Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2019-B-121 Trifluridin/Tipiracil

Stand: Juli 2019

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

Trifluridin/Tipiracil
[zur Therapie des vorbehandelten metastasierten Magenkarzinoms einschließlich Adenokarzinom 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 – 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:	
Trifluridin/ Tipiracil L01BC59 Lonsurf®	Geplantes Anwendungsgebiet laut Beratungsanforderung: Trifluridin/ Tipiracil wird angewendet zur Behandlung von erwachsenen Patienten mit metastasiertem Magenkarzinom einschließlich Adenokarzinom des gastroösophagalen Übergangs, die bereits mit mindestens zwei systemischen Therapieregimen für die fortgeschrittene Erkrankung behandelt wurden.
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 5-FU medac®	− Fortgeschrittenes Magenkarzinom
Doxorubicin L01DB01 Doxorubicin-hydrochlorid Bendalis®	− fortgeschrittenes Magenkarzinom
Epirubicin L01DB03 Epirubicin onkovis®	Epirubicin ist für die Behandlung folgender maligner Erkrankungen in Mono- und Kombinationsschemata angezeigt: − fortgeschrittenes Magenkarzinom

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Mitomycin L01DC03 Mitomycin medac	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
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).

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2019-B-121 (Trifluridin/Tipiracil)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	9. Juli 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis 3
1 Indikation 4
2 Systematische Recherche....4
3 Ergebnisse....5
3.1 G-BA Beschlüsse/IQWiG Berichte 5
3.2 Cochrane Reviews 7
3.3 Systematische Reviews....10
3.4 Leitlinien....17
4 Detaillierte Darstellung der Recherchestrategie 48
Referenzen....50
Anhang 53

Abkürzungsverzeichnis

5-FU	5-Fluorouracil
AE	adverse events
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BSC	Best Supportive Care
EGFR	epidermal growth factor receptor
G-BA	Gemeinsamer Bundesausschuss
GE	gastro-esophageal
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
OS	Overall survival
PFS	Progression-free survival
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Behandlung von erwachsenen Patienten mit metastasiertem Magenkarzinom einschließlich Adenokarzinom des gastroösophagalen Übergangs, die bereits mit mindestens zwei systemischen Therapieregimen für die fortgeschrittene Erkrankung behandelt wurden.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *metastasiertes Magenkarzinom und Adenokarzinom des gastroösophagalen Übergangs* durchgeführt. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, CCO, ESMO, G-BA, NCCN, NCI NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien.

Die Erstrecherche wurde am 12.11.2018 durchgeführt, die Folgerecherche am 12.06.2019. Die Recherchestrategie der Erstrecherche wurde für die Folgerecherche übernommen und der Suchzeitraum jeweils auf die letzten 5 Jahre eingeschränkt. Die letzte Suchstrategie ist am Ende der Synopse detailliert dargestellt.

Die Recherchen ergaben insgesamt 715 Quellen, die in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Es wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen und nur die Quellen der letzten 5 Jahre berücksichtigt. 14 Quellen wurden in die synoptische Evidenz-Übersicht aufgenommen

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2016 [5].

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

a) Ramucirumab 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.

b) Ramucirumab 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.

Zweckmäßige Vergleichstherapie

a) Therapie nach Maßgabe des Arztes unter Beachtung der jeweiligen Zulassung

b) Best-Supportive-Care

Fazit / Ausmaß des Zusatznutzens / Ergebnis

a) Ramucirumab in Kombination mit Paclitaxel: Anhaltspunkt für einen geringen Zusatznutzen.

b) Ramucirumab als Monotherapie, wenn die Patienten für eine Kombinationstherapie mit Paclitaxel nicht geeignet sind: Ein Zusatznutzen ist nicht belegt.

G-BA, 2012 [4].

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.

Vergleichstherapie

Die zweckmäßige Vergleichstherapie ist die Zweifachkombination von Cisplatin mit 5-Fluorouracil oder Capecitabin.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Der Zusatznutzen im Verhältnis zur zweckmäßigen Vergleichstherapie gilt als nicht belegt.

3.2 Cochrane Reviews

Janmaat VT et al., 2017 [7].

Palliative chemotherapy and targeted therapies for esophageal and gastroesophageal junction cancer.

Fragestellung

To assess the effects of cytostatic or targeted therapy for treating esophageal or gastroesophageal (GE) junction cancer with palliative intent.

Methodik

Population:

- People with advanced (T3-T4NxM0 non-resectable; and all TxNxM1), recurrent, or metastatic carcinoma of the esophagus and GE-junction Intervention:
- people with both SCC and adenocarcinoma, as well as people who had received prior chemotherapy.

Intervention:

- systemic intravenous and single oral chemotherapy or targeted therapy, as well as combination regimens in all doses and schedules
  - Chemotherapy encompassed all cytotoxic and anti-neoplastic drug treatment,
  - targeted therapy encompasses all anti-neoplastic drug treatment targeting a specific protein or small group of proteins.

Komparator:

- BSC or treatment with at least one chemotherapy agent whose composition, dose, and schedule were equal in both arms.

Endpunkte:

- OS, PFS, Toxicity

Recherche/Suchzeitraum:

- CENTRAL, MEDLINE, Embase, Web of Science etc. bis 09/2017
- WHO International Clinical Trials Registry Platform (09/20017)

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool to assess risk of bias and the quality of studies
- GRADE system to assess the quality of evidence for each analysis

Ergebnisse

Anzahl eingeschlossener Studien:

- N=41 included in qualitative synthesis
- N=11 included in meta-analysis

Charakteristika der Studien

- participants reported as having metastatic disease ranged from 69% to 100%, 5 studies with no information on % of people with metastasis
- participants with ECOG-2 or ECOG-3 was in the range of 0% to 35%.

11 Studien der Metaanalyse:

- Six studies were first-line therapy regimens (Bang 2010 [trastuzumab]; Bleiberg 1997[5-FU]; Levard 1998 [5-FU and cisplatin;] Lordick 2013 [cetuximab]; Lorenzen 2009 [cetuximab]; Nicolaou1982 [cyclophosphamide and doxorubicin]),
- one study was a mixed therapy (Huang 2009 [Shenyi Capsule)],
- four studies were second-line treatments (Ford 2014 [docetaxel]; Dutton 2014 [gefitinib]; Fuchs 2014 and Wilke 2014 [ramucirumab]

Studienergebnisse:

Hinweis: hier nur Ergebnisse der Second-line-Studien hier abgebildet

OS:

Analysis 5.1. Comparison 5 Subcomparison 2: studies with participants receiving second-line therapy, Outcome 1 Overall survival.

Review: Palliative chemotherapy and targeted therapies for esophageal and gastroesophageal junction cancer

Comparison: 5 Subcomparison 2: studies with participants receiving second-line therapy

Outcome: 1 Overall survival

Study or subgroup	Experimental N	Control N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
Dutton 2014	224	225	-0.1043 (0.0984)		36.8 %	0.90 [0.74, 1.09]
Ford 2014	45	47	-0.478 (0.2236)		21.0 %	0.62 [0.40, 0.96]
Wilke 2014	66	71	-0.652 (0.2065)		22.8 %	0.52 [0.35, 0.78]
Fuchs 2014	59	32	-0.2797 (0.24)		19.4 %	0.76 [0.47, 1.21]
Total (95% CI)	**394**	**375**			**100.0 %**	**0.71 [0.54, 0.94]**

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 7.04$, df = 3 (P = 0.07); $I^2 = 57\%$

Test for overall effect: Z = 2.43 (P = 0.015)

Test for subgroup differences: Not applicable

- Achtung: Dutton 2014 untersucht Gefitinib (keine Zulassung im AWG)
- Ford 2014: → stat. sign. superiority of docotaxel vs control
- Wilke 2014: → stat. sig. superiority of ramucirumab
- Fuchs 2014: → no stat. sign. superiority of ramucirumab

Ramucirumab+control intervention vs control intervention alone (2 studies): HR 0,62 [0,43; 0,88]

PFS

2 Studien (Wilke 2014, Fuchs 2014): HR 0,39 [0,28; 0,54] → superiority of ramucirumab

Toxicity:

- Ford 2014 found that grade 4 toxicities occurred more frequently in participants treated with docetaxel compared to participants in the control arm (21% vs 4%). Neutropenia,

infections, and febrile neutropenia were the toxicities that differed most between the study arms. None of the deaths were attributed to the treatment.

- In both arms of Fuchs 2014, 2% of the participants died due to drug-related toxicity Ramucirumab was not associated with increased rates of fatigue, decreased appetite, vomiting, anemia, or other notable toxic effects.
- Wilke 2014 found that the most frequently occurring grade 3, 4, and 5 adverse events in the ramucirumab arm vs the control arm were neutropenia (41% versus 19%), leukopenia (18% versus 7%), and hypertension (15% versus 3%). In both arms, 2% of participants had adverse events leading to death with a causal relation to the study drugs.

Anmerkung/Fazit der Autoren

People who receive more chemotherapeutic or targeted therapeutic agents have an increased overall survival compared to people who receive less. These agents, administered as both first-line or second-line treatments, also led to better overall survival than best supportive care. With the exception of ramucirumab, it remains unclear which other individual agents cause the survival benefit. Although treatment-associated toxicities of grade 3 or more occurred more frequently in arms with an additional chemotherapy or targeted therapy agent, there is no evidence that palliative chemotherapy and/or targeted therapy decrease quality of life. Based on this metaanalysis, palliative chemotherapy and/or targeted therapy can be considered standard care for esophageal and gastroesophageal junction carcinoma.

Kommentare zum Review

Keine Aussagen zur 3. Therapielinie

3.3 Systematische Reviews

Ter Veer E et al., 2016 [12].

Second- and third-line systemic therapy in patients with advanced esophago gastric cancer: a systematic review of the literature.

Fragestellung

The optimal 2nd and 3rd-line chemotherapy and targeted therapy for patients with advanced esophagogastric cancer is still a matter of debate. Therefore, we conducted a systematic review and metaanalysis of all currently available RCT.

Methodik

Population:

- patients with pathologically proven metastatic, unresectable, or recurrent adenocarcinoma of the esophagus, gastro-esophageal junction (GEJ), or stomach
- patients were previously treated with systemic therapy

Intervention/ Komparator:

Nicht genau spezifiziert (siehe Ergebnisteil)

Endpunkte:

- overall survival (OS), PFS and incidence of grade 3–4 adverse events (AEs)

Recherche/Suchzeitraum:

- bis Januar 2016

Qualitätsbewertung der Studien:

- Cochrane Risk of bias tool (version 5.1.0)

Ergebnisse

Anzahl eingeschlossener Studien:

- n=29

Charakteristika der Studien:

Studies derived from both database and conference search that were eligible for systematic review: n = 29
- Single agent chemotherapy versus BSC: n = 3
- Taxane- versus irinotecan-based chemotherapy: n = 4
- Doublet versus single agent chemotherapy: n = 10
- Single targeted agent versus BSC or placebo: n = 5
- Targeted agent versus chemotherapy-alone: n = 1
- Targeted agent combined with chemotherapy versus chemotherapy-alone: n = 7

Study	N	Treatment arms	Sex male (%)	Age median (range)	Disease status metastatic (%)	ECOG PS inclusion	ECOG PS distribution		Treatment line	Prior treatment	Primary endpoint
							0–1 (%)	2 (%)			
Chemotherapy											
Ford 2014 [17]	84	Docetaxel + BSC	69 (82)	65 (29–84)	73 (87)	0–2	70 (83)	14 (17)	2nd	Fluoropyrimidine + platinum	OS
	84	BSC	67 (80)	66 (36–84)	74 (88)		72 (86)	12 (14)			
Thuss-Patience 2011 [18]	21	Irinotecan	18 (86)	58 (43–73)	21 (100)	0–2	17 (81)	4 (19)	2nd	Fluoropyrimidine + platinum or taxane	OS
	19	BSC	11 (58)	55 (35–72)	19 (100)		14 (74)	5 (26)			
Kang 2012 [19]	133	Docetaxel or irinotecan	93 (70)	56 (31–83)	133 (100)	0–1	133 (100)	0 (0)	2nd or 3rd	Fluoropyrimidine + platinum	OS
	69	BSC	44 (64)	56 (32–74)	69 (100)		69 (100)	0 (0)			
Hironaka 2013 [20]	108	Paclitaxel	84 (78)	65 (37–75)	108 (100)	0–2	104 (96)	4 (4)	2nd	Fluoropyrimidine + platinum	OS
	111	Irinotecan	87 (78)	65 (38–75)	11 (100)		107 (96)	4 (4)			
Nishikawa 2015a [21]	43	Paclitaxel	35 (81)	65 (31–74)	NA	0–2	41 (95)	2 (5)	2nd	Fluoropyrimidine + platinum	OS
	42	Irinotecan	30 (71)	65 (44–74)	NA		42 (100)	0 (0)			
	20	Paclitaxel + S-1	12 (60)	63 (37–74)	NA		20 (100)	0 (0)			
	22	Irinotecan + S-1	15 (68)	67 (47–73)	NA		21 (95)	2 (5)			
Roy 2013 [22]	44	Docetaxel	34 (77)	58 (33–81)	43 (98)	0–2	40 (91)	4 (9)	2nd	Not specified	ORR
	44	Irinotecan	34 (77)	62 (33–79)	40 (91)		41 (93)	3 (7)			
	44	PEP-02	35 (79)	56 (38–81)	43 (98)		41 (93)	3 (7)			
Higuchi 2014 [23]	64	Irinotecan + cisplatin	49 (77)	66 (29–80)	44 (69)	0–2	64 (100)	0 (0)	2nd	Fluoropyrimidine + platinum or taxane	PFS
	63	Irinotecan	55 (87)	67 (49–78)	40 (63)		63 (100)	0 (0)			
Nishikawa 2015b [24]	84	Irinotecan + cisplatin	68 (81)	67 (36–85)	64 (78)	0–1	84 (100)	0 (0)	2nd	Fluoropyrimidine monotherapy	OS
	84	Irinotecan	63 (75)	68 (35–87)	71 (84)		84 (100)	0 (0)			
Kim 2015a [25]	23	Docetaxel + cisplatin	21 (87)	55 (38–74)	23 (100)	0–2	22 (92)	2 (8)	2nd	Fluoropyrimidine + cisplatin	ORR
	25	Docetaxel + S-1	15 (60)	55 (39–68)	25 (100)		23 (92)	2 (8)			
	23	Docetaxel	18 (78)	56 (34–68)	23 (100)		23 (100)	0 (0)			
Kim 2015b [26]	25	Docetaxel + oxaliplatin	18 (72)	59	NA	0–2	24 (96)	1 (4)	2nd	Fluoropyrimidine + cisplatin	ORR
	27	Docetaxel	24 (89)	54	NA		26 (96)	1 (4)			
Nakanishi 2015 [27]	38	Paclitaxel + S-1	29 (76)	64 (42–79)	NA	0–2	37 (97)	1 (3)	2nd	Fluoropyrimidine + platinum	PFS
	40	Paclitaxel	34 (85)	62 (38–80)	NA		46 (93)	3 (7)			
Tanabe 2015 [28]	145	Irinotecan + S-1	99 (68)	67 (37–84)	NA	0–1	145 (100)	0 (0)	2nd	Fluoropyrimidine-based regimen	OS
	148	Irinotecan	109 (74)	66 (22–83)	NA		148 (100)				
Sym 2013 [29]	30	Irinotecan + 5-FU/Lv	14 (47)	61 (30–75)	28 (93)	0–2	27 (90)	3 (10)	2nd	Fluoropyrimidine + platinum	ORR
	29	Irinotecan	20 (69)	60 (45–76)	27 (93)		27 (93)	2 (7)			
Maruta 2007 [30]	12	Docetaxel + 5′DFUR	9 (75)	61 (38–74)	NA	0–2	11 (92)	1 (8)	2nd	Fluoropyrimidine + platinum	ORR
	12	Docetaxel	9 (75)	65 (59–71)	NA		11 (92)	1 (8)			
Nishina 2015 [31]	49	5-FU + methotrexate	33 (67)	59 (30–74)	49 (100)	0–2	48 (98)	1 (2)	2nd	Fluoropyrimidine + cisplatin or methotrexate	OS
	51	Paclitaxel	36 (71)	64 (39–75)	51 (100)		49 (96)	2 (4)			

Study	N	Treatment arms	Sex male (%)	Age median (range)	Disease status metastatic (%)	ECOG PS inclusion	ECOG PS distribution		Treatment line	Prior treatment	Primary endpoint
							0–1 (%)	2 (%)			
Targeted therapy											
Fuchs 2014 [5]	238	Ramucirumab	169 (71)	60 (52–67)	NA	0–1	238 (100)	0 (0)	2nd	Fluoropyrimidine + platinum	OS
	117	BSC	79 (68)	60 (51–71)	NA		116 (99)	1 (1)			
Ohtsu 2013 [12]	439	Everolimus	322 (73)	62 (20–86)	439 (100)	0–2	413 (94)	25 (6)	2nd or 3rd	Fluoropyrimidine + platinum	OS
	217	Placebo + BSC	161 (74)	62 (20–88)	217 (100)		190 (87)	27 (12)			
Pavlakis 2015 [32]	97	Regorafenib	78 (80)	NA	NA	0-1	97 (100)	0 (0)	2nd or 3rd	Fluoropyrimidine + platinum	PFS
	50	BSC	40 (80)	NA	NA		50 (100)	0 (0)			
Wilke 2014 [6]	330	Ramucirumab + paclitaxel	229 (69)	61 (25–83)	NA	0–1	330 (100)	0 (0)	2nd	Fluoropyrimidine + platinum	OS
	335	Paclitaxel + placebo	243 (73)	61 (24–84)	NA		335 (100)	0 (0)			
Bang 2015a [33]	62	Olaparib + paclitaxel	49 (79)	63 (31–77)	NA	0-2	62 (100)	0 (0)	2nd	Fluoropyrimidine + platinum	PFS
	62	Paclitaxel	44 (71)	61 (26–79)	NA		60 (96.8)	2 (3)			
Yi 2012 [11]	56	Sunitinib + docetaxel	40 (71)	54 (20–72)	47 (84)	0–2	30 (89)	6 (11)	2nd or 3rd	Fluoropyrimidine + platinum	TTP
	49	Docetaxel	33 (67)	52 (36–70)	47 (96)		46 (94)	3 (6)			
Moehler 2013 [34]	45	Sunitinib + irinotecan + 5-FU/Lv	NA	NA	NA	KPS 100–70 %	NA	NA	2nd or 3rd	Taxane and/or platinum	PFS
	46	Irinotecan + 5-FU/Lv	NA	NA	NA		NA	NA			
Satoh 2015 [10]	40	Nimotuzumab + irinotecan	33 (82)	60 (27–75)	39 (97.5)	0–1	40 (100)	0 (0)	2nd or 3rd	Fluoropyrimidine-based regimen	PFS
	42	Irinotecan	33 (79)	63 (32–75)	42 (100)		42 (100)	0 (0)			
Bang 2015b [35]	41	AZD-4547	29 (71)	63	NA	NA	NA	NA	2nd or 3rd	Not specified	PFS
	30	Paclitaxel	22 (73)	62	NA		NA	NA			
Satoh 2014 [36]	132	Lapatinib + paclitaxel	101 (77)	61 (32–79)	127 (96)	0–1	132 (100)	0 (0)	2nd	Fluoropyrimidine + cisplatin	OS
	129	Paclitaxel	106 (82)	62 (22–80)	121 (94)		129 (100)	0 (0)			
Lorenzen 2015 [37]	18	Lapatinib + capecitabine	17 (94)	56 (44–75)	18 (100)	0–2	16 (88)	2 (11)	2nd	Fluoropyrimidine + platinum	ORR
	19	Lapatinib	14 (74)	62 (46–76)	19 (100)		18 (95)	1 (5)			
Li 2013 [13]	47	Apatinib 850 mg once daily	39 (83)	55	43 (91)	0–1	47 (100)	0 (0)	3rd or later	Fluoropyrimidine + platinum	PFS
	46	Apatinib 425 mg twice daily	34 (74)	53	45 (98)		46 (100)	0 (0)			
	48	Placebo	36 (75)	54	48 (100)		48 (100)	0 (0)			
Li 2016 [14]	176	Apatinib 850 mg once daily	132 (75)	58 (32–71)	NA	0–1	176 (100)	0 (0)	3rd or later	Fluoropyrimidine + platinum	OS
	91	Placebo + BSC	69 (76)	58 (28–70)	NA		91 (100)	0 (0)			

The most important baseline characteristics of all 28 studies are shown

5-FU 5-fluorouracil, *BSC* best supportive care, *ECOG PS* Eastern Collaborative Oncology Group performance status, *GEJ* gastro-esophageal junction, *KPS* Karnofsky performance status, *Lv* leucovorin, *NA* not available, *NR* not reached

Qualität der Studien:

- unclear or low risk of bias

Studienergebnisse (siehe auch Tabellen im Anhang)

Single cytotoxic agent vs. BSC:

OS:

- Total (3 studies [Ford 2014, Thuss-Patience 2011, Kang 2012]; N=410 patients): HR 0.65, [0.53–0.79] → stat. sign. difference
- Docetaxel vs BSC (Ford 2014, Kang 2012): HR 0,71 [0,56; 0,90] → stat. sign. difference
- Irinotecan vs BSC (Thuss-Patience 2011, Kang 2012): 0,55 [0,40; 0,77] → stat. sign. diff.

Toxicity:

- Both taxane and irinotecan were associated with statistically significant increased grade 3–4 neutropenia (33/207 vs. 2/198, RR 12.17, 3.41–43.50) and febrile neutropenia (9/100 vs. 0/91, RR 8.69, 1.14–66.42) compared to BSC.
  -

Taxane-based vs. irinotecan-based chemotherapy:

OS:

- Total (4 studies [Hironaka 2013, Kang 2012; Matsuyama 2014, Roy 2013]): no stat. sign. difference between groups

Toxicity

- Irinotecan was associated with increased grade 3–4 neutropenia, diarrhea and anorexia compared to taxane, whereas taxane was associated with increased neuropathy

Combination chemotherapy vs. single-agent taxane or irinotecan:

OS:

- Total (n=9): no stat. sign. difference between groups
- Cisplatin, oxaliplatin or fluoropyrimidine plus irinotecan or taxane vs. single agent irinotecan or taxane (n=3): no stat. sign. difference between groups
- Oxaliplatin –based chemotherapy vs single-agent (n=1): no stat. sign. difference between groups
- Fluoropyrimidine-based chemotherapy vs single agent (n=6): no difference between groups

Toxixity:

- none of the grade 3–4 adverse events showed statistically significant differences between doublet and monotherapy, although a general trend towards increased toxicity could be observed for doublets

Single targeted agents vs. BSC:

- In second-line setting, ramucirumab monotherapy showed increased benefit in OS, HR 0.78 (0.61–1.00) with absolute median OS gain of Δ1.4 months compared to BSC (Fuchs 2014)
- In second- or third-line setting, no OS benefit of the mammalian target of rapamycin (mTOR) inhibitor everolimus (Ohtsu 2013) and the multityrosine kinase inhibitor regorafenib (Pavlakis 2015) was found over BSC.
- As third- or later-line therapy, apatinib, a tyrosine kinase inhibitor that selectively inhibits VEGFR-2, showed increased OS, vs. BSC (HR 0.50 (0.32–0.79)), with a median OS gain ranging from Δ1.8 to Δ2.3 months (Li 2016; Li 2013).

The addition of a targeted agent to chemotherapy compared to chemotherapy-alone:

- In second-line setting, increased OS was shown for ramucirumab plus taxane (HR 0.81 0.68–0.96; [Wilke 2014]]), with a median survival gain of Δ2.2 months, and for the enzyme poly-ADP ribose polymerase [PARP] inhibitor olaparib plus taxane (HR 0.56, 0.35–0.87 [Bang 2015a]), with a median survival gain of Δ4.8 months compared to taxane alone.
- In second- or third-line setting, the EGFR inhibitor nimotuzumab plus irinotecan (Satoh 2015) and the multityrosine kinase inhibitor sunitinib plus irinotecan-based chemotherapy (Yi 2012, Moehler 2013) did not show any significant difference in OS compared to chemotherapy alone.
- Compared to chemotherapy-alone, second-line ramucirumab plus taxane was associated with increased grade 3–4 hypertension, fatigue and neuropathy and both second-line olaparib plus taxane and second-or third-line sunitinib plus chemotherapy were associated with increased neutropenia.
- None of the AEs associated with second- or third-line nimotuzumab plus taxane reached statistical significance compared to taxane-alone.

Anmerkung/Fazit der Autoren

This review indicates that, given the survival benefit in a phase III study setting, ramucirumab plus taxane is the preferred second-line treatment. Taxane or iriotecan monotherapy are alternatives, although the absolute survival benefit was limited. In third-line setting, apatinib monotherapy is preferred.

Kommentare zum Review

- Einschluss von Interventionen, die im AWG keine Zulassung haben
- Weitere relevante SR wurden über die Recherche identifiziert. Da sie ausschließlich RCT, die bereits im SR von Ter Veer (2016) eingeschlossen sind, berücksichtigt haben, werden nicht separat in der Evidenzsynopse abgebildet:
  - SR von Yang et al. 2018 [13] und Cho et al. 2017 [3] zu Irinotecan-basierter Kombinationstherapie vs Irinotecan-Monotherapie
    (eingeschlossene RCT in Yang 2018: Higuchi 2014, Nishikawa 2015, Satoh 2015, Sym 2013, Tanabe 2015;
    eingeschlossene RCT in Cho 2017: Higuchi 2014, Nishikawa 2015, Sym 2013, Tanabe 2015)
  - SR von Chan et al. 2017 [2] zur Drittlinientherapie vs. BSC/Placebo
    (eingeschlossene RCT: Kang 2012, Li 2013, Li 2016, Ohtsu 2013, Pavlakis 2015)

- SR von Iacovelli et al., 2014 [6] zur Zweitlinientherapie
  (eingeschlossene RCT: Ford 2014, Fuchs 2014, Kang 2012, Ohtsu 2013, Thuss-Patience 2011)

- Netzwerk-Meta-analyse von Zhu et al. 2017 [14] zur Zweitlinientherapie basierend auf 8 Studien: Aufgrund fehlender Informationen zur Ähnlichkeit der Studien (z.B. Vortherapien)/ Transitivitätsannahme und Heterogenität zwischen den Studien werden die Ergebnisse der NMA nicht in der Evidenzsynopse dargestellt. Die Ergebnisse der direkten Vergleiche (8 RCT) sind in Ter Veer et al. abgebildet.
  (Eingeschlossene RCT: Ford 2014, Fuchs 2014, Higuchi 2014, Hironaka 2013, Kang 2012, Ohtsu 2013, Thuss-Patience 2011, Wilke 2014)

Li B et al., 2019 [8].

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 solve the controversy, we conducted this meta-analysis of relevant studies to compare the survival outcomes [PFS, OS, ORR, and disease control rate (DCR)] and adverse effects (AEs) between DCF (docetaxel, cisplatin, and 5-fluorouracil) and ECF (epirubicin, cisplatin, and 5-fluorouracil) regimens.

Methodik

Population:

- Patients diagnosed with metastatic or advanced gastric cancer

Intervention:

- DCF

Komparator:

- ECF

Endpunkte:

- PFS, OS, ORR, DCR, and AEs

Recherche/Suchzeitraum:

- Systematische Recherche bis August 2018

Qualitätsbewertung der Studien:

- Jadad five-item scale & Newcastle-Ottawa Scale

Ergebnisse

Anzahl eingeschlossener Studien:

- n=4 RCTs und n=3 Kohortenstudien (N=7; 598 Patienten)
- 257 patients in the DCF group and 341 patients in the ECF

Charakteristika der Studien:

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		

Qualität der Studien:

- five studies were of high quality (four RCTs and one cohort study), and two cohort studies were of medium quality

Studienergebnisse

- **PFS (4 Studien, 288 Patienten)**
  - No statistically significant difference was found between the two groups (95%CI: 0.58-1.46, P = 0.73), with significant heterogeneity (P = 0.01; I2 = 72%)
- **OS (5 Studien, 431 Patienten)**
  - No statistically significant difference was found between the two groups (95%CI: 0.65-1.10, P = 0.21), with acceptable heterogeneity (P = 0.33; I2 = 13%)
- **ORR (7 Studien, 598 Patienten)**
  - ORR was significantly greater in the DCF group than in the ECF group (95%CI: 1.13-1.75, P = 0.002), with no heterogeneity (P = 0.52; I2 = 0%)
- **DCR (4 Studien, 351 Patienten)**
  - DCR was significantly greater in the DCF group than in the ECF group (95%CI: 1.03-1.41, P = 0.02), with no heterogeneity (P = 0.97; I2= 0%)
- **Sicherheitsendpunkte**
  - **Four studies including 288 patients reported total all-grade AEs**. No statistically significant difference was found between the two groups (95%CI: 0.93-1.29, P = 0.30), with significant heterogeneity (P = 0.03; I2 = 66%)
  - In the subgroup analysis, DCF induced a significantly greater rate of febrile neutropenia than ECF (95%CI: 1.05-4.00, P = 0.04). Similar incidence rates of leucopenia, neutropenia, thrombocytopenia, anemia, anorexia, nausea/vomiting, fatigue, diarrhea, and stomatitis were found between the two groups.

- **Four studies including 288 patients reported total grade 3-4 AEs**. The incidence rate of grade 3-4 AEs was significantly greater in the DCF group than in the ECF group (95%CI: 1.16-1.88, P = 0.002), with significant heterogeneity (P = 0.07; I2 = 57%).
- In the subgroup analysis, compared to ECF, DCF induced a significantly greater rate of neutropenia (95%CI: 1.25-2.16, P = 0.0003) and febrile neutropenia (95%CI: 1.17-4.12, P = 0.01). Similar incidence rates of leucopenia, anemia, anorexia, nausea/vomiting, fatigue, diarrhea, stomatitis, and paraesthesia were found between the two groups.

Anmerkung/Fazit der Autoren

In conclusion, Both DCF and ECF are effective regimens for advanced gastric cancer, with comparable PFS, OS, and total AEs. The DCF regimen has greater advantages over the ECF regimen in terms of ORR and DCR. However, the incidence rate of grade 3-4 AEs is also higher in the DCF group. Due to the inherent limitations of the study, more large-scale and high-quality RCTs are needed to support this conclusion.

Kommentare zum Review

Therapielinie unklar

3.4 Leitlinien

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

Oesophago-gastric cancer. Assessment and management in adults. NICE Guideline NG83.

Fragestellung

This guideline covers adults with newly-diagnosed or recurrent oesophago-gastric cancer; relevant topics:

- Management of oesophago-gastric cancer
- Curative treatment
- Palliative treatment

Methodik

Grundlage der Leitlinie

- Developed by multidisciplinary Guideline Committee (comprising healthcare professionals and lay members) convened by the National Guideline Alliance
- Definition of 20 review questions (interventions, diagnostics, prognosis)

Evidenzbasierung:

Full literature searches, critical appraisals and evidence reviews were completed for all review questions:

Recherche/Suchzeitraum:

- All searches were conducted in MEDLINE, Embase and The Cochrane Library. All searches were updated in May 2017.

Evidenzsynthese:

Durchführung von Meta-Analysen und Netzwerk-Meta-Analysen

LoE

- Bewertung des Risk of Bias der Einzelstudien (analog Cochrane Risk of bias-Tool)
- GRADE-Bewertung der Qualität der Evidenz für jedes Outcome (high, moderate, low, very low)

Ableitung der Empfehlungen/GoR

- Committee was presented with evidence tables of the clinical and economic evidence, summary of clinical and economic evidence and quality assessment, forest plots and a description of the methods and results of the cost-effectiveness analysis
- 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.
- This was either done formally, in an economic model, or informally. Firstly, the net benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. When this was done informally, the group took into account the clinical benefits and harms when one intervention was compared with another. The assessment of net benefit was moderated by the importance placed on the outcomes (the group's values and preferences) and the confidence the group had in the evidence (evidence quality). Secondly, the group assessed whether the net benefit justified any differences in costs.
- When clinical and economic evidence was of poor quality, conflicting or absent, the group drafted recommendations based on their expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs or implications compared with the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The group also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation.
- The wording of recommendations was agreed by the group and focused on the following factors:
  - the actions healthcare professionals need to take
  - the information readers of the guideline need to know
  - the strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weak recommendations)
  - the involvement of patients (and their carers if needed) in decisions about treatment and care
  - consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions.

Sonstige Hinweise

"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." (Technology appraisal guidance [TA378]: Ramucirumab alone or with paclitaxel is not recommended within its marketing authorisation for advanced gastric cancer or gastro–oesophageal junction adenocarcinoma previously treated with chemotherapy.)

Es finden sich in der LL keine Empfehlungen zur Therapielinie nach Second-Line.

Empfehlungen

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.

Hintergrund

9.3.2 Description of clinical evidence

Sixteen RCT (N=2353) were included in the review (Bang 2015, Bang 2016, Ford 2014, Higuchi 2014, Hironaka 2013, Kang 2012, Kim B 2015, Kim JY 2015, Maruta 2007, Moehler 2013, Nishikawa 2015, Nishina 2016, Roy 2013, Sym 2013, Tanabe 2015, Thuss-Patience 2011).

Median follow-up ranged from 6-59 months (where reported). Sample sizes ranged from 40-525 participants. Three studies were carried out in Europe (Ford 2014, Moehler 2013 and Thuss-Patience 2011) the remaining thirteen were from East Asia.

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.

Korean Gastric Cancer Association, 2019 [1].

Korean Practice Guideline for Gastric Cancer 2018: an Evidence-based, Multi-disciplinary Approach

Fragestellung

This guideline is intended to help medical staffs and educate training physicians at secondary and tertiary care medical institutions, including endoscopists, surgeons, medical oncologists, radiology oncologists, and pathologists. Additionally, the guideline was designed to allow patients and populations to receive optimum care by providing adequate medical information. Furthermore, it is intended for widespread adoption to increase the standard of gastric cancer treatment, thereby contributing to improving patient quality of life as well as national health care.

Methodik

Grundlage der Leitlinie

- The present guideline was initiated by the Korean Gastric Cancer Association (KGCA) based on the consensus for national need with the associated academic societies. This guideline was prepared in an integrated and comprehensive manner through an interdisciplinary approach that included the KGCA, the Korean Society of Medical Oncology (KSMO), the Korean Society of Gastroenterology (KSG), the Korean Society for Radiation Oncology (KOSRO), and the Korean Society of Pathologists (KSP), along with the participation of experts in the methodology of guideline development (National Evidence-based Healthcare Collaborating Agency).
- To complete this guideline, the Guideline Committee of the KGCA established the Development Working Group and Review Panel for Korean Practice Guidelines for Gastric Cancer 2018. The members were nominated by each participant association and society. This guideline will be revised every 3 to 5 years when there is solid evidence that can affect the outcomes of patients with gastric cancer.

Evidenzbasierung:

- We systematically searched published literature using databases including MEDLINE, EMBASE, and the Cochrane Library through January 2018. Manual searches were also performed to complement the results. The selection of relevant studies was performed by panels composed of pairs of clinical experts. The selection and exclusion criteria were predefined and tailored to key questions. The articles were screened by title and abstract and full texts were then retrieved for selection. In each step, 2 panels were independently selected and reached agreements.
- We critically appraised the quality of the selected studies using risk-of-bias tools. We used Cochrane Risk of Bias (ROB) for randomized controlled trials (RCTs), ROB for Nonrandomized Studies for non-RCTs, Quality Assessment of Diagnostic Accuracy Studies-2 for diagnostic studies, and A Measurement Tool to Assess Systematic Reviews for systematic reviews/meta-analysis [4-7]. The panels independently assessed and reached a consensus.
- Disagreements were resolved by discussion and the opinion of a third member. We extracted data using a predefined format and synthesized these data qualitatively. Evidence tables were summarized according to key questions.

Ableitung der Empfehlungen/GoR

Table 1. Levels of evidence

Class	Explanation
High	At least 1 RCT or SR/meta-analysis with no concern regarding study quality
Moderate	At least 1 RCT or SR/meta-analysis with minor concern regarding study quality or at least 1 cohort/case-control/diagnostic test design study with no concern regarding study quality
Low	At least 1 cohort/case-control/diagnostic test study with minor concern regarding study quality or at least 1 single arm before-after study, cross-sectional study with no concern regarding study quality
Very low	At least 1 cohort/case-control/diagnostic test design study with serious concern regarding study quality or at least 1 single arm before-after study, cross-sectional study with minor/severe concern regarding study quality

Table 2. Grading of recommendations

Grade classification	Explanation
Strong for	The benefit of the intervention is greater than the harm, with high or moderate levels of evidence. The intervention can be strongly recommended in most clinical practice.
Weak for	The benefit and harm of the intervention may vary depending on the clinical situation or patient/social value. The intervention is recommended conditionally according to the clinical situation.
Weak against	The benefit and harm of the intervention may vary depending on the clinical situation or patient/social values. The intervention may not be recommended in clinical practice.
Strong against	The harm of the intervention is greater than the benefit, with high or moderate levels of evidence. The intervention should not be recommended in clinical practice.
Inconclusive	It is not possible to determine the recommendation direction owing to a lack of evidence or a discrepancy in results. Thus, further evidence is needed.

Empfehlungen

Statement 17	Palliative gastrectomy is not recommended for metastatic gastric cancer except for palliation of symptoms.	High	Strong against
Statement 18-1	Palliative first-line combination platinum/fluoropyrimidine is recommended in patients with locally advanced unresectable or metastatic gastric cancer if the patient's performance status and major organ functions are preserved.	High	Strong for
Statement 18-2	Palliative trastuzumab combined with capecitabine or fluorouracil plus cisplatin is recommended in patients with HER2 IHC 3+ or IHC 2+ and ISH-positive advanced gastric cancer.	High	Strong for
Statement 19	Palliative second-line systemic therapy is recommended in patients with locally advanced unresectable or metastatic gastric cancer if the patient's performance status and major organ functions are preserved. Ramucirumab plus paclitaxel is preferably recommended and monotherapy with irinotecan, docetaxel, paclitaxel, or ramucirumab could also be considered.	High	Strong for
Statement 20	Palliative third-line systemic therapy is recommended in patients with locally advanced unresectable or metastatic gastric cancer if the patient's performance status and major organ functions are preserved.	High	Strong for
Statement 21	Palliative RT could be offered to alleviate symptoms and/or improve survival in recurrent or metastatic gastric cancer.	Moderate	Weak for
Statement 22	Peritoneal washing cytology is recommended for staging. Advanced gastric cancer patients with positive cancer cells in the peritoneal washing cytology are associated with frequent cancer recurrence and a poor prognosis.	Moderate	Strong for

PPG = preserving gastrectomy; DG = distal gastrectomy; LND = lymph node dissection; EGJ = esophagogastric junction; IHC = immunohistochemistry; ISH = in situ hybridization; RT = radiotherapy.

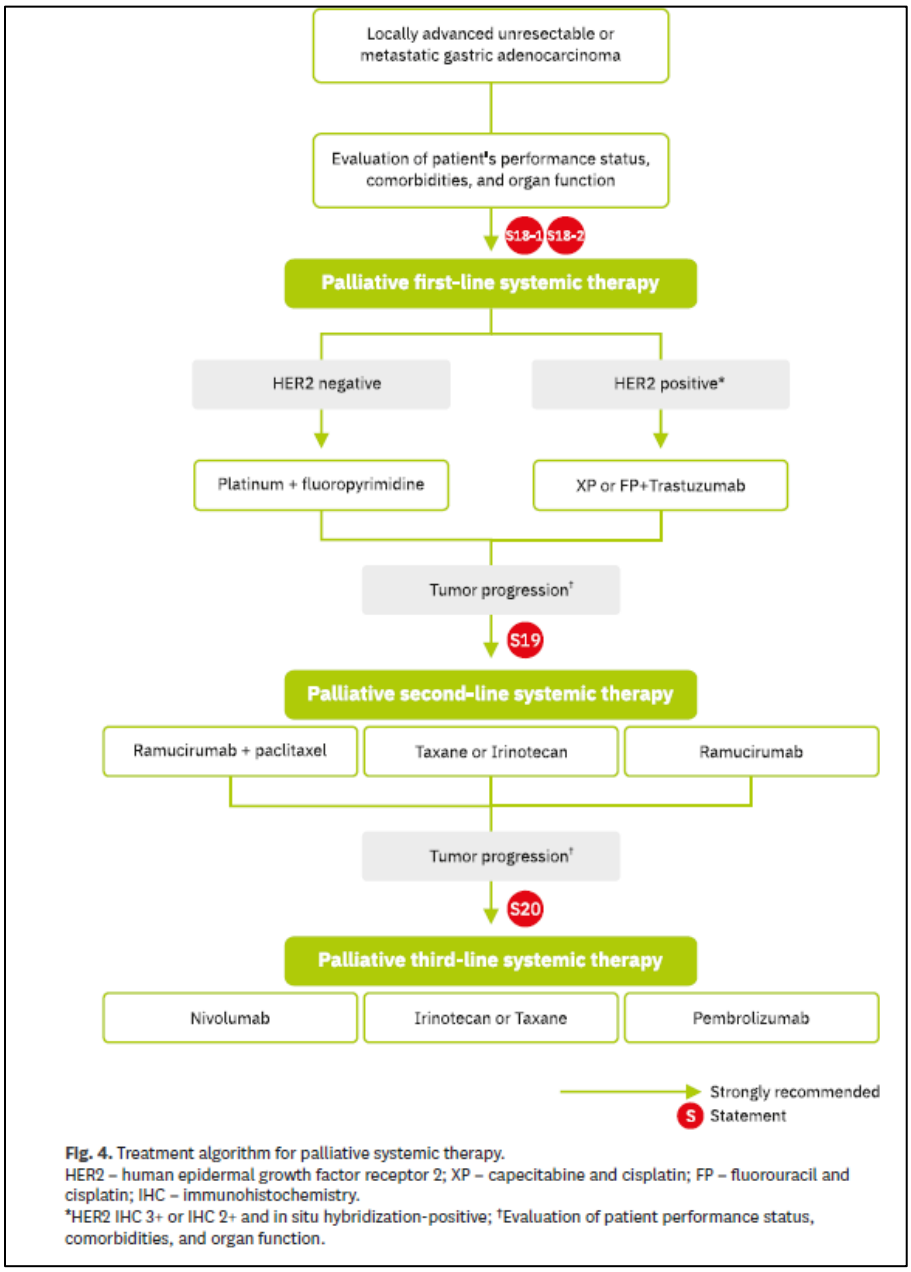

Fig. 4. Treatment algorithm for palliative systemic therapy.
HER2 – human epidermal growth factor receptor 2; XP – capecitabine and cisplatin; FP – fluorouracil and cisplatin; IHC – immunohistochemistry.
*HER2 IHC 3+ or IHC 2+ and in situ hybridization-positive; †Evaluation of patient performance status, comorbidities, and organ function.

PALLIATIVE THERAPY

The prognosis for locally advanced unresectable or metastatic gastric cancers is dismal, and these patients have a median OS of 6–13 months. The goals of therapy for these patients are to palliate disease-related symptoms and to prolong survival. Such palliative systemic therapy also provides a greater quality of life than best supportive care. Thus, systemic therapy is the primary treatment to be considered in patients with locally advanced unresectable (unresectable T4b or extensive nodal disease) or metastatic disease or those after non-curative resection. Palliative systemic therapy for advanced gastric cancer should be determined based on patient performance status, medical comorbidities, and organ function. Furthermore, systemic therapy regimens can be individualized for each patient, with the regimen determined by the clinician according to various patient or gastric cancer- related conditions and participation in clinical trials can be actively considered. A recent study conducted in Germany reported that patients' preferences impacted the specific responses, including low toxicity of chemotherapy, self-care ability, and additional survival benefits [172]. Therefore, patient preferences should also be considered in making decisions regarding palliative therapy

Surgery

Statement 17. Palliative gastrectomy is not recommended for metastatic gastric cancer except for palliation of symptoms (**evidence level: high, recommendation: strong against**).

Palliative surgery is usually indicated for metastatic gastric cancer for the control of urgent symptoms such as obstruction, bleeding, or perforation. However, the effect of palliative gastrectomy on the survival of patients with metastatic gastric carcinoma has long been debated. Several retrospective studies have reported inconsistent results depending on patient population and analytic methods. Some studies have reported significantly improved patient survival for gastrectomy plus chemotherapy compared to chemotherapy alone in carefully selected patients [173-179]. Some reports have suggested that patients with hepatic metastasis might benefit from gastrectomy plus partial hepatectomy when no other distant metastasis existed [180-183]. In contrast, other studies have reported that gastrectomy neither prolonged patient survival nor improved the quality of life in patients with metastatic gastric carcinoma [184-191]. Meanwhile, a meta-analysis of 14 retrospective studies showed that gastrectomy followed by chemotherapy could significantly improve patient survival (median survival, 14.96 vs. 7.07 months; HR, 0.56; 95% CI, 0.39–0.80), compared to that for chemotherapy alone [192]. Another meta-analysis of 19 non-randomized studies reported that gastrectomy could improve patient survival (1-year survival: OR, 2.6; 95% CI, 1.7–4.3; P<0.001) in metastatic gastric carcinoma [193]. However, these studies are mostly biased by patient selection, in which surgery was usually indicated for patients with relatively better performance status and less advanced disease.

To investigate the survival benefit of gastrectomy for metastatic gastric carcinoma, a large international phase III trial was performed in Korea, Japan, and Singapore (REGATTA trial) [194]. In this trial, 175 advanced gastric cancers with a single non-curable factor (liver, peritoneum, or distant nodal metastasis) were randomly assigned to receive gastrectomy plus chemotherapy or chemotherapy alone. The results of an interim analysis revealed that gastrectomy prior to chemotherapy had no effect on OS (HR, 1.08; 95% CI, 0.74–1.58; P=0.66) or PFS (HR, 1.01; 95% CI, 0.74–1.37; P=0.96). Based on these findings, this trial was interrupted in 2013, concluding that gastrectomy did not show any survival benefit compared to that for chemotherapy alone in advanced gastric carcinoma with a single non- curable factor. In conclusion, although some retrospective studies have reported a possible survival benefit of palliative gastrectomy for metastatic gastric carcinoma, a well-designed multi-institutional randomized trial proved that gastrectomy does not improve patient survival in metastatic gastric carcinoma. Therefore, gastrectomy should only be performed with a palliative intent to relieve patient symptoms (Fig. 1).

First-line systemic therapy

Statement 18-1. Palliative first-line platinum/fluoropyrimidine combination is recommended in patients with locally advanced unresectable or metastatic gastric cancer if the patient's performance status and major organ functions are preserved (**evidence: high, recommendation: strong for**).

The effective cytotoxic agents for advanced gastric cancer include infusional 5-FU, oral fluoropyrimidines, platinum agents, taxanes, irinotecan, and anthracyclines. Randomized studies have evaluated various 5-FU-based regimens for the treatment of locally advanced unresectable or metastatic gastric cancer [195-197]. In a meta-analysis, significant OS benefits were shown for chemotherapy versus best supportive care, with increased survival of approximately 6 months. In addition, combination chemotherapy showed a statistically significant survival benefit over single-agent chemotherapy, with a difference in weighted mean average survival of approximately 1 month [198] (Fig. 4).

Although infusional 5-FU is one of the most commonly used cytotoxic agents for advanced gastric cancer, continuous intravenous infusions can prolong hospital stays and result in thrombosis and infection. Randomized phase III studies have demonstrated that the oral fluoropyrimidines capecitabine [199-201] and S-1 [202,203] are as effective as infusional 5-FU. Therefore, oral fluoropyrimidines (capecitabine or S-1) are safe and convenient alternatives to 5-FU for combinations with platinum compounds in patients with advanced gastric cancer. For many years, cisplatin was the leading compound used for the treatment of patients with advanced gastric cancer. To avoid some of the associated side effects such as nausea, vomiting, nephrotoxicity, and ototoxicity, other platinum compounds were investigated. The results of the REAL-2 study suggested that pooled oxaliplatin- based regimens are not inferior to pooled cisplatin-based regimens in terms of OS [199]. A randomized trial in Germany showed that oxaliplatin had better efficacy than that of cisplatin in older adult patients and a more favorable overall toxicity profile [204]. The G-SOX study in Japan and the SOPP study in Korea showed that S-1 plus oxaliplatin is as effective as S-1 plus cisplatin for the treatment of advanced gastric cancer, with a favorable safety profile [205,206]. Therefore, oxaliplatin is at least as effective as cisplatin for prolonging survival and is generally better tolerated.

Regarding combination therapies, it remains unclear if there is a benefit from combining 3 rather than 2 cytotoxic agents. The phase III V325 study showed an increased overall response rate, PFS, and OS for docetaxel, cisplatin, 5-FU (DCF) compared to those of cisplatin/5-FU [207]. However, the implementation of DCF is difficult in clinical practice because the DCF regimen showed only a modest OS benefit (9.2 [DCF] vs. 8.6 months [CF]) but caused markedly increased hematological and gastrointestinal toxicity in this highly selected study population, with a median age of 55 years. In various clinical trials, modifications of this DCF regimen have demonstrated efficacy with improved safety profiles in patients with advanced gastric cancer. Therefore, selected patients can benefit from docetaxel-containing triplet combinations but increased side effects should be considered (high, weak for).

Statement 18-2. Palliative trastuzumab combined with capecitabine or fluorouracil plus cisplatin is recommended in patients with human epidermal growth factor receptor 2 (HER2) immunohistochemistry (IHC) 3+ or IHC 2+ and in situ hybridization (ISH)-positive advanced gastric cancer (**evidence: high, recommendation: strong for**).

Trastuzumab is a humanized anti-HER2 immunoglobulin G1 (IgG1) monoclonal antibody and the first successful biologic agent, with documented clinical activity as a first-line treatment in advanced gastric cancer (Fig. 4). The Trastuzumab for Gastric Cancer (ToGA) trial demonstrated clinically and statistically significant improvements in OS with the addition of trastuzumab to a cisplatin/fluoropyrimidine doublet (13.8 vs. 11.1 months; HR, 0.74; 95% CI, 0.60–0.91; P<0.01) [208]. A post hoc subgroup analysis revealed that the addition of trastuzumab to chemotherapy substantially improved the OS of patients whose tumors were IHC 3+ or ICH 2+ and ISH-positive (16.0 vs. 11.8 months; HR, 0.65; 95% CI, 0.51–0.83). Therefore, a trastuzumab-containing regimen is recommended in patients with HER2-positive gastric cancer and a combination of trastuzumab, cisplatin, and either capecitabine or infusional 5-FU is recommended in clinical practice based on the results of this trial.

Various agents targeting epidermal growth factor receptor, hepatocyte growth factor receptor, and vascular endothelial growth factor receptor (VEGFR) have been evaluated as first-line treatments for advanced gastric cancer; however, except for trastuzumab, none of these agents demonstrated a significant OS benefit in global phase III trials.

Second-line systemic therapy

Statement 19. Palliative second-line systemic therapy is recommended in patients with locally advanced unresectable or metastatic gastric cancer if the patient's performance status and major organ functions are preserved. Ramucirumab plus paclitaxel is preferably recommended and monotherapy with irinotecan, docetaxel, paclitaxel, or ramucirumab could also be considered (**evidence: high, recommendation, strong for**).

Randomized trials and a meta-analysis have demonstrated the survival benefit of second-line palliative chemotherapy (with irinotecan or taxanes) compared to best supportive care alone for patients with locally advanced unresectable or metastatic gastric cancer (HR, 0.64; 95% CI, 0.52–0.79; P<0.001) [209-212] (Fig. 4). Weekly paclitaxel resulted in a similar OS to that achieved with irinotecan in phase III trials [213,214]. In addition, ramucirumab, a monoclonal antibody targeting VEGFR-2, was shown to significantly improve survival in 2 phase III double-blind placebo-controlled trials. In the REGARD trial, patients receiving ramucirumab had improvements in both OS and PFS compared to those in patients receiving placebo [215]. Similarly, in the RAINBOW trial, the addition of ramucirumab to weekly paclitaxel significantly prolonged the median OS (9.6 vs. 7.4 months; HR, 0.807; 95% CI, 0.678–0.962; P=0.017) compared to that for paclitaxel plus placebo [216].

Based on the available data, ramucirumab in combination with paclitaxel is recommended as the most preferred second-line treatment. Irinotecan, docetaxel, paclitaxel, or ramucirumab as single agents can also be considered as a second-line option if not previously administered in the first-line treatment.

Pembrolizumab, an anti-programmed cell death 1 (PD-1) antibody, was recently approved by the Food and Drug Administration (FDA) for the treatment of unresectable or metastatic microsatellite instability-high (MSI-H) or deficient mismatch repair (MMR) solid tumors that have progressed after initial treatments, thus representing a second-line or later option for such gastric cancer cases [217].

Third-line systemic therapy

Statement 20. Palliative third-line systemic therapy is recommended in patients with locally advanced unresectable or metastatic gastric cancer if the patient's performance status and major organ functions are preserved (**evidence: high, recommendation: strong for**).

Despite the lack of clear evidence for third-line cytotoxic chemotherapy, data from several phase II and retrospective studies indicate a 15%–20% response rate with third-line taxane- or irinotecan-based chemotherapy [218-220] (Fig. 4). In a randomized phase III trial in Korea, second- or third-line salvage chemotherapy significantly prolonged patient survival compared to that for best supportive care [210]. Therefore, palliative third-line chemotherapy with cytotoxic agents (e.g., irinotecan, paclitaxel, or docetaxel) not used in second-line therapy can be recommended (moderate, strong for). Recently, a phase III study of patients with metastatic gastric cancer refractory to standard therapies showed a benefit in terms of OS with TAS-102 (trifluridine/tipiracil) compared to that for best supportive care [221]. TAS -102 can be considered if it is approved for use in gastric cancer (high, weak for).

In a randomized phase III trial, apatinib mesylate, a small-molecule inhibitor of VEGFR-2, significantly prolonged the survival of patients who experienced disease progression after 2 or more lines of systemic therapy [222]. However, with an increasing number of patients receiving ramucirumab in the second-line setting, the efficacy of apatinib mesylate in overcoming resistance to ramucirumab is unclear. Moreover, the only results with apatinib mesylate have been reported among Chinese patients; therefore, additional studies are needed to confirm these results (high, weak for).

Recently, immune checkpoint inhibitors have been shown to enhance antitumor T-cell activity via inhibition of the PD-1 receptor. Nivolumab is a humanized IgG4 anti-PD-1 monoclonal antibody. ATTRACTION-2 (ONO-4538-12), the first phase III trial of third-line or later nivolumab versus placebo, showed the efficacy and safety of nivolumab in heavily pretreated patients with advanced gastric cancer (median OS, 5.26 vs. 4.14 months; HR, 0.63; 95% CI, 0.51–0.78; P<0.001) [223]. Another such antibody, pembrolizumab, also showed promising activity and manageable safety in advanced gastric cancer patients who had received at least 2 lines of treatment in a phase Ib trial (KEYNOTE-012) (8) as

well as a phase II trial (KEYNOTE-059; cohort 1), in which the overall response rates trended higher in PD-L1-positive versus PD-L1-negative tumors [224,225]. Nivolumab improves OS as third-line treatment irrespective of PD-L1 status in Asian patients with gastric cancer and is registered in Korea, Japan, and Taiwan (high, strong for). Pembrolizumab shows significant efficacy as a third-line treatment, especially in PD-L1-positive patients in whom its use is approved by the US FDA (moderate, weak for).

Radiotherapy (RT)

Statement 21. Palliative RT could be offered to alleviate symptoms and/or improve survival in recurrent or metastatic gastric cancer (**evidence: moderate, recommendation: weak for**).

Systemic chemotherapy is the mainstay treatment for the management of recurrent or metastatic gastric cancer, even for isolated LRR [50]. However, the addition of local modalities including RT may add a benefit over chemotherapy alone in certain situations [226-231].

Unfortunately, no prospective randomized phase III trial has evaluated the efficacy of adding RT in recurrent or metastatic gastric cancer. However, successful symptom alleviation has been reported with the addition of RT in symptomatic advanced gastric cancer [228-230] and prolongation of survival is suggested according to the results of several prospective and retrospective reports [226-228,231]. Tey et al. [230] reported improvement of symptoms such as tumor bleeding (83/103, 80.6%), obstruction (9/17, 52.9%), and pain (5/11, 45.5%) after RT, with an acceptable rate (2.6%) of grade 3 gastrointestinal toxicities [230]. Sun et al.

[228] reported that clinical symptoms were relieved after RT in 19 of 21 patients (90.5%) with recurrent gastric cancer with abdominal LN metastasis. Hingorani et al. [227] reported the outcomes of a retrospective study comparing chemotherapy followed by RT to primary tumor and chemotherapy alone in metastatic EGJ cancer patients with responding or stable disease after 3 months of chemotherapy. Both OS and time to local progression were significantly improved in irradiated patients, at 23.3 vs. 14.0 months (P<0.001) and 17.3 vs. 8.3 months (P=0.006), respectively.

Despite a lack of evidence from randomized phase III trials on the efficacy of RT in recurrent or metastatic stomach cancer, RT could be used for palliation of symptoms in localized primary and/or metastatic disease and could possibly improve survival by maximizing local control in patients with responding or stable disease after chemotherapy (Fig. 1). The efficacy and necessity of RT in recurrent or metastatic stomach cancer should be evaluated in larger studies.

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National Comprehensive Cancer Network (NCCN), 2018 [10].

Gastric Cancer, Version 2.2019

Fragestellung

k.A.

Methodik

Grundlage der Leitlinie

Repräsentativität der Leitliniengruppe unklar, Interessenkonflikte und finanzielle Unabhängigkeit unklar, Systematik der Suche, Auswahl und Bewertung der Literatur unklar, Ableitung der Empfehlungen unklar

Evidenzbasierung:

For the ‘uniform NCCN consensus’ defined in Category 1 and Category 2A, a majority Panel vote of at least 85% is required. For the ‘NCCN consensus’ defined in Category 2B, a Panel vote of at least 50% (but less than 85%) is required. Lastly, for recommendations where there is strong Panel disagreement regardless of the quality of the evidence, NCCN requires a Panel vote of at least 25% to include and designate a recommendation as Category 3. The large majority of the recommendations put forth in the Guidelines are Category 2A. Where

categories are not specified within the Guidelines, the default designation for the recommendation is Category 2A.

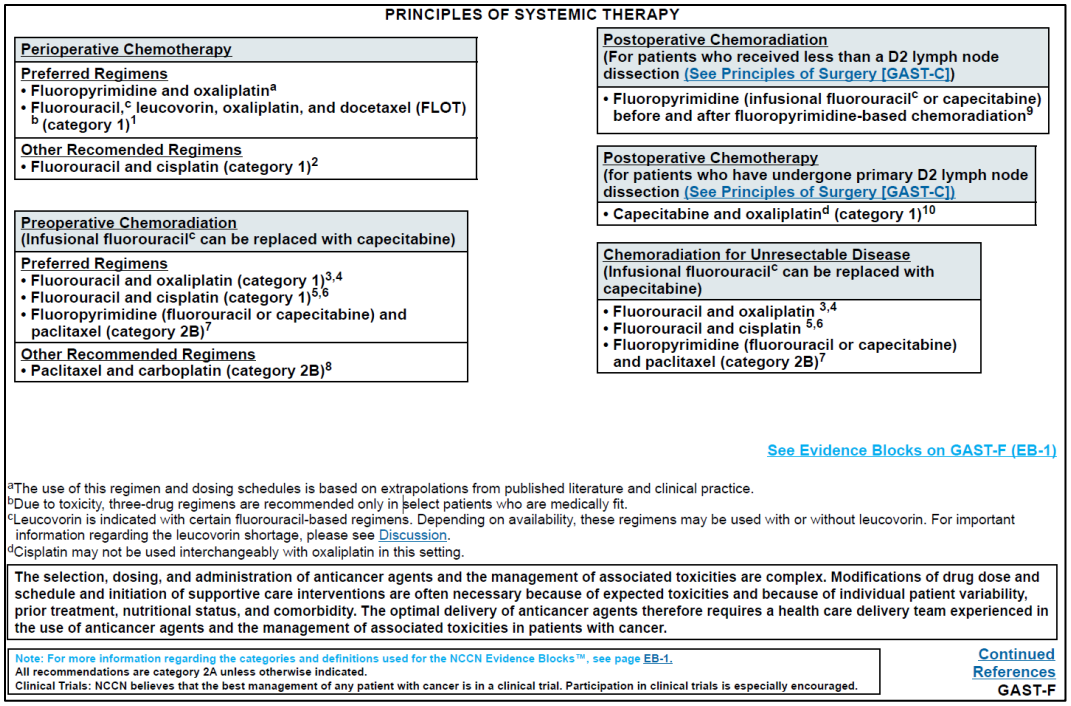
Ableitung der Empfehlungen/GoR

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

Sonstige methodische Hinweise

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt. Unklar ist u.a. die Repräsentativität der Gremien, der Auswahlprozess der Literatur, zudem erfolgte keine system. Bewertung der Validität der Studien, sondern "quality of data based on trial design"

Empfehlungen



PRINCIPLES OF SYSTEMIC THERAPY

Perioperative Chemotherapy

Preferred Regimens
- Fluoropyrimidine and oxaliplatin[a]
- Fluorouracil,[c] leucovorin, oxaliplatin, and docetaxel (FLOT)[b] (category 1)[1]

Other Recomended Regimens
- Fluorouracil and cisplatin (category 1)[2]

Preoperative Chemoradiation
(Infusional fluorouracil[c] can be replaced with capecitabine)

Preferred Regimens
- Fluorouracil and oxaliplatin (category 1)[3,4]
- Fluorouracil and cisplatin (category 1)[5,6]
- Fluoropyrimidine (fluorouracil or capecitabine) and paclitaxel (category 2B)[7]

Other Recommended Regimens
- Paclitaxel and carboplatin (category 2B)[8]

Postoperative Chemoradiation
(For patients who received less than a D2 lymph node dissection (See Principles of Surgery [GAST-C])

- Fluoropyrimidine (infusional fluorouracil[c] or capecitabine) before and after fluoropyrimidine-based chemoradiation[9]

Postoperative Chemotherapy
(for patients who have undergone primary D2 lymph node dissection (See Principles of Surgery [GAST-C])

- Capecitabine and oxaliplatin[d] (category 1)[10]

Chemoradiation for Unresectable Disease
(Infusional fluorouracil[c] can be replaced with capecitabine)

- Fluorouracil and oxaliplatin [3,4]
- Fluorouracil and cisplatin [5,6]
- Fluoropyrimidine (fluorouracil or capecitabine) and paclitaxel (category 2B)[7]

See Evidence Blocks on GAST-F (EB-1)

[a]The use of this regimen and dosing schedules is based on extrapolations from published literature and clinical practice.
[b]Due to toxicity, three-drug regimens are recommended only in select patients who are medically fit.
[c]Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see Discussion.
[d]Cisplatin may not be used interchangeably with oxaliplatin in this setting.

The selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, nutritional status, and comorbidity. The optimal delivery of anticancer agents therefore requires a health care delivery team experienced in the use of anticancer agents and the management of associated toxicities in patients with cancer.

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Continued
References
GAST-F

Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

- Trastuzumab should be added to first-line chemotherapy for HER2 overexpressing metastatic adenocarcinoma (See Principles of Pathologic Review and Biomarker Testing [GAST-B])
  - Combination with fluoropyrimidine and cisplatin (category 1)[11]
  - Combination with other chemotherapy agents (category 2B)
  - Trastuzumab is not recommended for use with anthracyclines

First-Line Therapy
- Two-drug cytotoxic regimens are preferred because of lower toxicity.
- Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.

Preferred Regimens
- Fluoropyrimidine (fluorouracil[c] or capecitabine) and oxaliplatin[12-14]
- Fluoropyrimidine (fluorouracil[c] or capecitabine) and cisplatin[12, 15-17]

Other Recommended Regimens
- Paclitaxel with cisplatin or carboplatin[18-20]
- Docetaxel with cisplatin[21,22]
- Fluoropyrimidine[16,23,24] (fluorouracil[c] or capecitabine)
- Docetaxel[25,26]
- Paclitaxel[27,28]
- Fluorouracil[c,e] and irinotecan[29]
- DCF modifications
  - Docetaxel, cisplatin, and fluorouracil[c,30]
  - Docetaxel, oxaliplatin, and fluorouracil[31]
  - Docetaxel, carboplatin, and fluorouracil (category 2B)[32]
- ECF (epirubicin, cisplatin, and fluorouracil) (category 2B)[33]
- ECF modifications (category 2B)[34,35]
  - Epirubicin, oxaliplatin, and fluorouracil
  - Epirubicin, cisplatin, and capecitabine
  - Epirubicin, oxaliplatin, and capecitabine

See Evidence Blocks on GAST-F (EB-2)

Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

Second-Line or Subsequent Therapy
- Dependent on prior therapy and PS

Preferred Regimens
- Ramucirumab and paclitaxel (category 1)[36]
- Docetaxel (category 1)[25,26]
- Paclitaxel (category 1)[27,28,37]
- Irinotecan (category 1)[37-40]
- Trifluridine and tipiracil (category 1)[41]
  - For third-line or subsequent therapy
- Fluorouracil[c,e] and irinotecan[38,42,43]
- Pembrolizumab
  - For second-line or subsequent therapy for MSI-H or dMMR tumors[44,45]

Other Recommended Regimens
- Ramucirumab (category 1)[46]
- Irinotecan and cisplatin[13,47]
- Pembrolizumab
  - For third-line or subsequent therapy for gastric adenocarcinoma with PD-L1 expression levels by CPS of ≥1[f,48]
- Docetaxel and irinotecan (category 2B)[49]

See Evidence Blocks on GAST-F (EB-3)

PRINCIPLES OF SYSTEMIC THERAPY

Perioperative Chemotherapy

Preferred Regimens
- Fluoropyrimidine and oxaliplatin[a]
- Fluorouracil,[c] leucovorin, oxaliplatin, and docetaxel (FLOT)[b] (category 1)[1]

Other Recomended Regimens
- Fluorouracil and cisplatin (category 1)[2]

Preoperative Chemoradiation
(Infusional fluorouracil[c] can be replaced with capecitabine)

Preferred Regimens
- Fluorouracil and oxaliplatin (category 1)[3,4]
- Fluorouracil and cisplatin (category 1)[5,6]
- Fluoropyrimidine (fluorouracil or capecitabine) and paclitaxel (category 2B)[7]

Other Recommended Regimens
- Paclitaxel and carboplatin (category 2B)[8]

Postoperative Chemoradiation
(For patients who received less than a D2 lymph node dissection (See Principles of Surgery [GAST-C])
- Fluoropyrimidine (infusional fluorouracil[c] or capecitabine) before and after fluoropyrimidine-based chemoradiation[9]

Postoperative Chemotherapy
(for patients who have undergone primary D2 lymph node dissection (See Principles of Surgery [GAST-C])
- Capecitabine and oxaliplatin[d] (category 1)[10]

Chemoradiation for Unresectable Disease
(Infusional fluorouracil[c] can be replaced with capecitabine)
- Fluorouracil and oxaliplatin [3,4]
- Fluorouracil and cisplatin [5,6]
- Fluoropyrimidine (fluorouracil or capecitabine) and paclitaxel (category 2B)[7]

See Evidence Blocks on GAST-F (EB-1)

[a]The use of this regimen and dosing schedules is based on extrapolations from published literature and clinical practice.
[b]Due to toxicity, three-drug regimens are recommended only in select patients who are medically fit.
[c]Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see Discussion.
[d]Cisplatin may not be used interchangeably with oxaliplatin in this setting.

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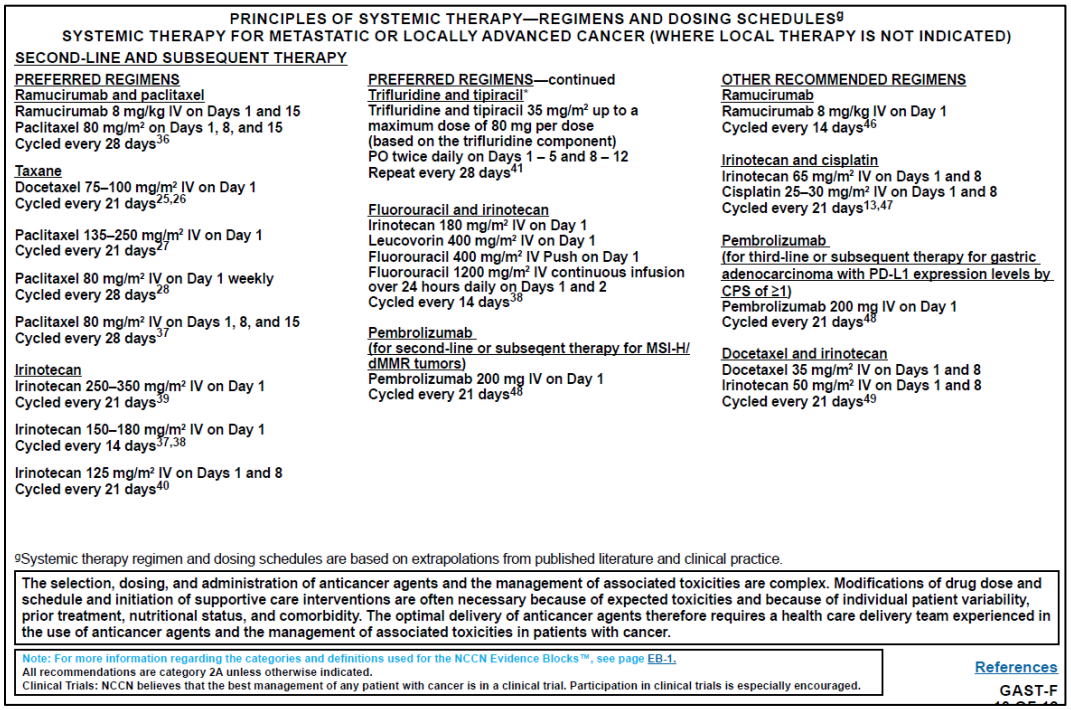
Continued
References
GAST-F

Second-Line and Subsequent Therapy



PRINCIPLES OF SYSTEMIC THERAPY—REGIMENS AND DOSING SCHEDULES[g]
SYSTEMIC THERAPY FOR METASTATIC OR LOCALLY ADVANCED CANCER (WHERE LOCAL THERAPY IS NOT INDICATED)

SECOND-LINE AND SUBSEQUENT THERAPY

PREFERRED REGIMENS

Ramucirumab and paclitaxel
Ramucirumab 8 mg/kg IV on Days 1 and 15
Paclitaxel 80 mg/m² on Days 1, 8, and 15
Cycled every 28 days[36]

Taxane
Docetaxel 75–100 mg/m² IV on Day 1
Cycled every 21 days[25,26]

Paclitaxel 135–250 mg/m² IV on Day 1
Cycled every 21 days[27]

Paclitaxel 80 mg/m² IV on Day 1 weekly
Cycled every 28 days[28]

Paclitaxel 80 mg/m² IV on Days 1, 8, and 15
Cycled every 28 days[37]

Irinotecan
Irinotecan 250–350 mg/m² IV on Day 1
Cycled every 21 days[39]

Irinotecan 150–180 mg/m² IV on Day 1
Cycled every 14 days[37,38]

Irinotecan 125 mg/m² IV on Days 1 and 8
Cycled every 21 days[40]

PREFERRED REGIMENS—continued

Trifluridine and tipiracil[h]
Trifluridine and tipiracil 35 mg/m² up to a maximum dose of 80 mg per dose (based on the trifluridine component)
PO twice daily on Days 1 – 5 and 8 – 12
Repeat every 28 days[41]

Fluorouracil and irinotecan
Irinotecan 180 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days[38]

Pembrolizumab
(for second-line or subseqent therapy for MSI-H/dMMR tumors)
Pembrolizumab 200 mg IV on Day 1
Cycled every 21 days[48]

OTHER RECOMMENDED REGIMENS

Ramucirumab
Ramucirumab 8 mg/kg IV on Day 1
Cycled every 14 days[46]

Irinotecan and cisplatin
Irinotecan 65 mg/m² IV on Days 1 and 8
Cisplatin 25–30 mg/m² IV on Days 1 and 8
Cycled every 21 days[13,47]

Pembrolizumab
(for third-line or subsequent therapy for gastric adenocarcinoma with PD-L1 expression levels by CPS of ≥1)
Pembrolizumab 200 mg IV on Day 1
Cycled every 21 days[48]

Docetaxel and irinotecan
Docetaxel 35 mg/m² IV on Days 1 and 8
Irinotecan 50 mg/m² IV on Days 1 and 8
Cycled every 21 days[49]

[g]Systemic therapy regimen and dosing schedules are based on extrapolations from published literature and clinical practice.

The selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, nutritional status, and comorbidity. The optimal delivery of anticancer agents therefore requires a health care delivery team experienced in the use of anticancer agents and the management of associated toxicities in patients with cancer.

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References

GAST-F

Second-Line and Subsequent Therapy

The selection of regimens for second-line or subsequent therapy is dependent upon prior therapy and performance status. Based on the available data and FDA approvals, the guidelines have included the targeted therapy ramucirumab as a single agent (category 1) or in combination with paclitaxel (category 1; preferred) as treatment options for second-line or subsequent therapy.[281,282] Additionally, pembrolizumab has been included as a second-line or subsequent therapy option for MSI-H/dMMR tumors (preferred)[108,283] and as a third-line or subsequent therapy option for gastric adenocarcinoma with PD-L1 expression levels by CPS of ≥1.[284] See *Targeted Therapies* below for more information on ramucirumab and pembrolizumab.

Category 1 preferred options for second-line or subsequent therapy include single-agent docetaxel,[234,275] paclitaxel,[276,277,285] and irinotecan.[235,285-287] In a randomized phase III trial (COUGAR-02) single-agent docetaxel was shown to significantly increase 12-month OS

compared to active symptom control alone (5.2 months vs. 3.6 months, respectively; HR = 0.67; *P* = .01).[234] Additionally, patients receiving docetaxel reported less pain, nausea, vomiting, dysphagia, and constipation. A randomized phase III trial comparing second-line therapy with paclitaxel to irinotecan in patients with advanced gastric cancer found similar OS between the two groups (9.5 months in the paclitaxel group vs. 8.4 months in the irinotecan group; HR = 1.13; *P* = .38).[285] Therefore, single-agent docetaxel, paclitaxel, and irinotecan are all recommended as preferred second-line treatment options for advanced gastric cancer.

Second-line therapy with FOLFIRI has also been shown to be active and well-tolerated in patients with metastatic gastric cancer.[258,287-290] A phase II trial investigating the efficacy and toxicity of FOLFIRI in patients (n = 40) with recurrent or metastatic gastric cancer reported an ORR of 29% and median OS of 6.4 months.[290] Another phase II trial reported similar results with an ORR of 20% and OS of 6.7 months in advanced gastric cancer patients (n = 59) treated with FOLFIRI in the second-line setting.[287] Additionally, FOLFIRI was shown to be an effective and safe treatment option in a cohort of patients with metastatic gastric or EGJ cancers refractory to docetaxel-based chemotherapy.[288] In this study, the ORR was 22.8% and median PFS and OS were 3.8 and 6.2 months, respectively. The most common grade 3–4 toxicities were neutropenia (28.5%) and diarrhea (14.5%). Therefore, FOLFIRI is considered as a preferred treatment option that can be safely used in the second-line setting if it was not previously used in first-line therapy. Other recommended combined regimens for second-line therapy include irinotecan and cisplatin[238,291] and irinotecan and docetaxel (category 2B).[292]

A recently published phase III trial (TAGS) has demonstrated activity for the combined regimen of trifluridine and tipiracil in metastatic gastric and EGJ adenocarcinoma in the third-line setting.[293] The trifluridine and tipiracil regimen, which was approved by the FDA in 2019 for previously treated recurrent or metastatic gastric and EGJ adenocarcinoma,[294] was initially

investigated in a phase II trial in Japan that reported a median OS of 8.7 months and a disease control rate of 65.5%.[295] In the global phase III TAGS trial, 507 patients with heavily pretreated metastatic gastric or EGJ cancer were randomized 2:1 to receive trifluridine and tipiracil plus best supportive care (n = 337) or placebo plus best supportive care (n = 170).[293] This study reported a significant improvement in median OS by 2.1 months (5.7 vs. 3.6 months) with the trifluridine and tipiracil regimen compared to placebo (HR = 0.69; 95% CI, 0.56–0.85; *P* = .0003). PFS was statistically significantly longer in the trifluridine and tipiracil group (2.0 vs. 1.7 months; HR = 0.57; 95% CI, 0.47–0.70; *P* < .0001). The most frequently reported grade 3–4 toxicities associated with the trifluridine and tipiracil regimen were neutropenia (38%), leukopenia (21%), anemia (19%), and lymphocytopenia (19%), which was consistent with other studies involving these agents. Trifluridine and tipiracil is recommended as a preferred category 1 treatment option for patients with recurrent or metastatic gastric cancer in the third-line or subsequent setting following prior fluoropyrimidine-, platinum-, taxane-, or irinotecan-based chemotherapy and anti-HER2 therapy (if HER2-positive). However, trifluridine and tipiracil did not result in any partial or complete responses and produced substantial grade 3–4 toxicities. Therefore, this treatment should be considered for a very select population of patients with low-volume gastric cancer who have minimal or no symptoms and the ability to swallow pills. Other recommended regimens for third-line or subsequent therapy include regimens recommended for second-line therapy that were not previously used and pembrolizumab for PD-L1–positive adenocarcinoma.

Targeted Therapies

At present, three targeted therapeutic agents, trastuzumab, ramucirumab, and pembrolizumab, have been approved by the FDA for use in gastric cancer.[107,111,296-298] Treatment with trastuzumab is based on testing for HER2 status.[103] Treatment with pembrolizumab is based on testing for microsatellite instability and PD-L1 expression.[108,283,284,299] Investigational agents targeting epidermal growth factor receptor (EGFR) or poly (ADP-ribose) polymerase (PARP) have also shown encouraging results in patients with advanced or metastatic gastric cancer.[238,300-303] However, further investigation of these agents is required before they can be recommended for clinical care.

Trastuzumab

The ToGA trial was the first randomized, prospective, multicenter, phase III trial that evaluated the efficacy and safety of trastuzumab in patients with HER2-positive advanced gastric or EGJ adenocarcinoma.[103] In this trial, 594 patients with HER2-positive, locally advanced, recurrent, or metastatic gastric or EGJ adenocarcinoma were randomized to receive trastuzumab plus chemotherapy (cisplatin plus fluorouracil or capecitabine) or chemotherapy alone.[103] The majority of patients had gastric cancer (80% in the trastuzumab group and 83% in the chemotherapy group). Median follow-up was 19 months and 17 months, respectively, in the two groups. Results showed significant improvement in median OS with the addition of trastuzumab to chemotherapy in HER2-positive patients (13.8 vs. 11 months, respectively; *P* = .046). This study established trastuzumab in combination with cisplatin and a fluoropyrimidine as the standard treatment for patients with HER2-positive metastatic gastroesophageal adenocarcinoma. The addition of trastuzumab was particularly beneficial in patients with a tumor score of IHC 3+ or IHC 2+ and FISH positivity for HER2. In a post-hoc subgroup analysis, the addition of trastuzumab to chemotherapy further improved OS in patients whose tumors were IHC 2+ and FISH positive or IHC 3+ (n = 446; 16 months vs. 11.8 months; HR = .65) compared to those with tumors that were IHC 0 or 1+ and FISH positive (n = 131; 10 months vs. 8.7 months; HR = 1.07).

In a retrospective study of 34 patients with metastatic gastric or EGJ adenocarcinoma, the combination of trastuzumab with a modified FOLFOX regimen (mFOLFOX6) improved tolerability compared with the cisplatin plus fluorouracil regimen in previously untreated patients with HER2-positive tumors.[304] The ORR with this regimen was 41% and median PFS and OS were 9.0 months and 17.3 months, respectively. The most frequent grade 3–4 toxicities were neutropenia (8.8%) and neuropathy (17.6%). These results suggest that the combination of mFOLFOX6 and trastuzumab is an effective regimen with an acceptable safety profile and warrants further study in patients with HER2-positive gastroesophageal cancers.

Ramucirumab

Ramucirumab, a VEGFR-2 antibody, has shown favorable results in patients with previously treated advanced or metastatic gastroesophageal cancers in two phase III clinical trials.[281,282] An international randomized multicenter phase III trial (REGARD) demonstrated a survival benefit for ramucirumab in patients with advanced gastric or EGJ adenocarcinoma progressing after first-line chemotherapy.[281] In this study, 355 patients were randomized to receive ramucirumab (n = 238; 178 had gastric cancer and 60 had EGJ adenocarcinoma) or placebo (n = 117; 87 had gastric cancer and 30 had EGJ adenocarcinoma). Median OS was 5.2 months in patients treated with ramucirumab compared to 3.8 months for those in the placebo group (*P* = .047). Ramucirumab was associated with higher rates of hypertension than placebo (16% vs. 8%), whereas rates of other adverse events were similar.

A more recent international phase III randomized trial (RAINBOW) evaluated paclitaxel with or without ramucirumab in patients (n = 665) with metastatic gastric or EGJ adenocarcinoma progressing on first-line chemotherapy.[282] Patients randomized to receive ramucirumab plus paclitaxel (n = 330) had significantly longer median OS (9.63 months) compared to patients receiving paclitaxel alone (n = 335; 7.36 months; *P* < .0001). The median PFS was 4.4 months and 2.86 months, respectively, for the two treatment groups. Additionally, the ORR was 28% for ramucirumab plus paclitaxel compared to 6% for paclitaxel alone (*P* = .0001). However, neutropenia and hypertension were more common with ramucirumab plus paclitaxel. Based on the results of these two studies, ramucirumab, as a single agent or in combination with paclitaxel, was approved by the FDA for the treatment of patients with advanced gastric or EGJ adenocarcinoma refractory to or progressive following first-line therapy with platinum- or fluoropyrimidine-based chemotherapy. Interestingly, an exposure-response analysis of these two trials revealed that ramucirumab was a significant predictor of OS and PFS in both trials.[305] Higher ramucirumab exposure was associated with longer OS and PFS, but also with higher rates of grade ≥3 hypertension, leukopenia, and neutropenia. This exploratory exposure-response analyses suggest a positive relationship between ramucirumab exposure and efficacy with manageable toxicities.

An international randomized phase III trial (RAINFALL) has recently completed investigation of ramucirumab in combination with a fluoropyrimidine and cisplatin in the first-line treatment of gastroesophageal adenocarcinoma.[306] This trial randomized 645 patients to receive capecitabine and cisplatin in combination with ramucirumab (n = 326) or placebo (n = 319). Preliminary results showed that median PFS was significantly longer in patients treated with ramucirumab versus placebo (5.7 vs. 5.4 months, respectively; *P* = .011; HR, 0.75; 95% CI, 0.61–0.94). However, no improvement in median OS was observed with the addition of ramucirumab (11.2 vs. 10.7 months; *P* = .68; HR, 0.96; 95% CI, 0.80–1.16). The ORR was 41.1% (95% CI, 35.8–46.4) in the ramucirumab arm compared to 36.4% (95% CI, 31.1–41.6) in the placebo arm. The most common grade ≥3 adverse events in the ramucirumab arm were neutropenia, anemia, and hypertension. These early results suggest

that the addition of ramucirumab may not reduce the risk of disease progression or death in treatment-naïve patients with metastatic gastroesophageal adenocarcinoma. Therefore, the addition of ramucirumab to first-line fluoropyrimidine and cisplatin chemotherapy is not recommended at this time. However, more data are needed to ascertain whether the addition of ramucirumab to other first-line chemotherapy regimens can improve OS in these patients.

Pembrolizumab

Pembrolizumab is a PD-1 antibody that was granted accelerated approval by the FDA in 2017 for the treatment of patients with unresectable or metastatic MSI-H or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.[107] This first-ever tissue- and site-agnostic approval was based on data from 149 patients with MSI-H/dMMR cancers (90 patients had colorectal cancer) enrolled across 5 multicenter single-arm clinical trials. The ORR was 39.6% (95% CI, 31.7–47.9) and responses lasted ≥6 months for 78% of those who responded to pembrolizumab. There were 11 complete responses and 48 partial responses to pembrolizumab, and the ORR was similar irrespective of whether patients were diagnosed with colorectal cancer (36%) or a different cancer type (46% across the 14 other cancer types).

One of the trials included in the FDA approval was KEYNOTE-016, a multicenter phase II trial that evaluated the activity of pembrolizumab in 41 patients with metastatic treatment-refractory dMMR colorectal cancers, MMR-proficient colorectal cancers, or dMMR non-colorectal cancers who had received at least two previous lines of chemotherapy.[108,283] In this study, the immune-related ORR for patients with dMMR non-colorectal cancers (n = 9) was 71% with an immune-related PFS rate of 67% at 20 weeks.[283] Median PFS was 5.4 months and OS was not reached. Adverse events of clinical interest included rash or pruritus (24%), thyroid dysfunction (10%), and asymptomatic pancreatitis (15%), which were similar to those reported in other trials involving pembrolizumab. In a recently reported expansion of this study, data from 86 patients with dMMR tumors representing 12 different cancer types, including gastroesophageal cancers, achieved an ORR of 53% with 21% of patients achieving a complete response to pembrolizumab.[108] While median PFS and OS have not yet been reached, estimates of these outcomes at 1 and 2 years are 64% and 53% for PFS and 76% and 64% for OS, respectively. The KEYNOTE-016 trial is still recruiting patients at several institutions (Clinical Trial ID: NCT01876511).

Another 2017 FDA approval for pembrolizumab was for the treatment of patients with recurrent, locally advanced, or metastatic PD-L1–positive gastric or EGJ adenocarcinoma who had progressed following two or more prior lines of therapy, including fluoropyrimidine- and platinum-containing chemotherapy and, if appropriate, HER2-targeted therapy.[111] This approval was based on the results of two KEYNOTE studies (KEYNOTE-012 and KEYNOTE-059). KEYNOTE-012 was a multicenter phase Ib study that evaluated the safety and activity of pembrolizumab in patients with PD-L1–positive recurrent or metastatic gastric or EGJ adenocarcinoma.[307] The ORR was 22% and 13% of patients had grade 3–4 treatment-related adverse events including fatigue, pemphigoid, hypothyroidism, peripheral sensory neuropathy, and pneumonitis. The results of this trial justified the study of pembrolizumab monotherapy in cohort 1 of the phase II KEYNOTE-059 trial, which included 259 patients with gastric or EGJ adenocarcinoma who had progressed on two or more prior lines of therapy.[284] Of those with PD-L1–positive tumors (57.1%; n = 143), the ORR was 15.5% (95% CI, 10.1–22.4), with 2% (95% CI, 0.4–5.8) of patients achieving a complete response. The median duration of response was 16.3 months. Investigations involving cohorts 2 and 3 of the KEYNOTE-059 trial, which examine the efficacy of first-line pembrolizumab as a single agent or in combination with chemotherapy, are ongoing (Clinical Trial ID: NCT02335411).[308-310] Preliminary results suggest that pembrolizumab as a single agent or in combination with cisplatin and fluorouracil demonstrates promising antitumor activity and acceptable toxicity as first-line therapy for PD-L1–positive advanced gastric and EGJ cancers.

One of the most recent KEYNOTE trials (KEYNOTE-061) compared monotherapy with pembrolizumab to paclitaxel in patients with advanced pre-treated gastric or EGJ cancers.[311] In this multicenter international phase III trial, 395 patients who had a PD-L1 CPS ≥1 were randomized to receive either pembrolizumab (n = 196) or standard-dose paclitaxel (n = 199). Median OS was 9.1 months (95% CI, 6.2–10.7) with pembrolizumab and 8.3 months (95% CI, 7.6–9.0) with paclitaxel (HR = 0.82, 95% CI, 0.66–1.03; *P* = .0421). Median PFS was 1.5 months (95% CI, 1.4–2.0) and 4.1 months (95% CI, 3.1–4.2), respectively (HR = 1.27; 95% CI, 1.03–1.57). Grade 3–5 treatment-related adverse events occurred in 14% of the patients treated with pembrolizumab compared to 35% of the patients treated with paclitaxel. Therefore, while pembrolizumab did not significantly improve OS compared with paclitaxel as second-line therapy for advanced gastric or EGJ cancer, pembrolizumab had a better safety profile and was better tolerated by patients.

Based on the KEYNOTE trials, pembrolizumab shows manageable toxicity and promising antitumor activity in patients with heavily pretreated PD-L1–positive or MSI-H/dMMR advanced gastroesophageal adenocarcinoma. Additional trials of pembrolizumab in gastric and EGJ cancers are ongoing. Please visit https://keynoteclinicaltrials.com for more information regarding ongoing KEYNOTE clinical trials of pembrolizumab in patients with gastric and EGJ cancers.

Other Immunotherapies

Preliminary studies have demonstrated the activity of the immune checkpoint inhibitors nivolumab (a PD-1 antibody) and ipilimumab (a CTLA-4 antibody) for the treatment of advanced, recurrent, or metastatic gastric and EGJ cancers.[312-314] While these data are encouraging, the panel considers these studies too preliminary for inclusion in the guidelines and will reevaluate once more mature data become available.

CheckMate-032 is a phase I/II study evaluating the safety and activity of nivolumab alone or in combination with ipilimumab for advanced or metastatic gastric, esophageal, and EGJ cancers.[312] Patients, irrespective of PD-L1 status, were randomized to receive nivolumab 3 mg/kg (N3, n = 59), nivolumab 1 mg/kg + ipilimumab 3 mg/kg (N1 + I3, n = 49), or nivolumab 3 mg/kg + ipilimumab 1 mg/kg (N3 + I1, n = 52). The ORR in each treatment group was 12%, 24%, and 8% for N3, N1+I3, and N3+I1, respectively. Among PD-L1–positive patients, the ORR was 19%, 40%, and 23%, respectively, in each treatment group. One-year PFS rates were 8%, 17%, and 10%, and one-year OS rates were 39%, 35%, and 24%, respectively. Grade 3–4 treatment-related adverse events occurred in 17%, 47%, and 27% of patients treated with N3, N1+I3, and N3+I1. Although nivolumab and nivolumab plus ipilimumab demonstrated clinically meaningful activity in patients with advanced gastroesophageal cancer, this will need to be confirmed in larger phase III trials. The phase III trial CheckMate-649, which is comparing first-line nivolumab + ipilimumab, nivolumab + chemotherapy, and chemotherapy alone in patients with advanced gastric and EGJ cancers, is currently recruiting patients (Clinical Trial ID: NCT02872116).[315] However, because of the high rate of grade 4 and 5 toxicities, enrollment for the nivolumab + ipilimumab arm of the study has been terminated. It is important to note that although encouraging in combination with nivolumab, ipilimumab monotherapy has not shown any benefit in the treatment of gastric or EGJ cancers. A phase II trial comparing ipilimumab to best supportive care for treatment of advanced gastric or EGJ cancers following first-line chemotherapy showed no significant improvement in OS or PFS for patients treated with ipilimumab.[313]

A recently published randomized phase III trial (ATTRACTION-2) investigating the safety and efficacy of nivolumab in Asian patients (n = 493) with heavily pretreated advanced gastric or EGJ cancer reported significantly improved OS with nivolumab compared to placebo (5.26 months vs. 4.14 months; HR = 0.63; $P < .0001$).[314] The 12-month OS rate was 26.2% in the nivolumab group (n = 330) compared to 10.9% in the placebo group (n = 163). OS in the nivolumab group was also higher than the placebo group at 18 months, indicating a persistent survival advantage with nivolumab over time. Grade 3–4 treatment-related adverse events, including fatigue and decreased appetite, were reported in 10% of patients receiving nivolumab and 4% of patients receiving placebo. The outcomes of this trial led the Japanese Ministry of Health, Labour and Welfare to approve nivolumab for the treatment of unresectable advanced or recurrent gastric cancer that has progressed after chemotherapy.[316] However, due to differences in gastric cancer gene expression patterns, these results may not be applicable to non-Asian populations.[314,317,318] A retrospective analysis that evaluated the gene expression profiles of more than 1000 gastric adenocarcinomas from Asian and non-Asian patients found that immune and inflammation signatures were differentially expressed between the two cohorts, suggesting that Asian and non-Asian patients may respond differently to immunotherapy drugs.[317] Therefore, a confirmatory randomized controlled trial investigating nivolumab for advanced gastric or EGJ cancers in non-Asian populations is needed.

The PD-L1 antibody avelumab has also been investigated in the third-line or first-line maintenance settings for advanced or metastatic gastric and EGJ cancers.[319,320] The randomized phase III JAVELIN Gastric 300 trial, which compared avelumab to physician's choice of chemotherapy in patients (n = 371) with advanced gastric or EGJ cancer, showed that treatment with single-agent avelumab in the third-line setting did not improve OS or PFS compared to chemotherapy.[319] However, avelumab showed a more favorable safety profile, with only 9.2% of patients experiencing grade ≥3 treatment-related adverse events compared with 31.6% in the chemotherapy arm. The phase III JAVELIN Gastric 100 trial, which will compare first-line maintenance therapy with avelumab to continuation of chemotherapy in patients with advanced or metastatic gastric or EGJ cancer, is ongoing (Clinical Trial ID: NCT02625610).[320]

Treatment Guidelines

The management of patients with gastric cancer requires the expertise of several disciplines, including surgical oncology, medical oncology, radiation oncology, gastroenterology, radiology, and pathology. In addition, the presence of nutritional services, social workers, nurses, palliative care specialists, and other supporting disciplines are also desirable.[130] Hence, the panel believes in an infrastructure that encourages multidisciplinary treatment decision-making by members of all disciplines taking care of patients with gastric cancer. The recommendations made by the multidisciplinary team may be considered advisory to the primary group of treating physicians. See *Principles of Multidisciplinary Team Approach for Esophagogastric Cancers* in the algorithm for more information.

Workup

Newly diagnosed patients should receive a complete history and physical examination, complete blood count (CBC), comprehensive chemistry profile, and upper GI endoscopy with biopsy of the primary tumor. CT scan (with oral and IV contrast) of the chest, abdomen, and pelvis should also be performed. FDG-PET/CT evaluation from skull base to mid-thigh is recommended, if clinically indicated and if metastatic disease is not evident. EUS should be performed if early-stage disease is suspected or if early-stage versus locally advanced disease needs to be determined (preferred). ER is also recommended since it is essential for the accurate staging of early-stage cancers (T1a or T1b). HER2, MSI-H/dMMR, and PD-L1 testing is recommended at the time of diagnosis if metastatic

Unresectable locally advanced, reccurent, or metastatic disease

Unresectable Locally Advanced, Recurrent, or Metastatic Disease

When locoregional recurrence develops after prior therapy, the clinician should determine whether surgery is an appropriate option. Surgery should be considered in medically fit patients with isolated resectable recurrences. Palliative management, which includes chemoradiation (only if locally unresectable and not previously received), systemic therapy, and/or best supportive care, is recommended for patients with unresectable or metastatic recurrence. If not done previously, HER2, MSI-H/dMMR, and PD-L1 testing should be performed in patients with suspected metastatic adenocarcinoma.

Palliative management and best supportive care are always indicated for patients with unresectable, locally advanced, recurrent, or metastatic disease. The decision to offer palliative/best supportive care alone or with systemic therapy is dependent upon the patient's performance status. The Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS) and the Karnofsky Performance Status Scale (KPS) are commonly used to assess the performance status of patients with cancer.[335-337] ECOG PS is a 5-point scale (0–4) based on the level of symptom interference with normal activity. Patients with higher ECOG PS scores are considered to have worse performance status. KPS is an ordered scale with 11 levels (0%–100%) in which patients are classified based on their degree of functional impairment (activity, work, and self-care). Lower KPS scores are associated with worse survival for most serious illnesses. Patients with a KPS score <60% or an ECOG PS score ≥3 should be offered palliative/best supportive care only. Systemic therapy or chemoradiation (only if locally unresectable and not previously received)

can be offered in addition to palliative/best supportive care for patients with better performance status (KPS score of ≥60% or ECOG PS score ≤2).

The survival benefit of systemic therapy compared to palliative/best supportive care alone for patients with advanced gastric cancer has been demonstrated in several randomized trials.[233-236] In an early comparison between chemotherapy and best supportive care versus best supportive care alone, OS (8 months vs. 5 months) and time to progression (5 months vs. 2 months) were longer in patients receiving chemotherapy in addition to best supportive care for advanced gastric cancer.[233] More patients in the chemotherapy group (45%) had an improved or prolonged quality of life for a minimum of 4 months compared to those who received best supportive care alone (20%). In a more recent randomized phase III study, the addition of second-line chemotherapy with irinotecan significantly prolonged OS compared to best supportive care alone in patients with metastatic or locally advanced gastric or EGJ adenocarcinoma (n = 40).[235] Median survival was 4 months in the irinotecan and best supportive care group compared to 2.4 months in the best supportive care alone group. However, the study was closed prematurely due to poor accrual. In a larger randomized trial (n = 193), second-line chemotherapy with irinotecan (or docetaxel) was also found to significantly improve OS (5.1 months vs. 3.8 months) compared to best supportive care alone in patients with advanced gastric cancer.[236] In another phase III randomized trial, the addition of docetaxel to best supportive care was associated with a survival benefit for patients with advanced adenocarcinoma of the esophagus (n = 33), EGJ (n = 59), or stomach (n = 76) that had progressed on or within 6 months of treatment with platinum and fluoropyrimidine-based combination chemotherapy.[234] After a median follow-up of 12 months, the median OS was 5.2 months for patients in the docetaxel and best supportive care group compared to 3.6 months for those in the best supportive care alone group (P = .01).

Therefore, the addition of systemic therapy to best supportive care can improve the quality of life and may prolong survival in patients with advanced gastric cancer.

See *Principles of Systemic Therapy* in the algorithm for a full list of specific regimens for unresectable, locally advanced, recurrent, or metastatic disease. Some of the chemotherapy regimens and dosing schedules included in the guidelines are based on extrapolations from published literature and clinical practice.

Leucovorin Shortage

Leucovorin is used with certain fluorouracil-based regimens. However, there is currently a shortage of leucovorin in the United States.[338] There are no specific data to guide management under these circumstances, and all proposed strategies are empiric. One is the use of levoleucovorin, which is commonly used in Europe. A levoleucovorin dose of 200 mg/m^2 is equivalent to 400 mg/m^2 of standard leucovorin. Another option is to use lower doses of leucovorin in all patients, since lower doses are likely to be as efficacious as higher doses, based on several studies in patients with colorectal cancer.[339-341] However, the panel recommends use of these regimens without leucovorin in situations where leucovorin is not available.

Palliative/Best Supportive Care

The goals of palliative/best supportive care are to prevent, reduce, and relieve suffering and improve the quality of life for patients and their caregivers, regardless of the stage of the disease or the need for other therapies. In patients with advanced or metastatic gastric cancer, palliative/best supportive care provides symptom relief, improvement in overall quality of life, and may result in prolongation of life. This is especially true when a multimodality interdisciplinary approach is pursued. Therefore, a multimodality interdisciplinary approach to palliative/best supportive care of gastric cancer patients is encouraged.

Referenzen

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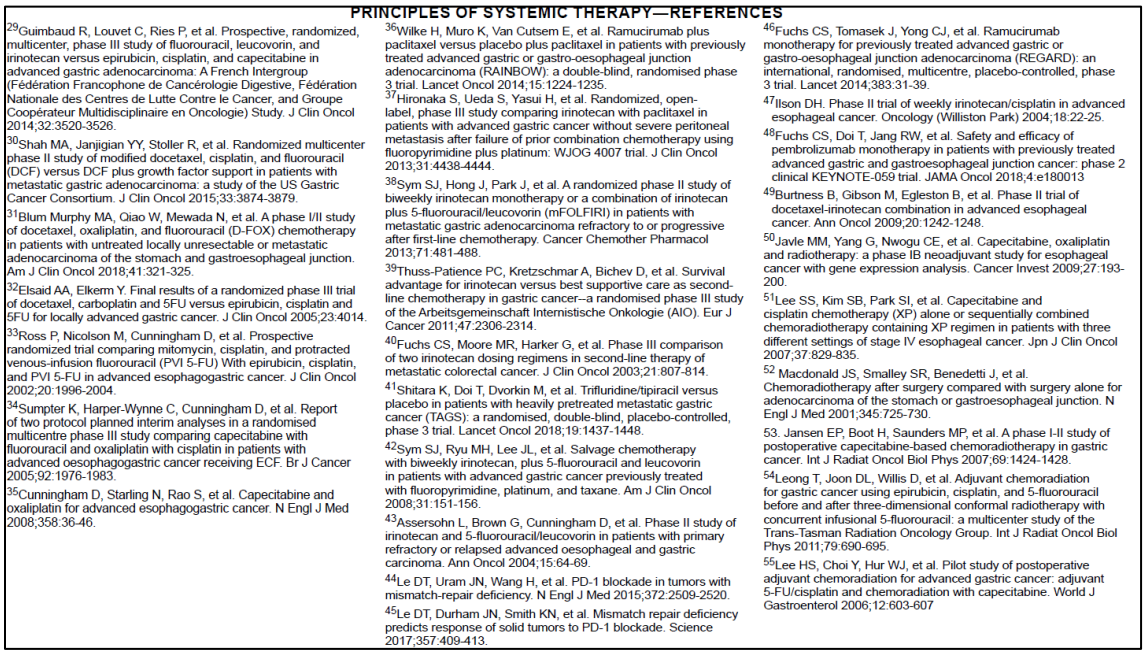

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National Comprehensive Cancer Network (NCCN), 2019 [9].

Esophageal and Esophagogastric Junction, Version 2.2019

Fragestellung

k.A.

Methodik

Grundlage der Leitlinie

Repräsentativität der Leitliniengruppe unklar, Interessenkonflikte und finanzielle Unabhängigkeit unklar, Systematik der Suche, Auswahl und Bewertung der Literatur unklar, Ableitung der Empfehlungen unklar

Evidenzbasierung:

For the ‘uniform NCCN consensus’ defined in Category 1 and Category 2A, a majority Panel vote of at least 85% is required. For the ‘NCCN consensus’ defined in Category 2B, a Panel vote of at least 50% (but less than 85%) is required. Lastly, for recommendations where there is strong Panel disagreement regardless of the quality of the evidence, NCCN requires a Panel vote of at least 25% to include and designate a recommendation as Category 3. The large majority of the recommendations put forth in the Guidelines are Category 2A. Where categories are not specified within the Guidelines, the default designation for the recommendation is Category 2A.

Ableitung der Empfehlungen/GoR

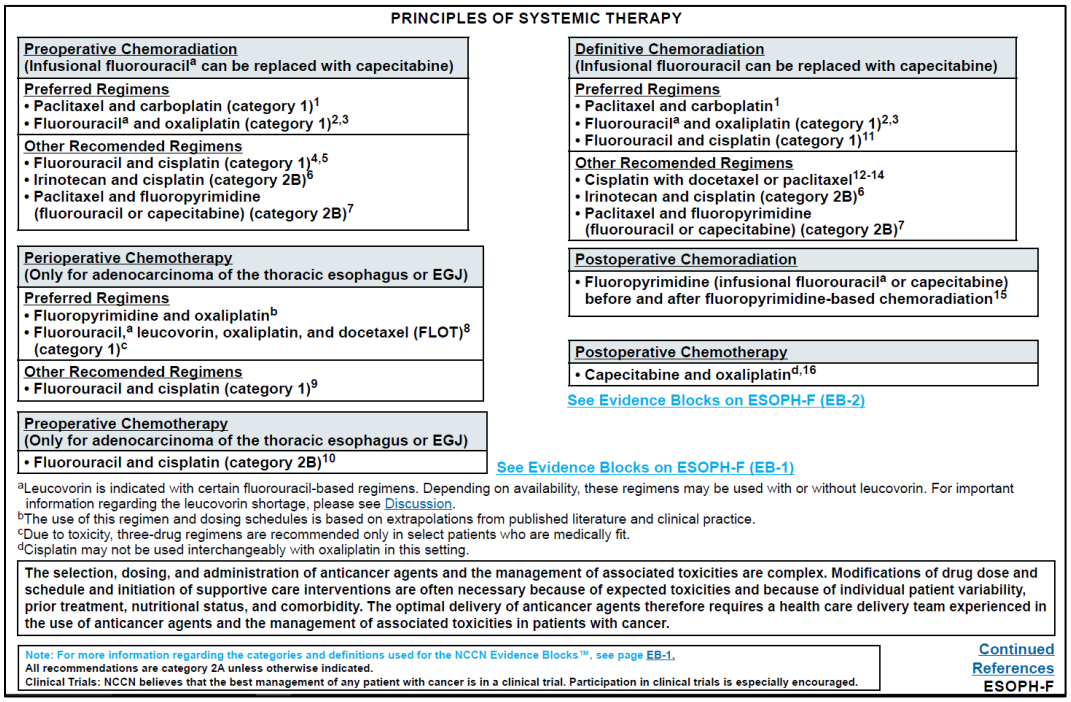
- Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate;
- Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate;

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

Sonstige methodische Hinweise

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt. Unklar ist u.a. die Repräsentativität der Gremien, der Auswahlprozess der Literatur, zudem erfolgte keine system. Bewertung der Validität der Studien, sondern "quality of data based on trial design"

Empfehlungen



PRINCIPLES OF SYSTEMIC THERAPY

Preoperative Chemoradiation
(Infusional fluorouracil[a] can be replaced with capecitabine)

Preferred Regimens
- Paclitaxel and carboplatin (category 1)[1]
- Fluorouracil[a] and oxaliplatin (category 1)[2,3]

Other Recomended Regimens
- Fluorouracil and cisplatin (category 1)[4,5]
- Irinotecan and cisplatin (category 2B)[6]
- Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)[7]

Perioperative Chemotherapy
(Only for adenocarcinoma of the thoracic esophagus or EGJ)

Preferred Regimens
- Fluoropyrimidine and oxaliplatin[b]
- Fluorouracil,[a] leucovorin, oxaliplatin, and docetaxel (FLOT)[8] (category 1)[c]

Other Recomended Regimens
- Fluorouracil and cisplatin (category 1)[9]

Preoperative Chemotherapy
(Only for adenocarcinoma of the thoracic esophagus or EGJ)
- Fluorouracil and cisplatin (category 2B)[10]

Definitive Chemoradiation
(Infusional fluorouracil can be replaced with capecitabine)

Preferred Regimens
- Paclitaxel and carboplatin[1]
- Fluorouracil[a] and oxaliplatin (category 1)[2,3]
- Fluorouracil and cisplatin (category 1)[11]

Other Recomended Regimens
- Cisplatin with docetaxel or paclitaxel[12-14]
- Irinotecan and cisplatin (category 2B)[6]
- Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine) (category 2B)[7]

Postoperative Chemoradiation
- Fluoropyrimidine (infusional fluorouracil[a] or capecitabine) before and after fluoropyrimidine-based chemoradiation[15]

Postoperative Chemotherapy
- Capecitabine and oxaliplatin[d,16]

See Evidence Blocks on ESOPH-F (EB-2)

See Evidence Blocks on ESOPH-F (EB-1)

[a]Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see Discussion.
[b]The use of this regimen and dosing schedules is based on extrapolations from published literature and clinical practice.
[c]Due to toxicity, three-drug regimens are recommended only in select patients who are medically fit.
[d]Cisplatin may not be used interchangeably with oxaliplatin in this setting.

The selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, nutritional status, and comorbidity. The optimal delivery of anticancer agents therefore requires a health care delivery team experienced in the use of anticancer agents and the management of associated toxicities in patients with cancer.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued
References
ESOPH-F

Second-Line and Subsequent Therapy

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

Second-Line or Subsequent Therapy
- Dependent on prior therapy and PS

Preferred Regimens
- Ramucirumab and paclitaxel for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[42]
- Docetaxel (category 1)[31,32]
- Paclitaxel (category 1)[33,34,43]
- Irinotecan (category 1)[43-46]
- Trifluridine and tipiracil for EGJ adenocarcinoma (category 1)[47]
  - For third-line or subsequent therapy
- Fluorouracil[a,e] and irinotecan[44,48,49]
- Pembrolizumab
  - For second-line or subsequent therapy for MSI-H or dMMR tumors[50,51]

Other Recommended Regimens
- Ramucirumab for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma)[52]
- Irinotecan and cisplatin[19,53]
- Pembrolizumab
  - For second-line therapy for esophageal squamous cell carcinoma, esophageal adenocarcinoma and EGJ adenocarcinoma with PD-L1 expression levels by CPS of ≥10 (category 2B)[54]
  - For third-line or subsequent therapy for esophageal and EGJ adenocarcinoma with PD-L1 expression levels by CPS of ≥1[f,55]
- Docetaxel and irinotecan (category 2B)[56]

See Evidence Blocks on ESOPH-F (EB-4)

[a]Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see Discussion.
[e]Capecitabine cannot be used interchangeably with fluorouracil in regimens containing irinotecan.
[f]Pembrolizumab is approved for the third-line treatment of patients with EGJ adenocarcinoma with PD-L1 expression levels by CPS of ≥1, as determined by an FDA-approved companion diagnostic test. The NCCN Panel recommends that this pembrolizumab treatment option be extended to patients with esophageal adenocarcinomas with PD-L1 expression levels by CPS of ≥1. For more information on PD-L1 testing, See Principles of Pathology and Biomarker Testing (ESOPH-B).

Continued
References

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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PRINCIPLES OF SYSTEMIC THERAPY–REGIMENS AND DOSING SCHEDULES[g]

SYSTEMIC THERAPY FOR METASTATIC OR LOCALLY ADVANCED CANCER (WHERE LOCAL THERAPY IS NOT INDICATED)

SECOND-LINE AND SUBSEQUENT THERAPY

PREFERRED REGIMENS

Ramucirumab and paclitaxel (for adenocarcinoma only)
Ramucirumab 8 mg/kg IV on Days 1 and 15
Paclitaxel 80 mg/m² on Days 1, 8, and 15
Cycled every 28 days[42]

Taxane
Docetaxel 75–100 mg/m² IV on Day 1
Cycled every 21 days[31,32]

Paclitaxel 135–250 mg/m² IV on Day 1
Cycled every 21 days[33]

Paclitaxel 80 mg/m² IV on Day 1 weekly
Cycled every 28 days[34]

Paclitaxel 80 mg/m² IV on Days 1, 8, 15
Cycled every 28 days[43]

Irinotecan
Irinotecan 250–350 mg/m² IV on Day 1
Cycled every 21 days[45]

Irinotecan 150–180 mg/m² IV on Day 1
Cycled every 14 days[43,44]

Irinotecan 125 mg/m² IV on Days 1 and 8
Cycled every 21 days[46]

PREFERRED REGIMENS–continued

Trifluridine and tipiracil (for EGJ adenocarcinoma)
For third-line or subsequent therapy
Trifluridine and tipiracil 35 mg/m² up to a maximum dose of 80 mg per dose (based on the trifluridine component)
PO twice daily on Days 1–5 and 8–12
Repeat every 28 days[47]

Fluorouracil and irinotecan
Irinotecan 180 mg/m² IV on Day 1
Leucovorin 400 mg/m² IV on Day 1
Fluorouracil 400 mg/m² IV Push on Day 1
Fluorouracil 1200 mg/m² IV continuous infusion over 24 hours daily on Days 1 and 2
Cycled every 14 days
(only for adenocarcinoma)[44]

Pembrolizumab
(for second-line or subseqent therapy for MSI-H/ dMMR tumors)
Pembrolizumab 200 mg IV on Day 1
Cycled every 21 days[55]

OTHER RECOMMENDED REGIMENS

Ramucirumab (for adenocarcinoma only)
Ramucirumab 8 mg/kg IV on Day 1
Cycled every 14 days[52]

Irinotecan and cisplatin
Irinotecan 65 mg/m² IV on Days 1 and 8
Cisplatin 25–30 mg/m² IV on Days 1 and 8
Cycled every 21 days[19,53]

Pembrolizumab
(for second-line therapy for esophageal squamous cell carcinoma, esophageal adenocarcinoma, and EGJ adenocarcinoma with PD-L1 expression levels by CPS of ≥10 or for third-line or subsequent therapy for esophageal and EGJ adenocarcinoma with PD-L1 expression levels by CPS of ≥1)
Pembrolizumab 200 mg IV on Day 1
Cycled every 21 days[54,55]

Docetaxel and irinotecan
Docetaxel 35 mg/m² IV on Days 1 and 8
Irinotecan 50 mg/m² IV on Days 1 and 8
Cycled every 21 days[56]

[g]Systemic therapy regimen dosing and schedules are based on extrapolations from published literature and clinical practice.

The selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, nutritional status, and comorbidity. The optimal delivery of anticancer agents therefore requires a health care delivery team experienced in the use of anticancer agents and the management of associated toxicities in patients with cancer.

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References

Second-Line and Subsequent Therapy

The selection of regimens for second-line or subsequent therapy is dependent upon prior therapy and performance status. Based on the available data and FDA approvals, the guidelines have included the targeted therapy ramucirumab (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma) as a single agent or in combination with paclitaxel (preferred) as treatment options for second-line or subsequent therapy.[361,362] Pembrolizumab has been included as a preferred second-line or subsequent therapy option for MSI-H/dMMR tumors.[147,363] Pembrolizumab has also been included as a second-line therapy option for esophageal cancers with PD-L1 expression levels by CPS of ≥10 (category 2B)[152] and as a third-line or subsequent therapy option for esophageal and EGJ adenocarcinomas with PD-L1 expression levels by CPS of ≥1.[151] See *Targeted Therapies* below for more information on ramucirumab and pembrolizumab.

Category 1 preferred options for second-line or subsequent therapy include single-agent docetaxel,[324,355] paclitaxel,[356,357,364] and irinotecan.[325,364-366] In a randomized phase III trial (COUGAR-02) single-agent docetaxel was shown to significantly increase 12-month OS compared to active symptom control alone (5.2 months vs. 3.6 months,

respectively; HR = 0.67; *P* = .01).[324] Additionally, patients receiving docetaxel reported less pain, nausea, vomiting, dysphagia, and constipation. A randomized phase III trial comparing second-line therapy with paclitaxel to irinotecan in patients with advanced gastric cancer found similar OS between the two groups (9.5 months in the paclitaxel group vs. 8.4 months in the irinotecan group; HR = 1.13; *P* = .38).[364] Therefore, single-agent docetaxel, paclitaxel, and irinotecan are all recommended as preferred second-line treatment options for advanced gastroesophageal cancers.

Second-line therapy with FOLFIRI has also been shown to be active and well-tolerated in patients with metastatic gastroesophageal cancers.[365,367,368] A phase II trial investigating the efficacy and toxicity of FOLFIRI in patients (n = 40) with refractory or relapsed esophageal or gastric cancer reported an ORR of 29% and median OS of 6.4 months. Another phase II trial reported similar results with an ORR of 20% and OS of 6.7 months in advanced gastric cancer patients (n = 59) treated with FOLFIRI in the second-line setting.[365] Additionally, FOLFIRI was shown to be an effective and safe treatment option in a cohort of patients with metastatic gastric or EGJ cancers refractory to docetaxel-based chemotherapy.[369] In this study, the ORR was 22.8% and median PFS and OS were 3.8 and 6.2 months, respectively. The most common grade 3–4 toxicities were neutropenia (28.5%) and diarrhea (14.5%). Therefore, FOLFIRI is considered as a preferred treatment option that can be safely used in the second-line setting if it was not previously used in first-line therapy. Other recommended combined regimens for second-line therapy include irinotecan and cisplatin[328,342] and irinotecan and docetaxel (category 2B).[345]

A recently published phase III trial (TAGS) has demonstrated activity for the combined regimen of trifluridine and tipiracil in metastatic gastric and EGJ adenocarcinoma in the third-line setting.[370] The trifluridine and tipiracil regimen, which was approved by the FDA in 2019 for previously

treated recurrent or metastatic gastric and EGJ adenocarcinoma,[371] was initially investigated in a phase II trial in Japan which reported a median OS of 8.7 months and a disease control rate of 65.5%.[372] In the global phase III TAGS trial, 507 patients with heavily pretreated metastatic gastric or EGJ cancer were randomized 2:1 to receive trifluridine and tipiracil plus best supportive care (n = 337) or placebo plus best supportive care (n = 170).[370] This study reported a significant improvement in median OS by 2.1 months (5.7 vs. 3.6 months) with the trifluridine and tipiracil regimen compared to placebo (HR = 0.69; 95% CI, 0.56–0.85; *P* = .0003). PFS was statistically significantly longer in the trifluridine and tipiracil group (2.0 vs. 1.7 months; HR = 0.57; 95% CI, 0.47–0.70; *P* < .0001). The most frequently reported grade 3–4 toxicities associated with the trifluridine and tipiracil regimen were neutropenia (38%), leukopenia (21%), anemia (19%), and lymphocytopenia (19%), which was consistent with other studies involving these agents. Trifluridine and tipiracil is recommended as a preferred category 1 treatment option for patients with recurrent or metastatic EGJ adenocarcinoma in the third-line or subsequent setting following prior fluoropyrimidine-, platinum-, taxane-, or irinotecan-based chemotherapy and anti-HER2 therapy (if HER2-positive). However, trifluridine and tipiracil did not result in any partial or complete responses and produced substantial grade 3–4 toxicities. Therefore, this treatment should be considered for a very select population of patients with low-volume EGJ adenocarcinoma who have minimal or no symptoms and the ability to swallow pills. Other recommended regimens for third-line or subsequent therapy for esophageal and EGJ cancers include regimens recommended for second-line therapy that were not previously used and pembrolizumab for adenocarcinomas with PD-L1 expression levels by CPS of ≥1.

Targeted Therapies

At present, three targeted therapeutic agents, trastuzumab, ramucirumab, and pembrolizumab, have been approved by the FDA for use in esophageal and EGJ cancers.[146,150,373-375] Treatment with trastuzumab is based on testing for HER2 status.[141] Treatment with pembrolizumab is based on testing for microsatellite instability and/or PD-L1 expression.[147,151,363,376] Investigational agents targeting EGFR have also shown encouraging results in patients with advanced or metastatic esophageal and EGJ cancers.[328,377-382] However, further investigation of these agents is required before they can be recommended for clinical care.

Trastuzumab

The ToGA trial was the first randomized, prospective, multicenter, phase III trial that evaluated the efficacy and safety of trastuzumab in HER2-positive advanced gastric and EGJ adenocarcinoma.[141] In this trial, 594 patients with HER2-positive, locally advanced, recurrent, or metastatic gastric or EGJ adenocarcinoma were randomized to receive trastuzumab plus chemotherapy (cisplatin plus fluorouracil or capecitabine) or chemotherapy alone.[141] The majority of patients had gastric cancer (80% in the trastuzumab group and 83% in the chemotherapy group). Median follow-up time was 19 months and 17 months, respectively, in the two groups. Results showed significant improvement in median OS with the addition of trastuzumab to chemotherapy in HER2-positive patients (13.8 vs.11 months, respectively; *P* = .046). This study established trastuzumab in combination with cisplatin and a fluoropyrimidine as the standard treatment for patients with HER2-positive metastatic gastroesophageal adenocarcinoma. The addition of trastuzumab was particularly beneficial in patients with a tumor score of IHC 3+ or IHC 2+ and FISH positivity for HER2. In a post-hoc subgroup analysis, the addition of trastuzumab to chemotherapy further improved OS in patients whose tumors were IHC 2+ and FISH positive or IHC 3+ (n = 446; 16 months vs. 11.8 months; HR = 0.65) compared to those with tumors that were IHC 0 or 1+ and FISH positive (n = 131; 10 months vs. 8.7 months; HR = 1.07).

In a retrospective study of 34 patients with metastatic gastric or EGJ adenocarcinoma, the combination of trastuzumab with a modified FOLFOX regimen (mFOLFOX6) improved tolerability compared with the cisplatin plus fluorouracil regimen in previously untreated patients with HER2-positive tumors.[383] The ORR with this regimen was 41% and median PFS and OS were 9.0 months and 17.3 months, respectively. The most frequent grade 3–4 toxicities were neutropenia (8.8%) and neuropathy (17.6%). These results suggest that the combination of mFOLFOX6 and trastuzumab is an effective regimen with an acceptable safety profile and warrants further study in patients with HER-2+ gastroesophageal cancers.

Ramucirumab

Ramucirumab, a VEGFR-2 antibody, has shown favorable results in patients with previously treated advanced or metastatic gastroesophageal cancers in two phase III clinical trials.[361,362] An international randomized multicenter phase III trial (REGARD) demonstrated a survival benefit for ramucirumab in patients with advanced gastric or EGJ adenocarcinoma progressing after first-line chemotherapy.[361] In this study, 355 patients were randomized to receive ramucirumab (n = 238; 178 had gastric cancer and 60 had EGJ adenocarcinoma) or placebo (n = 117; 87 had gastric cancer and 30 had EGJ adenocarcinoma). Median OS was 5.2 months in patients treated with ramucirumab compared to 3.8 months for those in the placebo group (*P* = .047). Ramucirumab was associated with higher rates of hypertension than placebo (16% vs. 8%), whereas rates of other adverse events were similar.

A more recent international phase III randomized trial (RAINBOW) evaluated paclitaxel with or without ramucirumab in patients (n = 665) with metastatic gastric or EGJ adenocarcinoma progressing on first-line chemotherapy.[362] Patients randomized to receive ramucirumab plus paclitaxel (n = 330) had significantly longer median OS (9.63 months) compared to patients receiving paclitaxel alone (n = 335; 7.36 months; *P* < .0001). The median PFS was 4.4 months and 2.86 months, respectively, for the two treatment groups. Additionally, the ORR was 28% for ramucirumab plus paclitaxel compared to 6% for paclitaxel alone (*P* = .0001). However, neutropenia and hypertension were more common with ramucirumab plus paclitaxel. Based on the results of these two studies, ramucirumab (as a single agent or in combination with paclitaxel) was approved by the FDA for the treatment of patients with advanced gastric or EGJ adenocarcinoma refractory to or progressive following first-line therapy with platinum- or fluoropyrimidine-based chemotherapy. Interestingly, an exposure-response analysis of these two trials revealed that ramucirumab was a significant predictor of OS and PFS in both trials.[384] Higher ramucirumab exposure was associated with longer OS and PFS, but also with higher rates of grade ≥3 hypertension, leukopenia, and neutropenia. This exploratory exposure-response analyses suggests a positive relationship between ramucirumab exposure and efficacy with manageable toxicities.

An international randomized phase III trial (RAINFALL) has recently completed investigation of ramucirumab in combination with a fluoropyrimidine and cisplatin in the first-line treatment of gastroesophageal adenocarcinoma.[385] This trial randomized 645 patients to receive capecitabine and cisplatin in combination with ramucirumab (n = 326) or placebo (n = 319). Preliminary results showed that median PFS was significantly longer in patients treated with ramucirumab versus placebo (5.7 vs. 5.4 months, respectively; *P* = .011; HR = 0.75; 95% CI, 0.61–0.94). However, no improvement in median OS was observed with

the addition of ramucirumab (11.2 vs. 10.7 months; *P* = .68; HR = 0.96; 95% CI, 0.80–1.16). The ORR was 41.1% (95% CI, 35.8–46.4) in the ramucirumab arm compared to 36.4% (95% CI, 31.1–41.6) in the placebo arm. The most common grade ≥3 adverse events in the ramucirumab arm were neutropenia, anemia, and hypertension. These early results suggest that the addition of ramucirumab may not reduce the risk of disease progression or death in treatment-naïve patients with metastatic gastroesophageal adenocarcinoma. Therefore, the addition of ramucirumab to first-line fluoropyrimidine and cisplatin chemotherapy is not recommended at this time. However, more data are needed to ascertain whether the addition of ramucirumab to other first-line chemotherapy regimens can improve OS in these patients.

Pembrolizumab

Pembrolizumab is a monoclonal PD-1 antibody directed against PD-1 receptors that was granted accelerated approval by the FDA in 2017 for the treatment of patients with unresectable or metastatic MSI-H or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.[146] This first-ever tissue- and site-agnostic approval was based on data from 149 patients with MSI-H/dMMR cancers (90 patients had colorectal cancer) enrolled across 5 multicenter single-arm clinical trials. The ORR was 39.6% (95% CI, 31.7–47.9) and responses lasted ≥6 months for 78% of those who responded to pembrolizumab. There were 11 complete responses and 48 partial responses to pembrolizumab and the ORR was similar irrespective of whether patients were diagnosed with colorectal cancer (36%) or a different cancer type (46% across the 14 other cancer types).

One of the trials included in the FDA approval was KEYNOTE-016, a multicenter phase II trial that evaluated the activity of pembrolizumab in 41 patients with metastatic treatment-refractory dMMR colorectal cancers, MMR-proficient colorectal cancers, or dMMR non-colorectal cancers who had received at least two previous lines of chemotherapy.[147,363] In this study, the immune-related ORR for patients with dMMR non-colorectal cancers (n = 9) was 71% with an immune-related PFS rate of 67% at 20 weeks.[363] Median PFS was 5.4 months and OS was not reached. Adverse events of clinical interest included rash or pruritus (24%), thyroid dysfunction (10%), and asymptomatic pancreatitis (15%), which were similar to those reported in other trials involving pembrolizumab. In a recently reported expansion of this study, data from 86 patients with dMMR tumors representing 12 different cancer types, including gastroesophageal cancers, achieved an ORR of 53% with 21% of patients achieving a complete response.[147] While median PFS and OS have not yet been reached, estimates of these outcomes at 1 and 2 years are 64% and 53% for PFS and 76% and 64% for OS, respectively. The KEYNOTE-016 trial is still recruiting patients at several institutions (Clinical Trial ID: NCT01876511).

Another 2017 FDA approval for pembrolizumab was for the treatment of patients with recurrent, locally advanced, or metastatic PD-L1–positive (CPS ≥1) gastric or EGJ adenocarcinoma who have progressed following two or more prior lines of therapy, including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2-targeted therapy.[150] This approval was based on the results of two KEYNOTE studies (KEYNOTE-012 and KEYNOTE-059). KEYNOTE-012 was a multicenter, phase Ib study that evaluated the safety and activity of pembrolizumab in patients with PD-L1–positive recurrent or metastatic gastric or EGJ adenocarcinoma.[386] The ORR was 22% and 13% of patients had grade 3–4 treatment-related adverse events including fatigue, pemphigoid, hypothyroidism, peripheral sensory neuropathy, and pneumonitis. The results of this trial justified the study of pembrolizumab monotherapy in cohort 1 of the phase II KEYNOTE-059 trial, which included 259 patients with gastric or EGJ adenocarcinoma who had progressed on two or more prior lines of therapy.[151] Of those with PD-L1–positive tumors (57.1%; n = 143), the ORR was 15.5% (95% CI, 10.1–22.4), with 2% (95% CI, 0.4–5.8) of patients achieving a complete response. The median duration of response was 16.3 months. Investigations involving cohorts 2 and 3 of the KEYNOTE-059 trial, which will examine the efficacy of first-line pembrolizumab in combination with chemotherapy or as a single agent, are ongoing (Clinical Trial ID: NCT02335411).[387-389] Preliminary results suggest that pembrolizumab as a single agent or in combination with cisplatin and fluorouracil demonstrates promising antitumor activity and acceptable toxicity as first-line therapy for PD-L1–positive advanced gastric and EGJ cancers. First-line treatment with pembrolizumab in combination with cisplatin and fluorouracil will also be investigated in the phase III randomized KEYNOTE-590 trial, which is actively recruiting participants with advanced esophageal adenocarcinoma, esophageal SCC, and EGJ adenocarcinoma (Clinical Trial ID: NCT03189719).[390]

The recently published KEYNOTE-061 trial directly compared monotherapy with pembrolizumab to paclitaxel in patients with advanced gastric or EGJ cancers that progressed following first-line therapy with combined fluoropyrimidine and platinum-based agents.[391] In this multicenter international phase III trial, 395 patients with PD-L1–positive tumors were randomized to receive either pembrolizumab (n = 196) or standard-dose paclitaxel (n = 199). Median OS was 9.1 months (95% CI, 6.2–10.7) with pembrolizumab and 8.3 months (95% CI, 7.6–9.0) with paclitaxel (HR = 0.82, 95% CI, 0.66–1.03; *P* = .0421). Median PFS was 1.5 months (95% CI, 1.4–2.0) and 4.1 months (95% CI, 3.1–4.2), respectively (HR = 1.27; 95% CI, 1.03–1.57). Grade 3–5 treatment-related adverse events occurred in 14% of the patients treated with pembrolizumab compared to 35% of the patients treated with paclitaxel. Therefore, while pembrolizumab did not significantly improve OS compared with paclitaxel as second-line therapy for advanced PD-L1–positive gastric or EGJ cancer, pembrolizumab had a better safety profile and was better tolerated by patients. Additionally, Doi et al recently analyzed preliminary data from the advanced esophageal cancer cohort (n = 23) of the KEYNOTE-028 trial, a multi-cohort phase Ib trial of pembrolizumab in patients with PD-L1–positive advanced solid tumors that have failed first-line therapy.[392] In patients with SCC or adenocarcinoma of the esophagus or EGJ, the ORR was 30% and the median duration of response was 15 months. By histologic subtype, the ORR was 28% for patients with SCC and 40% for patients with adenocarcinoma. Median PFS was 1.8 months (95% CI, 1.7–2.9) and the 6- and 12-month PFS rates were 30% and 22%, respectively. Median OS was 7 months (95% CI, 4.3–17.7) and the 6- and 12-month OS rates were 60% and 40%, respectively. Grade 3 immune-mediated adverse events, including decreased appetite and decreased lymphocyte count, occurred in 17% of patients, but no grade 4 adverse events were reported.

Two of the most recently published KEYNOTE trials (KEYNOTE-180 and KEYNOTE-181) examined the efficacy of pembrolizumab in patients with advanced PD-L1–positive SCC or adenocarcinoma of the esophagus or EGJ.[152,393] In these studies, PD-L1–positive tumors were defined as having a CPS ≥10, which is in contrast to previous studies which have defined PD-L1–positive tumors as having a CPS ≥1. In the phase II single-arm KEYNOTE-180 trial, which evaluated pembrolizumab monotherapy in 121 patients with progressive disease following two or more prior lines of therapy, the objective response rate was 9.9% (95% CI, 5.2%–16.7%) among all patients.[393] The objective response rate was 14.3% (95% CI, 6.7%–25.4%) among patients with esophageal SCC (n = 63), 5.2% (95% CI, 1.1%–14.4%) among patients with adenocarcinoma (n = 58), 13.8% (95% CI, 6.1%–25.4%) among patients with PD-L1–positive tumors (n = 58), and 6.3% (95% CI, 1.8%–15.5%) among patients with PD-L1–negative tumors (n = 63). Overall, 12.4% of patients experience grade 3–5 treatment-related adverse events and 5 patients

discontinued treatment because of toxicity. These results demonstrated the efficacy and tolerability of pembrolizumab as third-line or subsequent therapy in heavily pretreated esophageal cancers with high PD-L1 expression. The phase III KEYNOTE-181 trial evaluated pembrolizumab versus investigator's choice of chemotherapy (docetaxel, paclitaxel or irinotecan) as second-line therapy in 628 patients with advanced SCC or adenocarcinoma of the esophagus or EGJ.[152] Patients (401 with SCC and 222 with PD-L1 CPS ≥10) were randomized 1:1 to pembrolizumab or chemotherapy and randomization was stratified by histology (SCC vs. adenocarcinoma) and region (Asia vs. rest of world). Pembrolizumab significantly improved median OS (9.3 vs. 6.7 months; HR = 0.69; 95% CI, 0.52–0.93; *P* = .0074) and 12-month OS rates (43% vs. 20%) compared to chemotherapy in patients whose tumors had a PD-L1 CPS ≥10. There was improvement in OS with pembrolizumab compared to chemotherapy in patients with esophageal SCC, but this was not statistically significant per the prespecified boundaries of the study (8.2 vs. 7.1 months; HR = 0.78; 95% CI, 0.63–0.96; *P* = .0095). The difference in OS was also not statistically significant in the intention-to-treat population (7.1 vs 7.1 months; HR = 0.89; 95% CI, 0.75–1.05; *P* = .0560). Fewer patients had grade 3–5 (18% vs 41%) treatment-related adverse events with pembrolizumab compared to chemotherapy. These data suggest that pembrolizumab may be an effective second-line therapy for patients with advanced esophageal cancer with a PD-L1 CPS ≥10, with a more favorable safety profile than chemotherapy.

Based on the KEYNOTE trials, pembrolizumab shows manageable toxicity and promising antitumor activity in patients with pretreated PD-L1–positive or MSI-H/dMMR advanced gastroesophageal adenocarcinoma. Additional trials of pembrolizumab in gastroesophageal cancers are ongoing. Please visit https://keynoteclinicaltrials.com for more information regarding ongoing KEYNOTE trials of pembrolizumab in patients with gastric, esophageal, or EGJ cancers.

Other Immunotherapies

Preliminary studies have demonstrated the activity of the immune checkpoint inhibitors nivolumab (a PD-1 antibody) and ipilimumab (a CTLA-4 antibody) for the treatment of advanced, recurrent, or metastatic gastroesophageal cancers.[394-398] While these data are encouraging, the panel considers these studies too preliminary for inclusion in the guidelines and will reevaluate once more mature data become available.

CheckMate-032 is a phase I/II study evaluating the safety and activity of nivolumab alone or in combination with ipilimumab for advanced or metastatic gastric, esophageal, and EGJ cancers.[395] Patients, irrespective of PD-L1 status, were randomized to receive nivolumab 3 mg/kg (N3, n = 59), nivolumab 1 mg/kg + ipilimumab 3 mg/kg (N1 + I3, n = 49), or nivolumab 3 mg/kg + ipilimumab 1 mg/kg (N3 + I1, n = 52). The ORR for each treatment group was 12%, 24%, and 8% for N3, N1+I3, and N3+I1, respectively. Among PD-L1–positive patients, the ORR was 19%, 40%, and 23%, respectively, in each treatment group. One-year PFS rates were 8%, 17%, and 10%, and one-year OS rates were 39%, 35%, and 24%, respectively. Grade 3–4 treatment-related adverse events occurred in 17%, 47%, and 27% of patients treated with N3, N1+I3, and N3+I1. Although nivolumab and nivolumab plus ipilimumab demonstrated clinically meaningful activity in patients with advanced esophagogastric cancer, this will need to be confirmed in larger phase III trials. The phase III CheckMate-649 trial, which is comparing first-line nivolumab + ipilimumab, nivolumab + chemotherapy, and chemotherapy alone in patients with advanced gastric and EGJ cancers, is currently recruiting patients (Clinical Trial ID: NCT02872116).[399] However, because of the high rate of grade 4 and 5 toxicities, enrollment for the nivolumab + ipilimumab arm of the study has been terminated. It is important to note that although encouraging in combination with nivolumab, ipilimumab monotherapy has not shown any benefit in the treatment of gastric or EGJ cancers. A phase II trial comparing ipilimumab to best supportive care for treatment of gastric or EGJ cancers following first-line chemotherapy showed no significant improvement in OS or PFS for patients treated with ipilimumab.[396]

The safety and activity of nivolumab in Asian patients with treatment-refractory esophageal SCC was investigated in a single-arm phase II trial (ATTRACTION-01).[394] At a median follow-up of 10.8 months, the ORR was 17.2% and the median OS and PFS were 10.8 and 1.5 months, respectively, in patients (n = 64) treated with nivolumab. The most common grade 3–4 adverse events were dyspnea and hyponatremia (2% each), lung infection (8%), decreased appetite (3%), increased blood creatinine phosphokinase (3%), and dehydration (3%). After a minimum follow-up of two years, the ORR held steady at 17.2% and the median duration of response was 11.17 months.[398] Estimated 1-, 1.5-, and 2-year OS rates were 45.3%, 25%, and 17.2%, respectively, and estimated 1-, 1.5-, and 2-year PFS rates were 10.3%, 8.6%, and 8.6%, respectively. However, adverse events were reported in 86.2% of patients, the most common being diarrhea (21.5%), decreased appetite (18.5%), lung infection (13.8%), and cough (12.3%). The recently published randomized phase III ATTRACTION-2 trial, which investigated the safety and efficacy of nivolumab in Asian patients (n = 493) with heavily pretreated advanced gastric or EGJ cancer, reported significantly improved OS with nivolumab compared to placebo (5.26 months vs. 4.14 months; HR = 0.36; *P* < .0001).[397] The 12-month OS rate was 26.2% in the nivolumab group (n = 330) compared to 10.9% in the placebo group (n = 163). OS in the nivolumab group was also higher than the placebo group at 18 months, indicating a persistent survival advantage with nivolumab over time. Grade 3–4 treatment-related adverse events, including fatigue and decreased appetite, were reported in 10% of patients receiving nivolumab and 4% of patients receiving placebo. However, due to differences in gastroesophageal tumor gene expression patterns, these results may not be applicable to non-Asian populations.[397] Therefore, a confirmatory randomized controlled trial investigating nivolumab for advanced gastroesophageal cancers in non-Asian populations is needed. Preliminary results of the international, randomized, phase III ATTRACTION-3 trial, which compares nivolumab to chemotherapy in patients with unresectable, advanced or recurrent esophageal cancer, were recently disclosed.[400] Nivolumab demonstrated a significant extension in OS compared to chemotherapy with either docetaxel or paclitaxel in 390 patients with PD-L1–unselected esophageal cancer refractory to combination therapy with a fluoropyrimidine and platinum-based agent. The data from this trial is currently undergoing further analysis (Clinical Trial ID: NCT02569242) and publication/presentation of the full results is awaited.

The PD-L1 antibody avelumab has also been investigated in the third-line or first-line maintenance settings for advanced or metastatic gastroesophageal cancers.[401,402] The randomized phase III JAVELIN Gastric 300 trial, which compared avelumab to physician's choice of chemotherapy in patients (n = 371) with advanced gastric or EGJ cancer, showed that treatment with single-agent avelumab in the third-line setting did not improve OS or PFS compared to chemotherapy.[401] However, avelumab showed a more favorable safety profile, with only 9.2% of patients experiencing grade ≥3 treatment-related adverse events compared with 31.6% in the chemotherapy arm. The phase III JAVELIN Gastric 100 trial, which will compare first-line maintenance therapy with avelumab to continuation of chemotherapy in patients with advanced or metastatic gastric or EGJ cancer, is ongoing (Clinical Trial ID: NCT02625610).[402]

Treatment Guidelines

The management of patients with esophageal and EGJ cancers requires the expertise of several disciplines, including surgical oncology, medical oncology, gastroenterology, radiation oncology, radiology, and pathology.

Unresectable locally advanced, reccurent, or metastatic disease

Unresectable, Locally Advanced, Recurrent, or Metastatic Disease

When locoregional recurrence develops after prior chemoradiation therapy, the clinician should determine whether the patient is medically fit for surgery and if the recurrence is resectable. If both criteria are met, esophagectomy remains an option. Palliative management, which includes concurrent chemoradiation (preferred), surgery, chemotherapy, and best supportive care, is recommended for patients who develop a locoregional recurrence following prior esophagectomy. Those who are medically unable to tolerate major surgery and those who develop an unresectable or metastatic recurrence should also receive palliative management. If not done previously, HER2, MSI-H/dMMR, and PD-L1 testing should be performed in patients with suspected metastatic disease.

Palliative management and best supportive care are always indicated for patients with unresectable locally advanced, recurrent, or metastatic disease. The decision to offer palliative/best supportive care alone or with systemic therapy is dependent upon the patient's performance status. The Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS) and the Karnofsky Performance Status Scale (KPS) are commonly used to assess the performance status of patients with cancer.[418-420] ECOG PS is a 5-point scale (0–4) based on the level of symptom interference with normal activity. Patients with higher ECOG PS scores are considered to have worse performance status. KPS is an ordered scale with 11 levels (0%–100%) in which patients are classified based on their degree of functional impairment (activity, work, and self-care). Lower KPS scores are associated with worse survival for most serious illnesses. Patients with a KPS score <60% or an ECOG PS score ≥3 should be offered palliative/best supportive care only. Systemic therapy can be offered in addition to palliative/best supportive care for patients with better performance status (KPS score ≥60% or ECOG PS score ≤2).

The survival benefit of systemic therapy compared to palliative/best supportive care alone has been demonstrated in small cohorts of patients with esophageal or EGJ adenocarcinoma included in gastric adenocarcinoma trials.[324,325] In a phase III randomized trial, the addition of docetaxel to best supportive care was associated with a survival benefit for patients with advanced adenocarcinoma of the esophagus (n = 33), EGJ (n = 59), or stomach (n = 76) that had progressed on or within 6 months of treatment with platinum and fluoropyrimidine–based

combination chemotherapy.[324] After a median follow-up of 12 months, the median OS was 5.2 months for patients in the docetaxel and best supportive care group compared to 3.6 months for those in the best supportive care alone group (P = .01). In another randomized phase III study, the addition of second-line chemotherapy with irinotecan significantly prolonged OS compared to best supportive care alone in patients with metastatic or locally advanced gastric or EGJ adenocarcinoma (n = 40).[325] Median survival was 4 months in the irinotecan and best supportive care group compared to 2.4 months in the best supportive care alone group. However, the study was closed prematurely due to poor accrual.

A recent Cochrane database systematic review analyzed 5 randomized controlled trials (involving 750 patients) comparing palliative chemotherapy and/or targeted therapy to best supportive care alone in patients with advanced esophageal or EGJ cancer.[326] The analysis demonstrated a benefit in OS for patients receiving palliative therapy (chemotherapy or targeted therapy) compared to those receiving best supportive care alone (HR = 0.81; 95% CI, 0.71–0.92). The only individual agent found by more than one study to improve both OS and PFS was ramucirumab. Although the addition of palliative chemotherapy or targeted therapy increased the frequency of grade ≥3 adverse events, treatment-related deaths did not increase. Importantly, patient-reported quality of life often improved with the addition of palliative systemic therapy to best supportive care. Therefore, the addition of systemic therapy to best supportive care can improve the quality of life and may prolong survival in patients with advanced esophageal or EGJ cancers.

See *Principles of Systemic Therapy* in the algorithm for a full list of specific regimens for unresectable, locally advanced, recurrent, or metastatic disease. Some of the chemotherapy regimens and dosing schedules included in the guidelines are based on extrapolations from published literature and clinical practice.

Leucovorin Shortage

Leucovorin is used with certain fluorouracil-based regimens. However, there is currently a shortage of leucovorin in the United States.[421] There are no specific data to guide management under these circumstances, and all proposed strategies are empiric. One is the use of levoleucovorin, which is commonly used in Europe. A levoleucovorin dose of 200 mg/m^2 is equivalent to 400 mg/m^2 of standard leucovorin. Another option is to use lower doses of leucovorin in all patients, since lower doses are likely to be as efficacious as higher doses based on several studies in patients with colorectal cancer.[422-424] However, the panel recommends use of these regimens without leucovorin in situations where leucovorin is not available.

Palliative/Best Supportive Care

The goals of palliative/best supportive care are to prevent, reduce, and relieve suffering and improve the quality of life for patients and their caregivers, regardless of the stage of the disease or the need for other therapies. In patients with advanced or metastatic esophageal or EGJ cancer, palliative/best supportive care provides symptom relief, improvement in overall quality of life, and may result in prolongation of life. This is especially true when a multimodality interdisciplinary approach is pursued. Therefore, a multimodality interdisciplinary approach to palliative/best supportive care of patients with esophageal and EGJ cancers is encouraged.

Dysphagia

Dysphagia is the most common symptom in patients with esophageal cancer, especially those with locally advanced disease. Dysphagia most often arises due to obstruction, but can also be associated with tumor-related dysmotility. Assessing the extent of disease and severity of swallowing impairment, preferably through a standardized scoring scale,[425] is essential to initiate appropriate interventions for long-term palliation of

Referenzen

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ESOPH-F

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 6 of 12, November 2019) am 12.06.2019

#	Suchfrage
#1	MeSH descriptor: [Stomach Neoplasms] explode all trees
#2	MeSH descriptor: [Esophagogastric Junction] explode all trees
#3	MeSH descriptor: [Adenocarcinoma] explode all trees
#4	#2 AND #3
#5	(gastric or stomach or esophagogastric or oesophagogastric or gastroesophageal or gastrooesophageal or esophago-gastric or oesophago-gastric or gastro-esophageal or gastro-oesophageal):ti
#6	(tumor or tumors or tumour* or carcinoma* or adenocarcinoma* or neoplas* or sarcoma* or cancer*):ti
#7	#5 AND #6
#8	#1 OR #4 OR #7
#9	#8 with Cochrane Library publication date Between Jun 2014 and Jun 2019

Systematic Reviews in Medline (PubMed) am 12.06.2019

#	Suchfrage
1	"stomach neoplasms"[MeSH Major Topic]
2	(Esophagogastric Junction[MeSH Major Topic]) AND "adenocarcinoma"[MeSH Major Topic]
3	(((gastric[Title]) OR stomach[Title]) OR esophagogastric[Title]) OR oesophagogastric[Title] OR gastroesophageal[Title] OR gastrooesophageal[Title] OR esophago-gastric[Title]) OR oesophago-gastric[Title] OR gastro-esophageal[Title] OR gastro-oesophageal[Title]
4	(((((((tumor[ti]) OR tumors[ti]) OR tumour*[ti]) OR carcinoma*[ti]) OR adenocarcinoma*[ti]) OR neoplas*[ti]) OR sarcoma*[ti]) OR cancer*[ti])
5	(#3 AND #4)
6	(#1 OR #2 OR #5)
7	((((advanced[Title/Abstract]) OR metastat*[Title/Abstract]) OR metastas*[Title/Abstract]) OR recurr*[Title/Abstract]) OR progressed[Title/Abstract] OR "neoplasm metastasis"[MeSH Terms] OR “Neoplasm Recurrence, Local”[MeSH Terms]
8	(#6 AND #7)
9	(#8) 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 studies[pt] OR validation studies[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]))))))
10	(#9) AND ("2014/06/01"[PDAT] : "3000"[PDAT])
11	(#10) NOT "The Cochrane database of systematic reviews"[Journal]
12	(#11) NOT retracted publication[ptyp]

Leitlinien in Medline (PubMed) am 11.06.2019

#	**Suchfrage**
1	stomach neoplasms[MeSH Major Topic]
2	(Esophagogastric Junction[MeSH Major Topic]) AND "adenocarcinoma"[MeSH Major Topic]
3	(((gastric[Title]) OR stomach[Title]) OR esophagogastric[Title]) OR oesophagogastric[Title] OR gastroesophageal[Title] OR gastrooesophageal[Title] OR esophago-gastric[Title]) OR oesophago-gastric[Title] OR gastro-esophageal[Title] OR gastro-oesophageal[Title]
4	(((((((tumor[ti]) OR tumors[ti]) OR tumour*[ti]) OR carcinoma*[ti]) OR adenocarcinoma*[ti]) OR neoplas*[ti]) OR sarcoma*[ti]) OR cancer*[ti])
5	(#3 AND #4)
6	(#1 OR #2 OR #5)
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
8	(#7) AND ("2014/06/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT retracted publication[ptyp]

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Anhang

Ter Veer et al. (2016): Studienergebnisse zur Zweitlinienchemotherapie (Tab 3)

Table 3 Efficacy of second-line chemotherapy

Study	Efficacy sample	Arms	Overall survival				Progression-free survival			
			Median	Median difference	HR (95 % CI)	*P*	Median	Median difference	HR (95 % CI)	*P*
Taxane/irinotecan *vs.* BSC										
Ford 2014 [17]	84	Docetaxel	5.2	Δ 1.6	0.66 (0.48–0.92)	*0.01	NA	NA	NA	NA
	84	BSC	3.6				NA			
Thuss-Patience 2011 [18]	21	Irinotecan	4.0	Δ 1.6	0.48 (0.25–0.92)	*0.02	NA	NA	NA	NA
	19	BSC	2.4				NA			
Kang 2012 [19]	66	Docetaxel	5.2	Δ 1.4	0.76 (0.53–1.08)	0.13	NA	NA	NA	NA
	60	Irinotecan	6.5	Δ 2.7	0.58 (0.40–0.85)	*0.01	NA	NA	NA	NA
	69	BSC	3.8				NA			
Taxane-based *vs.* irinotecan-based regimens										
Kang 2012 [19]	66	Docetaxel	5.2	Δ −1.3	1.31 (0.78–2.20)	0.12	NA	NA	NA	NA
	60	Irinotecan	6.5				NA			
Hironaka 2013 [20]	108	Paclitaxel	9.5	Δ 1.1	0.88 (0.67–1.16)	0.38	3.6	Δ 1.3	0.87 (0.67–1.14)	0.33
	111	Irinotecan	8.4				2.3			
Nishikawa 2015a [21]	63	S-1 + paclitaxel and paclitaxel-alone	11.1	Δ −0.7	0.98 (0.68–1.42)	0.92	4.1	Δ 0.5	0.67 (0.47–0.97)	*0.03
	64	S-1 + irinotecan and irinotecan-alone	11.8				3.6			
Roy 2013 [22]	44	Docetaxel	7.7	Δ 0.2	0.83 (0.54–1.27)	0.51	2.7	Δ 0.1	1.00 (0.68–1.47)	0.38
	44	Irinotecan	7.8				2.6			
	44	PEP02	7.3				2.7			
Combination therapy *vs.* taxane/irinotecan-alone										
Cisplatin-based										
Nishikawa 2015b [24]	84	Cisplatin + irinotecan	13.9	Δ 1.2	0.83 (0.60–1.17)	0.29	2.6	Δ 0.5	0.86 (0.61–1.20)	0.38
	84	Irinotecan	12.7				2.1			
Higuchi 2014 [23]	64	Cisplatin + irinotecan	10.7	Δ 0.6	1.00 (0.69–1.44)	0.98	3.8	Δ 1.0	0.68 (0.47–0.98)	*0.04
	63	Irinotecan	10.1				2.8			
Kim 2015a [25]	23	Cisplatin + docetaxel	5.6	Δ −4.4	1.34 (1.02–1.77)	*0.03	1.8	Δ 0.5	0.96 (0.72–1.29)	0.80
	23	Docetaxel	10.0				1.3			
Oxaliplatin-based										
Kim 2015b [26]	25	Oxaliplatin + docetaxel	8.1	Δ 0.9	0.87 (0.65–1.16)	0.35	4.9	Δ 2.9	0.64 (0.48–0.85)	*<0.01
	27	Docetaxel	7.2				2.0			
Fluoropyrimidine-based										
Nishikawa 2015a [21]	42	S-1 + paclitaxel and S-1 + irinotecan	11.3	Δ 0.2	0.95 (0.64–1.41)	0.81	3.7	Δ 0.0	1.01 (0.69–1.49)	0.93
	85	Paclitaxel-alone and irinotecan-alone	11.1				3.7			
Kim 2015a [25]	25	S-1 + docetaxel	6.9	Δ 3.1	1.12 (0.84–1.50)	0.42	2.7	Δ 1.4	0.73 (0.54–0.98)	*0.03
	23	Docetaxel	10.0				1.3			
Nakanishi 2015 [27]	38	S-1 + paclitaxel	10.0	Δ 0.0	0.83 (0.51–1.36)	NA	4.6	Δ 0.0	0.86 (0.54–1.37)	NA
	40	Paclitaxel	10.0				4.6			
Tanabe 2015 [28]	145	S-1 + irinotecan	8.8	Δ −0.7	0.99 (0.78–1.25)	0.92	3.8	Δ 0.4	0.85 (0.67–1.07)	*0.02
	148	Irinotecan	9.5				3.4			
Sym 2013[29]	30	5-FU/Lv + irinotecan	6.7	Δ 0.9	0.83 (0.47–1.45)	0.51	3.0	Δ 0.8	0.83 (0.50–1.39)	0.48
	29	Irinotecan	5.8				2.2			
Maruta 2007 [30]	12	5′DFUR + docetaxel	7.6	Δ 3.6	NA	*<0.05	NA	NA	NA	NA

Table 3 (continued)

Study	Efficacy sample	Arms	Overall survival				Progression-free survival			
			Median	Median difference	HR (95 % CI)	*P*	Median	Median difference	HR (95 % CI)	*P*
	12	Docetaxel	4.0				NA			
5-FU + methotrexate										
Nishina 2015 [31]	49	5-FU + methotrexate	7.7	Δ 0.0	1.13 (0.73–1.75)	0.30	2.4	Δ -1.3	1.76 (1.15–2.70)	*<0.01
	51	Paclitaxel	7.7				3.7			

To summarize, treatment efficacy, median overall survival (months), median progression-free survival, hazard ratios (HR), 95 % confidence intervals (95 % CI), and *p* values are shown for all chemotherapy studies

Notes: $*P < 0.05$

5-FU 5-fluorouracil, *95 % CI* 95 % confidence interval, *BSC* best supportive care, *RR* risk ratio, *Lv* leucovorin, *NA* not available

Ter Veer (2016): Studienergebnisse zur Zweit- und Drittlinien-Target-Therapie (Tab 5)

Table 5 Efficacy and safety of second- or third-line targeted therapy

Study	Efficacy sample size	Arms	Treatment line	Overall survival				Progression-free survival				Safety		
				Median	Median difference	HR (95%CI)	*P*	Median	Median difference	HR (95%CI)	*P*	Safety sample size	Grade 3–4 Toxicity	Exp *n* (%) vs. control *n* (%)
Single targeted agent														
Ramucirumab			2nd											
Fuchs 2014 [5]	238 117	Ramucirumab BSC		5.2 3.8	Δ1.4	0.78 (0.60–1.00)	*0.05	2.1 1.3	Δ 0.8	0.48 (0.38–0.62)	*<0.01	236 115	No differences	
Everolimus			2nd or 3rd											
Ohtsu 2013 [12]	439 217	Everolimus Placebo		5.4 4.3	Δ 1.1	0.90 (0.75–1.08)	0.12	1.7 1.4	Δ 0.3	0.66 (0.56–0.78)	*<0.01	437 215	Anorexia Hypokalemia Thrombocytopenia Stomatitis	48 (11 %) vs. 12 (6 %) 26 (6 %) vs. 2 (1 %) 22 (5 %) vs. 3 (1 %) 20 (5 %) vs. 0 (0 %)
Regorafenib			2nd or 3rd											
Pavlakis 2015 [32]	97 50	Regorafenib Placebo		5.8 4.5	Δ 1.3	0.74 (0.51–1.08)	0.11	2.5 0.9	Δ 1.6	0.41 (0.28–0.59)	*<0.01	97 50	No differences	
Targeted agent + chemotherapy														
Ramucirumab + taxane			2nd											
Wilke 2014 [6]	330 335	Ramucirumab + P-aclitaxel Paclitaxel + placebo		9.6 7.4	Δ 2.2	0.81 (0.68–0.96)	*0.02	4.4 2.9	Δ 1.5	0.64 (0.54–0.75)	*<0.01	327 329	Hypertension Fatigue Neuropathy	48 (15 %) vs. 19 (6 %) 39 (12 %) vs. 18 (5 %) 27 (8 %) vs. 15 (5 %)
Sunitinib + chemotherapy			2nd or 3rd											
Yi 2012 [11]	56 49	Sunitinib + docetaxel Docetaxel		8.0 6.6	Δ 1.4	0.94 (0.60–1.49)	0.80	NA	NA	0.77 (0.52–1.16)	0.21	56 49		
Moehler 2013 [34]	45 46	Sunitinib + Irinotecan + 5-FU/Lv Irinotecan + 5-FU/Lv		I0.5 9.0	Δ 1.5	0.82 (0.50–1.34)	0.42	3.6 3.3	Δ 0.3	1.10 (0.70–1.74)	0.66	45 46		
Pooled		Sunitinib + CT *vs.* CT				0.88 (0.63–1.24)	0.47			0.91 (0.65–1.28)	0.59		Neutropenia	43 (43 %) vs. 19 (20 %)
Nimotuzumab + Irinotecan			2nd or 3rd											
Satoh 2015 [10]	40 42	Nimotuzumab + Irinotecan Irinotecan		8.2 7.6	Δ 0.6	0.99 (0.62–1.60)	0.98	2.4 2.8	Δ -0.4	0.86 (0.52–1.44)	0.57	40 42	No differences	
Olaparib + taxane			2nd											
	62 62	Olaparib + paclitaxel		13.1 8.3	Δ 4.8	0.56 (0.35–0.87)	*0.01	3.9 3.5	Δ 0.4	0.80 (0.54–1.18)	0.13	61 62	Neutropenia	34 (56 %) vs. 24 (39 %)

Table 5 (continued)

Study	Efficacy sample size	Arms	Treatment line	Overall survival				Progression-free survival				Safety		
				Median	Median difference	HR (95%CI)	*P*	Median	Median difference	HR (95%CI)	*P*	Safety sample size	Grade 3–4 Toxicity	Exp *n* (%) *vs.* control *n* (%)
Bang 2015a [33]		Paclitaxel												
Targeted agents for specific molecular prespecified subgroups														
HER-2 positive			2nd											
Satoh 2014 [36]	132 129	Lapatinib + paclitaxel Paclitaxel		11.0 8.9	Δ 2.1	0.84 (0.64–1.11)	0.10	5.5 4.4	Δ 1.1	0.85 (0.63–1.13)	0.15	131 129	Febrile neutropenia Diarrhea	9 (7 %) *vs.* 2 (2 %) 23 (18 %) *vs.* 0 (0 %)
Lorenzen 2015 [37]	18 19	Capecitabine + lapatinib Lapatinib		NR 4.7	NC	1.06 (0.34–3.29)	0.92	1.5 1.3	Δ 0.2	NA	NS	18 19	No differences	
Fibroblast growth factor receptor 2 amplification			2nd or 3rd											
Bang 2015b [35]	41 30	AZD-4547 Paclitaxel		NA NA	NA	NA NA		1.8 3.5	Δ 1.7	1.57 (1.12–2.21)	NS		Not reported	
Third- or further-line single targeted agent														
Apatinib			3rd or further											
Li 2016 [14]	176 91	Apatinib Placebo		6.5 4.7	Δ 1.8	0.71 (0.54–0.94)	*0.01	2.6 1.8	Δ 0.8	0.44 (0.33–0.60)	*<0.01	176 91		
Li 2013 [13]	47 46 48	Apatinib 850 mg Apatinib 425 mg Placebo		4.8 4.3 2.5	Δ 2.3 Δ 1.8	0.37 (0.22–0.62) 0.41 (0.24–0.71)	*<0.01 *<0.01	3.7 3.2 1.4	Δ 2.3 Δ 1.8	0.18 (0.10–0.34) 0.21 (0.11–0.38)	*<0.01 *<0.01	47 46 48		
Pooled		Apatinib *vs.* placebo				0.50 (0.32–0.79)	*<0.01			0.27 (0.14–0.51)	*<0.01		HFS Hypertension	23 (9 %) *vs.* 1 (%) 17 (6 %) *vs.* 0 (0 %)

To summarize treatment efficacy of targeted therapy, median overall survival (months), median progression-free survival and hazard ratios (HR) with 95 % confidence intervals (95 % CI) were shown. For safety of targeted therapy, only grade 3–4 AEs were reported for which a statistically significant difference exist between the occurrence in the treatments arms.

Notes: since more than one study was available for the comparisons for sunitinib and apatinib, also the pooled HRs were given.

*$P < 0.05$

5-FU 5-fluorouracil, *95 % CI* 95 % confidence interval, *BSC* best supportive care, *CT* chemotherapy, *d* days, *exp* experimental agent, *Lv* leucovorin, *HFS* hand-foot syndrome, *HR*: hazard ratio, *RR* risk ratio, *NA*: not available, *NC* not calculable, *NS*: not statistically significant