Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

sowie

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2016-B-017 Ramucirumab

Stand: März 2016

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Ramucirumab zur Behandlung des fortgeschrittenen Magenkrebses	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet"*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	▪ chirurgische Resektion
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse nach § 35a SGB V: ▪ Tegafur/Gimeracil/Oteracil vom 20.12.2012 ▪ Ramucirumab vom 16.07.2015
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu prüfendes Arzneimittel:	
Ramucirumab L01XC21 Cyramza®	Cyramza ist in Kombination mit Paclitaxel indiziert zur Behandlung von erwachsenen Patienten mit einem fortgeschrittenen Adenokarzinom des Magens oder des gastroösophagealen Übergangs mit Tumorprogress nach vorausgegangener Platin- und Fluoropyrimidin-haltiger Chemotherapie. Cyramza ist als Monotherapie indiziert zur Behandlung von erwachsenen Patienten mit einem fortgeschrittenen Adenokarzinom des Magens oder des gastroösophagealen Übergangs mit Tumorprogress nach vorausgegangener Platin- oder Fluoropyrimidin-haltiger Chemotherapie, wenn diese Patienten für eine Kombinationstherapie mit Paclitaxel nicht geeignet sind.
Tegafur/Gimeracil/ Oteracil L01BC53 Teysuno®	Teysuno ist für die Behandlung von fortgeschrittenem Magenkrebs bei Erwachsenen indiziert bei Gabe in Kombination mit Cisplatin.
Capecitabin L01BC06 Xeloda®, oral	Xeloda ist in Kombination mit einem platinhaltigen Anwendungsschema als First-line-Therapie des fortgeschrittenen Magenkarzinoms indiziert.
5-Fluorouracil L01BC02 5-FU medac®, i.v.	Fortgeschrittenes Magenkarzinom. 5-Fluorouracil wird in der Monochemotherapie sowie als Bestandteil einer Polychemotherapie angewendet.
Doxorubicin L01DB01 Adrimedac®, i.v.	Fortgeschrittenes Magenkarzinom. Doxorubicin wird in der Monochemotherapie bei Weichteilsarkomen sowie als Bestandteil einer Kombinationstherapie in etablierten Therapie-Protokollen angewendet.
Epirubicin L01DB03 Farmorubicin®, i.v.	Fortgeschrittenes Magenkarzinom.
Mitomycin L01DC03 Mito-extra®	Mitomycin wird in der palliativen Tumortherapie eingesetzt. Bei intravenöser Gabe ist es in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei folgenden metastasierenden Tumoren wirksam: […] fortgeschrittenes Magenkarzinom.
Carmustin L01AD01 Carmubris®	Carmubris ist zur unterstützenden Behandlung chirurgischer Operationen und Bestrahlungen, oder als Kombinationsbehandlung mit anderen Substanzen bei folgenden Gewebsneubildungen angezeigt: […] Maligne Tumoren im Gastrointestinalbereich: nur bei fortgeschrittener Erkrankung, wenn andere das Zellwachstum hemmende Mittel versagt haben.

Docetaxel L01CD02 (generisch)	Docetaxel ist in Kombination mit Cisplatin und 5-Fluorouracil angezeigt zur Behandlung von Patienten mit metastasiertem Adenokarzinom des Magens, einschließlich Adenokarzinom der gastroösophagealen Übergangszone, die keine vorherige Chemotherapie gegen ihre metastasierte Erkrankung erhalten haben. *(FI Docetaxel-ratiopharm® 20 mg/ml Konzentrat zur Herstellung einer Infusionslösung, 05-2013)*

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Indikation für die Recherche:

- in Kombination mit Paclitaxel indiziert zur Behandlung von erwachsenen Patienten mit einem fortgeschrittenen Adenokarzinom des Magens oder des gastroösophagealen Übergangs mit Tumorprogress nach vorausgegangener Platin- und Fluoropyrimidin-haltiger Chemotherapie (im nachfolgenden Text wird abkürzend von Magenkrebs gesprochen)
- als Monotherapie indiziert zur Behandlung von erwachsenen Patienten mit einem fortgeschrittenen Adenokarzinom des Magens oder des gastroösophagealen Übergangs mit Tumorprogress nach vorausgegangener Platin- oder Fluoropyrimidin-haltiger Chemotherapie, wenn diese Patienten für eine Kombinationstherapie mit Paclitaxel nicht geeignet sind (im nachfolgenden Text wird abkürzend von Magenkrebs gesprochen)

Berücksichtigte Wirkstoffe/Therapien:

siehe Tabellen „I. Zweckmäßige Vergleichstherapie“ und „II. Zugelassene Arzneimittel im Anwendungsgebiet.“

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation „fortgeschrittenes Adenokarzinom des Magens oder des gastroösophagealen Übergangs“ durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 24.02.2016 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, DAHTA, G-BA, IQWiG, NGC, TRIP, WHO. Aufgrund der onkologischen Indikation wurde zusätzlich in folgenden Datenbanken bzw. Internetseiten folgende Organisationen gesucht: CCO, ESMO, NCCN, NCI. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien (z.B. NICE). Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 688 Quellen, die anschließend in einem zweistufigen Screeningverfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 17 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen

5-FU	5-fluorouracil
AGC	advanced gastric cancer
Anti-EGFR	epidermal growth factor receptor
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
BSC	Best Supportive Care
CBCT	capecitabine based chemotherapy
CBR	Clinical benefit rate
CCO	Cancer Care Ontario
CI	Confidence Interval
CR	Completes response
DAHTA	Deutsche Agentur für Health Technology Assessment
ESMO	European Society for Medical Oncology
FOLFOX	5-fluorouracil/leucovorin plus oxaliplatin
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
HER2	human epidermal growth factor receptor 2
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
NCCN	National Comprehensive Cancer Network
NCI	U.S. National Cancer Institute
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
ORR	Overall response rate
OS	Overall survival
PD	progressive disease
PFS	Progression-free survival
PFS	Progression Free Survival

PR	Partial response
PS	Performance Status
PTX	paclitaxel
RR	Relative Risk
SBCT	S-1 based chemotherapy
ToGA	Trastuzumab for Gastric Cancer
TRIP	Turn Research into Practice Database
TTF	Time to Treatment Failure
TTP	time to progression
WHO	World Health Organization
XELOX	capecitabine plus oxaliplatin

IQWiG Berichte/ G-BA Beschlüsse

G-BA, 2012 [4]. Zusammenfassende Dokumentation über die Änderung der Arzneimittel -Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Tegafur, Gimeracil, Oteracil.	*Zugelassenenes Anwendungsgebiet:* Teysuno® ist für die Behandlung von fortgeschrittenem Magenkrebs bei Erwachsenen indiziert bei Gabe in Kombination mit Cisplatin. *Zweckmäßige Vergleichstherapie:* Die zweckmäßige Vergleichstherapie ist die Zweifachkombination von Cisplatin mit 5-Fluorouracil oder Capecitabin. *Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der Zweifach-kombination von Cisplatin mit 5-Fluorouracil oder Capecitabin:* Der Zusatznutzen im Verhältnis zur zweckmäßigen Vergleichstherapie gilt als nicht belegt.

Cochrane Reviews

Es konnten keine aktuellen Cochrane Reviews zum relevanten Anwendungsgebiet identifiziert werden

Systematische Reviews

Liu GF et al., 2014 [8]. S-1-based combination therapy vs S-1 monotherapy in advanced gastric cancer: a meta-analysis.	1. Fragestellung To assess the efficacy and safety of combination therapy based on S-1, a novel oral fluoropyrimidine, vs S-1 monotherapy in advanced gastric cancer (AGC).
	2. Methodik Population: patients with advanced gastric cancer Vergleich: combination therapy such as CDDP, docetaxel, paclitaxel and irinotecan based on S-1 (a novel oral fluoropyrimidine) vs. S-1 monotherapy Endpunkte: overall survival (OS), progression-free survival (PFS), overall response rate (ORR) and grade 3-4 adverse events Suchzeitraum (Aktualität der Recherche): bis 03/2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 4 studies (n=790) Qualitätsbewertung der Studien: The review team used a standardized form adapted from the Risk of Bias Criteria of the Cochrane Effective Practice and Organisation of Care (EPOC) Group to systematically identify study quality The quality of included studies was assessed by EPOC criteria, with the scores ranging from 6-7.
	3. Ergebnisdarstellung *Overall survival (3 studies)* • S-1-based combination therapy significantly improved OS

	(HR=0.77, 95%CI: 0.66-0.91, P = 0.002) *Progression-free survival (2 studies)* • S-1-based combination therapy significantly improved PFS (HR = 0.58, 95%CI: 0.46-0.72, P = 0.000) *Overall response rate (4 studies)* • S-1-based combination therapy significantly improved ORR (OR = 2.23, 95%CI: 1.54-3.21, P = 0.000) *Safety (4 studies)* • Lower incidence of grade 3-4 leucopenia (OR = 4.06, 95%CI: 2.11-7.81), neutropenia (OR = 3.94, 95%CI: 2.1-7.81) and diarrhea (OR = 2.41, 95%CI: 1.31-4.44) was observed in patients with S-1 monotherapy.
	4. Fazit der Autoren *S-1-based combination therapy is superior to S-1 monotherapy in terms of OS, PFS and ORR. S-1 monotherapy is associated with less toxicity.*
Chen XL et al., 2013 [2]. Docetaxel, Cisplatin and Fluorouracil (DCF) Regimen Compared with Non-Taxane-Containing Palliative Chemotherapy for Gastric Carcinoma: A Systematic Review and Meta- Analysis.	1. Fragestellung Present systematic review and meta-analysis were done to evaluate the survival outcomes and toxicities of DCF for palliatively resected, unresectable, recurrent or metastatic gastric carcinoma, compared with those of non-taxane-containing regimens.
	2. Methodik Population: patients diagnosed with palliatively resected, unresectable, recurrent or metastatic gastric carcinoma Vergleich: Docetaxel, Cisplatin and Fluorouracil (DCF) Regimen vs. Non-Taxane-Containing Palliative chemotherapy Endpunkte: response, survival outcomes, toxities Suchzeitraum (Aktualität der Recherche): 07/2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): 12 (n=1089 (549 in DCF and 540 in control)) Qualitätsbewertung der Studien: Jadad scale
	3. Ergebnisdarstellung *Response* • The overall response rate (ORR) combined of CR and PR, was 44.4% (244/549) vs 30.6% (165/540) in DCF and non-taxane-containing regimens, respectively. • significantly better ORR of DCF regimen (RR =1.45, 95% CI 1.24–1.69, p<0.00001) *Survival outcomes* • Significant improvement of 2-year OS rate was found in DCF regimen (RR = 2.03, p = 0.006), but not of 1-year OS rate (RR = 1.22, p = 0.08). • MST was significantly prolonged by DCF regimen (p = 0.039), but not median TTP (p = 0.054). • Both 1-year OS rate and median TTP had a trend of prolongation

	by DCF regimen. • Chemotherapy-related mortality was comparable (RR = 1.23, p = 0.49) in both regimens. *Toxities* • In grade I-IV toxicities, DCF regimen showed a major raise of febrile neutropenia (RR = 2.33, p<0.0001) and minor raises of leucopenia (RR = 1.25, p<0.00001), neutropenia (RR = 1.19, p<0.00001), and diarrhea (RR = 1.59, p<0.00001), while in other toxicities there were no significant differences.
	4. Fazit der Autoren *DCF regimen has better response than non-taxane containing regimen and could potentially improve the survival outcomes. The chemotherapy-related toxicity of DCF regimen is acceptable to some extent.*
Kim HS et al., 2013 [7]. Second-line chemotherapy versus supportive cancer treatment in advanced gastric cancer: a meta-analysis.	1. Fragestellung We conducted a meta-analysis of these trials and investigated whether second-line chemotherapy was more effective than best supportive care.
	2. Methodik Population: patients with advanced gastric cancer Vergleich: second-line chemotherapy vs. best supportive care Endpunkte: overall survival Suchzeitraum (Aktualität der Recherche): 03/2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 3 (n= 410 (150 received docetaxel chemotherapy, and 81 received irinotecan chemotherapy)) Qualitätsbewertung der Studien: Two review authors extracted data from each included study using an agreed-upon form and assessed the risk of bias.
	3. Ergebnisdarstellung *Overall survival* • Overall survival was compared for 238 patients who were assigned to irinotecan or docetaxel as salvage chemotherapy with 172 patients who received supportive care. • A significant reduction in the risk of death (HR = 0.64, 95% CI 0.52–0.79, P < 0.0001) was observed with salvage chemotherapy (no heterogeneity) • The HR was 0.71 (95% CI 0.56–0.90, P = 0.004) for docetaxel • no significant differences in treatment effect according to the chemotherapeutic agent
	4. Fazit der Autoren *This meta-analysis demonstrated evidence to support second-line chemotherapy in advanced gastric cancer.* 5. Hinweise durch FB Med • Irinotecan keine Zulassung in Deutschland
Ye JX et al., 2014 [17].	1. Fragestellung

Effectiveness and safety profile of S-1-based chemotherapy compared with capecitabine-based chemotherapy for advanced gastric and colorectal cancer: A meta-analysis.	The aim of the present analysis was to compare the efficacy and safety profile of S-1-based chemotherapy (SBCT) versus capecitabine-based chemotherapy (CBCT) for advanced gastric cancer (AGC) and advanced colorectal cancer (ACRC).
	2. Methodik Population: patients with advanced gastric cancer (AGC) and advanced colorectal cancer (ACRC). Vergleich: S-1-based chemotherapy (SBCT) versus capecitabine-based chemotherapy (CBCT) Endpunkte: overall survival, time to progession, overall response rate Suchzeitraum (Aktualität der Recherche): 08/2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 11 (n=k.A.) Qualitätsbewertung der Studien: According to the Cochrane Collaboration's tool for assessing risk of bias of RCTs.
	3. Ergebnisdarstellung Overall survival: [HR, 0.98; 95% CI, 0.85-1.12] Time to progression: [HR, 0.95; 95% CI, 0.80-1.12] Overall response rate: [OR, 1.06; 95% CI, 0.72-1.55] Safety: no statistically significant difference was observed in the incidence of grade 3-4 anemia, thrombocytopenia, leucopenia, neutropenia, diarrhea, stomatitis or nausea/vomiting.
	4. Fazit der Autoren *The SBCT treatment exhibited similar efficacy and an approximately equivalent safety profile compared with the CBCT treatment and was an alternative to CBCT for patients with AGC or ACRC; however, further investigation is required to provide confirmation.* 5. Hinweise durch FB Med • es wurden nur die Teilergebnisse dargestellt, welche die Patienten mit fortgeschrittenen Magenkrebs betrafen
Iacovelli R et al., 2014 [5]. Chemotherapy or targeted therapy as second-line treatment of advanced gastric cancer. A systematic review and meta-analysis of published studies	1. Fragestellung The aim of this meta-analysis was to estimate the effect of second-line treatment of GC and to analyze the differential role of chemotherapy or targeted agents. We also investigated if different strategies have the same role in patients with different performance status, with the intent to find the best strategy for second-line treatment of this tumor.
	2. Methodik Population: patients with advanced gastric cancer Intervention: chemotherapy or targeted therapy as single agents (second-line of therapy after first-line platinum- and fluoropyrimidine-based combination therapy)

	Komparator: placebo or the best supportive care (BSC) Endpunkt: k.A. Suchzeitraum: bis Februar 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): 5/1 424 Qualitätsbewertung der Studien: Jadad Score Heterogenität: k.A. Publication bias: k.A.
	3. Ergebnisdarstellung • 4 Studien zu nicht zugelassenen Wirkstoffen (Docetaxel, Irinotecan, Everolimus), 1 Studie zu Ramucirumab eingeschlossen (nur Ergebnisse letzterer hier dargestellt) **Fuchs CS, et al. 2014** (Ramucirumab, n = 238, ECOG 0 = 28%, ECOG 1 = 72%, ECOG ≥ 2 = 0, OS = 5,2 month vs. Pbo, n = 117, ECOG 0 = 31%, ECOG 1 = 85%, ECOG ≥ 2 = 1%, OS = 3,8 month): HR 0.78 (0.60–1.00), Jadad score: 5 <u>Survival by type of therapy</u> (chemotherapy vs. anti-VEGFR vs. mTORi) • chemotherapy able to decrease the risk of death by 27% (HR= 0.73; 95% CI, 0.58–0.96; posterior probability of HR≥1: 0.00942) • ramucirumab able to decrease the risk of death by 22% (HR= 0.78; 95% CI, 0.60–1.00) • no significant effect on OS seen with everolimus (HR =0.90; 95% CI, 0.75–1.08) <u>Survival by performance status</u> • 461 patients with ECOG 0 had greater benefit when treated with chemotherapy over BSC - reduction of risk of death by 43% (HR= 0.57; 95% CI, 0.36–0.91; posterior probability of HR≥1: 0.0092) • in this group of patients, no benefit was found for ramucirumab or everolimus over BSC • indirect comparison found a better outcome for patients treated with chemotherapy
	4. Fazit der Autoren *This analysis reports that active and available therapies are able to prolong survival in patients with advanced gastric cancer with a different outcome based on initial patient's performance status. New trials based on a better patient stratification are awaited.* 5. Hinweise durch FB Med • Funding: The authors received no specific funding for this work. • Competing Interests: The authors have declared that no

	competing interests exist.
Ma Y et al., 2012 [10]. Capecitabine for the treatment for advanced gastric cancer: efficacy, safety and ethnicity	1. Fragestellung We performed a focused analysis of capecitabine-based chemotherapy for the treatment for AGC as compared to 5-FUbased regimens, aiming to compare the efficacy and safety of the two regimens for both Caucasian and Asian subjects, through a meta-analysis of the available trial evidence.
	2. Methodik Population: patients with diagnosed AGC Intervention: capecitabine-based chemotherapy Komparator: infusional 5-FU-based chemotherapy Endpunkt: efficacy and safety Suchzeitraum: to September 20, 2010 Anzahl eingeschlossene Studien/Patienten (Gesamt): 18/2.175 Qualitätsbewertung der Studien: Jadad scale Heterogenitätsanalysen: The Q-test (Mantel–Haenszel chi-squared test) was used to examine the homogeneity of outcomes from the trials to statistically establish the validity of methods for combining the results of various trials using either the fixed or random effect models. Publication bias: not mentioned
	3. Ergebnisdarstellung • characteristics of the 18 included trials presented in Table 1 and 2 (siehe Anlage dieser Synopse). • Capecitabine-based chemotherapy for AGC prolonged the overall survival (OS; 10,7 months vs. 9,5 months, P = 0,03) and enhanced the response rate (RR; OR = 1,32; 95 CI, 1,11–1,57; P = 0,002) over 5-FU-based chemotherapy. • Similar trends were observed in both Caucasian and Asian patients. Capecitabine-based regimens were associated with reduced incidence rates of grade 3 or grade 4 leukopenia (OR = 0,42; P = 0,005), stomatitis (OR = 0,43; P = 0,004) and nausea and vomiting (OR = 0,60; P = 0,002) compared with 5-FU-based treatment. • Incidence of haematological toxicity such as anaemia (OR = 0,88; P = 0,53), thrombocytopenia (OR =0,58; P = 0,06), neutropenia (OR = 1,03; P = 0,78) and treatment-related mortality was similar between capecitabine- and 5-FU-based treatments. • Higher frequency of grade 3 or grade 4 hand-foot syndrome (HFS; OR = 2,45; P = 0,0007) was observed in capecitabine-based

	combination therapies. • Asian patients with AGC receiving capecitabine-based combination therapies showed less frequent occurrence of grade 3 or grade 4 gastrointestinal toxicity including nausea and vomiting (OR = 0,24; P = 0,0002) and stomatitis (OR = 0,33; P = 0,02) than those receiving 5-FU-based regimens. • These differences in GI toxicity between treatment regimens were not significant in Caucasian subjects. • No significant difference was found for the occurrence of anaemia (Caucasian
	4. Fazit der Autoren *Capecitabine-based chemotherapy shows prolonged OS and enhanced RR compared to traditional 5-FU-based treatments and therefore should be considered as one of the first choices for treatment for AGC, especially for Asian patients. Asian patients also showed less grade 3 or grade 4 gastrointestinal toxicity with the capecitabine-based regimens.* 5. Hinweise durch FB Med • The study was supported by The Leading Academic Discipline Project of The Shanghai Municipal Education Committee (J50208) and The Shanghai Municipal Natural Science Foundation (No. 09ZR1417900). • The authors declare that they have no conflict of interest • PTEN Expressionslevel nicht erwähnt
Petrelli F et al., 2013 [14]. Cisplatin or Not in Advanced Gastric Cancer: A Systematic Review and Meta- Analysis	1. Fragestellung We have therefore performed a systematic review and metaanalysis of randomised phase II and III treatment trials that compared the efficacy of two- and three-drug regimens containing CDDP (control arms) with the same regimens in which modern agents were substituted for CDDP (experimental arms) in patients with advanced GC.
	2. Methodik Population: patients with histologically confirmed, advanced, recurrent, or metastatic adenocarcinoma of the stomach or gastrooesophageal junction; and if they compared (first-line) chemotherapy Intervention: new active cytotoxic agents instead of CDDP Komparator: CDDP-based combination chemotherapy Endpunkt: efficacy and safety Suchzeitraum: to February 16, 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 14/2 981

	Qualitätsbewertung der Studien: Jadad scale Heterogenitätsanalysen: Cochran Q test, with a predefined significance threshold of 0.1, was used to assess the statistical heterogeneity among the studies. The assumption of homogeneity was considered invalid for p values less than 0.1; in this case, summary estimates were reported from the random effect models. Sources of heterogeneity were determined by subgroup stratification analysis based on study characteristics such as ethnicity, type of study (phase II or phase III), and chemotherapy regimen (CDDP versus oxaliplatin, CDDP versus not oxaliplatin, CDDP versus CPT-11, and CDDP versus taxanes). Potential publication biases were evaluated using funnel plots for OS analysis
	3. Ergebnisdarstellung *OS:* Nine of the 14 trials reported OS data in the form of HRs or these ratios were calculated from the published data. In particular, data for computing HRs were extracted from Kaplan-Meier curves in three studies and from the number of events in each arm and the p value (a randomization ratio of one to one) in one study. Using a random effects model, we found that, overall, CDDP-free chemotherapy significantly improved OS compared with CDDP-containing chemotherapy (HR, 0.79; 95% CI, 0.68–0.92; p =0.003) with moderate heterogeneity among the studies (I2 = 50%, p =0.04). The results remained unchanged after the leave-one-out procedure. *Subgroup analysis:* Compared with the phase III trials, the phase II trials showed better RRs (OR, 1.46 versus 1.19), OS (HR, 0.65 versus 0.93), and PFS (HR, 0.68 versus 0.89).
	4. Fazit der Autoren *In conclusion, we found that CDDP-free combination chemotherapy, containing new active cytotoxic agents instead of CDDP, significantly enhances OS, PFS, and RR when compared with CDDP-based combination chemotherapy as first-line treatment of metastatic GC.* 5. Hinweise durch FB Med • These authors have no support or funding to report. • The authors have declared that no competing interests exist. • Cisplatin hat keine Zulassung für das Magenkarzinom, jedoch über andere Wirkstoffe (wie Capecitabine, Docetaxel, Trastuzumab) als Kombinationstherapie zugelassen • Nur 4 der 9 Studien für Metaanalyse zum OS untersuchten in DL zugelassene Wirkstoffkombinationen – Ergebnis vorsichtig zu bewerten.

Janowitz T et al., 2016 [6]. Chemotherapy vs supportive care alone for relapsed gastric, gastroesophageal junction, and oesophageal adenocarcinoma: a meta-analysis of patient-level data.	1. Fragestellung Second-line chemotherapy treatment of patients with relapsed gastric and oesophageal cancers in comparison with supportive care (SC) alone has been supported by recent phase 3 clinical trials, but a meta-analysis of patient-level data is lacking.
	2. Methodik Population: Patients with relapsed gastric and oesophageal cancers Intervention: Second-line chemotherapy (siehe Ergebnisdarstellung) Komparator: Supportive Care (SC) (siehe Ergebnisdarstellung) Endpunkt: OS (primärer Endpunkt); risk of death Suchzeitraum: We searched Medline, the Cochrane Central Register of Controlled Trials (CENTRAL), and the Web of Science for phase 3 clinical trials that compared second-line chemotherapy with SC alone for gastric and oesophageal cancers. A metaanalysis of the comprehensive patient-level data from the three identified trials was performed. Anzahl eingeschlossene Studien/Patienten (Gesamt): 3 trials fulfilled eligibility criteria for this meta-analysis Qualitätsbewertung der Studien: Clinical trials that had not published results in peerreviewed medical journals or were not randomised phase 3 trials were not included in this meta-analysis. There is a risk that such trials would have identified different effects on OS. Most smaller studies, retrospective analysis, case series, and case reports, however, indicate benefit of chemotherapy. Reports on such smaller studies had already resulted in use of second-line chemotherapy in patients with relapsed gastric and oesophageal adenocarcinoma, before the establishment of level 1 evidence of OS benefit by phase 3 clinical trials (Ford and Gounaris, 2015).
	3. Ergebnisdarstellung A total of 410 patients with gastric (n=301), gastroesophageal junction (n=76), or oesophageal (n=33) adenocarcinoma were identified. In all, 154 patients received single-agent docetaxel and 84 patients received single-agent irinotecan, each with SC. SC alone was given to 172 patients. Chemotherapy significantly reduced the risk of death (hazard ratio (HR)=0.63, 95% confidence interval (CI)=0.51–0.77, P<0.0001). This effect was observed for treatment with docetaxel (HR=0.71, 95% CI=0.56–0.89, P=0.003) and irinotecan (HR=0.49, 95% CI=0.36–0.67, P<0.001). Overall survival (OS) benefit was greatest for patients who progressed 3–6 months following first-line chemotherapy (HR=0.39, 95% CI=0.26–0.59, P<0.0001).

	Performance status (PS) 0–1 compared with PS 2 (HR=0.66, 95% CI=0.46–0.94, P=0.02), locally advanced disease compared with metastatic disease (HR=0.41, 95% CI=0.25–0.67, P=0.0004) and older age (HR=0.94 per 5 years, 95% CI=0.90–0.99, P=0.01) were significant predictors of improved OS. Progression of disease during first-line treatment (HR=1.24, 95% CI=0.96–1.59) or within the first 3 months of completion of first-line treatment (HR=1.42, 95% CI=1.09–1.83) were predictors of an increased risk of death compared with progression between 3 and 6 months (P=0.03).
	4. Fazit der Autoren *This meta-analysis of patient-level data confirms that second-line chemotherapy treatment results in significantly better OS compared with SC alone in patients with platinum and fluoropyrimidine refractory gastric and oesphageal adenocarcinoma. Health-related quality of life outcomes should be included in future trials in this setting.*
Liu H et al., 2014 [9]. The Efficacy and Toxicity of Paclitaxel Plus S-1 Compared With Paclitaxel Plus 5-Fu for Advanced Gastric Cancer *A PRISMA Systematic Review and Meta-analysis of Randomized Controlled Trials*	1. Fragestellung To compare oral S-1 and infusional 5-fluorouracil (5-FU) to determine which agent was more efficacious and less toxic in combination with PTX.
	2. Methodik Population: patients with advanced gastric cancer (AGC) Vergleich: PTX plus S-1 vs. PTX plus 5-FU Endpunkte: survival outcomes, response rates, and toxicities Suchzeitraum (Aktualität der Recherche): bis 11/2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): Three RCTs were eligible for analysis and 352 patients with nonresectable, palliative-resected, recurrent, or metastatic GC were included: 182 patients in PTX plus S-1 group and 170 patients in PTX plus 5-FU group. Qualitätsbewertung der Studien: The quantitative 5-point Jadad scale was used to assess the quality of included trials based on the report of the methods and results of the studies. We assessed for heterogeneity in summary effects using the Cochrane Q and the I2 test (with 95% CIs). We considered a P value <0.05 and I^2>50% to indicate significant heterogeneity.
	3. Ergebnisdarstellung • *Response:* All 3 studies assessing 268 participants who were randomized to receive PTX plus S-1 (n=142) or PTX plus 5-FU (n=126) provided the information on complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The ORR (combined CR and PR) was 46.5% (66/142) versus 33.3% (42/126) in the PTX plus S-1 and PTX plus 5-FU regimens,

	respectively. Meta-analysis showed that there was no significant difference between these 2 groups (RR=1.08, 95% CI:0.53–2.19, P=0.84). The DCR (combined of CR, PR, and SD) was 83.8% (119/142) versus 73.0% (92/126) in the PTX plus S-1 and PTX plus 5-FU regimens, respectively. Meta-analysis (RR=1.14, 95% CI: 1.00–1.30, P=0.04) showed that there was a significantly better DCR with the PTX plus S-1 regimen. • *Survival Outcomes:* With respect to PFS and TTF, Huang et al. showed that the median PFS of the experimental and control arms was 153 and 129 days, respectively (HR=0.641, 95% CI: 0.473–0.868, P=0.004). These results were significantly different, which indicated a favorable outcome in the PTX plus S-1 group for PFS. The median TTF of the 2 arms was not reported. The HR of TTF in the 2 arms was 1.449 (95% CI: 0.705–2.980, P=0.229), which indicated there was no significant difference. The 6-month PFS rates in both the arms were similar (31.3% vs 31.8%). Only 1 RCT has reported a 10-month OS rate and median survival time (MST).21 The trial had 4 arms; only arms C (PTX plus 5-FU) and D (PTX plus S-1) were adopted. The 10-month OS rates were 61% and 73% in arms C and D, respectively. The MST values were 410 and 462 days in arms C and D, respectively. Kaplan–Meier survival curves did not show a significant difference between the 2 arms. Han et al. reported that the median TTPs were 6.5 and 5.5 months in the PTX plus S-1 and PTX plus 5-FU groups, respectively. There was no significant difference in TTP values in the 2 groups by log-rank test. • *Toxicities:* Grade I - IV and grade III – IV toxicities were compared. Most of the toxicities were hematologic and gastrointestinal in nature. Hematologic toxicities, including leucopenia, neutropenia, thrombocytopenia, and anemia, were not significantly different in the 2 groups. There was a significant increase in nausea (grade I - IV: RR: 0.60, 95% CI: 0.43–0.82, P=0.001) and vomiting (grade I - IV: RR:0.55, 95% CI:0.33–0.91, P=0.02) with the PTX plus 5-FU regimen. No significant differences were detected with respect to other toxicities
	4. Fazit der Autoren *Our meta-analysis indicated that PTX plus S-1 therapy had near-equivalent safety and a better DCR compared with PTX plus 5-FU therapy. With respect to the quality of life, PTX plus S-1 therapy is a favorable strategy especially for patients who cannot tolerate continuous intravenous infusion; however, more high-quality, large sample-size RCTs and Western studies are needed to confirm these findings.* 5. Anmerkungen: • Although the included studies were all RCTs, the scores of the studies were not high. • Second, the sample size was relatively small in the eligible trials and the scores were not high, which led to the relatively low statistical power of treatment effects, which were evaluated. • The authors could not conduct a pooled analysis on survival

	outcomes because the 3 trials adopted various survival outcome indicators. • All of the studies included in this meta-analysis were from Asia, the results need confirmation in Western countries
Oba K et al., 2013 [13]. Role of chemotherapy for advanced/recurrent gastric cancer: An individual-patient-data meta-analysis	1. Fragestellung Meta-analysis of the efficacy of chemotherapy on overall survival (OS) and progression-free survival (PFS) in advanced/recurrent gastric cancer (AGC).
	2. Methodik Population: Patients with advanced/recurrent gastric cancer (AGC) Vergleich: 10 group comparisons among eligible trials e defined, which investigated 5-FU, MMC, anthracyclines, platinum agents, irinotecan and taxanes. Endpunkte: OS, PFS Suchzeitraum (Aktualität der Recherche): bis 2010 Anzahl eingeschlossene Studien/Patienten (Gesamt): Individual patient data were available from 22 trials (4245 patients, representing 47% of the targeted data) of 55 eligible trials. Qualitätsbewertung der Studien: All data were centrally checked with standardized programs. Each trial was reanalysed and compared to the published results. Differences were queried to the corresponding author. In addition to the identification of inconsistencies and missing data, particular attention was paid to the randomisation process and patient follow-up. Randomisation was examined to identify possible differences with a true random process. Balance in the distribution of the main covariates was also investigated. Likewise, distributions of days/months of randomization were checked to detect anomalies. Heterogeneity between trials and groups of trials (e.g. defined by different chemotherapy regimens) was tested using chi-squared statistics and measured with the I^2 statistics, which estimates the proportion of variability due to heterogeneity between studies rather than sampling error
	3. Ergebnisdarstellung The overall comparison of experimental arms with the corresponding control arms showed statistically significant differences in terms of both OS and PFS. Hazard ratio was 0.88 (95%CI: 0.82–0.94, P< 0.0001) for OS and 0.81 (CI: 0.76–0.88, P< 0.0001) for PFS. The results of the sub-analysis of adding a given chemotherapeutic agent to any chemotherapy confirm the results of the overall analysis, with a hazard reduction of 11% for OS (P< 0.01) and 26% for PFS (P< 0.0001). The last set of analyses looked at the randomised comparisons of any treatment regimen not including an agent of interest with the same or a different treatment regimen including the agent: • For anthracyclines, analysis of 1320 patients (8 trials) showed no difference with regard to PFS or OS (10 trials). No statistically

	significant heterogeneity. • For platinum agents, analysis of 2337 patients from eight trials (53% of 4369 targeted patients) showed a statistically significant difference in favour of the platinum-based regimen with regard to PFS (HR= 0.88; 95%CI: 0.81–0.96) but not OS. There was, however, substantial heterogeneity between trials in terms of both PFS (P< 0.0001) and OS (P= 0.021). As a sensitivity analysis, we recomputed statistics without one study which had extreme results, which showed a borderline benefit on OS (HR= 0.92, P= 0.08) while across-trial heterogeneity remained statistically significant for PFS (P= 0.01). • Analysis of taxanes from three trials (n= 667, 69% of 971 targeted patients) showed no statistically significant difference with regard to either PFS or OS. Some indication of heterogeneity was seen for PFS (P= 0.05) but not for OS (P= 0.25). • Finally, analysis of 1380 patients (5 trials; 81% of 1698 targeted patients) showed a statistically significant benefit of irinotecan-based regimes over their comparator in terms of PFS (HR= 0.81; 95%CI: 0.72–0.90) and a marginally non-significant benefit in terms of OS. No statistically significant heterogeneity was detected.
	4. Fazit der Autoren *In conclusion, our IPD meta-analysis shows that OS and PFS have been modestly improved by the addition of experimental chemotherapeutic agents to pre-existing control or standard regimens. Nevertheless, median survival remains at less than 1 year for all investigated cytotoxic associations of chemotherapy, and none has emerged as a clear standard. We hope that molecularly targeted agents administered to subgroups of patients selected on the basis of biological characteristics may modify this disappointing situation.*
Xu HB et al., 2015 [16]. Capecitabine plus oxaliplatin (XELOX) compared with 5-fluorouracil/leucovorin plus oxaliplatin (FOLFOXs) in advanced gastric cancer: meta-analysis of randomized controlled trials.	1. Fragestellung The study aims to compare the efficacy and safety of capecitabine plus oxaliplatin (XELOX) with 5-fluorouracil/leucovorin plus oxaliplatin (FOLFOXs) in patients with advanced gastric cancer.
	2. Methodik Population: AGC patients Vergleich: capecitabine plus oxaliplatin (XELOX) vs. 5-fluorouracil/leucovorin plus oxaliplatin (FOLFOXs) Endpunkte: ORR, clinical benefit rate (CBR) and toxicity Suchzeitraum (Aktualität der Recherche): Five databases were searched up to June 2014, without language restrictions. The outcomes included overall response rate (ORR), clinical benefit rate

	(CBR), and toxicity Anzahl eingeschlossene Studien/Patienten (Gesamt): Twenty-six eligible trials were selected and included 1585 patients (787 in XELOX group and 798 in FOLFOXs group). Qualitätsbewertung der Studien: Methodological quality of the trials was assessed using modified Jadad score (7 points) for randomization, concealment of allocation, double blinding, withdrawals, and dropouts. Trials scoring 1–3 points are considered low quality and 4–7 points as high quality. Heterogeneity was assessed by chi-square test.
	3. Ergebnisdarstellung **Wirksamkeit:** • All trails reported ORR and CBR for XELOX comparing with FOLFOXs in patients with advanced gastric cancer therapy. • The pooled results by fixed effect model failed to show statistical significance of XELOX on ORR and CBR as compared with FOLFOXs. • Nine trails demonstrated ORR and CBR for XELOX comparing with FOLFOX4. Similarly, no significant difference was found on ORR and CBR between XELOX and FOLFOX4 group. **Sicherheit:** • Twenty-one trails reported toxicities for XELOX comparing with FOLFOXs. The common toxicities were leucopenia, nausea, and peripheral neuropathy, which were experienced by nearly half of patients both in XELOX and FOLFOXs group. Leucopenia and nausea were the most common adverse events in XELOX and FOLFOXs group, respectively. • As anticipated, the frequency of hand-foot syndrome was 40%in XELOX group and 13% in FOLFOXs group, with a significant difference between them (OR: 2.84, 95 % Cis: 2.19–3.69; P<0.001). • Significant difference between XELOX and FOLFOXs was also found for nausea (OR: 0.81, 95 % Cis: 0.68–0.97; P=0.023), stomatitis (OR: 0.77, 95 % Cis: 0.61–0.98; P=0.030), diarrhea (OR: 0.74, 95 % Cis: 0.58–0.94; P=0.012), and alopecia (OR: 0.50, 95 % Cis: 0.31–0.83; P=0.008). • Similarly, results were observed in two groups when comparing grades 3 and 4 hand-foot syndrome (OR: 3.45, 95%CI: 1.27–9.39; P=0.015), nausea (OR: 0.30, 95 % CI: 0.18–0.48; P<0.001), stomatitis (OR: 0.18, 95 % CI: 0.07–0.44; P<0.001), diarrhea (OR: 0.36, 95 % CI: 0.18–0.74; P= 0.005), and alopecia (OR: 0.14, 95 % CI: 0.02–0.90; P= 0.039). Additionally, grades 3 and 4 leucopenia was found significant difference between two groups (OR: 0.50, 95 % CI: 0.33–0.75; P<0.001).

	4. Fazit der Autoren *The evidence is limited to suggest that XELOX may share similar efficacy as FOLFOXs and reduce toxicities of chemotherapy in advanced gastric cancer therapy. However, owing to limited data and potential bias of the included studies, further rigorously controlled trials are required.* 5. Anmerkungen: • Stat. signifikanter Publikationsbias für ORR
Badiani B et al., 2015 [1]. Second-line treatments for advanced gastric cancer: Interpreting outcomes by network meta-analysis	1. Fragestellung To study the effectiveness of second-line treatments for advanced gastric cancer by application of Bayesian network meta-analysis.
	2. Methodik Population: Patients with advanced gastric cancer (AGC) Vergleich: The following 6 treatments were evaluated: (1) irinotecan (camptothecins); (2) paclitaxel (taxanes class); (3) docetaxel (taxanes); (4) everolimus (mammalian target of rapamycin inhibitors); (5) ramucirumab (vascular endothelial growth factor receptor 2 inhibitors); (6) ramucirumab + paclitaxel vs. best supportive care (BSC) Endpunkte: OS Suchzeitraum (Aktualität der Recherche): bis Februar 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): In total 7 studies selected. In 6 out of these 7 cases, the RCTs compared a second-line treatment with BSC. Overall, these 7 RCTs enrolled 2298 patients (in 15 treatment arms). As regards the methodological quality, the 7 RCTs showed a low risk of bias. Qualitätsbewertung der Studien: As regards the assessment of methodological quality, two reviewers (BB and DM) applied the Cochrane Collaboration's tool to evaluate the risk of bias in the studies included in our analysis. This tool assesses six domains (namely: random sequence generation, concealment of allocation, blinding of participants and personnel, incomplete data, selective outcome reporting of outcomes, and other sources of bias). Studies with adequate procedures in all domains were considered to have a low risk of bias. For our statistical analysis, we employed a Bayesian model of network meta-analysis. To evaluate the reproducibility of our results, we changed the initial parameter estimates from which the Markov chain Monte Carlo simulation begins according to a verification that is customary employed in these Bayesian analyses.
	3. Ergebnisdarstellung • Statistically significant difference in direct comparisons between two second-line active treatments vs BSC (namely, paclitaxel monotherapy and ramucirumab + paclitaxel). • Furthermore, 4 indirect head-to-head comparisons reached the

	threshold of statistical significance (namely, the comparisons of ramucirumab + paclitaxel with irinotecan or docetaxel or paclitaxel or everolimus).
	4. Fazit der Autoren *Our results indicate that both paclitaxel monotherapy and ramucirumab + paclitaxel determine a significant prolongation in survival as compared with BSC.* 5. Anmerkungen: • Netzwerkanalyse (z. T. basierend auf indirekten Vergleichen)

Leitlinien

<table>
<tr><td rowspan="2">Waddell T et al., 2013 [15]. Gastric cancer†: ESMO–ESSO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up.</td><td>Guideline developed by the European Society for Medical Oncology (ESMO), the European Society of Surgical Oncology (ESSO) and the European Society of Radiotherapy and Oncology (ESTRO)</td></tr>
<tr><td>Methodik

Grundlage der Leitlinie: The guideline covers incidence and epidemiology, diagnosis and pathology, staging and risk assessment, treatment planning, management of local/locoregional disease, management of advanced/metastatic disease, follow-up and long-term implications.

Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading Systema):
<table>
<tr><td colspan="2">Levels of evidence</td></tr>
<tr><td>I</td><td>Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or metaanalyses of well-conducted, randomised trials without heterogeneity</td></tr>
<tr><td>II</td><td>Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or metaanalyses of such trials or of trials with demonstrated heterogeneity</td></tr>
<tr><td>III</td><td>Prospective cohort studies</td></tr>
<tr><td>IV</td><td>Retrospective cohort studies or case–control studies</td></tr>
<tr><td>V</td><td>Studies without control group, case reports, experts opinions</td></tr>
</table>
<table>
<tr><td colspan="2">Grades of recommendation</td></tr>
<tr><td>A</td><td>Strong evidence for efficacy with a substantial clinical benefit, strongly recommended</td></tr>
<tr><td>B</td><td>Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended</td></tr>
<tr><td>C</td><td>Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,…), optional</td></tr>
<tr><td>D</td><td>Moderate evidence against efficacy or for adverse outcome, generally not recommended</td></tr>
</table>
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</table>

	E | Strong evidence against efficacy or for adverse outcome, never recommended [a]Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis 2001; 33: 139–144. By permission of the Infectious Diseases Society of America.
	Empfehlungen *Management of advanced/metastatic disease:* • Patients with stage IV disease should be considered for palliative chemotherapy, which improves survival compared with best supportive care alone [I, A] • Co-morbidities, organ function and performance status must always be taken into consideration [II, B] • Combination regimens based upon a platinum–fluoropyrimidine doublet are generally used, and there remains controversy regarding the need for triplet regimens. However, a meta-analysis has demonstrated significant benefit from adding an anthracycline to a platinum and fluoropyrimidine doublet [I, A] • Additionally, a meta-analysis has demonstrated that capecitabine is associated with improved OS compared with infused 5-FU within doublet and triplet regimes [I, A] • Alternative first-line chemotherapy options include taxane based regimens or irinotecan plus 5-FU. The addition of 3-weekly docetaxel to 5-FU/cisplatin (DCF) is associated with increased activity, but also adds toxic effects including increased rates of febrile neutropaenia [I, C]. • In patients of adequate performance status, second-line chemotherapy is associated with proven improvements in OS and quality of life compared with best supportive care, with treatment options including irinotecan, docetaxel or paclitaxel [I, A] • A randomised, phase III trial directly comparing weekly paclitaxel with irinotecan has demonstrated similar efficacy for both the regimens, with the median OS of 8 to 9 months in a Japanese population [I, A]. • Additionally, consideration should always be given to inclusion in any appropriate clinical trials [V, B]. • Alternatively, in patients with disease progression >3 months following first-line chemotherapy, it may be appropriate to consider a re-challenge with the same drug combination [IV, C]. • In patients with symptomatic locally advanced or recurrent disease, hypofractionated radiotherapy is an effective and well tolerated treatment modality which may palliate bleeding, obstructive symptoms or pain [III, B]. Personalised medicine: • Following the ToGA trial results, trastuzumab was licensed in Europe for use in HER-2 positive disease (IHC3+ or 2+/FISH-positive) in combination with capecitabine or 5- fluorouracil and cisplatin. This regimen now represents the standard of care for these patients [I, A]. • The AVAGAST trial evaluating bevacizumab in combination with first-line chemotherapy failed to demonstrate any improvement in OS, though both PFS and response rate were significantly improved [I, C]. • A second anti-angiogenic agent, ramucirumab, has recently been confirmed to have single-agent activity in the second-line setting with a modest 1.4-month improvement in OS compared with best supportive care [I, B].

<table>
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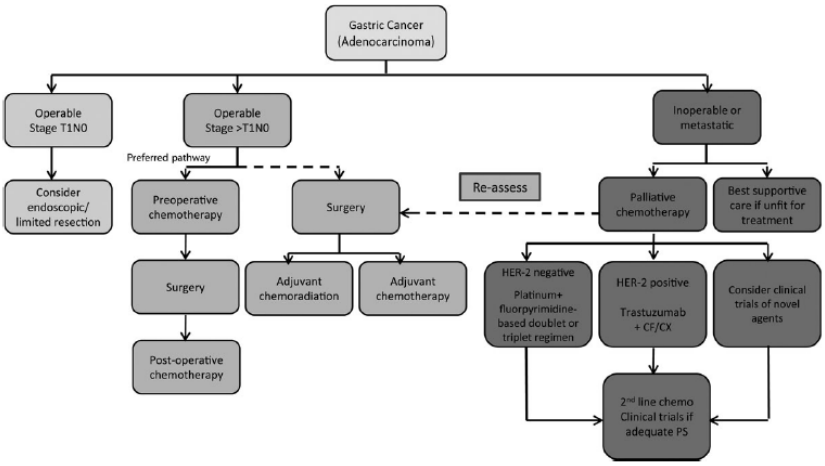
- Anti-EGFR therapies have failed to improve outcomes with recently reported negative phase III results when cetuximab or panitumumab was added to first-line chemotherapy, and a negative phase III trial of single-agent gefitinib compared with best supportive care in the second-line [I, D].

Algorithm for the management of gastric cancer



</td></tr>
<tr><td rowspan="2">National Comprehensive Cancer Network (NCCN), 2015 [12].

Gastric Cancer. Version 3.2015 (keine Änderungen/neuen Empfehlungen zum AWG auf Basis der aktualisierten Version)</td><td>Fragestellunge(n)

k.A.</td></tr>
<tr><td>

Methodik

<u>Grundlage der Leitlinie:</u>

Allgemeiner NCCN-Methodenreport beschreibt systematische Evidenzaufbereitung mit Konsensusprozessen - ob formalisierte Verfahren angewendet werden ist unklar

- Update: jährlich
- Suchzeitraum: between 06/27/2013 and 06/27/2014
- *Weitere Kriterien für die Qualität einer LL:*
  - *Repräsenativität des Gremiums unklar*
  - *industriefinanziert*
  - *Interessenkonflikte unklar (Link zu „NCCN Guideline Panel Disclosures“ nur über passwortgeschützten Zugang aktivierbar)*
  - *Empfehlungen nicht hervorgehoben*
  - *Empfehlungen, Algorithmen und Literatur nicht eindeutig miteinander verknüpft*

LoE/GoR:

Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

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<table>
<tr><td></td><td>Empfehlungen

<u>Locally advanced, metastatic or recurrent disease</u>

Palliative therapy (systemic therapy, clinical trial or best supportive care) is recommended for patients with locally advanced, metastatic or recurrent gastric cancer. Surgery should be considered as an option for resectable locoregional recurrence in medically fit patients. …

The selection of a second-line therapy regimen is dependent on prior therapy and performance status. The panel consensus was that there ist no category 1 evidence to support any specific regimen for second-line or third-line therapy for patients with advanced or metastatic gastric cancer. This area remains an active subject of investigation. …

Best supportive care is always indicated for patients with locally advanced, metastatic or recurrent gastric cancer. The decision to offer best supportive care alone or in combination with chemotherapy is dependent patient´s performance status.

• siehe auch Abbildungen im Anhang dieser Synopse

Some of the specific therapy regimens and dosing schedules included in the guidelines are based on extrapolations from published studies and institutional preferences that have support only from phase II studies.</td></tr>
<tr><td rowspan="2">Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS), 2012 [3].
Magenkarzinom Diagnostik und Therapie der Adenokarzinome des Magens und ösophagogastralen Übergangs.</td><td>S 3 Leitlinie der Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten</td></tr>
<tr><td>Methodik

Grundlage der Leitlinie: Die vorliegende Leitlinie wurde nach dem aktuellen Stand der wissenschaftlichen Literatur und Ergebnissen internationaler Studien erarbeitet. Neben der systematischen Recherche und Bewertung von Primärstudien wurden auch Quellen aggregierter Evidenz verwendet: nach systemischer Recherche und methodischer Bewertung mittels DELBI konnten 3 aktuelle, evidenzbasierte Quellleitlinien identifiziert und deren Empfehlungen z.T. eingearbeitet werden.

Die S3-Leitlinie soll kontinuierlich aktualisiert werden. Die Gültigkeitsdauer wird auf 3 Jahre geschätzt.

Schema der Evidenzgraduierung nach Oxford:

<table><tr><td>1a</td><td>SR (with homogeneity) of RCTs</td></tr><tr><td>1b</td><td>Individual RCT (with narrow Confidence Interval)</td></tr><tr><td>1c</td><td>All or none</td></tr><tr><td>2a</td><td>SR (with homogeneity) of cohort studies</td></tr><tr><td>2b</td><td>Individual cohort study (including low quality RCT; e.g., <80% follow-up)</td></tr></table></td></tr>
</table>

2c	"Outcomes" Research; Ecological studies
3a	SR (with homogeneity) of case-control studies
3b	Individual Case-Control Study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"
GCP	Good clinical practice

Empfehlungen

- Falls im Verlauf der neoadjuvanten Therapie klinisch Hinweise auf eine Tumorprogression bestehen (Verschlechterung tumorbedingter Symptome oder des Allgemeinzustandes), soll eine symptomadaptierte Diagnostik erfolgen. (LoE: GCP; Abstimmung im Plenum: starker Konsens)
- Bei Nachweis eines allgemeinen Tumorprogresses soll die Entscheidung über die weitere Therapie interdisziplinär erfolgen. (LoE: GCP; Abstimmung im Plenum: starker Konsens)
- Im Falle eines lokalen Tumorprogresses unter neoadjuvanter Therapie sollte eine frühzeitige Operation durchgeführt werden. (LoE: GCP; Abstimmung im Plenum: starker Konsens)

Hintergrund:
Falls im Verlauf der neoadjuvanten Therapie klinische Hinweise auf einen Tumorprogress bestehen (Verschlechterung tumorbedingter Symptome oder des Allgemeinzustandes) erscheint es sinnvoll, eine symptomorientierte Diagnostik durchzuführen. Im Falle eines lokalen Tumorprogresses unter neoadjuvanter Therapie sollte eine frühzeitige Operation durchgeführt werden, da Patienten mit einer lokalen Tumorprogression unter Therapie wahrscheinlich nicht von einem Fortsetzen dieser Therapie profitieren. Zudem gibt es keine Daten, die eine Therapieumstellung oder Therapieintensivierung rechtfertigen würden. Die präoperative Therapie sollte jedoch nicht abgebrochen werden, wenn keine Tumorprogression vorliegt. In den Phase III-Studien zur neoadjuvanten Therapie erfolgte bei fehlendem Hinweis auf Tumorprogress die neoadjuvante Therapie planmäßig und führte in dieser Form für die gesamte Patientengruppe zu einer Verbesserung des Überlebens.

- Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med2006 Jul 6;355(1):11-20.
- Stahl M, Walz MK, Stuschke M, Lehmann N, Meyer HJ, Riera-Knorrenschild J, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol2009 Feb 20;27(6):851-6.

Multimodale Therapie
Perioperative Chemotherapie:

- Bei lokalisierten Adenokarzinomen des Magens oder

	ösophagogastralen Übergangs mit Kategorie uT2 kann eine präoperative Chemotherapie durchgeführt und postoperativ fortgesetzt werden. (Empfehlungsgrad 0; LoE: 1b; Abstimmung im Plenum: Konsens) • Bei lokalisiertem Magenkarzinom der Kategorien uT3 und resektablen uT4a Tumoren „sollte/soll“***** eine perioperative Chemotherapie durchgeführt, d.h. präoperativ begonnen und postoperativ fortgesetzt werden. (Empfehlungsgrad A/B; LoE: 1b; Abstimmung im Plenum: Konsens) • Beim lokalisierten Adenokarzinom des ösophago-gastralen Übergangs der Kategorien uT3 und resektablen uT4 Tumoren *soll/sollte* eine perioperative Chemotherapie oder eine neoadjuvante Radiochemotherapie durchgeführt werden. (Empfehlungsgrad A/B; LoE: 1b [perioperative Chemotherapie], 1a-1b,1b-2b [neoadjuvante Radiochemotherapie]; Abstimmung im Plenum: Konsens) *Präoperative Radiochemotherapie:* • Eine präoperative Radiochemotherapie soll beim Magenkarzinom nicht durchgeführt werden. (LoE: GCP; Abstimmung im Plenum: starker Konsens) *Präoperative Antikörper-Therapie:* • Antikörper und „small molecules“ sollen in der präoperativen Therapie nicht eingesetzt werden. (LoE: GCP; Abstimmung im Plenum: starker Konsens) <u>Hintergrund:</u> In der palliativen Behandlung fortgeschrittener Magenkarzinome wurden vorläufige Daten publiziert, die einen Überlebensvorteil für Patienten mit HER-2-positiven Tumoren nachweisen, wenn sie zur Chemotherapie aus Cisplatin und einem Fluoropyrimid den Antikörper Trastuzumab erhielten (356). Es ist aber unklar, ob dieser Antikörper auch die Ergebnisse einer präoperativen Therapie bei lokalisierten, HER-2-positiven Karzinomen verbessert. Der Einsatz zielgerichteter Substanzen ist daher außerhalb klinischer Studien nicht indiziert. Die Ergebnisse laufender randomisierter Studien müssen abgewartet werden. ***Tumorgerichtete palliative Therapie*** *Medikamentöse Tumortherapie:* • Patienten in gutem Allgemeinzustand soll eine systemische Chemotherapie angeboten werden. Therapieziel ist die Verbesserung des Überlebens und der Erhalt der Lebensqualität. Ein erhöhtes Alter stellt keine Kontraindikation dar. (Empfehlungsgrad A; LoE: 1b; Abstimmung im Plenum: starker Konsens) • Eine palliative medikamentöse Tumortherapie sollte zum frühest möglichen Zeitpunkt nach Diagnosestellung der lokal fortgeschritten inoperablen oder metastasierten Erkrankung eingeleitet werden. (Empfehlungsgrad B; LoE: 1a; Abstimmung im Plenum: Konsens) • Über die Dauer der palliativen medikamentösen Tumortherapie sollte in Abhängigkeit vom Tumoransprechen, der therapieassoziierten Toxizität und der Patientenvorstellungen entschieden werden. (Empfehlungsgrad B; LoE: 1a; Abstimmung im Plenum: Konsens) • Vor dem Einsatz einer palliativen medikamentösen Tumortherapie sollte der HER-2-Status als positiver prädiktiver Faktor für eine Therapie mit Trastuzumab bestimmt werden. Die histopathologische

	Bestimmung am Tumorgewebe soll qualitätsgesichert durchgeführt werden. (LoE: GCP; Abstimmung im Plenum: starker Konsens) *Vorgehen bei Tumoren ohne HER-2-Überexpression:* • Die Kombinationstherapie ist der Monotherapie mit 5-FU bzw. oralen Fluoropyrimidinen in Bezug auf die Überlebenszeit signifikant überlegen. (LoE: 1a; Abstimmung im Plenum: starker Konsens) • Indiziert ist eine systemische Platin/Fluoropyrimidin-haltige Kombinationstherapie. Bei der Indikationsstellung sind mögliche Kontraindikationen zu berücksichtigen. (LoE: 1a; Abstimmung im Plenum: starker Konsens) • Eine Dreifachkombination mit Cisplatin/5-FU und Docetaxel (DCF) führt bei einer jüngeren Patientenpopulation (median 55 Jahre) im Vergleich zu einer Zweifachtherapie mit Cisplatin/5-FU zu einem statistisch signifikanten Überlebensvorteil, ist jedoch mit einer höheren Rate an Toxizitäten verbunden. (LoE: 1b; Abstimmung im Plenum: starker Konsens) • Die Docetaxel-haltige Dreifachkombination (DCF) sollte daher nur Patienten in gutem Allgemeinzustand ohne relevante Komorbidität angeboten werden. (Empfehlungsgrad: B; LoE: 1b; Abstimmung im Plenum: starker Konsens) • Die sogenannten modifizierten DCF-Schemata verfügen über ein im Vergleich zum klassischen DCF verbessertes Nebenwirkungsprofil. (LoE: GCP; Abstimmung im Plenum: starker Konsens) • Besteht eine Indikation zu einer Docetaxel-basierten Dreifachkombination, kann der Einsatz der modifizierten DCF-Schemata in Erwägung gezogen werden. (LoE: GCP; Abstimmung im Plenum: starker Konsens) • Oxaliplatin hat eine dem Cisplatin vergleichbare Wirksamkeit, die Toxizitätsprofile sind jedoch unterschiedlich. (LoE: 1b-; Abstimmung im Plenum: starker Konsens) • Die Therapieentscheidung zwischen diesen beiden Substanzen sollte deshalb die Begleiterkrankungen des jeweiligen Patienten berücksichtigen. (Empfehlungsgrad: B; LoE: 1b-; Abstimmung im Plenum: starker Konsens) • Capecitabin zeigt eine dem 5-FU vergleichbare Wirksamkeit. (LoE: 1a; Abstimmung im Plenum: starker Konsens) • Die orale Gabe von Capecitabin kann Patienten mit ausreichender Nierenfunktion und guter Compliance anstatt der intravenösen 5-FU-Dauerinfusion (wie z. B. bei ECF) angeboten werden. (Empfehlungsgrad: B; LoE: 1a; Abstimmung im Plenum: starker Konsens) • Im Rahmen von 5-FU-basierten Kombinationstherapien zeigt Irinotecan eine dem Cisplatin vergleichbare Wirksamkeit. (LoE: 1a-; Abstimmung im Plenum: starker Konsens) • Eine Irinotecan/Fluropyrimidin-basierte Kombinationstherapie kann Patienten angeboten werden, bei denen aufgrund des Nebenwirkungsprofils eine Alternative zu einer platinhaltigen Kombination sinnvoll ist. (Empfehlungsgrad: B; LoE: 1a-; Abstimmung im Plenum: starker Konsens) *Vorgehen bei HER-2-überexprimierenden/-amplifizierenden Tumoren:* • Aufgrund eines nachgewiesenen Überlebensvorteils besteht bei HER-2-überexprimierenden Tumoren (IHC3+ oder IHC2+ und FISH+) eine Indikation für den Einsatz von Trastuzumab in Kombination mit Cisplatin und Fluoropyrimidinen (5-FU oder Capecitabin). (LoE: 1b; Abstimmung im Plenum: Konsens) • Die Antikörper Cetuximab, Panitumumab und Bevacizumab sollten gegenwärtig außerhalb klinischer Studien nicht eingesetzt werden.

	(LoE: GCP; Abstimmung im Plenum: starker Konsens) *Zweit-Chemotherapie:* • Patienten in gutem Allgemeinzustand sollte eine Zweit-Chemotherapie angeboten werden. Das zu wählende Behandlungsschema sollte sich nach der jeweiligen Vortherapie richten. (Empfehlungsgrad: B; LoE: 2b-; Abstimmung im Plenum: Konsens)
National Comprehensive Cancer Network (NCCN), 2015 [11]. Esophageal and Esophagogastric Junction Cancers. Version 3.2015	Fragestellung: k.A.
	Methodik <u>Grundlage der Leitlinie:</u> Allgemeiner NCCN-Methodenreport beschreibt systematische Evidenzaufbereitung mit Konsensusprozessen - ob formalisierte Verfahren angewendet werden ist unklar – Update: jährlich – Suchzeitraum: between 06/27/2013 and 06/27/2014 – *Weitere Kriterien für die Qualität einer LL:* • *Repräsenativität des Gremiums unklar* • *industriefinanziert* • *Interessenkonflikte unklar (Link zu „NCCN Guideline Panel Disclosures“ nur über passwortgeschützten Zugang aktivierbar)* • *Empfehlungen nicht hervorgehoben* • *Empfehlungen, Algorithmen und Literatur nicht eindeutig miteinander verknüpft* LoE/GoR: eigenes Graduierungssystem (siehe Anlage dieser Synopse)
	Empfehlungen **Management of Metastatic, or Recurrent Cancer** Locoregional recurrence after esophagectomy can be treated with fluoropyrimidine-based or taxane-based concurrent chemoradiation in patients who have not received prior chemoradiation. Other options include best supportive care or surgery or chemotherapy. Selected patients with anastomotic recurrences can undergo re-resection. When recurrence develops after chemoradiation therapy with no prior esophagectomy, the clinician should determine whether the patient is medically fit for surgery and if the recurrence is resectable. If both criteria are met, esophagectomy remains an option. When patients experience another recurrence after surgery, the cancer is assumed to be incurable and palliative therapy should be provided as described for locally advanced or metastatic cancer. Palliative therapy is recommended for medically unfit patients and those who develop an unresectable or metastatic recurrence.

	Best supportive care is always indicated for patients with locally advanced, metastatic, or recurrent disease. The decision to offer best supportive care alone or with chemotherapy is dependent on the patient's performance status. The Karnofsky Performance Status Scale (KPS)[332,333] and the ECOG Performance Status Scale (ECOG PS)[334] are the two commonly used scales to assess the performance status in patients with cancer.

Primärstudien

Da ausreichend Literatur aus aggregierter Evidenz vorliegt, wurde eine Suche nach Primärstudien nicht durchgeführt.

Anlage

Table 1. Basic information of the trials included in the meta-analysis

Trials	No. of pts	Male *n* (%)	Median age (range)	Regimens (per arm)	No. of pts (per arm)	KPS/ECOG (%)
Cunningham *et al.*[10]	964	785 (81·4)	63 (22–83)	ECX	241 (237)[a]	0–1 (87·6)
				ECF	249 (246)	0–1 (88·4)
				EOX	239 (234)	0–1 (90·0)
				EOF	235 (231)	0–1 (91·5)
Kang *et al.*[11]	316	211 (66·8)	56 (22–74)	XP	160	70–100
				FP	156	70–100
Sun *et al.*[12]	58	41 (70·7)	54 (35–78)	OX	28	0–2
				OLF	30	0–2
Chen *et al.*[13]	48	32 (66·7)	54 (35–78)	XELOX	25	0–2
				$FOLFOX_4$	23	0–2
Qu *et al.*[14]	61	32 (52·5)	64 (45–78)	XELOX	30	80–100
				$FOLFOX_6$	31	80–100
Hu *et al.*[15]	55	32 (58·2)	54·2 (28–71)	XELOX	28	60–100
				OLF	27	60–100
Lei *et al.*[16]	60	38 (63·3)	62 (35–82)	XELOX	32	60–100
				OLF	28	60–100
Lee *et al.*[17]	52	38 (73·1)	66 (49–73)	XELOX	30	70–100
				$FOLFOX_4$	22	70–100
Cai *et al.*[18]	85	46 (54·1)	58 (37–79)	XELOX	41	60–100
				OLF	44	60–100
Shi *et al.*[19]	68	47 (69·1)	56 (34–77)	XELOX	31	60–100
				$FOLFOX_4$	37	60–100
Du and Chen[20]	30	22 (73·3)	59 (32–77)	XELOX	15	60–100
				OLF	15 (14)[b]	60–100
Xue *et al.*[21]	67	37 (53·7)	56·6 (34–78)	OX	32	60–90
				$mFOLFOX_7$	35	60–90
Zhao *et al.*[9]	72	45 (62·5)	55 (27–73)	XELOX	36	0–1
				$FLOFOX_4$	36	0–1
Wang *et al.*[22]	54	37 (68·5)	59 (32–72)	XELOX	28	0–2
				$FLOFOX_4$	26	0–2
Chen[23]	43	32 (74·4)	70 (62–78)	XELOX	20	50–100
				OLF	23	50–100
Wang[24]	56	42 (75·0)	55 (32–73)	XELOX	28	60–100
				OLF	28	60–100
Jia and Lee[25]	43	26 (60·5)	52 (35–72)	XELOX	23	0–2
				$FLOFOX_4$	20	0–2
Wang *et al.*[26]	43	28 (65·1)	62 (26–72)	XELOX	24	70–100
				$FLOFOX_4$	19	70–100

TC, tumour characteristics; Pts, patients; KPS, Karnofsky scoring performance status.
[a]In the REAL-2 study, the overall response could be evaluated only in 246 patients in the ECF group, 237 patients in the ECX group, 231 patients in the EOF group and 234 patients in the EOX group.
[b]In Du C's study, one patient in the OLF regimens could not be evaluated for efficacy because of upper gastrointestinal bleeding.

Table 2. Treatment for each group in the trials included in the meta-analysis

Trials	Arms	Regimens
Cunningham *et al.*[10]	ECX	Epi 50 mg/m^2 i.v. d_1, Cis 60 mg/m^2 i.v. d_1, Cap 625 mg/m^2 bid po d_{1-21}, q3w
	ECF	Epi 50 mg/m^2 i.v. d_1, Cis 60 mg/m^2 i.v. d_1, 5-FU 200 mg/m^2 d_{1-21}, q3w
	EOX	Epi 50 mg/m^2 i.v. d_1, Oxa 130 mg/m^2 i.v. 2h d_1, Cap 625 mg/m^2 bid po d_{1-21}, q3w
	EOF	Epi 50 mg/m^2 i.v. d_1, Oxa 130 mg/m^2 i.v. 2h d_1, 5-FU 200 mg/m^2 d_{1-21},q3w
Kang *et al.*[11]	XP	Cis 80 mg/m^2 i.v. d_1 with hyperhydration, Cap 1000 mg/m^2 bid d_{1-14}, q3w
	FP	Cis 80 mg/m^2 i.v. d_1 with hyperhydration, 5-FU 800 mg/m^2 CIV d_{1-5}, q3w
Sun *et al.*[12]	XELOX	Oxa 130 mg/m^2 i.v. d_1, Cap 1000 mg/m^2 bid d_{1-14}, q3w
	OLF	Oxa 130 mg/m^2 i.v. d_1, LV 100 mg/m^2 i.v. d_{1-5}, 5- FU 500 mg/m^2 i.v. d_{1-5}, q3w
Chen *et al.*[13]	XELOX	Cap 1000 mg/m^2 bid po d_{1-14}, Oxa 130 mg/m^2 i.v. d_1, q3w
	$FOLFOX_4$	Oxa 85 mg/m^2 i.v.d_1, LV 200 mg/m^2 i.v., 5-FU 400 mg/m^2 bolus and 600 mg/m^2 CIV d_{1-2}, q2w
Qu *et al.*[14]	XELOX	Oxa 65 mg/m^2 i.v. $d_{1,8}$, Cap 650 mg/m^2 bid d_{1-15}, q3w
	$FOLFOX_6$	Oxa 100 mg/m^2 d_1, LV 400 mg/m^2 i.v., 5-FU 400 mg/m^2 bolus and 2400–3000 mg/m^2 CIV, q3w
Hu *et al.*[15]	XELOX	Oxa 130 mg/m^2 i.v. d_1, Cap 1000 mg/m^2 bid d_{1-14}, q3w
	OLF	Oxa 130 mg/m^2 i.v. d_1, 5-FU 2500 mg/m^2 CIV, q3w;
Lei *et al.*[16]	XELOX	Oxa 130 mg/m^2 i.v. d_1, Cap 1000 mg/m^2 bid d_{1-14}, q3w
	OLF	Oxa 130 mg/m^2 i.v. d_1, LV 100 mg/m^2 i.v. d_2, 5-FU 350 mg/m^2 i.v. d_{2-6}, q3w
Lee *et al.*[17]	XELOX	Oxa 85 mg/m^2 i.v. d_1, Cap 825 mg/m^2 bid d_{1-7}, q2w
	$FOLFOX_4$	Oxa 85 mg/m^2 i.v. d_1, LV 200 mg/m^2 i.v. 5-FU 400 mg/m^2 bolus and 600 mg/m^2 CIV d_{1-2}, q2w;
Cai *et al.*[18]	XELOX	Oxa 130 mg/m^2 i.v. d_1, Cap 1000 mg/m^2 bid d_{1-14}, q3w
	OLF	Oxa 130 mg/m^2 i.v. d_1, LV 200 mg/m^2 i.v. d_{1-5}, 5- FU 500 mg/m^2 i.v. d_{1-5}, q3w
Shi *et al.*[19]	XELOX	Oxa 130 mg/m^2 i.v. d_1, Cap 1000 mg/m^2 bid d_{1-14}, q3w
	$FOLFOX_4$	Oxa 85 mg/m^2 i.v. d_1, LV 200 mg/m^2 i.v., 5-FU 400 mg/m^2 bolus and 600 mg/m^2 CIV d_{1-2}, q2w
Du and Chen[20]	XELOX	Oxa 130 mg/m^2 i.v. d_1, Cap 1000 mg/m^2 bid d_{1-14}, q3w
	OLF	Oxa 130 mg/m^2 i.v. d_1, LV 200 mg/m^2 2h i.v. d_{1-5}, 5-FU 500 mg/m^2 6h i.v. d_{1-5}, q3w
Xue *et al.*[21]	XELOX	Oxa 130 mg/m^2 i.v. d_1, Cap 1000 mg/m^2 bid d_{1-14}, q3w
	$mFOLFOX_7$	Oxa 100 mg/m^2 i.v. d_1, LV 200 mg/m^2 i.v., 5-FU 2400 mg/m^2 CIV, q3w
Zhao *et al.*[9]	XELOX	Oxa 130 mg/m^2 i.v. d_1, Cap 1000 mg/m^2 bid d_{1-14}, q3w
	$FLOFOX_4$	Oxa 85 mg/m^2 i.v.d_1, LV 200 mg/m^2 i.v., 5-FU 400 mg/m^2 bolus and 600 mg/m^2 CIV d_{1-2}, q2w
Wang *et al.*[22]	XELOX	Oxa 135 mg/m^2 i.v. d_1, Cap 1000 mg/m^2 bid po d_{1-14}, q3w
	$FLOFOX_4$	Oxa 85 mg/m^2 i.v.d_1, LV 200 mg/m^2 i.v., 5-FU 400 mg/m^2 bolus and 600 mg/m^2 CIV d_{1-2}, q2w
Chen[23]	XELOX	Oxa 85 mg/m^2 i.v. d_{1-2}, Cap 625 mg/m^2 bid d_{1-14}, q4w;
	OLF	Oxa 85 mg/m^2 d_{1-2}, LV 50 mg/m^2 d_{1-5}, 5-FU 500 mg/m^2 d_{1-5}, q4w
Wang[24]	XELOX	Oxa 85 mg/m^2 i.v. d_1, Cap 1000 mg/m^2 bid po d_{1-14}, q3w
	OLF	Oxa 85 mg/m^2 i.v. d_1, LV 200 mg/m^2 i.v. 2h d_{1-5}, 5-FU 5-h 300 mg/m^2 i.v. d_{1-5}, q3w
Jia and Lee[25]	XELOX	Oxa 85 mg/m^2 i.v. d_1, Cap 1000 mg/m^2 bid d_{1-10},q2w
	$FLOFOX_4$	Oxa 85 mg/m^2 i.v.d_1, LV 200 mg/m^2 i.v., 5-FU 400 mg/m^2 bolus and 600 mg/m^2 CIV d_{1-2}, q2w
Wang *et al.*[26]	XELOX	Oxa 85 mg/m^2 i.v. $d_{1/15}$, Cap 625 mg/m^2 bid d_{1-14}, q4w
	$FLOFOX_4$	Oxa 85 mg/m^2 i.vd_1, LV 200 mg/m^2 i.v.d_{1-2}, 5-FU 400 mg/m^2 bolus and 600 mg/m^2 CIV d_{1-2}, q2w

i.v., intravenous infusion; CIV, continuous infusion; Epi, epirubicin; Cis, cisplatin; Cap, capecitabine; 5-FU, 5-fluorouracil; Oxa, oxaliplatin; LV, leucovorin.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) **am 24.02.2016**

#	Suchfrage
#1	MeSH descriptor: [Stomach Neoplasms] explode all trees
#2	(gastric or stomach or esophagogastric or oesophagogastric or gastroesophageal):ti,ab,kw (Word variations have been searched)
#3	MeSH descriptor: [Stomach] explode all trees
#4	(cancer* or carcinoma* or adenocarcinoma* or tumor* or tumour* or neoplasm*):ti,ab,kw or (granular next cell next carcinoma*):ti,ab,kw or (malignant next adenoma*):ti,ab,kw (Word variations have been searched)
#5	MeSH descriptor: [Adenocarcinoma] explode all trees
#6	#2 or #3
#7	#4 or #5
#8	#6 and #7
#9	#1 or #8
#10	(advanced or metastat* or metastas* or recurr* or progress*):ti,ab,kw
#11	MeSH descriptor: [Neoplasm Metastasis] explode all trees
#12	MeSH descriptor: [Neoplasm Recurrence, Local] explode all trees
#13	#10 or #11 or #12
#14	#9 and #13
#15	#14 Publication Year from 2011 to 2016

SR, HTAs in Medline (PubMed) am 24.02.2016

#	Suchfrage
1	"stomach neoplasms"[MeSH Terms]
2	(((gastric[Title/Abstract]) OR stomach[Title/Abstract]) OR esophagogastric[Title/Abstract]) OR oesophagogastric[Title/Abstract] OR gastroesophageal[Title/Abstract] OR stomach[MeSH Terms]
3	((((((cancer*[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR adenocarcinoma*[Title/Abstract]) OR neoplasm*[Title/Abstract]) OR granular cell carcinoma*[Title/Abstract]) OR malignant adenoma*[Title/Abstract]) OR tumor*[Title/Abstract] OR tumour*[Title/Abstract] OR adenocarcinoma[MeSH Terms]
4	#2 AND #3
5	(#1 OR #4)
6	((((advanced[Title/Abstract]) OR metastat*[Title/Abstract]) OR metastas*[Title/Abstract]) OR recurr*[Title/Abstract]) OR progress*[Title/Abstract] OR "neoplasm metastasis"[MeSH Terms] OR “Neoplasm Recurrence, Local”[MeSH Terms]
7	(#5 AND #6)
8	(#7) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
9	(#7) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR

	Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
10	(#8 OR #9)
11	(#10) AND ("2011/02/01"[PDAT] : "2016/02/24"[PDAT])
12	#11 NOT "The Cochrane database of systematic reviews"[Journal]

Leitlinien in Medline (PubMed) am 23.02.2016

#	Suchfrage
1	"stomach neoplasms"[MeSH Terms]
2	(((gastric[Title/Abstract]) OR stomach[Title/Abstract]) OR esophagogastric[Title/Abstract]) OR oesophagogastric[Title/Abstract] OR gastroesophageal[Title/Abstract] OR stomach[MeSH Terms]
3	((((((cancer*[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR adenocarcinoma*[Title/Abstract]) OR neoplasm*[Title/Abstract]) OR granular cell carcinoma*[Title/Abstract]) OR malignant adenoma*[Title/Abstract]) OR tumor*[Title/Abstract] OR tumour*[Title/Abstract] OR adenocarcinoma[MeSH Terms]
4	#2 AND #3
5	(#1 OR #4)
6	((((advanced[Title/Abstract]) OR metastat*[Title/Abstract]) OR metastas*[Title/Abstract]) OR recurr*[Title/Abstract]) OR progress*[Title/Abstract] OR "neoplasm metastasis"[MeSH Terms] OR “Neoplasm Recurrence, Local”[MeSH Terms]
7	(#5 AND #6)
8	(#7) AND (Guideline[ptyp] OR Practice Guideline[ptyp] or guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title])
9	(#8) AND ("2011/02/01"[PDAT] : "2016/02/23"[PDAT])

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