/kg/weekly and are randomized to receive either MM-111 at 20 mg/kg/weekly or nothing.
Outcomes	The primary objective is PFS. Secondary objectives are OS, time to treatment failure, ORR, duration of response, safety, and health-related QoL.
Notes	Preliminary results: MM-111 did not improve PFS or OS in HER2+ GEC when added to PTX/T. HRG expression was lower than anticipated in the study population, potentially contributing to the effect of MM-111 on PFS and OS in the ITT. PTX/T alone appears promising in second-line therapy of GEC and further investigation is warranted.

Enzinger 2016

Methods	3 arm, phase II RCT
Participants	<p>245 participants were included with metastatic adenocarcinoma (222) or squamous cell carcinoma (23) of the esophagus or GEJ (type I or II by Siewert classification). All participants had esophageal or GE-junction cancer and all participants had metastasis. "No prior chemotherapy, radiotherapy, or anti-EGFR therapy was permitted."</p> <p>Participants had a median age of 59 years, 88% were males, study duration was 2 years and 8 months, median follow-up was 38.6 months. Participants were recruited from multiple centers. Setting of the trial, i.e. the type of hospitals, was not mentioned.</p>
Interventions	<p>All participants received cetuximab 400 mg/m² IV over 120 minutes on day 1 of the first cycle and then 250 mg/m² IV over 60 minutes once per week</p> <p>Arm 1 (N = 82): day 1 of each 3-week cycle epirubicin 50 mg/m² IV followed by cisplatin 60 mg/m² IV over 60 minutes and fluorouracil 200 mg/m² continuous IV infusion once per day for 21 days</p> <p>Arm 2 (N = 83): days 1 and 8 of each 3-week cycle cisplatin 30 mg/m² IV over 30 minutes followed by irinotecan 65 mg/m² IV over 90 minutes</p>

Enzinger 2016 (Continued)

Arm 3 (N = 80): day 1 of each 2-week cycle oxaliplatin 85 mg/m² IV and leucovorin 400 mg/m² IV, both over 120 minutes, followed by fluorouracil 400 mg/m² IV bolus injection and then fluorouracil 2,400 mg/m² IV infusion over 46-48 h

Outcomes	RR, OS, PFS, time to treatment failure, and toxicities
Notes	—

Hall 2017

Methods	Multicenter, 3-arm, phase II RCT
Participants	55 participants were recruited to the RCT. 24 had esophageal cancer, 9 GE-junction cancer, and 22 gastric cancer. (7 esophageal and GE-junction cancer participants were randomized to arm 1, 12 to arm 2 and 12 to arm 3. "Patients were excluded if they had previously received chemotherapy for gastric or oesophageal cancer;..." Participants had a median age of 75 years, 75% were males, study duration was 1 year and 6 months. Participants were recruited from 6 UK centers. Setting of the trial, i.e. the type of hospitals, was not mentioned.
Interventions	<p>Arm 1 (N = 17): epirubicin 40 mg/m² IV bolus and oxaliplatin 104 mg/m² IV infusion over 2 h and capecitabine 500 mg/m² twice a day on days 1-21, repeated every 21 days</p> <p>Arm 2 (N = 19): oxaliplatin 104 mg/m² IV infusion over 2 h and capecitabine 500 mg/m² twice a day on days 1-21, repeated every 21 days</p> <p>Arm 3 (N = 19): capecitabine 1000 mg/m² twice a day on days 1-14 only of a cycle repeated every 21 days</p>
Outcomes	Time to progression, OS, and toxicities
Notes	—

Hecht 2016

Methods	Multicenter, 2-arm, double-blind, phase III RCT
Participants	<p>545 participants randomly assigned to the intention-to-treat population. Participants had unresectable adenocarcinoma of the stomach, esophagus, or GE-junction. Of the 63 esophageal cancer participants 35 were randomized to the docetaxel group and 28 to the control group. "No prior palliative chemotherapy was allowed, and prior treatment with oxaliplatin-based neoadjuvant or adjuvant chemotherapy could not have been completed, 12 months before study entry."</p> <p>Participants had a median age of 61 and 59 years in arm 1 and 2, 76% and 74% were males, study duration was 3 years and 6 months, median follow-up was 23 months. Participants were recruited from 186 centers in 22 countries in Asia, Europe, North America, and South America. Setting of the trial, i.e. the type of hospitals, was not mentioned.</p>
Interventions	<p>Arm 1 (N = 249): CapeOx (capecitabine 1,700 mg/m² and oxaliplatin 130 mg/m²) + lapatinib 1250 mg (lapatinib arm)</p> <p>Arm 2 (N = 238): CapeOx + placebo (placebo arm)</p> <p>Treatment was administered in 21-day cycles, consisting of IV oxaliplatin on day 1 (for up to 8 cycles) and oral capecitabine in 2 daily doses (morning and evening) from day 1-14</p>

Hecht 2016 (Continued)

Outcomes	OS, PFS, duration of response, QoL, and safety
Notes	—

Huang 2016

Methods	Open-label, phase III RCT
Participants	Participants with with advanced esophageal squamous cell carcinoma refractory to platinum-based or taxane-based first-line chemotherapy
Interventions	Participants received either irinotecan (160 mg/m ² IV on day 1 every 2 weeks) and S-1 (initial oral dose 40 ~ 60 mg twice a day on days 1-10 every 2 weeks), or S-1 (initial oral dose 40 ~ 60 mg twice a day on days 1-14 every 3 weeks) alone.
Outcomes	The primary endpoint was PFS, and secondary end points were RR, disease control rate, and OS
Notes	Preliminary results: as compared with S-1 alone, irinotecan + S-1 regimen was associated with a significant PFS advantage. Irinotecan + S-1 regimen is an appropriate treatment option in participants with advanced esophageal squamous cell carcinoma after failure of prior platinum- or taxane-based chemotherapy.

Iqbal 2017

Methods	Phase II RCT
Participants	Participants with advanced esophagogastric cancer
Interventions	Either platinum 5- FU/LV/oxaliplatin (FOLFOX) vs non-platinum containing regimen irinotecan/taxotere differed according to ERCC1 levels
Outcomes	OS, PFS, and RR
Notes	Preliminary results: in all participants, FOLFOX had a statistically superior PFS and RR, when compared with irinotecan/taxotere. In participants with ERCC1 < 1.7 receiving FOLFOX, PFS and RR was statistically superior, with no difference in OS. There was no significant evidence of differential treatment effect on PFS across ERCC1 levels.

Janjigian 2017

Methods	Open-label, phase I/II RCT
Participants	Participants with advanced and metastatic, histologically confirmed gastric cancer (GC), esophageal cancer (EC), or gastroesophageal junction cancer (GEC), irrespective of PD-L1 status, who had progressed on chemotherapy
Interventions	Either nivolumab 3 mg/kg every 2 weeks (N3), nivolumab 1 mg/kg + ipilimumab 3 mg/kg (N1+I3), or nivolumab 3 mg/kg + ipilimumab 1 mg/kg (N3+I1) every 3 weeks x 4 cycles, followed by nivolumab 3 mg/kg every 2 weeks until confirmed disease progression or intolerable toxicity.

Janjigian 2017 (Continued)

Outcomes	Primary endpoint was ORR; other endpoints included safety, OS, and biomarker status.
Notes	Preliminary results: nivolumab ± ipilimumab led to durable responses and long-term OS in heavily pretreated Western participants with advanced gastric/esophageal/GE-junction cancer, which is consistent with the clinical activity observed in Asian patients in the ONO-12 study. Safety was consistent with prior reports. These data support ongoing investigation of nivolumab ± ipilimumab in participants with advanced gastric/esophageal/GE-junction cancer.

Kang 2017

Methods	Double-blinded, phase III RCT
Participants	Participants aged ≥ 20 years with ECOG PS 0-1 and unresectable advanced or recurrent advanced gastric cancer who had failed 2 or more previous chemotherapy regimens
Interventions	Participants received either 3 mg/kg nivolumab (N=330) or placebo (N=163) every 2 weeks until unacceptable toxicity or disease progression
Outcomes	OS, PFS, and ORR
Notes	NCT02267343 Preliminary results: Nivolumab was effective as the salvage treatment for pretreated advanced gastric cancer with significantly improved OS, PFS and ORR compared to placebo

Lee 2013

Methods	Multicenter, open-label, phase III RCT
Participants	Participants with metastatic or recurrent gastric or GE-junction AC who had not received prior chemotherapy
Interventions	Participants were randomized to receive either SP3 (SP3: S-1 80 mg/m ² /d on days 1-14, cisplatin 60 mg/m ² on day 1, every 3 weeks) or SP5 (S-1 80-120 mg/body/d on days 1-21, cisplatin 60 mg/m ² on day 8, every 5 weeks) until disease progression or unacceptable toxicities
Outcomes	OS, PFS, ORR, and toxicities
Notes	Preliminary results: SP3 was better than SP5 in terms of PFS and ORR. However, considering the small benefit in PFS and no difference in OS, both SP3 and SP5 can be recommended for the first-line treatment of advanced gastric carcinoma

Lee 2015

Methods	Single-center, 2-arm, open-label, phase II RCT
Participants	94 participants with recurrent or metastatic squamous cell carcinoma of the esophagus. "...who had not previously been treated palliative chemotherapy for metastatic disease were eligible." Participants had a median age of 63 years, 92% were males, study duration was 3 years and 11 months, median follow-up was 23 months. Participants were recruited from the Samsung Medical Center, Seoul, Korea. Setting of the trial, i.e. the type of hospitals, was the Samsung Medical Center

Lee 2015 (Continued)

Interventions	<p>Arm 1 (N = 46): capecitabine 1000 mg/m² orally twice a day on days 1-14 + 75 mg/m² of cisplatin IV on day 1.</p> <p>Arm 2 (N = 48): capecitabine as for CC + 80 mg/m² of paclitaxel IV on days 1 and 8</p>
Outcomes	RR, PFS, OS, toxicity, and QoL
Notes	—

Li 2015

Methods	Multicenter, 2-arm RCT
Participants	<p>255 participants with stomach or GE-junction cancer. 32 participants with GE-junction cancer (22 randomized to arm 1 and 10 to arm 2) and 61 participants with stomach and GE-junction cancer (28 randomized to arm 1 and 33 to arm 2). "The exclusion criteria included: "[p]rior systemic therapy for advanced or metastatic disease (for instance, cytotoxic chemotherapy or history of another malignancy within the last 5 years except cured basal cell carcinoma of skin and cured carcinoma in-situ of uterine cervix. active/passive immunotherapy)..."</p> <p>Participants had a mean age of 53 or 55 years for arms 1 and 2, 70% and 73% were males, study duration was 2 years and 7 months, median follow-up was 10 months. Participants were recruited from 15 centers in China. Setting of the trial, i.e. the type of hospitals, was not mentioned.</p>
Interventions	<p>Arm 1 (N = 127): S-1 was given as 40 mg/m² twice daily on days 1-21 and cisplatin was 20 mg/m² IV drip on days 1-4, repeated every 5 weeks in the CS group.</p> <p>Arm 2 (N = 128): 5-Fu was given as 800 mg/m²/d CI 120h, and the dosage of cisplatin was 20 mg/m² IV on days 1-4, repeated every 4 weeks</p>
Outcomes	TTP, OS, RR, and toxicities
Notes	—

Li 2016a

Methods	Multicenter, 3-arm, phase II RCT
Participants	<p>55 participants were recruited to the RCT. 24 participants had esophageal cancer, 9 GE-junction cancer, and 22 gastric cancer. (7 esophageal and GE-junction cancer participants were randomized to arm 1, 12 to arm 2 and 12 to arm 3. "Patients were excluded if they had previously received chemotherapy for gastric or oesophageal cancer;..." Participants had a median age of 75 years, 75% were males, study duration was 1 year and 6 months. Participants were recruited from 6 UK centers. Setting of the trial, i.e. the type of hospitals, was not mentioned.</p>
Interventions	<p>Arm 1 (N = 17): epirubicin 40 mg/m² IV bolus and oxaliplatin 104 mg/m² IV infusion over 2 h and capecitabine 500 mg/m² twice a day on days 1-21, repeated ever 21 days</p> <p>Arm 2 (N = 19): oxaliplatin 104 mg/m² IV infusion over 2 h and capecitabine 500 mg/m² twice a day on days 1-21, repeated ever 21 days</p> <p>Arm 3 (N = 19): capecitabine 1000 mg/m² twice a day on days 1-14 only of a cycle repeated every 21 days</p>

Li 2016a (Continued)

Outcomes	TTP, OS, and toxicities
Notes	—

Li 2016b

Methods	RCT
Participants	Participants with advanced esophageal cancer
Interventions	Participants were randomized to receive either nedaplatin and paclitaxel liposome and control group of chemotherapy with nedaplatin and paclitaxel regimen with 3-week as a course of treatment
Outcomes	Effectivity, QoL, and toxicities
Notes	Preliminary results: besides a favourable function in retention paclitaxel original medicinal mechanism, efficacy and indications, paclitaxel liposome can effectively avoid the risk of adverse events. Furthermore, paclitaxel liposome combined with nedaplatin for advanced esophageal cancer is worthy of wide application, due to the better curative effect and safety

Liu 2016

Methods	Multicenter, 2-arm, phase III RCT
Participants	273 participants were recruited to the RCT. 36 participants had GE-junction cancer, 112 had gastric cancer, (22 GE-junction cancer participants were randomized to arm 1 and 14 to arm 2. "Patients had to have had at least 2 lines of chemotherapy fail before participating in the study." Participants had a median age of 58 years, 75% were males, study duration was 1 year and 9 months. Participants were recruited from 32 centers in China. Setting of the trial, i.e. the type of hospitals, was not mentioned.
Interventions	Arm 1 (N = 181): oral apatinib 850 mg in tablet form once daily Arm 2 (N = 92): apatinib matching placebo tablets once daily
Outcomes	OS, PFS, ORR, disease control rate, QoL, and safety
Notes	—

Luelmo 2008

Methods	Phase II RCT
Participants	Participants with measurable histologically confirmed metastatic gastric cancer and ACs of the GE-junction
Interventions	Participants were randomized into 2 groups, either arm 1 (N = 50): weekly 5-FU (2.0 g/m ² days 1, 8, 15, 22, 29, 36) + leucovorin (500 mg/m ²) and biweekly cisplatin (50 mg/m ² days 1,15, 29) with cycles

Luelmo 2008 (Continued)

repeated every 7 weeks. Or arm 2 (N = 45): weekly 5-FU (2.0 g/m² days 1, 8, 15) + leucovorin (500 mg/m²) and weekly paclitaxel (80 mg/m² on days 1, 8, 15) with cycles repeated every 4 weeks

Outcomes	The primary outcome was response rate. Secondary outcomes were TTP, OS, and toxicities.
Notes	Preliminary results: the results indicate both treatments to have comparable overall response rates, TTP, and OS. However, paclitaxel + high dose 5-FU/leucovorin had a slightly better toxicity profile.

Moehler 2013

Methods	Multicenter, double-blinded, placebo-controlled, phase II RCT
Participants	Advanced esophagogastric cancer participants with failure of any prior docetaxel and/or platinum-based chemotherapy
Interventions	Participants were randomized to receive 6-week cycles including FOLFIRI+ Na-Folate twice weekly and sunitinib (25 mg) versus placebo daily for 4 consecutive weeks followed by a 2-week rest
Outcomes	Primary outcome was PFS, secondary outcomes were OS, RR, and toxicities
Notes	Preliminary results: sunitinib added to FOLFIRI increased hematotoxicity and did not improve response rates or PFS in chemotherapy-resistant gastric cancer participants. Since the regimen was safe and participants had a trend toward a better OS, biomarker analyses will be performed to identify subgroups that benefit from add-on of sunitinib.

Moehler 2016a

Methods	Multicenter, open-label, phase II RCT
Participants	Participants with histologically confirmed, unresectable locally advanced or metastatic gastric or GE-junction cancer without disease progression after first-line chemotherapy with a fluoropyrimidine and platinum doublet. Exclusion criteria are: radiological evidence of brain metastases, autoimmune/immune-mediated disease, inadequate hematologic, renal, and hepatic function, or HER2+.
Interventions	Participants are randomized either to: Arm 1: ipilimumab, 4 doses 10 mg/kg, IV every 3 weeks, followed by every 12 weeks, until confirmed immune-related disease progression or unacceptable toxicity Arm 2: BSC, continuing fluoropyrimidine used in lead-in chemotherapy or no active systemic therapy
Outcomes	Primary outcome is immune-related PFS: immune-related response criteria were derived from World Health Organization (WHO) criteria to better capture ipilimumab response patterns. Secondary outcomes are to compare PFS per WHO criteria and OS, and estimate immune-related best overall response rate.
Notes	NCT01585987 Preliminary results: The irPFS was similar and median OS for both arms was approximately 1 yr. AEs were consistent with other ipi studies. These results suggest ipi in combination with chemotherapy warrants further study in patients with advanced/metastatic gastric/GE junction cancer.

Moehler 2017

Methods	Multinational, open-label, phase III RCT
Participants	Participants with non-resectable, advanced or metastatic esophageal SCC, not eligible for definitive radiochemotherapy, are included. Participants have to have measurable or non-measurable disease according to RECIST 1.1. Participants with previous chemotherapy for esophageal SCC in the metastatic setting, concurrent radiotherapy involving target lesions and previous exposure to EGFR-targeted therapy are excluded.
Interventions	Arm 1: cisplatin 100 mg/m ² on day 1 and 5-FU 1000 mg/m ² /d on days 1-4 Arm 2: arm 1 + panitumumab 9 mg/kg on day 1 Cycles are repeated every 3 weeks until progression of disease.
Outcomes	Primary outcome is OS. Secondary outcomes are PFS, 1-year survival, response rate, safety and tolerability, and quality of life.
Notes	Preliminary results: addition of panitumumab to CF provided no additional benefit to chemotherapy alone as first-line treatment of ESCC. Biomarker program is going on for further analyses.

Pavlakakis 2015

Methods	Multinational, double-blind, placebo-controlled, phase II RCT
Participants	Participants with refractory advanced esophagogastric cancer
Interventions	Eligible participants received BSC + 160 mg regorafenib or matching placebo orally on days 1-21 each 28-day cycle until disease progression or prohibitive adverse events.
Outcomes	Primary outcome was PFS; secondary outcomes were toxicity and OS
Notes	Preliminary results: REG was highly effective in prolonging PFS across a broad range of participants, with a non-significant positive OS trend. Regional differences were found in the magnitude of effect but REG was effective in all regions and subgroups.

Ryu 2016

Methods	Multicenter, open-label, phase III RCT
Participants	Participants with metastatic or recurrent gastric or gastroesophageal junction adenocarcinoma and no prior chemotherapy
Interventions	Participants received either SOX (S-180 mg/m ² /d on days 1-14, oxaliplatin 130 mg/m ² on day 1, every 3 weeks) or SP (S-180 mg/m ² /d on days 1-14, cisplatin 60 mg/m ² on day 1, every 3 weeks) until disease progression or unacceptable toxicities
Outcomes	OS, PFS, ORR, and toxicities
Notes	Preliminary results: SOX was non-inferior to SP in terms of PFS, ORR, and OS. The 2 regimens were well tolerated with different toxicity profiles. SOX regimen can be also recommended as a first-line treatment of advanced GC.

Sahin 2015

Methods	Phase I RCT
Participants	Participants with CLDN18.2 + chemorefractory GEC
Interventions	Participants received IMAB362 (800 in cycle [cy] 1, followed by 600 mg/m ² in subsequent cy, IV every 3 weeks) + ZA (4 mg, IV, day 1 of cy 1 & 3) in arm 1; IMAB362, ZA + low IL2 (1 x 106 IU, subcutaneous, days 1-3 of cy 1 and 3) in arm 2; IMAB362, ZA + intermediate IL2 (3 x 106 IU, subcutaneous, days 1-3 of cy 1 and 3) in arm 3; and IMAB362 alone in arm 4.
Outcomes	Primary endpoints are biomarkers to assess immunomodulatory effects of treatments (modulation of immune cell populations, ADCC; data not available at time of this analysis). Here we report data on safety (NCICTCAE v4.0, primary endpoint) and anti-tumor activity (disease control rate, PFS, OS, secondary endpoint).
Notes	Preliminary results: IMAB362 (every 3 weeks) can safely be combined with ZA/IL2. IMAB362's safety profile is unaltered by ZA/IL2. Signs of activity were observed with IMAB362 as single agent and in combination with ZA/IL2. Emerging primary endpoint data will show whether adding ZA/IL2 achieves the desired augmentation of IMAB362-mediated immune effects.

Schuler 2016

Methods	Multinational, open-label, phase II RCT
Participants	Participants with histologically confirmed AC of the stomach, the esophagus or the GE-junction, either as inoperable locally advanced disease or as resections with R2 outcome or as recurrent or metastatic disease. Participants are not allowed to have received previous chemotherapy for advanced disease or previous perioperative chemotherapy with curative intent within 6 months of start of study treatment.
Interventions	<p>Arm 1: epirubicin 50 mg/m², day 1, oxaliplatin 130 mg/m², day 1, capecitabine 625 mg/m², orally day 1-21 twice daily, cycles are 3 weeks and participants received the drugs for a maximum of 8 cycles</p> <p>Arm 2: arm 1 + IMAB362 800/600 mg/m², 800 mg/m² loading dose on cycle 1. 600 mg/m² every 3 weeks</p> <p>Arm 3: arm 1 + IMAB362 1000 mg/m² 1000 mg/m² every 3 weeks</p>
Outcomes	Primary outcomes are PFS, safety, and tolerability. Secondary outcomes are survival rate at 12 months, OS, TTP, objective tumor response rate, disease control rate, and duration of response
Notes	Preliminary results: this final analysis confirms that addition of IMAB362 to first-line chemotherapy provides a clinically relevant benefit in participants with inoperable or recurrent gastric and GEJ cancer.

Shah 2015

Methods	Multicenter, 2-arm, phase II RCT
Participants	90 participants were recruited to the RCT. 28 participants had GE-junction cancer, 57 had gastric cancer, (28 GE-junction cancer participants were randomized to arm 1 and 18 to arm 2. "Prior chemotherapy or chemoradiotherapy for locoregional disease was allowed if 6 months had

Shah 2015 (Continued)

elapsed since completion of prior therapy and registration in the clinical trial. participants could not have received prior cisplatin or docetaxel; however, prior fluorouracil as part of adjuvant therapy was allowed." Participants had a median age of 58 years, 61% were males, study duration was 3 years and 7 months. Participants were recruited from 10 sites in the USA. Setting of the trial, i.e. the type of hospitals, was not mentioned.

Interventions	<p>Arm 1 (N = 57): docetaxel 40 day 1 IV piggyback (60 minutes), leucovorin 400 day 1 IV piggyback (30 minutes), Fluorouracil 400 day 1 IV push, fluorouracil 1,000 (per day) IV continuous infusion daily 2 days, Cisplatin 40 day 2 or 3 IV piggyback (30 minutes).</p> <p>Arm 2 (N = 33): docetaxel 75 Day 1 IV piggyback (60 minutes), Cisplatin 75 day 1 IV piggyback (60 minutes), fluorouracil 750 (per day) IV continuous infusion daily 5 days, neulasta 6 mg subcutaneous on day 8, 9, or 10 or neupogen 300 or 480 g subcutaneous 7 days (days 10-17). Either neulasta or neupogen administered, not both</p>
Outcomes	PFS, time to treatment failure, OS, and safety
Notes	—

Shah 2016

Methods	Multicenter, 2-arm, phase II RCT
Participants	123 participants were recruited to the RCT. 29 participants had GE-junction cancer, 94 had gastric cancer, (16 GE-junction cancer participants were randomized to arm 1 and 13 to arm 2. "Key exclusion criteria ... previous chemotherapy for locally advanced or metastatic disease" Participants had a median age of 58.5 years in arm 1 and 57.0 years in arm 2, 62% were males, study duration was 10 months. Participants were recruited from 30 sites across Australia, Korea, Singapore, Taiwan, Thailand, and the USA. Setting of the trial, i.e. the type of hospitals, was not mentioned.
Interventions	<p>Arm 1 (N = 62): onartuzumab (10 mg/kg)</p> <p>Arm 2 (N = 61): placebo</p> <p>All participants receive mFOLFOX6 (400 mg/m² bolus and 2,400 mg/m² IV 5-FU for 46-48 hours, 200 mg/m² leucovorin, and 85 mg/m² oxaliplatin for 2 hours)</p>
Outcomes	PFS, OS, ORR, and safety
Notes	—

Shah 2017a

Methods	Multicenter, 2-arm, phase III RCT
Participants	562 participants were recruited to the RCT. 130 participants had GE-junction cancer, 432 had gastric cancer, (65 GE-junction cancer participants were randomized to arm 1 and 65 to arm 2. "Key exclusion criteria included ... previous chemotherapy for locally advanced or metastatic gastric carcinoma," Participants had a median age of 60 years, 67% were males, study duration was 1 year and 3 months. Participants were recruited from multiple centers that were not specified. Setting of the trial, i.e. the type of hospitals, was not mentioned.
Interventions	<p>Arm 1 (N = 279): onartuzumab (10 mg/kg)</p> <p>Arm 2 (N = 283): placebo</p>

Shah 2017a (Continued)

	All participants receive mFOLFOX6 (400 mg/m ² bolus and 2400 mg/m ² IV 5-FU for 46-48 h, 200 mg/m ² leucovorin, and 85 mg/m ² oxaliplatin for 2 h)
Outcomes	OS, PFS, ORR, disease control rate, duration of response, participant reported outcomes, and safety
Notes	—

Smyth 2011

Methods	Reanalysis of the data of US institutions of the multinational, placebo-controlled, 2-arm RCT (AVAGAST)
Participants	Participants with metastatic/unresectable gastric cancer. 103/774 participants had esophageal cancer, 745 participants had metastasis. "(Neo)adjuvant chemotherapy was permitted if completed 6 months before random assignment. Surgery or radiotherapy was permitted if completed 28 days before random assignment."
Interventions	Participants were randomized either to bevacizumab 7.5 mg/kg or to placebo, both followed by cisplatin 80 mg/m ² on day 1 + capecitabine 1000 mg/m ² twice daily for 14 days every 3 weeks
Outcomes	Outcomes were bevacizumab-specific toxicity, OS, PFS, and participant characteristics
Notes	Preliminary results: participants with advanced gastric cancer treated on US phase II trials with bevacizumab differ significantly from the AVAGAST cohort. Bevacizumab may be active in some gastric cancer subtypes

Song 2016

Methods	RCT
Participants	Participants had to have advanced esophageal cancer without disease progression after 4-6 cycles of platinum-based first-line regimen chemotherapy.
Interventions	Participants in the maintenance group received maintenance chemotherapy with S-1 (80 mg, 100 mg or 120 mg in 2 divided doses. Twice daily for 4 weeks; 6 weeks for a treatment cycle) until disease progression or with intolerant toxicity, and those in the control group received optimal supportive care.
Outcomes	The primary endpoints were tumor RR and disease control ratio. The PFS and adverse events were also evaluated as secondary endpoints.
Notes	Preliminary results: indicate that S-1 maintenance chemotherapy, with a tolerable toxicity profile, can improve the RR and median PFS in advanced esophageal cancer participants who respond to first-line regimen. Additional randomized, double-blind, placebo-controlled, multicenter investigations will be required to verify findings

Tebbutt 2013

Methods	Phase II RCT
---------	--------------

Tebbutt 2013 (Continued)

Participants	Eligible participants had histologically confirmed metastatic esophagogastric cancer (AC and SCC)
Interventions	Participants received docetaxel 30 mg/m ² days 1,8, cisplatin 60 mg/m ² day 1, fluoropyrimidine, 5-FU infusion 160 mg/m ² /d or capecitabine 500 mg/m ² twice daily continuous at the discretion of the investigator, either with or without panitumumab 9 mg/kg day 1 every 3 weeks. Treatment was administered for 8 cycles or until disease progression
Outcomes	The primary outcome was RR according to RECIST
Notes	Preliminary results: the addition of panitumumab to docetaxel-based chemotherapy in advanced esophagogastric cancer did not improve efficacy and was associated with an increase in some toxicities.

Tebbutt 2016

Methods	Multicenter, 2-arm, phase II RCT
Participants	77 participants were recruited to the RCT. 49 participants had oesophageal or GE-junction cancer, 28 had gastric cancer, (24 GE-junction cancer participants were randomized to arm 1 and 25 to arm 2. "The ATTAX3 study was available for ... who had received no prior therapy other than neoadjuvant or adjuvant treatment completed at least 12 months earlier or palliative radiotherapy completed at least 14 days before enrolment." Participants had a median age of 59 years in arm 1 and 64 years in arm 2, 77% and 87% were males, study duration was 1 year and 7 months. Participants were recruited from multiple centers that were not specified. Setting of the trial, i.e. the type of hospitals, was not mentioned.
Interventions	Arm 1 (N = 39): docetaxel 30 mg/m ² days 1 and 8, cisplatin 60 mg/m ² day 1, and a fluoropyrimidine (investigator choice of 5-fluorouracil infusion 160 mg/m ² per day or capecitabine 500 mg/m ² twice a day continuous), with panitumumab 9 mg/kg on day 1 every 3 weeks Arm 2 (N = 38): docetaxel 30 mg/m ² days 1 and 8, cisplatin 60 mg/m ² day 1, and a fluoropyrimidine (investigator choice of 5-fluorouracil infusion 160 mg/m ² per day or capecitabine 500 mg/m ² twice a day continuous)
Outcomes	Objective tumor response, OS, PFS, toxicity, and QoL
Notes	—

Thuss-Patience 2015

Methods	Phase II RCT
Participants	Participants with metastatic or locally advanced gastric or gastroesophageal junction adenocarcinoma, HER2 negative and with measurable disease
Interventions	Either 5-FU (2.6g/m ² /d, day 1) + leukovorin (200 mg/m ² , day 1) + oxaliplatin (85 mg/m ² , day 1) (FLO) + pazopanib (800 mg/d days 1-14, every 2 weeks) (arm 1) or the same chemotherapy without pazopanib (arm 2)
Outcomes	Analysis was planned with a Simon Minimax design with PFS rate at 6 month in arm 1 as the primary endpoint expecting a minimum of 40% of patients progression free

Thuss-Patience 2015 (Continued)

Notes	Preliminary results: both arms had an inferior PFS than expected from the literature. Pazopanib in combination with 5-FU/oxaliplatin showed marginal efficacy in this randomized phase II study regarding PFS. Further follow up for interesting OS data is needed. Histology specimen and multiple serum samples were collected from each participant and need to be analyzed for potential subgroups that may benefit most from Pazopanib.
-------	--

Thuss-Patience 2017

Methods	International, 2-arm, phase II/III RCT
Participants	415 participants were recruited to the RCT. 100 participants had GE-junction cancer, 235 had gastric cancer, (33 GE-junction cancer participants were randomized to arm 1 and 77 to arm 2. "The last dose of chemotherapy or HER2-targeted therapy had to be at least 21 days before randomisation." Participants had a median age of 62 years, 81% were males, study duration was 1 year. Participants were recruited from 107 centres in 28 countries worldwide. Setting of the trial, i.e. the type of hospitals, was not mentioned.
Interventions	Arm 1 (N = 117): IV docetaxel 75 mg/m ² every 3 weeks or paclitaxel 80 mg/m ² weekly; one cycle was 21 days Arm 2 (N = 228): trastuzumab emtansine 2.4 mg/kg weekly
Outcomes	OS, PFS, ORR, duration of response, safety, participant-reported outcome measures, and pharmacokinetics
Notes	—

Wang 2010

Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	—

Wang 2016

Methods	Multicenter, 2-arm, phase III RCT
Participants	243 participants were recruited to the RCT. 49 participants had GE-junction cancer, 205 had gastric cancer (20 GE-junction cancer participants were randomized to arm 1 and 29 to arm 2.) "Major inclusion criteria were age 18 years or older ... no prior palliative chemotherapy" Participants had a median age of 56 years, 72% were males, study duration was not mentioned. Participants were recruited from 15 centers across China. Setting of the trial, i.e. the type of hospitals, was not mentioned.

Wang 2016 (Continued)

Interventions	<p>Arm 1 (N = 121): docetaxel at 60 mg/m² (1-h IV infusion) + cisplatin at 60 mg/m² (1- to 3-h IV infusion) on day 1, followed by 5-FU at 600 mg/m²/d (continuous IV infusion) for 5 days (mDCF regimen)</p> <p>Arm 2 (N = 122): cisplatin at 75 mg/m² on day 1 followed by 5-FU at 600 mg/m²/d for 5 days (CF regimen)</p>
Outcomes	PFS, OS, ORR, time to treatment failure, and safety
Notes	—

Wang 2017

Methods	Multicenter RCT
Participants	Participants with advanced esophageal cancer, Karnofsky Performance Status (KPS) score ≥60 and expected survival time ≥ 3 months
Interventions	Participants were randomized to receive either Xiaoaiping combined with S-1 and cisplatin or S-1 and cisplatin
Outcomes	The efficacy and adverse events in participants of the 2 groups were observed and compared
Notes	Preliminary results: Xiaoaiping combined with S-1 and cisplatin significantly increased response rate and prolonged participants' survival in participants with advanced esophageal cancer

Wu 2013

Methods	RCT
Participants	Participants with advanced esophageal carcinoma
Interventions	Participants were randomized to Aidi injection combined with chemotherapy with the regimen of docetaxel and cisplatin or the same chemotherapy without Aidi injection
Outcomes	ORR and toxicity
Notes	Preliminary results: Aidi injection can improve the response rate, decrease the toxicity and improve the tolerance of chemotherapy in advanced esophageal carcinoma

Xie 2016

Methods	RCT
Participants	Participants with advanced esophageal cancer
Interventions	Participants were randomized to receive either chemotherapy with docetaxel + oxaliplatin or docetaxel + cisplatin

Xie 2016 (Continued)

Outcomes	The short-term curative effects, survival and adverse reactions were compared between the 2 groups.
Notes	Preliminary results: docetaxel combined with oxaliplatin was effective in the treatment of advanced esophageal cancer, and adverse reactions could be tolerated. Therefore, the chemotherapy of docetaxel + oxaliplatin could be popularly applied in clinic.

Yeh 2012

Methods	Phase II RCT
Participants	Participants with radiologically confirmed gastric or GE-junction AC, who had progressed following 1 prior line of chemotherapy
Interventions	Participants were randomized to receive either AUY922 once weekly, 70 mg/m ² IV, or docetaxel 3 times weekly, 75 mg/m ² IV, or irinotecan 3 times weekly, 350 mg/m ² IV
Outcomes	The primary outcome was PFS. Secondary outcomes were OS, ORR, safety, and tolerability
Notes	Preliminary results: AUY922 had an acceptable safety profile, which was different than that observed with docetaxel or irinotecan chemotherapy. There were fewer drug-related grade 3/4 toxicities with AUY922, in particular grade 3/4 neutropenia and neutropenic sepsis, were significantly more common with docetaxel and irinotecan. Grade 1/2 eye disorders were more common in the AUY922 treatment group.

Yoon 2016

Methods	Multicenter, 2-arm, phase II RCT
Participants	168 participants were recruited to the RCT. 119 participants had esophageal or GE-junction cancer, 39 had gastric cancer, (55 GE-junction cancer participants were randomized to arm 1 and 64 to arm 2. Previous chemotherapy in participants was not described. Participants had a median age of 46.5 years in arm 1 and 60 years in arm 2, 75% and 72.6% were males, study duration was 1 year and 3 months. Participants were recruited from centers across the USA. Setting of the trial, i.e. the type of hospitals, was not mentioned.
Interventions	Arm 1 (N = 84): ramucirumab 8 mg/kg IV every 2 weeks Arm 2 (N = 84): placebo All participants received oxaliplatin (85 mg/m ²) and leucovorin (400 mg/m ²) IV, followed by 5-FU as an IV bolus (400 mg/m ²) and continuous IV over 46-48 h (2400 mg/m ²)
Outcomes	PFS, OS, ORR, duration of response, and safety
Notes	—

Zaanan 2015

Methods	Open label, phase Ib/II RCT
---------	-----------------------------

Zaanan 2015 (Continued)

Participants	Participants with measurable locally advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction
Interventions	Either masitinib (MAS) (6 mg/kg/d) in combination with 5-FU (400 mg/m ² bolus then 2400 mg/m ² , 46 h/2 weeks), or irinotecan (IRI) (350 mg/m ² /3 weeks), or FOLFIRI, after progression to platinum based first line chemotherapy
Outcomes	OS, PFS, RR, and toxicities
Notes	Preliminary results: MAS + IRI seems to be active in advanced gastric cancer patients (cf median OS ~7.5 months; average from 7 studies reporting second line IRI*) with an acceptable safety profile. A confirmatory phase III trial evaluating MAS at 6 mg/kg/d in combination with IRI in second line has been initiated.

Zhang 2015

Methods	Multicenter, phase III RCT
Participants	Participants with advanced gastric cancer
Interventions	Either PACX or XP group
Outcomes	The primary endpoint assessed PFS. The secondary endpoints assessed OS, ORR, disease control rate, QoL, and safety.
Notes	Preliminary results: suggest that combination therapy of paclitaxel and capecitabine as first-line chemotherapy followed by capecitabine monotherapy as maintenance therapy might be effective and safe in treatment of advanced gastric cancer.

Zhou 2016

Methods	RCT
Participants	Participants with advanced esophageal cancer
Interventions	Participants received either S-I orally as maintenance treatment or placebo orally
Outcomes	PFS, and toxicities
Notes	Preliminary results: S-I is effective and well tolerated in the maintenance treatment of advanced esophageal cancer

5-FU: fluorouracil; **AC**: adenocarcinoma; **ADCC**: antibody-dependent cellular cytotoxicity; **AE**: adverse event; **BSC**: best supportive care; **ECOG**: Eastern Cooperative Oncology Group; **GC**: gastric cancer; **GE(C)**: gastroesophageal (cancer); **GEJ**: gastroesophageal junction; **irPFS**: immune-related progression-free survival; **IV**: intravenous; **ORR**: objective response rate; **OS**: overall survival; **PFS**: progression-free survival; **QoL**: quality of life; **RCT**: randomized controlled trial; **RECIST**: response evaluation criteria in solid tumors; **RR**: response rate; **SCC**: squamous cell carcinoma; **TTP**: time to progression.

Characteristics of ongoing studies [ordered by study ID]

Aanur 2017

Trial name or title	FRACTION (Fast Real-time Assessment of Combination Therapies in Immuno-ONcology)-gastric cancer (GC): a randomized, open-label, adaptive, phase 2 study of nivolumab in combination with other immuno-oncology (IO) agents in patients with advanced GC
Methods	Open-label, phase II, adaptive RCT
Participants	Participants with advanced gastric cancer or GE-junction cancer
Interventions	Participants receive nivolumab + BMS-986016 (fully human IgG4 mAb that targets lymphocyte activation gene or nivolumab + ipilimumab. Enrollment is continuous and may offer participants consecutive treatment options based on their treatment exposure and response.
Outcomes	The primary endpoints are ORR, duration of response, and PFS rate at 24 weeks. The secondary endpoint is safety.
Starting date	—
Contact information	—
Notes	—

Bang 2014

Trial name or title	JAGUAR: A randomised phase II study of the AKT inhibitor Ipatasertib (GDC-0068) versus placebo in combination with mFOLFOX6 chemotherapy in patients with locally advanced or metastatic HER2-negative gastric or GE-junction AC
Methods	Double-blind, placebo-controlled, global, phase II RCT
Participants	Participants with previously untreated locally advanced or metastatic gastric or GE-junction cancers. Participants have to have measurable HER2-negative or HER2-unknown gastric or GE-junction cancers to be eligible
Interventions	Participants are randomized to receive mFOLFOX6 + either ipatasertib or placebo
Outcomes	The primary outcome is PFS. Secondary outcomes include OS, ORR, duration of response, safety, pharmacokinetics, and correlative biomarkers
Starting date	August 2013
Contact information	Study director: clinical trials Genentech Inc
Notes	This study was ongoing in May 2015 but not recruiting participants

Bendell 2017

Trial name or title	A phase 3 randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of GS-5745 combined with mFOLFOX6 as first-line treatment in patients with advanced gastric or gastroesophageal junction adenocarcinoma
Methods	Multicenter, double-blind, phase III RCT

Bendell 2017 (Continued)

Participants	Participants with untreated gastric and GE-junction adenocarcinoma
Interventions	Either mFOLFOX6 + GS-5745 or mFOLFOX6 + placebo. mFOLFOX6 will be administered on Days 1 and 15 of each 28-day treatment cycle for a total of 6 cycles followed thereafter by leucovorin (LV) and 5-fluorouracil (5-FU) dosing on days 1 and 15 of each 28-day treatment cycle until disease progression. GS-5745/placebo 800 mg will be infused on days 1 and day 15 of each 28-day cycle until disease progression.
Outcomes	Primary endpoint is OS, and secondary endpoints include PFS, ORR (RECIST 1.1), and safety
Starting date	—
Contact information	—
Notes	—

Cafferkey 2016

Trial name or title	PLATFORM: Planning treatment of oesophago-gastric (OG) cancer randomised maintenance therapy trial
Methods	Multicenter, open label, phase II RCT
Participants	Eligible participants are those who have measurable stable disease or better following completion of first line chemotherapy (at least 6 cycles) for locally advanced unresectable or metastatic disease. First line chemotherapy regimen should contain a platinum and 5-fluoropyrimidine (with trastuzumab if HER2 +); doublet or triplet drug combinations are permitted.
Interventions	Maintenance strategies are split by HER2 status. For HER2 negative participants these are: arm 1a: surveillance, arm 1b: capecitabine, arm 1c: MEDI 4736 (anti PDL1 inhibitor) and for HER2 positive participants; arm 2a: trastuzumab, arm 2b: in development
Outcomes	Primary endpoint is PFS. Secondary endpoints are progression free rate at 3, 6, and 12 months, OS, ORR by RECIST 1.1, toxicity and analysis of efficacy endpoints according to biomarker status for selected arms.
Starting date	February 2015
Contact information	Bijal Patel, bijal.patel@rmh.nhs.uk
Notes	—

CTRI/2016/01/006474

Trial name or title	A randomized clinical trial of best supportive care compared with best supportive care with chemotherapy in advanced unresectable or metastatic esophageal cancer
Methods	RCT
Participants	Participants with advanced unresectable or metastatic esophageal and gastroesophageal junction cancer that is not amenable to curative intent therapy

CTRI/2016/01/006474 (Continued)

Interventions	Best supportive care will be offered when appropriate and clinically indicated or paclitaxel injections, administered at a dose of 80 mg/m ² in a glass bottle with non-PVC tubing every week until disease progression
Outcomes	OS, PFS, and QoL
Starting date	3 January 2016
Contact information	Bhavesh Bandekar, bhavesh.bandekar1988@gmail.com
Notes	—

Doi 2016

Trial name or title	KEYNOTE-181: Phase 3, open-label study of second-line pembrolizumab vs single-agent chemotherapy in patients with advanced/metastatic esophageal adenocarcinoma
Methods	Open-label, phase III RCT
Participants	Key eligibility criteria include age ≥ 18 years, advanced, metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or Siewert type I adenocarcinoma of the GE-junction, measurable disease, documented PD during/after first-line therapy, ECOG PS 0-1, no active autoimmune disease or central nervous system metastases, and provision of a tissue sample for biomarker analysis. HER2 status must be determined for participants with EGJ adenocarcinoma; if HER2+, there must be documentation of PD on trastuzumab-containing therapy.
Interventions	Participants are to be randomized (unblinded) 1:1 to IV pembro 200 mg every 3 weeks or investigator's choice of paclitaxel 80-100 mg/m ² on days 1, 8, and 15 every 4 weeks, docetaxel 75 mg/m ² every 3 weeks, or irinotecan 180 mg/m ² every 2 weeks. Treatment is to continue until documented PD, intolerable toxicity, participant/investigator decision, or (for pembro) until 35 cycles (~2 years)
Outcomes	Adverse events are to be monitored throughout treatment and for 30 days thereafter (90 days for serious adverse events). Tumor response will be assessed every 9 weeks per RECIST v1.1 and adapted immune-related RECIST (irRECIST; central imaging vendor review). All participants will be followed up every 9 weeks for OS until death, withdrawal of consent, or end of study. Primary efficacy end points are PFS (per RECIST v1.1, blinded central imaging vendor review) and OS. Secondary endpoints include ORR (per RECIST v1.1, blinded central imaging vendor review).
Starting date	—
Contact information	—
Notes	—

Esaki 2017

Trial name or title	ACT (WJOG7112G): 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
Methods	Phase II RCT

Esaki 2017 (Continued)

Participants	Participants with unresectable or metastatic HER2-positive G/GEJ cancer who failed first-line chemotherapy with Tmab + fluoropyrimidine + platinum
Interventions	Either PTX (80 mg/m ² , on day 1, 8, 15, every 4 weeks) + Tmab (8 mg/kg loading dose and 6 mg/kg thereafter, on day 1, every 3 weeks) or PTX alone
Outcomes	The primary endpoint is PFS. Secondary endpoints include OS, time to treatment failure, RR, disease control rate, safety, and translational biomarker research.
Starting date	—
Contact information	—
Notes	—

EUCTR 2016-001514-20

Trial name or title	A randomized phase 3 study of nivolumab plus ipilimumab or nivolumab combined with fluorouracil plus cisplatin versus fluorouracil plus cisplatin in subjects with unresectable advanced, recurrent or metastatic previously untreated esophageal squamous cell carcinoma
Methods	—
Participants	—
Interventions	—
Outcomes	—
Starting date	—
Contact information	—
Notes	—

Haag 2017

Trial name or title	Randomized controlled trial of S-1 maintenance therapy in metastatic esophagogastric cancer - the multinational MATEO study
Methods	Multinational, phase II RCT
Participants	Participants with HER2 negative, advanced esophagogastric adenocarcinoma
Interventions	After a 12-week first line platinum-fluoropyrimidine-based chemotherapy, participants without tumour progression are randomized in a 2:1 allocation to receive S-1 alone or continue with the same regimen as during the primary period.
Outcomes	The primary endpoint is OS. Secondary endpoints include safety, toxicity, PFS, and QoL.
Starting date	—

Haag 2017 (Continued)

Contact information	—
Notes	—

Malka 2011

Trial name or title	Met or EGFR inhibition in gastresophageal AC (MEGA): FOLFOX alone or in combination with AMG 102 or panitumumab as first-line treatment in patients with advanced GE AC: FNCLCC-FFCD-AGEO-GERCOR PRODIGE 17-ACCORD 20 randomised phase II trial
Methods	Multicenter, open-label, phase II RCT
Participants	Participants with histologically proven AC of the stomach, esophagus or GE-junction; locally advanced or metastatic disease; measurable disease (RECIST 1.1); no known HER2 overexpression; no prior palliative chemotherapy
Interventions	Participants are randomized to modified FOLFOX6 (oxaliplatin 85 mg/m ² , FA 400 mg/m ² , 5-FU 400 mg/m ² bolus then 2400 mg/m ² over 46 h) alone or combined to either panitumumab (6 mg/kg) or AMG 102 (10 mg/kg) every 2 weeks until unacceptable toxicity or disease progression
Outcomes	Primary outcome is 4-month PFS rate. Secondary outcomes are: OS, ORR, and safety. Ancillary studies aim to identify candidate predictive and prognostic biomarkers among functional of molecular alterations of the EGFR/RAS/RAF and HGF/c-Met pathways, and to monitor circulating tumor cells and circulating immune cells
Starting date	January 2013
Contact information	Akos Czibere, MD, PhD Merrimack pharmaceuticals
Notes	This study was ongoing in May 2015 but not recruiting participants.

NCT00515411

Trial name or title	A phase II study of modified docetaxel, cisplatin, and fluorouracil (mDCF) in patients with unresectable or metastatic gastric and gastroesophageal junction AC
Methods	Multicenter, open-label, phase II RCT
Participants	Participants with histologically or cytologically confirmed metastatic or unresectable gastric or GE-junction AC. GE-junction AC may be classified according to Siewert's classification type I, II, or III. Participants are excluded if they received previous chemotherapy for the treatment of metastatic or unresectable gastric or GE-junction AC, or if they received previous pre- or post-operative chemotherapy or chemoradiation if therapy was completed less than 6 months prior to study registration, or if they had received previous docetaxel or cisplatin.
Interventions	<p>Arm 1: docetaxel 40 mg/m² day 1 IV, leucovorin 400 mg/m² day 1 IV, fluorouracil 400 mg/m² IV day 1, fluorouracil 1000 mg/m²/d daily x 2 days, cisplatin 40 mg/m² day 2 or 3 IV, the regimen is repeated every 2 weeks, and a cycle is considered 6 weeks (e.g. 3 treatments).</p> <p>Arm 2: docetaxel 75 mg/m² day 1 IV, cisplatin 75 mg/m² day 1 IV, fluorouracil 750 mg/m² IV daily x 5 days, neulasta 6 mg subcutaneous on days 8, 9, or 10 or neupogen 300 or 480 µg subcutaneous x 7 days 10-17, 300 µg for weight < 60 kg, 480 µg for weight > 60 kg</p>

NCT00515411 (Continued)

Outcomes	The primary outcome is PFS. Secondary outcomes are OS and 1-year survival
Starting date	October 2006
Contact information	Yelena Janjigian, MD, 646-888-4186
Notes	—

NCT00680901

Trial name or title	A phase III study for ErbB2 positive advanced or metastatic gastric, esophageal, or gastroesophageal GE-junction AC treated with capecitabine plus oxaliplatin with or without lapatinib
Methods	Multinational, double blind, phase III RCT
Participants	Participants with histologically confirmed gastric, esophageal, or GE-junction AC. Either locally advanced (unresectable), metastatic, or locally recurrent disease. Participants with prior palliative chemotherapy for the treatment of gastric cancer, or prior treatment with oxaliplatin less than 12 months ago are excluded.
Interventions	Arm 1: lapatinib, 5 pills at 250 mg each once daily Arm 2: placebo, 5 pills once daily. All participants received capecitabine 1700 mg/m ² /d in 2 daily doses, oxaliplatin 130 mg/m ² on day 1
Outcomes	Primary outcome is OS. Secondary outcomes are PFS, complete response or confirmed partial response, clinical benefit, time to response, duration of response, adverse events, QoL, and toxicity.
Starting date	June 2008
Contact information	GSK Clinical Trials, GlaxoSmithKline
Notes	—

NCT00816634

Trial name or title	A randomized phase II trial of capecitabine plus cisplatin (XP) versus capecitabine plus paclitaxel (XT) as a first-line treatment for advanced or recurrent esophageal squamous cell carcinoma
Methods	Randomized, open-label, phase II RCT
Participants	Participants with histologically confirmed metastatic, or recurrent esophageal SCC. Participants may have received prior adjuvant chemotherapy with 5-FU and/or cisplatin as long as it has been 12 months before start of the study. No previous palliative chemotherapy. Prior radiotherapy must be completed 4 weeks before study entry.
Interventions	Arm 1: capecitabine 1000 mg/m ² twice daily days 1-14, cisplatin 75 mg/m ² day 1, + NS 150 mL MIV over 1 h, repeat every 3 weeks. Arm 2: capecitabine 1000 mg/m ² twice daily days 1-14, paclitaxel 80 mg/m ² , day 1, day 8, + D5W 500 mL MIV over 3 h, repeat every 3 weeks.
Outcomes	Primary outcome is RR. Secondary outcomes are PFS, QoL, toxicity, OS, and predictive markers

NCT00816634 (Continued)

Starting date	October 2008
Contact information	Young-Hyuck Im, MD, PhD, 82-2-3410-3445, imyh00@skku.edu
Notes	—

NCT00824785

Trial name or title	REAL 3: A randomised open-labelled multicentre trial of the efficacy of epirubicin, oxaliplatin and capecitabine (EOX) with or without panitumumab in previously untreated advanced oesophago-gastric cancer
Methods	Multicenter, open-label RCT
Participants	Participants with histologically verified inoperable locally advanced or metastatic AC or undifferentiated carcinoma of the esophagus, GE-junction, or stomach. Participants are excluded if they had received prior chemotherapy including previous adjuvant chemotherapy.
Interventions	Arm 1: epirubicin 50 mg/m ² IV on day 1, oxaliplatin 130 mg/m ² IV on day 1 with hydration, capecitabine 1250 mg/m ² /d orally in 2 divided doses continuously from days 1-21 Arm 2: epirubicin 50 mg/m ² IV on day 1 oxaliplatin 100 mg/m ² IV on day 1 with hydration, capecitabine 1000 mg/m ² /d orally in 2 divided doses continuously from days 1-21, panitumumab 9 mg/kg every 21 days
Outcomes	Primary outcome is OS. Secondary outcomes are RR, toxicity, QoL, and PFS
Starting date	May 2008
Contact information	Prof Cunningham, David, Royal Marsden NHS Foundation Trust
Notes	—

NCT00982592

Trial name or title	A randomized, double blind placebo controlled phase 2 study of FOLFOX plus or minus GDC-0449 in patients with advanced gastric and gastroesophageal junction (GEJ) carcinoma
Methods	Double-blind, placebo controlled, phase II RCT
Participants	Participants with histologically or cytologically confirmed gastric or GE-junction carcinoma not amenable to surgical resection. Participants who have had chemotherapy or radiotherapy within 6 months prior to entering the study are excluded.
Interventions	Participants received FOLFOX: oxaliplatin IV over 2 h, leucovorin calcium IV over 2 h, and fluorouracil IV over 46-48 h on day 1 with either arm 1: placebo orally days 1-14 or arm 2: vismodegib orally days 1-14. Courses repeat every 2 weeks in the absence of unacceptable toxicity or disease progression.
Outcomes	Primary outcome is PFS. Secondary outcomes are ORR, OS, and toxicities
Starting date	September 2009

NCT00982592 (Continued)

Contact information	Deirdre Cohen, New York University Langone Medical Center
Notes	—

NCT00991952

Trial name or title	A multicenter random assignment phase II study of irinotecan and alvocidib (Flavopiridol) versus irinotecan alone for patients with p53 wild type gastric AC
Methods	Multicenter, phase II RCT
Participants	Participants with pathologically confirmed advanced or metastatic carcinoma of the stomach or GE-junction (Siewert's type I, II, or III) not amenable to surgical resection. The participant must have received one prior chemotherapy regimen for his or her unresectable or metastatic disease; this does not include therapy administered in the adjuvant or neoadjuvant setting. At least 2 weeks must have elapsed since the participant received prior chemotherapy, anti-angiogenic therapy, or other targeted therapy; 2 weeks since prior radiation therapy; or, 4 weeks if the last regimen included carmustine (BCNU) or mitomycin C. The participant may not have previously received irinotecan or flavopiridol. The participant may not be receiving any other investigational agents.
Interventions	Arm 1: irinotecan hydrochloride IV over 30 min and aralvocidib IV over 1 h on days 1 and 8 Arm 2: irinotecan hydrochloride as in arm 1. Courses repeat every 21 days in the absence of disease progression or unacceptable toxicity
Outcomes	Primary outcome is overall RR
Starting date	September 2009
Contact information	Yelena Janjigian, Memorial Sloan Kettering Cancer Center
Notes	—

NCT01020630

Trial name or title	A randomized, placebo-controlled phase II trial investigating SUNITINIB versus placebo in patients with chemorefractory advanced AC of the stomach or lower esophagus treated with chemotherapy FOLFIRI
Methods	Multicenter, double-blind, placebo-controlled, phase II RCT
Participants	Participants with histological proven gastric AC including AC of the GE-junction or lower esophagus. Participants had to have failure of any prior chemotherapy (docetaxel and/or platinum-based chemotherapy), but participants are not allowed to have received FOLFIRI treatment.
Interventions	Arm 1: sunitinib 25 mg orally once daily for 4 consecutive weeks followed by a 2-week rest period to comprise a complete cycle of 6 weeks Arm 2: placebo orally once daily
Outcomes	Primary outcome is PFS. Secondary outcomes are ORR, safety, and tolerability
Starting date	November 2009

NCT01020630 (Continued)

Contact information	Markus Moehler, MD, Johannes Gutenberg University Mainz, 1. Med Klinik
Notes	—

NCT01246960

Trial name or title	Randomized, placebo-controlled, double-blind phase 2 study of mFOLFOX6 chemotherapy plus ramucirumab drug product (IMC-1121B) versus mFOLFOX6 plus placebo for advanced AC of the esophagus, gastroesophageal junction or stomach
Methods	Multi-center, double-blind, placebo-controlled, phase II RCT
Participants	Participants with histologic or cytologic confirmation of metastatic or locally advanced AC of the esophagus, GE-junction, or stomach. Participants that received prior first-line systemic therapy for advanced/unresectable and/or metastatic disease are excluded, prior adjuvant or neo-adjuvant therapy is permitted.
Interventions	Participants all received oxaliplatin 85 mg/m ² , leucovorin 400 mg/m ² , 5-FU 400 mg/m ² bolus all given on day 1 of a 2-week cycle, 5-FU 2400 mg/m ² continuously given over 46-48 h on day 1 of a 2-week cycle, and are randomized to either arm 1: ramucirumab 8 mg/kg or to arm 2: placebo both given on day 1 of a 2-week cycle
Outcomes	Primary outcome is PFS, secondary outcomes are OS, ORR, duration of response, TTP, and number of participants with treatment-emergent anti-ramucirumab antibodies
Starting date	April 2011
Contact information	Call 11-877-285-4559 or 1-317-615-4559, Eli Lilly and Company
Notes	—

NCT01474642

Trial name or title	A randomized phase II trial of capecitabine plus cisplatin (XP) versus capecitabine plus genexol (XG) as a first-line treatment for advanced or recurrent esophageal squamous cell carcinoma
Methods	Monocenter, open-label, phase II RCT
Participants	Participants with histologically confirmed metastatic, or recurrent esophageal SCC that have not had prior palliative chemotherapy except for prior adjuvant chemotherapy with 5-FU with cisplatin as long as it has been 6 months since completion of regimen
Interventions	Arm 1: capecitabine 2000 mg/m ² days 1-14, twice daily orally and cisplatin 75 mg/m ² IV day 1 every 3 weeks Arm 2: days 1-14 capecitabine 2000 mg/m ² day 2 orally day 1, 8 paditaxel 80 mg/m ² IV every 3 weeks
Outcomes	Primary outcome is response rate. Secondary outcomes are PFS, quality of life, number of adverse events, OS, and predictive markers
Starting date	September 2008

NCT01474642 (Continued)

Contact information	Jeeyun Lee, MD, PhD, Samsung Medical Center, Seoul, Korea
Notes	—

NCT01498289

Trial name or title	A randomized phase II pilot study prospectively evaluating treatment for patients based on ERCC1 (Excision Repair Cross-Complementing 1) for advanced/metastatic esophageal, gastric or gastroesophageal junction (GEJ) cancer
Methods	Multicenter, phase II RCT
Participants	Participants with unresectable advanced or metastatic histologically or cytologically confirmed AC of the esophagus, stomach, or GE-junction. Participants are not allowed to have had treatment for metastatic or unresectable disease
Interventions	<p>Arm 1: fluorouracil 400 mg/m², IV bolus on day 1 of each 14 day cycle; 2400 mg/m² IV over 46-48 h on days 1-2. Leucovorin calcium 400 mg/m², IV over 2 h on day 1. Oxaliplatin 85 mg/m², IV over 2 h on day 1</p> <p>Arm 2: docetaxel 30 mg/m², IV over 30 minutes on day 1, 8 of each 21 day cycle. Irinotecan hydrochloride 65 mg/m², IV over 90 min on days 1 and 8</p>
Outcomes	Primary outcome is PFS. Secondary outcomes are OS, RR, and toxicity
Starting date	February 2012
Contact information	Syma Iqbal, MD, University of Southern California
Notes	—

NCT01503372

Trial name or title	Pazopanib with 5-FU, leucovorin and oxaliplatin (FLO) as 1st-line treatment in advanced gastric cancer; a randomized phase-II-study of the Arbeitsgemeinschaft Internistische Onkologie
Methods	Single-center, open-label, phase II RCT
Participants	Participants with histologically confirmed AC of the stomach or the GE-junction with either metastatic or locally advanced disease, incurable by operation and no preceding cytotoxic therapy, however, neoadjuvant or adjuvant treatment is allowed if it was finished more than 6 months before inclusion
Interventions	<p>Arm 1: FLO + 800 mg (2 x 400 mg or 4 x 200 mg) pazopanib days 1-14 each 2 week cycle. After 12 cycles chemotherapy FLO will be discontinued and Pazopanib will be given alone until disease progression.</p> <p>Arm 2: 5-FU IV 2600 mg/m² over 24 h, oxaliplatin IV 85 mg/m² over 2 h, leucovorin IV 200 mg/m² over 2 h, every 2 weeks for 12 cycles, or FLO and pazopanib</p>
Outcomes	Primary outcome is PFS at 6 months. Secondary outcomes are PFS at 9 and 12 months, duration of response, toxicity, tolerability, OS, time to treatment failure, and evaluation of the predictive and prognostic relevance of biomarkers

NCT01503372 (Continued)

Starting date	November 2011
Contact information	Peter Thuss-Patience, MD, Charite University Medicine
Notes	—

NCT01627379

Trial name or title	An open-label, randomized phase III trial of cisplatin and 5-FU with or without panitumumab for patients with nonresectable, advanced or metastatic esophageal squamous cell cancer
Methods	Open-label, phase III RCT
Participants	Participants with histologically proven SCC of the esophagus, which is not curatively resectable or locally recurrent disease and both not eligible for definitive radiochemotherapy, or clearly metastatic disease (Tx, Nx, M1, locally unresectable T4, Nx, M0 or TX, N3, M0) or residual (post-resection) disease not eligible for definitive radiochemotherapy. Participants with previous chemotherapy of esophageal cancer in the metastatic setting are excluded. Participants with previous neoadjuvant chemotherapy or definitive radiochemotherapy with a maximum cumulative dose of 120 mg cisplatin and without recurrence of disease within 4 months after the end of treatment is allowed.
Interventions	Arm 1: cisplatin 80 mg/m ² IV over 2 h on day 1, followed by 5-FU 1000 mg/m ² IV daily as continuous infusion over 24 h, days 1-4, every 3 weeks Arm 2: arm 1 + panitumumab 9 mg/kg, day 1, every treatment cycle
Outcomes	Primary outcome is OS. Secondary outcome is PFS, 1-year survival, RR, adverse events, and QoL
Starting date	May 2012
Contact information	Ralph Keller, 0049 30 814534434, ralph.keller@aio-studien-ggmbh.de
Notes	—

NCT01704690

Trial name or title	Combination treatment of S-1 with paclitaxel versus paclitaxel + cisplatin and 5-Fu + cisplatin as first-line treatment in advanced esophageal cancer
Methods	Multicenter, open-label RCT
Participants	Participants who have a histologically confirmed diagnosis of esophageal cancer without prior palliative treatment or an interval of at least 6 months from the last operation, adjuvant radiation therapy and adjuvant chemotherapy. Paclitaxel and more than 300 mg/m ² of cisplatin are not allowed as a prior palliative treatment
Interventions	Arm 1: S-1, 80-120 mg orally, twice a day, days 1-14, and paclitaxel, 175 mg/m ² , IV on day 1 Arm 2: paclitaxel, 175 mg/m ² , IV on day 1, and cisplatin, 30 mg/m ² , IV on day 1 and day 2 Arm 3: 5-FU, 2500 mg/m ² , continuous IV for 120 h, and cisplatin, 35 mg/m ² , IV on days 1-2, cycles for all 3 arms are repeated every 21 days

NCT01704690 (Continued)

Outcomes	Primary outcome is response rate. Secondary outcomes are OS, PFS, and number of participants with adverse events and the degree of each adverse event
Starting date	August 2012
Contact information	Xiaodong Zhang, MD, 86-10-88196956, vm ² 6@netease.com
Notes	—

NCT01747551

Trial name or title	Randomized, double-blind, placebo controlled phase II study of FOLFOX +/- ziv-aflibercept in patients with advanced esophageal and gastric cancer
Methods	Multicenter, double-blind, placebo controlled, phase II RCT
Participants	Participants with confirmed AC of esophagus, GE-junction or gastric origin which is not amenable to curative resection and is unresectable, locally advanced, or metastatic. These participants have not received any prior chemotherapy, investigative or biologic agents for esophagogastric cancer except in the neoadjuvant or adjuvant setting.
Interventions	<p>Participants all receive mFOLFOX6, which will be infused every 2 weeks: oxaliplatin IV over 2 h, folinic acid IV over 2 h, 5-FU IV bolus followed by continuous infusion via ambulatory infusion pump for 46-48 h, in addition to:</p> <p>Arm 1: ziv-aflibercept IV over 1 h every 2 weeks</p> <p>Arm 2: placebo IV over 1 h every 2 weeks</p>
Outcomes	Primary outcome is PFS. Secondary outcomes are safety and tolerability, RR, duration of objective response, blood plasma levels of VEGFA and VEGFR2, and the baseline expression of tumor tissue neuropilin 1 (NRP 1), neuropilin 2 (NRP 2), transforming growth factor-b1 (TGFB-type1 receptor), and Smad 2/3
Starting date	September 2013
Contact information	Peter Enzinger, MD, Dana-Farber Cancer Institute, 617-632-5960
Notes	—

NCT01896531

Trial name or title	A randomized, phase II, placebo-controlled study of GDC-0068, an inhibitor to Akt, in combination with fluoropyrimidine plus oxaliplatin in patients with locally advanced or metastatic gastric or gastroesophageal junction AC
Methods	Multinational, placebo controlled, phase II RCT
Participants	Participants with histologically documented, inoperable locally advanced or metastatic or recurrent gastric/GE-junction AC, not amenable to curative therapy. Participants are excluded if they had previous chemotherapy for inoperable locally advanced or metastatic gastric or GE-junction AC. Participants may have had prior neoadjuvant or adjuvant chemotherapy and/or radiation

NCT01896531 (Continued)

	treatment for locally advanced gastric or GE-junction AC, provided all treatments were completed 6 months prior to randomization or before
Interventions	Arm 1: GDC-0068, orally days 1-7 of each 14-day cycle and modified FOLFOX6 IV on day 1 of each cycle Arm 2: GDC-0068 replaced by placebo
Outcomes	Primary outcome is PFS. Secondary outcomes are OS, confirmed ORR in participants with measurable soft tissue disease at baseline, duration of confirmed ORR in participants with measurable soft tissue disease at baseline
Starting date	August 2013
Contact information	Clinical trials, Genentech, Inc
Notes	—

NCT02137343

Trial name or title	A phase 3, multicenter, randomized, double-blind, placebo controlled study of rilotumumab (AMG 102) with cisplatin and capecitabine (CX) as first-line therapy in advanced MET-positive gastric or gastroesophageal junction AC
Methods	Multicenter, double-blind, placebo controlled, phase III RCT
Participants	Participants with pathologically confirmed unresectable locally advanced or metastatic gastric or GE-junction AC. Participants are excluded if they had previous systemic therapy for locally advanced or metastatic gastric or GE-junction or lower esophageal AC
Interventions	Arm 1: rilotumumab + cisplatin and capecitabine Arm 2: placebo + cisplatin and capecitabine
Outcomes	Primary outcomes are OS and PFS. Secondary outcomes are TTP, ORR, disease control rate, time to response, incidence of subject adverse events, laboratory abnormalities, and immunogenicity
Starting date	July 2014
Contact information	MD, Amgen
Notes	—

NCT02177552

Trial name or title	Study assessing the effects of chemotherapy in advanced esophagogastric AC - carboplatin, docetaxel and capecitabine (CTX) or epirubicin, oxaliplatin and capecitabine: a randomised phase 2 trial
Methods	Randomized, phase II RCT
Participants	Participants with histologically verified, unresectable or metastatic, HER2-negative, AC of the esophagus or stomach. Participants with progression on first-line chemotherapy for unresectable

NCT02177552 (Continued)

	or metastatic AC of the esophagus or stomach or with prior chemotherapy for AC of the esophagus or stomach if the chemotherapy-free interval is less than 6 months
Interventions	<p>Arm 1: carboplatin IV AUC5 day 1, docetaxel IV 60 mg/m² day 1, and capecitabine orally 1000 mg/m² twice daily days 1-14, every 4 weeks</p> <p>Arm 2: epirubicin IV 50 mg/m² day 1, oxaliplatin IV 130 mg/m² day 1, and capecitabine orally 625 mg/m² twice daily continuously, every 3 weeks</p>
Outcomes	Primary outcome is OS at 1 year. Secondary outcomes are TTP, toxicities, OS, quality of life, and safety
Starting date	June 2014
Contact information	Peter C Petersen, MD, Finsen Center, Rigshospitalet
Notes	—

NCT02178956

Trial name or title	A phase III clinical trial of BBI608 plus weekly paclitaxel vs. placebo plus weekly paclitaxel in adult patients with advanced, previously treated gastric and gastro-esophageal junction adenocarcinoma
Methods	Multinational, double-blind, phase III RCT
Participants	Participants with cytologically or histologically confirmed advanced gastric or GE-junction AC that is metastatic or locally advanced and unresectable. Participants with failed treatment with one regimen containing at least a platinum/fluoropyrimidine doublet for unresectable or metastatic disease
Interventions	<p>All participants receive paclitaxel 80 mg/m² IV on days 1, 8, and 15 of every 4-week cycle, and are randomized to additionally receive:</p> <p>Arm 1: BBI608 480 mg orally twice daily</p> <p>Arm 2: placebo orally twice daily</p>
Outcomes	Primary outcome is OS. Secondary outcome is: PFS, ORR, disease control rate, and number of participants with adverse events
Starting date	August 2014
Contact information	Boston Biomedical, Inc
Notes	—

NCT02344810

Trial name or title	A phase I and randomized phase II double blinded placebo controlled study of mFOLFOX6 +/- AMG 337 in the first-line treatment of patients with Her2/Neu negative and high MET expressing advanced gastric and esophageal AC
Methods	Double-blind, placebo-controlled, phase II RCT

NCT02344810 (Continued)

Participants	Participants with AC or poorly differentiated carcinoma of the stomach, esophagus or GE-junction that is histologically or cytologically confirmed HER2/neu negative and locally advanced or metastatic and inoperable and not amenable to curative therapy. Participants are excluded if they received an investigational agent concurrently and must not have received any other investigational agents within 4 weeks prior to registration. Participants are not allowed to have received prior chemotherapy for advanced disease or prior oxaliplatin or anti-MET therapy. Previous neo-adjuvant or adjuvant treatment is allowed if it was discontinued at least 6 months prior to registration
Interventions	All participants receive oxaliplatin IV over 2 h, leucovorin calcium IV over 2 h, and fluorouracil IV over 46-48 h on days 1 and 15, participants are randomized to additionally receive either: Arm 1: c-Met inhibitor AMG 337 orally 4 times daily on days 1-28 Arm 2: placebo orally 4 times daily on days 1-28
Outcomes	Primary outcome measures are maximum tolerated dose of c-Met inhibitor AMG 337 and PFS. Secondary outcome measures are OS, response rate, disease control rate, incidence of toxicity, time to development of new metastasis, evaluation of MET amplification, evaluation of MET amplification and MET expression, comparison of DAKO IHC to Ventana IHC and comparison of amplification by FISH to over expression by Ventana IHC
Starting date	January 2015
Contact information	Lakshmi Rajdev, ECOG-ACRIN Cancer Research Group
Notes	—

NCT02409849

Trial name or title	Randomized phase II study of octreotide LAR as maintenance treatment after first-line chemotherapy for patients with unresectable or metastatic gastro-entero-pancreatic or esophageal neuroendocrine carcinomas
Methods	Randomized, open-label RCT
Participants	Participants with histologic diagnosis of high grade (poorly differentiated) gastro-entero-pancreatic neuroendocrine carcinoma, high-grade neuroendocrine carcinoma of esophageal or unknown primary site (if a pulmonary primary has been excluded) and metastatic or unresectable disease. Participants are included if they accepted chemotherapy with EP or IP regimen for no less than 3 months
Interventions	Octreotide lar 30 mg, deep intramuscular, every 28 days
Outcomes	Primary outcome is PFS and secondary outcome is OS
Starting date	April 2015
Contact information	in Shen, Prof, +86 10 88196175, lin100@medmail.com.cn
Notes	—

NCT02569242

Trial name or title	ONO-4538 phase III study a multicenter, randomized, open-label study in patients with unresectable advanced or recurrent esophageal cancer
Methods	Open-label RCT
Participants	Participants with histologically confirmed unresectable advanced or recurrent esophageal cancer, refractory to or intolerant of standard therapy, ECOG Performance Status score 0 or 1, and a life expectancy of at least 3 months. Participants were excluded if they had a current or past history of severe hypersensitivity to any other antibody products, multiple primary cancers, metastasis in the brain or meninx that is symptomatic or requires treatment, or active, known or suspected autoimmune disease.
Interventions	Nivolumab 240 mg/body solution IV every 2 weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends or docetaxel: intravenously administered at a dose of 75 mg/m ² every 2 weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends/paclitaxel: intravenously administered at a dose of 100 mg/m ² weekly for 6 weeks followed by 2-week drug holiday until documented disease progression, discontinuation due to toxicity, withdrawal of consent or study end
Outcomes	OS, PFS, ORR, duration of response, adverse events and laboratory abnormalities
Starting date	December 2015
Contact information	Mitsunobu Tanimoto
Notes	—

NCT02625610

Trial name or title	Avelumab in first-line maintenance gastric cancer (JAVELIN Gastric 100)
Methods	Multicenter, open-label, global, RCT
Participants	Key eligibility criteria are: histologically confirmed, unresectable, locally advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction; age ≥ 18 years; ECOG performance status score of 0 or 1; no prior therapy with any drug targeting T cell coregulatory proteins; no prior chemotherapy for locally advanced/metastatic disease; and no concurrent anticancer treatment or immunosuppressive agents. Fresh or archival tumor tissue for PD-L1 expression assessment is required for all participants, but participants are not preselected based on PD-L1 expression; participants with HER2+ tumors are excluded
Interventions	Eligible participants will receive 12-week induction chemotherapy (with either oxaliplatin + 5-fluorouracil + leucovorin or oxaliplatin + capecitabine), and upon completion, approximately 466 participants without disease progression will be randomized to receive treatment in the maintenance phase. Participants entering the maintenance phase are randomized to receive either avelumab 10 mg/kg as a 1-hour IV infusion Q2W or to continue 1L chemotherapy.
Outcomes	OS, PFS, best overall response, 5-level EQ-5D version, EORTC QLQ-C30, QLQ-STO22, and National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE)
Starting date	24 December 2015
Contact information	+49 6151 72 5200, service@merckgroup.com
Notes	—

NCT02625623

Trial name or title	JAVELIN gastric 300: Phase 3 trial of avelumab (anti-PD-L1 antibody) + best supportive care (BSC) vs BSC ± chemotherapy as third-line treatment for advanced gastric or gastroesophageal junction cancer
Methods	Multicenter, open-label, phase III RCT
Participants	Key eligibility criteria are: histologically confirmed, unresectable, locally advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction; age ≥18 years; ECOG performance status score of 0 or 1; progression after 2 prior lines of systemic treatment, no prior therapy with any drug targeting T cell coregulatory proteins, and no concurrent anticancer treatment or immunosuppressive agents. Fresh or archival tumor tissue for PD-L1 expression assessment is required for all participants, but participants are not preselected based on PD-L1 expression.
Interventions	Participants will receive either BSC + avelumab 10 mg/kg as a 1-h IV infusion every 2 weeks, or BSC + chemotherapy if eligible (physician's choice of irinotecan 150 mg/m ² every 2 weeks or paclitaxel 80 mg/m ² weekly for 3 out of 4 weeks, in a 4-week treatment cycle); participants not eligible for chemotherapy will receive BSC only.
Outcomes	The primary endpoint is OS. Secondary endpoints include PFS, best overall response, QoL (assessed via EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-STO22 questionnaires), and safety. Additional endpoints include duration of response, time to response, and association between PD-L1 expression in tumor cells or immune cells within the tumor microenvironment (measured by immunohistochemistry) and clinical responses
Starting date	28 December 2015
Contact information	EMD Serono Inc, a business of Merck KGaA, Darmstadt, Germany
Notes	—

NCT02743494

Trial name or title	An investigational immuno-therapy study of nivolumab or placebo in patients with resected esophageal or gastroesophageal junction cancer (CheckMate 577)
Methods	Multicenter, double blind, phase III RCT
Participants	Subjects with resected esophageal, or gastroesophageal junction cancer. Diagnosed with stage II/III carcinoma of the esophagus or gastroesophageal junction. Completed pre-operative chemo radiotherapy followed by surgery. Diagnosed with residual pathologic disease after being surgically rendered free of disease with negative margins following complete resection. Potential participants were excluded if they were diagnosed with cervical esophageal carcinoma, had stage IV resectable disease, or did not receive concurrent chemoradiotherapy prior to surgery.
Interventions	Nivolumab or placebo
Outcomes	OS and PFS
Starting date	23 May 2016
Contact information	Clinical.Trials@bms.com

NCT02743494 (Continued)

Notes

—

NCT02773524

Trial name or title	Integrate II: A randomised phase 3 double-blind placebo-controlled study of regorafenib in refractory advanced gastro-oesophageal cancer (AGOC). An international study organized by the Australasian Gastrointestinal Trials Group (AGITG)
Methods	International, double-blind, placebo-controlled, phase III RCT
Participants	participants are eligible if they have histologically confirmed advanced gastric or oesophageal cancer, with evaluable metastatic or locally advanced disease refractory to, or relapsed following second line chemotherapy.
Interventions	Participants receive best supportive care + 160 mg REG or matched placebo orally on days 1-21 of each 28 day cycle until disease progression or prohibitive adverse events
Outcomes	Primary endpoint is OS. Secondary endpoints: PFS, RR, QoL, safety, identification of prognostic/predictive biomarkers for study endpoints, and REG PK across geographical regions
Starting date	June 2016
Contact information	—
Notes	—

NCT02872116

Trial name or title	CheckMate 649: A randomized, multicenter, open-label, phase 3 study of nivolumab (nivo) + ipilimumab (ipi) or nivo + chemotherapy (CTX) vs CTX alone in pts with previously untreated advanced (adv) gastric (G) or gastroesophageal junction (GEJ) cancer
Methods	Open-label, phase III RCT
Participants	Participants aged ≥ 18 years with untreated, inoperable advanced/metastatic G/GEJ cancer (histologically confirmed adenocarcinoma) regardless of PD-L1 status. Tumor tissue for determination of PD-L1 status (Dako assay) must be provided from ≤ 6 months before study treatment. No prior systemic therapy, including HER2 inhibitors, are allowed. Participants with known HER2+ status, suspected autoimmune disease, grade > 1 peripheral neuropathy, or active infection are excluded.
Interventions	Either nivo + ipi, nivo + CTX (capecitabine/oxaliplatin (XELOX) or fluorouracil/leucovorin/oxaliplatin (FOLFOX)), or investigator choice of XELOX or FOLFOX
Outcomes	Primary endpoint is OS in patients with PD-L1+ ($\geq 1\%$) tumors. Other endpoints include OS in all patients; PFS and time to symptom deterioration in all patients and in patients with PD-L1+ tumors; and safety
Starting date	4 October 2016
Contact information	Clinical.Trials@bms.com
Notes	—

NCT03002064

Trial name or title	Docetaxol plus cisplatin versus 5-Fu plus cisplatin as 1st-line chemotherapy in advanced ESCC patients
Methods	Open-label RCT
Participants	Participants with metastatic esophageal squamous cell cancer
Interventions	All participants receive cisplatin: 60 mg per square metre on day 1, repeated every 3 weeks till progression or at most 6 cycles. Arm 1: docetaxel, 60 mg/m ² on day 1, repeated every 3 weeks till progression or at most 6 cycles. Arm 2: fluorouracil, 5-fluorouracil 3750 mg/m ² , continuous IV 120 h every 3 weeks till progression or at most 6 cycles
Outcomes	PFS, OS, RR, toxicities and EORTC QLQ-C30 and QLQ-OES18 questionnaires
Starting date	December 2016
Contact information	Rui-Hua Xu, MD, PhD, xurh@sysucc.org.cn
Notes	—

NCT03006432

Trial name or title	Phase III randomised trial to evaluate FOLFOX with or without docetaxel (TFOX) as 1st line chemotherapy for locally advanced or metastatic oesophago-gastric carcinoma (GASTFOX)
Methods	Open-label RCT
Participants	Participants with locally advanced or metastatic gastroesophageal carcinoma
Interventions	All participants receive oxaliplatin and folinic acid. Arm 1: 5-FU bolus and continuous Arm 2: 5-FU continuous and docetaxel
Outcomes	PFS, OS, ORR, and toxicities
Starting date	December 2016
Contact information	Marie Moreau, marie.moreau@u-bourgogne.fr
Notes	—

NCT03019588

Trial name or title	Efficacy and safety study of pembrolizumab (MK-3475) versus paclitaxel in Asian participants with advanced gastric or gastroesophageal junction adenocarcinoma who progressed after first-line therapy with platinum and fluoropyrimidine (MK-3475-063/KEYNOTE-063)
---------------------	---

NCT03019588 (Continued)

Methods	Open label, phase III RCT
Participants	Participants with advanced gastric or GE-junction adenocarcinoma who progressed after first-line therapy with platinum and fluoropyrimidine
Interventions	Participants receive pembrolizumab 200 mg IV infusion on day 1 of each 3-week cycle, or paclitaxel 80 mg/m ² IV infusion on days 1, 8 and 15 of each 4-week cycle for up to approximately 2 years
Outcomes	OS, PFS, ORR, and adverse events
Starting date	16 February 2017
Contact information	Trialsites@merck.com
Notes	—

NCT03042611

Trial name or title	A prospective, randomized, double-blinded, placebo-controlled, phase III study to evaluate the efficacy and safety of apatinib plus best supportive care (BSC) compared to placebo plus BSC in patients with advanced or metastatic gastric cancer: the ANGEL study
Methods	Multinational, placebo-controlled, phase III RCT
Participants	Eligibility criteria include participants with advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction for whom at least 2 prior lines of standard chemotherapy had failed, ECOG performance status ≤ 1, and disease progression < 6 months after last chemotherapy treatment
Interventions	Participants will be randomized in a 2:1 ratio to receive continuous 28-day cycles of apatinib 700 mg or a matched placebo daily with best supportive care until disease progression, intolerable toxicity or withdrawal of consent
Outcomes	Primary endpoint is OS in the intent-to-treat population, and secondary endpoints are PFS, ORR, disease control rate, QoL, and safety
Starting date	24 February 2017
Contact information	AM301Study@lskglobal.com
Notes	—

NCT03168594

Trial name or title	Study to compare irinotecan combined with cisplatin (IP) versus etoposide combined with cisplatin (EP) in advanced and metastatic gastrointestinal pancreatic and esophageal neuroendocrine carcinoma
Methods	Prospective, phase II RCT
Participants	Participants with advanced and metastatic gastrointestinal pancreatic and esophageal neuroendocrine carcinoma

NCT03168594 (Continued)

Interventions	<p>Arm 1: irinotecan: 60 mg/m² IV drip for 90 min days 1, 8 every 3 weeks + cisplatin: 60 mg/m² IV drip for 120 min, day 1 every 3 weeks.</p> <p>Arm B: Etoposide: 100 mg/m² IV drip for 60 min days 1-3 every 3 weeks + cisplatin: 75 mg/m² IV drip for 120 min, day 1 every 3 weeks.</p>
Outcomes	ORR, PFS, OS and safety and tolerability
Starting date	29 April 2017
Contact information	linshenpku@163.com
Notes	—

NCT03189719

Trial name or title	First-line esophageal carcinoma study with chemo vs. chemo plus pembrolizumab (MK-3475-590/KEYNOTE-590)
Methods	Double-blind, placebo-controlled, phase III RCT
Participants	Participants with locally advanced or metastatic esophageal carcinoma
Interventions	<p>All participants receive cisplatin 80 mg/m² administered IV every 3 weeks on day 1 of each cycle. Duration of cisplatin treatment will be capped at 6 cycles. They also receive 5-FU 800 mg/m²/d (4000 mg/m² total per cycle) administered as continuous IV infusion on days 1-5 (120 hours) of each cycle, or per local standard for 5-FU administration</p> <p>Arm 1: pembrolizumab 200 mg administered IV every 3 weeks on day 1 of each cycle</p> <p>Arm 2: placebo to pembrolizumab (saline) administered IV every 3 weeks on day 1 of each cycle</p>
Outcomes	PFS, OS, ORR, duration of response, adverse events, EORTC QLQ-C30, and EORTC QLQ-OES18
Starting date	25 July 2017
Contact information	Trialsites@merck.com
Notes	—

NCT03279601

Trial name or title	Study to compare capecitabine combined with dacarbazine (CAPDTIC) versus capecitabine combined temozolomide (CAPTEM) in advanced and metastatic gastrointestinal pancreatic and esophageal neuroendocrine tumor
Methods	Phase II RCT
Participants	Participants with advanced or metastatic gastrointestinal pancreatic and esophageal neuroendocrine tumors
Interventions	<p>All participants receive capecitabine: 1000 mg/m², orally twice a day on days 1-14, every 4 weeks</p> <p>Arm 1: dacarbazine: 200 mg/m², IV drip, days 1-5, every 4 weeks</p>

NCT03279601 (Continued)

Arm 2: temozolomide: 200 mg/m², orally twice a day on days 10-14, every 4 weeks

Outcomes	ORR, PFS, OS, and adverse events
Starting date	1 September 2017
Contact information	linshenpku@163.com
Notes	—

NCT03281369

Trial name or title	A study of multiple immunotherapy-based treatment combinations in patients with locally advanced unresectable or metastatic gastric or gastroesophageal junction cancer(G/GEJ) (UMBRELLA)
Methods	Multicenter, open-label, phase Ib/II RCT
Participants	Participants with locally advanced unresectable or metastatic gastric or GE-junction cancer
Interventions	Multiple immunotherapy-based treatment combinations (mFOLFOX6, atezolizumab, cobimetinib, ramucirumab, paclitaxel, PEGylated recombinant human hyaluronidase (PEGPH20), BL-8040, and linagliptin)
Outcomes	Objective response, adverse events, PFS, OS, duration of response, disease control, serum concentration of atezolizumab and plasma concentration of cobimetinib, PEGPH20, BL-8040, and linagliptin. Percentages of participants with anti drug antibodies to atezolizumab, PEGPH20 of BL-8040
Starting date	15 November 2017
Contact information	Hoffmann-La Roche
Notes	—

Ohtsu 2015

Trial name or title	KEYNOTE-061: Pembrolizumab (MK-3475) versus paclitaxel as second-line therapy for advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma
Methods	Open-label, phase III RCT
Participants	Key eligibility criteria are metastatic or unresectable gastric or GEJ adenocarcinoma that progressed after first-line platinum + fluoropyrimidine chemotherapy (with trastuzumab for patients with HER2/neu+ tumors, measurable disease per RECIST v1.1, ECOG PS 0-1, no chemotherapy within 2 weeks of first dose of study drug, and provision of a newly obtained or archival tumor sample for assessing PD-L1 status
Interventions	Either pembro 200 mg every 3 weeks or paclitaxel 80 mg/m ² IV on days 1, 8, and 15 of each 28-d cycle. Treatment will continue until progression, intolerable toxicity, or participant or investigator decision. In the pembro arm, participants who have complete remission after ≥ 24 weeks may discontinue after ≥ 2 doses following initial complete remission; maximum duration of pembro is 24

Ohtsu 2015 (Continued)

months. Clinically stable patients who progress per RECIST v1.1 may continue pembro at the discretion of the investigator until a confirmatory scan performed ≥ 4 wk later.

Outcomes	Response will be assessed every 6 weeks for the first 6 months and every 12 weeks thereafter per RECIST v1.1 by central review and per RECIST adapted for the unique response patterns that may be observed with immunotherapy. Adverse events will be assessed throughout treatment and for 30 days thereafter (up to 90 d for serious Adverse events). Primary efficacy endpoints are PFS and OS in patients with PD-L1+ tumors. Secondary endpoints include PFS and OS in all participants, time to progression, ORR, and duration of response.
Starting date	—
Contact information	—
Notes	—

Shah 2017b

Trial name or title	A phase II, open-label, randomized study to evaluate the efficacy and safety of GS-5745 combined with nivolumab versus nivolumab alone in subjects with unresectable or recurrent gastric or gastroesophageal junction adenocarcinoma
Methods	Open-label, phase II, RCT
Participants	Key inclusion criteria: metastatic or inoperable adenocarcinoma of the stomach or GEJ which has progressed after ≥ 1 prior systemic therapy, ECOG performance status ≤ 1 , RECIST v1.1 measurable disease, archival tissue adequate for PD-L1 evaluation
Interventions	Participants receive either GS-5745 800 mg IV + nivolumab 3 mg/kg IV, or nivolumab alone. Treatment will be administered every 2 weeks and stratified by PD-L1 status
Outcomes	The primary endpoint of the study is ORR; secondary endpoints include PFS, OS, and occurrence of adverse events
Starting date	—
Contact information	—
Notes	—

Tabernero 2013

Trial name or title	Pertuzumab with trastuzumab and chemotherapy in patients with HER2-positive metastatic gastric or GE-junction cancer: an international phase III study (JACOB)
Methods	Double-blind, placebo controlled, phase III RCT
Participants	Participants with HER2-positive 1L metastatic gastric or GE-junction cancer
Interventions	All participants receive cisplatin: 80 mg/m ² , 5-FU: 800 mg/m ² /24 h given continuously for 120 h or capecitabine: 1000 mg/m ² twice daily for 14 days. Participants are randomized to either receive: Arm 1: pertuzumab: 840 mg, and trastuzumab: 8 mg/kg first dose, then 6 mg/kg, every 3 weeks

Tabernero 2013 (Continued)

	Arm 2: placebos in the same regimen
	Pertuzumab/placebo and trastuzumab will be given until progressive disease or unacceptable toxicity. On or before cycle 6, chemotherapy will only be discontinued for progressive disease or unacceptable toxicity. Continuation of chemotherapy after cycle 6 is at the discretion of the participant and the physician.
Outcomes	Primary outcome is OS. Secondary outcomes include PFS, ORR, duration of response, clinical benefit rate, safety, pharmacokinetics of pertuzumab, and participant-reported outcomes
Starting date	June 2013
Contact information	Clinical trials Hoffmann-La Roche
Notes	—

Tabernero 2016

Trial name or title	KEYNOTE-062: phase III study of pembrolizumab (MK-3475) alone or in combination with chemotherapy versus chemotherapy alone as first-line therapy for advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma
Methods	Phase III RCT
Participants	Key eligibility criteria include age > 18 years, locally advanced or metastatic PD-L1+/HER2- gastric or GEJ adenocarcinoma, ECOG PS 0-1, no active autoimmune disease or brain metastases, and no prior therapy for advanced disease
Interventions	Participants receive either pembro 200 mg every 3 weeks (arm 1), pembro + cisplatin 80 mg/m ² every 3 weeks + 5-fluorouracil (5-FU) 800 mg/m ² on days 1-5 of each every 3 weeks cycle (arm 2), or placebo every 3 weeks + cisplatin + 5-FU (arm 3); 5-FU may be replaced with capecitabine 1000 mg/m ² twice daily on days 1-14 of each cycle
Outcomes	Participants will be followed for survival every 3 months. OS and PFS per RECIST v1.1 are the primary study endpoints; secondary endpoints include ORR and duration of response
Starting date	31 July 2015
Contact information	Merck Sharp & Dohme Corp
Notes	NCT02494583

Toshihiko 2016

Trial name or title	Pembrolizumab versus physician-choice chemotherapy for previously treated patients with advanced/metastatic squamous or adenocarcinoma of the esophagus or Siewert I adenocarcinoma of the esophagogastric junction (EGJ): randomized, phase 3 KEYNOTE-18
Methods	Multicenter, open-label, phase III RCT
Participants	Key eligibility criteria include age ≥ 18 years; histologically or cytologically confirmed diagnosis of adenocarcinoma or squamous cell carcinoma of the esophagus or Siewert type I adenocarcinoma of the EGJ; metastatic disease or locally advanced, unresectable disease; measurable disease per Response Evaluation Criteria In Solid Tumors (RECIST), version 1.1 (v1.1), as determined by the lo-

Toshihiko 2016 (Continued)

cal site investigator/radiology assessment; documented disease progression during or after first-line therapy; no prior anticancer therapy within 2 weeks of study treatment; ECOG performance status 0-1; no active autoimmune disease or brain metastases; and provision of a tissue sample for biomarker analysis. Human epidermal growth factor receptor 2 (HER2) status must be determined for participants with EGJ adenocarcinoma; if HER2 positive, there must be documentation of disease progression on trastuzumab-containing therapy.

Interventions	Participants receive either pembrolizumab 200 mg every 3 weeks or investigator's choice of 1 of 3 standard chemotherapy regimens (paclitaxel 80-100 mg/m ² on days 1, 8, and 15 every 4 weeks, docetaxel 75 mg/m ² every 3 weeks, or irinotecan 180 mg/m ² every 2 weeks)
Outcomes	Primary efficacy end points are progression-free survival (per RECIST v1.1, blinded central imaging vendor review) and OS. Secondary end points include ORR (per RECIST v1.1, blinded central imaging vendor review)
Starting date	1 December 2015
Contact information	1-888-577-8839
Notes	NCT02564263

5-FU: fluorouracil; **AC**: adenocarcinoma; **BSC**: best supportive care; **ECOG**: Eastern Cooperative Oncology Group; **GE**: gastroesophageal; **IV**: intravenous; **ORR**: objective response rate; **OS**: overall survival; **PFS**: progression-free survival; **PS**: performance status; **QoL**: quality of life; **RCT**: randomized controlled trial; **RECIST**: response evaluation criteria in solid tumors; **RR**: response rate; **SCC**: squamous cell carcinoma; **TTP**: time to progression; **VEGFA**: vascular endothelial growth factor A; **VEGFR2**: vascular endothelial growth factor receptor 2.

DATA AND ANALYSES

Comparison 1. Main analysis: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	11	1347	Hazard Ratio (Random, 95% CI)	0.75 [0.68, 0.84]
1.1 Subcomparison 3: chemotherapeutic agent(s) plus control intervention versus control intervention alone	5	358	Hazard Ratio (Random, 95% CI)	0.73 [0.63, 0.85]
1.2 Subcomparison 4: targeted therapy agent plus control intervention versus control intervention alone	6	989	Hazard Ratio (Random, 95% CI)	0.75 [0.63, 0.90]
2 Progression-free survival	5		Hazard Ratio (Random, 95% CI)	Subtotals only
2.1 Subcomparison 4: targeted therapy agent plus control intervention versus control intervention alone	5	883	Hazard Ratio (Random, 95% CI)	0.64 [0.45, 0.92]

Analysis 1.1. Comparison 1 Main analysis: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone, Outcome 1 Overall survival.

Analysis 1.2. Comparison 1 Main analysis: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone, Outcome 2 Progression-free survival.

Comparison 2. Sensitivity analysis: studies that also included participants with gastric cancer

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	8	1755	Hazard Ratio (Random, 95% CI)	0.94 [0.83, 1.05]

Analysis 2.1. Comparison 2 Sensitivity analysis: studies that also included participants with gastric cancer, Outcome 1 Overall survival.

Comparison 3. Sensitivity analysis: effect of intervention on participants with GE-junction cancer versus effect of intervention on participants with gastric cancer

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival, GE-junction cancer outcomes	5	538	Hazard Ratio (Random, 95% CI)	0.66 [0.54, 0.81]
2 Overall survival, gastric cancer outcomes	5	2093	Hazard Ratio (Random, 95% CI)	0.89 [0.76, 1.04]

Analysis 3.1. Comparison 3 Sensitivity analysis: effect of intervention on participants with GE-junction cancer versus effect of intervention on participants with gastric cancer, Outcome 1 Overall survival, GE-junction cancer outcomes.

Analysis 3.2. Comparison 3 Sensitivity analysis: effect of intervention on participants with GE-junction cancer versus effect of intervention on participants with gastric cancer, Outcome 2 Overall survival, gastric cancer outcomes.

Comparison 4. Subcomparison 1: chemotherapy or targeted therapy plus BSC versus BSC

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	5	750	Hazard Ratio (Random, 95% CI)	0.81 [0.71, 0.92]
2 Progression-free survival	2	540	Hazard Ratio (Random, 95% CI)	0.58 [0.28, 1.18]

Analysis 4.1. Comparison 4 Subcomparison 1: chemotherapy or targeted therapy plus BSC versus BSC, Outcome 1 Overall survival.

Analysis 4.2. Comparison 4 Subcomparison 1: chemotherapy or targeted therapy plus BSC versus BSC, Outcome 2 Progression-free survival.

Comparison 5. Subcomparison 2: studies with participants receiving second-line therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	4	769	Hazard Ratio (Random, 95% CI)	0.71 [0.54, 0.94]
2 Progression-free survival	3	677	Hazard Ratio (Random, 95% CI)	0.51 [0.29, 0.90]

Analysis 5.1. Comparison 5 Subcomparison 2: studies with participants receiving second-line therapy, Outcome 1 Overall survival.

Analysis 5.2. Comparison 5 Subcomparison 2: studies with participants receiving second-line therapy, Outcome 2 Progression-free survival.

Comparison 6. Subgroup analysis 4a: EGFR-targeting agent plus control intervention versus control intervention alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	3	655	Hazard Ratio (Random, 95% CI)	0.86 [0.73, 1.01]
2 Progression-free survival	3	655	Hazard Ratio (Random, 95% CI)	0.85 [0.73, 1.00]

Analysis 6.1. Comparison 6 Subgroup analysis 4a: EGFR-targeting agent plus control intervention versus control intervention alone, Outcome 1 Overall survival.

Analysis 6.2. Comparison 6 Subgroup analysis 4a: EGFR-targeting agent plus control intervention versus control intervention alone, Outcome 2 Progression-free survival. **Comparison 7. Subgroup analysis 4b: cetuximab plus control intervention versus control intervention alone**

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Overall survival	2	206	Hazard Ratio (Random, 95% CI)	0.76 [0.55, 1.04]
2 Progression-free survival	2	206	Hazard Ratio (Random, 95% CI)	0.90 [0.59, 1.37]

Analysis 7.1. Comparison 7 Subgroup analysis 4b: cetuximab plus control intervention versus control intervention alone, Outcome 1 Overall survival. **Analysis 7.2. Comparison 7 Subgroup analysis 4b: cetuximab plus control intervention versus control intervention alone, Outcome 2 Progression-free survival.**

Comparison 8. Subgroup analysis 4c: ramucirumab plus control intervention versus control intervention alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	2	228	Hazard Ratio (Random, 95% CI)	0.62 [0.43, 0.88]
2 Progression-free survival	2	228	Hazard Ratio (Random, 95% CI)	0.39 [0.28, 0.54]

Analysis 8.1. Comparison 8 Subgroup analysis 4c: ramucirumab plus control intervention versus control intervention alone, Outcome 1 Overall survival.

Analysis 8.2. Comparison 8 Subgroup analysis 4c: ramucirumab plus control intervention versus control intervention alone, Outcome 2 Progression-free survival.

Comparison 9. Subcomparison 5: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone in participants with AC of the esophagus

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	5	538	Hazard Ratio (Random, 95% CI)	0.66 [0.54, 0.81]
2 Progression-free survival	4	713	Hazard Ratio (Random, 95% CI)	0.62 [0.38, 1.00]

Analysis 9.1. Comparison 9 Subcomparison 5: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone in participants with AC of the esophagus, Outcome 1 Overall survival.

Analysis 9.2. Comparison 9 Subcomparison 5: chemotherapy or targeted therapy agent(s) plus control intervention versus control intervention alone in participants with AC of the esophagus, Outcome 2 Progression-free survival.

Comparison 10. Subcomparison 6: chemotherapy or targeted therapy agent(s) plus control arm versus control arm in participants with SCC of the esophagus

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	4	268	Hazard Ratio (Random, 95% CI)	0.76 [0.65, 0.90]
2 Progression-free survival	2	168	Hazard Ratio (Random, 95% CI)	0.72 [0.55, 0.96]

Analysis 10.1. Comparison 10 Subcomparison 6: chemotherapy or targeted therapy agent(s) plus control arm versus control arm in participants with SCC of the esophagus, Outcome 1 Overall survival.

Analysis 10.2. Comparison 10 Subcomparison 6: chemotherapy or targeted therapy agent(s) plus control arm versus control arm in participants with SCC of the esophagus, Outcome 2 Progression-free survival.

APPENDICES

Appendix 1. Glossary

Chemotherapy: a drug treatment that uses chemicals to kill fast-growing cells in the body in a fairly aspecific manner.

Dysphagia: the symptom of difficulty in swallowing.

Metastatic: the spread of cancer from one part of the body to another without being directly connected to it.

Non-resectable: not able to be removed by surgery. This can have multiple possible causes, for instance, the cancer has grown into a vital organ which cannot be removed, or the removal of the cancer would not cure the person because metastases are present, or the person is in such physical condition that exposure to surgery would cause a significant risk of dying.

Palliative care: treatment that reduces the effects or symptoms of a medical condition without curing it.

Cytostatic therapy: a drug treatment that is directed at fast-dividing cells in general.

Targeted therapy: a drug treatment, often a monoclonal antibody or a small molecule, to block the growth and spread of cancer by interfering with specific molecules.

Toxicity: any unfavourable event, symptom, or disease associated with the use of a treatment that may or may not be considered related to the treatment.

Appendix 2. CENTRAL search strategy

```
((esophag* OR oesophag* OR gastroesophag* OR gastrooesophag* OR junction* ) NEAR/6 (neoplas* OR cancer* OR tumo* OR metasta* OR meta-stasis OR meta-static OR malign* OR carcinom* OR adenocarcinom*)) :ab,ti) AND ((chemotherap* OR chemoradi* OR radiochemo* OR photochemo* OR ((drug* OR chemo*) NEAR/6 (radi* OR therap*))) :ab,ti) AND ((palliat* OR unresect* OR irresect* OR nonresect* OR inopera* OR unopera* OR nonopera* OR advanced OR (non NEAR/1 (opera* OR resect*))) :ab,ti) NOT ((preopera* OR ((pre OR post) NEAR/1 opera*) OR postopera*) :ab,ti)
```

Appendix 3. MEDLINE OvidSP

```
("Esophageal Neoplasms"/ OR (exp "Esophagogastric Junction"/ AND exp "Digestive System Neoplasms"/) OR ((esophag* OR oesophag* OR gastroesophag* OR gastrooesophag* OR junction* ) ADJ6 (neoplas* OR cancer* OR tumo* OR metasta* OR meta-stasis OR meta-static OR malign* OR carcinom* OR adenocarcinom*)) :ab,ti.) AND (exp "drug therapy"/ OR exp "digestive system cancer"/dt OR (chemotherap* OR chemoradi* OR radiochemo* OR photochemo* OR ((drug* OR chemo*) ADJ6 (radi* OR therap*))) :ab,ti.) AND ("Palliative Care"/ OR (palliat* OR unresect* OR irresect* OR nonresect* OR inopera* OR unopera* OR nonopera* OR advanced OR (non ADJ1 (opera* OR resect*))) :ab,ti.) AND ("randomized controlled trial".pt. OR "evaluation studies".pt. OR "comparative study".pt. OR "Follow-Up Studies"/ OR "Prospective Studies"/ OR (random* OR factorial* OR crossover* OR (cross ADJ over*) OR placebo* OR ((doubl* OR singl* OR tripl*) ADJ (mesk* OR blind*)) OR assign* OR allocat* OR volunteer* OR comparat* OR evaluat* OR follow-up OR followup OR prospectiv* OR control*) :ab,ti.) NOT ("preoperative period"/ OR exp "postoperative period"/ OR (preopera* OR ((pre OR post) ADJ1 opera*) OR postopera*) :ab,ti.)
```

Appendix 4. Embase search strategy

```
('esophagus cancer'/exp OR ('lower esophagus sphincter'/de AND 'digestive system cancer'/exp) OR ((esophag* OR oesophag* OR gastroesophag* OR gastrooesophag* OR junction* ) NEAR/6 (neoplas* OR cancer* OR tumo* OR metasta* OR meta-stasis OR meta-static OR malign* OR carcinom* OR adenocarcinom*)) :ab,ti) AND ('drug therapy'/exp OR 'digestive system cancer'/exp/dm_dt OR (chemotherap* OR chemoradi* OR radiochemo* OR photochemo* OR ((drug* OR chemo*) NEAR/6 (radi* OR therap*))) :ab,ti) AND ('advanced cancer'/de OR 'palliative therapy'/exp OR (palliat* OR unresect* OR irresect* OR nonresect* OR inopera* OR unopera* OR nonopera* OR advanced OR (non NEAR/1 (opera* OR resect*))) :ab,ti) AND ('crossover procedure'/de OR 'double-blind procedure'/de OR 'randomized controlled trial'/de OR 'single-blind procedure'/de OR evaluation/de OR 'comparative study'/exp OR 'follow up'/de OR 'prospective study'/de OR (random* OR factorial* OR crossover* OR (cross NEXT/1 over*) OR placebo* OR ((doubl* OR singl* OR tripl*) NEXT/1 (mesk* OR blind*)) OR assign* OR allocat* OR volunteer* OR comparat* OR evaluat* OR follow-up OR followup OR prospectiv* OR control*) :ab,ti) NOT ('preoperative period'/exp OR 'postoperative period'/exp OR (preopera* OR ((pre OR post) NEAR/1 opera*) OR postopera*) :ab,ti)
```

Appendix 5. Web of Science

```
TS=(((esophag* OR oesophag* OR gastroesophag* OR gastrooesophag* OR junction* ) NEAR/6 (neoplas* OR cancer* OR tumo* OR metasta* OR meta-stasis OR meta-static OR malign* OR carcinom* OR adenocarcinom*)) AND ((chemotherap* OR chemoradi* OR radiochemo* OR photochemo* OR ((drug* OR chemo*) NEAR/6 (radi* OR therap*))) AND ((palliat* OR unresect* OR irresect* OR nonresect* OR inopera* OR unopera* OR nonopera* OR advanced OR (non NEAR/1 (opera* OR resect*))) NOT ((preopera* OR ((pre OR post) NEAR/1 opera*) OR postopera*)) AND (random* OR factorial* OR crossover* OR (cross NEAR/1 over*) OR placebo* OR ((doubl* OR singl* OR tripl*) NEAR/1 (mesk* OR blind*)) OR assign* OR allocat* OR volunteer* OR comparat* OR evaluat* OR follow-up OR followup OR prospectiv* OR control*))
```

Appendix 6. PubMed publisher

```
((esophag*[tiab] OR oesophag*[tiab] OR gastroesophag*[tiab] OR gastrooesophag*[tiab] OR junction*[tiab] ) AND (neoplas*[tiab] OR cancer*[tiab] OR cancers[tiab] OR tumor[tiab] OR tumors[tiab] OR tumor*[tiab] OR metasta*[tiab] OR meta-sta*[tiab] OR malign*[tiab] OR carcinom*[tiab] OR adenocarcinom*[tiab])) AND ((chemotherap*[tiab] OR chemoradi*[tiab] OR radiochemo*[tiab] OR photochemo*[tiab] OR ((drug[tiab] OR drugs[tiab] OR chemo[tiab]) AND (radio[tiab] OR radiother[tiab] OR therapy[tiab] OR therapies[tiab]))) AND ((palliat*[tiab] OR unresect*[tiab] OR irresect*[tiab] OR nonresect*[tiab] OR inopera*[tiab] OR unopera*[tiab] OR nonopera*[tiab] OR advanced OR non opera*[tiab] OR non resect*[tiab])) AND ((random*[tiab] OR factorial*[tiab] OR crossover*[tiab] OR cross over*[tiab] OR placebo*[tiab] OR ((doubl*[tiab] OR singl*[tiab] OR tripl*[tiab]) AND (mesk*[tiab] OR blind*[tiab])) OR assign*[tiab] OR
```


allocat*[tiab] OR volunteer*[tiab] OR comparat*[tiab] OR evaluat*[tiab] OR follow-up OR followup OR prospectiv*[tiab] OR control[tiab] OR controlled[tiab])) NOT ((preopera*[tiab] OR pre opera*[tiab] OR post opera*[tiab] OR postopera*[tiab])) AND publisher[sb]

Appendix 7. Google scholar

"(esophagus|esophageal|oesophagus|esophageal|junction)(neoplasm|neoplasms|cancer|malignant|carcinoma)"(chemotherapy|chemoradiotherapy|radiochemotherapy)(palliative|inoperable|advanced)(random|randomized|randomised|comparative|evaluation|prospective)

Appendix 8. Clinicaltrials.gov

(esophageal OR esophagus OR gastresophageal) AND (neoplasm OR neoplasms OR cancer OR tumors) AND (chemotherapy OR chemoradiotherapy OR radiochemotherapy) AND (palliative OR unresectable OR irresectable OR nonresectable OR inoperable OR advanced)

Appendix 9. WHO International Clinical Trials Registry Platform (ICTRP) search strategy

Esophag* AND neoplas* AND palliat* OR Oesophag* AND neoplas* AND palliat* OR Esophag* AND cancer* AND palliat* OR Oesophag* AND cancer* AND palliat* OR Esophag* AND neoplas* AND unresectable* OR Oesophag* AND neoplas* AND unresectable* OR Esophag* AND cancer* AND unresectable* OR Oesophag* AND cancer* AND unresectable*

WHAT'S NEW

Date	Event	Description
15 October 2017	New search has been performed	We reran searches and placed the studies of interest that were identified from this updated search in "studies awaiting classification" or "ongoing studies". These will be incorporated in the next version of the review, as appropriate.
15 October 2017	New citation required and conclusions have changed	Inclusion of new citations enabled us to perform a meta-analysis.

HISTORY

Protocol first published: Issue 1, 2003

Review first published: Issue 4, 2006

Date	Event	Description
22 April 2009	New search has been performed	Updated
30 October 2008	Amended	Converted to new review format
14 July 2006	New search has been performed	Minor update
11 January 2006	Amended	New studies found and included or excluded

CONTRIBUTIONS OF AUTHORS

EJK reviewed the draft manuscript. AvdG supervised the analyses and reviewed the draft manuscript. RHJM supervised the analyses and reviewed the draft manuscript. MPP supervised the analyses and reviewed the draft manuscript. MJB supervised the analyses and reviewed the draft manuscript. EWS consulted on the statistical methodology and the interpretation of the outcomes of the analyses and reviewed the draft manuscript. MCWS selected inclusions based on abstract and full text, extracted descriptive data, risk of bias data and outcome data, supervised the analyses and reviewed the draft manuscript. VTJ selected inclusions based on abstract and full text, extracted

descriptive data, risk of bias data and outcome data, attempted to contact study authors, performed analyses, wrote the draft manuscript, made revisions to the draft manuscript, and submitted the final paper.

DECLARATIONS OF INTEREST

VTJ: none known.

EWS: none known.

AvdG: none known.

RHJM: none known.

MJB: none known.

MPP: none known.

EJK: none known.

MCWS: none known.

SOURCES OF SUPPORT

Internal sources

- Dept. of Gastroenterology & Hepatology, Erasmus MC / University Medical Center Rotterdam, Netherlands.
- Dept. of Public Health, ErasmusMC, University Medical Center Rotterdam, Netherlands.
- Biomedical information specialists, Medical Library ErasmusMC, University Medical Center Rotterdam, Netherlands.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences between the protocol of the previous review and the protocol of the current review

Types of participants

Besides people with metastatic disease, we also included people with advanced (T3-T4NxM0 if technically inoperable) disease, with the exception of those with locally advanced cancer who received systemic therapy in order to assess secondary resectability. We included people with advanced, non-metastasized disease when the intent of the treatment was palliation. We included studies involving only a subset of eligible participants if they contained at least 15 eligible participants, and we only included these studies in a meta-analysis if there were enough studies to perform a meaningful sensitivity analysis by meta-regression.

Types of interventions

Interventions studying targeted therapies fall explicitly within the types of interventions studied in this review. This was not specified in the previous version.

Electronic searches

In addition to researching CENTRAL, MEDLINE, Embase, and PUBMED, we also searched the Web of Science, Google Scholar, ClinicalTrials.gov, and WHO International Clinical Trials Registry Platform (ICTRP).

Individual participant data

We attempted to contact the authors of all studies that included suitable participants and asked them to provide individual participant data for studies included after the search of 3 October 2013. We did the same for studies that included some suitable participants but did not report the outcomes separately for this group.

Quality assessment of studies

We included an additional quality assessment domain on selective reporting bias. We no longer subdivided studies into categories of quality depending on the risk of bias criteria. We defined baseline comparability and intention-to-treat analysis.

Measures of treatment effect

We extracted or estimated HRs and 95% CIs as relevant effect measures directly or indirectly from the given data. This was not specified in the previous version.

Dealing with missing data

In case of missing outcomes, we contacted the trial authors. If the authors were not willing or able to share their data, we estimated the missing outcomes if possible, and if not, we included the studies and described the outcomes that were reported. We then noted missing data on individuals and missing study level characteristics in the 'Risk of bias' tables.

Assessment of reporting biases

We assessed small study effects such as publication bias in a qualitative manner using a funnel plot. This was not specified in the previous version.

Data synthesis

Given the heterogeneous methods of the included studies, we calculated pooled estimates of effect using an inverse variance random-effects model for meta-analysis. We synthesized the Ln(HR) for overall survival and progression-free survival as well as median overall and progression-free survival, which was not specified in the previous version. We summarized toxicity and quality of life data narratively for comparison one as was done in the previous version, but we did not repeat them for the subcomparisons.

Summary of findings tables

We used the GRADE system to assess the quality of the evidence for each analysis, presenting our assessments in 'Summary of findings' tables using RevMan 5. This was not specified in the previous version.

Sensitivity analysis

The effect modifier identified was the presence of ineligible participants in the study. If we performed data synthesis including studies from this subgroup, we ran a sensitivity analysis by meta-regression to quantify the amount of heterogeneity between the two subgroups.

INDEX TERMS

Medical Subject Headings (MeSH)

*Esophagogastric Junction; Adenocarcinoma [drug therapy] [mortality]; Antibodies, Monoclonal [therapeutic use]; Antibodies, Monoclonal, Humanized; Antineoplastic Agents [therapeutic use]; Antineoplastic Combined Chemotherapy Protocols [*therapeutic use]; Carcinoma, Squamous Cell [drug therapy] [mortality]; Disease-Free Survival; Esophageal Neoplasms [*drug therapy] [mortality]; Molecular Targeted Therapy [*methods] [mortality]; Palliative Care [*methods]; Quality of Life; Randomized Controlled Trials as Topic; Stomach Neoplasms [*drug therapy] [mortality]

MeSH check words

Humans