Prognostic and predictive factors for overall survival in metastatic oesophagogastric cancer: A systematic review and meta-analysis

ter Veer, Emil; van Kleef, Jessy Joy; Schokker, Sandor; van der Woude, Stephanie O.; Laarman, Marety; Haj Mohammad, Nadia; Sprangers, Mirjam A. G.; van Oijen, Martijn G. H.; van Laarhoven, Hanneke W. M.

Published in:
European journal of cancer (Oxford, England

DOI:
10.1016/j.ejca.2018.07.132

Published: 01/01/2018

Document Version
Publisher's PDF, also known as Version of record

Citation for pulished version (APA):
ter Veer, E., van Kleef, J. J., Schokker, S., van der Woude, S. O., Laarman, M., Haj Mohammad, N., Sprangers, M. A. G., van Oijen, M. G. H., & van Laarhoven, H. W. M. (2018). Prognostic and predictive factors for overall survival in metastatic oesophagogastric cancer: A systematic review and meta-analysis. *European journal of cancer (Oxford, England*, *103*, 214-226. https://doi.org/10.1016/j.ejca.2018.07.132

European Journal of Cancer 103 (2018) 214–226

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Review

Prognostic and predictive factors for overall survival in metastatic oesophagogastric cancer: A systematic review and meta-analysis

Emil ter Veer [a,1], Jessy Joy van Kleef [a,1], Sandor Schokker [a], Stephanie O. van der Woude [a], Marety Laarman [a], Nadia Haj Mohammad [b], Mirjam A.G. Sprangers [c], Martijn G.H. van Oijen [a], Hanneke W.M. van Laarhoven [a,*]

[a] *Cancer Center Amsterdam, Amsterdam University Medical Centers, University of Amsterdam, Department of Medical Oncology, Academic Medical Center, Meibergdreef 9, Amsterdam, The Netherlands*
[b] *Department of Medical Oncology, University Medical Center Utrecht, University Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands*
[c] *Cancer Center Amsterdam, Amsterdam University Medical Centers, University of Amsterdam, Department of Medical Psychology, Academic Medical Center, Meibergdreef 9, Amsterdam, The Netherlands*

Received 29 April 2018; received in revised form 26 July 2018; accepted 31 July 2018

KEYWORDS
Advanced oesophagogastric cancer;
Prognostic factors;
Predictive factors;
Systematic review;
Meta-analysis;
Palliative systemic therapy

Abstract ***Background:*** Consistent evidence on prognostic and predictive factors for advanced oesophagogastric cancer is lacking. Therefore, we performed a systematic review and meta-analysis.

Methods: We searched PubMed, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL) databases for phase II/III randomised controlled trials (RCTs) until February 2017 on palliative systemic therapy for advanced oesophagogastric cancer that reported prognostic or predictive factors for overall survival (PROSPERO-CRD42014015177). Prognostic factors were identified from multivariate regression analyses in study reports. Factors were considered potentially clinically relevant if statistically significant ($P \leq 0.05$) in multivariate analysis in $\geq$50% of the total number of patients in the pooled sample of the RCTs and were reported with a pooled sample size of $\geq$600 patients in the first-line or $\geq$300 patients in the beyond first-line setting. Predictive factors were identified from time-to-event stratified treatment comparisons and deemed potentially clinically relevant if the P-value for interaction between subgroups was $\leq$0.20 and the hazard ratio in one of the subgroups was significant ($P \leq 0.05$).

* *Corresponding author*: Department of Medical Oncology, Academic Medical Center, 1100 DD Amsterdam, The Netherlands.
E-mail address: h.vanlaarhoven@amc.uva.nl (H.W.M. van Laarhoven).
[1] Contributed equally.

https://doi.org/10.1016/j.ejca.2018.07.132

Results: Forty-six original RCTs were included (n = 15,392 patients) reporting on first-line (n = 33) and beyond first-line therapy (n = 13). Seventeen prognostic factors for overall survival in the first-line and four in the beyond first-line treatment setting were potentially clinically relevant. Twenty-one predictive factors in first-line and nine in beyond first-line treatment setting were potentially relevant regarding treatment efficacy.

Conclusions: The prognostic and predictive factors identified in this systematic review can be used to characterise patients in clinical practice, be included in future trial designs, enrich prognostic tools and generate hypotheses to be tested in future research to promote patient-centred treatment.

Research in context

Evidence before this study

Prognostic and predictive factors are important for estimation of prognosis, clinical decision making and trial design, and are key in a transition towards more personalised medicine. A variety of factors have been described in past trials on palliative treatment of oesophagogastric cancer, and available prognostic indexes use different sets of factors which are based on relatively small numbers of patients. Of predictive factors only HER-2 status is currently used in clinical practice. We therefore searched PubMed, EMBASE, and CENTRAL for phase II/III randomised controlled trials (RCTs) until February 2017 on palliative systemic therapy for advanced oesophagogastric cancer that reported prognostic or predictive factors for overall survival. Forty-six original RCTs were included, of which 33 were rated as having a low risk of bias. Adopting self-defined criteria for potential clinical relevance we identified 17 prognostic factors for first-line and four potential factors for beyond first-line palliative treatment, as well as 21 predictive factors for first-line and nine predictive factors for beyond first-line palliative treatment.

Added value of this study

In this systematic review we are the first to identify all prognostic and predictive factors that have been reported as statistically significant in previous RCTs. This review therefore reports more robust evidence on prognostic and predictive factors in the palliative treatment of advanced oesophagogastric cancer.

Implications of all the available evidence

Prognostic factors identified in this review can be used to better characterise patients in clinical practice, guide the development of better prognostic models, and be used in future trial design as stratification factors or to be included in regression analyses. The predictive factors we identified can generate hypotheses to be tested in future trials, and can in combination with prognostic factors eventually be used for more personalised medicine.

1. Introduction

Survival of patients with metastatic oesophagogastric cancer varies greatly among patient subpopulations [1]. There is no international consensus on standard first-line palliative treatment, but regimens usually consist of a fluoropyrimidine (e.g., 5-fluorouracil, capecitabine, S-1) and a platinum compound (e.g., cisplatin, oxaliplatin) [2–4]. Recently, targeted therapies such as monoclonal antibodies and tyrosine kinase inhibitors have been added as treatment options in both first- and beyond first-line treatment [2–4].

Identifying which patients have a dismal prognosis and which treatments they are most likely to benefit from would enable personalised treatment strategies and improve survival. Prognostic and predictive factors are key in this process. Prognostic factors are patient and tumour characteristics that can be used to estimate the prognosis of a patient, independent of a specific treatment regimen. Cohort studies or, preferably, well-conducted randomised controlled trials (RCTs) are suitable for evaluating the prognostic relevance of such patient and tumour characteristics [5]. In contrast, predictive factors indicate which patient (sub)populations may benefit more from a certain treatment over others [6]. Predictive factors, therefore, imply a differential treatment benefit that depends on the absence or presence of a particular patient or tumour characteristic. Predictive factors can be evaluated with stratified analyses in an RCT including a control group [5]. If there is evidence that a certain factor may have predictive value for the efficacy of the experimental intervention over the control treatment, the next step may be to repeat the RCT but with a selected patient group.

The tumour-node-metastasis (TNM) classification is an established combination of prognostic factors, which uses the following tumour characteristics: tumour size and invasion of surrounding structures, lymph node metastases and distant metastases [7]. Besides the TNM classification, other prognostic factors such as the performance status and peritoneal metastasis are also

recognised as clinically important and are, therefore, used as stratification factors in RCTs. Many trials have been performed in the last decades, reporting a variety of statistically significant prognostic factors. Previously, several gastric and oesophageal cancer–specific prognostic models have been proposed [8–12]. A well-known example is the Royal Marsden Hospital prognostic index. However, these prognostic indices were based on relatively small numbers of patients from a limited number of studies, and the evidence of prognostic factors is inconsistent. As for predictive factors, human epidermal growth factor receptor 2 (HER-2) status is currently the only predictive factor in oesophagogastric cancer that is used in clinical practice to select patients for a specific (in this case, HER-2 targeted) therapy [13].

In sum, the current evidence of prognostic factors is inconsistent, and evidence of predictive factors (other than HER-2 status) in the palliative treatment of oesophagogastric cancer is lacking. We, therefore, performed a systematic review and meta-analysis to identify clinically relevant prognostic and predictive factors for overall survival (OS) in the palliative systemic treatment of oesophagogastric cancer.

2. Methods

2.1. Literature search

The search protocol of a previous project registered in PROSPERO with registration number CRD42014015177 was used. Adopting the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, we searched the databases PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) and meeting abstracts from the American Society of Clinical Oncology and European Society for Medical Oncology for RCTs up to February 2017. Medical subject headings and text words for oesophagogastric cancer and for each treatment option were used (Supplementary Table 1). E.t.V. and N.H.M. screened the titles, abstract and full texts of the articles before January 2016, and J.J.v.K. and S.S. screened the titles, abstracts and full texts of the update search after January 2016. Disagreements were discussed with H.W.M.v.L. until consensus was reached.

2.2. Study selection and quality assessment

We included prospective phase II or III RCTs comparing palliative systemic therapies for patients with pathologically proven metastatic, unresectable or recurrent adenocarcinoma of the stomach, oesophagus or gastro-esophageal junction. In addition, RCTs needed to report on prognostic factors in multivariate regression analyses and/or predictive subgroup analyses concerning OS. The Cochrane risk of bias tool (version 5.1.0) was used to assess the quality of the included studies and was performed by two authors independently. Items were scored as low, high or unknown risk of bias.

2.3. Data extraction and statistical analysis

Data extraction was independently conducted by J.J.v.K., S.S., S.O.v.d.W. and M.L. A final check was conducted by E.t.V. Prognostic factors for OS were identified from multivariate Cox or logistic regression analyses in the study reports. In absence of previously established criteria, we adopted self-constructed criteria to determine the potential clinical relevance of prognostic and predictive factors for OS. For prognostic factors, first a factor should be statistically significant ($P \leq 0.05$) in a multivariate regression analysis in at least one RCT and the pooled sample size of RCTs in which the factor was statistically significant should be more than 50% of the sample size of all RCTs reporting that factor. Second, a factor should be reported in first-line treatment RCTs including $\geq$600 patients or in beyond first-line RCTs including $\geq$300 patients. For example, if the factor 'age' was analysed in five first-line RCTs with a total sample size of 1000 but only statistically significant in two of five first-line RCTs with a pooled sample size of 400 of 1000 (40%), then the factor was not deemed clinically relevant.

Furthermore, as usually only statistically significant hazard ratios (HRs) are reported, while non-significant HRs are not; we extracted the available multivariate HRs with 95% confidence intervals from Cox proportional hazards regression analyses in the study reports for exploratory reasons only. If possible, the reported HRs were pooled with random-effects pairwise meta-analysis using Review Manager, 5.3.

Predictive factors were identified from time-to-event stratified treatment comparisons. To determine potentially clinically relevant predictive factors, we adopted the following self-constructed criteria: first, the P-value for interaction between two or more specific subgroups should be $\leq$0.20 and second, the HR in one of the subgroups should be significant ($P \leq 0.05$). We calculated P-values for subgroup interaction and HRs with Review Manager, 5.3, if study reports did not report them.

The funder of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all data and had the final responsibility for the decision to submit for publication.

3. Findings

3.1. Description of the included studies

A total of 5765 unique titles were retrieved through the database search, of which 191 references remained after title and abstract screening. After full-text assessment,

134 references were excluded and 57 references were found eligible. Two references were additionally retrieved from the conference search (Fig. 1). In total, 59 references [8,13–70] on 46 original RCTs [13, 25–56, 58–70] were included. From the 46 original RCTs (n = 15,392 patients), 33 investigated first-line therapy [13, 25–56] and thirteen investigated beyond first-line therapy [58–70]. Thirteen of the 59 references [8,14–24,57] were secondary reports of the original RCTs that contained data on prognostic or predictive factors.

3.2. Risk of bias

Of the 46 original RCTs, 33 (72%) RCTs were rated as low risk of bias (Supplementary Fig. 1). The number of RCTs that were rated as unclear risk of bias on one item, on two items or on three items were four (9%), seven (15%) and two (4%), respectively. No major differences in study design were observed (Supplementary Table 2).

3.3. Prognostic factors

A total of 50 factors were investigated in multivariate regression analyses in the first-line setting and twelve factors in the beyond first-line setting. From these factors, seventeen first-line factors and four beyond first-line factors met the criteria for potential clinical relevance. The factors with clinically relevant prognostic value in the first-line setting were the following: performance status, peritoneal metastasis, alkaline phosphatase, primary tumour resection, liver metastasis, disease status (locally advanced versus metastatic and unresectable versus recurrent), histology (Lauren classification), primary tumour location (oesophagus versus stomach), the number of metastatic sites, white blood cell count, health-related quality of life (European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire Core 30 Global Health Status, Physical Functioning and Role Functioning scales), neutrophil-to-lymphocyte ratio (NLR), lactate dehydrogenase, aspartate aminotransferase, C-reactive protein and tumour size (Fig. 2; Table 1). In beyond first-line treatment, the following factors met the criteria for clinical relevance: age, performance status, disease status (locally advanced or metastatic) and time-to-progression on first-line therapy (Fig. 2; Table 1). More details of the results of our selection strategy for clinically relevant prognostic factors are shown in Supplementary Fig. 2A. As the number of studies reporting an HR for a certain factor was only a

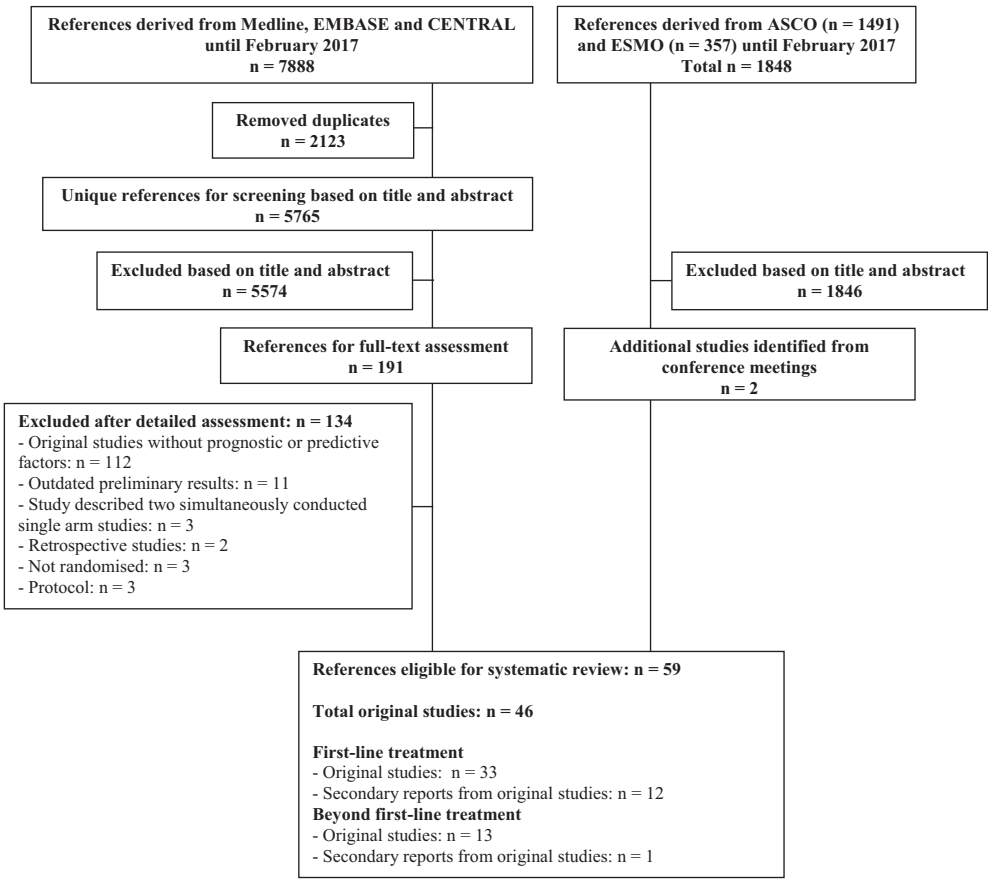

Fig. 1. **Flowchart of included studies**. Using PRISMA guidelines, a flowchart of our literature search used in the identification of prognostic and predictive factors. CENTRAL, Cochrane Central Register of Controlled Trials; ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

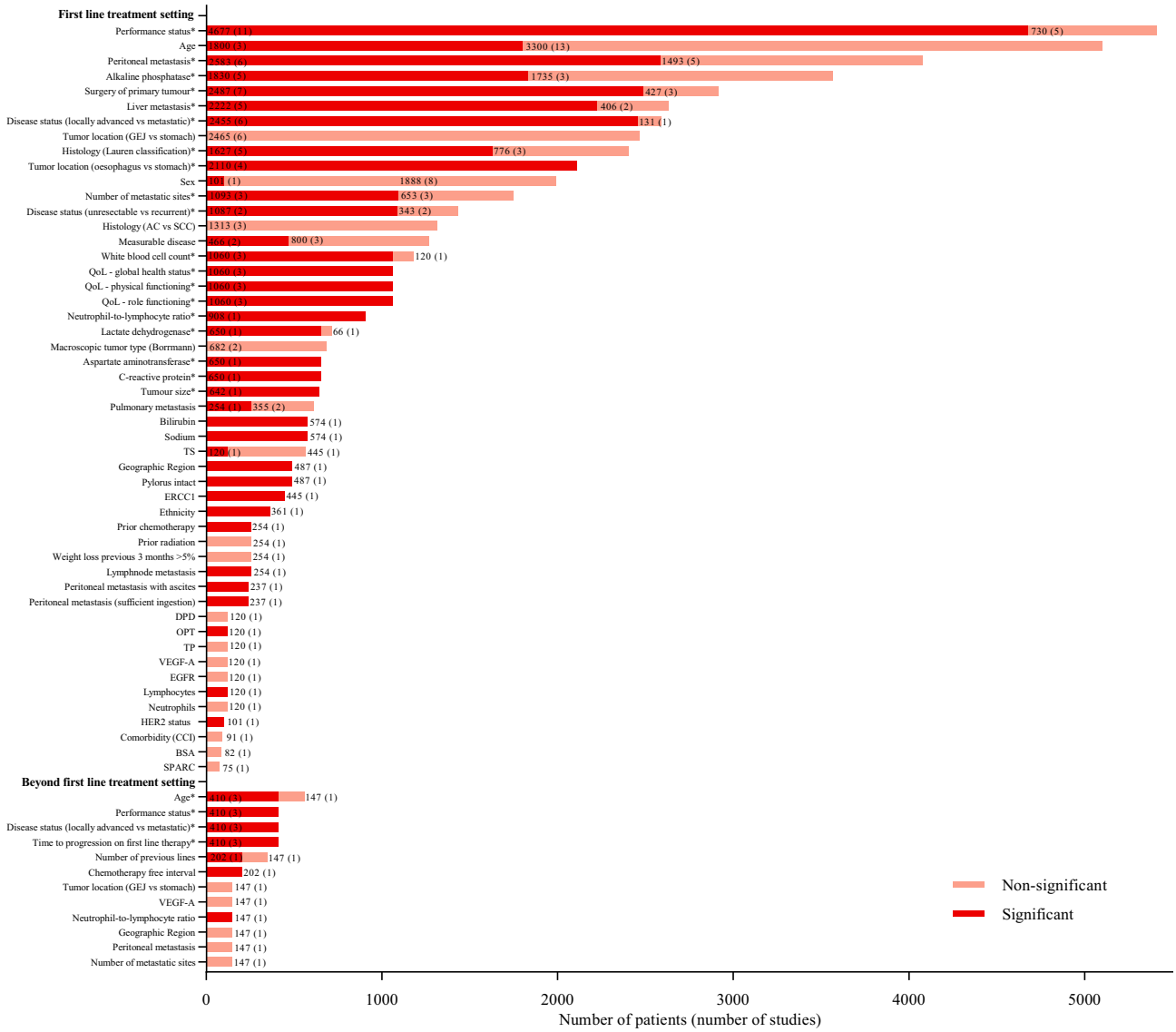

Fig. 2. **Prognostic factors for overall survival**. The full set of factors that have been included in a multivariate regression analysis in at least one RCT. *The factors that met the criteria for clinical relevance. GEJ, gastroesophageal junction; VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; BSA, bovine serum albumin; AC, adenocarcinoma; SCC, squamous cell carcinoma; QoL, quality of life; TS, thymidylate synthase; ERCC1, excision repair cross-complementing group 1; DPD, dihydropyrimidine dehydrogenase; OPT, orotate phosphoribosyltransferase; TP, thymidine phosphorylase; SPARC, secreted protein acidic and rich in cysteine.

fraction of the total number of studies reporting the factor (Fig. 2), the HRs are shown in Supplementary Table 3 for exploratory purposes only.

3.4. Predictive factors

Stratified treatment comparisons in RCTs were performed for 46 predictive factors in the first-line setting and 26 in the beyond first-line setting. From these factors, 21 in first-line and nine in beyond first-line RCTs met the criteria for potentially clinically relevant predictive value for survival benefit of certain treatment regimens. Table 2 shows the subgroups with significant HRs for specific treatment comparisons. The following 21 factors in the first-line treatment setting met the criteria for potential clinical relevance: age, performance status, disease status (unresectable versus recurrent and locally advanced versus metastatic), measurable disease, histology (according to Lauren), clinical nodal stage, number of metastatic sites, number of metastatic lesions, metastasis in liver, peritoneum, lymph nodes or lung, presence of primary tumour, primary tumour location, geographic region and specific biomarkers related to anti-HER2, anti-MET, anti-EGFR and antiangiogenic therapies. For specific beyond first-line treatment regimens, the following nine predictive factors were

Table 1
Prognostic factors for overall survival.

First-line treatment setting	Subgroup
Performance status	ECOG **0** versus 1–2, **0–1** versus 2, **0–1** versus 2–3, **0** versus 1, **0** versus 1 versus 2 KPS **100–90** versus 80–60
Peritoneal metastasis	**Absent** versus present
Alkaline phosphatase	Continuous (**lower** is better survival), **<ULN** versus ≥ULN, **<100 U/L** versus ≥100U/L
Surgery of primary tumour	**Yes** versus no
Liver metastasis	**Absent** versus present
Disease status	**Locally advanced** versus metastatic
Histology	**Intestinal type** versus diffuse type (Lauren classification)
Tumour location	**Oesophagus** versus stomach
Number of metastatic sites	**0–1** versus ≥2
Disease status	**Recurrent** versus unresectable at diagnosis
White blood cell count	<**Median** versus >median
Quality of Life EORTC QLQ-C30	
Global Health Status subscale	Continuous (**higher score** is better survival)
Physical Functioning subscale	Continuous (**higher score** is better survival)
Role Functioning subscale	Continuous (**higher score** is better survival)
Neutrophil-to-lymphocyte ratio	**>3** versus ≤3
Lactate dehydrogenase	**<ULN** versus ≥ULN
Aspartate aminotransferase	**<ULN** versus ≥ULN
C-reactive protein	**<ULN** versus ≥ULN
Tumour size	**<76.5 mm** versus ≥76.5 mm
Beyond first-line treatment setting	**Subgroup**
Age	Continuous (**lower age** is better survival)
Performance status	**0–1** versus 2
Disease status	**Locally advanced** versus metastatic
Time-to-progression on first-line treatment	**Within 3–6 months after completion** versus during treatment versus within 3 months after completion

ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status; EORTC, European Organisation for Research and Treatment of Cancer; QLQ-C30, Quality of Life Questionnaire Core 30; ULN, upper limit of normal.
*Median not specified.
This table gives an overview of all prognostic factors that met the criteria of clinical relevance. The patient subgroups with the better survival were stated as first and indicated in bold. Subgroups with worse survival were stated as second.

identified as potentially clinically relevant: performance status, measurable disease, tumour histology (according to Lauren), number of metastatic sites, sex, primary tumour location, geographic region, objective response to first-line therapy and time-to-progression on first-line therapy. More details on the results of the selection strategy for potential clinically relevant predictive factors are shown in Supplementary Fig. 2B. The full overview including the opposite subgroups within each study in which no significant difference between treatments were found is shown in Supplementary Table 4.

4. Discussion

We identified all prognostic and predictive factors for first-line and beyond first-line treatment described in phase II/III RCTs published up to February 2017.

4.1. Prognostic factors for OS of oesophagogastric cancer

In the past years, several prognostic indices have been developed for patients with previously untreated advanced oesophagogastric cancer [11,71]. An example is the Royal Marsden Hospital prognostic index that is based on data of three RCTs [8] and was validated in the REAL-2 RCT population [24]. This prognostic index includes four factors: performance status, liver metastases, peritoneal metastases and alkaline phosphatase, which are confirmed to be clinically relevant in the current systematic review [8]. Other prognostic models incorporate a variety of prognostic factors to predict survival, e.g., bone metastasis, albumin, ascites and haemoglobin [9–12]. However, these factors are not confirmed by our analysis. The usefulness of these factors may, therefore, be questioned.

As our review includes evidence from all RCTs in advanced oesophagogastric cancer, we were able to identify more factors with prognostic value in the first-line treatment setting as compared with the prognostic models that have been previously reported. For example, the disease status (locally advanced versus metastatic or unresectable versus recurrent), primary tumour location (oesophagus versus stomach), tumour histology (diffuse versus intestinal), several health-

Table 2
Clinically relevant predictive factors for specific treatment comparisons.

Factor	First-line			Beyond first-line		
	Experimental versus Comparator	HR (95% CI)	N	Experimental versus Comparator	HR (95% CI)	N
Sex						
Male sex (versus female)				Ramucirumab > BSC	0.68 (0.50–0.92)	355
Age						
Age <65 (versus ≥65)	S-1 + Cis > S-1	0.75 (0.61–0.92)	298			
Age <60 (versus ≥60)	Lapatinib + Cap + Ox > Cap + Ox	0.69 (0.51–0.94)	487			
PS (ECOG)						
1–2 (versus 0)	S-1 + Iri > S-1	0.61 (0.40–0.94)	315	Ramucirumab > PCB	0.68 (0.51–0.92)	355
1 (versus 0)	S-1 + Cis > 5-FU + Cis	0.71 (0.70–0.94)	1390			
	S-1 + Ox + Lv > S-1 + Cis	0.34 (0.12–0.96)	95			
Disease status						
Unresectable (versus recurrent)	S-1 > 5-FU	0.75 (0.60–0.94)	468			
	S-1 + Ox + Lv > S-1 + Cis	0.51 (0.31–0.83)	95			
Locally advanced (versus metastatic)	Nimotuzumab + Cis + S-1 < Cis + S-1	6.01 (1.78–20.23)	62			
Clinical node stage N0-1 (versus N2-3)	Gastrectomy + S-1 + Cis < S-1 + Cis	1.79 (1.14–2.83)	175			
Measurable disease						
Measurable disease: no (versus yes)	S-1 + Cis > S-1	0.54 (0.35–0.83)	298	DTX/Iri + BSC > BSC	0.36 (0.20–0.67)	202
	S-1 + DTX > S-1	0.65 (0.46–0.91)	635			
Measurable disease: yes (versus no)	Cis + Iri > 5-FU	0.73 (0.58–0.89)	470	Ramucirumab + PTX > PTX + PCB	0.75 (0.62–0.91)	665
	Trastuzumab + Cis + 5-FU/Cap > Cis + 5-FU/Cap	0.66 (0.53–0.82)	584			
Histology						
Intestinal histology (versus diffuse)				Iri + Cis > Iri	0.57 (0.35–0.92)	162
Diffuse histology (versus intestinal, mixed and unknown)	Cetuximab + Cis + Cap < Cis + Cap	1.44 (1.01–2.03)	883			
Diffuse histology (versus intestinal)	Cis + Iri > 5-FU	0.70 (0.45–0.94)	470	Ramucirumab > PCB	0.56 (0.37–0.86)	355
Prior therapy						
Prior objective response (versus no prior response)				DTX/Iri + BSC > BSC	0.48 (0.30–0.77)	202
TTP on first-line therapy ≥6 months (versus <6 months)				Ramucirumab + PTX > PTX + PCB	0.62 (0.42–0.90)	665
TTP on first-line therapy within 3 months (versus during treatment)				DTX/Iri > BSC	0.70 (0.49–0.99)	410
TTP on first-line therapy within 3–6 months (versus during treatment)				DTX/Iri > BSC	0.39 (0.26–0.59)	410
Metastatic sites						
Number of metastatic sites						
>1 (versus 1)	Panitumumab + EOX < EOX	1.79 (1.20–2.68)	494			
>2 (versus 1–2)	Trastuzumab + Cis + 5-FU/Cap > Cis + 5-FU/Cap	0.57 (0.43–0.77)	583			
≥2 (versus 0–1)				PTX > Iri	1.64 (1.08–2.49)	219
>4 metastatic lesions (versus 1–4 metastatic lesions)	Trastuzumab + Cis + 5-FU/Cap > Cis + 5-FU/Cap	0.64 (0.49–0.84)	583			
Liver metastasis: yes (versus no)	S-1 + Ox + Lv > S-1 + Cis	0.31 (0.14–0.67)	95			
Lymph node metastasis: no (versus yes)	S-1 + DTX > S-1	0.68 (0.51–0.92)	635			
Peritoneal metastasis: yes (versus no)	S-1 + Cis > S-1	0.52 (0.33–0.82)	298			
Peritoneal metastasis: no (versus yes)	Cis + Iri > 5-FU	0.70 (0.56–0.91)	470			
Visceral (lung or liver) metastasis: yes (versus no)	Trastuzumab + Cis + 5-FU/Cap > Cis + 5-FU/Cap	0.65 (0.49–0.85)	584			

Table 2 (*continued*)

Factor	First-line			Beyond first-line		
	Experimental versus Comparator	HR (95% CI)	N	Experimental versus Comparator	HR (95% CI)	N
Primary tumour						
Primary tumour present (versus not present)	Nimotuzumab + Cis + S-1 < Cis + S-1	2.31 (1.12–4.76)	62			
GEJ (versus stomach)				Ramucirumab + PTX > PTX + PCB	0.52 (0.35–0.78)	665
Upper third stomach (versus lower middle third)	Gastrectomy + S-1 + Cis < S-1 + Cis	2.23 (1.14–4.37)	175			
Geographic region						
Asia (versus North America versus rest of the world)	Lapatinib + Cap + Ox > Cap + Ox	0.68 (0.48–0.96)	487			
Rest of the world (versus Asia and Western countries)				Ramucirumab > PCB	0.46 (0.27–0.81)	355
Non-East Asia (versus East Asia)				Ramucirumab + PTX > PTX + PCB	0.73 (0.59–0.91)	665
China (versus Japan)*				Lapatinib + PTX > PTX	0.62 (0.39–0.98)	261
Biomarkers						
KRAS wild type (versus mutation)	Panitumumab + EOX < EOX	1.50 (1.03–2.18)	174			
HER2 IHC2+/FISH+ or IHC3+ (versus IHC 0–1/FISH+)	Trastuzumab + Cis + 5-FU/Cap > Cis + 5-FU/Cap	0.65 (0.51–0.83)	577			
VEGF-A ≥111 ng/L (versus <111 ng/L)	Bevacizumab + Cis + 5-FU/Cap > Cis + 5-FU/Cap	0.72 (0.57–0.93)	712			
Neuropilin-1 H-score <80 (versus H-score ≥80)	Bevacizumab + Cis + 5-FU/Cap > Cis + 5-FU/Cap	0.75 (0.59–0.97)	679			
High VEGF + low Ang-2 (versus low VEGF + low Ang-2)	Bevacizumab + Cis + 5-FU/Cap > Cis + 5-FU/Cap	0.64 (0.42–0.97)	319			
25% MET expression positive (versus negative)	Rilotumumab + ECX > ECX	0.46 (0.24–0.87)	91			
50% MET expression positive (versus negative)	Rilotumumab + ECX > ECX	0.38 (0.16–0.88)	91			

5-FU, 5-fluorouracil; Ang, angiopoietin; BSC, best supportive care, Cap, capecitabine; Cis, cisplatin; DTX, docetaxel; ECX, epirubicin, cisplatin, capecitabine; ECOG, Eastern Cooperative Oncology Group; EOX, epirubicin, oxaliplatin, capecitabine; FISH, fluorescence *in situ* hybridisation; HER2, human epidermal growth factor receptor 2; GEJ, gastroesophageal junction; HR, hazard ratio; IHC, immunohistochemistry; Iri, irinotecan; KRAS, kirsten rat sarcoma; Lv, leucovorin; MET, mesenchymal–epithelial transition; Ox, oxaliplatin; N, sample-size; PCB, placebo; PS, performance status; PTX, paclitaxel; TTP, time-to-progression; VEGF, vascular endothelial growth factor.

*Results from this study were given for China and Japan only, and all patients in this study were HER2 positive, defined as IHC3+ or *in situ* hybridization positive, regardless of IHC score.

For clinically relevant predictive factors in first-line and beyond first-line palliative treatment, the P-value for subgroup interaction between two or more specific subgroups was ≤0.20, and the HR in one of the subgroups was significant ($P \leq 0.05$). The > or < indicates which specific treatment showed a significant survival benefit over the other treatment in the particular patient subgroup.

related quality of life domains and laboratory factors were additionally found in the current systematic review. Also, for patients receiving beyond first-line treatment, little evidence regarding prognostic factors is available in the literature. Therefore, the current systematic review offers a more robust overview of factors with potential clinical value for this patient population.

Besides demographic and tumour characteristics, the prognostic value of laboratory factors is becoming more recognised. For example, the NLR is a relatively new prognostic factor that has previously been identified in other solid malignancies [72,73]. In addition, the NLR was included in one of the previous prognostic models on oesophagogastric cancer [9] and by two large well-conducted RCTs included in this review. Therefore, the NLR may be regarded a valuable prognostic marker in oesophagogastric cancer.

The prognostic factors that we identified can be used by clinicians to better characterise their patients and therefore support clinical decision-making. For future trial design, the current findings can be used to prespecify factors to include in statistical analyses, for example, to control for confounding when estimating conditional treatment effects, or to choose evidence-based stratification factors.

An important next step would be to validate the factors that were found to be clinically relevant in large cohort studies, e.g., the Prospective Observational

Cohort study of Oesophageal-gastric cancer Patients [74]. Subsequently, a comprehensive prognostic index can be developed.

4.2. Predictive factors for treatment efficacy in oesophagogastric cancer

We identified a variety of predictive factors, which included both regular patient and tumour characteristics and biomarkers. Ideally, potential predictive factors should be further tested in a new RCT, including patients from the predictive subgroup only. A good example of testing the treatment effect on the predictive subgroup for a regular patient and tumour characteristic based on previous evidence is tumour histology in the FLAGS and DIGEST trials, both also included in the current review. Subgroup analysis within the FLAGS trial showed that patients with a diffuse histology had an increased survival rate with S-1 plus cisplatin over 5-fluorouracil (5-FU) plus cisplatin, whereas there was no difference in efficacy between the two arms in the intestinal histology subgroup [55]. Subsequently, this hypothesis was tested in the DIGEST trial, comparing the same treatment strategies but now in patients with diffuse histology tumours only [75]. As there was no survival benefit from S-1 plus cisplatin over 5-FU plus cisplatin, the hypothesis was not confirmed, but clearly, those negative findings are also valuable evidence.

For biomarkers, the predictive value of HER2 expression for trastuzumab treatment is the prime example of the relevance of such an approach. An important subanalysis within the ToGA trial indicated that trastuzumab plus chemotherapy is more effective compared with chemotherapy alone in patients with HER2 positivity defined as IHC3+ or IHC2+ and gene amplification by *in situ* hybridisation (ISH+) but not in patients with just ISH+ and IHC1+/0 expression [13]. Therefore, trastuzumab is the treatment of choice for HER2-positive disease defined as IHC3+ or IHC2 and fluorescence *in situ* hybridisation positive in most countries [4]. The same strategy illustrated, however, that MET expression could eventually not be used as a predictive factor for MET inhibitors. Initial subanalysis of a phase II trial generated the hypothesis that the MET inhibitor rilotumumab would be effective in MET-positive patients [46]. However, this hypothesis was not confirmed as the subsequent phase III RILOMET-1 trial with solely MET-positive patients was stopped prematurely because of inferior survival in the rilotumumab arm compared with the control arm [76]. These findings correspond with the results of the phase II YO28252 study [77] and the phase III METGastric study [78], in which the MET inhibitor onartuzumab added to chemotherapy also failed to improve clinical outcomes compared with chemotherapy alone in an MET-positive population.

In addition, we identified some other patient characteristics that showed predictive value for common treatment regimens, meriting attention. First, although fluoropyrimidine-based regimens with capecitabine, 5-FU and S-1 may be equally effective, there is some evidence in the current review that S-1 may have survival benefit over 5-FU in certain subgroups (e.g., patients with Eastern Cooperative Oncology Group >0 or unresectable disease rather than recurrent disease). For platinum-based regimens, oxaliplatin has been associated with prolonged survival compared with cisplatin in several subgroups. This finding is in line with previous reports, indicating that oxaliplatin may be slightly more effective and less toxic compared with cisplatin [2,4,52,79–82].

Our systematic review underscores the difficulties of extrapolating findings from one population to another. Geographic region as a predictive factor may confound the outcomes of a trial. In multinational trials, region should, therefore, be considered as a stratification factor and should be included in stratified subgroup analyses to assess its influence on treatment efficacy.

4.3. Strengths and limitations

This review has limitations. First, because HRs for prognostic factors tend to be reported predominantly for statistically significant factors only, pooling of these results leads to bias. Second, as no formal criteria to determine clinical relevance are available, we devised the criteria used in this study ourselves. One could argue the arbitrariness of the criterion to include the cut-off P-value for interaction of 0.20 as it may have led to chance findings. However, stricter cut-off criteria—for example a P-value for subgroup interaction of 0.05 instead of 0.2—might have excluded valuable evidence from trials with smaller sample sizes. Third, most evidence for predictive factors is based on single RCT, and the results are difficult to translate into clinical practice. This evidence can, however, be used to generate hypotheses and guide further research like in the aforementioned examples of the FLAGS [55] and DIGEST [75] trials.

The major strength is that we were able to identify more factors in the RCTs than all previously generated prognostic models, which were mostly based on non-randomised patient cohorts. The factors identified in this systematic review are based on a large number of randomised patients, consistent over different studies, and therefore, the results are more robust. In this systematic review, we only included RCTs and did not consider cohort studies to identify prognostic and predictive factors. As for predictive factors, randomisation is essential for identification of these factors, whereas cohort studies are undermined with confounding factors for this purpose [83]. Also, using RCTs to identify prognostic factors has advantages over using cohort studies. Most importantly, RCTs usually have a more strict prespecified protocol of which patient population

to include, which baseline characteristics to obtain from the population and which treatment regimens to use. Cohort studies might not always have a prespecified protocol, which may lead to missing data on baseline characteristics and treatment types. In RCTs, usually the type of treatment is included as a separate factor in multivariate analysis to control for its effect when identifying independent prognostic factors in RCTs. In addition, the majority of RCTs were conducted in multiple healthcare institutions, whereas in many cohort studies, the cohort is drawn from only one institution.

5. Conclusion

In conclusion, we identified prognostic and predictive factors studied in phase II and III RCTs on the palliative treatment of oesophagogastric cancer. The evidence for prognostic factors can be used to better characterise patients and may indicate which factors to include in prognostic models. Also, evidence could be used to indicate which factors to include in future trial designs and analyses, e.g., as a stratification variable. The evidence for predictive factors may generate hypotheses to be tested in future research and can eventually promote patient-centred treatment.

Author contributions

H.W.M.v.L., M.G.H.v.O., M.A.G.S., E.t.V. and J.J.v.K. contributed to study concepts. H.W.M.v.L., M.G.H.v.O., M.A.G.S., E.t.V., J.J.v.K., S.S. and S.O.v.d.W. contributed to study design. E.t.V., J.J.v.K., S.S., S.O.v.d.W. and M.L. contributed to data acquisition. E.t.V., J.J.v.K., S.S., S.O.v.d.W., M.L. and N.H.M. contributed to quality control of data and algorithms. E.t.V., S.S., J.J.v.K., M.G.H.v.O., N.H.M, M.A.G.S., H.W.M.v.L. and S.O.v.d.W. contributed to data analysis and interpretation. E.t.V., J.J.v.K., S.S. and M.L. contributed to statistical analysis. E.t.V., S.S., J.J.v.K., M.G.H.v.O., N.H.M., M.A.G.S., H.W.M.v.L. and S.O.v.d.W. contributed to manuscript preparation. E.t.V., S.S., J.J.v.K., M.G.H.v.O., N.H.M., M.A.G.S., H.W.M.v.L. and S.O.v.d.W. contributed to manuscript editing. M.G.H.v.O., H.W.M.v.L. and M.A.G.S. contributed to manuscript review. All authors gave the final approval for submission of the manuscript.

Funding

This project is supported by a grant of the Dutch Cancer Society (KWF), grant number UVA 2014-7000.

Conflict of interest statement

Dr. Nadia Haj Mohammad has served as a consultant for Celgene and BMS. Dr. Martijn G. H. van Oijen has received unrestricted research grants from Bayer, Lilly, Merck Serono and Roche. Prof. Dr. Hanneke W. M. van Laarhoven has served as a consultant for Philips, Celgene, Lilly and Nordic and has received unrestricted research funding from Philips, Bayer, BMS, Celgene, Lilly, Merck Serono, MSD, Nordic and Roche. The other authors have nothing to declare.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejca.2018.07.132.

References

[1] Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA Oncol 2017;3(4):524–48.

[2] Ter Veer E, Haj Mohammad N, van Valkenhoef G, Ngai LL, Mali RMA, Anderegg MC, et al. The efficacy and safety of first-line chemotherapy in advanced esophagogastric cancer: a network meta-analysis. J Natl Cancer Inst 2016;108(10).

[3] Ter Veer E, Haj Mohammad N, van Valkenhoef G, Ngai LL, Mali RM, van Oijen MG, et al. Second- and third-line systemic therapy in patients with advanced esophagogastric cancer: a systematic review of the literature. Cancer Metastasis Rev 2016;35(3):439–56.

[4] Wagner AD, Syn NL, Moehler M, Grothe W, Yong WP, Tai BC, et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev 2017;8, Cd004064.

[5] Clark GM. Prognostic factors versus predictive factors: examples from a clinical trial of erlotinib. Mol Oncol 2008;1(4):406–12.

[6] Italiano A. Prognostic or predictive? It's time to get back to definitions! J Clin Oncol 2011;29(35):4718. author reply 4718-9.

[7] Edge S, Byrd D, Compton C, Fritz A, Greene F, Trotti A. AJCC cancer staging manual. 7th ed. Springer; 2010.

[8] Chau I, Norman AR, Cunningham D, Waters JS, Oates J, Ross PJ. Multivariate prognostic factor analysis in locally advanced and metastatic esophago-gastric cancer – pooled analysis from three multicenter, randomized, controlled trials using individual patient data. J Clin Oncol 2004;22(12):2395–403.

[9] Custodio A, Carmona-Bayonas A, Jimenez-Fonseca P, Sanchez ML, Viudez A, Hernandez R, et al. Nomogram-based prediction of survival in patients with advanced oesophagogastric adenocarcinoma receiving first-line chemotherapy: a multicenter prospective study in the era of trastuzumab. Br J Cancer 2017;116(12):1526–35.

[10] Kanagavel D, Pokataev IA, Fedyanin MY, Tryakin AA, Bazin IS, Narimanov MN, et al. A prognostic model in patients treated for metastatic gastric cancer with second-line chemotherapy. Ann Oncol 2010;21(9):1779–85.

[11] Koo DH, Ryoo BY, Kim HJ, Ryu MH, Lee SS, Moon JH, et al. A prognostic model in patients who receive chemotherapy for metastatic or recurrent gastric cancer: validation and comparison with previous models. Canc Chemother Pharmacol 2011;68(4):913–21.

[12] Lee J, Lim T, Uhm JE, Park KW, Park SH, Lee SC, et al. Prognostic model to predict survival following first-line chemotherapy in patients with metastatic gastric adenocarcinoma. Ann Oncol 2007;18(5):886–91.

[13] 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.

[14] Yamada Y, Boku N, Nishina T, Yamaguchi K, Denda T, Tsuji A, et al. Impact of excision repair cross-complementing gene 1 (ERCC1) on the outcomes of patients with advanced gastric cancer: correlative study in Japan Clinical Oncology Group Trial JCOG9912. Ann Oncol 2013;24(10):2560–5.

[15] Van Cutsem E, De Haas S, Kang YK, Ohtsu A, Tebbutt NC, Xu JM, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a biomarker evaluation from the AVAGAST randomized phase III trial. J Clin Oncol 2012;30(17):2119–27.

[16] Tsuburaya A, Sugimoto N, Imamura H, Nishikawa K, Imamoto H, Tsujinaka T, et al. Molecular biomarker study in a randomised phase III trial of irinotecan plus S-1 versus S-1 for advanced gastric cancer (GC0301/TOP-002). Clin Oncol (R Coll Radiol) 2016;28(8):e45–51.

[17] Trumper M, Ross PJ, Cunningham D, Norman AR, Hawkins R, Seymour M, et al. Efficacy and tolerability of chemotherapy in elderly patients with advanced oesophago-gastric cancer: a pooled analysis of three clinical trials. Eur J Cancer 2006;42(7): 827–34.

[18] Takahari D, Boku N, Mizusawa J, Takashima A, Yamada Y, Yoshino T, et al. Determination of prognostic factors in Japanese patients with advanced gastric cancer using the data from a randomized controlled trial, Japan clinical oncology group 9912. Oncologist 2014;19(4):358–66.

[19] 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.

[20] Okines AFC, Norman AR, McCloud P, Kang YK, Cunningham D. Meta-analysis of the REAL-2 and ML17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. Ann Oncol 2009;20(9):1529–34.

[21] 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. Int J Cancer 2010;126(1):162–70.

[22] Hacker UT, Escalona-Espinosa L, Consalvo N, Goede V, Schiffmann L, Scherer SJ, et al. Evaluation of Angiopoietin-2 as a biomarker in gastric cancer: results from the randomised phase III AVAGAST trial. Br J Cancer 2016;114(8):855–62.

[23] Grenader T, Waddell T, Peckitt C, Oates J, Starling N, Cunningham D, et al. Prognostic value of neutrophil-to-lymphocyte ratio in advanced oesophago-gastric cancer: exploratory analysis of the REAL-2 trial. Ann Oncol 2016;27(4):687–92.

[24] Chau I, Ashley S, Cunningham D. Validation of the Royal Marsden hospital prognostic index in advanced esophagogastric cancer using individual patient data from the REAL 2 study. J Clin Oncol 2009;27(19):e3–4.

[25] 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-naive patients with advanced gastric cancer. Ann Oncol 2015;26(1):141–8.

[26] 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. J Clin Oncol 1997; 15(1):261–7.

[27] Wang X, Wang ML, Zhou LY, Lu XY, Yang JF, Yu HG. Randomized phase II study comparing paclitaxel with S-1 vs. S-1 as first-line treatment in patients with advanced gastric cancer. Clin Transl Oncol 2013;15(10):836–42.

[28] Wang J, Xu R, Li J, Bai Y, Liu T, Jiao S, 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.

[29] Waddell T, Chau I, Cunningham D, Gonzalez D, Frances A, Okines C, et al. 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 Oncol 2013;14(6):481–9.

[30] 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. Ann Oncol 2015;26(1): 149–56.

[31] Tebbutt N, 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. Ann Oncol 2002:1568–75.

[32] 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). Jpn J Clin Oncol 2013:972–80.

[33] 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. J Clin Oncol 2002:1996–2004.

[34] 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. J Clin Oncol 2011;29(30): 3968–76.

[35] 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 2011:72–80.

[36] Moehler M, Eimermacher A, Siebler J, Hohler T, Wein A, Menges M, et al. Randomised phase II evaluation of irinotecan plus high-dose 5-fluorouracil and leucovorin (ILF) vs 5-fluorouracil, leucovorin, and etoposide (ELF) in untreated metastatic gastric cancer. Br J Canc 2005;92(12):2122–8.

[37] Lu Y, Liu Z, 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. J Chemother (Florence, Italy) 2014:159–64.

[38] 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 Oncol 2013;14(6):490–9.

[39] Lee J, Kang Y, Kang H, Lee K, Zang D, Ryoo B, et al. A randomised multicentre phase II trial of capecitabine vs S-1 as first-line treatment in elderly patients with metastatic or recurrent unresectable gastric cancer. Br J Cancer 2008:584–90.

[40] Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 2008;9(3):215–21.

[41] 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). J Canc Res Clin Oncol 2014;140(2):319–28.

[42] 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. Canc Chemother Pharmacol 2014;73(1):163–9.
[43] Kim N, Park Y, Heo D, Suh C, Kim S, Park K, et al. A phase III randomized study of 5-fluorouracil and cisplatin versus 5-fluorouracil, doxorubicin, and mitomycin C versus 5-fluorouracil alone in the treatment of advanced gastric cancer. Cancer 1993:3813–8.
[44] 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. Ann Oncol 2009;20(4):666–73.
[45] 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;117(10):2050–7.
[46] 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 Oncol 2014;15(9):1007–18.
[47] Icli F, Celik I, Aykan F, Uner A, Demirkazik A, Ozet A, et al. A randomized phase III trial of etoposide, epirubicin, and cisplatin versus 5-fluorouracil, epirubicin, and cisplatin in the treatment of patients with advanced gastric carcinoma. Cancer 1998;83(12):2475–80.
[48] Hironaka S, Sugimoto N, Yamaguchi K, Moriwaki T, Komatsu Y, Nishina T, et al. S-1 plus leucovorin versus S-1 plus leucovorin and oxaliplatin versus S-1 plus cisplatin in patients with advanced gastric cancer: a randomised, multicentre, open-label, phase 2 trial. Lancet Oncol 2016;17(1):99–108.
[49] 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. J Clin Oncol 2016;34(5):443–51.
[50] Fujitani K, Yang HK, Mizusawa J, Kim YW, Terashima M, Han SU, et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. Lancet Oncol 2016;17(3):309–18.
[51] 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 2015:e958.
[52] Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008:36–46.
[53] Cullinan SA, Moertel CG, Fleming TR. A comparison of three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma. Fluorouracil vs fluorouracil and doxorubicin vs fluorouracil, doxorubicin, and mitomycin. J Am Med Assoc 1985;253(14):2061–7.
[54] 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 Oncol 2009;10(11):1063–9.
[55] 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. J Clin Oncol 2010;28(9):1547–53.
[56] 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. Ann Oncol 2017;28(9):2142–8.
[57] Janowitz T, Thuss-Patience P, Marshall A, Kang JH, Connell C, Cook N, et al. Chemotherapy vs supportive care alone for relapsed gastric, gastroesophageal junction, and oesophageal adenocarcinoma: a meta-analysis of patient-level data. Br J Cancer 2016;114(4):381–7.
[58] Wilke H, Muro K, Cutsem E, Oh S, 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 Oncol 2014:1224–35.
[59] Thuss-Patience PC, Kretzschmar A, Bichev D, Deist T, Hinke A, Breithaupt K, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer - a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer 2011;47(15):2306–14.
[60] Tanabe K, Fujii M, Nishikawa K, Kunisaki C, Tsuji A, Matsuhashi N, et al. Phase II/III study of second-line chemotherapy comparing irinotecan-alone with S-1 plus irinotecan in advanced gastric cancer refractory to first-line treatment with S-1 (JACCRO GC-05). Ann Oncol 2015;26(9):1916–22.
[61] Satoh T, Doi T, Ohtsu A, Tsuji A, Omuro Y, Mukaiyama A, et al. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN - a randomized, phase III study. J Clin Oncol 2014;32(19):2039–49.
[62] Pavlakis N, Sjoquist KM, Martin AJ, Tsobanis E, Yip S, Kang YK, et al. Regorafenib for the treatment of advanced gastric cancer (INTEGRATE): a multinational placebo-controlled phase II trial. J Clin Oncol 2016;34(23):2728–35.
[63] 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. J Clin Oncol 2013;31(31):3935–43.
[64] Nishikawa K, Imamura H, Kawase T, Gotoh M, Kimura Y, Ueda S, et al. A randomized phase II factorial design trial of CPT-11 versus PTX versus each combination with S-1 in patients with advanced gastric cancer refractory to S-1: final results of OGSG0701. J Clin Oncol 20 January 2015;33(3_suppl). https://doi.org/10.1200/jco.2015.33.3_suppl.117. 117–117.
[65] Nishikawa K, Fujitani K, Inagaki H, Akamaru Y, Tokunaga S, Takagi M, et al. Randomised phase III trial of second-line irinotecan plus cisplatin versus irinotecan alone in patients with advanced gastric cancer refractory to S-1 monotherapy: TRICS trial. Eur J Cancer 2015;51(7):808–16.
[66] Nakanishi K, Kobayashi D, Mochizuki Y, Ishigure K, Ito S, Kojima H, et al. Phase II multi-institutional prospective randomized trial comparing S-1 plus paclitaxel with paclitaxel alone as second-line chemotherapy in S-1 pretreated gastric cancer (CCOG0701). Int J Clin Oncol 2016;21(3):557–65.
[67] Kang JH, Lee SI, Lim DH, Park KW, Oh SY, Kwon HC, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. J Clin Oncol 2012;30(13):1513–8.
[68] Hironaka S, Ueda S, Yasui H, Nishina T, Tsuda M, Tsumura T, et al. 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. J Clin Oncol 2013;31(35):4438–44.
[69] 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.

[70] Ford H, Marshall A, Bridgewater J, Janowitz T, Coxon F, Wadsley J, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. Lancet Oncol 2014:78–86.

[71] van den Boorn HG, Engelhardt EG, van Kleef J, Sprangers MAG, van Oijen MGH, Abu-Hanna A, et al. Prediction models for patients with esophageal or gastric cancer: a systematic review and meta-analysis. PLoS One 2018;13(2), e0192310.

[72] Xue P, Kanai M, Mori Y, Nishimura T, Uza N, Kodama Y, et al. Neutrophil-to-lymphocyte ratio for predicting palliative chemotherapy outcomes in advanced pancreatic cancer patients. Cancer Med 2014;3(2):406–15.

[73] Kim JH, Lee JY, Kim HK, Lee JW, Jung SG, Jung K, et al. Prognostic significance of the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in patients with stage III and IV colorectal cancer. World J Gastroenterol 2017;23(3):505–15.

[74] Coebergh van den Braak RRJ, van Rijssen LB, van Kleef JJ, Vink GR, Berbee M, van Berge Henegouwen MI, et al. Nationwide comprehensive gastro-intestinal cancer cohorts: the 3P initiative. Acta Oncol 2017:1–8.

[75] Ajani J, Abramov M, Bondar V, Bondarenko I, Shparyk Y, Gorbunova V, et al. Untreated metastatic diffuse gastric adenocarcinoma (DGAC): randomized phase III study of S-1 and cisplatin vs. 5-FU and cisplatin (the DIGEST trial). J Clin Oncol 20 May 2015;33(15_suppl). https://doi.org/10.1200/jco.2015.33.15_suppl.4015. 4015–4015.

[76] Cunningham D, Tebbutt N, Davidenko I, Murad A, Al-Batran S-E, Ilson D, et al. Phase III, randomized, double-blind, multicenter, placebo (P)-controlled trial of rilotumumab (R) plus epirubicin, cisplatin and capecitabine (ECX) as first-line therapy in patients (pts) with advanced MET-positive (pos) gastric or gastroesophageal junction (G/GEJ) cancer: RILOMET-1 study. J Clin Oncol 20 May 2015;33(15_suppl). https://doi.org/10.1200/jco.2015.33.15_suppl.4000. 4000–4000.

[77] 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. Oncol 2016;21(9): 1085–90.

[78] 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 Oncol 2017;3(5):620–7.

[79] Petrelli F, Zaniboni A, Coinu A, Cabiddu M, Ghilardi M, Sgroi G, et al. Cisplatin or not in advanced gastric cancer: a systematic review and meta-analysis. PLoS One 2013;8(12), e83022.

[80] Huang J, Zhao Y, Xu Y, Zhu Y, Huang J, Liu Y, et al. Comparative effectiveness and safety between oxaliplatin-based and cisplatin-based therapy in advanced gastric cancer: a meta-analysis of randomized controlled trials. Oncotarget 2016;7(23): 34824–31.

[81] 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. J Clin Oncol 2008;26(9): 1435–42.

[82] Chen WW, Wang F, Xu RH. Platinum-based versus non-platinum-based chemotherapy as first line treatment of inoperable, advanced gastric adenocarcinoma: a meta-analysis. PLoS One 2013;8(7), e68974.

[83] Noordzij M, Dekker FW, Zoccali C, Jager KJ. Study designs in clinical research. Nephron Clin Pract 2009;113:c218–21.