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: 2024-B-268-z Tislelizumab

Stand: Dezember 2024

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

Tislelizumab
[Erstlinienbehandlung des HER2-negativen Adenokarzinoms des Magens oder des gastroösophagealen Übergangs]

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:** - Tegafur/Gimeracil/Oteracil: Beschluss vom 20. Dezember 2012 - Pembrolizumab: Beschlüsse vom 5. Mai 2022 und 20. Juni 2024 - Nivolumab: Beschluss vom 19. Mai 2022
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:	
Tislelizumab L01FF09 Tevimbra	Anwendungsgebiet laut Zulassung vom 25.11.2024: <u>Adenokarzinom des Magens oder des gastroösophagealen Übergangs (G/GEJ)</u> Tislelizumab in Kombination mit platin- und fluoropyrimidinbasierter Chemotherapie wird angewendet zur Erstlinienbehandlung des lokal fortgeschrittenen, nicht resezierbaren oder metastasierten HER-2-negativen Adenokarzinom des Magens oder des gastroösophagealen Übergangs (G/GEJ) bei erwachsenen Patienten, deren Tumore eine PD-L1-Expression mit einem TAP-Score (Tumour Area Positivity) von ≥ 5 % aufweisen.
Zytostatika	
Capecitabin L01BC06 generisch	Xeloda wird angewendet: - in Kombination mit einem platinhaltigen Anwendungsschema als First-line-Therapie des fortgeschrittenen Magenkarzinoms.
Cisplatin L01XA01 generisch	Cisplatin ist als Monosubstanz bzw. in Kombination mit anderen Zytostatika bei der Chemotherapie folgender Tumoren angezeigt: - Zur Kombinationschemotherapie (auch in Verbindung mit Radiotherapie) bei fortgeschrittenen Oesophaguskarzinomen.
Docetaxel L01CD02 generisch	Adenokarzinom des Magens Docetaxel ist in Kombination mit Cisplatin und 5-Fluorouracil angezeigt zur Behandlung von Patienten mit metastasiertem Adenokarzinom des Magens, einschließlich Adenokarzinom der gastroösophagealen Übergangszone, die keine vorherige Chemotherapie gegen ihre metastasierte Erkrankung erhalten haben.
Doxorubicin L01DB01 generisch	- fortgeschrittenes Magenkarzinom
Epirubicin L01DB03 generisch	Epirubicin wird zur Behandlung einer Reihe von neoplastischen Erkrankungen eingesetzt, einschließlich: - Magenkarzinom

II. Zugelassene Arzneimittel im Anwendungsgebiet	
5-Fluorouracil L01BC02 generisch	- fortgeschrittenes Magenkarzinom - fortgeschrittenes Ösophaguskarzinom
Folinsäure V03AF03 generisch	Calciumfolinat ist indiziert: - in Kombination mit 5-Fluorouracil in der zytotoxischen Therapie.
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 - fortgeschrittenes Ösophaguskarzinom
Tegafur / Gimeracil / Oteracil L01BC53 Teysuno	Teysuno ist bei Erwachsenen indiziert: für die Behandlung von fortgeschrittenem Magenkrebs bei Gabe in Kombination mit Cisplatin.
Antikörper	
Nivolumab L01FF01 Opdivo	<u>Adenokarzinome des Magens, des gastroösophagealen Übergangs (GEJ) oder des Ösophagus</u> Nivolumab ist in Kombination mit fluoropyrimidin- und platinbasierter Kombinationschemotherapie für die Erstlinienbehandlung der HER2-negativen fortgeschrittenen oder metastasierten Adenokarzinome des Magens, des gastroösophagealen Übergangs oder des Ösophagus bei Erwachsenen indiziert, deren Tumoren PD-L1 (Combined Positive Score [CPS] ≥ 5) exprimieren.
Pembrolizumab L01FF02 Keytruda	<u>Ösophaguskarzinom</u> Pembrolizumab ist in Kombination mit einer Platin- und Fluoropyrimidin-basierten Chemotherapie zur Erstlinienbehandlung des lokal fortgeschrittenen nicht resezierbaren oder metastasierenden Ösophaguskarzinoms bei Erwachsenen mit PD-L1-exprimierenden Tumoren (CPS ≥ 10) angezeigt. <u>Magenkarzinom:</u> Pembrolizumab ist in Kombination mit einer Fluoropyrimidin- und Platin-basierten Chemotherapie zur Erstlinienbehandlung des lokal fortgeschrittenen nicht resezierbaren oder metastasierenden HER2-negativen Adenokarzinoms des Magens oder des gastroösophagealen Übergangs bei Erwachsenen mit PD-L1-exprimierenden Tumoren (CPS ≥ 1) angezeigt.
Zolbetuximab	Zolbetuximab ist in Kombination mit Fluoropyrimidin- und Platin-haltiger Chemotherapie zur Erstlinienbehandlung von erwachsenen Patienten

II. Zugelassene Arzneimittel im Anwendungsgebiet	
L01FX31 Vyloy	mit lokal fortgeschrittenem inoperablem oder metastasiertem HER2-negativem Adenokarzinom des Magens oder des gastroösophagealen Übergangs (gastro-oesophageal junction, GEJ) angezeigt, deren Tumore Claudin (CLDN) 18.2 positiv sind.
Anmerkung: Für Cisplatin und Oxaliplatin besteht trotz umfangreicher klinischer Daten keine Zulassung für das Magenkarzinom, jedoch sind die Wirkstoffe über andere Wirkstoffe (z.B. Capecitabin, Docetaxel, Trastuzumab) als Kombinationstherapie zugelassen.	

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2024-B-268-z (Tislelizumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	12. November 2024

Inhaltsverzeichnis

Abkürzungsverzeichnis

5-FU	5-fluorouracil
AE	adverse event
AGC	advanced gastric cancer
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CPS	combined positive score
DCR	disease control rate
DORR	disease objective response rate
EAC	esophageal adenocarcinoma
ECRI	Emergency Care Research Institute
FOLFOX	fluorouracil plus oxaliplatin
G-BA	Gemeinsamer Bundesausschuss
GEA	gastroesophageal junction adenocarcinoma
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment Development and Evaluation
HR	Hazard Ratio
ICI	immune checkpoint inhibitors
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
NM	not mentioned
OR	Odds Ratio
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed death ligand-1
PFS	progression-free survival
PPE	palmar-plantar erythrodysesthesia
RCT	randomized control trial
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database

WHO	World Health Organization
XELOX	oxaliplatin plus capecitabine

1 Indikation

Erstlinienbehandlung von Erwachsenen mit HER2-negativem, lokal fortgeschrittenem, nicht resezierbarem oder metastasierendem Adenokarzinom des Magens oder des gastroösophagealen Übergangs (G/GEJ), deren Tumoren PD-L1 mit einem tumour area positivity (TAP) score ≥ 5% exprimieren.

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Magenkarzinom, Adenokarzinom des Magens und des ösophago-gastralen Übergangs* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.startpage.com*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 30.10.2024 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 2227 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. 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 Referenzen 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 9 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten CR identifiziert.

3.2 Systematische Reviews

Cai T et al., 2024 [2].

Comparative efficacy and tolerability of first-line treatments for untreated, HER2-negative, advanced gastric cancer: systematic review and network meta-analysis.

Fragestellung

to compare the efficacy and safety of first-line treatments for gastric cancer.

Methodik

Population:

- untreated, HER2-negative, unresectable advanced (stage III/IV) gastric or GEJ adenocarcinoma confirmed either histologically or cytologically

Intervention/Komparator:

- any two or more different means of first-line treatments for patients with HER2-negative gastric or GEJ adenocarcinoma

Endpunkte:

- OS, PFS, ORR, AEs

Recherche/Suchzeitraum:

- PubMed, EMBASE, Cochrane Library, and ClinicalTrials.gov, ranging from January 1, 2000 to May 1, 2023

Qualitätsbewertung der Studien:

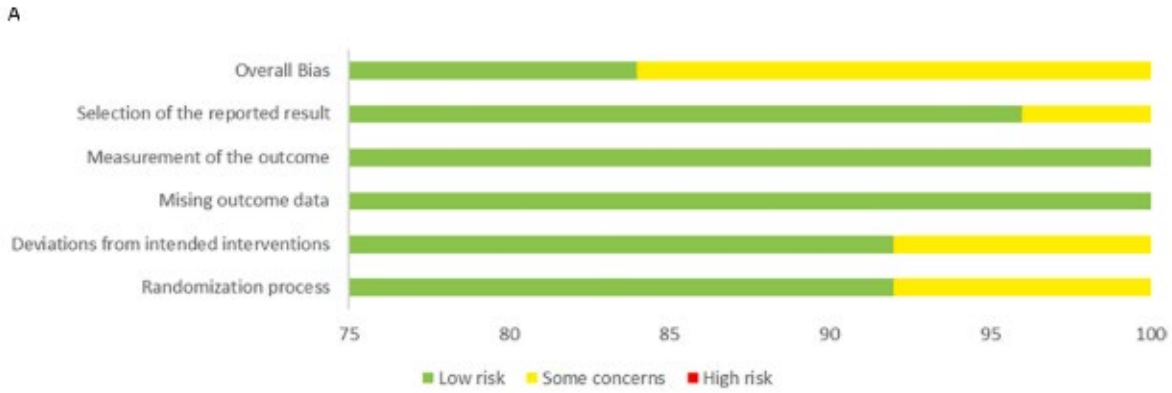
- Cochrane risk of bias assessment tool (RoB-2)

Egebnisse

Anzahl eingeschlossener Studien:

- 25 studies including 14389 patients and 23 first-line treatments

Qualität der Studien:



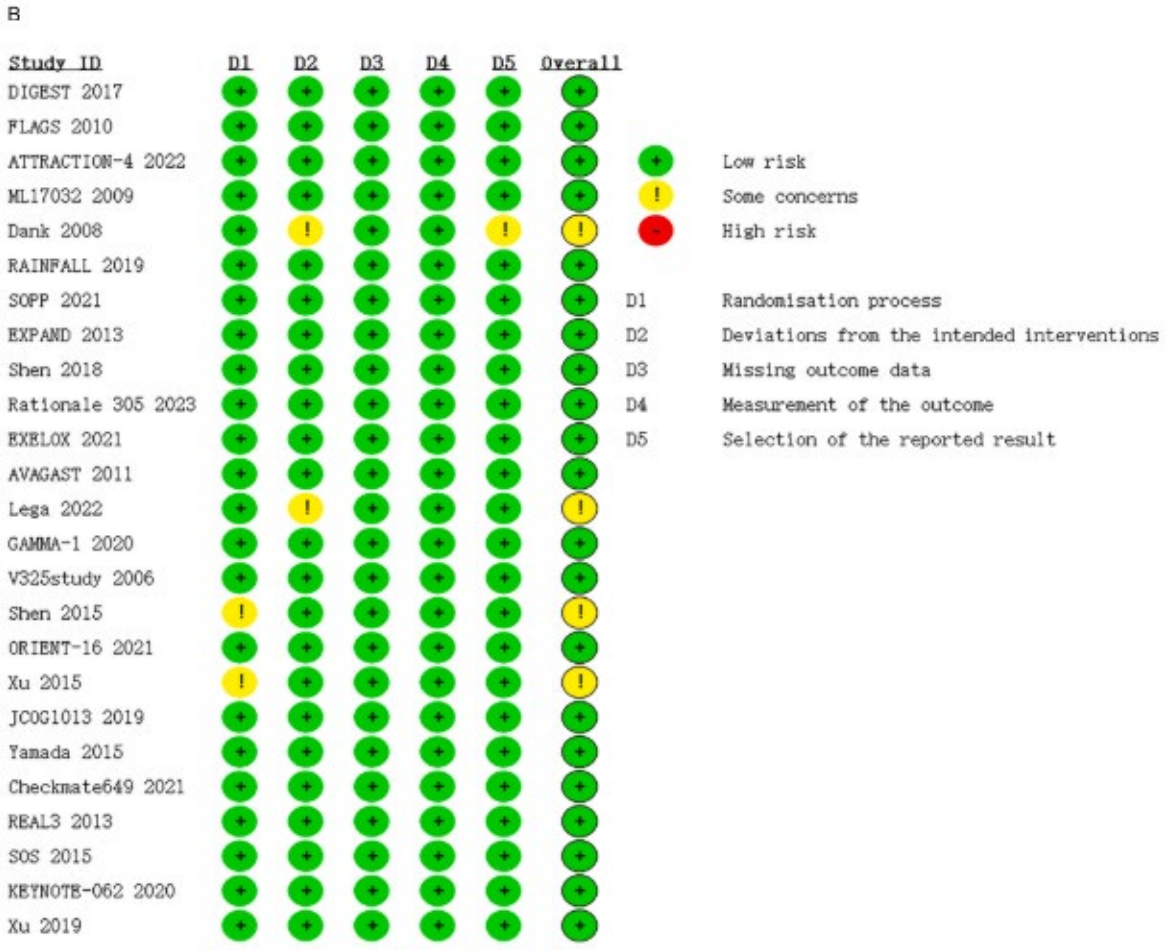


Fig. 2. Risk of bias assessment.

Studienergebnisse:

Hinweis: Ergebnisdarstellung -sofern möglich - fokussiert auf zugelassene Arzneimittel.

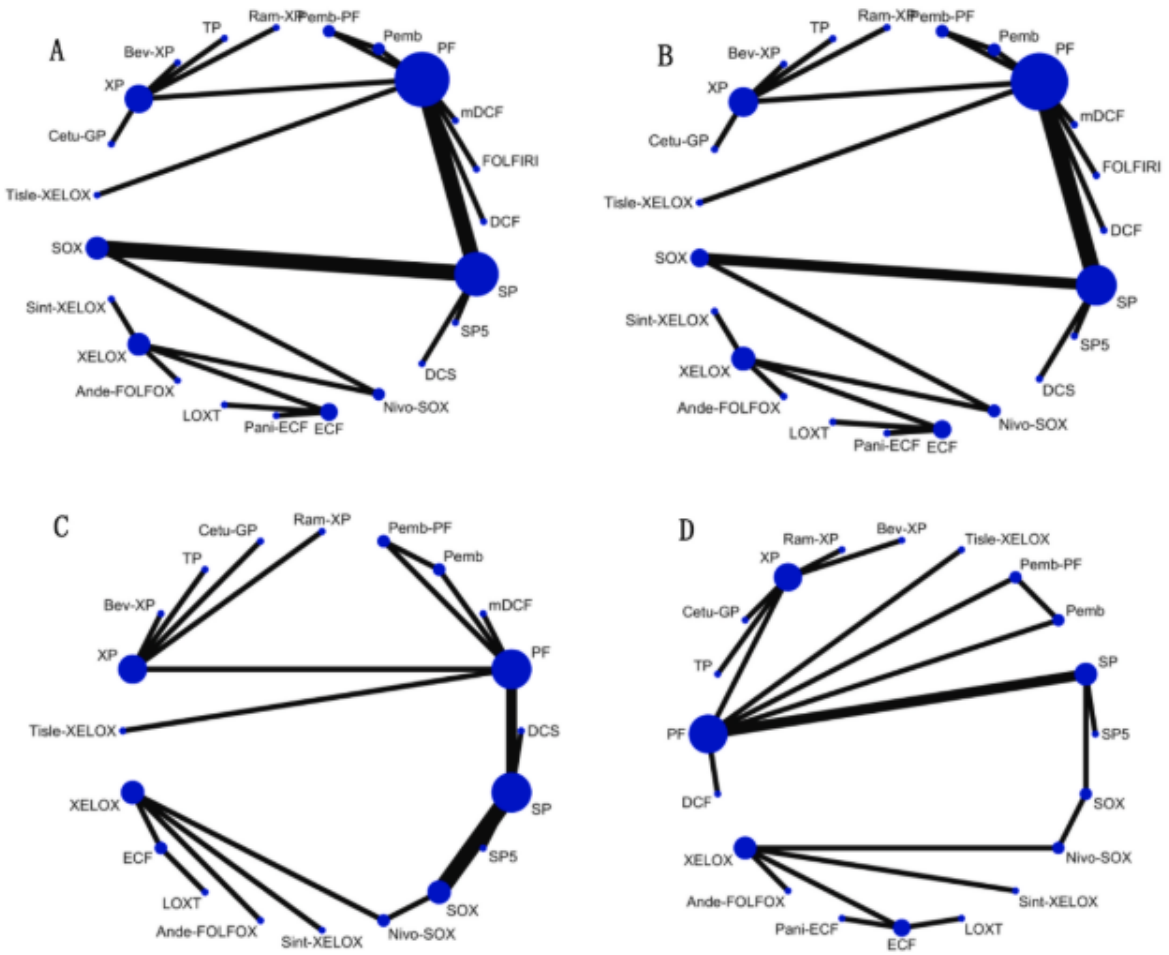


Fig. 3. Network diagram. Network diagram of comparison on different outcomes in different treatment groups for patients with HER2-negative advanced GC. (A) Comparison of network diagrams for OS in HER2-negative advanced GC. (B) Comparison of network diagrams for ORR in HER2-negative advanced GC. (C) Comparison of network diagrams for PFS in HER2-negative advanced GC. (D) Comparison of network diagram for grade 3 or higher adverse events in patients with HER2-negative advanced GC.

- Nivolumab plus tegafur (S-1) plus oxaliplatin (Nivo-SOX) and tislelizumab plus capecitabine plus oxaliplatin (Tisle-XELOX) were also found to be better than PF in providing OS benefit (HR = 0.73, 95%CI: 0.57–0.93 and HR = 0.74, 95% CI: 0.59–0.93, respectively).
- Nivo-SOX and Tisle-XELOX were also found to be better to PF in providing PFS benefit (HR = 0.58, 95%CI: 0.42–0.80 and HR = 0.67, 95%CI: 0.54–0.82, respectively).
- OS:
  - In terms of OS patients who received immunotherapy combinations were more likely to obtain greater OS benefit than those who received chemotherapy alone
    - Nivo-SOX and TisleXELOX was also found to be better to PF in providing OS benefit (HR = 0.73, 95%CI: 0.57–0.93 and HR = 0.74, 95%CI: 0.59–0.93, respectively).
    - However, Pemb-PF was the only immunotherapy regimen that did not benefit from OS compared to standard chemotherapy. In addition, the three-drug combination regimen of reduced-dose chemotherapy (mDCF) was superior to the PF regimen (HR = 0.71, 95%CI: 0.52–0.97).
    - Similarly, (…) Nivo-SOX all show greater benefits compared to XELOX ((…) Nivo-SOX vs. XELOX [HR = 0.79, 95%CI: 0.71–0.88]).

- PFS:
  - Immune checkpoint inhibitor (ICI) with chemotherapy also revealed consistently better PFS than standard chemotherapy except Pemb-PF.
  - Nivo-SOX and Tisle-XELOX was also found to be better to PF in providing PFS benefit (HR = 0.58, 95%CI: 0.42–0.80 and HR = 0.67, 95%CI: 0.54–0.82, respectively).
  - The three-drug chemotherapy regimen did not significantly improve patients' PFS compared to the PF regimen. The only exception was mDCF, which was found to have better PFS than standard chemotherapy (HR = 0.58, 95%CI: 0.42–0.80).
- ORR:
  - the combination of immunotherapy and chemotherapy seemed to have not achieved the expected results in OS or PFS. In general, the combined treatment strategy was superior to the dual drug chemotherapy scheme, whether it was immunotherapy combined with chemotherapy or chemotherapy combined with targeted therapy except TP and XP. As expected, Pemb was still the worst solution for improving ORR.
- Safety:
  - Compared to standard chemotherapy, Pemb had the least toxicity and the best safety profile, whereas Pani-ECF (SUCRA, 83.7%) was noted with the most grade 3 or higher adverse events, and ECF (SUCRA, 80%) was second only to Pani-ECF
  - The three-drug chemotherapy regimen had the strongest toxic response, ranking in the top four. In addition, compared with standard chemotherapy, both immunotherapy combined with chemotherapy and targeted therapy combined with chemotherapy had increased toxicity.

Ranking Ranking analysis:

- The ranking results were consistent with the direct and indirect pooled results obtained using HR and OR, implying the stability and reliability of the framework. For patients with HER-2 negative advanced gastric cancer, Sint-XELOX was most likely to be ranked first for overall survival and progression-free survival, TP for ORR, and PaniECF for adverse events of grade 3 or higher. Besides, not only could SintXELOX achieve excellent clinical efficacy, but its safety or toxicity had not significantly increased. Conversely, although Pemb had the lowest toxicity, its efficacy was not satisfactory, especially with PFS ranking at the bottom.

Anmerkung/Fazit der Autoren

The treatment strategies of advanced HER2-negative gastric or GEJ adenocarcinoma have significantly changed over the past few years, mainly due to the rapid development of immunotherapy. Immunotherapy combined with chemotherapy is now considered the standard first-line treatment for patients with advanced gastric cancer. In our network meta-analysis, all immunotherapy combined with chemotherapy demonstrated greater OS and PFS benefits compared to standard chemotherapy, except for the combination therapy strategy based on pembrolizumab. These findings could supplement the current treatment standard and strengthen the design of trials of gastric or GEJ adenocarcinoma with advanced HER2-negative in the future.

Ma X et al., 2023 [6].

Efficacy and safety of combination chemotherapy regimens containing taxanes for first-line treatment in advanced gastric cancer

Fragestellung

In view of the inconsistent efficacy results of the current studies on the combination of taxanes and basic chemotherapy regimen for AGC, we performed a meta-analysis to analyze the efficacy and safety of basic chemotherapy regimen combined with or without taxanes in the first-line treatment of patients with AGC.

Methodik

Population:

- cytological or histopathological diagnosis of untreated AGC

Intervention/Komparator:

- comparing taxanes combined with basic chemotherapy and basic chemotherapy without taxanes;

Endpunkte:

- objective response rate (ORR) and disease control rate (DCR), and the hazard ratio (HR) and its 95% confidence intervals (95% CI) of progression-free survival (PFS) and overall survival (OS)

Recherche/Suchzeitraum:

- August 1, 2021
- PubMed, PMC, MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE databases, as well as the American Society of Clinical Oncology (ASCO) and European Medical Oncology (ESMO) databases

Qualitätsbewertung der Studien:

- Cochrane collaboration tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 studies involving 2263 patients

Charakteristika der Population/Studien:

Table 1 Characteristics of the included studies

Study/ Year	Trial	Region	Phase	Regimens	Number of patients	Median OS (months)	Median PFS (months)	ORR (%)	DCR (%)
Koizumi 2013	START	Asian	III	Docetaxel + S-1 vs. S-1	316 323	12.5 10.8 (HR 0.84, 95% CI 0.71–0.99, $p=0.032$)	5.3 4.2 (HR 0.77, 95% CI 0.65–0.90, $p<0.001$)	29 20	–
Wang 2015	CASPIAN	Asian	III	Docetaxel + cisplatin + 5-Fu vs. cisplatin + 5-Fu	121 122	10.2 8.5 (HR 0.71, 95% CI 0.52 -0.97, $p=0.0319$)	7.2 4.9 (HR 0.58, 95% CI 0.42–0.80, $p=0.0008$)	41 34	–
Vancutsem2006	V325	Western	III	Docetaxel + cisplatin + 5-Fu vs. cisplatin + 5-Fu	227 230	9.2 8.6 (HR 0.78, 95% CI 0.63–1.00, $p=0.02$)	5.6 3.7 (HR 0.68, 95% CI 0.55–0.84, $p<0.001$)	36 25	65 55
Wang 2013	CA184-041	Asian	II	paclitaxel + S-1 vs. S-1	41 41	14 11 (HR 0.55, 95% CI 0.34–0.90, $p=0.02$)	6 4 (HR 0.60, 95% CI 0.37–0.97, $p=0.04$)	46 24	85 66
Yamada 2019	JCOG1013	Asian	III	docetaxel + cisplatin + S-1 vs. cisplatin + S-1	371 370	14.2 15.3 (HR1.01 95% CI0.86–1.18), $p=0.47$)	7.4 6.5 (HR 0.99, 95% CI 0.86–1.15, $p=0.92$)	36 33	46 38
Nakajima 2020	JCOG1108	Asian	III	paclitaxel + 5-FU + LV vs. 5-FU + LV	50 51	7.3 6.1 (HR0.79 95% CI0.60–1.05, $p=0.145$)	5.4 1.9 (HR0.64 95% CI0.43–0.96, $p=0.029$)	–	–

PFS progression-free survival, *OS* overall survival, *ORR* objective response rate, *DCR* disease control rate, *HR* hazard rate, *CI* confidence interval

Qualität der Studien:

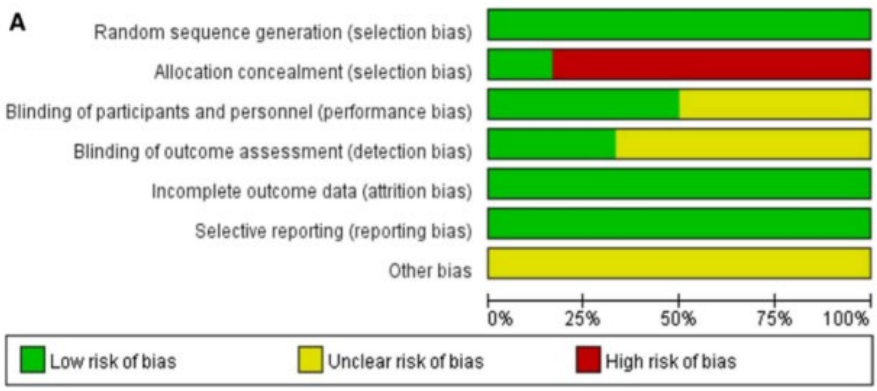
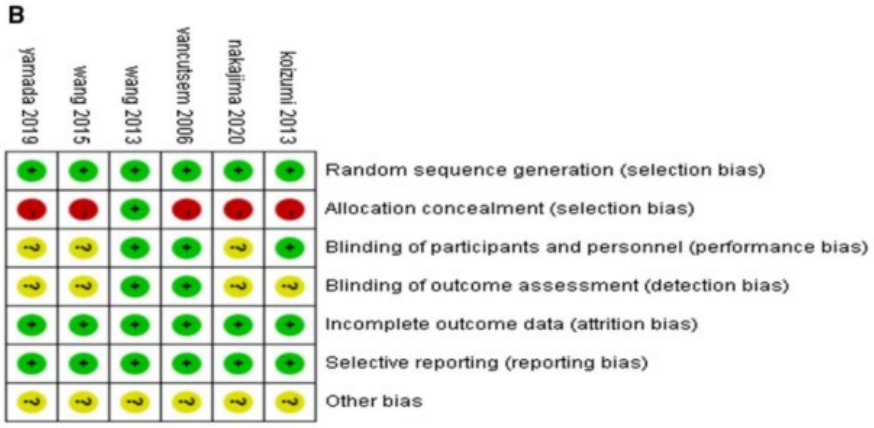


Fig. 2 Assessment of risk of bias. **A** Risk of bias summary. **B** Risk of bias graph



Studienergebnisse:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Taxanes	Non-taxanes	Relative (95% CI)	Absolute (95% CI)		
ORR												
5	randomised trials	not serious	serious	not serious	not serious	none	385/1074 (35.8%)	295/1086 (27.2%)	**RR 1.32** (1,16 to 1.49)	**12 more per 1,000** (from 52 fewer to 91 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
DCR												
5	randomised trials	not serious	serious	not serious	not serious	none	353/639 (55.2%)	294/641 (45.9%)	**RR 1.21** (1.08 to 1.34)	**42 fewer per 1,000** (from 18 fewer to 93 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
PFS												
6	randomised trials	not serious	serious	not serious	not serious	none	-/0	-/0	**HR 0.87** (0.80 to 0.95)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
OS												
6	randomised trials	not serious	serious	not serious	not serious	none	-/0	-/0	**HR 0.93** (0.89 to 0.97)	**1 fewer per 1,000** (from 1 fewer to 1 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard Ratio

Fig. 10 Summary of GRADE on evidences of outcomes

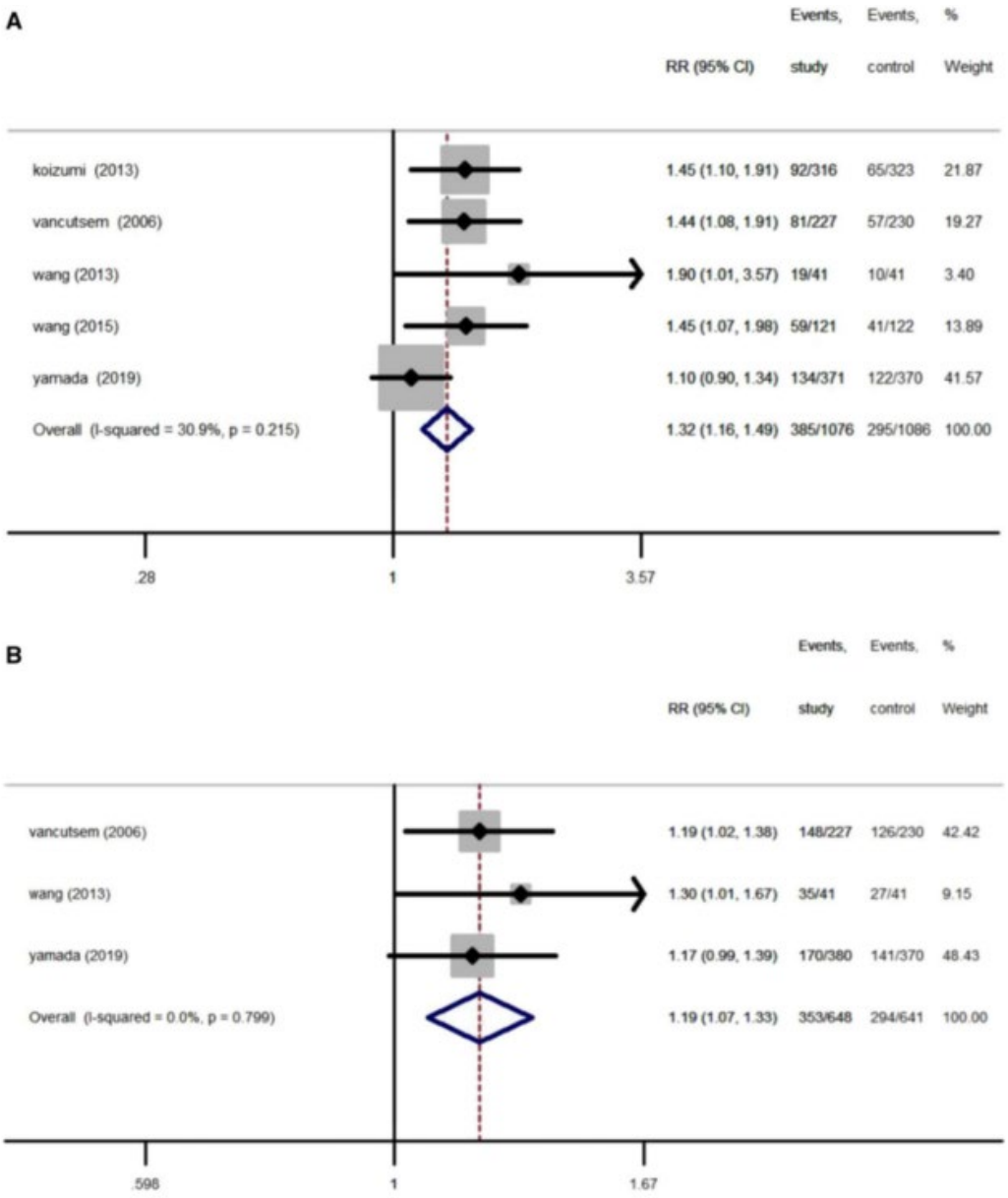


Fig. 3 Forest plot and pooled RR and 95% CI for ORR (**A**) and DCR (**B**): "taxanes combined with basic chemotherapy" versus "chemotherapy without taxanes". RR, relative ratio; CI, confidence interval

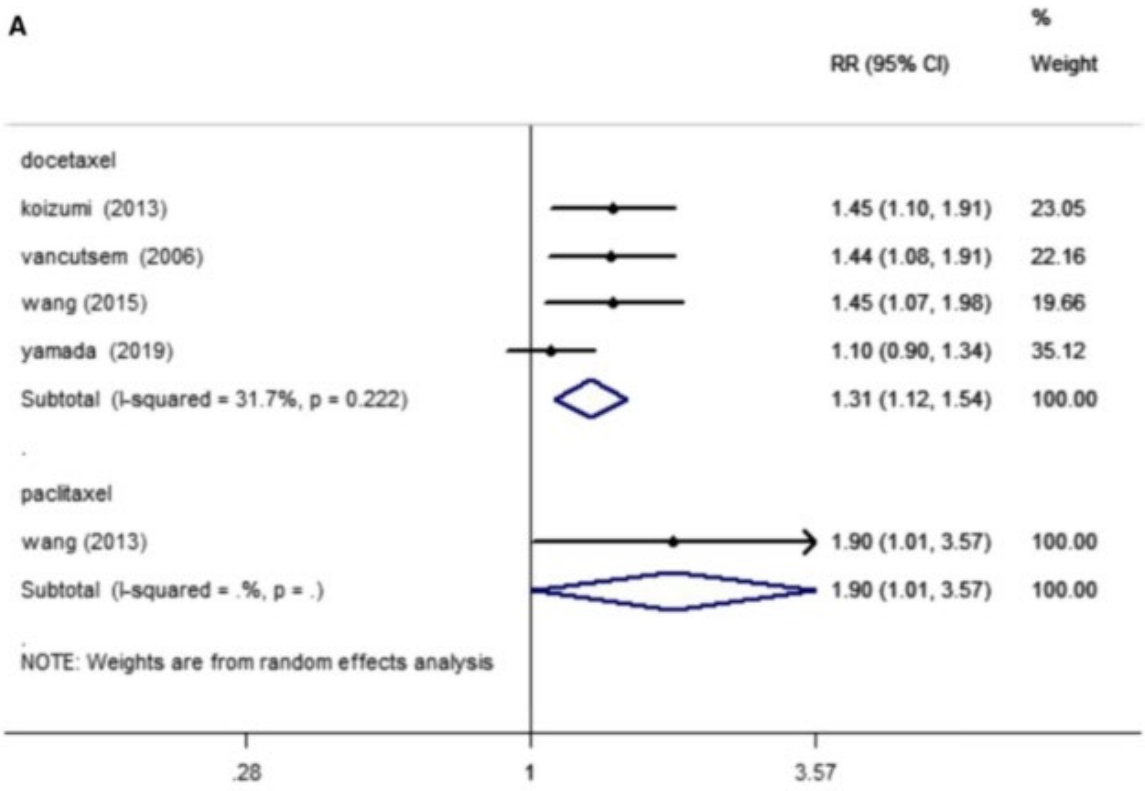


Fig. 4 Forest plot and pooled RR and 95% CI for subgroup ORR: "taxanes combined with basic chemotherapy" versus "chemotherapy without taxanes". RR risk ratios, CI confidence intervals, ORR objective response rate. (**A** ORR of subgroups of paclitaxel or docetaxel combined with basic chemotherapy; **B** ORR of subgroups of the Westerners and Asians)

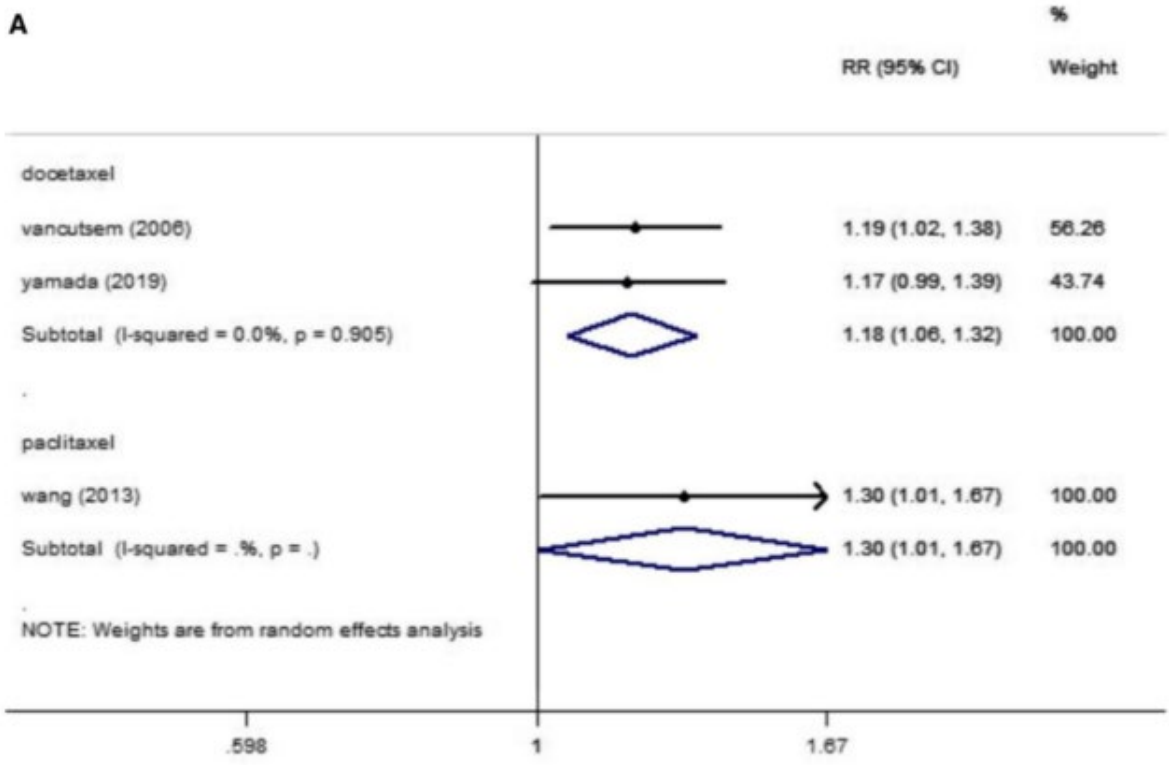


Fig. 5 Forest plot and pooled RR and 95% CI for subgroup DCR: "taxanes combined with basic chemotherapy" versus "chemotherapy without taxanes". RR risk ratios, CI confidence intervals, DCR disease control rate. (**A** DCR of subgroups of paclitaxel or docetaxel combined with basic chemotherapy; **B** DCR of subgroups of the Westerners and Asians)

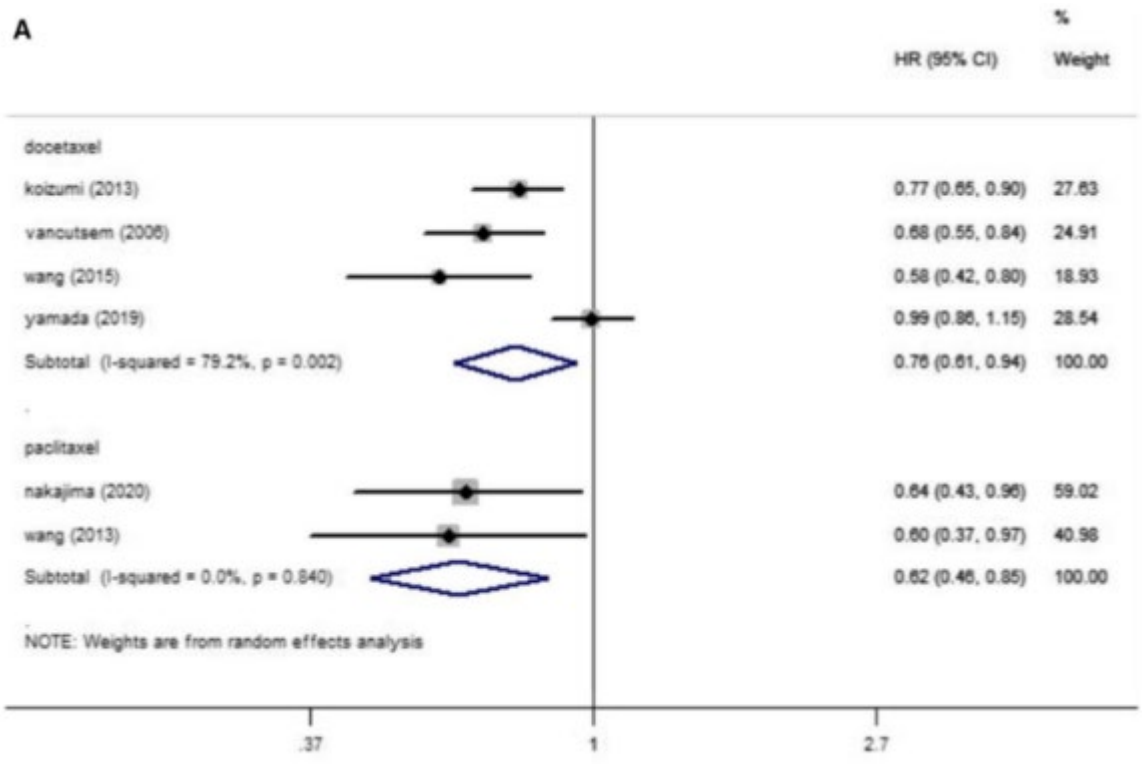


Fig. 7 Forest plot and pooled HR and 95% CI for subgroup PFS: "taxanes combined with basic chemotherapy" versus "chemotherapy without taxanes". HR hazard ratios, CI confidence intervals, PFS progression-free survival. (**A** PFS of subgroups of paclitaxel or docetaxel combined with basic chemotherapy; **B** PFS of subgroups of the Westerners and Asians)

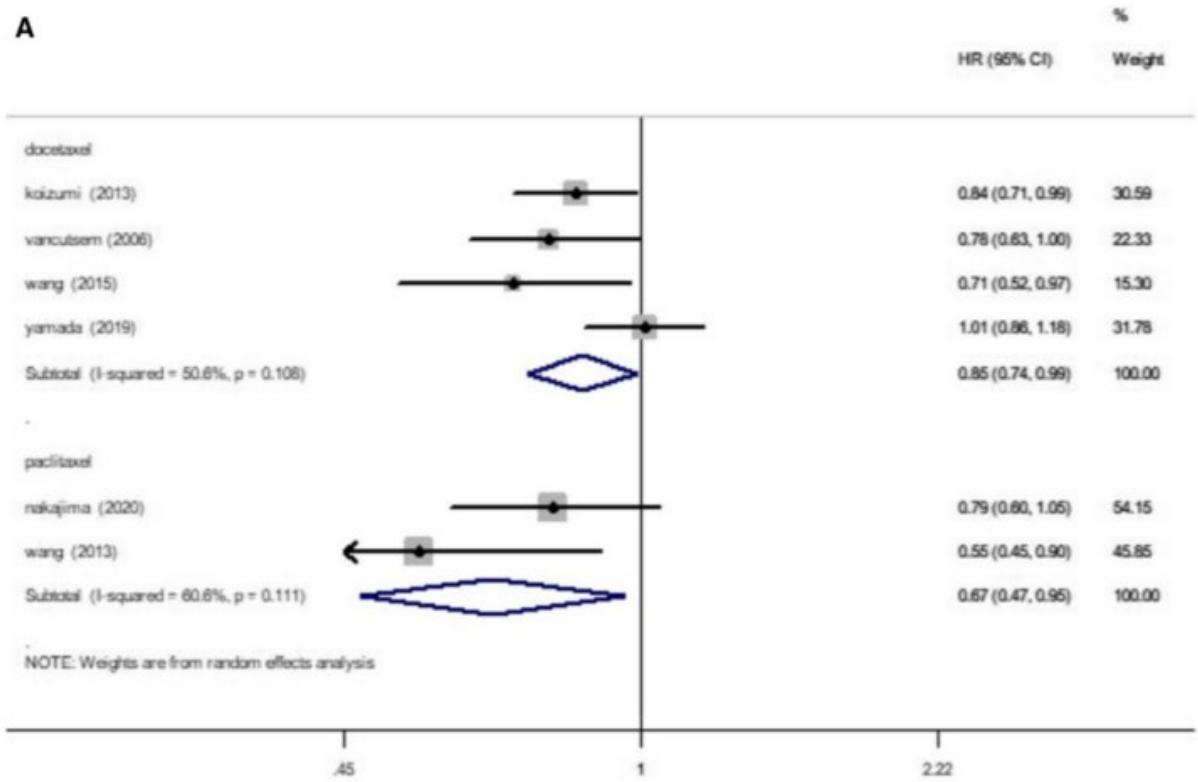


Fig. 8 Forest plot and pooled HR and 95% CI for subgroup OS: "taxanes combined with basic chemotherapy" versus "chemotherapy without taxanes". HR hazard ratios, CI confidence intervals, OS overall survival. (A: OS of subgroups of paclitaxel or docetaxel combined with basic chemotherapy; B: OS of subgroups of the Westerners and Asians)

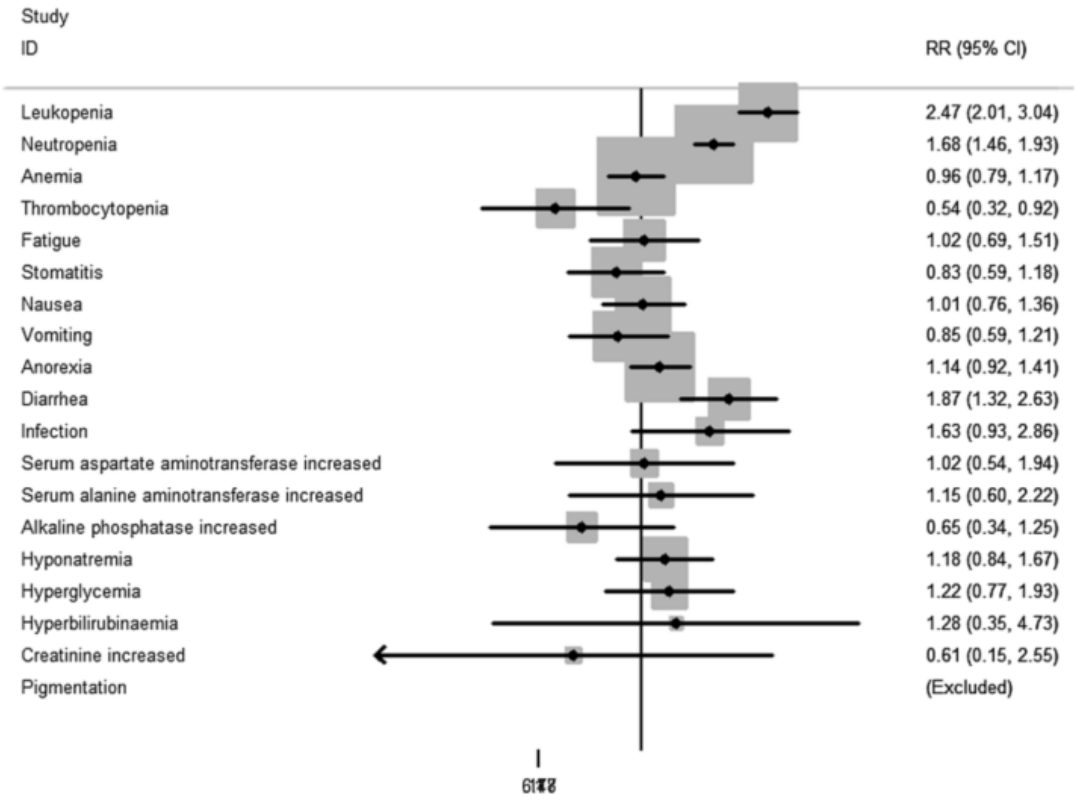


Fig. 9 RR of high-grade toxic side effects in patients with advanced gastric cancer treated with taxanes combined with basic chemotherapy

Anmerkung/Fazit der Autoren

Regardless of paclitaxel or docetaxel, the ORR and DCR of combined treatment were superior to those of non-taxanes, but the effect of docetaxel combination was relatively better. It has been reported that although taxanes drugs have many similarities in pharmacological characteristics and mechanisms of action, such as microtubule stabilizers and cell cycle inhibitors, there are significant differences between them. Preclinical studies have shown that docetaxel has stronger affinity for microtubules, longer plasma half-life, and longer intracellular retention time than paclitaxel [27], which is also consistent with our results.

Taxanes combined with basic chemotherapy are superior to basic chemotherapy without taxanes in ORR, DCR, OS and PFS. Further research is needed to explore the action mechanism of taxanes in the treatment of AGC patients and adjust the scheme to reduce toxic and side effects, so as to improve clinical benefits and improve the prognosis of patients.

Wu Z et al., 2023 [9].

Meta-Analysis of Capecitabine versus 5-Fluorouracil in Advanced Gastric Cancer

Fragestellung

Tis study aimed to investigate the effect of capecitabine versus 5fuorouracil on overall response rate, neutropenia, thrombocytopenia, nausea and vomiting, alopecia, and diarrhea through a meta-analysis.

Methodik

Population:

- individuals aged ≥ 18 years with a definite diagnosis of advanced gastric cancer, despite of sex, and race

Intervention/Komparator:

- capecitabine-based chemotherapy was used in the experimental group and 5-fuorouracil-based chemotherapy was used in the control group

Endpunkte:

- data on overall response rate and adverse events were provided in the study

Recherche/Suchzeitraum:

- PubMed, Embase, and Cochrane Library
- to June 2022

Qualitätsbewertung der Studien:

- Cochrane collaboration's risk of bias evaluation tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs
- 1998 individuals with advanced gastric cancer
- 982 patients in the capecitabine arm
- 1016 patients in the 5-fuorouracil arm

Charakteristika der Population/Studien:

Table 1: Clinical characteristics of included literature.

First author	Year	Sample size (capecitabine/ 5-fluorouracil)	Age, years (capecitabine/ 5-fluorouracil)	Number of males (capecitabine/ 5-fluorouracil)	Capecitabine arm chemotherapy regimen	5-Fluorouracil arm chemotherapy regimen
Cunningham [8]	2008	494/508	63/63	392/393	Epirubicin/cisplatin/capecitabine, or epirubicin/oxaliplatin/capecitabine	Epirubicin/cisplatin/5-fluorouracil, or epirubicin/oxaliplatin/5-fluorouracil
Kang [9]	2009	139/137	56/56	103/108	Cisplatin/capecitabine	Cisplatin/5-fluorouracil
Li [10]	2016	55/50	52/52	35/34	Epirubicin/oxaliplatin/capecitabine	Irinotecan/5-fluorouracil/leucovorin calcium
Ochenduszko [11]	2015	29/27	58/60	16/13	Epirubicin/oxaliplatin/capecitabine	Docetaxel/cisplatin/5-fluorouracil
Ocvirk [12]	2012	40/45	56/55	32/34	Epirubicin/cisplatin/capecitabine	Epirubicin/cisplatin/5-fluorouracil
Sumpter [13]	2005	96/108	63/62	82/79	Epirubicin/cisplatin/capecitabine, or epirubicin/oxaliplatin/capecitabine	Epirubicin/cisplatin/5-fluorouracil, or epirubicin/oxaliplatin/5-fluorouracil
Tebbutt [14]	2010	47/53	59/61	42/42	Docetaxel/capecitabine	Docetaxel/cisplatin/5-fluorouracil
Van Cutsem [15]	2014	82/88	59/58	74/69	Docetaxel/oxaliplatin/capecitabine	Docetaxel/oxaliplatin/5-fluorouracil

Qualität der Studien:

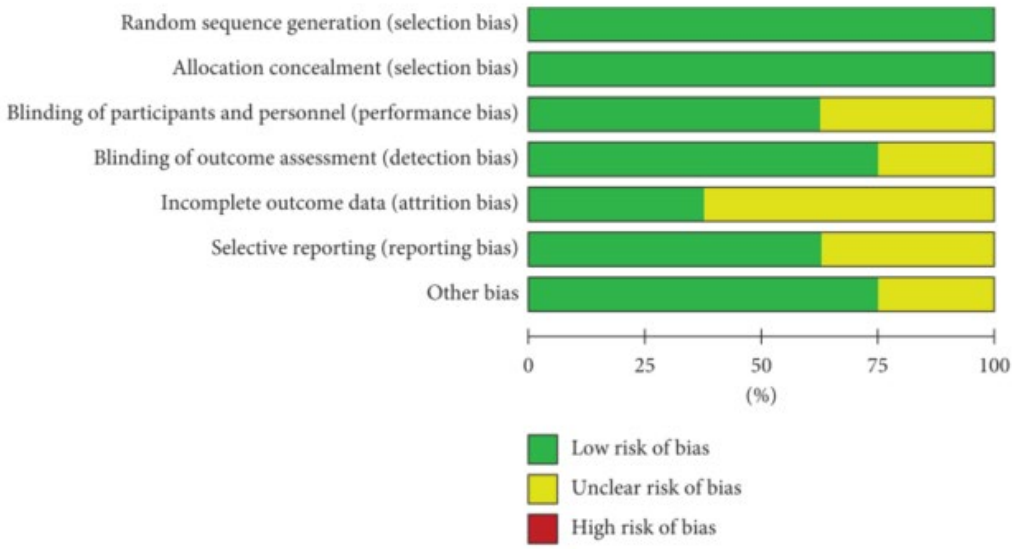


FIGURE 2: Risk of bias of included literature.

Studienergebnisse:

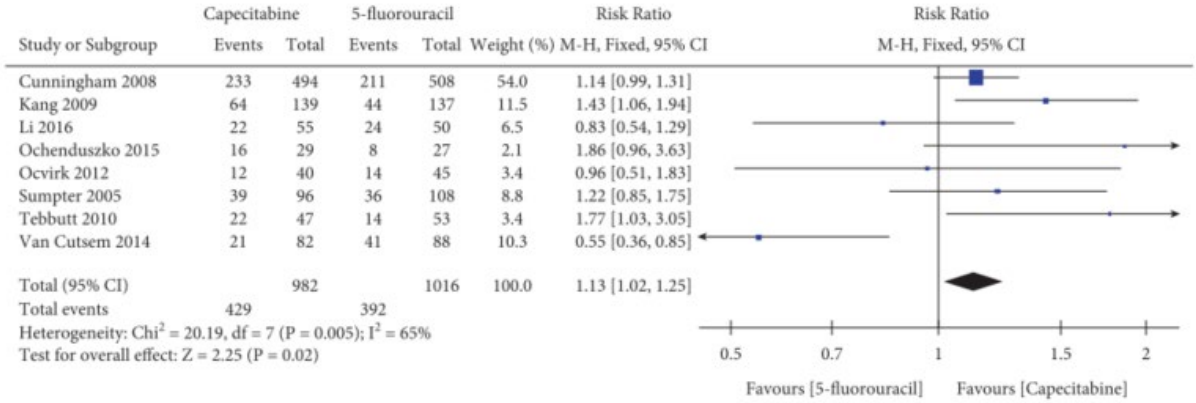


FIGURE 3: Effect of capecitabine and 5-fluorouracil on overall response rate.

3.4. Effect of Capecitabine and 5-Fluorouracil on Overall Response Rate. A total of 8 articles were included in Figure 3 to show the effect of capecitabine and 5-fuorouracil on the overall response rate. Capecitabine use was significantly associated with an increased overall response rate compared with 5-fuorouracil (RR 1.13, 95% CI 1.02–1.25, I^2=65%, P=0.02).

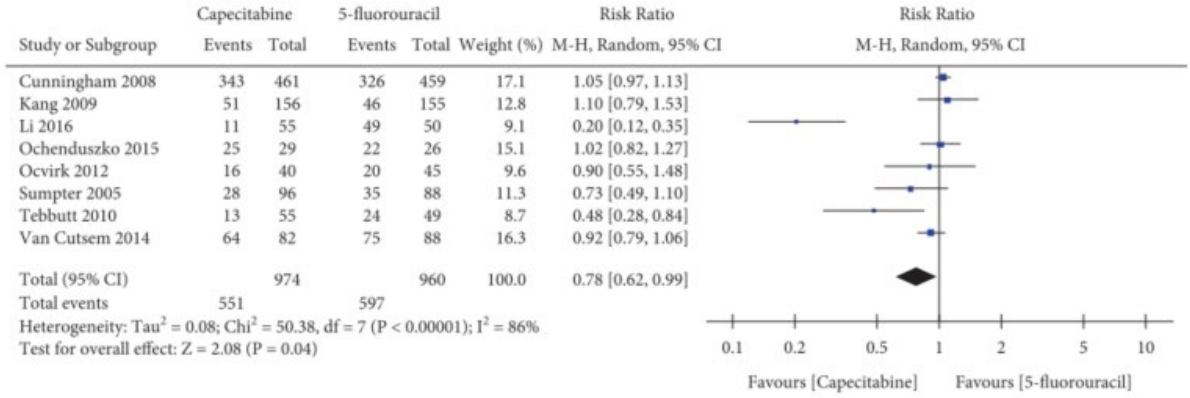


FIGURE 4: Effect of capecitabine and 5-fluorouracil on neutropenia.

3.5. Effect of Capecitabine and 5-Fluorouracil on Neutropenia and Trombocytopenia. Figure 4 shows the effect of capecitabine versus 5-fuorouracil on neutropenia. Compared with 5fuorouracil, treatment with capecitabine was significantly associated with decreased neutropenia events in advanced gastric cancer patients (RR 0.78, 95% CI 0.62–0.99, I2=86%, P=0.04). Capecitabine tended to reduce the occurrence of thrombocytopenia compared with the 5-fuorouracil group (RR 0.79, 95% CI 0.38 to 1.62, I^2=82%, P=0.52) (Table 2).

Table 2: Safety analysis of capecitabine and 5-fluorouracil.

Adverse reactions	Capecitabine arm (number of events/sample size)	5-Fluorouracil group (# events/sample size)	RR	95% CI	*P* Value	I^2 (%)
Thrombocytopenia	130/811	146/813	0.79	0.38–1.62	0.52	82
Nausea and vomiting	580/969	598/969	0.97	0.91–1.03	0.27	0
Hand-foot syndrome	300/878	173/872	2.00	1.21–3.31	0.007	69
Alopecia	454/689	477/693	0.95	0.89–1.02	0.17	26
Stomatitis	238/878	322/872	0.73	0.64–0.84	<0.0001	40
Diarrhea	372/878	364/872	1.02	0.78–1.33	0.90	67

4. Nonhematologic Adverse Events

Compared with 5-fuorouracil, the intervention with capecitabine was significantly associated with decreased stomatitis events (RR 0.73, 95% CI 0.64–0.84, I^2=40%, P< 0.0001). In terms of hand-foot syndrome, capecitabine was associated with increased hand-foot syndrome events than 5-fuorouracil (RR 2.00, 95% CI 1.21–3.31, I^2=69%, P=0.007). Capecitabine was not significantly different from 5-fuorouracil in nausea and vomiting (RR 0.97, 95% CI 0.91–1.03, I^2=0%, P=0.27). Capecitabine did not differ significantly from 5-fuorouracil in alopecia (RR 0.95, 95% CI 0.89–1.02, I^2=26%, P=0.17). Compared with 5-fuorouracil treatment, capecitabine did not significantly affect diarrhea (RR 1.02, 95% CI 0.78–1.33, I^2=67%, P=0.90)

Anmerkung/Fazit der Autoren

In summary, capecitabine treatment improves overall response rates and reduces the risk of neutropenia and stomatitis compared with 5-fuorouracil. It should be noted that treatment with capecitabine may also increase the occurrence of hand-foot syndrome. Capecitabine is similar to 5-fuorouracil in causing thrombocytopenia, nausea and vomiting, alopecia, and diarrhea.

Liu BW et al., 2023 [5].

Efficacy and safety of PD-1/PD-L1 inhibitor combined with chemotherapy versus chemotherapy alone in the treatment of advanced gastric or gastroesophageal junction adenocarcinoma: a systematic review and meta-analysis

Fragestellung

Thus, we integrated and summarized the data of published studies, compared the efficacy and safety of immunotherapy combined with chemotherapy and chemotherapy alone, and comprehensively analyzed and drew conclusions to provide an evidence base for the treatment of previously untreated, unresectable advanced, or metastatic gastroesophageal adenocarcinoma.

Methodik

<u>Population:</u>

- patients with unresectable, untreated (if prior therapy was more than 180 days), and metastatic EAC/GEA

Intervention/Komparator:

- Comparisons between chemotherapy combined with PD-1 or PDL1 inhibitors and chemotherapy alone (either FLOT or other standard regimens) were performed

Endpunkte:

- PFS, OS, adverse events

Recherche/Suchzeitraum:

- before 31 December 2021
- PubMed, Embase, Cochrane, and ClinicalTrials.gov

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 4 RCTs
- 3,013 patients

Charakteristika der Population/Studien:

TABLE 1 Basic characteristics of the included studies.

Study (year)	Design	Arms	Country	Population (N, age)	Sex (male/female)	Primary endpoint	Main outcome measures
Janjigian et al. (21)	RCT; multicenter; open-label; phase 3 study	Nivolumab plus chemotherapy (XELOX every 3 weeks or FOLFOX every 2 weeks) or chemotherapy alone	USA	N = 1,581, NM	1,100/481	OS/PFS	OS; PFS; ORR; AE
Jong-Mu Sun et al.	RCT; multicenter; double-blind, phase 3 study	Pembrolizumab plus chemotherapy (5-fluorouracil plus cisplatin every 3 weeks) or chemotherapy alone	USA	N = 201, NM	NM	OS/PFS	OS; PFS; ORR; DORR; AE
Yoon-Koo Kang et al. (21)	RCT; multicenter; double-blind, phase 3 study	Nivolumab plus chemotherapy (oxaliplatin plus S-1 or capecitabine every 3 weeks) or chemotherapy alone	Japan	N = 724, 25–89	523/201	OS/PFS	OS; PFS; ORR; DORR; DCR; AE
Kohei Shitara et al. (25)	RCT; partially blinded; phase 3 study	Pembrolizumab plus chemotherapy (cisplatin plus fluorouracil or capecitabine every 3 weeks) or chemotherapy alone	USA	N = 507, 22–87	374/133	OS/PFS	OS; ORR; DORR; PFS; AE

DORR, disease objective response rate; ORR, objective response rate; AE, adverse event; PFS, progression-free survival; OS, overall survival; NM, not mentioned; RCT, randomized control trial; DCR, disease control rate; XELOX, oxaliplatin plus capecitabine; FOLFOX, fluorouracil plus oxaliplatin.

Qualität der Studien:

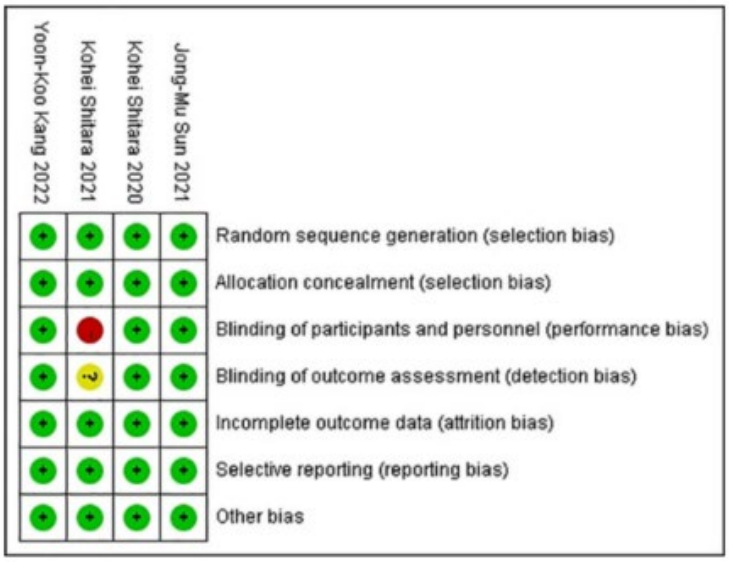


FIGURE 2
Quality assessment result of included studies according to the Cochrane risk of bias tool.

Studienergebnisse:

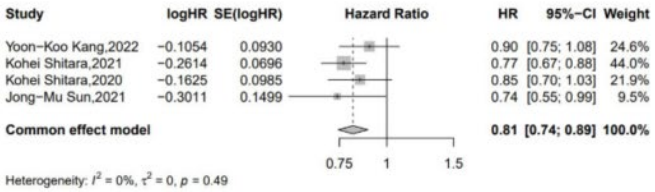


FIGURE 3
Forest plot of the hazard ratio comparing the overall survival (OS) in patients treated with immune checkpoint inhibitors (ICIs) + chemotherapy and chemotherapy alone.

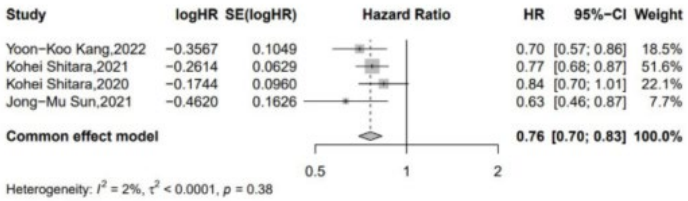


FIGURE 4
Forest plot of the hazard ratio comparing the progression-free survival (PFS) in patients treated with immune checkpoint inhibitors (ICIs) + chemotherapy and chemotherapy alone.

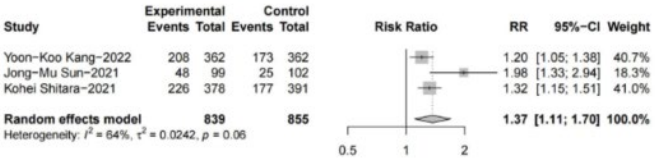


FIGURE 5
Forest plot of the hazard ratio comparing the disease objective response rate (DORR) in patients treated with immune checkpoint inhibitors (ICIs) + chemotherapy and chemotherapy alone.

TABLE 2 Pooled results of adverse effects in patients during treatment.

Variables	No. of subjects	OR (95% CI)	p-Value
ALA increased	216	1.55 (1.17–2.07)	**0.003**
Anemia	678	1.16 (0.98–1.38)	0.09
ASA increased	289	1.63 (1.17–2.10)	**<0.000**
Decreased appetite	828	1.01 (0.86–1.19)	0.89
Diarrhea	819	1.22 (1.03–1.43)	**0.02**
Fatigue	702	1.08 (0.91–1.28)	0.37
Nausea	1,268	1.24 (1.07–1.44)	**0.005**
Neutropenia	594	0.99 (0.82–1.19)	0.9
NCD	661	1.35 (1.14–1.61)	**<0.000**
Peripheral neuropathy	550	1.21 (1.00–1.46)	**0.05**
PSN	691	1.18 (1.00–1.41)	0.06
PLT count decreased	617	1.14 (0.96–1.37)	0.14
PPE syndrome	367	1.30 (1.05–1.63)	**0.02**
Pruritus	88	2.88 (1.74–4.76)	**<0.000**
Rash	96	3.23 (2.00–5.20)	**<0.000**
Thrombocytopenia	395	1.14 (0.92–1.41)	0.24
Vomiting	633	1.12 (0.94–1.34)	0.21
WBC count decreased	380	1.40 (1.13–1.73)	**0.002**

Statistically significant value ($p < 0.05$) favors ICIs + chemotherapy.
ALA, alanine aminotransferase; ASA, aspartate aminotransferase; PCD, neutrophil count decreased; PLT, platelet; PSN, peripheral sensory neuropathy; PPE, palmar-plantar erythrodysesthesia syndrome; WBC, white blood cell; ICIs, immune checkpoint inhibitors.
Bold values represent that ICIs plus chemotherapy had a higher incidence of side effects and was statistically significant.

Anmerkung/Fazit der Autoren

In conclusion, ICIs plus chemotherapy improved median OS, PFS, and ORR when compared with chemotherapy in patients with advanced, unresectable, and metastatic EAC/GEA, with manageable higher TRAEs. Therefore, the optimal timing, dose, and combination regimen of neoadjuvant ICI combined with chemotherapy in the treatment of esophageal cancer are worthy of further study.

3.3 Leitlinien

Leitlinienprogramm Onkologie., 2023 [3,4].

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft (DKG); Deutsche Krebshilfe (DKH); Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)

Diagnostik und Therapie der Plattenepithelkarzinome und Adenokarzinome des Ösophagus; S3-Leitlinie, Langversion 4.0

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- - 04.03.2022

LoE/GoR

Tabelle 2: Schema der Empfehlungsgraduierung

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll/soll nicht
B	Empfehlung	sollte/sollte nicht
0	Empfehlung offen	kann/kann verzichtet werden

Tabelle 3: Festlegungen hinsichtlich der Konsensstärke

Konsensstärke	Prozentuale Zustimmung
Starker Konsens	> 95% der Stimmberechtigten
Konsens	>75 – 95% der Stimmberechtigten
Mehrheitliche Zustimmung	>50 – 75% der Stimmberechtigten
Keine mehrheitliche Zustimmung	<50% der Stimmberechtigten

Empfehlungen

8.14	Konsensbasierte Empfehlung	modifiziert 2023
EK	Bei präoperativem Nachweis von Fernmetastasen soll keine Operation erfolgen. Bei intraoperativem Befund vorher nicht bekannter, sehr limitierter Fernmetastasen können diese zusammen mit dem Primärtumor entfernt werden.	
	Konsens	

9.2	Evidenzbasierte Empfehlung	geprüft 2023
Empfehlungsgrad A	Patienten mit einem metastasierten oder lokal fortgeschrittenen, nicht kurativ behandelbaren **Adenokarzinom** des Ösophagus und des ösophagogastralen Übergangs soll eine Systemtherapie angeboten werden. Therapieziel ist die Verlängerung der Überlebenszeit und der Erhalt der Lebensqualität.	
Level of Evidence 1a	[123], [610], [611], [612], [613], [60]	
	Starker Konsens	

9.5	Evidenzbasierte Empfehlung	neu 2023
Empfehlungsgrad A	Bei negativem HER2-Status und einem erhöhten PD-L1 CPS Cut-off Wert (für Nivolumab PD-L1 CPS≥5, für Pembrolizumab PD-L1 CPS≥10) soll eine Platin (Oxaliplatin oder Cisplatin)/Fluoropyrimidin-Kombination zusammen mit einem der genannten Immun-Checkpoint-Inhibitoren eingesetzt werden.	
Level of Evidence 1b	[618], [619] 1b: 2: LoE nach Oxford 2011 - einzelnes RCT Für Evidenzbewertung nach GRADE siehe Evidenztabelle (Leitlinienreport)	

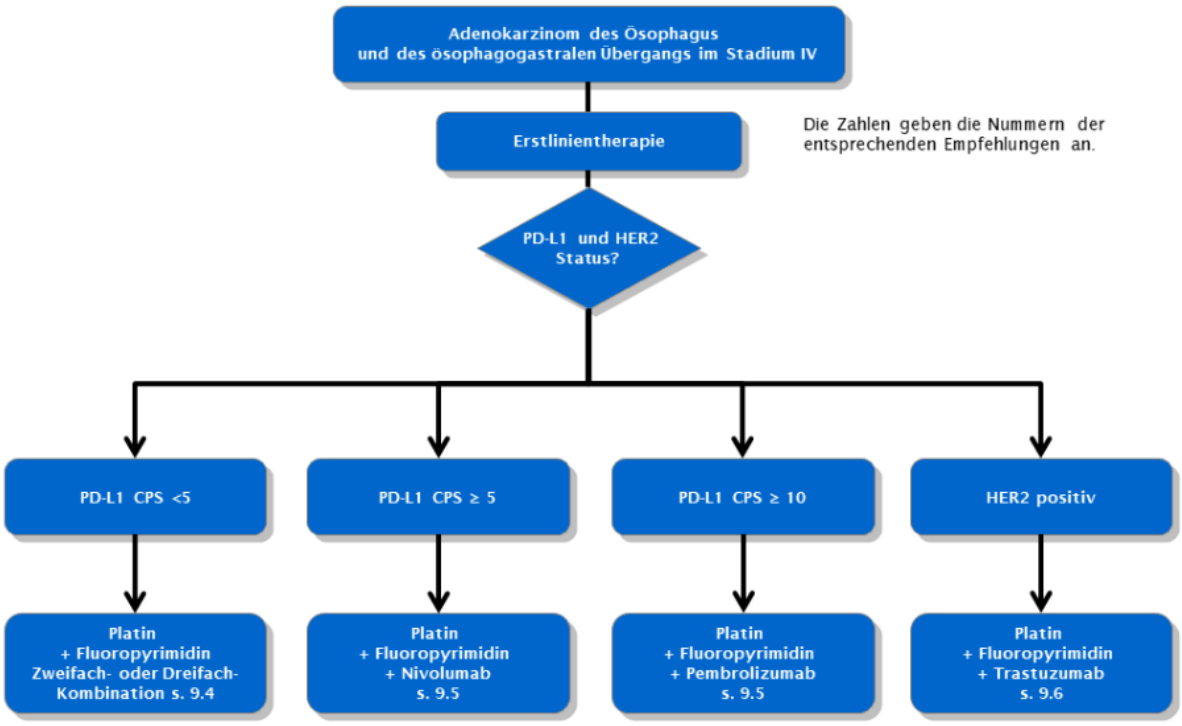


Abbildung 6: Therapiealgorithmus für die Erstlinientherapie des metastasierten oder lokal fortgeschrittenen, nicht kurativ behandelbaren Adenokarzinoms des Ösophagus und des gastroösophagealen Übergangs

9.14	Konsensbasierte Empfehlung	geprüft 2023
EK	Die perkutane Radiotherapie des Ösophaguskarzinoms – ggfs. in Kombination mit einer simultanen Chemotherapie – kann bei lokalen Symptomen (z. B. Blutung, Stenose, Kompression) im Rahmen der multidisziplinären Betreuung eingesetzt werden.	
	Konsens	

9.15	Evidenzbasierte Empfehlung	geprüft 2023
Empfehlungsgrad **B**	Die palliative Brachytherapie sollte im Rahmen der multidisziplinären Betreuung von Patienten mit Ösophaguskarzinom zur Linderung der Dysphagie gegebenenfalls in Kombination einer perkutanen Radiochemotherapie oder einer Stentimplantation angeboten werden.	
Level of Evidence **1a**	[663], [664], [662], [661]	
	Starker Konsens	

9.16	Evidenzbasierte Empfehlung	geprüft 2023
Empfehlungsgrad **B**	Zur raschen Linderung einer Dysphagie bei Patienten mit Ösophaguskarzinom sollte ein selbstexpandierender Metallstent eingesetzt werden.	
Level of Evidence **1a**	[666]	
	Konsens	

9.18	Konsensbasierte Empfehlung	geprüft 2023
EK	Eine intraluminale thermoablative Therapie bei Patienten mit exophytischem Ösophaguskarzinom in der palliativen Situation kann erwogen werden. Eine additive Brachytherapie oder Radiatio nach lokaler Tumorablation kann das dysphagiefreie Intervall verlängern.	
	Starker Konsens	

Referenzen

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NICE, 2023 [7].

National Institute for Health and Care Excellence (NICE)

Oesophago-gastric cancer: assessment and management in adults

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- All searches were updated in May 2017
- Last updated: 4 July 2023

LoE/GoR

- GRADE

Empfehlungen

Non-metastatic oesophageal cancer that is not suitable for surgery

1.5.1 Consider chemoradiotherapy for people with non-metastatic oesophageal cancer that can be encompassed within a radiotherapy field. [2018]

1.5.2 When the cancer cannot be encompassed within a high-dose radiotherapy field, consider one or more of:

• chemotherapy

• local tumour treatment, including stenting or palliative radiotherapy

• best supportive care.

Discuss the benefits, risks and treatment consequences of each option with the person with oesophageal cancer and those who are important to them (as appropriate). [2018]

1.5.3 After a person with oesophageal cancer has had treatment, assess the tumour's response to chemotherapy or chemoradiotherapy and reconsider if surgery is an option. [2018]

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

1.5.5 Offer first-line palliative combination chemotherapy to people with advanced oesophago-gastric cancer who have a performance status 0 to 2 and no significant comorbidities. Possible drug combinations include:

• doublet treatment: 5-fluorouracil or capecitabine in combination with cisplatin or oxaliplatin

• triplet treatment: 5-fluorouracil or capecitabine in combination with cisplatin or oxaliplatin plus epirubicin.

Discuss the benefits, risks and treatment consequences of each option with the person and those important to them (as appropriate).

In January 2018, this was an off-label use of capecitabine, cisplatin, epirubicin and oxaliplatin. See NICE's information on prescribing medicines.

For all NICE technology appraisal guidance on first-line palliative chemotherapy, see the NICE topic pages for oesophageal cancer and stomach cancer. [2018]

Shah MA et al., 2023 [8].

American Society of Clinical Oncology (ASCO)

Immunotherapy and Targeted Therapy for Advanced Gastroesophageal Cancer: ASCO Guideline.

Zielsetzung/Fragestellung

To develop recommendations involving targeted therapies for patients with advanced gastroesophageal 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.

Recherche/Suchzeitraum:

- PubMed (January 1, 2010-March 4, 2022)

LoE/GoR

- Cochrane Risk of Bias tool and elements of the GRADE quality assessment and recommendations development process / GRADE quality assessment labels

TABLE A2. Recommendation Rating Definitions

Term	Definitions
Quality of evidence	
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Strength of recommendation	
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects. In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects. All or almost all informed people would make the recommended choice for or against an intervention.
Weak	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists. In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists. Most informed people would choose the recommended course of action, but a substantial number would not.

Recommendations

First-line therapy

- Recommendation 1.1. For human epidermal growth factor receptor 2 (HER2)–negative patients with gastric adenocarcinoma (AC) and programmed death-ligand 1 (PD-L1) combined positive score (CPS) $ 5, first-line therapy with nivolumab in combination with fluoropyrimidine- and platinum-based chemotherapy (CT) is recommended (Type: Evidence based; benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).
- Qualifying statements:
  - For HER2-negative patients with gastric AC and PD-L1 CPS 1-5, first-line therapy with nivolumab in combination with fluoropyrimidine- and platinum-based CT may be considered on a case-by-case basis.
  - For HER2-negative patients with gastric AC and PD-L1 CPS 0, first-line therapy with fluoropyrimidine- and platinumbased CT, without the addition of nivolumab, is recommended.
- Recommendation 1.2. For HER2-negative patients with esophageal or gastroesophageal junction (GEJ) AC, first-line therapy with nivolumab for patients with PD-L1 CPS ≥5, or pembrolizumab for PD-L1 CPS ≥ 10, in combination with fluoropyrimidine- and platinum-based CT is recommended (Type: Evidence based; benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Strong).
- Qualifying statements:
  - For HER2-negative patients with esophageal or GEJ AC, first-line therapy with nivolumab for patients with PD-L1 CPS 1-5, or pembrolizumab for patients with PD-L1 CPS 1-10, in combination with fluoropyrimidine- and platinum-based CT may be recommended on a case-by-case basis.
  - For HER2-negative patients with gastric AC and PD-L1 CPS 0 or PD-L1 tumor proportion score (TPS) 0%, first-line therapy with fluoropyrimidine- and platinum-based CT, without the addition of programmed cell death protein 1 inhibitors, is recommended.

- Recommendation 1.4. For patients with HER2-negative ESCC and PD-L1 TPS ≥ 1%, nivolumab plus fluoropyrimidine- and platinum-based CT or nivolumab plus ipilimumab is recommended (Type: Evidence based; benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong).
- Qualifying statement:
  - Data from the primary analysis of CheckMate 648 supports Recommendation 1.4 in patients with ESCC and PD-L1 TPS ≥1%. Additional exploratory analyses from CheckMate 648 found that 91% of patients across three study arms had PD-L1 CPS $ 1; therefore, CPS ≥ 1 may be used as a threshold for treatment decision making if TPS is not available.
- Qualifying statements for Recommendations 1.1-1.4:
  - The PD-L1 cutoffs in Recommendations 1.1-1.4 are based on subgroup analyses presented in included studies. All possible cutoffs have not been assessed; therefore, optimal PD-L1 cutoffs are unknown.
  - Several additional studies of immunotherapy with programmed cell death protein 1 inhibitors plus CT, compared with placebo plus CT have shown efficacy; however, these therapy options are not currently US Food and Drug Administration–approved
- Recommendation 1.5. For patients with HER2-positive gastric or GEJ previously untreated, unresectable or metastatic AC, trastuzumab plus pembrolizumab is recommended, in combination with fluoropyrimidine- and oxaliplatin-based CT (Type: Evidence based; benefits outweigh harms; Evidence quality: Low; Strength of recommendation: Strong).
- Qualifying statements:
  - Recommendation 1.5 is applicable irrespective of CPS or TPS levels; however, the Expert Panel notes that PD-L1 CPS was ≥ 1 in 87% of patients included in the KEYNOTE-811 randomized controlled trial.
  - HER2 positivity was defined in KEYNOTE-811 as immunohistochemistry 31 or immunohistochemistry 21 with positive in-situ hybridization (details of testing methodology are contained in the Literature review and analysis section).
  - Trastuzumab plus pembrolizumab and CT is recommended based on an interim analysis showing a response benefit in the first 264 patients enrolled in KEYNOTE-811.12 progression-free survival.

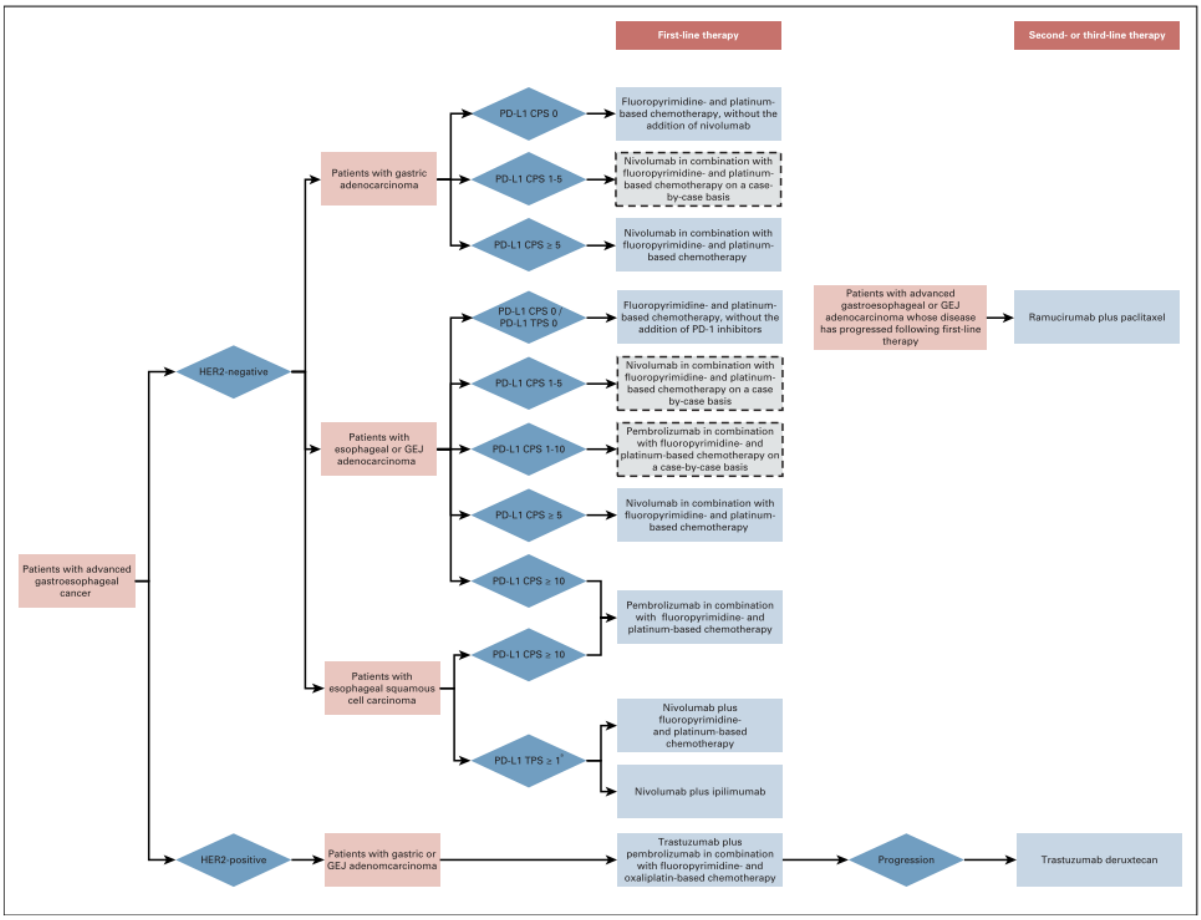

FIG 1. Immunotherapy and targeted therapy for advanced gastroesophageal cancer algorithm. [a]Data from the primary analysis of CheckMate 648 supports Recommendation 1.3 in patients with ESCC and PD-L1 TPS ≥ 1%. Additional exploratory analyses from CheckMate 648 found that 91% of patients across three study arms had PD-L1 CPS ≥ 1; therefore, CPS ≥ 1 may be used as a threshold for treatment decision making if TPS is not available. CPS, combined positive score; ESCC, esophageal squamous cell carcinoma; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

Alberta Health Services, 2021 [1].

Gastric cancer, Version 6.

Zielsetzung/Fragestellung

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

Methodik

<u>Grundlage der Leitlinie</u>

- Repräsentatives Gremium; trifft teilweise zu (Patientenvertretung unklar)
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt; trifft zu
- Systematische Suche, Auswahl und Bewertung der Evidenz; trifft zu
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt; trifft zu
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt; trifft teilweise zu
- Regelmäßige Überprüfung der Aktualität gesichert

Recherche/Suchzeitraum:

- Suchzeitraum: 01.01.2018 – 31.12.2020

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

Der Empfehlungsgrad ist in der vorliegenden Leitlinie nicht berichtet.

Recommendations

Stage IV (First Line)

- Palliative maneuvers to maintain and/or improve quality of life are indicated (e.g.: stent placement or radiotherapy to relieve dysphagia, obstruction, or bleeding).
- Palliative chemotherapy regimens are generally continued as long as tumour shrinkage or stability is confirmed, as long as the side effects remain manageable, as long as the patient wishes to continue, and as long as the treatment remains medically reasonable.
- Consider an early referral to palliative care

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/ m^2 IV over ninety minutes) and Leucovorin (400 mg/ m^2 IV over two hours) followed by 5-Fluorouracil (2400 mg/ m^2 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/m^2 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.

- Nivolumab with FOLFOX/CAPOX CPS≥5
  i. In the ATTRACTION-4 study patients in Japan, Korea or Taiwan were randomized to nivolumab or placebo with chemotherapy (SOX or CapeOx). In this study with dual primary endpoints, the nivolumab + chemotherapy patients had improved progression free survival (median PFS 10.45 months versus 8.34 months with chemotherapy alone (HR: 0.68, 95%CI: 0.51-0.90, p<0.001). However, there was no improvement in overall survival.
  ii. The Checkmate 649 study study was an international trial (including poppulations from Asia, North America and the rest of the world) which randomized patients to nivolumab with chemotherapy (Nivolumab + XELOX or Nivolumab + FOLFOX) or chemotherapy alone (XELOX or FOLFOX). This study demonstrated a statistically significant improvement in overall survival in patients with the addition of nivolumab in the PD-L1 CPS≥5 (median OS 14.4 months versus 11.1 months in the chemotherapy alone arm; HR: 0.71, 95%CI: 0.59-0.86, p<0.001). Furthermore, OS benefit was also seen in the secondary endpoints analyzing patients with PD-L1 CPS≥1 as well as in all randomized patients. Similarly, benefits were seen in PFS, overall responses and duration of response in the patients receiving nivolumab†.
- Pembrolizumab
  i. In the phase III KEYNOTE-062 trial, 763 patients with previously untreated advanced gastric or GE junction adenocarcinoma patients with a CPS > 1 were randomized to pembrolizumab, chemotherapy (cisplatin plus a fluoropyrimidine) or combined therapy. Pembrolizumab was non-inferior to chemotherapy alone for overall survival. In an exploratory analysis of patients with a CPS > 10, there was a clinically meaningful improvement in median overall survival with pembrolizumab compared to chemotherapy alone (17.4 vs 10.8 months, HR 0.69, 95% CI 0.49-0.97). Pembrolizumab is not currently funded.
  ii. At this time, the addition of pembrolizumab to chemotherapy has not demonstrated sufficient improvement in outcomes to justify the associated toxicities.
- 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.

<u>Capecitabine-based Combination Regimens:</u>

i. Capecitabine-based combination regimens (e.g.: ECX, EOX, CX) offer a superior response rate (45.6% versus 38.4%, OR 1.38, CI95% 1.10-1.73, p = 0.006) and overall survival (HR 0.87, CI95% 0.77-0.98, p = 0.02) when compared to 5-Fluorouracil-based combination chemotherapies (e.g.: ECF, EOF, CF).26

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

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 10 of 12, October 2024) am 30.10.2024

#	Suche
1	[mh "Esophageal Neoplasms"]
2	[mh "Stomach Neoplasms"]
3	[mh "Esophagogastric Junction"]
4	(esophag* OR oesophag* OR gastroesophag* OR gastrooesophag* OR ((gastric OR gastro) NEXT esophag*) OR ((gastric OR gastro) NEXT oesophag*)):ti,ab,kw
5	#4 AND (cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR squamo* OR malignan*):ti,ab,kw
6	stomach NEXT (cancer* OR tum*r* OR carcinoma* OR neoplasm* OR adenocarcinoma* OR squamo* OR malignan*):ti,ab,kw
7	{OR #1-#3, #5-#6}
8	#7 with Cochrane Library publication date from Okt 2019 to present

Systematic Reviews und Leitlinien in PubMed am 30.10.2024

verwendeter Suchfilter für Systematic Reviews ohne Änderung:

Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

verwendeter Suchfilter für Leitlinien ohne Änderung:

Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suche nach SR/MA/HTA
1	Esophageal Neoplasms/TH
2	Stomach Neoplasms/TH
3	Esophagogastric Junction/ AND Adenocarcinoma/TH
4	esophageal[ti] OR esophagogastric[ti] OR oesophagogastric[ti] OR stomach[ti] OR gastric[ti] OR gastroesophag*[ti] OR gastrooesophag*[ti] OR gastro-esophag*[ti] OR gastro-oesophag*[ti]
5	(#4) AND (cancer[ti] OR tumo*r[ti] OR tumo*rs[ti] OR tumour*[ti] OR carcinoma*[ti] OR neoplas*[ti] OR adenocarcinoma*[ti] OR malignan*[ti])
6	(#5) AND (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] OR untreat[tiab])
7	#1 OR #2 OR #3 OR #6

8	(#7) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
9	(((#8) AND ("2019/10/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))) NOT ("retracted publication"[Publication Type] OR "retraction of publication"[Publication Type] OR "preprint"[Publication Type])
	Suche nach Leitlinien
10	Esophageal Neoplasms[mh]
11	Stomach Neoplasms[mh]
12	Esophagogastric Junction[mh] AND Adenocarcinoma [mh]
13	#10 OR #11 OR #12 OR #5
14	(#13) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
15	((((#14) AND ("2019/10/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])
	Ergebnisse SR ohne Leitlinien
16	(#9) NOT (#15)

Iterative Handsuche nach grauer Literatur, abgeschlossen am 30.10.2024

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)

- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- *Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)*
- *Alberta Health Service (AHS)*
- *European Society for Medical Oncology (ESMO)*
- *National Comprehensive Cancer Network (NCCN)*
- *National Cancer Institute (NCI)*

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

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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