Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

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

Vorgang: 2020-B-408 Pembrolizumab

Stand: März 2021

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

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

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	*Es liegen keine vor.*
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Pembrolizumab L01XC18 Keytruda	<u>Zu prüfendes Anwendungsgebiet:</u> Keytruda ist als Monotherapie zur Behandlung der folgenden Tumoren mit MSI-H oder mit einer dMMR bei Erwachsenen angezeigt: - nicht resezierbares oder metastasierendes […] Dünndarmkarzinom […] mit einem Fortschreiten der Erkrankung während oder nach mindestens einer vorherigen Therapie
	Es ist kein Arzneimittel im vorliegenden Anwendungsgebiet zugelassen.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2020-B-408 (Pembrolizumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	8. Februar 2021

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWG	Anwendungsgebiet
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CBC	complete blood count
CEA	carcinoembryonic antigen
CRC	colorectal carcinoma
CT	computed tomography
DA	duodenal adenocarcinoma
dMMR	deficient mismatch repair
ECRI	ECRI Guidelines Trust
EGD	esophagogastroduodenoscopy
EUS	endosonography
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IAA	intestinal type ampullary adenocarcinoma
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LL	Leitlinie
LoE	Level of Evidence
MCBS	magnitude of clinical benefit scale
MMR	mismatch repair
MRI	magnetic resonance imaging
MSI-H	microsatellite instability-high
MSS	microsatellite stable
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
OS	overall survival
PET/CT	positron emission tomography – computed tomography
pMMR	proficient mismatch repair
RCT	randomized controlled trial
RR	Relatives Risiko
RT	radiation therapy

SBA	small bowel adenocarcinoma
SIGN	Scottish Intercollegiate Guidelines Network
SR	systematic review
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

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

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Dünndarmkarzinom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 19.01.2021 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 591 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 3 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

Es wurden keine relevanten G-BA-Beschlüsse/IQWiG-Berichte identifiziert.

3.2 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.3 Systematische Reviews

Nishikawa Y et al., 2020 [3].

Chemotherapy for patients with unresectable or metastatic small bowel adenocarcinoma: a systematic review.

Fragestellung

The aim of this systematic review was to assess the efficacy and safety of chemotherapy for patients with unresectable or metastatic SBA.

Methodik

Population:

- patients diagnosed histologically as advanced SBA (unresectable or metastatic SBA)
- age > 18 years
- no restriction regarding sex, ethnicity, or socioeconomic status
- exclusion of studies including only adenocarcinoma of the ampulla of Vater

Intervention:

- chemotherapy

Komparator:

Not reported

Endpunkte:

- tumor response, survival time, or toxicity

Recherche/Suchzeitraum:

- to September 29, 2018
- included study types: RCTs, nonrandomized, or observational studies

Qualitätsbewertung der Studien:

ROBINS-I (no RCTs could have been included)

Ergebnisse

Anzahl eingeschlossener Studien:

- RCTs could not have been included in this review
- 7 prospective single-arm Phase II studies

Charakteristika der Population:

Table 1 Characteristics of the included studies

References	Country	Number of centers	Number of patients	Median follow up period (month) (range)	Median age (years old) (range)	Sex (male/female)	Regimen	Primary endpoint	Unresectable (Locally advanced/metastatic) (*n*)	Prior adjuvant chemotherapy (*n*)
1st line systemic chemotherapy										
Gibson et al. [10]	USA	multi-institutional	Total 38 eligible, 36 evaluable for response, [duodenum 17, jejunum 12, Ileum 5, (ampullary) 4]	NR	63 (38–80)	(27/11)	FAM	NR	36	NR
Overman et al. [11]	USA	1	Total 30 (duodenum 7, jejunum 8, Ileum 3, (ampullary) 12)	14	62 (41–79)	(18/12)	CAPOX	Overall response rate	30 (5/25)	2 (5-FU), 2 (FU with concurrent radiation)
Xiang et al. [12]	China	3	Total 33, [duodenum 26, jejunum 7 (J + I), Ileum 7 (J + I), (ampullary) 0]	16.5 (3–45)	57 (32–76)	(23/10)	FOLFOX	Overall response rate and safety	33 (4/29)	3 (cisplatin/FU: *n* = 2, FU/LV: *n* = 1)
Horimatsu et al. [13]	Japan	12	Total 24, [duodenum 14, jejunum 10, Ileum 0, (ampullary) 0]	14.7 (3.7–40.3)	63 (31–79)	(18/6)	mFOLFOX6	1-year progression-free survival	24 (2/22)	0
Gulhati et al. [14]	USA	1	Total 30, (duodenum 18, jejunum + Ileum 5, (ampullary) 7)	25.9 (NR)	63 (33–78)	(13/17)	CAPOX + BV	6-months progression-free survival	30 (0/30)	NR (accepted)
McWilliams et al. [15]	USA	15	Total 33 [duodenum 19, jejunum 10, Ileum 3, cannot discern 1, (ampullary) 0]	NR	64 (41–77)	(24/9)	CAPIRINOX*	The percentage of patients with a confirmed tumor response	33	2 (accepted)

Table 1 (continued)

References	Country	Number of centers	Number of patients	Median follow up period (month) (range)	Median age (years old) (range)	Sex (male/female)	Regimen	Primary endpoint	Unresectable (Locally advanced/metastatic) (*n*)	Prior adjuvant chemotherapy (*n*)
2nd or further line systemic chemotherapy										
Overman et al. [16]	USA	1	Total 13 (duodenum 4, ileum or jejunum 9), and 21 patients with CIMP-high CRC. Among 13 patients, 10 were asessable[a]	NR	58 (40–76)	(6/7)	Nab-paclitaxel	Response rate (as per RECIST version 1.1)	13 (0/13)	Median number of prior lines 2 (range 1–7): fluoropyrimidine and oxaliplatin

All included studies were Phase II single arm studies. Horimatsu et al. reported there were patients who received prior surgery (six primary resection and seven bypass), and subsequent chemotherapy (12). Other studies did not record the number of patients treated with prior surgery or subsequent chemotherapy. As for recurrent cases, there were zero case in Overman (2006) and three cases in Horimatsu (2017). Other studies did not record the number of recurrent patients

NR not recorded, *FAM* 5-fluorouracil, Adriamycin, and mitomycin-C, *CAPOX* capecitabine and oxaliplatin, *FOLFOX* folinic acid, 5-fluorouracil, and oxaliplatin, *BV* bevacizumab, *LV* leucovorin, *CAPIRINOX* capecitabine, irinotecan, and oxaliplatin

[a]defined as those who had received at least three cycles of nab-paclitaxel

Qualität der Studien:

- Because all studies were single-arm, the review authors were unable to assess the risk of bias of confounding and classification criteria.

Study	Domain 1: Confounding	Domain 2: Selection	Domain 3: Classification	Domain 4: Deviations from interventions	Domain 5: Missing Data	Domain 6: Measurement of Outcomes	Domain 7: Selection of Reported Result	Overall
Gibson et al. (2005)	NA	Low	NA	NI	Serious	Moderate	Serious	Serious
Overman et al. (2009)	NA	Low	NA	Low	Low	Moderate	Low	Moderate
Xiang et al. (2012)	NA	Low	NA	Moderate	Low	Moderate	Low	Moderate
Horimatsu et al. (2017)	NA	Low	NA	Low	Low	Moderate	Low	Moderate
Gulhati et al. (2017)	NA	Low	NA	NI	Low	Moderate	Low	Moderate
McWilliams et al. (2017)	NA	Low	NA	Low	Low	Moderate	Low	Moderate
Overman et al. (2018)	NA	Low	NA	Low	Low	Moderate	Low	Moderate

NA Not applicable because of single-arm study. NI No information.

(Source: Supplementary Material 2)

Studienergebnisse:

Meta-analyses of the study results for tumor response, survival time, or toxicity were not feasible because of the differences in chemotherapeutic agents and toxicity assessment measurements.

- Efficacy

Table 2 Efficacy in the included studies

References	Regimen	Object response rate %	Disease control rate %	Median progression free survival (month)	Median overall survival (month)	Used criteria
1st line systemic chemotherapy						
Gibson et al. [10]	FAM	18% (7/36)	29% (11/36)	5 (NR)	8 (NR)	Its own criteria
Overman et al. [11]	CAPOX	50% (15/30)	NR (SD + PR + CR 87% 26/30)	11.3 (95% CI 4.7 to > 35)	20.4 (95% CI 14.4 to > 35)	RECIST (version 1.0)
Xiang et al. [12]	FOLFOX	48.5% (16/33)	84.9% (28/33)	7.8 (95% CI 6.0–9.6)	15.2 (95% CI 11.0–19.4)	RECIST (version 1.0)
Horimatsu et al. [13]	FOLFOX	45% (9/20) four patients were excluded because of no target lesion	80% (16/20)	5.4 (95% CI 4.8–6.0)	17.3 (11.7–19.0)	RECIST (version 1.1)
Gulhati et al. [14]	CAPOX + BV	48.3% (14/30)	80% (24/30)	8.7 (95% CI 4.9–10.5)	12.9 (95% CI 9.2–19.7)	RECIST (version 1.1)
McWilliams et al. [15]	CAPIRINOX	37.5% (12/32)	81% (26/32)	8.9 (95% CI 4.7–10.8)	13.4 (95% CI 10.5–18.1)	RECIST (version unspecified)
2nd or further line systemic chemotherapy						
Overman et al. [16]	Nab-paclitaxel	20%	50%	3.2 (95% CI 2.1–not reached), ITT 2.2 (95% 2–2.4)	10.9 (7.0–not reached), ITT 8.7 (95% CI 5.3–not reached)	RECIST (version 1.1)

NR not recorded, *RECIST* response evaluation criteria in solid tumors

Table 3 Severe toxicity in the included studies

Author (Year)	Total Number of patients	Regimen	Stomatitis	Hand foot syndrome	Neutropenia	Febrile neutropenia	Thrombocytopenia	Anemia	Nausea	Vomiting	Diarrhea	Peripheral Neuropathy	Fatigue	Treatment related death	Used criteria
Gibson et al. (2005) [10]	38	FAM	1 (3%)	NR [skin 0 (0%)]	NR [blood 22 (58%)]	NR	NR [blood 22 (58%)]	NR [blood 22 (58%)]	NR	6 (16%)	1 (3%)	NR	NR	1 (3%) (blood)	Its own criteria
Overman et al. (2009) [11]	30	CAPOX	NR	0 (0%)	3 (10%)	0 (0%)	2 (7%)	0 (0%)	1 (3%)	3 (10%)	3 (10%)	3 (10%)	9 (30%)	0 (0%)	CTCAE[a] v3.0
Xiang et al. (2012) [12]	33	FOLFOX	0 (0%)	NR	4 (12%)	0 (0%)	1 (3%)	0 (0%)	2 (6%)	1 (3%)	1 (3%)	3 (9%)	1 (3%)	0 (0%)	CTCAE v2.0
Horimatsu et al. (2017) [13]	24	FOLFOX	0 (0%)	0 (0%)	9 (38%)	NR	0 (0%)	6 (25%)	0 (0%)	0 (0%)	1 (4%)	6 (25%)	2 (8%)	0 (0%)	CTCAE v3.0
Gulhati et al. (2017) [14][b]	30	CAPOX + BV	NR	NR	7 (23%)	NR	0 (0%)	0 (0%)	2 (7%)	0 (0%)	3 (10%)	2 (7%)	7 (23%)	0 (0%)	CTCAE v4.0
McWilliams et al. (2017) [15]	33	CAPIRINOX	0 (0%)	0 (0%)	9 (27%)	2 (6%)	3 (9%)	3 (9%)	8 (24%)	6 (18%)	7 (21%)	1 (3%)	4 (12%)	0 (0%)	CTCAE v3.0
Overman et al. (2018) [16]	34[c]	Nab-paclitaxel	0 (0%)	NR	3 (9%)	3 (9%)	2 (6%)	0 (0%)	1 (3%)	1 (3%)	1 (3%)	0 (0%)	4 (12%)	0 (0%)	CTCAE v4.0

NR not recorded

[a]CTCAE The National Cancer Institute Common Terminology Criteria for Adverse Events [18]

[b]Seven patients experienced hypertension (CTCAE grade 3 −)

[c]Both small bowel adenocarcinoma ($n = 13$) and colorectal cancer patients ($n = 21$) were included

Anmerkung/Fazit der Autoren

There are some limitations.

- First, all included studies were single-arm studies, and the number of included studies was small because of the rarity of SBA.
- Second, a variety of chemotherapeutic regimens were used for SBA; however, many of them were fluoropyrimidine-based.
- Third, the inclusion criteria of the tumor location of SBA appeared to be heterogeneous in the included studies.

Systemic chemotherapy with fluoropyrimidine-based regimens was mainly used for unresectable or metastatic SBA. While this therapy may achieve favorable outcomes with acceptable adverse effects, further evidence is needed.

Kommentare zum Review

Single-arm-studies, no RCTs included in this review, narrative review

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Meijer LL et al., 2018 [1].

Outcomes and Treatment Options for Duodenal Adenocarcinoma: A Systematic Review and Meta-Analysis.

Fragestellung

The aim of this review of the literature and meta-analysis is to describe the outcomes of DA after curative and palliative treatment strategies, including optimal type of resection and the value of (neo)adjuvant therapy, and to determine the role of prognostic factors.

Methodik

Population:

- patients with confirmed DA or intestinal type ampullary adenocarcinoma (IAA) (including signet cell carcinoma and mucinous adenocarcinoma); primary tumor
- disease stages, or T and N classification, or treatment modality specified for the included patients
- age ≥ 18 year, male and female

Intervention und Komparator:

- surgical intervention: curative intent vs. palliative surgery
- adjuvant therapy (including chemotherapy, radiotherapy and chemoradiation) vs. no adjuvant therapy
- involvement of nodal metastases vs. no involvement

Endpunkte:

- OS

Recherche/Suchzeitraum:

- PubMed, EMBASE, and Wiley/Cochrane Library
- to 25April 2017

Qualitätsbewertung der Studien:

- The Newcastle – Ottawa quality assessment scale (0 – 9 points) was implemented to assess the quality and risk of bias of the included studies. A follow-up duration of at least 3 years was considered sufficient, and the maximum loss to follow-up of less than 10% was awarded a point. Studies with scores below 4 were considered to have a high risk of bias, those with scores of 4 - 6 to have an intermediate risk of bias, and those with scores of 7 or more to have a low risk of bias.

Ergebnisse

Anzahl eingeschlossener Studien:

- n=26 studies comprising 6438 patients
- 23 retrospective cohort studies, 2 prospective cohort studies and 1 case-control study

Charakteristika der Population:

- Weighted mean age: 63 years
- 53% male

TABLE 1 General characteristics of the included studies

Author (year of publication)	*N*	Study period	Trial setting	Country	Age (SD)[a]	Males [*n* (%)]	Follow-up (months, median)	Interventions for which survival is reported	Type of survival outcome studied (in years)	Tumor location				AJCC edition
										D1 + D1/2	D2 + D2/3	D3 + D3/4	D4 + Treitz	
Bakaeen[31]	101	1976–1996	RCS	USA	63 (14)	51 (50)	39.6[b]	CR, PT	OS-3,5	3	50	9	6	5
Bhatti[47]	12	1999–2012	RCS	Pakistan	55 (10)	8 (67)	–	CR	M, OS-5	–	–	–	–	7
Buchbjerg[2]	71	1997–2012	RCS	Denmark	67 (13)	43 (61)	–	CR, PT	M, OS-1,3,5	7	36	19	10	5
Cecchini[32]	169	1982–2010	RCS	USA	62 (13)	93 (55)	26.5	CR, PT	M, OS-3,5	10	72	10	11	7
Cloyd[43]	1611	1988–2010	RCS	USA	–	745 (46)	41.9	CR	M, OS-5	–	–	–	–	6
Ecker[50]	3122	1998–2012	CCS	USA	66 (14)	1683 (54)	79.2	Adj. CRTx, adj. CTx	M, OS-5	–	–	–	–	–
Han[10]	32	1990–2006	RCS	China	56 (7)	19 (59)	106	CR, PT	OS-1,3,5	2	8	17	5	6
Hung[33]	23	1994–2005	RCS	Taiwan	68 (12)	15 (65)	15.1	CR, PT	M, OS-1,3,5	9	14	–	–	–
Hurtuk[44]	52	1984–2005	RCS	USA	65 (12)	36 (69)	24	CR, PT	M, OS-3,5	–	–	–	–	–
Jiang[34]	201	1999–2015	RCS	China	55 (10)	78 (61)[b]	20	CR, PT	M, OS-1,3,5	5	113	9	4	7
Kaklamanos[12]	63	1978–1988	RCS	USA	61 (18)	33 (52)	–	CR, PT	M, OS-5	7	41	–	4	5
Kawahira[35]	21	1977–2007	RCS	Japan	61 (–)	11 (52)	–	CR, PT	M, OS-1,3,5	–	–	–	–	7
Kelsey[22]	32	1975–2005	RCS	USA	57 (11)	23 (72)	32	CR, CR + adj. CRTx	OS-5	0	14	11	7	–
Kim[45]	24	1991–2002	RCS	South Korea	58 (11)	14 (58)	32	CR, CR + adj. CRTx	OS-5	–	–	–	–	6
Kim[36]	50	1995–2010	RCS	South Korea	61 (11)	35 (70)	–	CR, PT	M, OS-3,5	9	24	2	1	7
Lee[37]	53	1995–2007	RCS	South Korea	60 (10)	33 (62)	41.7	CR, PT	OS-3,5	6	30	13	4	–
Lee[38]	76	1999–2009	RCS	South Korea	56 (11)	55 (72)	–	CR, PT	M, OS-1,3,5	–	41	7	–	7
Liang[41]	36	1993–2010	RCS	Taiwan	64 (13)	24 (67)	41	CR	M, OS-3,5	8	25	2	1	7
Malleo[40]	37	2000–2009	RCS	Italy	57 (11)	21 (57)	25	CR, PT	M, OS-5	–	25	12	–	7
Onkendi[11]	124	1994–2009	RCS	USA	65 (14)	75 (59)	–	CR, PT	M, OS-2,5,10	8	73	24	15	7
Poultsides[42]	122	1984–2006	RCS	USA	67 (14)	66 (54)	33	CR, CR + adj. CRTx	OS-5,10	–	–	–	–	7
Sarela[46]	137	1983–2001	PCS	USA	63 (11)	75 (55)	36	CR	OS-5,10	–	–	–	–	5
Solaini[24]	178	2000–2013	PCS	UK	61 (4)	101 (57)	39	CR, PT	M, OS-1,3,5	25	94	29	12	7
Struck[48]	30	1989–2006	RCS	USA	61 (10)	22 (73)	15.2	CR	M, OS-1,5	–	–	–	–	6
Swartz[49]	14	1994–2003	RCS	USA	53 (9)	10 (71)	42	CR, CR + adj. CTx	M, OS-5	–	–	–	–	6
Tocchi[39]	47	1980–2000	RCS	Italy	58 (8)	26 (45)	24	CR, PT	M, OS-5	–	–	37	10	–
All studies	6438				63[c]	3395 (53)				99	660	201	90	

n number of patients included, *PCS* prospective cohort study, *RCS* retrospective cohort study, *CCS* case–control study, *SD* standard deviation, *AJCC* American Joint Committee on Cancer, *M* median survival reported, *OS* overall survival, *CR* resection with curative intent (R0/R1 resection, pancreaticoduodenectomy or segmental resection), *PT* palliative treatment (R2 resection, bypass, stent placement, palliative or supportive treatment), – Indicates not reported

[a]Age: mean in years (range in years)

[b]Only reported for resection with curative intent

[c]Weighted mean

Qualität der Studien:

„…the quality of the included studies was mainly compromised by clinical incomparability of both factors that could influence survival, such as age, sex, and tumor stage, as well as limited therapy specifications. In addition, adjusted estimates of OS were insufficiently reported to be included for our meta-analysis.“

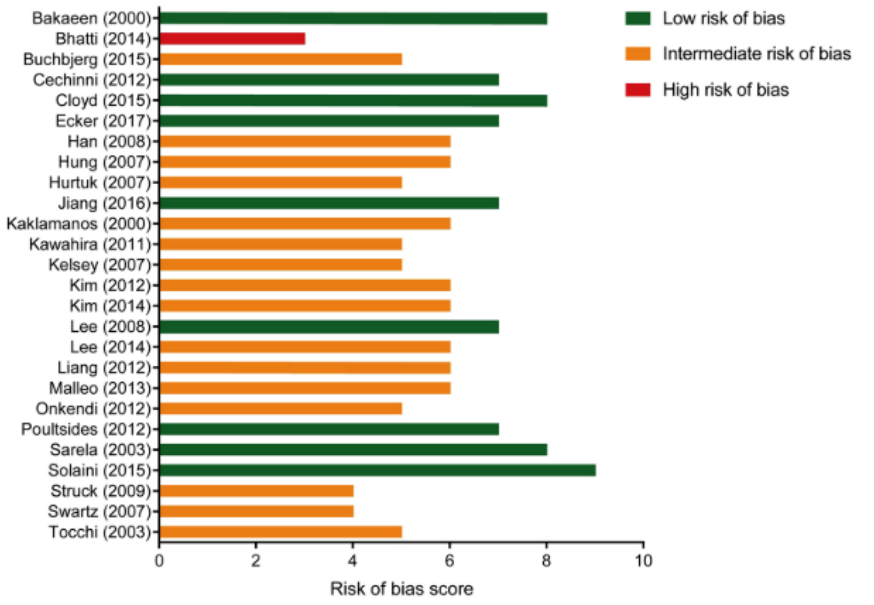
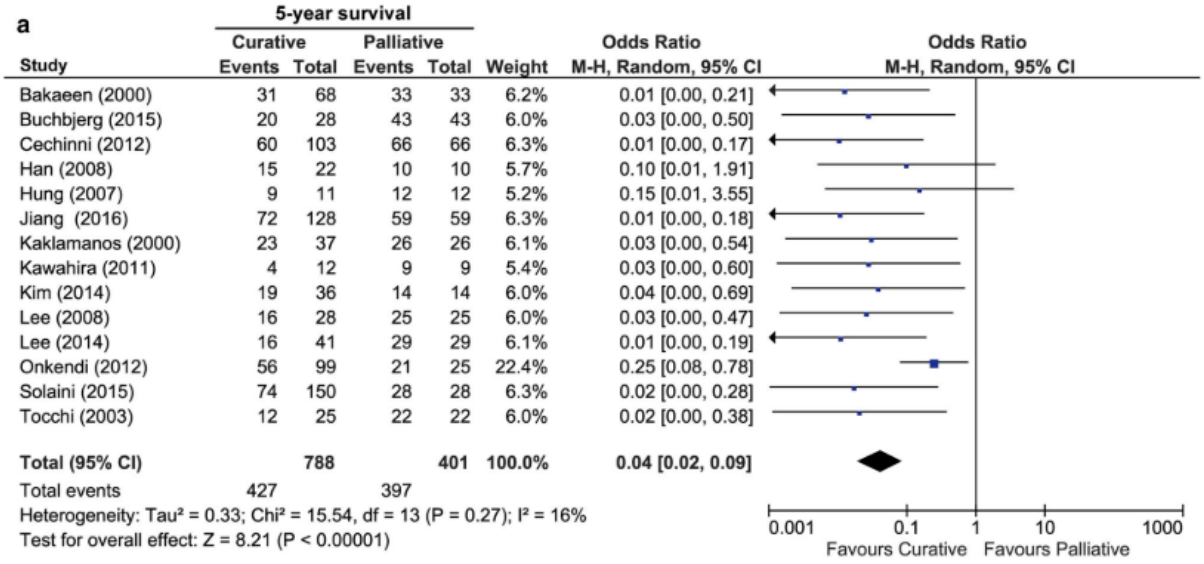


FIG. 3 Quality assessment of the included studies based on the Newcastle–Ottawa quality assessment scale for case–control studies. The maximum score is 9

Studienergebnisse:

- **Survival after Resection with Curative Intent vs. Palliative Treatment**

  In the 14 studies comparing curative and palliative treatment, the pooled 5-year survival rate was significantly longer when treatment with curative intent was feasible (46 vs. 1%, respectively; OR 0.04, 95% CI 0.02–0.09; I2 = 16%, p<0.0001).



Pooling of studies to estimate survival per disease stage could not be performed due to the lack of specification of survival per disease stage. Only three studies specified survival rates.[36–38,41]

36. Kim MJ, Choi SB, Han HJ, et al. Clinicopathological analysis and survival outcome of duodenal adenocarcinoma. Kaohsiung J Med Sci. 2014;30(5):254–9.

37. Lee HG, You DD, Paik KY, Heo JS, Choi SH, Choi DW. Prognostic factors for primary duodenal adenocarcinoma. World J Surg. 2008;32(10):2246–52.

38. Lee SY, Lee JH, Hwang DW, Kim SC, Park KM, Lee YJ. Longterm outcomes in patients with duodenal adenocarcinoma. ANZ J Surg. 2014;84(12):970–5.

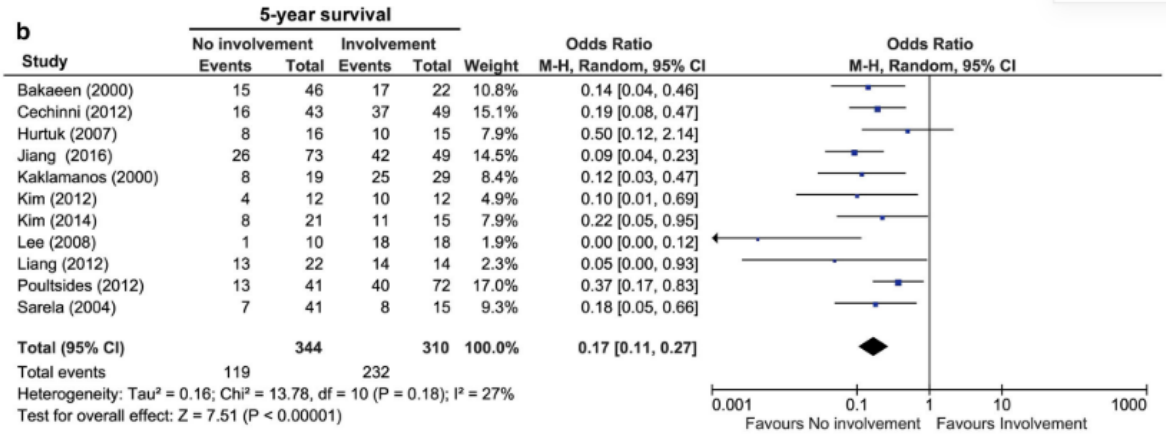
41. Liang TJ, Wang BW, Liu SI, et al. Number of involved lymph nodes is important in the prediction of prognosis for primary duodenal adenocarcinoma. J Chin Med Assoc. 2012;75(11):573–80.

- no significant differences in survival comparing segmental resection with pancreaticoduodenectomy (n=8 studies)

- **Nodal involvement (N+ vs. N0)**

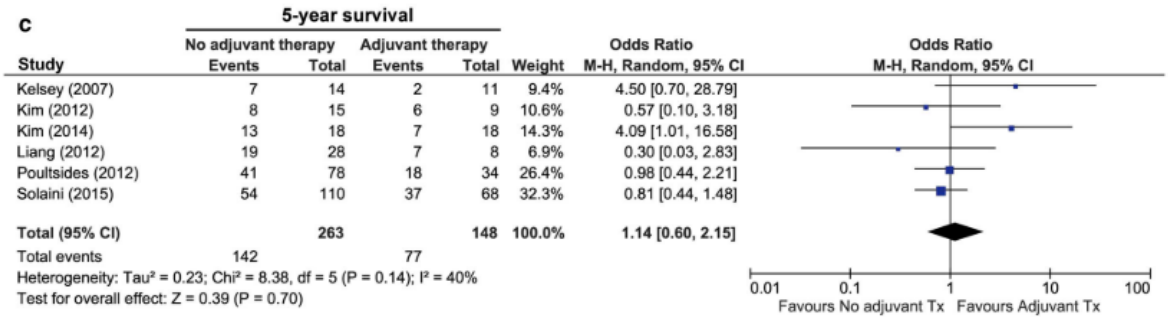
  The pooled 5-year survival rate was 65% for N0, compared with 21% for N+ , resulting in significantly shorter survival when involvement of lymph nodes was present (OR 0.17, 95% CI 0.11–0.27, p<0.0001) (n=11 studies).

  Lymph node involvement remained an independent prognostic factor in most studies after correction for other clinicopathological factors, including tumor size, differentiation grade, and disease stage



- **Adjuvant therapy**

  There was no difference in the pooled 5-year OS for any type of adjuvant therapy and control groups (48 vs. 46%, respectively; OR 1.14, 95% CI 0.60–2.15, I2 = 40%) (n=6 studies).



Due to heterogenous groups and missing results no specific analysis stratified per treatment could be made.

Anmerkung/Fazit der Autoren

This systematic review of the literature and meta-analysis shows a clear survival benefit for patients with DA after curative surgical resection, compared with palliativetreated patients. Both segmental duodenal resection and pancreaticoduodenectomy allow for adequate removal of lymph nodes and result in similar OS when negative resection margins can be achieved.

The included studies show no associated survival benefit for the use of any type of adjuvant therapy for DA, although this remains debatable due to the inequality of regimes used and insufficient patient stratification. No consensus regarding palliative treatment was found.

Kommentare zum Review

Inclusion of primary tumor, no RCTs included in this review, no subgroup analysis regarding type of treatment resp. chemotherapeutic regimen

3.4 Leitlinien

NCCN, 2020 [2]

Small Bowel Adenocarcinoma: NCCN Evidence Blocks; Version 2.2020

Zielsetzung/Fragestellung

- The treatment recommendations in this guideline only refer to small bowel adenocarcinoma (SBA), which comprise an estimated 30% to 40% incidence of small intestinal cancer diagnoses.
- Due to the rarity of this disease, there are very few established guidelines for management of SBA.

Methodik

Grundlage der Leitlinie

- Interessenkonflikte dargelegt; keine Angaben zum Umgang
- Systematische Suche, Auswahl und Bewertung der Evidenz: keine Angaben
- Formaler Konsensusprozess: keine Angaben
- Externes Begutachtungsverfahren: keine Angaben
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: Evidence Blocks geben Hinweise, genaue Bewertung und Begründung der Bewertung der dazugehörigen Studien wird allerdings nicht dargestellt
- Regelmäßige Aktualisierung

Recherche/Suchzeitraum:

- Datenbank: PubMed
- Einschlusskriterien: humans, english, clinical trial, multicenter studies, practice guidelines, RCTs, Meta-analysis, SRs, validation studies
- Aktualität der Recherche: „prior to annual update“ (nccn.org)

LoE/GoR

NCCN Categories of Evidence and Consensus	
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.

All recommendations are category 2A unless otherwise indicated.

uniform NCCN consensus: ≥85% agreement

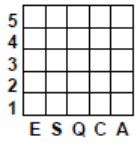
Anmerkung:

Leitlinie entspricht nicht den Kriterien einer evidenzbasierten Leitlinie. Es fehlen u.a. Angaben zur Literaturrecherche und Literaturbewertung sowie Konsensfindung. Aufgrund fehlender höherwertiger Evidenz in dem vorliegenden AWG wird die LL ergänzend dargestellt.

Sonstige methodische Hinweise:

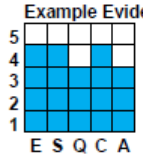
Hintergrund Evidence Blocks

NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Cure likely and often provides long-term survival advantage
4	**Very effective:** Cure unlikely but sometimes provides long-term survival advantage
3	**Moderately effective:** Modest impact on survival, but often provides control of disease
2	**Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal toxicities; no interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only; little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs
2	**Moderately toxic:** Significant toxicities often occur but life threatening/fatal toxicity is uncommon; interference with ADLs is frequent
1	**Highly toxic:** Significant toxicities or life threatening/fatal toxicity occurs often; interference with ADLs is usual and severe

Note: For significant chronic or long-term toxicities, score decreased by 1

Quality of Evidence

5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** One or more well-designed randomized trials
3	**Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s)
2	**Low quality:** Case reports or extensive clinical experience
1	**Poor quality:** Little or no evidence

Consistency of Evidence

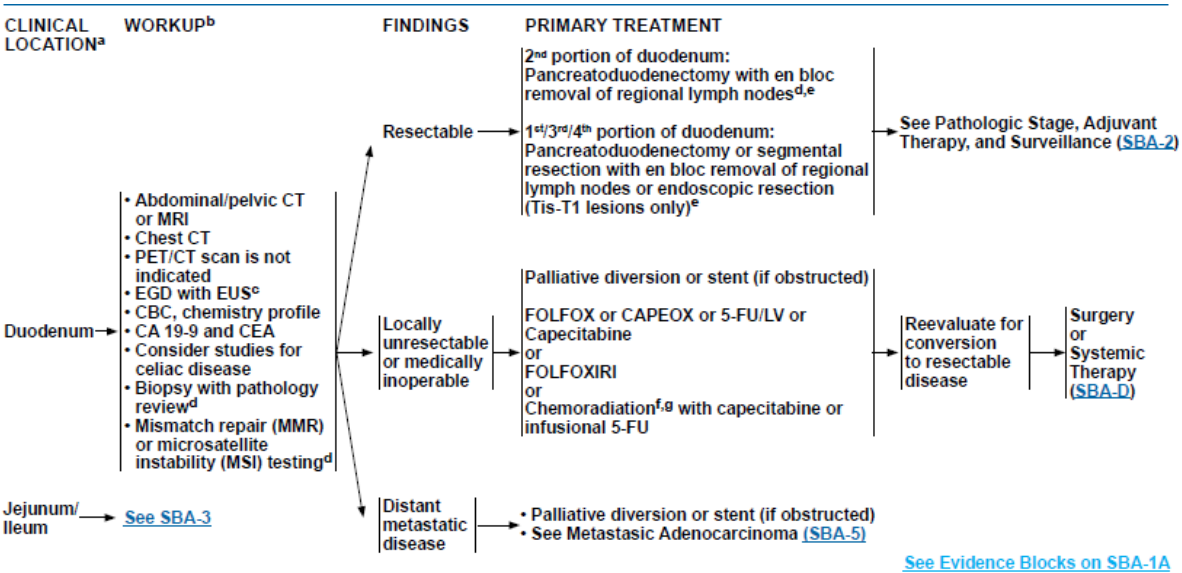
5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	Very inexpensive
4	Inexpensive
3	Moderately expensive
2	Expensive
1	Very expensive

Empfehlungen

Duodenum – Workup and Primary Treatment (SBA-1)



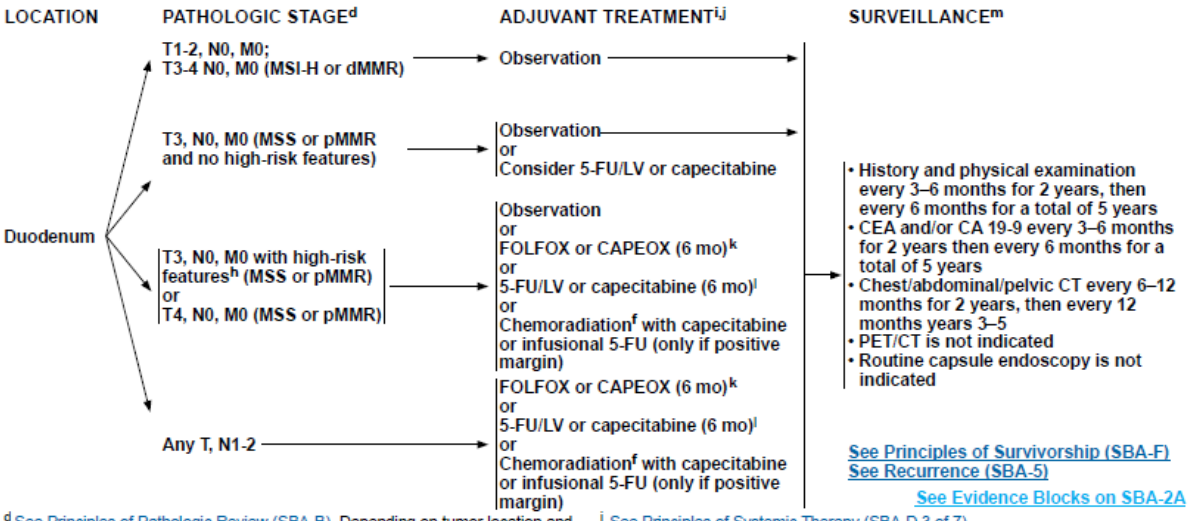
See Evidence Blocks on SBA-1A

[a] All patients with small bowel adenocarcinoma (SBA) should be counseled for familial malignancies and considered for risk assessment, including Lynch syndrome (HNPCC), FAP, and other polypoid mutations. Refer to the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
[b] See Principles of Imaging and Endoscopy (SBA-A).
[c] EUS should be considered when needed to discern duodenal malignancy from ampullary, distal common bile duct, or pancreatic head malignancy. Also consider if other radiologic imaging is insufficient for clinical staging.
[d] See Principles of Pathologic Review (SBA-B). Depending on tumor location and patient history, celiac disease or Crohn's disease may need to be assessed.
[e] See Principles of Surgery (SBA-C).
[f] See Principles of Radiation Therapy (SBA-E).
[g] Preoperative chemoradiation should be considered in patients who remain unresectable following a course of induction chemotherapy.

EVIDENCE BLOCKS FOR PRIMARY TREATMENT FOR LOCALLY UNRESECTABLE OR MEDICALLY INOPERABLE CANCER OF THE DUODENUM

CHEMOTHERAPY REGIMENS	
FOLFOX	
CAPEOX	
5-FU/leucovorin	
Capecitabine	
FOLFOXIRI	
Capecitabine + RT	
Infusional 5-FU + RT	

Duodenum – Adjuvante Therapie (SBA-2)



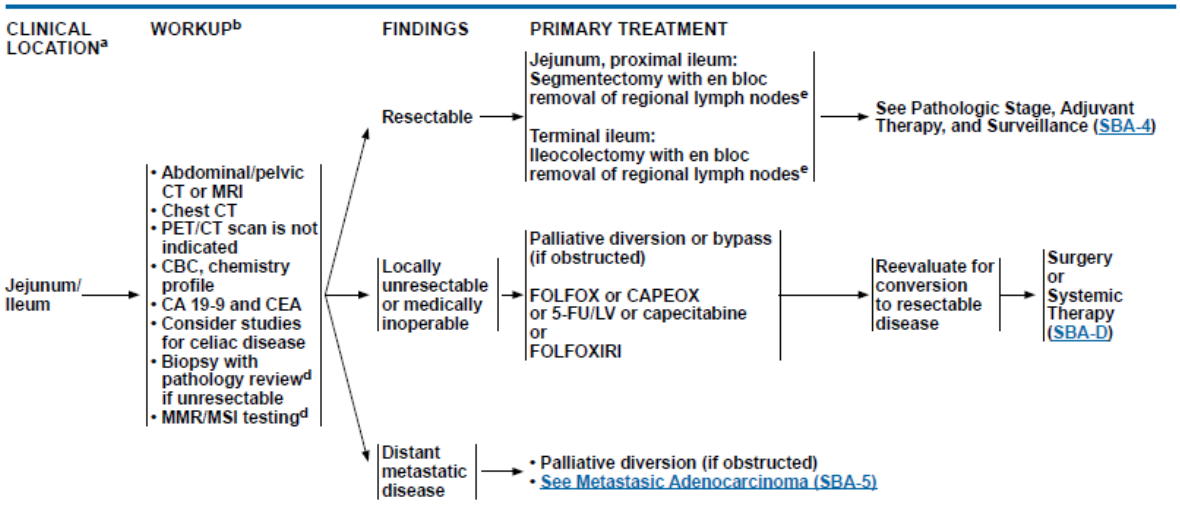
[d] See Principles of Pathologic Review (SBA-B). Depending on tumor location and patient history, celiac disease or Crohn's disease may need to be assessed.
[f] See Principles of Radiation Therapy (SBA-E).
[h] High-risk features in stage II SBA include close or positive resection margins, <5 lymph nodes examined if duodenal location or <8 lymph nodes examined if jejunal/ileal primary tumor location, and tumor perforation. Further consideration may be made for administering chemotherapy in patients with stage II disease who have lymphovascular or perineural invasion, or poorly differentiated histology due to data extrapolated from colorectal cancer studies.
[i] Enrollment in a clinical trial is encouraged [eg, Phase III Trial Investigating the Potential Benefit of Adjuvant Chemotherapy for Small Bowel Adenocarcinoma (BALLAD): https://clinicaltrials.gov/ct2/show/NCT02502370].
[j] See Principles of Systemic Therapy (SBA-D 3 of 7).
[k] The IDEA trial, which successfully showed non-inferior 3-year disease-free survival with 3 months of CAPEOX compared to 6 months of CAPEOX enrolled no patients with SBAs, which tend to have a higher risk for recurrence when compared to colon cancer. As a result, data extrapolation is not recommended for SBA patients receiving adjuvant therapy.
[l] Survival benefit in adding oxaliplatin to fluoropyrimidine has not been demonstrated in geriatric patients (>70 years) for colon cancer adjuvant management.
[m] No studies have been performed to assess ideal surveillance intervals for SBA. The data in colorectal cancer surveillance is generally accepted as appropriate for SBA.

EVIDENCE BLOCKS FOR ADJUVANT TREATMENT FOR STAGE II AND STAGE III CANCER OF THE DUODENUM

STAGE II			
LOW-RISK		HIGH-RISK	
5-FU/leucovorin	▦	FOLFOX	▦
Capecitabine	▦	CAPEOX	▦
		5-FU/leucovorin	▦
		Capecitabine	▦
		Capecitabine + RT (if positive margin)	▦
		Infusional 5-FU + RT (if positive margin)	▦

STAGE III	
FOLFOX	▦
CAPEOX	▦
5-FU/leucovorin	▦
Capecitabine	▦
Capecitabine + RT (if positive margin)	▦
Infusional 5-FU + RT (if positive margin)	▦

Jejunum/Ileum – Workup and Primary Treatment (SBA-3)



EVIDENCE BLOCKS FOR PRIMARY TREATMENT FOR LOCALLY UNRESECTABLE OR MEDICALLY INOPERABLE CANCER OF THE JEJUNUM/ILEUM

CHEMOTHERAPY REGIMENS	
FOLFOX	
CAPEOX	
5-FU/leucovorin	
Capecitabine	
FOLFOXIRI	

Primary Treatment of Unresectable Disease:

For some patients with locally unresectable or medically inoperable SBA, conversion to resectable disease may be a goal. A limited amount of data has demonstrated that neoadjuvant therapy may be beneficial in converting unresectable SBA to resectable disease. A retrospective study of patients with unresectable or recurrent duodenal adenocarcinoma who were treated with neoadjuvant chemotherapy or chemoradiation found that 9 out of 10 patients showed conversion to resectable disease following neoadjuvant therapy. At the time of data collection, 5 patients were still alive (ranging from 18–83 months postoperatively), suggesting prolonged survival following conversion to resectable disease.[89] In addition, neoadjuvant chemoradiation was studied in two small prospective trials. A phase II trial including patients with duodenal or pancreatic adenocarcinomas reported that 4 of 5 patients with tumors in the duodenum were able to undergo resection following neoadjuvant chemoradiation.[90] Another small prospective study of patients with duodenal or pancreatic adenocarcinomas reported that all 4 patients with duodenal cancer underwent curative resection following neoadjuvant chemoradiation and experienced a complete pathologic response.[91]

Since many small bowel cancers present at an advanced stage, malignant small bowel obstruction is a common complication. One retrospective Eastern European study reported that most patients with small bowel cancer presented due to an emergency situation,[39] with obstruction being a common complication for SBA, accounting for 22% to 57.9% of these cases.[39,92-94] Malignant small bowel obstruction may be treated palliatively with either surgical diversion or stenting. While most of the literature on palliative treatment of malignant small bowel obstruction comes from pancreatic cancer, there are a few studies that include SBA cases.[39,95-97] One retrospective study concluded that there was no difference in poststent survival between patients with pancreatic and nonpancreatic cancers, and that patients with nonpancreatic cancers (including SBA) showed a longer OS.[95]

Based on these data, the panel recommends that patients with locally unresectable or medically inoperable SBA may undergo neoadjuvant therapy, during which they should be routinely monitored for conversion to resectable disease. Neoadjuvant chemoradiation may be indicated for duodenal disease that remains unresectable following a course of induction chemotherapy, but is controversial and should be considered on an individual case basis. Alternatively, in cases where conversion to resectable disease is not feasible, palliative chemotherapy may be considered. Palliative diversion or stenting is recommended if a small bowel obstruction is present.

39. Negoi I, Paun S, Hostiuc S, et al. Most small bowel cancers are revealed by a complication. Einstein (Sao Paulo) 2015;13:500-505. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26676271.

89. Onkendi EO, Boostrom SY, Sarr MG, et al. Neoadjuvant treatment of duodenal adenocarcinoma: a rescue strategy. J Gastrointest Surg

2012;16:320-324. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21956430.

90. Yeung RS, Weese JL, Hoffman JP, et al. Neoadjuvant chemoradiation in pancreatic and duodenal carcinoma. A Phase II Study. Cancer 1993;72:2124-2133. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8374871.

91. Coia L, Hoffman J, Scher R, et al. Preoperative chemoradiation for adenocarcinoma of the pancreas and duodenum. Int J Radiat Oncol Biol Phys 1994;30:161-167. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8083109.

92. Minardi AJ, Jr., Zibari GB, Aultman DF, et al. Small-bowel tumors. J Am Coll Surg 1998;186:664-668. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9632155.

93. Ciresi DL, Scholten DJ. The continuing clinical dilemma of primary tumors of the small intestine. Am Surg 1995;61:698-702; discussion 702693. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7618809.

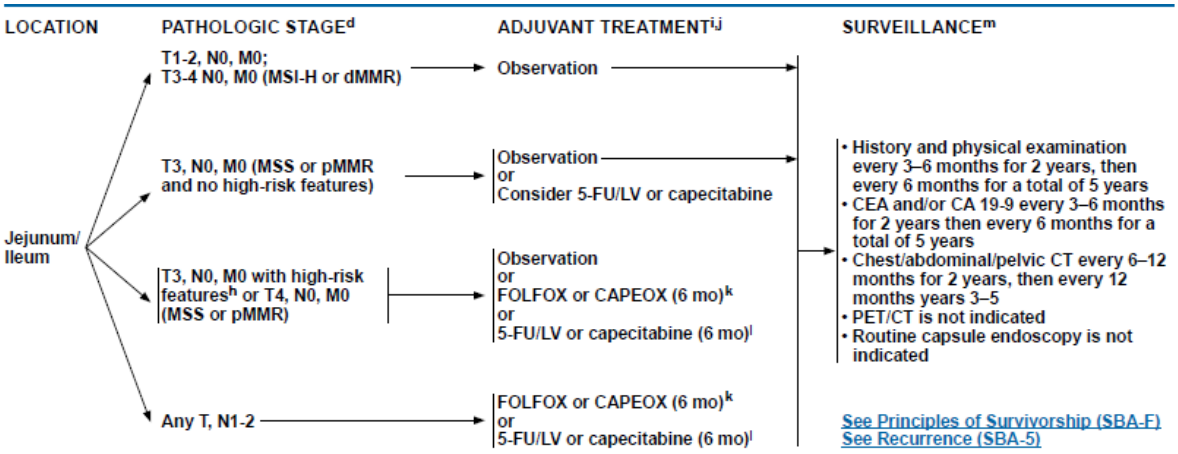
94. Ojha A, Zacherl J, Scheuba C, et al. Primary small bowel malignancies: single-center results of three decades. J Clin Gastroenterol 2000;30:289-293. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10777190.

95. Oh SY, Edwards A, Mandelson M, et al. Survival and clinical outcome after endoscopic duodenal stent placement for malignant gastric outlet obstruction: comparison of pancreatic cancer and nonpancreatic cancer. Gastrointest Endosc 2015;82:460-468.e462. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25851162.

96. van den Berg MW, Haijtink S, Fockens P, et al. First data on the Evolution duodenal stent for palliation of malignant gastric outlet obstruction (DUOLUTION study): a prospective multicenter study. Endoscopy 2013;45:174-181. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23348890.

97. Upchurch E, Ragusa M, Cirocchi R. Stent placement versus surgical palliation for adults with malignant gastric outlet obstruction. Cochrane Database Syst Rev 2018;5:CD012506. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29845610.

Jejunum/Ileum – Adjuvante Therapie (SBA-4)



See Evidence Blocks on SBA-4A

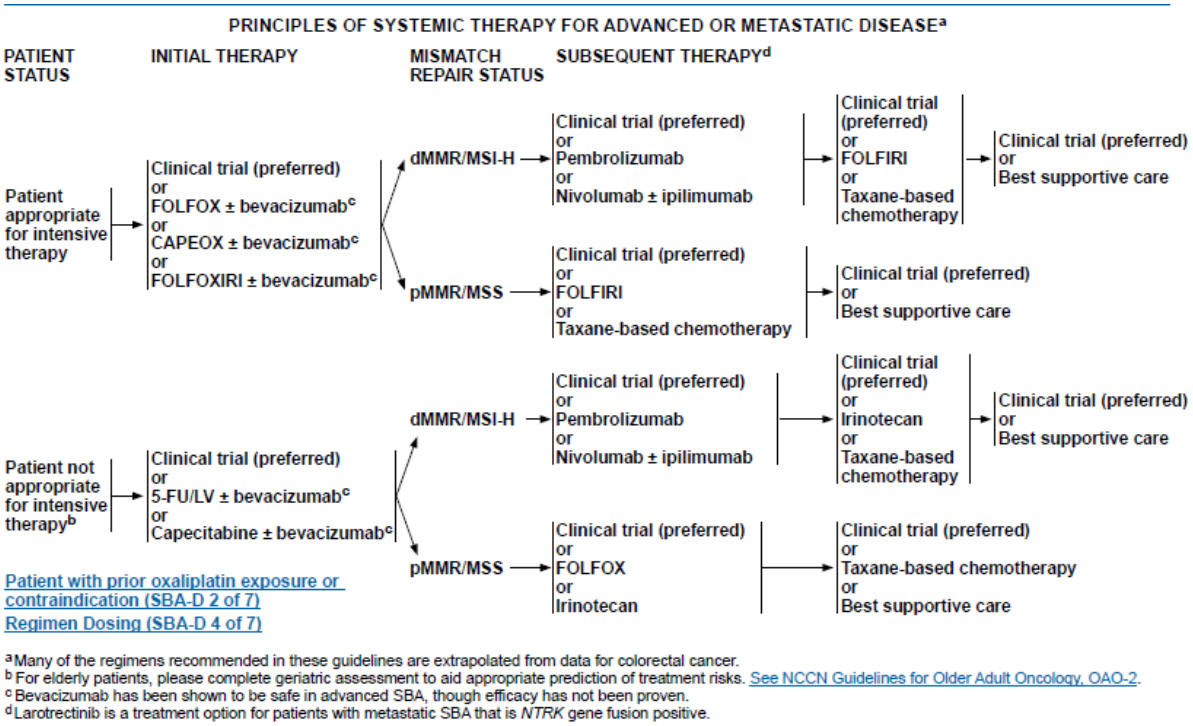
[d] See Principles of Pathologic Review (SBA-B). Depending on tumor location and patient history, celiac disease or Crohn's disease may need to be assessed.
[h] High-risk features in stage II SBA include close or positive resection margins, <5 lymph nodes examined if duodenal location or <8 lymph nodes examined if jejunal/ileal primary tumor location, and tumor perforation. Further consideration may be made for administering chemotherapy in patients with stage II disease who have lymphovascular or perineural invasion, or poorly differentiated histology due to data extrapolated from colorectal cancer studies.
[i] Enrollment in a clinical trial is encouraged [eg, Phase III Trial Investigating the Potential Benefit of Adjuvant Chemotherapy for Small Bowel Adenocarcinoma (BALLAD): https://clinicaltrials.gov/ct2/show/NCT02502370].
[j] See Principles of Systemic Therapy (SBA-D 3 of 7).
[k] The IDEA trial, which successfully showed non-inferior 3-year disease-free survival with 3 months of CAPEOX compared to 6 months of CAPEOX enrolled no patients with SBAs, which tend to have a higher risk for recurrence when compared to colon cancer. As a result, data extrapolation is not recommended for SBA patients receiving adjuvant therapy.
[l] Survival benefit in adding oxaliplatin to fluoropyrimidine has not been demonstrated in geriatric patients (>70 years) for colon cancer adjuvant management.
[m] No studies have been performed to assess ideal surveillance intervals for SBA. The data in colorectal cancer surveillance is generally accepted as appropriate for SBA.

EVIDENCE BLOCKS FOR ADJUVANT TREATMENT FOR
STAGE II AND STAGE III CANCER OF THE JEJUNUM/ILEUM

STAGE II			
LOW-RISK		HIGH-RISK	
5-FU/leucovorin		FOLFOX	
Capecitabine		CAPEOX	
		5-FU/leucovorin	
		Capecitabine	

STAGE III	
FOLFOX	
CAPEOX	
5-FU/leucovorin	
Capecitabine	

Metastatic Adenocarcinoma – Principles of systemic therapy (SBA-D)



[a] Many of the regimens recommended in these guidelines are extrapolated from data for colorectal cancer.
[b] For elderly patients, please complete geriatric assessment to aid appropriate prediction of treatment risks. See NCCN Guidelines for Older Adult Oncology, OAO-2.
[c] Bevacizumab has been shown to be safe in advanced SBA, though efficacy has not been proven.
[d] Larotrectinib is a treatment option for patients with metastatic SBA that is *NTRK* gene fusion positive.

Systematic Therapy for Metastatic Disease:

Data supporting systemic therapy for advanced adenocarcinoma of the small bowel were also almost entirely limited to retrospective reports,[109-112] although recently several small phase II trials for SBA have been reported. Based on the results from these studies, several systemic therapy regimens are recommended for treatment of metastatic SBA. However, participation in clinical trials is especially encouraged for patients with SBA based on the lack of data.

The choice of therapy is based on consideration of the goals of therapy, the type and timing of prior therapy, and the differing toxicity profiles of the constituent drugs. Furthermore, an evaluation of the efficacy and safety of these regimens for an individual patient must take into account the performance status of the patient. As initial therapy for advanced disease in a patient appropriate for intensive therapy (ie, one with a good tolerance for this therapy for whom a high tumor response rate would be potentially beneficial) without prior platinum resistance, the panel recommends a choice of 3 chemotherapy regimens: FOLFOX, CAPEOX, or FOLFOXIRI (infusional 5-FU, LV, oxaliplatin, irinotecan); any of which may be combined with bevacizumab. For patients who are not appropriate for intensive therapy, treatment options would exclude the more toxic components of these regimens with 5-FU/LV or capecitabine with or without bevacizumab recommended as first-line therapy for these patients.

The choice of second-line therapy depends on the MMR/MSI status of the tumor. For tumors that are dMMR or MSI-H, checkpoint inhibitor therapy with anti-PD-1 inhibitors, alone or in combination with an anti-CTLA4 inhibitor, is recommended in the second-line setting. FOLFIRI or taxanebased chemotherapies are options in the second line for pMMR/MSS tumors, or those that are refractory to checkpoint inhibitor therapies. Larotrectinib is an option in subsequent lines of therapy for metastatic SBA with neurotrophic tyrosine receptor kinase (NTRK) gene fusion and no satisfactory alternative treatments.

Genetic Alterations in SBA

Emerging research has shown that SBA has a distinct genetic profile, which sets it apart from CRC or gastroesophageal cancers, the two cancer types SBA is most often likened to. While KRAS and TP53 alterations are frequently identified in both SBA and CRC, APC mutations are significantly less common in SBA (27% in SBA vs. 76% in CRC; P < .001).[34] Considering the near ubiquity of APC mutation and its well-established role in CRC carcinogenesis, this suggests that neoplastic transformation in SBA is unique compared to CRC.[33,34]

SMAD4 and CDKN2A mutations are more commonly seen compared to gastroesophageal cancers and CRC. Though BRAF mutations occur at a similar rate as seen in CRC, only 10% of BRAF-mutant SBAs have a V600E alteration, compared with >70% in BRAF-mutant CRC.[34] Importantly, human epidermal growth factor receptor 2 (HER2) alterations, MSI-H/dMMR, programmed death-ligand 1 (PD-L1) expression, and high tumor mutational burden are enhanced in SBA compared to CRC,[34,113-115] and may reveal greater importance of targeted or immunotherapeutic treatments compared to current CRC treatment algorithms.

Regimens Not Recommended for SBA

While many of the systemic therapy regimens recommended for treatment of metastatic SBA are extrapolated from data for CRC, there are several regimens commonly used for metastatic CRC that are not recommended for SBA based either on a lack of data supporting their use or data suggesting that these regimens do not work for metastatic SBA.

A 2017 retrospective analysis reported that the efficacy of cetuximabcontaining chemotherapy for RAS wild-type SBA was inconclusive.[116] Subsequently, a phase II trial published in 2018 showed that panitumumab has no clinically meaningful activity in RAS wild-type SBA;[117] therefore, cetuximab or panitumumab should not be used for treatment of SBA.

While trifluridine-tipiracil or regorafenib are recommended as subsequent therapy options for metastatic CRC, there are no data to support their use for SBA and are, therefore, not recommended.

FOLFOX or CAPEOX as First-line Therapy

Both FOLFOX and CAPEOX have been evaluated prospectively for firstline treatment of advanced SBA in phase II clinical trials. One of these trials evaluated CAPEOX in 30 patients with advanced adenocarcinomas of the small bowel and ampulla of Vater. The overall response rate (ORR) (the primary endpoint) was 50%, with 10% achieving complete response.[118] A similar response rate of 48.5% (95% CI, 31%–67%) was seen in another small phase II study of 33 patients that assessed the efficacy of FOLFOX in first-line treatment of advanced SBA.[119] Likewise, another phase II study reported an ORR of 45% for 24 patients with metastatic or unresectable SBA who were treated with FOLFOX, with a median progression-free survival (PFS) and OS of 5.9 and 17.3 months, respectively.[120] These response rates to CAPEOX and FOLFOX were much higher than the 18% response rate seen in another small phase II study that evaluated 5-FU/doxorubicin/mitomycin C in patients with metastatic SBA.[121] Adverse events reported across these three trials were similar, with neutropenia, thrombocytopenia, nausea, vomiting, diarrhea, peripheral neuropathy, and fatigue reported most frequently.[118-120] Retrospective studies have supported the results of these trials, reporting that the combination of a fluoropyrimidine with oxaliplatin was the most effective first-line therapy for advanced SBA.[111,122,123] Based on these data, FOLFOX or CAPEOX are recommended as first-line therapy options for treatment of patients with advanced SBA who are appropriate for intensive therapy.

FOLFOXIRI as First-line Therapy

While the role of FOLFOXIRI for treatment of SBA has not been formally evaluated, CAPIRINOX (capecitabine, irinotecan, oxaliplatin) has been tested as first-line treatment in a phase II trial of 33 patients with advanced SBA.[124] In this trial, CAPIRINOX—dose-adjusted according to UGT1A1 genotype—showed a response rate of 37.5% (95% CI, 21%–56%), with a median PFS and OS of 8.9 and 13.4 months, respectively. Neither hematologic toxicity nor tumor response rate differed significantly by UGT1A1 genotype, supporting the feasibility of genotype-directed dosing for CAPIRINOX. The NCCN Panel does not recommend use of CAPIRINOX for SBA due to concerns about toxicity, but the recommendation for FOLFOXIRI is extrapolated from the results of this study.

FOLFOX, CAPEOX, or FOLFOXIRI Plus Bevacizumab as First-line Therapy

While data supporting the addition of biologics to FOLFOX, CAPEOX, or FOLFOXIRI are currently extremely limited, a single-phase II trial has reported that CAPEOX in combination with bevacizumab is safe and efficacious in patients with SBA.[125] Retrospective analyses have supported these results, reporting favorable outcomes in patients treated with bevacizumab-containing chemotherapy regimens without adding significant toxicity.[116,126] Based on these data, FOLFOX, CAPEOX, or FOLFOXIRI may be given with or without bevacizumab as first-line therapy for advanced SBA.

Pembrolizumab or Nivolumab ± Ipilimumab (for dMMR/MSI-H tumors) as Subsequent-line Therapy

Pembrolizumab is a PD-1 inhibitor that was evaluated as a subsequentline therapy for treatment-refractory metastatic cancers in a phase 2 study that included 3 cohorts: 1) dMMR colorectal adenocarcinomas, 2) MMR-proficient colorectal adenocarcinomas, and 3) dMMR cancers of types other than CRC.[127] This third cohort included 2 patients with small bowel cancers. The immune-related objective response rate and immune-related PFS rate were 40% and 78%, respectively, for patients with dMMR CRC and 71% and 67% for patients with dMMR non-CRC. Common adverse events of clinical interest included rash or pruritus; thyroiditis, hypothyroidism, or hypophysitis; and asymptomatic pancreatitis.[127] Based on the results of this study, the FDA granted accelerated approval to pembrolizumab in May 2017 for patients with unresectable or metastatic dMMR or MSI-H solid tumors that have progressed following prior treatment and have no satisfactory alternative treatment options.[128] More recently, an abstract reported results of ZEBRA, a multicenter, phase 2 study of pembrolizumab in patients with previously treated, advanced SBA.[129] The results of this study confirmed efficacy of pembrolizumab for dMMR/MSI-H SBA. Furthermore, while pembrolizumab did not achieve the goal ORR for this study, there was some evidence that this therapy may control disease in some patients with MSS SBA. Of 18 patients with confirmed MSS SBA, there was a 50% disease control rate, although further study is needed to confirm this result.[129]

Another PD-1 inhibitor, nivolumab—alone or in combination with the CTLA-4 inhibitor, ipilimumab—has been studied in patients with dMMR metastatic CRC in the phase II, multi-cohort CheckMate-142 trial.[130,131] One cohort of this trial included 74 patients with dMMR CRC who were treated with nivolumab. ORR for these patients was 31.1% (95% CI, 20.8– 42.9), with 69% of patients having disease control for at least 12 weeks. Median duration of response had not yet been reached at the time of data collection. PFS and OS were 50% and 73%, respectively, at 1 year. Grade 3 or 4 drug-related adverse events occurred in 20% of patients, with increased amylase and increased lipase being the most common.[130] Another cohort of the CheckMate-142 trial included 119 patients with dMMR CRC who were treated with nivolumab in combination with ipilimumab. For this cohort, ORR was 55% (95% CI, 45.2–63.8) and the disease control rate for at least 12 weeks was 80%. PFS and OS were 71% and 85%, respectively, at 1 year. In addition, significant, clinically meaningful improvements were observed in patient-reported outcomes of functioning, symptoms, and quality of life. Grade 3 to 4 treatment-related adverse events occurred in 32% of patients, but were manageable.[131]

Based on these positive results for CRC, and the data showing benefit of pembrolizumab in SBA, the NCCN Panel recommends either pembrolizumab or nivolumab, with or without ipilimumab, as second-line treatment options for dMMR/MSI-H advanced SBA. SBA has been reported to have a higher incidence of dMMR/MSI-H and higher rates of PD-L1 IHC positivity compared to CRC,[33,34,113] making checkpoint inhibition an important treatment option for some SBA patients.

Taxane-based Chemotherapy as Subsequent-line Therapy

While almost all of the phase II trials of systemic therapy for SBA have focused on first-line therapy, a phase II trial including 13 patients with SBA studied the efficacy of nab-paclitaxel in the refractory disease setting.[132] Patients with SBA in this trial had received a median of 2 prior lines of therapy including a fluoropyrimidine and oxaliplatin. Of the 10 patients with SBA who were evaluable for efficacy, 2 showed a partial response to nabpaclitaxel and an additional 3 had stable disease per RECIST criteria, yielding a disease control rate of 50%. Common grade 3 or 4 toxicities across the entire study population included fatigue (12%), neutropenia (9%), febrile neutropenia (9%), dehydration (6%), and thrombocytopenia (6%).[132]

A single-center, retrospective review reported on 20 patients with advanced SBA who were treated with taxane-based therapy (either as single therapy or in combination).[133] Of these cases, 30% showed disease response, 35% showed stable disease, and 35% showed progression. Median time to progression was 3.8 months (95% CI, 2.9–4.6) and median OS was 10.7 months (95% CI, 3.1–18.3). Based on these data, taxanebased chemotherapy is a recommended option for second- or subsequent-line therapy, although only nab-paclitaxel has prospective, published data to support its use for treatment of SBA.

FOLFIRI as Subsequent-line Therapy

A retrospective, multicenter study evaluated the efficacy of FOLFIRI as second-line therapy for patients with advanced SBA who had received platinum-based chemotherapy in the first-line setting.[134] Of the 28 patients who fit this treatment paradigm, the ORR was 20% and disease control rate was 52%. The median PFS and OS were 3.2 and 10.5 months. Grade 3–4 toxicity was reported in 48% of patients. Based on these data, FOLFIRI is recommended as a treatment option for second- or subsequent-line treatment of advanced SBA.

Larotrectinib as Subsequent-line Therapy

A pooled analysis of 3 studies (a phase 1 including adults, a phase 1/2 involving children, and a phase 2 involving adolescents and adults) studied the safety and efficacy of larotrectinib in patients with NTRK gene fusion-positive tumors, including 4 patients with colon cancer and 1 with cancer of the appendix.[135] For the whole population, the ORR was 75% (95% CI, 61%–85%) by independent review and 80% (95% CI, 67%–90%) by investigator assessment. Larotrectinib was found to be well-tolerated as the majority (93%) of adverse events were grades 1 or 2 and no treatment-related adverse events of grades 3 or 4 occurred in more than 5% of patients.[135] Based on these data, the FDA approved larotrectinib for metastatic solid tumors with NTRK gene fusion and no satisfactory alternative treatments on November 26, 2018.[136]

33. Aparicio T, Svrcek M, Zaanan A, et al. Small bowel adenocarcinoma phenotyping, a clinicobiological prognostic study. Br J Cancer 2013;109:3057-3066. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24196786.

34. Schrock AB, Devoe CE, McWilliams R, et al. Genomic profiling of small-bowel adenocarcinoma. JAMA Oncol 2017;3:1546-1553. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28617917.

109. Czaykowski P, Hui D. Chemotherapy in small bowel adenocarcinoma: 10-year experience of the British Columbia Cancer Agency. Clin Oncol (R Coll Radiol) 2007;19:143-149. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17355111.

110. Jigyasu D, Bedikian AY, Stroehlein JR. Chemotherapy for primary adenocarcinoma of the small bowel. Cancer 1984;53:23-25. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6690001.

111. Zhang L, Wang LY, Deng YM, et al. Efficacy of the FOLFOX/CAPOX regimen for advanced small bowel adenocarcinoma: a three-center study from China. J BUON 2011;16:689-696. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22331723.

112. Aydin D, Sendur MA, Kefeli U, et al. Evaluation of prognostic factors and treatment in advanced small bowel adenocarcinoma: report of a multiinstitutional experience of Anatolian Society of Medical Oncology (ASMO). J BUON 2016;21:1242-1249. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27837629.

113. Pedersen K, Smyrk TC, Harrington S, McWilliams RR. Programmed death-ligand 1 (PD-L1) expression in small bowel adenocarcinomas (SBA) [abstract]. J Clin Oncol 2015;33:3619-3619. Available at: http://ascopubs.org/doi/abs/10.1200/jco.2015.33.15_suppl.3619.

114. Thota R, Gonzalez RS, Berlin J, et al. Could the PD-1 pathway be a potential target for treating small intestinal adenocarcinoma? Am J Clin Pathol 2017;148:208-214. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28821192.

115. Laforest A, Aparicio T, Zaanan A, et al. ERBB2 gene as a potential therapeutic target in small bowel adenocarcinoma. Eur J Cancer 2014;50:1740-1746. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24797764.

116. Takayoshi K, Kusaba H, Uenomachi M, et al. Suggestion of added value by bevacizumab to chemotherapy in patients with unresectable or recurrent small bowel cancer. Cancer Chemother Pharmacol 2017;80:333342. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28653251.

117. Gulhati P, Raghav K, Shroff R, et al. Phase II study of panitumumab in RAS wild-type metastatic adenocarcinoma of small bowel or ampulla of Vater. Oncologist 2018;23:277-e226. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29259073.

118. Overman MJ, Varadhachary GR, Kopetz S, et al. Phase II study of capecitabine and oxaliplatin for advanced adenocarcinoma of the small bowel and ampulla of Vater. J Clin Oncol 2009;27:2598-2603. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19164203.

119. Xiang XJ, Liu YW, Zhang L, et al. A phase II study of modified FOLFOX as first-line chemotherapy in advanced small bowel

adenocarcinoma. Anticancer Drugs 2012;23:561-566. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22481063.

120. Horimatsu T, Nakayama N, Moriwaki T, et al. A phase II study of 5fluorouracil/L-leucovorin/oxaliplatin (mFOLFOX6) in Japanese patients with metastatic or unresectable small bowel adenocarcinoma. Int J Clin Oncol 2017;22:905-912. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28536826.

121. Gibson MK, Holcroft CA, Kvols LK, Haller D. Phase II study of 5fluorouracil, doxorubicin, and mitomycin C for metastatic small bowel adenocarcinoma. Oncologist 2005;10:132-137. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15709215.

122. Tsushima T, Taguri M, Honma Y, et al. Multicenter retrospective study of 132 patients with unresectable small bowel adenocarcinoma treated with chemotherapy. Oncologist 2012;17:1163-1170. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22622149.

123. Zaanan A, Costes L, Gauthier M, et al. Chemotherapy of advanced small-bowel adenocarcinoma: a multicenter AGEO study. Ann Oncol 2010;21:1786-1793. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20223786.

124. McWilliams RR, Foster NR, Mahoney MR, et al. North Central Cancer Treatment Group N0543 (Alliance): A phase 2 trial of pharmacogenetic-based dosing of irinotecan, oxaliplatin, and capecitabine as first-line therapy for patients with advanced small bowel adenocarcinoma. Cancer 2017;123:3494-3501. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28493308.

125. Gulhati P, Raghav K, Shroff RT, et al. Bevacizumab combined with capecitabine and oxaliplatin in patients with advanced adenocarcinoma of the small bowel or ampulla of vater: A single-center, open-label, phase 2 study. Cancer 2017;123:1011-1017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27859010.

126. Aydin D, Sendur MA, Kefeli U, et al. Evaluation of bevacizumab in advanced small bowel adenocarcinoma. Clin Colorectal Cancer 2017;16:78-83. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27247089.

127. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509-2520. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26028255.

128. U.S. Food and Drug Administration. FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication. 2017. Available at: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm5600 40.htm. Accessed January 8, 2019.

129. Pedersen K, Foster N, Overman M, et al. ZEBRA: an ACCRU/IRCI multicenter phase 2 study of pembrolizumab in patients with advanced small bowel adenocarcinoma (SBA) [abstract]. Wold Congress on Gastrointestinal Cancer 2019; Abstract # O-007. Available at: https://www.oncnet.com/meeting-materials/world-congressgastrointestinal-cancer/3823.

130. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instabilityhigh colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol 2017;18:1182-1191. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28734759.

131. Overman MJ, Lonardi S, Wong KYM, et al. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repairdeficient/microsatellite instability-high metastatic colorectal cancer. J Clin Oncol 2018;36:773-779. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29355075.

132. Overman MJ, Adam L, Raghav K, et al. Phase II study of nabpaclitaxel in refractory small bowel adenocarcinoma and CpG island methylator phenotype (CIMP)-high colorectal cancer. Ann Oncol 2018;29:139-144. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29069279.

133. Aldrich JD, Raghav KPS, Varadhachary GR, et al. Retrospective analysis of taxane-based therapy in small bowel adenocarcinoma. Oncologist 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30598498.

134. Zaanan A, Gauthier M, Malka D, et al. Second-line chemotherapy with fluorouracil, leucovorin, and irinotecan (FOLFIRI regimen) in patients with advanced small bowel adenocarcinoma after failure of first-line platinum-based chemotherapy: a multicenter AGEO study. Cancer 2011;117:1422-1428. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21425142.

135. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. N Engl J Med 2018;378:731-739. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29466156.

136. U.S. Food and Drug Administration. FDA approves larotrectinib for solid tumors with NTRK gene fusions. 2018. Available at: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm6267 20.htm. Accessed November 30, 2018.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 1 of 12, Monat 2021) am 19.01.2021

#	Suchfrage
1	[mh ^"intestinal neoplasms"]
2	[mh "Duodenal Neoplasms"]
3	[mh "Ileal Neoplasms"]
4	[mh "Jejunal Neoplasms"]
5	[mh "Cecal Neoplasms"]
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7	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesions* OR malignan* OR carcinoid OR lymphoma):ti,ab,kw
8	#6 AND #7
9	(Intestin* AND (tumor OR tumors OR tumour* OR carcinoma* OR adenocarcinoma* OR neoplas* OR sarcoma* OR cancer* OR lesions* OR malignan* OR carcinoid OR lymphoma)):ti
10	#1 OR #2 OR #3 OR #4 OR #5 OR #8 OR #9
11	#10 with Cochrane Library publication date from Jan 2016 to Jan 2021, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 19.01.2021

#	Suchfrage
1	Intestinal Neoplasms[mh:noexp]
2	Duodenal Neoplasms[mh]
3	Ileal Neoplasms[mh]
4	Jejunal Neoplasms[mh]
5	Cecal Neoplasms[mh]
6	Carcinoid Tumors, Intestinal[nm]
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8	tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR neoplas*[tiab] OR sarcoma*[tiab] OR cancer*[tiab] OR lesions*[tiab] OR malignan*[tiab] OR carcinoid[tiab] OR lymphoma[tiab]
9	#7 AND #8
10	Intestin*[ti] AND (tumor[ti] OR tumors[ti] OR tumour*[ti] OR carcinoma*[ti] OR adenocarcinoma*[ti] OR neoplas*[ti] OR sarcoma*[ti] OR cancer*[ti] OR lesions*[ti] OR malignan*[ti] OR carcinoid[ti] OR lymphoma[ti])
11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #9 OR #10

#	Suchfrage
12	(#11) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
13	(#12) AND ("2016/01/01"[PDAT] : "3000"[PDAT])
14	(#13) NOT "The Cochrane database of systematic reviews"[Journal]
15	(#14) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 19.01.2021

#	Suchfrage
1	Intestinal Neoplasms[mh:noexp]
2	Duodenal Neoplasms[mh]
3	Ileal Neoplasms[mh]
4	Jejunal Neoplasms[mh]
5	Cecal Neoplasms[mh]

#	Suchfrage
6	Carcinoid Tumors, Intestinal[nm]
7	((Small[tiab] AND (intestine[tiab] OR intestinal[tiab] OR bowel[tiab])) OR Duoden*[tiab] OR Ileal[tiab] OR ileum[tiab] OR Jejunal[tiab] OR jejunum[tiab] OR cecal[tiab] OR cecum[tiab])
8	tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR neoplas*[tiab] OR sarcoma*[tiab] OR cancer*[tiab] OR lesions*[tiab] OR malignan*[tiab] OR carcinoid[tiab] OR lymphoma[tiab]
9	#7 AND #8
10	Intestin*[ti] AND (tumor[ti] OR tumors[ti] OR tumour*[ti] OR carcinoma*[ti] OR adenocarcinoma*[ti] OR neoplas*[ti] OR sarcoma*[ti] OR cancer*[ti] OR lesions*[ti] OR malignan*[ti] OR carcinoid[ti] OR lymphoma[ti])
11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #9 OR #10
12	(#11) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
13	(#12) AND ("2016/01/01"[PDAT] : "3000"[PDAT])
14	(#13) NOT (retracted publication [pt] OR retraction of publication [pt])

Referenzen

1. **Meijer LL, Alberga AJ, de Bakker JK, van der Vliet HJ, Le Large TYS, van Grieken NCT, et al.** Outcomes and treatment options for duodenal adenocarcinoma: a systematic review and meta-analysis. Ann Surg Oncol 2018;25(9):2681-2692.
2. **National Comprehensive Cancer Network (NCCN).** Small Bowel Adenocarcinoma: NCCN Evidence Blocks; Version 2.2020 [online]. Plymouth Meeting (USA): NCCN; 2020. [Zugriff: 15.01.2021]. (NCCN Clinical Practice Guidelines in Oncology). URL: https://www.nccn.org/professionals/physician_gls/pdf/small_bowel_blocks.pdf.
3. **Nishikawa Y, Hoshino N, Horimatsu T, Funakoshi T, Hida K, Sakai Y, et al.** Chemotherapy for patients with unresectable or metastatic small bowel adenocarcinoma: a systematic review. Int J Clin Oncol 2020;25(8):1441-1449.

Gemeinsamer Bundesausschuss

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

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