Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2020-B-407 Pembrolizumab

Stand: Februar 2021

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Pembrolizumab
[zur Therapie des vorbehandelten nicht-resezierbaren oder metastasierenden Magenkarzinoms]

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.	*Nicht angezeigt.*
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Trifluridin/Tipiracil: Beschluss vom 2. April 2020 – Ramucirumab: Beschluss vom 20. Oktober 2016 – Tegafur/Gimeracil/Oteracil: Beschluss vom 20. Dezember 2012
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 bewertendes Arzneimittel:	
Pembrolizumab L01XC18 Keytruda	Zu prüfendes Anwendungsgebiet: Keytruda ist als Monotherapie zur Behandlung der folgenden Tumoren mit MSI -H oder mit einer dMMR bei Erwachsenen angezeigt: - nicht resezierbares oder metastasierendes Magenkarzinom […] mit einem Fortschreiten der Erkrankung während oder nach mindestens einer vorherigen Therapie.
Tegafur / Gimeracil / Oteracil L01BC53 Teysuno	Teysuno ist für die Behandlung von fortgeschrittenem Magenkrebs bei Erwachsenen indiziert bei Gabe in Kombination mit Cisplatin.
5-Fluorouracil L01BC02 generisch	– Fortgeschrittenes Magenkarzinom
Doxorubicin L01DB01 generisch	– fortgeschrittenes Magenkarzinom
Epirubicin L01DB03 generisch	Epirubicin ist für die Behandlung folgender maligner Erkrankungen in Mono- und Kombinationsschemata angezeigt: – fortgeschrittenes Magenkarzinom
Mitomycin L01DC03 generisch	Mitomycin wird in der palliativen Tumortherapie eingesetzt. Die intravenöse Anwendung von Mitomycin ist in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei Erwachsenen mit folgenden Erkrankungen angezeigt: – fortgeschrittenes Magenkarzinom

II. Zugelassene Arzneimittel im Anwendungsgebiet	
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.
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 (siehe Abschnitt 5.1).
Trifluridin/Tipiracil L01BC59 Lonsurf	Lonsurf wird angewendet als Monotherapie zur Behandlung von erwachsenen Patienten mit metastasiertem Magenkarzinom einschließlich Adenokarzinom des gastroösophagealen Übergangs, die bereits mit mindestens zwei systemischen Therapieregimen für die fortgeschrittene Erkrankung behandelt worden sind (siehe Abschnitt 5.1).

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2020-B-407 (Pembrolizumab)

Auftrag von:	Abteilung Arzneimittel
Bearbeitet von:	Abteilung Fachberatung Medizin
Datum:	11. Januar 2021

Gemeinsamer Bundesausschuss, Berlin 2022

Inhaltsverzeichnis

Abkürzungsverzeichnis

5-FU	5-Fluorouracil
AEG-Tumore	Karzinome des gastroösophagealen Übergangs
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CDR	Clinical Decision Rule
CI	Confidence Interval
DCF	Docetaxel, Cisplatin und 5-Fluorouracil
ECF	Epirubicin, Ciasplatin und 5-Fluorouracil
ECRI	ECRI Guidelines Trust
ECX	Epirubicin, Cisplatin und Capecitabin
EK	Expertenkonsens
Embase	Excerpta Medica Database
EOX	Epirubicin, Oxaliplatin und Capecitabin
FAMTX	5-Fluorouracil, Doxorubicin und Methotrexat
FFS	Failure Free Survival
FISH	Fluoreszenz-in-situ-Hybridisierung
FLO	5-Fluorouracil/Folinsäure und Oxaliplatin
FLOT	Docetaxel, Oxaliplatin, und 5-Fluorouracil/Folinsäure
FOLFIRI	Folinsäure, 5-Fluorouracil und Irinotecan
FUP	5-Fluorouracil und Cisplatin
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hazard Ratio
IHC	Immunhistochemie
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IV	Intravenous

LoE	Level of Evidence
MEDLINE	Medical Literature Analysis and Retrieval System Online
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
OS	Overall Survival
PFS	Progression-Free Survival
PLF	5-Fluorouracil, Folinsäure und Cisliplatin
RCT	Randomisierte kontrollierte Studie
RR	Relative Risk
SIGN	Scottish Intercollegiate Guidelines Network
SR	Systematic Review
TRIP	Turn Research into Practice Database
WHO	World Health Organization
XP	Capecitabin und Cisplatin

1 Indikation

Behandlung des nicht resezierbaren oder metastasierenden Magenkarzinoms bei Fortschreiten der Erkrankung nach vorheriger Therapie bei Erwachsenen.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Magenkarzinom, Karzinoms des gastroösophagealen Übergangs und des Adenokarzinoms des Ösophagus* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 05.11.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 2641 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 16 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA-Beschlüsse / IQWiG-Berichte

G-BA, 2020 [5].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Trifluridin/Tipiracil (neues Anwendungsgebiet: metastasiertes Magenkarzinom, vorbehandelte Patienten) vom 2. April 2020.

Anwendungsgebiet

Lonsurf wird angewendet als Monotherapie zur Behandlung von erwachsenen Patienten mit metastasiertem Magenkarzinom einschließlich Adenokarzinom des gastroösophagealen Übergangs, die bereits mit mindestens zwei systemischen Therapieregimen für die fortgeschrittene Erkrankung behandelt worden sind (siehe Abschnitt 5.1).

Zweckmäßige Vergleichstherapie

Erwachsene Patienten mit metastasiertem Magenkarzinom einschließlich Adenokarzinom des gastroösophagealen Übergangs, die bereits mit mindestens zwei systemischen Therapieregimen für die fortgeschrittene Erkrankung behandelt wurden: Best-Supportive-Care

Fazit / Ausmaß des Zusatznutzens

Hinweis auf einen geringen Zusatznutzen.

G-BA, 2016 [7].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 20. Oktober 2016 – Ramucirumab.

Anwendungsgebiet

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 (siehe Abschnitt 5.1 der Fachinformation).

Zweckmäßige Vergleichstherapie & Ausmaß des Zusatznutzens

a) Ramucirumab in Kombination mit Paclitaxel

- Zweckmäßige Vergleichstherapie: Therapie nach Maßgabe des Arztes unter Beachtung der jeweiligen Zulassung.

- Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer Therapie nach Maßgabe des Arztes: Anhaltspunkt für einen geringen Zusatznutzen.

b) Ramucirumab als Monotherapie, wenn die Patienten für eine Kombinationstherapie mit Paclitaxel nicht geeignet sind

- Zweckmäßige Vergleichstherapie: Best-Supportive-Care
- Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-Supportive-Care: Ein Zusatznutzen ist nicht belegt.

G-BA, 2012 [6].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 20. Dezember 2012 - Tegafur / Gimeracil / Oteracil.

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 5-Fluorouracil oder Capecitabin.

Fazit / Ausmaß des Zusatznutzens

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der Zweifachkombination von Cisplatin mit 5-Fluorouracil oder Capecitabin: Der Zusatznutzen im Verhältnis zur zweckmäßigen Vergleichstherapie gilt als nicht belegt.

3.2 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.3 Systematische Reviews

Guo, X. et al., 2020 [8].

A comparison between triplet and doublet chemotherapy in improving the survival of patients with advanced gastric cancer: a systematic review and meta-analysis.

Fragestellung

to compare the efficacy, prognosis, and toxicity of triplet chemotherapy with doublet chemotherapy in patients with advanced gastric cancer.

Methodik

Population:

- patients have pathologically proven advanced, recurrent, metastatic, or unresectable adenocarcinoma of the stomach or gastroesophageal junction

Intervention/Komparator:

- first-line chemotherapy setting: studies that compared at least two arms that consisted of the following chemotherapeutic drugs: fluoropyrimidine (F, either 5-fluorouracil [5-FU], capecitabine [Cap], or S-1), platinum (cisplatin [Cis] and oxaliplatin [Ox]), taxane ([T] and paclitaxel), anthracycline (doxorubicin [D] and epirubicin [E]), irinotecan (I), etoposide (E), semustine (Me), mitomycin (MMC), methotrexate (Mtx), uracil (U), or tegafur (Te)

Endpunkte:

- overall survival, progression-free survival (PFS), time to progress (TTP), objective response rate (ORR), and toxicity.

Recherche/Suchzeitraum:

- PubMed, Embase, and the Cochrane Register of Controlled Trials and all abstracts from the annual meetings of the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology conferences up to October 2018

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 23 RCTs involving 4540 patients and 8 types of triplet and doublet chemotherapy regimens
- Of these studies, 2380 were assigned to the triplet and 2160 to the doublet group / patients in every study ranged from 25 to 741

Charakteristika der Population:

- Median age was 51 to 70 years. In these studies, 2039 and 2501 (44.9 and 55.1%, respectively) patients were Asians and Westerners, respectively. PS was well balanced in all studies. All patients had an ECOG PS of 0 or 1.

Studienergebnisse:

- Triplet chemotherapy was superior compared with doublet chemotherapy in terms of improving median OS (HR = 0.92; 95% CI, 0.86–0.98; P = 0.02) and PFS (HR = 0.82; 95% CI, 0.69–0.97; P = 0.02) and TTP (HR = 0.92; 95% CI, 0.86–0.98; P = 0.02) and ORR (OR = 1.21; 95% CI, 1.12–1.31; P < 0.0001) among overall populations.
- Compared with doublet chemotherapy, subgroup analysis indicated that OS improved with
  - fluoropyrimidine-based (HR = 0.80; 95% CI, 0.66–0.96; P = 0.02), platinum-based (HR = 0.75; 95% CI, 0.57–0.99; P = 0.04), and
  - other drug-based triplet (HR = 0.79; 95% CI, 0.69–0.90; P = 0.0006) chemotherapies while
  - not with anthracycline-based (HR = 0.70; 95% CI, 0.42–1.15; P = 0.16), mitomycin-based (HR = 0.81; 95% CI, 0.47–1.39; P = 0.44), taxane-based (HR = 0.91; 95% CI, 0.81–1.01; P = 0.07), and irinotecan-based triplet (HR = 1.01; 95% CI, 0.82–1.24; P = 0.94) chemotherapies.
- For different patients, compared with doublet chemotherapy, triplet chemotherapy improved OS (HR = 0.89; 95% CI, 0.81–0.99; P = 0.03) among Western patients but did not improve (HR = 0.96; 95% CI, 0.86–1.07; P = 0.47) that among Asian patients.

Anmerkung/Fazit der Autoren

In conclusion, compared with doublet chemotherapy, triplet chemotherapy, as a first-line treatment, improved OS, PFS, TTP, and OS in patients with advanced gastric cancer among overall populations, especially for fluoropyrimidine- or platinum-based triplet chemotherapy, which showed a significant improvement in OS. In the subgroup analyses, triplet chemotherapy improved OS in Western but not in Asian patients.

Zheng, Z. et al., 2020 [16].

Oncological outcomes of addition of anti-PD1/PD-L1 to chemotherapy in the therapy of patients with advanced gastric or gastro-oesophageal junction cancer: A meta-analysis.

Fragestellung

The purpose of this study is to analyze the significance of antiPD1/PD-L1 for advanced GC/GEJC.

Methodik

Population:

- patients were clinical diagnosis of advanced G/GEJ progresses on chemotherapy after failure of prior therapy

Intervention:

- chemotherapy plus PD-1/PD-L1 versus

Komparator:

- chemotherapy alone

Endpunkte:

- efficacy and toxicity (siehe Ergebnisteil)

Recherche/Suchzeitraum:

- Pubmed, Embase, Cochrane library up to June 2019

Qualitätsbewertung der Studien:

- Cochrane Collaboration's "Risk of bias" tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 3 RCTs

Charakteristika der Population:

Table 1

Brief description of included eligible studies.

	Treatment regimen		No. of patients		Age (mean)		Sex (male)	
Study year	PD-1/PD-L1	Chemotherapy alone	PD-1/PD-L1	Chemotherapy alone	PD-1/PD-L1	Chemotherapy alone	PD-1/PD-L1	Chemotherapy alone
Kohei Shitara 2018	Pembrolizumab	Paclitaxel	296	296	62.5	60	202	208
Kang 2017	Nivolumab	Placebo	330	163	62	61	229	119
Y.-J. Bang 2018	Avelumab	Irinotecan; paclitaxel; BSC only	185	186	59	61	140	127

BSC = best supportive care, PD-1 = programmed death 1, PD-L1 = programmed death ligand-1.

Qualität der Studien:

- Moderate evidence

Studienergebnisse:

- Pooled analysis of overall survival (OS) comparing chemotherapy plus PD-1/PD-L1 with chemotherapy alone Pooling the OS demonstrated that PD-1/PD-L1 targeted agents did lead to an OS advantage (OR=0.66, 95%CI= 0.47–0.92, P=.02).
- Also, subgroup analysis revealed GEJC (OR=0.73, 95%CI=0.58–0.93, P=.01) was associated with better OS, but the GC group (OR=0.88, 95%CI=0.64–1.20, P=.41).
- Pooled analysis of progression-free survival (PFS) comparing chemotherapy plus PD-1/PD-L1 with chemotherapy alone Pooled estimates of effect sizes showed that the difference of PFS between two groups was no statistically significant (OR= 0.93, 95%CI=0.62–1.39, P=.72).
- Pooled analysis of AE comparing chemotherapy plus PD-1/ PD-L1 with chemotherapy alone: The pooling AE data did not achieve advantage in the PD-1/PD-L1 targeted agents (OR=0.53, 95%CI=0.13–2.10, P=.36). And results showed that the difference of grade 3 to 5 serious adverse events between two groups was no statistically significant (OR=0.53, 95%CI=0.16–1.74, P=.30)

Anmerkung/Fazit der Autoren

Our study confirms that patients treated with anti-PD-1/PD-L1 therapy had a better superior survival benefit with some but not all survival endpoints and with a comparable adverse event

for advanced GC/GEJC. From an efficacy standpoint, further trials into immune checkpoint therapy that will benefit patients by specific molecular subtype and genomic alterations, which can be instructive in driving therapy decisions, while conferring with manageable safety profile. To further validate this treatment, the effect and safety of PD-1/PD-L1 agents should systematically subgroup analyzed in the near future.

Pan, W. T. et al., 2020 [12].

Role of Systemic Treatment for Advanced/Metastatic Gastric Carcinoma in the Third-Line Setting: A Bayesian Network Analysis.

Fragestellung

To compare the effectiveness and safety of current third-line therapies for metastatic Gastric Cancer (mGC), we conducted this network analysis.

Methodik

Population:

- metastatic GC (mGC) patients

Intervention/Komparator:

- chemotherapy, nivolumab, avelumab, apatinib, ramucirumab, and Trifluridine/tipiracil

Endpunkte:

- PFS, OS, AEs

Recherche/Suchzeitraum:

- Up to Sep 30, 2019

Qualitätsbewertung der Studien:

- Cochrane Handbook's Risk of Bias Assessment Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 24 studies, 7 phase III RCTs (2,655 patients) were included in this network meta-analysis, with an average of 189 (range 69–337) per group and at least 100 cases per group.

Charakteristika der Population:

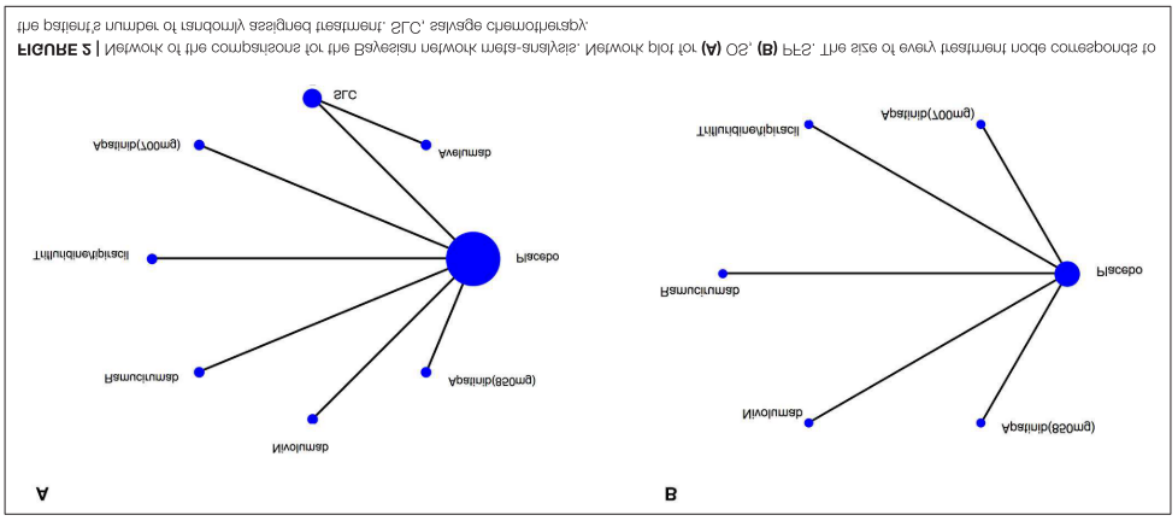
TABLE 1 | Studies included in the meta-analysis.

Study	Number of patients	Age (years) median(range)	Sex (% male)	Median OS in months (range)	OS HR (95%CI)	Median PFS In months (range)	PFS HR (95% CI)	HighGrade AE, %	Phase of the trial
Li et al. (12)									3
Apatinib (800 mg)	176	58 (23–71)	75	6.5 (4.8–7.6)	0.7 (0.5–0.9)	2.6 (2–2.9)	0.4 (0.3–0.6)	69.2	
Placebo	91	58 (28–70)	75.8	4.7 (3.6–5.4)	1 (Ref)	1.8 (1.4–1.9)	1 (Ref)	42.9	
Kang et al. (8)									3
Nivolumab	330	62 (54–69)	69	5.3 (4.6–6.4)	0.6 (0.5–0.8)	1.6 (1.5–2.3)	0.6 (0.5–0.8)	10	
Placebo	163	61 (53–68)	73	4.1 (3.4–4.9)	1 (Ref)	1.5 (1.4–1.5)	1 (Ref)	4	
Fuchs et al. (13)									3
Ramucirumab	238	60 (52–67)	71	5.2 (2.3–9.9)	0.8 (0.6–0.9)	2.1 (1.3–4.2)	0.5 (0.4–0.6)	57	
Placebo	117	60 (51–71)	68	3.8 (1.7–7.1)	1 (Ref)	1.3 (1.1–2.1)	1 (Ref)	58	
Shitara et al. (14)									3
Trifluridine/tipiracil	337	64 (56–70)	75	5.7 (4.8–6.2)	0.7 (0.6–0.9)	2 (1.9–2.3)	0.6 (0.5–0.7)	80	
Placebo	170	63 (56–69)	69	3.6 (3.1–4.1)	1 (Ref)	1.8 (1.7–1.9)	1 (Ref)	58	
Ryu et al. (15)									3
Apatinib(700 mg)	308	60 (21–91)	78.3	5.8	0.9 (0.7–1.2)	2.8	0.6 (0.5–0.8)	47.6	
Placebo	105	61 (27–82)	73.7	5.1	1 (Ref)	1.8	1 (Ref)	43.7	
Kang et al. (9)									3
SLC	133	56 (31–83)	70	5.3 (4.1–6.5)	0.7 (0.5–0.9)	NR	NR	87	
Placebo	69	56 (32–74)	64	3.8 (3.1–4.5)	1 (Ref)			75	
Bang et al. (11)									3
avelumab	185	59 (29–86)	75.7	4.6 (3.6–5.7)	1.1 (0.9–1.4)	1.4 (1.4–1.5)	1.7 (1.4–2.2)	9.7	
SLC	186	61 (18–82)	68.3	5 (4.5–6.3)	1 (Ref)	2.7 (1.8–2.8)	1 (Ref)	38.9	

Qualität der Studien:

- Of the included studies, the methodological quality was good, with only one trial verbally reported and not accurately assessing its risk bias. Overall, all remaining studies had no significant high risk of bias with respect to random sequence generation, allocation concealment, incomplete outcome data, and selective reporting of outcomes

Studienergebnisse:



- It turns out that for overall survival, nivolumab has the highest probability to be the optimal choice for overall survival (OS).

- For patients with no peritoneal metastases, the network meta-analysis showed that Nivolumab (HR: 0.64; 95% CI: 0.48–0.85) and Trifluridine/tipiacil (HR: 0.66; 95% CI: 0.51–0.86) were associated with significantly higher improvement in OS than placebo.
- However, patients with peritoneal metastases could not benefit from nivolumab, ramucirumab, or Trifluridine/tipiacil, when compared with a placebo.
- For progression-free survival, apatinib (850mg) was the most likely candidate, followed by ramucirumab. Statistically, Apatinib (850mg), Trifluridine/tipiacil, and SLC had higher incidences of high-grade adverse events (AEs) than placebo.

Anmerkung/Fazit der Autoren

Our results indicated that nivolumab could provide the best OS benefit for mGC. Apatinib (850mg) is the best choice for PFS. Nivolumab might also be a potential option for mGC, as it had the most favorable balance between effectiveness and safety. Given the limitations of this study, more head-to-head comparative RCTs are needed to verify our conclusions.

Kommentar zum Review:

- Siehe auch: Chan, W. L. et al., 2017 [2]

Zheng, T. et al., 2020 [15].

Efficacy and safety of paclitaxel with or without targeted therapy as second-line therapy in advanced gastric cancer: A meta-analysis.

Fragestellung

to evaluate the efficacy and safety of the two therapy regimes.

Methodik

Population:

- advanced gastric cancer patients

Intervention/Komparator:

- PTX + targeted therapy vs. PTX alone as second-line chemotherapy;

Endpunkte:

- progression-free survival and overall survival, objective response rate and adverse events

Recherche/Suchzeitraum:

- PubMed, Embase, Web of Science and the Cochrane Library published between January 2000 and August 2019

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- A total of 4 randomized controlled trials with 1574 patients (PTX + targeted therapy, n=786; PTX, n=788)

Charakteristika der Population:

Table 1
Characteristics of included study.

Study	Research time	Country	Phase	Regimen	Number	Male (%)	Mean age (range)	NCT number	Published journal
Wilke.2014	Dec 2010 to Sept 2012	27 countries	III	Ramucirumab + paclitaxel	330	229 (69%)	61 (25–83)	NCT01170663	Lancet Oncol
				Placebo + paclitaxel	335	243 (73%)	61 (24–84)		
Satoh.2014	March 2008 to January 2012	Asia	III	Lapatinib + paclitaxel	132	101 (77%)	60.8 (32-79)	NCT00486954	J Clin Oncol
				paclitaxel	129	106 (82%)	60.4 (22–80)		
Bang.2015	February 2010 to May 2012	Korea	II	olaparib + paclitaxel	62	49 (79%)	63.0 (31–77)	NCT01063517	J Clin Oncol
				Placebo + paclitaxel	62	44 (71%)	60.5 (25–79)		
Bang.2017	Sept 2013 to March 2016	Asia	III	olaparib + paclitaxel	263	174 (66%)	58 (49–67)	NCT01924533	Lancet Oncol
				Placebo + paclitaxel	262	185 (71%)	59 (50–65)		

Dec = december, J Clin Oncol = journal of clinical oncology, Sept = september.

Qualität der Studien:

- In terms of the Cochrane Risk of Bias assessment, only 1 study has not described the blinding of participants and personnel, so it has “unclear” risk of corresponding bias. No other additional risk of bias was present in all trials. Hence, all the included trials were of high quality.

Studienergebnisse:

- As compared with PTX monotherapy, PTX + targeted therapy significantly improved progression-free survival (hazard ratio =0.88, 95% confidence interval [CI] 0.84–0.92, P<.001), overall survival (hazard ratio =0.90, 95% CI: 0.86–0.95, P<.001) and was associated with a better objective response rate (RR=1.80; 95% CI: 1.45–2.24; P<.001).
- PTX+targeted therapy group significantly increased incidences of grade 3 to 5 neutropenia, fatigue and neuropathy (P<.05).
- No statistically significant differences were observed in the incidences of grade 3 to 5 anemia, decreased appetite, nausea, diarrhea and abdominal pain between the two treatments (P >.05)

Anmerkung/Fazit der Autoren

In conclusion, PTX+targeted therapy showed significantly better survival outcomes compared with PTX alone due to the results of our meta-analysis of RCTs. Major grade 3 to 5 adverse events associated with PTX + targeted therapy were generally manageable and tolerable. Therefore, PTX + targeted therapy could be a considerable second-line option for AGC. In the future, more larger multicenter RCTs should be carried out to verify the efficacy and safety of PTX+targeted therapy.

Zhang, D. et al., 2019 [14].

A Bayesian Network Meta-Analysis for Identifying the Optimal Taxane-Based Chemotherapy Regimens for Treating Gastric Cancer.

Fragestellung

to compare the efficacy and safety of different taxane-based chemotherapy regimens against gastric cancer.

Methodik

Population:

- participants were diagnosed as gastric cancer

Intervention/Komparator:

- Taxane-based chemotherapy regimens

Endpunkte:

- PFS, ORR, AEs

Recherche/Suchzeitraum:

- PubMed, Cochrane Library, and OVID were searched for all eligible randomized controlled trials (RCTs) from inception to May 29, 2017

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 37 RCTs involving 7,178 patients with gastric cancer (NMA incorporated 10 taxane-based chemotherapy regimens)

Charakteristika der Population:

- ages ranged from 19 to 87 years old

Qualität der Studien:

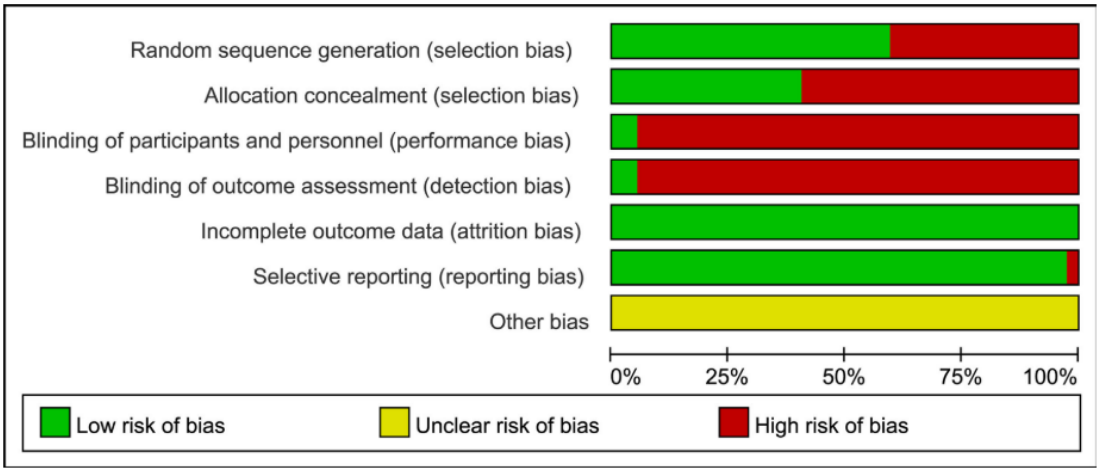


FIGURE 3 | Risk of bias graph.

Studienergebnisse:

TABLE 2 | The NMA result of comparisons with significant difference.

Outcome	Comparison	OR (95% CI)	Outcome	Comparison	OR (95% CI)	Outcome	Comparison	OR (95% CI)
OS	TO vs. mTCF	3.04 (1.13,7.75)	ORR	F vs. IC	7.83 (1.34,78.44)	Neutropenia	RT vs. mTCF	0.043 (0.0034,0.51)
OS	T vs. TF	2.72 (1.19,6.33)	ORR	F vs. mCF	7.08 (1.38,62.19)	Neutropenia	RT vs. T	0.19 (0.063,0.53)
OS	TC vs. TF	2.79 (1.26,5.87)	ORR	CF vs. TO	2.57 (1.43,4.59)	Neutropenia	TOF vs. mTCF	0.067 (0.0064,0.62)
OS	I vs. TF	3.88 (1.27,12.98)	ORR	F vs. TC	6.49 (1.44,57.02)	Neutropenia	TCF vs. mTCF	0.18 (0.041,0.77)
OS	TO vs.TOF	2.90 (1.63,5.04)	ORR	F vs. TCF	6.44 (1.46,54.55)	Neutropenia	TC vs. mTCF	0.16 (0.030,0.87)
OS	TF vs. TO	0.25 (0.14,0.48)	ORR	CF vs. TF	2.63 (1.57,4.42)	Leukopenia	CF vs. EOF	40.09 (1.01,17)
OS	TF vs. mTOF	0.28 (0.11,0.77)	ORR	F vs. TO	9.00 (1.96,80.7)	Leukopenia	IF vs. mTCF	31.71 (1.06,1145)
OS	TCF vs. TO	0.40 (0.20,0.86)	ORR	F vs. TF	9.32 (2.02,81.72)	Leukopenia	ECF vs. mTCF	35.27 (1.73,1004)
OS	TOF vs. mTOF	0.39 (0.17,0.89)	ORR	EOF vs. F	0.085 (0.0079,0.53)	Leukopenia	IC vs. mTCF	5.87 (1.88,2292)
OS	RT vs. T	0.61 (0.41,0.91)	ORR	TF vs. mTCF	0.32 (0.14,0.72)	Leukopenia	I vs. mTCF	78.15 (2.09,3545)
OS	OF vs. TO	0.41 (0.19,0.93)	ORR	OF vs. RT	0.49 (0.33,0.75)	Leukopenia	TOF vs. mTCF	31.66 (2.09,705.4)
PFS	TO vs. TOF	3.80 (1,17.87)	ORR	TO vs. mTCF	0.32 (0.14,0.77)	Leukopenia	TO vs. mTCF	31.77 (2.36,629.7)
PFS	F vs. RT	24.38 (1.07,1227)	ORR	EOF vs. mTCF	0.25 (0.072,0.91)	Leukopenia	TF vs. mTCF	41.55 (3.14,819.4)
PFS	F vs. TOF	41.09 (1.09,3852)	ORR	TC vs. mTCF	0.45 (0.20,0.97)	Leukopenia	TCF vs. mTCF	39.38 (3.43,699)
ORR	F vs. OF	6.73 (1.01,70.23)	ORR	TCF vs. mTCF	0.46 (0.21,0.98)	Leukopenia	T vs. mTCF	71.42 (3.58,1889)
ORR	ECF vs. TC	1.65 (1.02,2.67)	Neutropenia	CF vs. TOF	8.58 (1.10,71.92)	Leukopenia	TC vs. mTCF	52.76 (3.68,1145)
ORR	F vs. TOF	5.69 (1.03,54.36)	Neutropenia	CF vs. RT	13.6 (1.31,134.9)	Leukopenia	OF vs. mTCF	79.97 (5.26,1821)
ORR	I vs. TF	3.42 (1.04,11.04)	Neutropenia	I vs. mTOF	44 (1.53,1576)	Leukopenia	F vs. mTCF	120.6 (7.20,2709)
ORR	IF vs. TF	1.81 (1.04,3.06)	Neutropenia	TF vs. mTOF	47.1 (1.65,1685)	Leukopenia	CF vs. mTCF	75.34 (7.90,1085)
ORR	CF vs. TCF	1.81 (1.06,3.15)	Neutropenia	F vs. mTOF	45.58 (1.66,1546)	Leukopenia	mTCF vs. mTF	0.016 (0.00058,0.34)
ORR	IF vs. TO	1.76 (1.06,2.83)	Neutropenia	CF vs. TO	9.09 (2.01,41.02)	Leukopenia	mTCF vs. mTOF	0.029 (0.00093,0.63)
ORR	T vs. TC	1.62 (1.08,2.33)	Neutropenia	TO vs. mTOF	19.06 (2.04,249.3)	Leukopenia	EOF vs. F	0.016 (0.00025,0.88)
ORR	F vs. mTF	5.94 (1.10,57.33)	Neutropenia	TOF vs. mTOF	19.9 (2.18,258)	Vomiting	EOF vs. TOF	13.35 (1.15,518.5)
ORR	F vs. IF	5.13 (1.12,46.13)	Neutropenia	EOF vs. mTOF	113.3 (3.41,4490)	Vomiting	TF vs. TOF	4.18 (1.29,12.63)
ORR	CF vs. EOF	3.26 (1.13,9.66)	Neutropenia	TC vs. mTOF	49.29 (4.02,837.2)	Vomiting	ECF vs. TOF	5.50 (1.31,29.62)
ORR	ECF vs. TO	2.29 (1.17,4.53)	Neutropenia	T vs. mTOF	69.65 (4.26,1502)	Vomiting	TO vs. TOF	6.87 (2.15,25.18)
ORR	CF vs. mCF	1.97 (1.19,3.37)	Neutropenia	TCF vs. mTOF	55.13 (4.67,883.8)	Vomiting	IF vs. TOF	19.34 (270,157.5)
ORR	T vs. TO	2.25 (1.21,4.07)	Neutropenia	OF vs. mTOF	100.2 (7.10,1751)	Vomiting	F vs. IF	0.029 (0.00083,0.46)
ORR	ECF vs. TF	2.36 (1.24,4.47)	Neutropenia	CF vs. mTOF	174.7 (12.56,3152)	Vomiting	CF vs. TO	0.29 (0.11,0.90)
ORR	CF vs. TC	1.84 (1.33,2.60)	Neutropenia	mTCF vs. mTOF	305.8 (18.62,6592)	Vomiting	CF vs. IF	0.11 (0.013,0.94)
ORR	T vs. TF	2.31 (1.34,3.95)	Neutropenia	TO vs. mTCF	0.063 (0.010,0.37)	Vomiting	TOF vs. mTCF	0.21 (0.042,0.99)

- According to the results of cluster analysis, compared with other taxane-based chemotherapy regimens, the regimens of TOF, mTCF, and TF were associated with the most favorable clinical efficacy in improving OS, PFS, and ORR. On the other hand, the regimens of T and mTF had the potential to be the most tolerable and acceptable therapeutic alternative in terms of ADRs.

Anmerkung/Fazit der Autoren

In conclusion, the current evidence suggests that the combination of taxanes (paclitaxel or docetaxel) and fluorouracil was associated with the most preferable and beneficial option for patients with gastric cancer, although additional results from multicenter trials and high-quality studies will be pivotal for supporting our findings.

Kommentare zum Review

- Siehe auch: Shi, J. et al., 2017 [13]

Li, B. et al., 2019 [10].

Docetaxel, cisplatin, and 5-fluorouracil compared with epirubicin, cisplatin, and 5-fluorouracil regimen for advanced gastric cancer: A systematic review and meta-analysis.

Fragestellung

To compare the efficacy and safety of DCF and ECF regimens by conducting this meta-analysis.

Methodik

Population:

- Patients diagnosed with metastatic or advanced gastric cancer

Intervention:

- docetaxel, cisplatin, and 5-fluorouracil (DCF)

Komparator:

- epirubicin, cisplatin, and 5fluorouracil (ECF)

Endpunkte:

- PFS, OS, DCR, ORR, AEs

Recherche/Suchzeitraum:

- PubMed, EMBASE, Ovid Medline, Science Direct, Web of Science, The Cochrane Library and Scopus was performed up to August 31, 2018

Qualitätsbewertung der Studien:

- Jadad scale (5-point) & the Newcastle-Ottawa Scale (NOS, 9-point)

Ergebnisse

Anzahl eingeschlossener Studien:

- seven studies involving a total of 598 patients / four RCTs and three cohort studies

Charakteristika der Population:

Table 2 Characteristics of the included studies

Ref.	Yr	Intervention and control	Samples	ORR (%)	OS	PFS	Design	Quality (score)
Sadighi *et al*[18]	2006	DCF: D 60 mg/m^2, d1, C 60 mg/m^2, d1, F 750 mg/m^2/d, d1-5 (21)	44	42.0	-	-	RCT	5/5
		ECF: E 60mg/m^2, d1, C 60 mg/m^2, d1, F 750 mg/m^2/d, d1-5 (21)	42	37.0	-	-		
Roth *et al*[10]	2007	DCF: D 85mg/m^2, d1, C 75 mg/m^2, d1, F 300 mg/m^2/d, d1-14 (21)	41	36.6	10.4	4.6	RCT	4/5
		ECF: E 50 mg/m^2, d1, C 60 mg/m^2, d1, F 200 mg/m^2/d, d1-21 (21)	40	25.0	8.3	4.9		
Abbasi *et al*[19]	2010	DCF: D 75mg/m^2, d1, C 75 mg/m^2, d1, F 750 mg/m^2/d, d1-5 (21)	30	56.3	10.81	6.81	RS	6/9
		ECF: E 50 mg/m^2, d1, C 60 mg/m^2, d1, F 200 mg/m^2/d, d1-21 (21)	113	31.3	8.06	5.13		
Gao *et al*[11]	2010	DCF: D 60 mg/m^2, d1, C 25 mg/m^2, d1-3, F 1000 mg/m^2, 46 h, pumping (21)	32	59.3	-	-	RCT	5/5
		ECF: E 50 mg/m^2, d1, C 25 mg/m^2, d1-3, F 1000 mg/m^2, 46 h, pumping (21)	32	32.6	-	-		
Kilickap *et al*[8]	2011	DCF: D 75 mg/m^2, d1, C 75 mg/m^2, d1, F 750 mg/m2/d, d1-5 (21)	40	40.0	9.6	5.8	RS	7/9
		ECF: E 50 mg/m^2, d1, C 60 mg/m^2, d1, F 250 mg/m^2/d, d1-21 (21)	40	30.0	10.1	4.4		
Teker *et al*[12]	2014	DCF: D 50-75 mg/m^2, d1, C 50-75 mg/m^2, d1, F 500-750 mg/m^2/d, d1-5 (21)	42	26.2	11	6.0	RS	9/9
		ECF: E 50 mg/m^2, d1, C 60 mg/m^2, d1, F 200 mg/m^2/d, d1-21 (21)	44	29.5	10	6.0		
Babu *et al*[9]	2017	DCF: D 75 mg/m^2, d1, C 60 mg/m^2, d1, F 750 mg/m^2/d, d1-5 (21)	28	46.4	12.5	7.5	RCT	3/5
		ECF: E 50 mg/m^2, d1, C 60 mg/m^2, d1, F 750 mg/m^2/d, d1-5 (21)	30	26.7	9.4	5.8		

ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; ECF: Epirubicin, cisplatin, and 5-fluorouracil; DCF: Docetaxel, cisplatin, and 5-fluorouracil; RCT: Randomized controlled trial.

Qualität der Studien:

- According to the Jadad scale and NOS, five studies were of high quality (four RCTs and one cohort study), and two cohort studies were of medium quality

Table 1 Quality assessment of all included studies

Study	Selection	Comparability	Exposure	Randomization	Masking	Accountability of all patients	Quality (score)
Randomized controlled trial							
Sadighi *et al*[18], 2006				**	**	*	5
Roth *et al*[10], 2007				**	*	*	4
Gao *et al*[11], 2010				**	**	*	5
Babu *et al*[9], 2017				*	*	*	3
Retrospective study							
Abbasi *et al*[19], 2010	***	**	*				6
Kilickap *et al*[8], 2011	***	**	**				7
Teker *et al*[12], 2014	****	**	***				9

Studienergebnisse:

- The pooled hazard ratios between the DCF and ECF groups were comparable in PFS (95%CI: 0.58-1.46, P = 0.73), OS (95%CI: 0.65-1.10, P = 0.21), and total AEs (95%CI: 0.93-1.29, P = 0.30).
- The DCF group was significantly better than the ECF group in terms of ORR (95%CI: 1.13-1.75, P = 0.002) and DCR (95%CI: 1.03-1.41, P = 0.02).
- However, the incidence rate of grade 3-4 AEs was also greater in the DCF group than in the ECF group (95%CI: 1.16-1.88, P = 0.002), especially for neutropenia and febrile neutropenia.

Anmerkung/Fazit der Autoren

This study is the latest meta-analysis to compare DCF and ECF regimens for advanced gastric cancer. From this result, we conclude that DCF regimen seems to be more suitable for advanced gastric cancer than the ECF regimen. This finding is extremely important for the research and guidance of clinical medication in related fields. DCF regimen, like most drugs, is not perfect and in some respects shows some unsatisfactory aspects. We cannot deny the effectiveness of DCF in the treatment of advanced gastric cancer, but we cannot ignore its side effects.

Cheng, J. et al., 2019 [4].

Systemic therapy for previously treated advanced gastric cancer: A systematic review and network meta-analysis.

Fragestellung

a systematic review and network meta-analysis featuring systemic therapy for previously treated advanced gastric cancer.

Methodik

Population:

- Participant (patients with locally advanced inoperable, recurrent or metastatic gastric cancer, including gastro-esophageal junction cancer)

Intervention:

- second or further line systemic therapies with cytotoxic chemotherapies or targeted medications after previous treatments

Komparator:

- paclitaxel plus ramucirumab in second-line setting and placebo in refractory setting

Endpunkte:

- survival or safety analysis

Recherche/Suchzeitraum:

- PubMed, Web of Science, Cochrane Central Register of Controlled Trials and Embase were comprehensively examined. Additionally, we also thoroughly searched major databases for meeting abstracts, including ASCO and ESMO Meeting Library. The searching process started at June 1st until August 12th of 2018, covering the possible trials published from inception to August 2018.

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 36 randomized controlled trials were eligibly included into our systematic review, corresponding to 8436 participants
- Among 36 eligible trials, 27, 5, 1 and 3 studies reported second-line only, second and further line, third-line only as well as third and further line treatment respectively

Charakteristika der Population:

- Median age was around 60 and the sex ratio was male dominant
- The majority of trials recruited unselected patients in terms of pathological specificity (n=31), while only a few investigations focused on HER2 (n=4) and FGFR2 (n=1) positive patients respectively
- Moreover, patients from 30 studies received fluoropyrimidine-based first-line regimens and predominantly, patients were metastatic measurable cases and had a PS of either 0 or 1.

Qualität der Studien:

- Overall, the included studies had low risk of bias since more than half of the assessment parameters were scored as low risk of bias (60%), while unclear risk (24%) or high risk of bias (16%) took up relatively small proportions. None of the eligible studies were in high risk of bias concerning methodological design.
    - Specifically, since the majority of trials were centrally allocated and adequately randomized, 56% and 67% of the studies were evaluated as low risk of bias concerning random sequence generation and allocation concealment respectively, while no high risk of bias was reported in these two key domains. Largely due to open-label design, 69% of the include trials were scored as high risk of bias in terms of blinding or participants and personnel. Due to independent response reviewing, nearly half of the studies were

assessed as low risk of bias in terms of blinding of outcome assessment (47%). In addition, because most of the studies were analyzed based on the intention-to-treat population as well as had reported enough endpoints, 89% and 83% of the eligible trials had low risk of bias in terms of incomplete outcome data and selective reporting respectively. Moreover, since the majority of studies were completely performed without early termination and also described adequate baseline details, half of the studies were appraised as low risk of bias with respect to other source of bias (50%).

Studienergebnisse:

- Second-line unselected patients with fluoropyrimidine-based first-line regimens

  OS:

  - Since paclitaxel plus ramucirumab (PRa) was the standard second-line regimen, “PRa” was therefore selected as the common comparator. Based on P-score ranking of the network meta-analysis, Paclitaxel plus olaparib (“PO”) (network HR 95% CI: 1.00 (0.70–1.28), P-score=0.909) was the best ranking node, however which was nearly identical to common comparator “PRa” (network HR 1.00, P-score= 0.907).
  - Since no direct evidences between “PO” and “PRa” had been reported, this ranking was statistically generated by network estimation via the pairwise comparisons between Paclitaxel (“P”) versus “PO” (random HR 95% CI: 1.34 (1.12–1.61)) and “P” versus “PRa” (random HR 95%CI: 1.34 (1.12–1.59)).
  - Subgroups: There were totally 6 subgroups, including fluoropyrimidine monotherapy, fluoropyrimidine plus platinum, eastern population, western population, performance status (0) and performance status (1). Due to insufficient studies to construct networks, we could not analyze the subgroup results of fluoropyrimidine monotherapy and western population in a quantitative way. As a result, “PO” was the top-ranking node with insignificant slight margin over “PRa” in subgroups of fluoropyrimidine plus platinum first-line regimen, eastern population as well as performance status (0), while “PRa” reigned the hierarchy among patients with performance status (1).

  PFS:

  - PRa became the optimal node in the entire hierarchy (network HR 1.00, P-score=0.983) and showed significant superiority against “PO” which ranked in the second place (network HR 95% CI: 1.39 (1.10–1.76), P-score=0.701).

  ORR:

  - PRa again ranked in the first place for achieving objective response rate (network RR 1.00, P-score=0.925), displaying insignificant superiority over “PO” (network RR 95% CI: 0.88 (0.54–1.42), P-score=0.840).

  Hematological adverse events:

  - Pembrolizumab (“Pe”) was the most tolerable node in the ranking (network RR 95% CI: 0.09 (0.03-0.26), P-score=1.000). Meanwhile, “PO” ranked in the middle of the hierarchy (network RR 95% CI: 0.80 (0.42–1.54), P-score=0.434) and was slightly better than “PRa” (network RR 1.00, P-score=0.267). Irinotecan plus cisplatin (“IC”) versus Irinotecan (“I”) was the major cause of significant heterogeneity inside the network (I2=65.64%, P=0.027). After removing either study responsible for “IC” versus “I”, including Nishikawa 2015-1 (Nishikawa et al., 2015a) and (Higuchi et al., 2014), the overall heterogeneity reduced to low level (I2=21.42%) and the relative ranking of nodes remained unchanged (data not shown).

Non-hematological adverse events:

- Again, “Pe” was the most tolerable node concerning non-hematological adverse events (network RR 95% CI: 0.42 (0.16–1.08), P-score=0.942). Moreover, “PO” ranked in the third place (network RR 95% CI: 0.68 (0.32–1.45), P-score=0.755) and was also slightly superior than “PRa” (network RR 1.00, P-score=0.505).

- Second-line HER2 positive patients: In terms of survival efficacies, among patients with trastuzumab-free first-line regimens, neither capecitabine plus lapatinib (HR 95% CI: 1.06 (0.34–3.29)) nor paclitaxel plus lapatinib (HR 95%CI: 0.84 (0.64–1.11)) surpassed their corresponding monotherapies lapatinib and paclitaxel respectively. Similarly, despite of adding trastuzumab into first-line regimens, trastuzumabbased second-line regimens failed to gain significant survival superiority over taxane monotherapy (HR 95% CI: 1.23 (0.75–1.99) and 1.15 (0.87–1.51) respectively). However, it was noteworthy that paclitaxel plus lapatinib was significantly better than paclitaxel among patients with greater HER2 positivity (IHC3+, n=101, HR 95% CI: 0.59 (0.37-0.93)). In addition, all doublets were comparable to monotherapies regarding adverse events.
- Refractory unselected patients (previously treated by at least two-lines of systemic regimens)

OS:

- “A8” was the best ranking node (network HR 95% CI: 0.49 (0.29-0.84), P-score=0.795) and the only one that was significantly better than common comparator “B”. After removing the source of heterogeneity (Li 2016 (Li et al., 2016)) from the calculation, the systemic heterogeneity level significantly reduced (I2=0%) and “A8” remained as the top node with even more advantage (network HR 95% CI: 0.35 (0.23-0.54), P-score=0.965).

Overall survival for third-line only:

- Again, “A8” topped the ranking as the best node (network HR 95% CI: 0.70 (0.490.99), P-score=0.793) without detecting any systemic heterogeneity (I2=0%), which was significantly better than common comparator “B”.

Table 3
Survival and safety data of studies among refractory patients (third-line or more).

Study	Regimen	Node	Sample size	Overall survival: all refractory cases		Overall survival: third-line only	
				Hazard ratio	Network meta-analysis	Hazard ratio	Network meta-analysis
Bang et al. (2018)	Avelumab Chemotherapy	A C	185 186	1.10 (95% CI, 0.90-1.40)	Included	1.10 (95% CI, 0.90-1.40)	Included
Kang et al. (2012)	Nivolumab Placebo	N B	330 163	0.63 (95% CI, 0.51-0.78)	Included	0.82 (95% CI, 0.50-1.35)	Included
Tebbutt et al. (2016)	Regorafenib Placebo plus BSC	R B	97 50	NA	NA	NA	NA
Li (2016)	Apatinib-850 Placebo	A8 B	176 91	0.71 (95% CI, 0.54-0.94)	Included	0.70 (95% CI, 0.49-0.99)	Included
Ohtsu et al. (2013)	Everolimus Placebo plus BSC	E B	439 217	0.90 (95% CI, 0.70-1.15)	Included	0.90 (95% CI, 0.70-1.15)	Included
Li et al. (2013)	Apatinib-425 Apatinib-850 Placebo	A4 A8 B	46 47 48	A4 vs A8: 1.28 (95% CI, 0.75-2.17) A4 vs B: 0.41 (95% CI, 0.24-0.72) A8 vs B: 0.37 (95% CI, 0.22-0.62)	Included	NA	NA
Kang et al. (2012)	Chemotherapy BSC	C B	133 69	0.81 (95% CI, 0.45-1.46)	Included	0.81 (95% CI, 0.45-1.46)	Included

Study	Progression-free survival: all refractory cases		Objective response rate: all refractory cases		Hematological adverse events: all refractory cases		Non-hematological adverse events: all refractory cases	
	Hazard ratio	Network meta-analysis	Response/total	Network meta-analysis	Event/total	Network meta-analysis	Event/total	Network meta-analysis
Bang et al. (2018)	1.73 (95% CI, 1.40-2.20)	**Not included**	4/185 8/186	**Not included**	0/184 28/177	**Not included**	19/184 70/177	**Not included**
Kang et al. (2012)	0.60 (95% CI, 0.49-0.75)	Included	30/268 0/131	Included	38/330 19/161	Included	153/330 65/161	Included
Tebbutt et al. (2016)	0.32 (95% CI, 0.19-0.55)	Included	NA	NA	NA	NA	NA	NA
Li (2016)	0.44 (95% CI, 0.33-0.60)	Included	5/176 0/91	Included	29/176 6/91	Included	93/176 33/91	Included
Ohtsu et al. (2013)	NA	NA	NA	NA	NA	NA	NA	NA
Li et al. (2013)	A4 vs A8: 1.22 (95% CI, 0.68-2.20) A4 vs B: 0.21 (95% CI, 0.11-0.38) A8 vs 8: 0.18 (95% CI, 0.10-0.34)	Included	6/46 3/47 0/48	Included	11/46 4/47 9/48	Included	22/46 11/47 6/48	Included
Kang et al. (2012)	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: CI: confidence interval; NA: not available.
Naming rules for nodes: Avelumab: A; Chemotherapy: C; Nivolumab: N; Placebo, Placebo plus BSC and BSC: B; Regorafenib: R; Apatinib-850: A8; Everolimus: E; Apatinib-425: A4;
Notes: “Not included” suggested that these data were not included into the specific network calculations due to failure of forming a single network (Since a complete network could not be formed in terms of progression-free survival, objective response rate, hematological and non-hematological adverse events, the network calculations were based on their largest sub-networks accordingly).

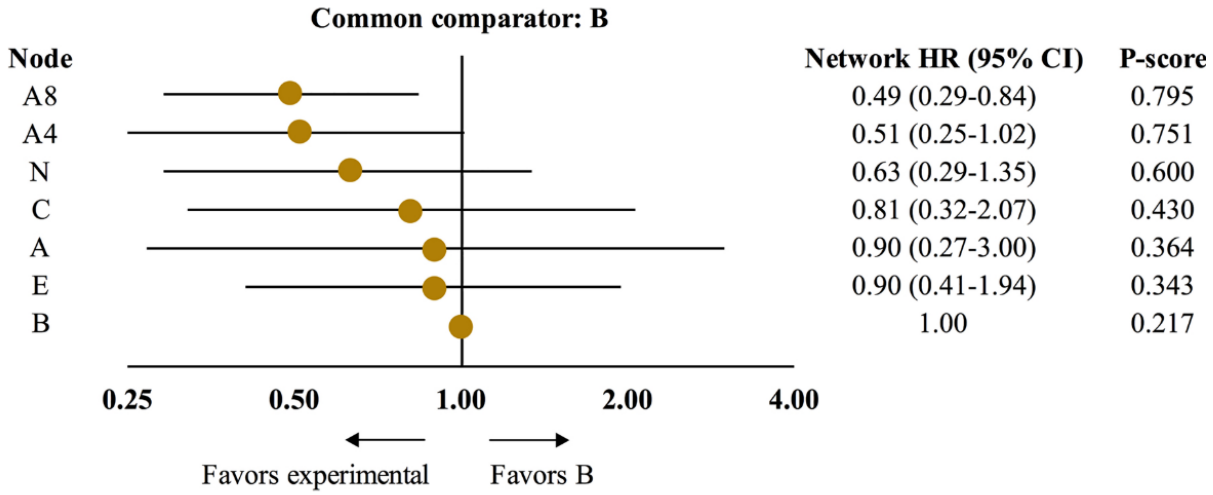


Fig. 2. Network forest plot of overall survival for refractory unselected patients.

Secondary endpoints:

- In terms of progression-free survival, “A4” and “A8” closely ranked as the top two nodes in the hierarchy, both of which were significantly superior to “B”. However, regarding objective response rate, “N” reigned the entire hierarchy by surpassing both “A4” as well as “A8”, all of which were significantly better than common comparator “B”. Moreover, “A8” was the most tolerable node and slightly better than “B” concerning hematological adverse events however significantly worse than common comparator in terms of non-hematological adverse events.

Anmerkung/Fazit der Autoren

In conclusion, paclitaxel plus ramucirumab is the optimal regimen for second-line unselected patients with fluoropyrimidine-based first line regimens while olaparib-based medications also have the potential to become vital alternatives against advanced gastric cancer, especially among eastern population where paclitaxel plus ramucirumab seems less effective. Paclitaxel monotherapy should be recommended as the preferred second-line regimen among HER2 positive patients who receive standard first-line treatment. Both apatinib and nivolumab could be potentially recommended as refractory regimens due to their significant superiority against placebo, however their mutual efficacies still need to be verified in further global investigations.

Chen, C. et al., 2019 [3].

Efficacy and safety of immune checkpoint inhibitors in advanced gastric or gastroesophageal junction cancer: a systematic review and meta-analysis.

Fragestellung

To evaluate the efficacy and safety of ICI in G/GEJ cancer.

Methodik

Population:

- previously treated unresectable locally advanced or metastatic G/GEJ cancer

Intervention/Komparator:

- Treatment with ICI such as CTLA-4, PD-1 or PD-L1 antibodies (siehe Ergebnisteil)

Endpunkte:

- efficacy and safety (siehe Ergebnisteil)

Recherche/Suchzeitraum:

- PubMed, Cochrane Library, Embase, Web of Science were searched up to 30/09/2018

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- A total of 2003 patients from nine clinical trials

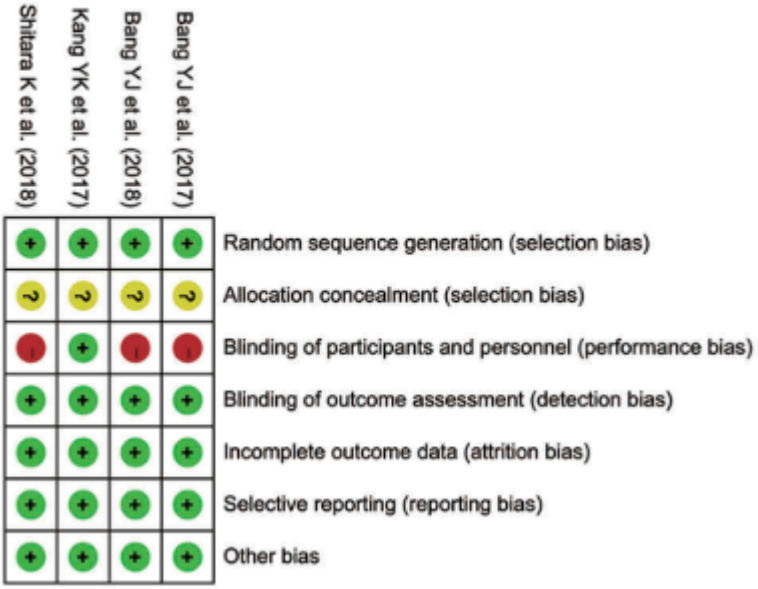
Charakteristika der Population:

Table 1. Main characteristics of included studies.

Study author (year)	Study design	Case experimental *vs* control	Patients characteristics	Intervention methods
Janjigian YY *et al.* (2018)[21]	Non-RCT phase 2	59	Locally advanced or metastatic G/GEJ or esophageal adenocarcinoma with disease progression while taking or intolerance of at least one chemotherapy regimen	Nivolumab (PD-1) 3 mg/kg/2 weeks *i.v.*
Kang YK *et al.* (2017)[22]	RCT phase 3	493 330 *vs* 163	Advanced G/GEJ cancer; refractory to, or intolerant of, at least two previous chemotherapy regimens; ECOG 0-1; ≥ 20 years old	Nivolumab (PD-1) 3 mg/kg/2 weeks *i.v.* *vs* placebo (saline)
Shitara K *et al.* (2018)[23]	RCT phase 3	592 296 *vs* 296	Unresectable metastatic or locally advanced G/GEJ cancer; progression after first-line therapy with a platinum and fluoropyrimidine, or trastuzumab; ECOG 0-1; ≥ 18 years old	Pembrolizumab (PD-1) 200 mg/3 weeks *i.v.* *vs* paclitaxel 80 mg/m^2 *i.v.* d1,8,15/4 weeks
Fuchs CS *et al.* (2018)[24]	Non-RCT phase 2	259	Previously treated advanced G/GEJ cancer; had disease progression after 2 or more prior chemotherapy regimens; ECOG 0-1; ≥ 18 years old	Pembrolizumab (PD-1) 200 mg/3 weeks *i.v.*
Kim ST *et al.* (2018)[25]	Non-RCT phase 2	61	metastatic or recurrent G/GEJ cancer; failure at least 1 line of chemotherapy; ECOG 0-1; ≥ 19 years old	Pembrolizumab (PD-1) 200 mg/3 weeks *i.v.*
Muro K *et al.* (2016)[26]	Non-RCT phase 1b	36	PD-L1-positive advanced GC; did not set a limit for the number of previous treatment regimens; ECOG 0-1; ≥ 18 years old	Pembrolizumab (PD-1) 10 mg/kg/2 weeks *i.v*
Bang YJ *et al.* (2018)[27]	RCT phase 3	371 185 *vs* 186	Recurrent, unresectable, locally advanced, or metastatic G/GEJ cancer; received two prior lines of systemic treatment; ECOG 0-1; ≥ 18 years old	Avelumab (PD-L1) 10 mg/kg/2 weeks *i.v.* *vs* paclitaxel 80 mg/m^2 *i.v.* d1,8,15/4 weeks or irinotecan 150 mg/m^2 *i.v.* d1,15/4 weeks
Bang YJ *et al.* (2017)[28]	RCT phase 2	114 57 *vs* 57	Unresectable locally advanced/metastatic G/GEJ cancer; received a platinum and fluoropyrimidine based chemotherapy regimen; ECOG 0-1; ≥ 18 years old	Ipilimumab (CTLA-4) 10 mg/kg/3 weeks *i.v.* *vs* best supportive care
Ralph C et al. (2010)[29]	Non-RCT phase 2	18	locally advanced or metastatic GC or esophageal adenocarcinoma; previously received at least one cisplatin-based chemotherapy; ECOG 0-1; ≥ 18 years old	tremelimumab (CTLA-4) 15 mg/kg/90 days *i.v.*

Abbreviations: ECOG, Eastern Cooperative Oncology Group, GC, gastric cancer; G/GEJ, gastric or gastroesophageal junction; *i.v.* intravenously; RCT, randomized controlled trial; *vs* versus.

Qualität der Studien:



Studienergebnisse:

- Anti-PD-1 treatment improved the 12-month, 18-month overall survival (OS) rate (RR, 1.79 p =0.013; 2.20 p = 0.011) and prolonged the duration of response (DOR) (MSR, 3.27 p < 0.001).
- The objective response rate (ORR) in PD-L1+ patients was greater than PD-L1− (RR, 4.31 p < 0.001).
- Microsatellite instability-high (MSI-H) patients had higher ORR and disease control rate (DCR) than microsatellite stability (MSS) (RR, 3.40 p< 0.001; 2.26 p= 0.001).
- The most common grade ≥3 treatment-related adverse events (TRAEs) were fatigue, aspartate aminotransferase increased, hepatitis, pneumonitis, colitis, hypopituitarism.
- The TRAE incidence of anti-PD-1/PD-L1 was less than chemotherapy (TRAE RR = 0.64 p<0.001; ≥3 TRAE RR = 0.37 p < 0.001).
- The incidence of ≥3 TRAEs of antiPD-1/PD-L1 treatment was less than that of anti-CTLA-4 (11.7% vs 43.9%).

Anmerkung/Fazit der Autoren

ICI therapy has no particular advantage over standard chemotherapy and has some hysteresis, but once it works, it can achieve long-term clinical benefit for patients with advanced G/GEJ cancer. Moreover, the incidence of adverse events to anti-PD-1/PD-L1 treatment was significantly lower than that of chemotherapy. The patient's response was associated with PD-L1 expression and molecular subtypes in gastric cancer, and PD-L1+, MSI-H, EBV+ or TMB-high patients were more effective. The efficacy of anti-PD-1/PD-L1 was generally better than that of anti-CTLA-4 treatment with fewer adverse reactions. The reason for the inconspicuous results may be that most of the current studies used ICI as a 3rd-line or later monotherapy. Most of the patients included were advanced patients who were relapsed or metastasized after chemotherapy, these patient's physical condition and immune level were poor. What's more, it

is of worth noting the possibility of synergism of ICI with chemotherapy, targeted biologics like VEGFR2 blockade or other ICI drugs and earlier in the adjuvant setting. Thus, ICI, especially PD-1/PD-L1 antibodies, is still very promising in the treatment of gastric cancer.

3.4 Leitlinien

Alberta Health Services, 2020 [1].

Gastric cancer, Version 5.

Zielsetzung/Fragestellung

What are the treatment recommendations for adult patients with gastric cancer?

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert: A formal review of the guideline will be conducted in 2021

Recherche/Suchzeitraum:

- Update: 2020 (This guideline was originally developed in 2010)

LoE/GoR

Levels of Evidence

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinion

Strength of Recommendations

A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Recommendations

HER2 Normal:

- Preferred
  - Oxaliplatin/fluoropyrimidine or FOLFIRI [Level of evidence: I]

    i. A network meta-analysis of systemic therapy for advanced gastric cancer demonstrated that anthracycline triplet chemotherapy and docetaxel, cisplatin, fluorouracil (5FU) triplets showed no benefit over fluoropyrimidine (FP: 5-fluorouracil (5FU) or capecitabine) doublets for overall survival (OS) or progression-free survival (PFS), and increased toxicity was noted.

    ii. A fluoropyrimidine doublet containing oxaliplatin or irinotecan significantly improved overall survival compared with a fluoropyrimidine plus cisplatin (for a fluoropyrimidine plus irinotecan, the HR for death was 0.85, 95% CI 0.71-0.99; for a fluoropyrimidine plus oxaliplatin, the HR was 0.83, 95% CI 0.71-0.98). The cisplatin-fluoropyrimidine doublet was also associated with more grade 3 or 4 toxicity.

    FOLFOX/CAPOX Four phase III trials have compared oxaliplatin to cisplatin based regimens (including ECF) suggesting similar efficacy. A meta-analysis of the REAL-2 trial and two randomized phase II trials comparing oxaliplatin to cisplatin based regimens demonstrated that oxaliplatin was associated with significant improvements in PFS (HR 0.88, 95% CI 0.80-0.98) and overall survival (HR for death 0.88, 95% CI 0.78-0.99), and with less neutropenia, anemia, alopecia, and thromboembolic events, but with more neurotoxicity and diarrhea.

    FOLFIRI

    i. Suitable first or second line regimen for patients with an ECOG of 0-2: Irinotecan (180 mg/m2 IV over ninety minutes) and Leucovorin (400 mg/m2 IV over two hours) followed by 5-Fluorouracil (2400 mg/m2 as 46 hour infusion) every 2 weeks.

    ii. FOLFIRI followed by ECX was compared to the reverse sequence in the first line setting of metastatic GE junction/gastric adenocarcinoma. The dosing and duration of Capecitabine in the ECX arm (oral Capecitabine 1g/m2 twice per day from day 2 to day 15 every 3 weeks) was different than in the REAL-2 trial.

    iii. FOLFIRI followed by ECX was superior to the reverse strategy for the primary endpoint of time to treatment failure (5.08 months versus 4.24 months, HR 0.77, CI 95% 0.63-0.83, p = 0.008). There were no significant differences in PFS or OS between the two sequences.

    iv. Patients who received first line ECX had higher rates of grade 3/4 toxicities, especially hematological ones.

    Palliative Chemotherapy Options (Established in the REAL-2 Clinical Trial) include:

    Triplet regimens with anthracyclines are historically considered as options, but no longer preferred due to increased rates of toxicity, without clear improvements in PFS or OS.

    i. ECX or EOX: Epirubicin (50 mg/m2 IV over twenty minutes) and either Cisplatin (60 mg/m2 IV over one hour) or Oxaliplatin (130 mg/m2 IV over two to five hours) are

administered on day one, and Capecitabine 625 mg/m2 PO Q12h is administered for twenty-one consecutive days.

ii. ECF or EOF: Epirubicin (50 mg/m2 IV over twenty minutes) and either Cisplatin (60 mg/m2 IV over one hour) or Oxaliplatin (130 mg/m2 IV over two to five hours) are administered on day one, and 5Fluorouracil (200 mg/m2/day) is administered as a continuous intravenous infusion through a central venous catheter ("CVC"), peripherally inserted central catheter ("PICC line"), or port.

iii. Capecitabine-based combination regimens (e.g.: ECX, EOX, CX) offer a superior response rate (45.6% versus 38.4%, OR 1.38, CI 95% 1.10-1.73, p = 0.006) and overall survival (HR 0.87, CI 95% 0.77-0.98, p = 0.02) when compared to 5-Fluorouracil-based combination chemotherapies (e.g.: ECF, EOF, CF).

iv. Oxaliplatin is the preferred platinum as it reduces the risk of death (HR 0.88, CI 95% 0.78-0.99, p = 0.04), progression (HR 0.88, CI95% 0.80-0.98, p = 0.02), and thromboembolism.

HER2 Positive:

HER2 over-expression can be demonstrated in 16% of gastric cancers. The addition of Trastuzumab to six three-week cycles of Cisplatin 80 mg/m2 IV on day one plus either Capecitabine 1,000 mg/m2 po BID for fourteen days or 5-Fluorouracil 800 mg/m2 continuous IV infusion on days one through five was associated with a superior progression-free (6.7 months versus 5.5 months, HR 0.71, CI95% 0.59-0.85, p = 0.0002) and overall survival (13.8 months versus 11.1 months, HR 0.74, CI95% 0.60-0.91, p = 0.0046).28 In a pre-planned exploratory analysis, the subset of patients with high-level HER2 expression (immunohistochemistry scores (IHC) of 2+ with FISH positivity or IHC3+) achieved a median overall survival of 16.0 months. [Level of evidence: I]

In the updated survival analysis, the median overall survival for the addition of trastuzumab was 13.1 months as compared to 11.7 months for the chemotherapy alone arm (HR 0.80, CI95% 0.67- 0.91). In the updated preplanned analysis, only the patients in the IHC3+ subgroup showed a statistically significant survival benefit (18.0 months vs 13.2 months, HR 0.66 (CI95% 0.50-0.87)). [Level of evidence: 1]

Contraindications to platinum/fluoropyrimidine or FOLFIRI

- In patients who have a contraindication to a platinum/fluoropyrimidine combination, or FOLFIRI, the following regimen may be considered as an alternative but it does not have the same degree of survival benefit: a. ELF: Three-week cycles where Etoposide (120 mg/m2 IV), Leucovorin (300 mg/m2 IV), and 5Fluorouracil (500 mg/m2 IV) are administered on days one, two, and three.

Stage IV (Second Line)

Combination Systemic Therapy

i. In patients with a preserved performance status, modest benefits have been achieved with second-line chemotherapy. For patients who are fit enough, combination systemic therapy is preferred. Options include:

a. Paclitaxel 80 mg/m^2 on days 1, 8, 15 every 4 weeks with Ramucirumab 8 mg/kg IV days 1, 15

1. Compared to Paclitaxel alone, in patients with ECOG 0-1 the addition of Ramucirumab significantly improved overall survival (7.6 months *versus* 9.6 months, HR 0.807, $CI_{95\%}$ 0.678-0.962, p = 0.017)[30] [Level of evidence: I]

2. Similar time to deterioration in performance status was reported in the paclitaxel arm and the paclitaxel plus ramucirumab arm (p=0.0941) according to QLQ-C30 scales. EQ-5D scores were comparable between treatment arms, stable during treatment, and worsened at discontinuation.[25,31]

b. FOLFIRI as above can be considered in the second line setting, after a fluoropyrimide/platinum combination.[25]

c. A fluoropyrimidine/platinum combination such as FOLFOX or CAPOX can be considered in the second line setting after FOLFIRI.[25] While combinations like ECX, EOX, ECF or EOF have more direct evidence in this setting, it is reasonable to omit the anthracycline in the second line setting due to the added toxicities and lack of increased efficacy observed in the first line setting. [19,25]

Single Agent Systemic Therapy:

i. Paclitaxel 80 mg/m^2 IV on days one, eight, and fifteen every four weeks [Level of evidence: I]

a. Paclitaxel is equivalent to Irinotecan every 2 weeks[32] in terms of median overall survival (8.4 months for Irinotecan *versus* 9.5 months for Paclitaxel, HR 1.132, $CI_{95\%}$ 0.86-1.49, p = 0.38); median progression-free survival (2.3 months for Irinotecan and 3.6 months for Paclitaxel, HR 1.14, $CI_{95\%}$ 0.88-1.49, p = 0.33); and overall response rate (13.6% for Irinotecan and 20.9% for Paclitaxel, p = 0.20).However, Paclitaxel confers less grade 3/4 neutropenia (28.7% *versus* 39.1%), anemia (21.3% *versus* 30.0%), anorexia (7.4% *versus* 17.3%), and fatigue (6.5% *versus* 12.7%).

ii. Irinotecan 250 to 350 mg/m^2 IV every three weeks or 150mg/m^2 IV every two weeks [Level of evidence: I]

a. Irinotecan 250 to 350 mg/m^2 IV three weeks demonstrated a median overall survival of 4.0 months *versus* 2.4 months, (HR 0.48, $CI_{95\%}$ 0.25-0.92, p = 0.012) compared to best supportive care.[33]

b. Irinotecan 150 mg/m^2 IV every two weeks (or Docetaxel) demonstrated a median overall survival of 5.3 months *versus* 3.8 months, HR 0.657, $CI_{95\%}$ 0.485-0.891, p = 0.007 compared to best supportive care.[34]

iii. Docetaxel 60 or 75 mg/m^2 IV every three weeks [Level of evidence: I]

a. Docetaxel 60 mg/m^2 IV every three weeks or Irinotecan improves overall survival when

compared with best supportive care (5.3 months *versus* 3.8 months, HR 0.657, $CI_{95\%}$ 0.485-0.891, $p = 0.007$).[34]

b. Docetaxel 75 mg/m^2 IV every three weeks improves overall survival (5.2 months *versus* 3.6 months, HR 0.67, $CI_{95\%}$ 0.49-0.92, $p = 0.01$) and pain scores when compared with best supportive care.[35]

iv. Ramucirumab 8mg/kg IV every 2 weeks [Level of evidence: I]

a. This improved overall survival when compared to best supportive care (5.2 versus 3.8 months, multivariable HR 0.774, $CI_{95\%}$ 0.605-0.991, $p = 0.042$) with no difference in quality of life scores at 6 weeks. [36] Patients enrolled in the study had an ECOG 0-1 and Ramucirumab was also associated with a delay to median time to deterioration of performance status. Ramicirumab is not currently funded for single agent use.

Stage IV (Third Line)

i. TAS-102 (Trifluridine/tipiracil) 35 mg/m2 po twice daily on days 1-5 and days 8-12 every 28 days [Level of evidence: I]
ii. In patients with an ECOG 0-1 who had received 2 or more lines of systemic therapy, TAS-102 demonstrated an improvement in median overall survival to 5.7 months from 3.6 months, compared to placebo (HR 0.69, $CI_{95\%}$ 0.56-0.85, $p = 0.00029$, two-sided p=0.00058).[37]
iii. Higher rates of grade 3 or higher were observed with TAS-102 in terms of neutropenia (n=114, 35=4%) and anemia (n=64, 19%), while with placebo abdominal pain (n=15, 9%) and general deterioration of physical health (n=15, 9%) were more common. No differences were seen in quality of life between patients treated with TAS-102 and placebo.
iv. TAS-102 is not currently funded, but has been approved by pCODR [link].

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF), 2018 [9].

Diagnostik und Therapie der Adenokarzinome des Magens und ösophagogastralen Übergangs; S3-Leitlinie, Langversion 2.0.

Zielsetzung/Fragestellung

Therapie des Magenkarzinoms und der Karzinome des ösophagogastralen Übergangs.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert: Spätestens 2023 wird eine erneute Überarbeitung erfolgen

Recherche/Suchzeitraum:

- pubmed und CENTRAL

- Zeitraum: 01/2012- 03/2017 (letzte Aktualisierung AG2: 26.09.2017)

LoE/GoR

Tabelle 8: Schema der Empfehlungsgraduierung

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll
B	Empfehlung	sollte
0	Empfehlung offen	kann

Tabelle 9: Schema der Konsensstärke

Konsenstärke	Prozentuale Zustimmung
Starker Konsens	> 95% der Stimmberechtigten
Konsens	> 75 – 95% der Stimmberechtigten
Mehrheitliche Zustimmung	> 50 – 75% der Stimmberechtigten
Dissens	< 50% der Stimmberechtigten

Empfehlungen

Informationen zu Mikrosatelliten-Instabilität:

13.14.	Konsensbasierte Empfehlung	Modifiziert 2019
EK	Bei Patienten mit nachgewiesener Mikrosatelliten-Instabilität kann nach Ausschöpfung zugelassener Therapien eine Therapie mit Immuncheckpoint-Inhibitoren erwogen werden.	
	Starker Konsens (100%), 7 Enthaltungen wegen Interessenkofnlikten (siehe Leitlinienreport)	

13.15.	Konsensbasiertes Statement	Modifiziert 2019
EK	Der Stellenwert einer Therapie mit Immuncheckpoint-Inihibitoren ist bei unselektierten Patienten unklar.	
	Konsens (93%), 4 Enthaltungen wegen Interessenkofnlikten (siehe Leitlinienreport)	

Hintergrund

In der Therapie des Magenkarzinoms befinden sich derzeit zahlreiche ImmunCheckpoint-Inhibitoren, so z.B. Antikörper gegen PD-1 (Pembrolizumab und Nivolumab) gegen PD-L1 Avelumab, Atezolizumab und Durvalumab, in klinischer Erprobung.

(…) Status bei nachgewiesener Mikrosatelliteninstabilität bzw. defizientem Mismatch-repairSystem („MSI high“- bzw. „dMMR“-Status)

Im Mai 2017 hat die U.S. Food and Drug Administration Pembrolizumab zugelassen für erwachsene und pädiatrische Patienten mit irresektablen oder metastasierten Tumoren mit MSI-high-Status, bzw. defizientem Mismatch-repair-System, wenn keine sonstige sinnvolle (“satisfactory“) Therapiealternative besteht. Diese Zulassung gründet sich auf einer Studie beim kolorektalen Karzinom, die unter einer Therapie mit einem Fluoropyrimidin, Oxaliplatin, und Irinotecan progredient waren, sowie auf die Daten aus fünf weiteren, einarmigen, unkontrollierten Multikohorten-Studien, in die 90 Patienten mit kolorektalem Karzinom und 59 Patienten mit insgesamt 14 weiteren Tumorentitäten eingeschlossen waren [376, 739, 740]. In der Kohorte 1 der KEYNOTE-059 Studie [729], bei Patienten mit gastroösophagealem Adenokarzinom in der Dritt- und Viertliniensituation und Therapie mit Pembrolizumab, wurde über 7 Patienten mit MSIhigh Status berichtet (7 von 174 hierfür getestet =4%). Von diesen hatten 57% ein objektives Ansprechen (davon 14% CR), im Vergleich dazu betrugen die Ansprechraten (wie oben erwähnt) bei PD-L1 Positivität 15,5 (bzw. bei Negativität 6,4). Die Krankheitskontrollrate bei MSI-high betrug 71,4%. Dies bestätigt die hohe Immunogenität von MSI-high-Tumoren und den besonderen Nutzen von CheckpointInhibitoren bei diesen Patienten. (…)

(…) Fazit: Immuncheckpoint-Inhibitoren sind in verschiedenen Studien bei ösophagogastralen Adenokarzinomen untersucht und zeigen bei einer Subgruppe von Patienten eine deutliche Aktivität. Bislang lässt sich mit prädiktiven Biomarkern diese Subgruppe nur ungenügend definieren. Patienten mit MSI-high-Status scheinen jedoch mit hoher Wahrscheinlichkeit auf die Behandlung anzusprechen. (…)

Medikamentöse Tumortherapie

12.1.	Evidenzbasierte Empfehlung	Geprüft 2019
Empfehlungsgrad **A**	Patienten in gutem Allgemeinzustand (ECOG 0-1) soll eine systemische Chemotherapie angeboten werden. Therapieziel ist die Verbesserung des Überlebens und der Erhalt der Lebensqualität. Ein erhöhtes Alter stellt keine Kontraindikation dar.	
Level of Evidence **1a**	DeNovo [609, 638-658]	
	Starker Konsens (96%)	

12.2.	Evidenzbasierte Empfehlung	Geprüft 2019
Empfehlungsgrad **B**	Eine palliative medikamentöse Tumortherapie sollte zum frühestmöglichen Zeitpunkt nach Diagnosestellung der lokal fortgeschritten inoperablen oder metastasierten Erkrankung eingeleitet werden.	
Level of Evidence **1a**	DeNovo (alt) [539, 540, 575, 638, 647, 665-669]	
	Starker Konsens (100%)	

12.6.	Konsensbasierte Empfehlung	Modifiziert 2019
EK	Vor dem Einsatz einer palliativen medikamentösen Tumortherapie soll der HER-2-Status als positiver prädiktiver Faktor für eine Therapie mit Trastuzumab bestimmt werden.	
	Starker Konsens (100%)	

Vorgehen bei Tumoren ohne HER-2-Überexpression

12.7.	Evidenzbasierte Empfehlung	Modifiziert 2019
Empfehlungsgrad A	In der Palliativsituation soll in der Erstlinientherapie eine Platin-/Fluoropyrimidin-haltige Kombinationstherapie durchgeführt werden.	
0	Bei Vorliegen von Kontraindikationen gegen Platin kann alternativ eine Irinotecan/Fluoropyrimidinhaltige Kombinationstherapie durchgeführt werden. Dabei handelt es sich um einen Off-Label-Use.	
Level of Evidence 1a	De Novo [638]	
	Starker Konsens (100%)	

12.8.	Evidenzbasierte Empfehlung	Modifiziert 2019
Empfehlungsgrad 0	Eine Docetaxel-haltige Dreifachkombination kann unter Berücksichtigung von Alter, Allgemeinzustand und Komorbidität erwogen werden.	
Level of Evidence 1a	De Novo [638]	
	Konsens (86%)	

12.9.	Evidenzbasierte Empfehlung	Modifiziert 2019
Empfehlungsgrad A	Wenn eine taxan-basierte Dreifachkombination geplant ist, soll ein modifiziertes DCF-Schema (z.B. FLOT) durchgeführt werden.	
Level of Evidence 1a	DeNovo [638]	
	Starker Konsens (100%)	

Tabelle 17: Randomisierte Studien zum Vergleich Oxaliplatin- versus Cisplatin-haltiger Kombinationstherapien

Referenz	Patienten N =	Therapie-Regime	Ansprechrate	Medianes Gesamtüberleben
Van Cutsem [679]	445	DCF vs. CF	36,7% vs. 25,4%	9,2 Monate vs. 8,2 Monate
Lorenzen [687]	60	T-PLF	47%	17,3 Monate *
Al Batran [665]	59	FLOT	57,7%	11,1 Monate
Shah [685]	85	mDCF vs. DCF	49% vs. 33%	18,8 Monate vs. 12,6 Monate
* 20 Patienten hatten lokal fortgeschrittene nicht metastasierte Stadien				

12.10.	Evidenzbaiserte Empfehlung	Modifiziert 2019
Empfehlungsgrad **A**	Bei der Therapieentscheidung zwischen Oxaliplatin und Cisplatin sollen aufgrund vergleichbarer Wirksamkeit und unterschiedlicher Nebenwirkungen die Begleiterkrankungen des jeweiligen Patienten berücksichtigt werden.	
Level of Evidence **1a**	DeNovo [638]	
	Starker Konsens (100%)	

Tabelle 18: Randomisierte Studien zum Vergleich Capecitabin - versus 5-FU-haltige Kombinationstherapien [638]

Referenz	Patienten N =	Therapieregime	Ansprechrate	Medianes Überleben
Al-Batran [542]	112	FLO	34,8%.	10,7 Monate
	106	FLP	24,5%	8,8 Monate
Al-Batran [542] Subgruppe >64 Jahre	46	FLO	41,3%	13,9 Monate
	48	FLP	16,7%	7,2 Monate
Cunningham [540]	245	ECF	42,4%	9,3 Monate
	244	EOX	47,9%	11,2 Monate

12.11.	Evidenzbasierte Empfehlung	Modifiziert 2019
Empfehlungsgrad **A**	Die Therapieentscheidung zwischen oralen und infusionalen Fluoropyrimidinen soll aufgrund vergleichbarer Wirksamkeit und unterschiedlicher Nebenwirkungen die Begleiterkrankungen und Präferenz des jeweiligen Patienten berücksichtigen.	
Level of Evidence **1a**	DeNovo [638]	
	Starker Konsens (100%)	

Tabelle 19: Randomisierte Studien zum Vergleich Capecitabin - versus 5-FU-haltige Kombinationstherapien

Studie	Patienten N=	Therapieregime	Ansprechrate	Medianes Überleben
Cunningham [540]	480	Capecitabin-haltig ECX oder EOX	44,6%	10,9 Monate
Cunningham [540]	484	5-FU-haltig ECF oder EOF	39,4%	9,6 Monate
Kang [539]	160	XP Capecitabin/Cisplatin	41%	10,5 Monate
Kang [539]	156	FP 5-FU/Cisplatin	29%	9,5 Monate
Ajani [690]	527	SP S-1/Cisplatin	29,1%	8,6 Monate
Ajani [690]	526	FP 5-FU/Cisplatin	31,9%	7,9 Monate

Vorgehen bei metastasierten Karzinomen mit HER-2- Überexpression/-Amplifikation

12.12.	Evidenzbasierte Empfehlung	Modifiziert 2019
Empfehlungsgrad **A**	Bei HER2-überexprimierenden Tumoren soll eine Cisplatin-/Fluoropyrimidin-basierte Erstlinienchemotherapie um Trastuzumab ergänzt werden.	
Level of Evidence **1b**	DeNovo (alt): [575, 692]	
	Konsens (92%) – 8 Enthaltungen wegen Interessenkonflikten	

12.13.	Evidenzbasierte Empfehlung	Geprüft 2019
Empfehlungsgrad **B**	Die Antikörper Cetuximab, Panitumumab und Bevacizumab sollten gegenwärtig außerhalb klinischer Studien nicht eingesetzt werden.	
Level of Evidence **1a**	DeNovo [693]	
	Starker Konsens (100%)	

Zweitlinientherapie

12.14.	Evidenzbasierte Empfehlung	Geprüft 2019
Empfehlungsgrad **A**	Patienten in gutem Allgemeinzustand soll eine Zweitlinien-Chemotherapie angeboten werden. Das zu wählende Behandlungsschema soll sich nach der jeweiligen Vortherapie richten.	
Level of Evidence **1a**	DeNovo [659, 660, 694, 696-700]	
	Starker Konsens (100%)	

12.15.	Evidenzbasierte Empfehlung	Neu 2019
Empfehlungsgrad **B**	Eine Zweitlinientherapie sollte Irinotecan*, Docetaxel*, Paclitaxel*, Ramucirumab oder Paclitaxel mit Ramucirumab beinhalten, wobei der Zulassungsstatus zu berücksichtigen ist. * = off-Label Use	
Level of Evidence **1a**	DeNovo [659, 660, 694, 696-700]	
	Starker Konsens (100%) – 7 Enthaltungen wegen Interessenkonflikten	

Tabelle 20: Randomisierte Phase III-Studien zur Zweitlinien-Therapie des Magenkarzinoms

Autor	Patienten N=	Vergleichsarme	Medianes Überleben	Hazard Ratio
Thuss-Patience [659]	40	Irinotecan vs. BSC	4,0 Monate 2,4 Monate p=0,012	0,48
Kang [694]	202	Irinotecan /Docetaxel vs. BSC	5,3 Monate 3,8 Monate p=0,007	0,657
Ford [696]	168	Docetaxel vs. BSC	5,2 Monate 3,6 Monate p=0,001	0,67
Hironaka [697]	223	Paclitaxel vs. Irinotecan	9,5 Monate 8,4 Monate p=0,38	-
Fuchs [698]	355	Ramucirumab vs. Placebo (2:1)	5,2 Monate 3,8 Monate p=0,047	0,776
Wilke [699]	665	Paclitaxel + Ramucirumab vs. Paclitaxel + Placebo (2:1)	9,6 Monate 7,4 Monate p=0,017	0,807

National Institute for Health and Care Excellence (NICE), 2018 [11].

Oesophago-gastric cancer – Assessment and management in adults.

Zielsetzung

This guideline focuses on the assessment and management of oesophago-gastric cancer in adults. This includes oesophageal cancer, gastric cancer, and cancer occurring at the oesophageal-gastric junction.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium,

- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt,
- Systematische Suche, Auswahl und Bewertung der Evidenz,
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt,
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt,
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- All searches were conducted in MEDLINE, Embase and The Cochrane Library. All searches were updated in May 2017. Any studies added to the databases after this date (even those published prior to this date) were not included unless specifically stated in the text.

LoE

Tabelle 3: Overall quality of outcome evidence in GRADE level

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

GoR

Recommendations were drafted on the basis of the group's interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. [...] When clinical and economic evidence was of poor quality, conflicting or absent, the group drafted recommendations based on their expert opinion.

[...] the word "offer" was used for strong recommendations and "consider" for weak recommendations.

Empfehlungen

Second-line palliative chemotherapy

9.3.8 Recommendations

Second-line palliative chemotherapy for locally advanced or metastatic oesophago-gastric cancer

37. **Consider second-line palliative chemotherapy for people with oesophago-gastric cancer.**

38. **Discuss the risks, benefits and treatment consequences of second-line palliative chemotherapy for oesophago-gastric cancer with the person and those who are important to them (as appropriate). Cover:**
    - how different treatments can have similar effectiveness but different side effects
    - how the treatments are given
    - if the person has any preference for one treatment over another.

39. **Consider a clinical trial (if a suitable one is available) as an alternative to second-line chemotherapy for people with oesophago-gastric cancer.**

9.3.6 Evidence statements

9.3.6.1 Overall survival

Moderate quality evidence about the effectiveness of second line chemotherapy in terms of overall survival came from 15 randomised trials including 3442 patients and comparing 13 treatments. Almost all treatments appeared to improve overall survival compared to best supportive care alone, though only seven were clinically significant. Docetaxel + fluoropyrimidine was most likely to be the most effective treatment, however, it was only tested on 12 participants.

9.3.6.2 Progression free survival

Moderate quality evidence about the effectiveness of second line chemotherapy in terms of progression free survival came from 11 randomised trials including 2131 patients and comparing 11 treatments. For PFS, results were less clear than for OS as there were slightly fewer studies included and the direct estimates tended to be more imprecise than for OS. The only treatment that appeared to be significantly better than placebo was docetaxel, although fluoropyrimidine and Irinotecan + cisplatin did reasonable effectiveness compared to the other treatments

9.3.6.3 Nausea (grade 3 or greater)

Low quality evidence about the rates of nausea during second line chemotherapy came from 10 randomised trials including 1271 patients and comparing 10 treatments. None of the odds ratios for patients reporting experiencing nausea was clinically significant, and there was considerable uncertainty in results, mainly due to the low event rates.

9.3.6.4 Neutropaenic sepsis (grade 3 or greater)

Low quality evidence about the rates of neutropaenic sepsis during second line chemotherapy came from 12 randomised trials including 1505 patients and comparing 14 treatments. There was very little information for this adverse event due to relatively low event rates. However, placebo / best supportive care was included in this network, and (as expected) it seemed to be better than all other treatments and significantly better than three.

9.3.6.5 Neutropaenia (grade 3 or greater)

Low quality evidence about the rates of neutropaenia during second line chemotherapy came from 18 randomised trials including patients and comparing 10 treatments. Placebo / best supportive care had the lowest risk of neutropenia and this was significant for four treatments. However, paclitaxel had much lower risk than many other treatments whereas docetaxel + oxaliplatin had higher risk than many others

9.3.6.6 Diarrhoea (grade 3 or greater)

Low quality evidence about the rates of diarrhoea during second line chemotherapy came from 9 randomised trials including 1247 patients and comparing 9 treatments. This was a very sparse network here with relatively few events. Although docetaxel performed fairly well

in comparison to the other treatments and fluoropyrimidine quite poorly these results are very uncertain.

9.3.6.7 Treatment related mortality

Low quality evidence about the rates of mortality related to second line chemotherapy came from 10 randomised trials including 1271 patients and comparing 10 treatments. This was a very small network with very few events and as a result there was serious uncertainty about relative effectiveness.

9.3.7 Evidence to recommendations

9.3.7.1 Relative value placed on the outcomes considered

The most important outcomes considered for this topic were treatment related morbidity and mortality, health-related quality of life and overall survival. Overall survival and health-related quality of life were considered to be important because achieving improvements in these outcomes is the main aim of treatment in this patient group. Treatment related morbidity and mortality are important as chemotherapy is known to have detrimental side-effects.

Taken together, the outcomes characterise the key trade-off between interventions in this patient group. There is the potential for benefits in terms of improved survival and quality of life but this must be weighed against the harms in terms of treatment-related mortality and morbidity and an associated decrease in quality of life.

9.3.7.2 Quality of the evidence

Network meta-analyses (NMA) provided moderate quality evidence that second line chemotherapy improves overall survival compared to best supportive care but low quality evidence about treatment related morbidity and mortality. Second line chemotherapy was associated with an increased risk of neutropaenia compared to best supportive care, but the evidence about nausea, neutropaenic sepsis, diarrhoea and treatment related mortality was uncertain, largely due to low event rates. The group thought here was insufficient evidence to recommend a specific chemotherapy regimen and instead made a general recommendation about second line chemotherapy.

9.3.7.3 Consideration of benefits and harms

The evidence for second-line chemotherapy showed that chemotherapy appeared to improve overall survival compared to supportive care (with median overall survival of 4.4 to 17 months in chemotherapy compared to 3.6 months in supportive care). There was some evidence for increased adverse events such as nausea, neutropaenia and neutropaenic sepsis, although there was some uncertainty around this. The Committee agreed the balance of benefits and harms, and particularly the increase in survival seen in this population, allowed them to recommend second-line palliative chemotherapy but that it should be offered after a discussion of the risks and benefits with the patient.

While the committee agreed that there was enough evidence to recommend second-line chemotherapy, they did not think that the evidence was strong enough to be able to recommend one chemotherapy regimen over another.

The Committee considered that the recommendations are unlikely to significantly change practice and so the primary benefit of the recommendation is that it should encourage shared decision making and ensure that an informed discussion takes place with the patient. The use of second line chemotherapy could potentially improve survival and quality of life in some patients but this must bebalanced against the potential for a diminished quality of life as a

result of treatment morbidity. However, it should be noted that the changes in quality of life are hypothesised since there was no evidence identified on this outcome.

There are some patients who may not benefit from treatment. Therefore, the recommendations suggest an individualised approach to treatment selection, which should ensure that the harms and benefits are appropriately balanced for each patient.

9.3.7.4 Consideration of economic benefits and harms

Two relevant studies were identified in a literature review of published cost-effectiveness analyses on this topic; Lam et al. 2016 and Meads et al. 2015. The analysis by Lam et al. 2016 suggests that chemotherapy may be a cost-effective alternative to palliative care. However the analysis was only partially applicable to the decision problem in the UK setting as they were based on the health care perspective of the United States. The analysis by Meads et al. 2015 suggests that docetaxel is not a cost-effective addition to active symptom control when considering the typical threshold of £20,000 per QALY. If the treatment was deemed to meet the end of life criteria, then the addition of docetaxel may be considered cost-effective at an increased threshold of £50,000 per QALY. However, some potentially serious limitations were identified in the analysis (including uncertainty around some of the cost estimates). Overall, the analyses indicate that chemotherapy may be cost-effective in this setting but further research is required before drawing decisive conclusions.

The economic implications of this topic were thought to be negligible as the recommendations largely reflect current clinical practice. The recommendations suggest an emphasis on patient discussion, for which there would be an associated cost. However, the committee anticipate that such discussions should already be taking place in practice and so no additional cost is expected in terms of consultation time.

If there are centres where practice is not currently in line with the recommendations then there could be increased costs associated with the use of chemotherapy (and managing the associated side effects). However, the use of chemotherapy would be expected to be cost-effective as the benefits in terms of overall and disease-free survival would be expected to translate into QALY gains.

9.3.7.5 Other considerations

The Committee were aware of the NICE technology appraisal covering ramicurimab, and since there were already NICE recommendations for ramicurimab, it was excluded from consideration in the evidence review.

9.3.7.6 Key conclusions

The Committee agreed that second line chemotherapy could be a useful treatment modality for some patients and so it should be considered. It was also thought important to make it clear that the potential risks and benefits of the treatment should be discussed with the patient to allow an informed decision to be made. This approach should help to ensure that an individualised treatment approach is taken. As this is an area where further research into emerging treatments is being considered it was also thought important to consider entry into clinical trials as an alternative to second line chemotherapy.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 11 of 12, November 2020) am 04.11.2020

#	Suchfrage
1	[mh “Esophageal Neoplasms”] OR [mh “Stomach Neoplasms”]
2	[mh Adenocarcinoma]
3	[mh Esophagogastric Junction]
4	#1 OR (#2 AND #3)
5	(gastric OR stomach OR esophag* OR oesophag* OR gastroesophag* OR gastrooesophag*):ti,ab,kw
6	(tumor* OR tumour* OR carcinoma* OR adenocarcinoma* OR neoplas* OR cancer*):ti,ab,kw
7	{AND #5-#6}
8	(siewert*):ti,ab,kw
9	{OR #4, #7-#8}
10	#9 with Cochrane Library publication date from Nov 2015 to present

Systematic Reviews in Medline (PubMed) am 04.11.2020

#	Suchfrage
1	"Esophageal Neoplasms/therapy"[mh] OR “Stomach Neoplasms/therapy”[mh]
2	adenocarcinoma[mh] AND esophagogastric junction[mh]
3	"Adenocarcinoma Of Esophagus"[nm]
4	#1 OR #2 OR #3
5	gastric[tiab] OR stomach[tiab] OR esophag*[tiab] OR oesophag*[tiab] OR gastroesophag*[tiab] OR gastrooesophag*[tiab]
6	tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR neoplas*[tiab] OR cancer*[tiab]
7	treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab]
8	#5 AND #6 AND #7
9	siewert*[tiab]
10	#4 OR #8 OR #9
11	(#10) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR

	(study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
12	((#11) AND ("2015/11/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
13	(#12) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 04.11.2020

#	Suchfrage
1	"Esophageal Neoplasms"[mh] OR “Stomach Neoplasms”[mh]
2	adenocarcinoma[mh] AND esophagogastric junction[mh]
3	"Adenocarcinoma Of Esophagus"[nm]
4	#1 OR #2 OR #3
5	gastric[tiab] OR stomach[tiab] OR esophag*[tiab] OR oesophag*[tiab] OR gastroesophag*[tiab] OR gastrooesophag*[tiab]
6	tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR neoplas*[tiab] OR cancer*[tiab]
7	#5 AND #6
8	siewert*[tiab]
9	#4 OR #7 OR #8
10	(#9) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
11	(#10) AND ("2015/11/01"[PDAT] : "3000"[PDAT])
12	(#11) NOT (retracted publication [pt] OR retraction of publication [pt])

Referenzen

1. **Alberta Health Services.** Gastric cancer, Version 5 [online]. Edmonton (CAN): Alberta Health Services; 2020. [Zugriff: 09.11.2018]. (Band GI-008). URL: https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-gi008-gastric.pdf.

2. **Chan WL, Yuen KK, Siu SW, Lam KO, Kwong DL.** Third-line systemic treatment versus best supportive care for advanced/metastatic gastric cancer: a systematic review and meta-analysis. Crit Rev Oncol Hematol 2017;116:68-81.

3. **Chen C, Zhang F, Zhou N, Gu YM, Zhang YT, He YD, et al.** Efficacy and safety of immune checkpoint inhibitors in advanced gastric or gastroesophageal junction cancer: a systematic review and meta-analysis. Oncoimmunology 2019;8(5):e1581547.

4. **Cheng J, Cai M, Shuai X, Gao J, Wang G, Tao K.** Systemic therapy for previously treated advanced gastric cancer: a systematic review and network meta-analysis. Crit Rev Oncol Hematol 2019;143:27-45.

5. **Gemeinsamer Bundesausschuss (G-BA).** Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Trifluridin/Tipiracil (neues Anwendungsgebiet: metastasiertes Magenkarzinom, vorbehandelte Patienten) vom 02. April 2020 [online]. Berlin (GER): G-BA; 2020. [Zugriff: 11.11.2020]. URL: https://www.g-ba.de/downloads/39-261-4245/2020-04-02_AM-RL-XII_TrifluridinTipiracil_D-493_BAnz.pdf.

6. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 20. Dezember 2012 - Tegafur / Gimeracil / Oteracil [online]. Berlin (GER): G-BA; 2012. [Zugriff: 06.11.2020]. URL: https://www.g-ba.de/downloads/91-1385-35/2012-12-20_Geltende-Fassung_Tegafur_Gimeracil_Oteracil_D-033.pdf.

7. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 20. Oktober 2016 - Ramucirumab [online]. Berlin (GER): GBA; 2016. [Zugriff: 06.07.2020]. URL: https://www.g-ba.de/downloads/91-1385-229/2016-10-20_Geltende-Fassung_Ramucirumab_D-224.pdf.

8. **Guo X, Zhao F, Ma X, Shen G, Ren D, Zheng F, et al.** A comparison between triplet and doublet chemotherapy in improving the survival of patients with advanced gastric cancer: a systematic review and meta-analysis. BMC Cancer 2019;19(1):1125.

9. **Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften).** Diagnostik und Therapie der Adenokarzinome des Magens und ösophagogastralen Übergangs; S3-Leitlinie, Langversion 2.0 [online]. AWMF-Registernummer 021-023OL. 08.2019. Berlin (GER): Leitlinienprogramm Onkologie; 2018. [Zugriff: 05.11.2020]. URL: https://www.awmf.org/uploads/tx_szleitlinien/032-009l_S3_Magenkarzinom_Diagnostik_Therapie_Adenokarzinome_oesophagogastraler_Uebergang_2019-12.pdf.

10. **Li B, Chen L, Luo HL, Yi FM, Wei YP, Zhang WX.** Docetaxel, cisplatin, and 5-fluorouracil compared with epirubicin, cisplatin, and 5-fluorouracil regimen for advanced gastric cancer: a systematic review and meta-analysis. World J Clin Cases 2019;7(5):600-615.

11. **National Institute for Health and Care Excellence (NICE).** Oesophago-gastric cancer: assessment and management in adults [online]. London (GBR): NICE; 2018. [Zugriff: 05.11.2020]. (NICE Guideline; Band 83). URL: https://www.nice.org.uk/guidance/ng83/evidence/full-guideline-pdf-4723230493.

12. **Pan WT, Zhou SN, Pan MX, Luo QY, Zhang L, Yang DJ, et al.** Role of systemic treatment for advanced/metastatic gastric carcinoma in the third-line setting: a bayesian network analysis. Front Oncol 2020;10:513.

13. **Shi J, Gao P, Song Y, Chen X, Li Y, Zhang C, et al.** Efficacy and safety of taxane-based systemic chemotherapy of advanced gastric cancer: a systematic review and meta-analysis. Sci Rep 2017;7(1):5319.

14. **Zhang D, Wu JR, Duan XJ, Wang KH, Zhao Y, Ni MW, et al.** A bayesian network meta-analysis for identifying the optimal taxane-based chemotherapy regimens for treating gastric cancer. Front Pharmacol 2019;10:717.

15. **Zheng T, Jin J, Zhang Y, Zhou L.** Efficacy and safety of paclitaxel with or without targeted therapy as second-line therapy in advanced gastric cancer: a meta-analysis. Medicine (Baltimore) 2020;99(25):e20734.

16. **Zheng Z, Guo Y, Zou CP.** Oncological outcomes of addition of anti-PD1/PD-L1 to chemotherapy in the therapy of patients with advanced gastric or gastro-oesophageal junction cancer: a meta-analysis. Medicine (Baltimore) 2020;99(7):e18332.

Gemeinsamer Bundesausschuss

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO