**Supplemental content**

**Supplementary Table 1. Full search strategy**
Note:In the database searches, squamous cell carcinoma was also added as search term to make sure that studies with mixed populations of patients with both adenocarcinoma and squamous cell carcinoma were not missed.

 **PubMed**

|  |  |
| --- | --- |
| 1 | "Esophageal Neoplasms"[Mesh] OR "Stomach Neoplasms"[Mesh] OR "Carcinoma, Squamous Cell"[Mesh] |
| 2 | (esophag\*[tiab] OR oesophag\*[tiab] OR gastric[tiab] OR gastroesophag\*[tiab] OR gastrooesophag\*[tiab] OR stomach[tiab] OR squamous[tiab] OR barrett\*[tiab]) AND (cancer\*[tiab] OR neoplas\*[tiab] OR tumor\*[tiab] OR tumour\*[tiab] OR malignan\*[tiab] OR carcino\*[tiab] OR adeno\*[tiab] OR metastas\*[tiab]) |
| 3 | #1 OR #2 |
| 4 | "Receptor, ErbB-2"[Mesh] OR "Genes, erbB-2"[Mesh] |
| 5 | HER2[tiab] OR HER 2[tiab] OR epidermal growth factor receptor 2[tiab] OR ERBB2[tiab] OR ERBB-2[tiab] OR ERB B 2[tiab] OR c-erbb-2[tiab] OR cerbb2[tiab] OR neu[tiab] OR neu protein[tiab] OR neu receptor[tiab] OR receptor neu[tiab] OR neuregulin receptor[tiab] |
| 6 | #4 OR #5 |
| 7 | #3 AND #6 |

**EMBASE**

|  |  |
| --- | --- |
| **#** | **Searches** |
| 1 | exp \*esophagus tumor/ or exp \*stomach tumor/ or exp \*squamous cell carcinoma/ or ((esophag\* or oesophag\* or gastric or gastroesophag\* or gastrooesophag\* or stomach or squamous or barrett\*) adj3 (cancer\* or neoplas\* or tumor\* or tumour\* or malig\* or carcino\* or adeno\* or metastas\*)).ti,ab,kw. |
| 2 | epidermal growth factor receptor 2/ or proto oncogene/ or (epidermal growth factor receptor 2 or HER2 or HER 2 or epidermal growth factor receptor 2 or ERBB2 or ERBB-2 or ERB B 2 or c-erbb-2 or cerbb2 or neu protein or neu receptor or receptor neu or neuregulin receptor).ti,ab,kw. |
| 3 | 1 and 2 |

**Cochrane Central Register of Controlled Trials**

#1 MeSH descriptor: [Esophageal Neoplasms] explode all trees
#2 MeSH descriptor: [Stomach Neoplasms] explode all trees
#3 MeSH descriptor: [Carcinoma, Squamous Cell] explode all trees
#4 (esophag\* or oesophag\* or gastric or gastroesophag\* or gastrooesophag\* or stomach or squamous or barrett\*) near/3 (cancer\* or neoplas\* or tumor\* or tumour\* or malignan\* or carcino\* or adeno\* or metastas\*):ti,ab,kw (Word variations have been searched)
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Receptor, ErbB-2] explode all trees
#7 MeSH descriptor: [Genes, erbB-2] explode all trees
#8 epidermal growth factor receptor 2 or HER2 or HER 2 or epidermal growth factor receptor 2 or ERBB2 or ERBB-2 or ERB B 2 or c-erbb-2 or cerbb2 or neu protein or neu receptor or receptor neu or neuregulin receptor:ti,ab,kw (Word variations have been searched)
#9 #6 or #7 or #8
#10 #5 and #9 in Trials

**ASCO**
trastuzumab AND gastric

**ESMO**
trastuzumab AND gastric

**Supplementary Table 2. Quality assessment**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Non-randomized studies** |  |  |  |  |  |
| **Category** | **Selection** | **Design** | **Comparability of studies** | **Outcome** | **Published** | **Overall quality** |
| **Items** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |   |
| Narita 2016 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | High |
| Li 2016 | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | High |
| Palle 2017 | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | High |
| Makiyama 2017 | Yes | Yes | Yes | No | Yes | NA/No | Yes | Yes | Yes | No | Moderate |
| **Randomized studies** |
| **Items** | A | B | C | D | E | F |  |  |  |  |  |
| Makiyama 2018 | Unclear | Unclear | Low | Low | Low | Unclear (conference abstract) |  |  |  |  | Unclear |

|  |
| --- |
| **Legend** |
| Modified version of the Newcastle Ottawa Scale for single-arm cohort studies. Studies were scored as low (0-4 points), moderate (5-8 points) or high quality (9-10 points).  |
| 1. Representativeness of exposed cohort: drawn from target population and at least baseline age and performance status should be described2) The non exposed cohort: drawn from the same community as the exposed cohort and at least baseline age and performance status should be described3. Ascertainment of exposure: description of number of patients who actually received treatment4. Prospective study 5. Multicenter study6. Majority of patients (>80%) in the study received second-line taxane- or irinotecan-based chemotherapy regimens 7. Assessment of outcome was adequate 8.Follow-up long enough for events to occur: if the upper bound of the 95%CI of the median OS was reached, the follow-up time was deemed long enough.9. Adequacy of follow-up: state reasons for dropout10.Published report in peer reviewed journalCochrane Risk of Bias tool for randomized controlled trials. Studies were scored as Low, High or Unclear risk of bias.A. Random sequence generationB. Allocation concealmentC. Blinding of outcomeD. Incomplete outcome dataE. Selective ReportingF. Other bias  |

**Supplementary Figure 1. Flowchart of included studies**

**References derived from ASCO (n = 222) and ESMO (n = 296) until June 2018**

**Total n = 518**

**References derived from Pubmed (n = 3275), EMBASE**

**(n = 5944) and CENTRAL (n = 575) until June 2018**

**Total n = 9478**

**Removed duplicates**

**n = 2664**

**Unique references for screening based on title and abstract**

**n = 6814**

**Excluded based on title and abstract**

**n = 516**

**Excluded based on title and abstract**

**n = 6800**

**Additional studies identified from conference meetings**

**n = 2**

**References for full-text assessment**

**n = 14**

**Excluded after detailed assessment: n = 11**

- Trastuzumab-naïve patients: n = 1
- No comparison with chemotherapy-alone: n = 8

- Case report: n = 2

**Studies eligible for systematic review**

**n = 3**

**Studies derived from both database and conference search: n = 5**

**Supplementary Figure 2. Funnel plot for the assessment of publication bias.

(A) Overall Survival**

****
**(B) Progression Free Survival**

**(C) Objective Response Rate**

**Supplementary Table 3. Grade 1-2 Adverse Events**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Grade 1-2 toxicity** | **Tmab + CT** | **CT-alone** | **Estimate**  | **Heterogeneity**  |
|  | **n/N** | **%** | **n/N** | **%** | **RR (95%CI)** | ***P*** | **Trials** | ***I²* (%)** | ***P*** |
| **Haematological** |  |  |  |  |  |  |  |  |  |
| Neutropenia | 26/70 | 37% | 20/65 | 31% | 1.20 (0.75-1.92) | 0.46 | 2 | 0 | 0.33 |
| Leukopenia | 30/70 | 43% | 24/65 | 37% | 1.16 (0.77-1.77) | 0.48 | 2 | 0 | 0.90 |
| Anemia | 24/70 | 34% | 19/65 | 29% | 1.13 (0.69-1.85) | 0.62 | 2 | 0 | 0.79 |
| Thrombocytopenia | 4 | 6% | 7 | 11% | 0.55 (0.17-1.83) | 0.33 | 2 | 0 | 0.41 |
| **Non-haematological** |  |  |  |  |  |  |  |  |  |
| Nausea | 14/70 | 20% | 16/65 | 25% | 0.75 (0.25-2.27) | 0.62 | 2 | 66 | 0.09 |
| Diarrhea | 14/70 | 20% | 14/65 | 22% | 0.97 (0.50-1.87) | 0.92 | 2 | 0 | 0.40 |
| Stomatitis  | 3 | 12% | 2 | 10% | 1.15 (0.21-6.26) | 0.87 | 1 | NA | NA |
| Mucositis  | 7 | 16% | 3 | 7% | 2.39 (0.66-8.64) | 0.19 | 1 | NA | NA |
| Anorexia | 23/70 | 33% | 16/65 | 25% | 1.08 (0.30-3.97) | 0.90 | 2 | 75 | 0.06 |
| Fatigue | 23/70 | 33% | 22/65 | 34% | 0.98 (0.55-1.77) | 0.96 | 2 | 27 | 0.24 |
| Neuropathy | 32/70 | 46% | 33/65 | 51% | 0.91 (0.64-1.28) | 0.58 | 2 | 0 | 0.58 |
| Febrile neutropenia | 0/70 | 0% | 0/65 | 0% | NA | NA | 2 | NA | NA |
| Cardiovasculair | 1/168 | 1% | 2/156 | 1% | 0.51 (0.02-16.03) | 0.70 | 4 | 60 | 0.11 |
| Nephrotoxicity  | 0/32 | 0% | 0/27 | 0% | NA | NA | 1 | NA | NA |
| Allergic reaction | 1 | 2% | 0/26 | 0% | 1.35 (0.06-32.08) | 0.85 | 1 | NA | NA |
| Infusion related events | 10 | 12% | 3 | 7% | 1.47 (0.44-4.90) | 0.53 | 2 | NA | NA |

No significant differences were detected between the trastuzumab-continuation arm and the chemotherapy-alone arm. A Risk Ratio < 1 indicates less adverse events for trastuzumab-continuation. A Risk Ratio > 1 indicates more adverse events for trastuzumab-continuation.
Abbreviations: 95%CI: 95% confidence interval, CT: chemotherapy, n: number of patients with an adverse event, N: sample size, NA: Not available, RR: Risk Ratio, Tmab: trastuzumab.