Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

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

Vorgang: 2024-B-296-z Repotrectinib

Stand: Januar 2025

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

Entrectinib
[zur Behandlung von NTRK-Fusions-positiven soliden Tumoren]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	- Chirurgische Resektion
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: - Entrectinib (Beschlüsse vom 18.02.2021 und 06.02.2025) - Larotrectinib (Beschluss vom 02.04.2020)
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:	
Repotrectinib L01EX28 Augtyro	<u>Zugelassenes Anwendungsgebiet:</u> Repotrectinib ist als Monotherapie zur Behandlung von fortgeschrittenen soliden Tumoren mit NTRK-Genfusion bei Erwachsenen und pädiatrischen Patienten ab 12 Jahren indiziert, - die zuvor einen NTRK-Inhibitor erhalten haben oder - die bisher keinen NTRK-Inhibitor erhalten haben und bei denen Therapieoptionen, die nicht auf NTRK abzielen, einen begrenzten klinischen Nutzen bieten oder ausgeschöpft sind
Entrectinib L01EX14 Rozlytrek	<u>Neurothrophe Tyrosin-Rezeptor-Kinase (NTRK)-Genfusion</u> Rozlytrek als Monotherapie wird zur Behandlung von erwachsenen und pädiatrischen Patienten älter als 1 Monat mit soliden Tumoren mit NTRK-Genfusion angewendet, - bei denen eine lokal fortgeschrittene oder metastasierte Erkrankung vorliegt oder eine Erkrankung, bei der eine chirurgische Resektion wahrscheinlich zu schwerer Morbidität führt, und - die bisher keinen NTRK-Inhibitor erhalten haben - für die keine zufriedenstellenden Therapieoptionen zur Verfügung stehen (siehe Abschnitte 4.4 und 5.1).
Larotrectinib L01EX12 Vitrakvi	VITRAKVI als Monotherapie wird zur Behandlung von erwachsenen und pädiatrischen Patienten mit soliden Tumoren mit einer neurotrophen Tyrosin-Rezeptor-Kinase (NTRK)-Genfusion angewendet, - bei denen eine lokal fortgeschrittene oder metastasierte Erkrankung vorliegt oder eine Erkrankung, bei der eine chirurgische Resektion wahrscheinlich zu schwerer Morbidität führt, und - für die keine zufriedenstellenden Therapieoptionen zur Verfügung stehen siehe Abschnitte 4.4 und 5.1).

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2024-B-296z (Repotrectinib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	20. Dezember 2024

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ALK	Anaplastic lymphoma kinase
AE	Adverse event
ASCO	American Society of Clinical Oncology
ATC	Anaplastic thyroid cancer
BTC	Biliary tract cancer
CCA	Cholangiocarcinoma
CRS	Colorectal cancers
DGP	Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin
DKG	Deutsche Krebsgesellschaft
DOR	Duration of response
ECRI	Emergency Care Research Institute
ESMO	European Society for Medical Oncology
FDA	U.S. Food and Drug Administration
GB	Glioblastom
G-BA	Gemeinsamer Bundesausschuss
GEINO	Spanish Group of Investigation in Neuro-Oncology
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HCC	Hepatocellular Carcinoma
HER2	Human Epidermal Ggrowth Factor Receptor 2
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI/CI	Konfidenzintervall
LoE	Level of Evidence
MTC	Medullary thyroid cancer
NCCN	National Comprehensive Cancer Network
NGS	Next-generation sequencing
NICE	National Institute for Health and Care Excellence
NSCLC	Non–Small-Cell Lung Cancer
NTRK	Neurotropher Tyrosinkinaserezeptor
OR	Odds Ratio
ORR	Objektive Ansprechrate

PDTC	Poorly differentiated thyroid cancer
PFS	Progressionsfreies Überleben
PS	Performance status
PTC	Papillary thyroid cancer
RCT	Randomized clinical trial
RET	Rezeptortyrosinkinase
RR	Relatives Risiko
SBA	Small Bowel Adenocarcinoma
SC	Secretory carcinomas
SEOM	Spanish Society of Medical Oncology
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
TKI	Tyrokinase-Inhibitor
TRK	Tropomyosinrezeptorkinasen
WHO	World Health Organization

1 Indikation

Behandlung von erwachsenen und pädiatrischen Patienten ab 12 Jahren mit lokal fortgeschrittenen oder metastasierten NTRK-Fusions-positiven Tumoren.

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

2 Systematische Recherche

Es wurde eine orientierende Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zu den Indikationen Tumore mit Expression einer neurotrophen Tyrosinrezeptorkinase (NTRK)-Genfusion, sekretorisches Mammakarzinom, Fibrosarkom, sekretorisches mamma-analoges Speicheldrüsenkarzinom, pigmentierter Spindelzellnävus Reed, pleomorphes Adenom, papilläres Schilddrüsenkarzinom, differenziertes Schilddrüsenkarzinom, konnatales mesoblastisches Nephrom, Gliom und Mukoepidermoidkarzinom durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen nach NTRK-Genfusion, Larotrectinib und Entrectinib sowie weiterer Indikationen (nicht-kleinzelliges Lungenkarzinom (NSCLC); Bauchspeicheldrüsenkarzinom und Kolorektalkarzinom).

Die Erstrecherche wurde am 24.02.2023 durchgeführt, die folgenden am 15.01.2024 und 04.12.2024. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 2903 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 23 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten Quellen identifiziert.

3.2 Systematische Reviews

Es wurden keine relevanten Quellen identifiziert.

3.3 Leitlinien

Leitlinienprogramm Onkologie, 2024 [5].

Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin (DGP); Deutsche Krebsgesellschaft vertreten durch Ihre Arbeitsgemeinschaften (DKG)

Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms

Zielsetzung/Fragestellung

Ziele der vorliegenden S3-Leitlinie sind:

- Unterstützung von Ärzten, betroffenen Patienten und Bürgern mit einem erhöhten Risiko für ein Lungenkarzinom bei medizinischen Entscheidungen durch evidenzbasierte und formal konsentierte Empfehlungen
- Schaffung einer Grundlage für inhaltlich gezielte ärztliche Aus-, Fort- und Weiterbildungsmaßnahmen
- flächendeckende Umsetzung einer multidisziplinären, qualitätsgesicherten und sektorübergreifenden Versorgung des Lungenkarzinoms
- Optimierung der Diagnosekette und der stadiengerechten Therapie sowohl bei der Ersterkrankung als auch beim Rezidiv bzw. bei einer Metastasierung

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium zutreffend;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz dargelegt;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Jährliche Überprüfung der Aktualität. Diese Version der S3-Leitlinie ist bis zur nächsten Aktualisierung gültig maximal jedoch 5 Jahre. Vorgesehen sind zukünftig jedoch jährliche Überprüfungen der Aktualität und Anpassungen bei dringendem Änderungsbedarf.

LoE

- Bei der Ersterstellung Leitlinie (2006-2010) wurde für die Graduierung der Evidenz das in der folgenden Tabelle aufgeführte System des Oxford Centre for Evidence-based Medicine in der Version von 2001verwendet. Die in den Empfehlungen aus 2010 aufgeführten Level of Evidence beziehen sich auf dieses Schema.

GoR

- Bei den im Rahmen der Aktualisierung 2013-2018 konsentierten Empfehlungen kamen die in Tabelle 6 aufgeführten, in den OL-Leitlinien etablierten, Empfehlungsstärken zur Anwendung. Diese spiegeln sich auch in den Formulierungen der Empfehlungen wider. Erläuterungen zur Festlegung der Empfehlungsstärken können dem Leitlinienreport entnommen werden

Tabelle 6: Schema der Empfehlungsgraduierung für Empfehlungen ab 2018

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

Tabelle 7: Kategorien der Konsensstärke

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

8.6.8 Systemtherapie bei Patienten mit NTRK-Fusion

8.139	Evidenzbasierte Empfehlung	geprüft 2024
Empfehlungsgrad **A**	Patienten mit NSCLC Stadium IV mit nachgewiesener NTRK 1-3 Fusion soll eine Therapie mit Larotrectinib oder Entrectinib angeboten werden.	
Level of Evidence **3b**	[1175]	
	Starker Konsens	

8.140	Konsensbasierte Empfehlung	geprüft 2024
EK	Bei oligoprogredienten Fällen soll die Möglichkeit einer Lokaltherapie interdisziplinär geprüft werden. Wegen der Möglichkeiten der lokalen Therapie bei ZNS-Metastasen sollte eine regelmäßige Bildgebung des ZNS, auch bei asymptomatischen Patienten, alle 3-9 Monate erfolgen.	
	Starker Konsens	

Hintergrund

Genfusionen, die die NTRK (neurotropher Tyrosinkinaserezeptor) 1-3 Gene betreffen und zur Aktivierung der Tropomyosinrezeptorkinasen 1-3 (TRK 1-3,) führen, finden sich in einer Vielzahl von Krebserkrankungen. Beim fortgeschrittenen NSCLC liegt die Häufigkeit unter 1% (REF). Die TRK-Inhibitoren der 1. Generation Larotrectinib und Entrectinib sind tumoragnostisch für die Behandlung fortgeschrittener solider Tumore mit NTRK-Fusionen, die nicht reseziert werden können und für die keine bessere Behandlung zur Verfügung steht, zugelassen.

Der Zulassung von Larotrectinib lag die integrierte Auswertung von 3 frühen Studien (Phase I,II) zugrunde, in die insgesamt 55 Patienten (Kinder und Erwachsene) mit einem breiten Spektrum an fortgeschrittenen,

zumeist rezidivierten soliden Tumoren und NTRK1-3 Genfusionen eingeschlossen wurden [1198]. Die Ansprechrate betrug 75% (95% CI 61-85). Die PFS-Rate nach 12 Mon. betrug 67% (95%CI 58-76), das Gesamtüberleben nach 12 Mon. 88% (95% CI 83-94). Die Verträglichkeit war augezeichnet, nur wenige Grad 3,4 Toxizitäten wurden beobachtet. Erhöhte Leberwerte, Müdigkeit, Schwindel, gastrointestinale Symptome und Gewichtszunahme waren die häufigsten Nebenwirkungen. Ein spätere Subgruppenanalyse von Lungenkarzinompatienten (14, davon 7 mit ZNS-Metastasen) ergab eine ORR von 71% (95% CI 42-92) in allen Patienten und von 57% (95% CI 18-90) in den Patienten mit ZNS-Metastasen [1199].
Der Zulassung von Entrectinib lag ebenfalls die integrierte Auswertung von 3 Phase I-II Studien zugrunde [1200], in denen Entrectinib bei erwachsenen Patienten mit einer Vielzahl von Tumorerkrankungen evaluiert wurde. Bei 54 Patienten betrug die ORR 57% (95% CI 43-71), die Dauer des Ansprechens 10.1 Mon. (95% CI 7 – n.r.). Das Sicherheitsprofil war dem des Larotrectinib vergleichbar (s.o.). Die Subgruppenanalyse beim NSCLC (10 Pat.) ergab eine ORR von 70% (95% CI 34.8 – 93), beim intrakraniellen Ansprechen vom 67%. Das med. PFS betrug 14.9 Mon [1201].

Referenzen

1198. Drilon A, Laetsch T, Kummar S, DuBois S, Lassen U, Demetri G, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. N Engl J Med. 2018;378(8):731-739. URL: https://pubmed.ncbi.nlm.nih.gov/29466156/
1199. Drilon A, Oxnard G, Tan D, Loong H, Johnson M, Gainor J, et al. Efficacy of Selpercatinib in. N Engl J Med. 2020;383(9):813-824. URL: https://pubmed.ncbi.nlm.nih.gov/32846060/
1200. Doebele RC, Drilon A, Paz-Ares L, Siena S, Shaw AT, Farago AF, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol. 2020;21:271-282

American Society of Clinical Oncology, 2024 [1,21,23].

American Society of Clinical Oncology (ASCO) and Ontario Health (Cancer Care Ontario)

Therapy for Stage IV Non–Small-Cell Lung Cancer With Driver Alterations: ASCO Living Guideline

Zielsetzung/Fragestellung

This clinical practice guideline addresses one overarching clinical question with three subquestions: What systemic therapy treatment options should be offered to patients with stage IV NSCLC with driver alterations,depending on the subtype of the patient's cancer?

Methodik

Grundlage der Leitlinie

Update 2024 (Aktualisierung GoR)

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

Recherche/Suchzeitraum:

- The current recommendations were developed by using a systematic review of evidence identified through a targeted electronic literature search of PubMed from June 2018 through December 2021 to identify any trials meeting the inclusion criteria of the 2021 update, published since then, and clinical experience.
- *Version 2024.2:* Based on routine literature searches (up to August 22, 2024)

LoE/GoR

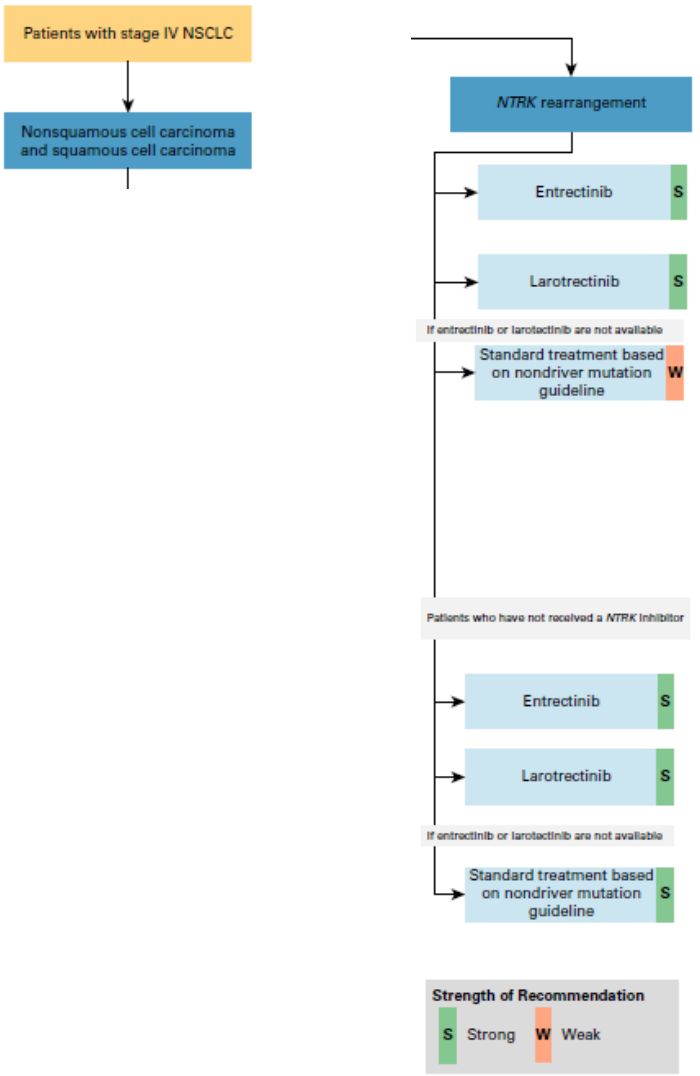
- The quality of the evidence for each outcome was assessed using the Cochrane Risk of Bias tool and elements of the GRADE quality assessment and recommendations development process.

Empfehlungen (2022)

What is the most effective second-line therapy for patients with stage IV NSCLC with a *NTRK* rearrangement and PS 0-2?	Recommendation 14.1: For patients with *NTRK* fusion previously treated with a NTRK inhibitor, clinicians may offer standard therapy following the non-driver mutation guideline (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate) Recommendation 14.2: For patients with *NTRK* fusion previously treated lung cancer who have not received an NTRK inhibitor, clinicians may offer entrectinib or larotrectinib (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate)

Empfehlungen (2024 Version 1 und 2)

Driver Alteration	Recommendation	Evidence Quality	Strength of Recommendation
NTRK rearrangement	2.15. For patients who have not received an *NTRK* inhibitor, clinicians should offer entrectinib or larotrectinib	Low	Strong
	2.16. If entrectinib or larotrectinib is not available, clinicians may offer standard therapy following the nondriver alteration guideline	Low	Strong



Bible K. C. et al., 2021 [2].

American Thyroid Association

American Thyroid Association Guidelines for Management of Patients with Anaplastic Thyroid Cancer

Zielsetzung/Fragestellung

The aim of these guidelines is to inform clinicians, patients, and researchers on published evidence relating to the diagnosis and management of Anaplastic thyroid cancer (ATC).

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- Ovid Medline In-Process and Other Non- Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. Databases were searched from inception to the date of the search (February 15, 2017, initially and updated in May 11, 2020), without restriction of publication date or language

LoE/GoR

- The quality and strength of the authors' recommendations based on the body of evidence were reported using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Group, GRADE workgroup system; a detailed description of the grading scheme has been published elsewhere (6). In this system, recommendations are classified as strong or conditional. Strong recommendations (''we recommend'') are those in which the panel is confident that the anticipated desirable effects of following a recommendation clearly outweigh undesirable effects and that the recommendation should be implemented into practice. Conditional recommendations (''we suggest'') are those in which the panel concludes that the anticipated desirable effects of following these recommendations probably outweigh undesirable effects, but is not confident about this conclusion and there may be reasonable alternative options for consideration in clinical practice.
- In the GRADE system, there are four categories of quality of evidence: high quality, moderate quality, low quality, and very low quality

RECOMMENDATION 23

In NTRK or RET fusion ATC patients with stage IVC disease, we suggest initiation of a TRK inhibitor (either larotrectinib or entrectinib) or RET inhibitor (either selpercatinib or pralsetinib), preferably in a clinical trial, if available.

Strength of Recommendation: Conditional

Quality of Evidence: Very Low

Hintergrund:
NTRK and RET fusions are rare events found in solid tumors—including in PTC, PDTC, and ATC—and are almost always mutually exclusive of other oncogenic driver mutations. Thus, in a patient without another candidate oncogenic driver, fusion testing should be performed. The TRK inhibitors, larotrectinib and entrectinib, are FDA approved for pediatric and adult patients with NTRK fusion, but not NTRK-mutated, solid tumors. While trials did enroll thyroid cancer patients, specific histologies were not teased out in initial reports. Thus, we recommend that patients who are able to participate in clinical trials with these drugs continue to do so until more data specifically relevant to response and progression-free survival in ATC patients with NTRK fusions are available. If a trial is not available, consideration of commercial use of the drug is recommended if available, with parallel close monitoring for PD. Currently, clinical trials with selective NTRK inhibitors are ongoing (e.g., NCT02576431, NCT02122913, NCT02568267, NCT02650401). Larotrectinib is an inhibitor of TRK 1–3 and was studied in 55 patients with NTRK fusion solid tumors, of whom 5 had thyroid cancer (histologies not specified) (267). All thyroid cancer patients achieved a response (four PR and one CR), but it is unclear whether any of these were ATCs. Entrectinib also inhibits TRK 1–3 but in addition also inhibits the ALK and ROS1 tyrosine kinases, and is also approved for NTRK fusion solid tumors. Five thyroid cancer patient were included in the clinical trial that led to the FDA approval, however, histologies were not specified (268). One of five thyroid cancer patients achieved a PR to therapy. ROS1 fusions, which are exceedingly rare in PTC, are likely also seen in ATC, in very rare instances. A case of a patient with PTC successfully treated with entrectinib has been reported (269). Clinical trials for ROS1 fusion thyroid cancers should be sought, if available. The selective RET inhibitor, selpercatinib, is also now FDA approved as of May 2020 for patients with RET fusion thyroid and lung cancer, as well as for patients with RETmutated MTC. This approval was based on the results of a phase 1/2 trial that enrolled 170 thyroid cancer patients, of
whom 19 had RET fusion thyroid cancer (270). Only two ATC patients were enrolled in the trial and one of these patients responded for 18 months to selpercatinib. Given the sparse data in ATC with respect to selective RET inhibitors, we recommend their use in ATC in the clinical trial setting. ALK fusions are very rare in ATC and there is only case report of patients with ALK fusion who were successfully treated with ALK inhibitors (120,271). Again, given limited information, ALK inhibitors are preferably used in a clinical trial setting.

Referenzen:
120. Godbert Y, Henriques de Figueiredo B, Bonichon F, et al. 2015 Remarkable response to crizotinib I woman with anaplastic lymphoma kinase-rearranged anaplastic thyroid carcinoma. J Clin Oncol 33:e84–e87.
267. Drilon A, Laetsch TW, Kummar S, et al. 2018 Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 378:731–739.
268. Doebele RC, Drilon A, Paz-Ares L, et al. 2020 Entrectinib in patients with advanced or metastatic NTRK fusionpositive solid tumours: integrated analysis of three phase 1–2 trials. Lancet Oncol 21:271–282.
269. Liu SV, Macke LA, Colton BS, et al. 2017 Response to entrectinib in differentiated thyroid cancer with a ROS1 fusion. JCO Precis Oncol 1, PO.17.00105.
270. Wirth LJ, Sherman E, Robinson B, et al. 2020 Efficacy of selpercatinib in RET-altered thyroid cancers. N Engl J Med 383:825–835.
271. Leroy L, Bonhomme B, Le Moulec S, et al. 2020 Remarkable response to ceritinib and brigatinib in an anaplastic lymphoma kinase-rearranged anaplastic thyroid carcinoma previously treated with crizotinib. Thyroid 30: 343–344.

Geiger J.L. et al., 2021 [4].

American Society of Clinical Oncology (ASCO)

Management of salivary gland malignancy

Zielsetzung/Fragestellung

To provide evidence-based recommendations for practicing physicians and other healthcare providers on the management of salivary gland malignancy

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- The recommendations were developed by using an SR (January 2000-December 2020) of SRs, phase III randomized clinical trials (RCTs), observational studies, and clinical experience.

LoE

Table 1. Definitions for Quality of Evidence Grades[7]

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

GoR

- Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like “must,” “must not,” “should,” and “should not” indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases.

Recommendation 6.5

For patients with nonadenoid cystic salivary gland cancer who are candidates for initiation of systemic therapy, targeted therapy based on tumor molecular alterations (ie, AR, HER2, and NTRK) may be offered if a clinical trial is not available (Type: evidence based; Evidence quality: low; Strength of recommendation: moderate).

Hintergrund
Patients with secretory carcinomas (SCs) of the salivary glands, harboring NTRK gene fusion without a known acquired resistance mutation, may be offered first-line or subsequent-line NTRK inhibitor therapy rather than chemotherapy, given the high response rates and favourable toxicity profile. In a combined analysis of two phase I and one phase II studies of larotrectinib in patients with advanced NTRK fusion–positive cancers, objective responses were observed in 18 of 20 patients (90%) with NTRK fusion–positive SC of the salivary glands (median duration of response 35 months).[350] In a pooled analysis of two phase I and one phase II trials, seven patients with NTRK fusion–positive SC received entrectinib and 86% had an objective response.[351]

Referenzen:
350. Hong DS, DuBois SG, Kummar S, et al: Larotrectinib in patients with TRK fusion-positive solid tumours: A pooled analysis of three phase 1/2 clinical trials. Lancet Oncol 21:531-540, 2020
351. Doebele RC, Drilon A, Paz-Ares L, et al: Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: Integrated analysis of three phase 1-2 trials. Lancet Oncol 21:271-282, 2020

Segura P.P. et al., 2023 [22].

GEINO (Spanish Group of Investigation in Neuro-Oncology) and SEOM (Spanish Society of Medical Oncology)

SEOM-GEINO clinical guidelines for high-grade gliomas of adulthood

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz für NTRK-Fusions-positive Gliome, wird die LL jedoch ergänzend dargestellt

Grundlage der Leitlinie

- Repräsentatives Gremium teilweise zutreffend (keine Patientenvertretung ersichtlich);
- Interessenkonflikte und finanzielle Unabhängigkeit teilweise zutreffend;
- Systematische Suche, Auswahl und Bewertung der Evidenz nicht explizit dargelegt;
- Formale Konsensusprozesse und externes Begutachtungsverfahren nicht explizit dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist teilweise über den Hintergrundtext dargestellt;
- Regelmäßige Überprüfung der Aktualität trifft nicht zu.

Recherche/Suchzeitraum:

- This guideline is based on a systematic review of relevant published studies

LoE/ GoR:

- The Infectious Diseases Society of America-US Public Health Service Grading System for Ranking Recommendations in Clinical Guidelines has been used to assign levels of evidence and grades of recommendation

Empfehlung

Targeted therapies have not been approved for GB recurrence in our country; nevertheless, we recommend screening for BRAF mutations and NTRK fusions. BRAF inhibitors + MEK inhibitors could be a treatment option in cases of brain tumors harboring the BRAF V600E mutation (II, B), as well as Larotrectinib in patients with brain tumors and NTRK fusions (II, B).

Hintergrund:
For those harboring NTRK fusions, preliminary and exploratory data from early basket trials with NTRK inhibitors (larotrectinib and entrectinib) pointed toward a favourable safety profile and potential benefit in terms of response [63,64].

Referenzen:
63. Rangaraju S, Farago A, Heym KM, Ahn M, Drilon A, Potts S, et al. Preclinical and clinical efficacy of entrectinib in primary and metastatic brain tumors harboring NTRK, ROS1, or ALK gene fusions. Neuro Oncol. 2017;19:106.
64. Doz F, Tilburg CM Van, Geoerger B, Højgaard M, Øra I, BoniV, et al. Efficacy and safety of larotrectinib in TRK fusionpositive primary central nervous system tumors. Neuro Oncol. 2022;24(6):997–1007

NCCN, 2024 [7].

National Comprehensive Cancer Network

Central Nervous System Cancers, vers. 3.2024

Zielsetzung/Fragestellung

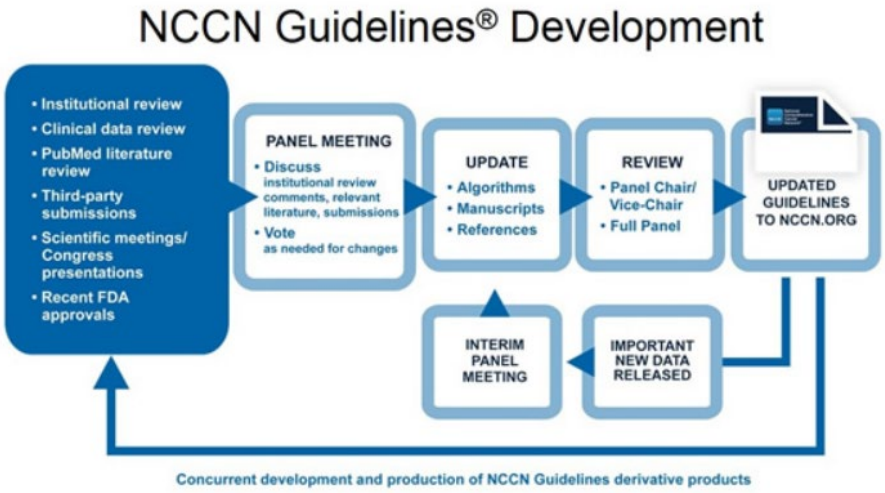
The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche wird beschrieben, keine Angaben bezüglich Auswahl und Bewertung der Evidenz; Es werden auch weitere Evidenzquellen außerhalb der systematischen Suche als Grundlage für LL-Empfehlungen herangezogen
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie anhand von Behandlungspfaden, die Verbindung zu der zugrundeliegenden Evidenz ist nicht immer klar ersichtlicht;
- Regelmäßige Überprüfung der Aktualität gesichert.



Recherche/Suchzeitraum:

- Pubmed Recherche, Zeitpunkt unklar

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.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Empfehlungen

CIRCUMSCRIBED GLIOMA: SYSTEMIC THERAPY OPTIONS

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Adjuvant Treatment	• None	• None	• PA, circumscribed ganglioglioma/neuroglioma/glioneuronal tumor, PXA (grade 2) with *BRAF* V600E activation mutation ‣ BRAF/MEK inhibitors: ◊ Dabrafenib/trametinib[4,5] ◊ Vemurafenib/cobimetinib[6,7] • SEGA ‣ mTOR inhibitor (eg, everolimus)[8,9]
Recurrent[a] or Progressive Disease	• None	• RT + adjuvant PCV[b,c] • RT + adjuvant TMZ[c] • RT + concurrent and adjuvant TMZ[c] • TMZ[d,1,2] • Lomustine or carmustine • PCV[b,3]	• *NTRK* gene fusion tumors ‣ Larotrectinib[10] ‣ Entrectinib[11] ‣ Repotrectinib (category 2B)[12] • BRAF V600E activation mutation ‣ BRAF/MEK inhibitors: ◊ Dabrafenib/trametinib[4,5] ◊ Vemurafenib/cobimetinib[6,7] • *BRAF* fusion or *BRAF* V600E activating mutation or in *NF1*-mutated glioma ‣ MEK inhibitor ◊ Selumetinib[13] • PAs ‣ Cisplatin/etoposide[14] ‣ Carboplatin[15] ‣ Carboplatin + vincristine (category 2B)[16] ‣ Thioguanine + PCV[b] (category 2B)[16,17]

GLIOBLASTOMA: SYSTEMIC THERAPY OPTIONS[o]

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Adjuvant Treatment, KPS ≥60	• RT + concurrent and adjuvant TMZ[45,46] ± tumor treating fields (TTF)[p,47]	• None	• TMZ (for patients with MGMT promoter-methylated or indeterminate tumors and age >70 years)[45,64] • Standard RT + concurrent and adjuvant lomustine and TMZ (for patients with MGMT promoter-methylated or indeterminate tumors and age ≤70 years) (category 2B)[q,65]
Adjuvant Treatment, KPS <60	• None	• None	• Hypofractionated RT + concurrent or adjuvant TMZ (for patients aged ≤70 years)[j,66] • TMZ (for patients with MGMT promoter-methylated tumors)[64]
Recurrent or Progressive Disease[e,m,n]	• Bevacizumab[g,h,48-51] • TMZ[2,25,52,53] • Lomustine or carmustine[54-57] • PCV[b,58,59] • Regorafenib[60]	• Systemic therapy[m] + bevacizumab[g,h] ‣ Carmustine or lomustine + bevacizumab[g,h,61] ‣ TMZ + bevacizumab[g,h,62,63]	• If disease progression or intolerance to the preferred or other recommended regimens ‣ Etoposide (category 2B)[38] ‣ Platinum-based regimens[r,40-42] (category 3) • *NTRK* gene fusion tumors ‣ Larotrectinib[10] ‣ Entrectinib[11] ‣ Repotrectinib (category 2B)[12] • *BRAF* V600E activation mutation ‣ BRAF/MEK inhibitors: ◊ Dabrafenib/trametinib[4,5] ◊ Vemurafenib/cobimetinib[6,7]

*10 Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. Lancet Oncol 2020;21:531-540.

11 Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2
trials. Lancet Oncol 2020;21:271-282.
12 Solomon BJ, Drilon A, Lin JJ, et al. Repotrectinib in patients (pts) with NTRK fusion-positive (NTRK+) advanced solid tumors, including NSCLC: update from the
phase I/II TRIDENT-1 trial. Annals of Oncology 2023;34:S755-S851.

NCCN, 2024 [3].

National Comprehensive Cancer Network

Pediatric Central Nervous System Cancers, Version 2.2023

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt.

*Grundlage der Leitlinie, Recherche/Suchzeitraum, LoE / GoR ist der zuvor dargestellten NCCN-LL „*Central Nervous System Cancers“ *[7] zu entnehmen*

Empfehlungen

PRINCIPLES OF SYSTEMIC THERAPY[a,b]
(PARTICIPATION IN A CLINICAL TRIAL IS STRONGLY ENCOURAGED)

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Adjuvant Therapy	RT + concurrent TMZ + adjuvant TMZ + lomustine[1]	RT + concurrent TMZ + adjuvant TMZ[2] Age <3 years: • Chemotherapy only ▸ Cyclophosphamide/vincristine/cisplatin/etoposide[3] ▸ Vincristine/carboplatin/TMZ[4] • Targeted therapy only ▸ Targeted therapy including, but not limited to the following: – If *BRAF* V600E mutated: ▪ Dabrafenib/trametinib[5] ▪ Vemurafenib[6] – If *TRK* fusion-positive: ▪ Larotrectinib[7] ▪ Entrectinib[8] – If hypermutant tumor: ▪ Nivolumab[9,10] ▪ Pembrolizumab[11]	RT ± concurrent TMZ[1,2] + adjuvant targeted therapy including, but not limited to the following: If *BRAF* V600E mutated: • Dabrafenib/trametinib[5] • Vemurafenib[6] If *TRK* fusion-positive: • Larotrectinib[7] • Entrectinib[8] If hypermutant tumor: • Nivolumab[9,10] • Pembrolizumab[11]
Recurrent or Progressive Disease	Targeted therapy including, but not limited to the following: If *BRAF* V600E mutated: • Dabrafenib/trametinib[5] • Vemurafenib[6] If *TRK*-fusion positive: • Larotrectinib[7] • Entrectinib[8] If hypermutant tumor: • Nivolumab[9,10] • Pembrolizumab[11]	Reirradiation if feasible	For palliation: • Oral etoposide[12] • Bevacizumab[13,c] • Nitrosoureas (lomustine or carmustine)[1]

[a] Regimens and recommendations on this page are for those patients who elect not to participate in clinical trials.
[b] Monitor (labs and/or imaging) as clinically indicated.
[c] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

Hintergrund:
Gene fusions involving NTRK1, NTRK2, or NTRK3 encode for TRK fusion proteins (TRKA, TRKB, TRKC) which have increased kinase function and are implicated in the oncogenesis of many solid tumors.[95,96] The small-molecule TRK inhibitors larotrectinib and entrectinib have demonstrated activity in several trials of adults and children with various cancers.[97–100] In the multicenter phase I SCOUT trial, 24 pediatric and adolescent patients (aged 1 month to 21 years; median age, 4.5 years) with advanced solid or primary CNS tumors were treated with larotrectinib, regardless of TRK fusion status.[99] In patients with TRK-fusion positive tumors, the objective response rate (ORR) was 93% compared with 0% in patients without TRK fusion. In addition to a high ORR, larotrectinib was also well tolerated, with most patients experiencing only grade 1 adverse events and dose-limiting toxicity in one patient. The phase II part of this trial is currently ongoing and recruiting patients (ClinicalTrials.gov identifier: NCT02637687).
The phase I/II STARTRK-NG trial assessed the activity of entrectinib in 43 pediatric patients (aged,22 years) with solid tumors including primary CNS tumors, regardless of TRK fusion status.[98] In patients with TRK-

fusion–positive tumors, the ORR was 58%and the median duration of treatment was 11 months. The median duration of response was not reached. Treatment with entrectinib resulted in antitumor activity in patients with TRK-fusion–positive tumors; however, it also led to dose-limiting toxicities in 4 patients (9%). The most common treatment-related adverse events were weight gain (49%) and bone fractures (21%). The phase II part of this trial is currently ongoing (ClinicalTrials.gov identifier: NCT02650401).

Referenzen:
95. Gatalica Z, Xiu J, Swensen J, et al. Molecular characterization of cancers with NTRK gene fusions. Mod Pathol 2019;32:147–153.
96. Amatu A, Sartore-Bianchi A, Siena S. NTRK gene fusions as novel targets of cancer therapy across multiple tumour types. ESMO Open 2016;1:e000023.
97. 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.
98. Desai AV, Robinson GW, Gauvain K, et al. Entrectinib in children and young adults with solid or primary CNS tumors harboring NTRK, ROS1, or ALK aberrations (STARTRK-NG). Neuro Oncol 2022;24:1776–1789.
99. Laetsch TW, DuBois SG,Mascarenhas L, et al. Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: phase 1 results fromamulticentre, open-label, phase 1/2 study. LancetOncol 2018;19:705–714.
100. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:271–282.

NCCN, 2024 [18].

National Comprehensive Cancer Network

Soft Tissue Sarcoma, vers. 4.2024

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie, Recherche/Suchzeitraum, LoE / GoR ist der zuvor dargestellten NCCN-LL „Central Nervous System Cancers „[7] zu entnehmen

Empfehlungen

SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN SOFT TISSUE SARCOMA SUBTYPES[a,b,c,d] AND AGGRESSIVE SOFT TISSUE NEOPLASMS

Regimens Appropriate for General Soft Tissue Sarcoma[e,f]; see other sections for histology-specific recommendations[g]

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Neoadjuvant/ Adjuvant Therapy	• AIM (doxorubicin, ifosfamide, mesna)[1-4] • Ifosfamide, epirubicin, mesna[5]	• AD[1,2,10,11] for LMS, or if ifosfamide is not considered appropriate • Doxorubicin[1,2,6,7]	• Ifosfamide[5,7,21-25] • Trabectedin (for myxoid liposarcoma)[30] • Gemcitabine and docetaxel[21,22] (category 2B)
First-Line Therapy Advanced/ Metastatic	• Anthracycline-based regimens: ▸ Doxorubicin[1,2,6,7] ▸ Epirubicin[8] ▸ Liposomal doxorubicin[9] ▸ AD (doxorubicin, dacarbazine)[1,2,10,11,12] ▸ AIM[1-4,6] ▸ Ifosfamide, epirubicin, mesna[5] • *NTRK* gene fusion-positive sarcomas only (regardless of soft tissue sarcoma subtype) ▸ Larotrectinib[h,13] ▸ Entrectinib[i,14] ▸ Repotrectinib[15]	• Gemcitabine • Gemcitabine and docetaxel[21,22] (category 2B)	• Pazopanib[k,16] (patients ineligible for IV systemic therapy or patients who are not candidates for anthracycline-based regimens) • MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[1,2,31,32] • Trabectedin and doxorubicin (for LMS)[33,34] • Selpercatinib (for *RET* gene fusion-positive tumors)[35] (regardless of soft tissue sarcoma subtype) • Gemcitabine and dacarbazine[23] (category 2B)
Subsequent Lines of Therapy for Advanced/ Metastatic Disease	• Pazopanib[j,k,16] • Eribulin[j,17] (category 1) recommendation for liposarcoma, category 2A for other subtypes • Trabectedin[j,18-20] (category 1 recommendation for liposarcoma and LMS, category 2A for other subtypes) • Gemcitabine and docetaxel[21,22] • *NTRK* gene fusion-positive sarcomas only (regardless of soft tissue sarcoma subtype) ▸ Repotrectinib[15] (if not previously given)	• Dacarbazine[23] • Ifosfamide[5,7,22,24,25,26] • Temozolomide[j,27] • Vinorelbine[j,28] • Regorafenib[k,29] • Gemcitabine • Gemcitabine and dacarbazine[23]	• Gemcitabine and vinorelbine[24] (category 2B) • Gemcitabine and pazopanib[36] (category 2B) • Pembrolizumab[37,38] or nivolumab ± ipilimumab[39-42] ▸ For myxofibrosarcoma, UPS,[f] dedifferentiated liposarcoma, cutaneous angiosarcoma, and undifferentiated sarcomas OR ▸ For TMB-H (≥10 mutations/megabase [mut/Mb])[l] regardless of soft tissue sarcoma subtype • Pembrolizumab[43] ▸ For MSI-H or dMMR tumors[m] (regardless of soft tissue sarcoma subtype) • Cabozantinib[44] (category 2B) • Afamitresgene autoleucel[117] ▸ HLA-A*02:01P, HLA-A*02:02P, HLA-A*02:03P or HLA-A*02:06P positive and whose tumor expresses the MAGE-A4 antigen (synovial sarcomas only)

*13 Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusionpositive cancers in adult and children. N Engl J Med 2018;378:731-739.

14 Demetri GD, Paz-Ares L, Farago AF, et al. Efficacy and safety of entrectinib in patients with NTRK fusio positive tumours: pooled analysis of STARTRK-2, STARTRK-1 and ALKA-372-001. Presented at the European Society for Medical Oncology Meeting in Munich, Germany; October 12-23, 2018. Oral Presentation.
15 Solomon BJ, Drilon A, Lin JJ, et al. Repotrectinib in patients (pts) with NTRK fusion-positive (NTRK+) advanced solid tumors, including non-small cell lung cancer: update from the phase 1/2 TRIDENT-1 trial. Ann Oncol. 2023;34:S787-S788.
284. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:271-282. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31838007.

NCCN, 2024 [10].

National Comprehensive Cancer Network

Gastric Cancer, vers. 4.2024

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie, Recherche/Suchzeitraum, LoE / GoR ist der zuvor dargestellten NCCN-LL „Central Nervous System Cancers „[7] zu entnehmen.

Empfehlungen

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 (category 1)[46] • Fam-trastuzumab deruxtecan-nxki for HER2 overexpression positive adenocarcinoma[47] • Docetaxel (category 1)[40,41] • Paclitaxel (category 1)[36,37,48] • Irinotecan (category 1)[48-51] • Fluorouracil[a,i] and irinotecan[49,52,53] • Trifluridine and tipiracil for third-line or subsequent therapy (category 1)[54]
Other Recommended Regimens • Ramucirumab (category 1)[55] • Irinotecan and cisplatin[23,56] • Fluorouracil and irinotecan + ramucirumab[a,i,57] • Irinotecan and ramucirumab[58] • Docetaxel and irinotecan (category 2B)[59]
Useful in Certain Circumstances • Entrectinib, larotrectinib, or repotrectinib[k] for *NTRK* gene fusion-positive tumors[60-62] • Pembrolizumab[g,h] for MSI-H/dMMR tumors[63-65] • Nivolumab and ipilimumab[g,h] for MSI-H/dMMR tumors[20] • Pembrolizumab[g,h] for TMB high (≥10 mutations/megabase) tumors[66] • Dostarlimab-gxly[g,h,l] for MSI-H/dMMR tumors[31] • Dabrafenib and trametinib for *BRAF* V600E mutated tumors[67] • Selpercatinib for *RET* gene fusion-positive tumors[68]

[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.
[g] If no prior tumor progression while on therapy with a checkpoint inhibitor.
[h] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[i] Capecitabine may not be used interchangeably with fluorouracil in regimens containing irinotecan.
[k] Repotrectinib can be used in patients whose disease progressed on a prior NTRK targeted therapy.
[l] For patients whose cancer is progressing on or following prior treatment (that did not include a checkpoint inhibitor like PD-1i, PD-L1i, or CTLA4i) and who have no satisfactory alternative treatment options. Prior use of immuno-oncology therapy in these patients will make them ineligible for dostarlimab-gxly.

*60. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusionpositive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:271-282.
61. 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.
62. Solomon BJ, Drilon A, Lin JJ, et al. 1372P Repotrectinib in patients (pts) with NTRK fusionpositive (NTRK+) advanced solid tumors, including NSCLC: Update from the phase I/II TRIDENT-1 trial. Annals of Oncology 2023;34:S787-S788.

Hintergrund:
Gene fusions involving NTRK1, NTRK2, or NTRK3 encode TRK fusion proteins (TRKA, TRKB, TRKC), which have increased kinase function and are implicated in the oncogenesis of many solid tumors including head and neck, thyroid, soft tissue, lung, and colon.[319,334] Although believed to be extremely rare in gastroesophageal cancers, one case report provides evidence that NTRK gene fusions do occur in gastric adenocarcinoma and may be associated with an aggressive phenotype.[335-337] In 2018, the FDA granted accelerated approval of the TRK inhibitor larotrectinib for the treatment of adult and pediatric patients (aged 12 years and older) with solid tumors that have an NTRK gene fusion without a known acquired resistance mutation, that are either metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment.[323] This second-ever tissue-agnostic FDA approval for the treatment of patients with cancer was based on data from three multicenter single-arm clinical trials. Patients with prospectively identified NTRK gene fusion-positive cancers were enrolled into one of three protocols: a phase I trial involving adults (LOXO-TRK- 14001), a phase I–II trial involving children (SCOUT), and a phase II trial involving adolescents and adults (NAVIGATE).[319] A total of 55 patients with unresectable or metastatic solid tumors harboring an NTRK gene fusion who experienced disease progression following systemic therapy were enrolled across the three trials and treated with larotrectinib. The most common cancer types represented were salivary gland tumors (22%), soft tissue sarcoma (20%), infantile fibrosarcoma (13%), and thyroid cancer (9%). The ORR across the three trials was 75%, with a complete response rate of 22%. At a median follow-up of 9.4 months, 86% of the patients with a response were either continuing treatment with larotrectinib or had undergone curative-intent surgery. At 1 year, 71% of the responses were ongoing and 55% of the patients remained progression-free. Response duration was ≥6 months for 73%, ≥9 months for 63%, and ≥12 months for 39% of patients. At the time of data analysis, the median duration of response and PFS had not been reached. Adverse events were predominantly grade 1, the most common being increased aspartate aminotransferase (AST) levels, vomiting, constipation, and dizziness. The SCOUT (Clinical Trial ID: NCT02637687) and NAVIGATE (Clinical Trial ID: NCT02576431) trials are still actively recruiting patients with NTRK gene fusion-positive tumors. In 2019, the FDA approved the second TRK inhibitor, entrectinib, for the same indications as larotrectinib, as well as for adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ROS1- positive.[322] The approval of entrectinib for the treatment of NTRK gene fusion-positive tumors was based on data from three multicenter singlearm phase I and phase II clinical trials. A total of 54 patients aged 18 years or older with metastatic or locally advanced NTRK gene fusionpositive solid tumors were enrolled into one of the three protocols (ALKA- 372-001, STARTRK-1, and STARTRK-2).[318] The most common cancer types represented were sarcoma, NSCLC, mammary analogue secretory carcinoma, breast, thyroid, and colorectal. The ORR across the three trials was 57%, with a complete response rate of 7%. Response duration was ≥6 months for 68% of patients and ≥12 months for 45% of patients. The median duration of response was 10 months. The most common grade 3–4 treatment-related adverse events were increased weight and anemia while the most common serious treatment-related adverse events were nervous system disorders. STARTRK-2 (Clinical Trial ID: NCT02568267) is still actively recruiting patients with NTRK gene fusionpositive tumors. These data demonstrate that entrectinib and larotrectinib induce durable and clinically meaningful responses in patients with NTRK gene fusionpositive tumors with manageable safety profiles. Therefore, entrectinib and larotrectinib are recommended as second-line or subsequent treatment options for patients with NTRK gene fusion-positive gastric tumors.

Referenzen:
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NCCN, 2024 [17].

National Comprehensive Cancer Network

Small Bowel Adenocarcinoma, vers. 5.2024

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie, Recherche/Suchzeitraum, LoE / GoR ist der zuvor dargestellten NCCN-LL „Central Nervous System Cancers „[7] zu entnehmen

Empfehlungen

PRINCIPLES OF SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,c]

INITIAL THERAPY (pMMR/MSS)

Intensive Therapy Recommended

- FOLFOX[d] ± bevacizumab[e]
- CAPEOX[d] ± bevacizumab[e]
- FOLFIRI ± bevacizumab[e,f]
- FOLFIRINOX[d] ± bevacizumab[e]

Intensive Therapy NOT Recommended[g]

- 5-FU/LV ± bevacizumab[e]
- Capecitabine ± bevacizumab[e]

Initial Therapy if previous FOLFOX/ CAPEOX in the adjuvant setting within past 12 months or contraindication

- FOLFIRI ± bevacizumab[e]
- Taxane-based chemotherapy
- If *BRAF* V600E mutation-positive:
  - Dabrafenib + trametinib
- If TMB-high (≥10 mut/Mb)[h,i]:
  - Pembrolizumab (category 2B)

SECOND-LINE AND SUBSEQUENT THERAPY (if not previously given)

- FOLFOX[d] ± bevacizumab[e]
- CAPEOX[d] ± bevacizumab[e]
- FOLFIRI ± bevacizumab[e]
- Irinotecan
- Taxane-based chemotherapy
- If *BRAF* V600E mutation-positive:
  - Dabrafenib + trametinib
- If TMB-high (≥10 mut/Mb)[h,i]:
  - Pembrolizumab (category 2B)
- If *NTRK* gene fusion-positive:
  - Entrectinib
  - Larotrectinib
  - Repotrectinib[j]
- If *RET* gene fusion-positive:
  - Selpercatinib
- If HER2-amplified (IHC 3+)[k]:
  - Fam-trastuzumab deruxtecan-nxki
- If *KRAS* G12C mutation positive:
  - (Sotorasib or adagrasib)[l]
- Best supportive care

FOR ANY LINE OF THERAPY (if dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb])[h,i,m]

- Cemiplimab-rwlc
- Dostarlimab-gxly
- Nivolumab
- Nivolumab + ipilimumab
- Pembrolizumab
- Retifanlimab-dlwr
- Tislelizumab-jsgr
- Toripalimab-tpzi

*j On the TRIDENT-1 trial, repotrectinib showed activity both in NTRK TKI naïve and NTRK TKI-pretreated patients.

Hintergrund:
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.168 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 AEs were grades 1 or 2 and no treatment-related AEs of grades 3 or 4 occurred in >5% of patients.[168] An integrated analysis of three global phase I/II studies (ALKA-372-001, STARTRK-1, and STARTRK-2) tested the efficacy and safety of entrectinib in 54 adult patients with advanced or metastatic NTRK gene fusion-positive solid tumors.[169] For the whole population, ORR was 57% (95% CI, 43.2%–70.8%), median PFS was 11 months (95% CI, 8.0–14.9), and median OS was 21 months (95% CI, 14.9–not estimable) by independent review. Median duration of response was 10 months (95% CI, 7.1–not estimable). Of the four patients with CRC on this study, one was recorded as having a response. Notably, a similar ORR (50% vs. 60%) was

observed among those with central nervous system metastasis, indicating that entrectinib has activity in this population. Entrectinib was found to be well-tolerated as most treatment-related AEs were grade 1 or 2 and managed with dose reduction, leading few (4%) patients to discontinue therapy due to treatment-related AEs. The phase I/II TRIDENT-1 trial tested repotrectinib in two cohorts of patients with NTRK gene fusion-positive advanced solid tumors; 40 patients in the NTRK TKI-naïve cohort, who received repotrectinib as their first NTRK TKI treatment, and 48 patients in the NTRK TKI-pretreated cohort, who had already received larotrectinib or entrectinib.[170] One patient on the NTRK TKI-naïve cohort had CRC and two had CRC in the NTRK TKI-pretreated cohort. An abstract presented at ESMO Congress 2023 reported a confirmed ORR of 58%, 12-month DOR of 86%, and 12-month PFS of 56% for the TKI-naïve group and a confirmed ORR of 50%, 12- month DOR of 39%, and 12-month PFS of 22% for the TKI-pretreated population. Grade ≥3 treatment-emergent AEs occurred in 51% of patients (29% were treatment-related), with dizziness being most common. Treatment discontinuation due to AEs occurred in 7% of patients. Although there were no SBA patients in the TRIDENT trial, treatment implications are based on the data extrapolated from the patients with CRC. Based on these data, the FDA has approved larotrectinib, entrectinib, and repotrectinib for metastatic solid tumors with NTRK gene fusion and no satisfactory alternative treatment,[105] and the NCCN Panel recommends these therapies as options for subsequent-line treatment of metastatic SBA that is NTRK gene fusion positive.

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NCCN, 2024 [9].

National Comprehensive Cancer Network

Colon Cancer, vers. 5.2024

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie, Recherche/Suchzeitraum, LoE / GoR ist der zuvor dargestellten NCCN-LL „Central Nervous System Cancers „[7] zu entnehmen

CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,o]
pMMR/MSS (or dMMR/MSI-H or *POLE/POLD1* mutation that is ineligible for or progressed on checkpoint inhibitor immunotherapy)

SECOND-LINE AND SUBSEQUENT THERAPY OPTIONS (if not previously given)[c,p]		
Previous oxaliplatin-based therapy without irinotecan	Previous therapy with oxaliplatin and irinotecan	Biomarker-directed therapy
• FOLFIRI[i] or irinotecan[i] • FOLFIRI[i] + (bevacizumab[e,q] [preferred] or ziv-aflibercept[q,r] or ramucirumab[q,r]) • Irinotecan[i] + (bevacizumab[e,q] [preferred] or ziv-aflibercept[q,r] or ramucirumab[q,r]) • If *KRAS/NRAS/BRAF* WT[h]: ‣ FOLFIRI[i] + (cetuximab or panitumumab)[f,s] ‣ (Cetuximab or panitumumab)[f,s] ± irinotecan[i] • Biomarker-directed therapy (see Biomarker-directed therapy)	• If *KRAS/NRAS/BRAF* WT[h]: ‣ (Cetuximab or panitumumab)[f,s] ± irinotecan[i] • Biomarker-directed therapy (see Biomarker-directed therapy) • For disease that has progressed through all available regimens: ‣ Fruquintinib ‣ Regorafenib ‣ Trifluridine + tipiracil ± bevacizumab[e] (bevacizumab combo preferred) • Best supportive care (NCCN Guidelines for Palliative Care)	• *BRAF* V600E mutation positive[f] ‣ Encorafenib + (cetuximab or panitumumab)[t] • HER2-amplified and *RAS* and *BRAF* WT[f] ‣ (Trastuzumab[j] + [pertuzumab or lapatinib or tucatinib])[m] • HER2-amplified (IHC 3+) ‣ Fam-trastuzumab deruxtecan-nxki[u] • *KRAS* G12C mutation positive[f] ‣ (Sotorasib or adagrasib)[v] + (cetuximab or panitumumab) • *NTRK* gene fusion-positive ‣ Entrectinib ‣ Larotrectinib ‣ Repotrectinib[w] • *RET* gene fusion-positive ‣ Selpercatinib
Previous irinotecan-based therapy without oxaliplatin	Previous therapy without oxaliplatin or irinotecan	
• FOLFOX[d] or CAPEOX[d] • FOLFOX[d] + bevacizumab[e] • CAPEOX[d] + bevacizumab[e] • If *KRAS/NRAS/BRAF* WT[h]: ‣ FOLFOX[d] + (cetuximab or panitumumab)[f] ‣ CAPEOX[d] + (cetuximab or panitumumab)[f] ‣ (Cetuximab or panitumumab)[f,s] ± irinotecan[i] • Biomarker-directed therapy (see Biomarker-directed therapy)	• FOLFOX[d] or CAPEOX[d] • (FOLFOX or CAPEOX)[d] + bevacizumab[e] • FOLFIRI[i] or irinotecan[i] • (FOLFIRI or irinotecan)[i] + (bevacizumab[e,q] [preferred] or ziv-aflibercept[q,r] or ramucirumab[q,r]) • Irinotecan[i] + oxaliplatin[d] ± bevacizumab[e] • FOLFIRINOX[d,k] ± bevacizumab[e] • If *KRAS/NRAS/BRAF* WT[h]: ‣ FOLFIRI[h] + (cetuximab or panitumumab)[f,s] ‣ (Cetuximab or panitumumab)[f,s] ± irinotecan[i] • Biomarker-directed therapy (see Biomarker-directed therapy)	

*w On the TRIDENT-1 trial, repotrectinib showed activity in both NTRK TKI-naïve and NTRK TKI-pretreated patients.

Hintergrund:

NTRK Fusions

Three NTRK genes encode the TRK proteins. TRK expression is primarily in the nervous system where these kinases help to regulate pain, perception of movement/position, appetite, and memory. NTRK gene fusions lead to overexpression of the TRK fusion protein, resulting in constitutively active downstream signaling.[746] Studies have estimated that about 0.2% to 1% of CRCs carry NTRK gene fusions.[747,748] A study of 2314 CRC specimens, of which 0.35% had NTRK fusions, found that NTRK fusions were limited to cancers that were wild-type for KRAS, NRAS, and BRAF. Furthermore, a majority of the CRCs harboring NTRK fusions were also MMR-deficient.[749] Similarly, in a smaller study that aimed to characterize the molecular and clinical landscape of ALK, ROS1, and NTRK rearranged mCRC, 76.9% of NTRK rearranged tumors were MMR-deficient.[750] NTRK inhibitors are treatment options for patients with mCRC that is NTRK gene fusion-positive (see Systemic Therapy Options for NTRK Fusion-Positive Disease in the Non-First-Line Setting, below). Systemic Therapy Options for NTRK Gene Fusion-Positive Disease in the Non–First-Line Setting Studies have estimated that about 0.2% to 1% of CRCs carry NTRK gene fusions.[747,748] Three targeted therapies: larotrectinib, entrectinib, and repotrectinib have been FDA-approved for the treatment of patients with metastatic, unresectable solid tumors that have an NTRK gene fusion and no satisfactory alternative treatment options, regardless of the location of the primary tumor. The Panel recommends larotrectinib, entrectinib, or repotrectinib as subsequent treatment options for patients with NTRK gene fusion-positive disease, acknowledging that these therapies will not be appropriate for most patients due to the rarity of the NTRK fusion in CRC.

Larotrectinib: A pooled analysis of three studies (a phase I including adults, a phase I/II involving children, and the phase II NAVIGATE study involving adolescents and adults) studied the safety and efficacy of larotrectinib in 55 patients with NTRK gene fusion-positive tumors, including four patients with colon cancer.[746] For the whole population, the ORR was 75% (95% CI, 61–85) by independent review and 80% (95% CI, 67–90) by investigator assessment,[746] although the package insert cites a 25% ORR for colon tumors specifically.[988] Larotrectinib was found to be well-tolerated as the majority (93%) of AEs were grades 1 or 2 and no treatment-related AEs of grades 3 or 4 occurred in >5% of patients.746 A subsequent analysis of these three studies included 159 patients, eight with colon cancer, and reported similar results compared to the earlier analysis.[989] In this later analysis, the ORR was 79% (95% CI, 72–85) by investigator assessment with 16% complete responses. An analysis of 14 patients with GI cancer who were treated with larotrectinib in the NAVIGATE study reported a median PFS of 5.3 months (95% CI, 2.2–9.0) and a median OS of 33.4 months (95% CI, 2.8–36.5).[990] Responses were ongoing for five patients, leading their

results to be censored. Of the 8 patients with colon cancer, 50% showed a partial response and 50% had stable disease.

Entrectinib: An integrated analysis of three global phase I/II studies (ALKA-372-001, STARTRK-1, and STARTRK-2) tested the efficacy and safety of entrectinib in 54 adult patients with advanced or metastatic NTRK gene fusion-positive solid tumors.[991] For the whole population, ORR was 57% (95% CI, 43.2–70.8), median PFS was 11 months (95% CI, 8.0– 14.9), and median OS was 21 months (95% CI, 14.9–NE) by independent the four patients with CRC in this study, one was recorded as having a response. Notably, a similar ORR (50% vs. 60%) was observed among those with central nervous system metastasis, indicating that entrectinib has activity in this population. Entrectinib was found to be well-tolerated as most treatment-related AEs were grade 1 or 2 and managed with dose reduction, leading few (4%) patients to discontinue therapy due to treatment-related AEs.

Repotrectinib: The phase I/II TRIDENT-1 trial tested repotrectinib in two cohorts of patients with NTRK gene fusion-positive advanced solid tumors; 40 patients in the NTRK TKI-naïve cohort, who received repotrectinib as their first NTRK TKI treatment, and 48 patients in the NTRK TKI-pretreated cohort, who had already received larotrectinib or entrectinib.[992] One patient on the NTRK TKI-naïve cohort had CRC and two had CRC in the NTRK TKI-pretreated cohort. An abstract presented at ESMO Congress 2023 reported a confirmed ORR of 58%, 12-month DOR of 86%, and 12-month PFS of 56% for the TKI-naïve group and a confirmed ORR of 50%, 12- month DOR of 39%, and 12-month PFS of 22% for the TKI-pretreated population. Grade ≥3 treatment-emergent AEs occurred in 51% of patients (29% were treatment-related), with dizziness being most common. Treatment discontinuation due to AEs occurred in 7% of patients.

Referenzen:

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NCCN, 2024 [16].

National Comprehensive Cancer Network

Rectal Cancer, vers. 4.2024

Methodik

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Empfehlungen

CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,n]
pMMR/MSS (or dMMR/MSI-H or *POLE/POLD1* mutation that is ineligible for or progressed on checkpoint inhibitor immunotherapy)

SECOND-LINE AND SUBSEQUENT THERAPY OPTIONS (if not previously given)[c,o]		
Previous oxaliplatin-based therapy without irinotecan	Previous therapy with oxaliplatin and irinotecan	Biomarker-directed therapy
• FOLFIRI[h] or irinotecan[h] • FOLFIRI[h] + (bevacizumab[e,p] [preferred] or ziv-aflibercept[p,q] or ramucirumab[p,q]) • Irinotecan[h] + (bevacizumab[e,p] [preferred] or ziv-aflibercept[p,q] or ramucirumab[p,q]) • If *KRAS/NRAS/BRAF* WT[g]: ‣ FOLFIRI[h] + (cetuximab or panitumumab)[f,r] ‣ (Cetuximab or panitumumab)[f,r] ± irinotecan[h] • Biomarker-directed therapy (see Biomarker-directed therapy)	• If *KRAS/NRAS/BRAF* WT[g]: ‣ (Cetuximab or panitumumab)[f,r] ± irinotecan[h] • Biomarker-directed therapy (see Biomarker-directed therapy) • For disease that has progressed through all available regimens: ‣ Fruquintinib ‣ Regorafenib ‣ Trifluridine + tipiracil ± bevacizumab[e] (bevacizumab combo preferred) • Best supportive care (NCCN Guidelines for Palliative Care)	• *BRAF* V600E mutation positive[f] ‣ Encorafenib + (cetuximab or panitumumab)[s] • HER2-amplified and *RAS* and *BRAF* WT[f] ‣ (Trastuzumab[k] + [pertuzumab or lapatinib or tucatinib])[l] • HER2-amplified (IHC 3+) ‣ Fam-trastuzumab deruxtecan-nxki[t] • *KRAS* G12C mutation positive[f] ‣ (Sotorasib or adagrasib)[u] + (cetuximab or panitumumab) • *NTRK* gene fusion-positive ‣ Entrectinib ‣ Larotrectinib ‣ Repotrectinib[v] • *RET* gene fusion-positive ‣ Selpercatinib
Previous irinotecan-based therapy without oxaliplatin	Previous therapy without oxaliplatin or irinotecan	
• FOLFOX[d] or CAPEOX[d] • FOLFOX[d] + bevacizumab[e] • CAPEOX[d] + bevacizumab[e] • If *KRAS/NRAS/BRAF* WT[g]: ‣ FOLFOX[d] + (cetuximab or panitumumab)[f] ‣ CAPEOX[d] + (cetuximab or panitumumab)[f] ‣ (Cetuximab or panitumumab)[f,r] ± irinotecan[h] • Biomarker-directed therapy (see Biomarker-directed therapy)	• FOLFOX[d] or CAPEOX[d] • (FOLFOX or CAPEOX)[d] + bevacizumab[e] • FOLFIRI[h] or irinotecan[h] • (FOLFIRI or irinotecan)[h] + (bevacizumab[e,p] [preferred] or ziv-aflibercept[p,q] or ramucirumab[p,q]) • Irinotecan[h] + oxaliplatin[d] ± bevacizumab[e] • FOLFIRINOX[d,j] ± bevacizumab[e] • If *KRAS/NRAS/BRAF* WT[g]: ‣ FOLFIRI[h] + (cetuximab or panitumumab)[f,r] ‣ (Cetuximab or panitumumab)[f,r] ± irinotecan[h] • Biomarker-directed therapy (see Biomarker-directed therapy)	

*v On the TRIDENT-1 trial, repotrectinib showed activity in both NTRK TKI-naïve and NTRK TKI-pretreated patients.

NCCN, 2024 [15].

National Comprehensive Cancer Network

Pancreatic adenocarcinoma, vers. 3.2024

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie, Recherche/Suchzeitraum, LoE / GoR ist der zuvor dargestellten NCCN-LL „Central Nervous System Cancers „[7] zu entnehmen

Empfehlungen

Subsequent Therapy for Locally Advanced/Metastatic Disease and Therapy for Recurrent Disease

	Preferred Regimens	Other Recommended Regimens		Useful in Certain Circumstances
Good PS 0–1	• Entrectinib (if *NTRK* gene fusion-positive) • Larotrectinib (if *NTRK* gene fusion-positive) • Repotrectinib (if *NTRK* gene fusion-positive)[o,21] If no prior immunotherapy: • Pembrolizumab[j] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb])	• Dabrafenib + trametinib (if *BRAF* V600E mutation-positive)[19,20] • Selpercatinib (if *RET* gene fusion-positive)[30] If no prior immunotherapy: • Dostarlimab-gxly[j] (if MSI-H or dMMR) • Nivolumab + ipilimumab[j] (if TMB-H [≥10 mut/Mb]) (category 2B) If prior gemcitabine-based therapy: • 5-FU + leucovorin + liposomal irinotecan[31] (category 1 for metastatic disease) • Bolus 5-FU + leucovorin • Capecitabine • CapeOx • Continuous infusion 5-FU • FOLFIRI[32-34] • FOLFIRINOX or modified FOLFIRINOX[e,35] • FOLFOX • OFF	If prior fluoropyrimidine-based therapy: • 5-FU + leucovorin + liposomal irinotecan[31] (if no prior irinotecan) • Gemcitabine • Gemcitabine + albumin-bound paclitaxel • Gemcitabine + cisplatin (only for known *BRCA1/2* or *PALB2* mutations) • Gemcitabine + erlotinib[f,36] • Gemcitabine + albumin-bound paclitaxel + cisplatin[14,15] (category 2B)	• Adagrasib (if *KRAS G12C* mutation-positive) • Sotorasib (if *KRAS G12C* mutation-positive) • Fam-trastuzumab deruxtecan-nxki (if HER2 positive [IHC3+])[37] • Chemoradiation,[b] if not previously given, only an option for: ▸ Locally advanced disease if primary site is the sole site of progression ▸ Select patients with recurrent disease in combination with systemic therapy

PRINCIPLES OF SYSTEMIC THERAPY

Subsequent Therapy for Locally Advanced/Metastatic Disease and Therapy for Recurrent Disease

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances	
Intermediate PS 2	• None	If prior fluoropyrimidine-based therapy: • 5-FU + leucovorin + liposomal irinotecan[31] (if no prior irinotecan) • Gemcitabine + albumin-bound paclitaxel If prior gemcitabine-based therapy: • 5-FU + leucovorin + liposomal irinotecan[31] (category 1 for metastatic disease)	• Adagrasib (if *KRAS G12C* mutation positive) • Sotorasib (if *KRAS G12C* mutation-positive) • Dabrafenib + trametinib (if *BRAF* V600E mutation-positive)[19,20] • Entrectinib (if *NTRK* gene fusion-positive) • Larotrectinib (if *NTRK* gene fusion-positive) • Repotrectinib (if *NTRK* gene fusion-positive) (category 2B)[o,21] • Chemoradiation[b] if not previously given, only an option for: ▸ Locally advanced disease if primary site is the sole site of progression ▸ Selected patients with recurrent disease in combination with systemic therapy	If no prior immunotherapy: • Dostarlimab-gxly[j] (if MSI-H or dMMR) • Pembrolizumab[j] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • Nivolumab + ipilimumab[j] (if TMB-H [≥10 mut/Mb]) (category 2B)
Poor PS 3	• Entrectinib (if *NTRK* gene fusion-positive) • Larotrectinib (if *NTRK* gene fusion-positive) • Repotrectinib (if *NTRK* gene fusion-positive) (category 2B)[o,21] If no prior immunotherapy: • Pembrolizumab[j] (if MSI-H, dMMR, or TMB-H [≥10 mut/Mb]) • Dostarlimab-gxly[j] (if MSI-H or dMMR) (category 2B)	• Capecitabine (category 2B) • Continuous infusion 5-FU (category 2B) • Gemcitabine ▸ 1000 mg/m² over 30 minutes, weekly for 3 weeks every 28 days (category 1) ▸ Fixed-dose-rate gemcitabine (10 mg/m²/min) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B)	• Dabrafenib + trametinib (if *BRAF* V600E mutation positive)[19,20] • Adagrasib (if *KRAS G12C* mutation-positive) (category 2B) • Sotorasib (if *KRAS G12C* mutation-positive) (category 2B)	

[b] Chemoradiation (PANC-F 10 of 12).

*o If disease progressed on a prior NTRK targeted agent.

21. Solomon BJ, Drilon A, Lin JJ, et al. Repotrectinib in patients with NTRK fusionpositive advanced soli tumors, including non-small cell lung cancer: update from the phase 1/2 TRIDENT-1 trial. Ann Oncol. 2023;34:S787-S788.

Hintergrund:

Larotrectinib, Entrectinib, and Repotrectinib NTRK gene fusions, although rare, have been implicated in the oncogenesis of pancreatic cancer. The efficacy and safety of larotrectinib, an NTRK inhibitor, was investigated in three multicenter, open-label, single-arm trials (a phase I study in adults, a phase I/II study in children, and a phase II study in adolescents and adults).[239,240] The primary endpoint was set to be ORR and the secondary endpoints were determined to be PFS, duration of response (DOR), and safety. Among 12 tumor types, the ORR during independent review was 75% (95% CI, 61%–85%). After 9.4 months, 86% of participants had either undergone curative surgery or were continuing treatment. At 1 year, 55% of

patients were free of disease progression and the toxicity profile of the agent was minimal.[239] Based on these data, larotrectinib was approved by the FDA in 2018 for the treatment of NTRK gene fusion-positive solid tumors in adult and pediatric patients with known acquired resistance, with either metastatic disease or in whom surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment.[240] Updated data published in 2020 reported that 79% of patients had an objective response (95% CI, 72%–85%) with 16% showing a complete response.[241] Similarly, entrectinib, another NTRK inhibitor, was approved in 2019 by the FDA for adult and pediatric patients (aged ≥12 years) with advanced, morbid, or unresectable NTRK gene fusion-positive solid tumors with acquired resistance to standard treatment.[242] Data from three phase I–II trials (ALKA-372-001, STARTRK-1, and STARTRK-2) revealed that entrectinib was associated with an ORR of 75% and a median DOR of 12.9 months. Like its predecessor, it had a tolerable safety profile.[243,244] Thus, the NCCN Panel recommends larotrectinib and entrectinib as first-line and subsequent treatment options for patients with NTRK gene fusion-positive locally advanced or metastatic pancreatic adenocarcinoma and for recurrent disease. The only setting in which these NTRK inhibitors are not recommended by the Panel is as first-line therapy for patients with locally advanced disease and poor PS. The FDA issued accelerated approval for repotrectinib, another NTRKbased regimen, for adult and pediatric patients 12 years and older with solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity, and that have progressed following treatment or have no satisfactory alternative therapy.[245] A small number of patients with pancreatic adenocarcinoma were evaluated in the TRIDENT trial,[246] resulting in a category 2A recommendation as firstline therapy for patients with locally advanced (PS 0-2) or metastatic disease (PS 0-2), and subsequent therapy or therapy for recurrent disease for patients (PS 0-1). Repotrectinib is a category 2B recommendation as first-line for patients with metastatic disease (PS 3) and subsequent therapy or therapy for recurrent disease for patients with intermediate/poor PS (PS 2-3).

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242. FDA approves entrectinib for NTRK solid tumors and ROS-1 NSCLC. 2019. Available at: https://www.fda.gov/drugs/resources- information-approved-drugs/fda-approves-entrectinib-ntrk-solid-tumorsand- ros-1-nsclc. Accessed July 16, 2024.
243. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:271-282. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31838007.
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246. Solomon BJ, Drilon A, Lin JJ, et al. 1372P Repotrectinib in patients (pts) with NTRK fusion-positive (NTRK+) advanced solid tumors, including NSCLC: Update from the phase I/II TRIDENT-1 trial. Annals of Oncology 2023;34:S787-S788. Available at: https://doi.org/10.1016/j.annonc.2023.09.2405

NCCN, 2024 [6].

National Comprehensive Cancer Network

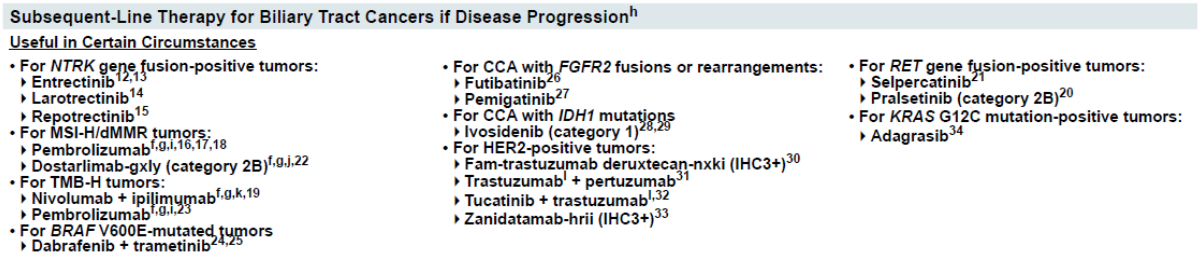
Biliary Tract Cancers, vers. 5

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie, Recherche/Suchzeitraum, LoE / GoR ist der zuvor dargestellten NCCN-LL „Central Nervous System Cancers „[7] zu entnehmen

Empfehlungen



Subsequent-Line Therapy for Biliary Tract Cancers if Disease Progression[h]

Useful in Certain Circumstances

- For *NTRK* gene fusion-positive tumors:
  - Entrectinib[f,12,13]
  - Larotrectinib[14]
  - Repotrectinib[15]
- For MSI-H/dMMR tumors:
  - Pembrolizumab[f,g,i,16,17,18]
  - Dostarlimab-gxly (category 2B)[f,g,j,22]
- For TMB-H tumors:
  - Nivolumab + ipilimumab[f,g,k,19]
  - Pembrolizumab[f,g,i,23]
- For *BRAF* V600E-mutated tumors
  - Dabrafenib + trametinib[24,25]
- For CCA with *FGFR2* fusions or rearrangements:
  - Futibatinib[26]
  - Pemigatinib[27]
- For CCA with *IDH1* mutations
  - Ivosidenib (category 1)[28,29]
- For HER2-positive tumors:
  - Fam-trastuzumab deruxtecan-nxki (IHC3+)[30]
  - Trastuzumab[l] + pertuzumab[31]
  - Tucatinib + trastuzumab[l,32]
  - Zanidatamab-hrii (IHC3+)[33]
- For *RET* gene fusion-positive tumors:
  - Selpercatinib[21]
  - Pralsetinib (category 2B)[20]
- For *KRAS* G12C mutation-positive tumors:
  - Adagrasib[34]

12. Drilon A, Siena S, Ou SI, et al. Safety and antitumor activity of the multitargeted pan-TRK, ROS1, and ALK inhibitor entrectinib: Combined results from two phase I trials (ALKA-372-001 and STARTRK-1). Cancer Discov 2017;7:400-409.
13. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusio positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:271-282.
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15. Solomon BJ, Drilon A, Lin JJ, et al. Repotrectinib in patients with NTRK fusion-positive advanced solid tumors, including non-small cell lung cancer: Update from the phase 1/2 TRIDENT-1 trial [abstract]. Ann Oncol 2023;34:Abstract 1372P.

Hintergrund:
NTRK Fusions
NTRK is a membrane-bound receptor that autophosphorylates and activates downstream pathways that drive oncogenesis. NTRK1/NTRK2/NTRK3 fusions are estimated to occur at <1% prevalence in BTCs.[310,311] Three NTRK inhibitors have been approved by the U.S. Food and Drug Administration (FDA) for a tumor agnostic indication in NTRK fusion-positive solid tumors: larotrectinib[312] in 2018, entrectinib[313] in 2019, and repotrectinib[314] in 2024. Studies with entrectinib and larotrectinib have demonstrated response rates in the 57% to 75% range in pre-treated NTRK fusion-positive tumors.[311-313] These studies have included small numbers of patients with CCA and demonstrated evidence of clinical benefit. Abstract data for repotrectinib showed a confirmed ORR of 50% in patients with TKI-pretreated NTRK fusion-positive tumors.[314] Entrectinib, larotrectinib, and repotrectinib are useful in certain circumstances first-line or subsequent-line (for progressive disease) systemic therapy options for unresectable or metastatic NTRK gene fusion-positive tumors. Testing for NTRK fusions is recommended for patients with unresectable or metastatic gallbladder cancer, intrahepatic CCA, or extrahepatic CCA. These assessments are feasible in the context of multi-target assessment in NGS gene panels currently in clinical use and NTRK fusion-positive CCAs have demonstrated responses in clinical trials.

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313. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:271-282. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31838007.
314. Solomon BJ, Drilon A, Lin JJ, et al. Repotrectinib in patients (pts) with NTRK fusion-positive (NTRK+) advanced solid tumors, including NSCLC: Update from the phase I/II TRIDENT-1 trial [abstract]. Ann Oncol 2023;34:Abstract 1372P. Available at: https://www.annalsofoncology.org/article/S0923-7534(23)03242-8/fulltext.

NCCN, 2024 [12].

National Comprehensive Cancer Network

Hepatocellular Carcinoma, vers. 3

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie, Recherche/Suchzeitraum, LoE / GoR ist der zuvor dargestellten NCCN-LL „Central Nervous System Cancers „[7] zu entnehmen

Empfehlungen

PRINCIPLES OF SYSTEMIC THERAPY[a,b,c]

First-Line Systemic Therapy

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Atezolizumab[d] + bevacizumab (category 1)[e,f,g,1] • Tremelimumab-actl + durvalumab (category 1)[f,2]	• Durvalumab (category 1)[f,2] • Lenvatinib (category 1)[3,4] • Sorafenib (category 1)[5,6] • Tislelizumab-jsgr (category 1)[f,7] • Pembrolizumab (category 2B)[f,8]	• For *NTRK* gene-fusion positive tumors: ‣ Repotrectinib (category 2B)[9]

Subsequent-Line Systemic Therapy if Disease Progression[h,i,j]

Options	Other Recommended Regimens	Useful in Certain Circumstances
• Cabozantinib (category 1)[12] • Regorafenib (category 1)[13] • Lenvatinib • Sorafenib	• Nivolumab + ipilimumab[e,k,14-16] • Pembrolizumab[f,l,m,n,17-19]	• Ramucirumab (AFP ≥400 ng/mL) (category 1)[20] • Nivolumab[f,l,m,21-24] • For MSI-H/dMMR tumors ‣ Dostarlimab-gxly (category 2B)[f,l,m,o,25] • For *RET* gene fusion-positive tumors: ‣ Selpercatinib (category 2B)[26]

[a] Order does not indicate preference.
[b] See Principles of Liver Functional Assessment (HCC-E) and assess portal hypertension (eg, varices, splenomegaly, thrombocytopenia).
[c] Caution: Therapies listed may have limited safety data available for Child-Pugh Class B or C liver function. Use with extreme caution in patients with elevated bilirubin levels. Consult the prescribing information for individual agents.
[d] Atezolizumab and hyaluronidase-tqjs subcutaneous injection may be substituted for IV atezolizumab. Atezolizumab and hyaluronidase-tqjs has different dosing and administration instructions compared to atezolizumab for intravenous infusion.
[e] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[f] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[g] Patients on atezolizumab + bevacizumab should have adequate endoscopic evaluation and management for esophageal varices within approximately 6 months prior to treatment or according to institutional practice and based on the assessment of bleeding risk.
[h] There are no comparative data to define optimal treatment after first-line systemic therapy.
[i] Principles of Molecular Testing (HCC-J).
[j] Larotrectinib and entrectinib are treatment options for patients with *NTRK* gene-fusion positive HCC.[10,11] Repotrectinib (category 2B) is a treatment option for patients with *NTRK* gene-fusion positive HCC that has progressed on a prior NTRK-targeted treatment.[9]
[k] For patients who have not been previously treated with a checkpoint inhibitor unless following atezolizumab + bevacizumab.
[l] There is a lack of data for subsequent use of single agent immunotherapy in patients who have previously been treated with a checkpoint inhibitor.
[m] For patients who have not been previously treated with a checkpoint inhibitor.
[n] Pembrolizumab is a recommended treatment option for patients with or without microsatellite instability-high (MSI-H) HCC. Pembrolizumab is FDA-approved for MSI-H tumors.
[o] Dostarlimab-gxly is a recommended treatment option for patients with MSI-H/mismatch repair deficient (dMMR) recurrent or advanced tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.

*9 Solomon BJ, Drilon A, Lin JJ, et al. Repotrectinib in patients with NTRK fusion-positive advanced solid tumors, including non-small cell lung cancer: Update from the phase 1/2 TRIDENT-1 trial [abstract]. Ann Oncol 2023;34:Abstract 1372P.
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11 Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: Integrated analysis of three phase 1-2 trials Lancet Oncol 2020;21:271-282

Hintergrund:
NTRK1/NTRK2/NTRK3 fusions have not been reported in HCC. However, as studies have demonstrated response rates in the 57% to 75% range in pre-treated NTRK fusion-positive tumors, larotrectinib and entrectinib are subsequent-line systemic therapy options for patients with HCC that is NTRK gene fusion positive.[525,526]

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NCCN, 2024 [11].

National Comprehensive Cancer Network

Head and Neck Cancers, vers. 1.2025

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie, Recherche/Suchzeitraum, LoE / GoR ist der zuvor dargestellten NCCN-LL „Central Nervous System Cancers „[7] zu entnehmen

Empfehlungen

SYSTEMIC THERAPY FOR SALIVARY GLAND TUMORS

Recurrent, Unresectable, or Metastatic Salivary Gland Tumors (with no surgery or RT option)

- **The choice of systemic therapy should be individualized based on patient characteristics (eg, PS, goals of therapy).**
- **An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.**

Preferred Regimens
- None

Other Recommended Regimens
- Cisplatin/vinorelbine[1]
- Cisplatin/doxorubicin/cyclophosphamide[2] (category 2B)
- Paclitaxel (category 2A for non-adenoid cystic carcinoma [ACC]; category 2B for ACC)[3]
- Carboplatin/paclitaxel[4,5]
- Carboplatin/gemcitabine[6]

Useful in Certain Circumstances
- Androgen receptor (AR) therapy for AR+ tumors
  - Leuprolide[7]
  - Bicalutamide[8]
  - Abiraterone[9] + prednisone + luteinizing hormone-releasing hormone (LHRH) agonist (triptorelin, leuprolide, or goserelin)
  - Goserelin (category 2B)[10,11,12]
- *NTRK* therapy for *NTRK* gene fusion-positive tumors
  - Larotrectinib[13,14]
  - Entrectinib[15]
  - Repotrectinib[16]
- HER2-targeted therapy for HER2+ tumors[a]
  - Trastuzumab[17]
  - Ado-trastuzumab emtansine (TDM-1)[18]
  - Trastuzumab/pertuzumab[19]
  - Docetaxel/trastuzumab[20]
  - Fam-trastuzumab deruxtecan-nxki[21]
- Sorafenib (category 2B)[22]
- Axitinib (category 2B)[23]
- Axitinib + avelumab for ACC (category 2B)[24]
- Erdafitinib for *FGFR* mutations or fusions and disease progression with at least one line of prior systemic therapy and no availability of an alternative systemic therapy (category 2B)[25]
- Lenvatinib for ACC (category 2B)[26]
- Pembrolizumab (for microsatellite instability-high [MSI-H], mismatch repair deficient [dMMR], TMB-H [≥10 mut/Mb] tumors, or PD-L1 tumors)[27]
- Dabrafenib/trametinib for *BRAF* V600E-positive tumors[28]
- Selpercatinib for *RET* gene fusion-positive tumors[29]

*13 Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusionpositive cancers in adults and children. N Engl J Med 2018;378:731-739. 14 Hong DS, Bauer TM, Lee JJ, et al. Larotrectinib in adult patients with solid tumours: a multi-centre, open-label, phase I dose-escalation study. Ann Oncol 2019;30:325-331. 15 Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:271-282.
16 Solomon B, Drilon A, Lin JJ, et al. Repotrectinib in patients with NTRK fusionpositive advanced solid tumors, including non-small cell lung cancer: update from the phase 1/2 TRIDENT-1 trial. Poster presented at the European Society for Medical Oncology Congress, Madrid, Spain, October 20-24, 2023.

Hintergrund:
Two phase I/II studies including patients with advanced NTRK gene fusion-positive cancer (with 22%–38% being salivary gland tumors) showed promising objective response rates of 75% to 100% with the TRK inhibitor larotrectinib.[710,711] A pooled analysis from a phase II trial and two phase I trials including 54 patients with NTRK gene fusion-positive cancer (13% being mammary analogue secretory carcinoma of the salivary gland) showed an objective response rate of 57.4% for entrectinib, another TRK inhibitor.[712]

Finally, repotrectinib was evaluated in a phase I/II study including 88 patients with NTRK gene fusion-positive advanced solid tumors (48 previously treated with a TRK TKI, and 40 who were TRK TKInaive). [717] Eleven patients (12.5%) had a salivary gland tumor. The analysis showed an objective response rate of 58% for those who were TRK TKI-naïve, and 50% in those who were previously treated with a TRK TKI. The FDA approved larotrectinib, entrectinib, and repotrectinib for treatment of patients with NTRK gene fusion-positive tumors, and the panel also recommends these three NTRK therapy options for patients with recurrent NTRK gene fusion-positive salivary gland tumors and distant metastases.

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NCCN, 2024 [14].

National Comprehensive Cancer Network

Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer, vers. 3

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie, Recherche/Suchzeitraum, LoE / GoR ist der zuvor dargestellten NCCN-LL „Central Nervous System Cancers „[7] zu entnehmen

Empfehlungen

PRINCIPLES OF SYSTEMIC THERAPY
Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)[p]/Fallopian Tube/Primary Peritoneal Cancer[q]

Recurrence Therapy for Platinum-Sensitive Disease[r] (alphabetical order)

Preferred Regimens	Other Recommended Regimens[u]	Useful in Certain Circumstances
Carboplatin/ gemcitabine[14] ± bevacizumab[k,s,t,15] Carboplatin/liposomal doxorubicin[16] ± bevacizumab[k,s,17] Carboplatin/paclitaxel[9,18] ± bevacizumab[k,s,t,19] Cisplatin/gemcitabine[20] Targeted Therapy (single agents) Bevacizumab[k,s,21,22]	Capecitabine Carboplatin[14] Carboplatin/docetaxel[23, 24] Carboplatin/paclitaxel (weekly)[9,25] Cisplatin[18] Cyclophosphamide Doxorubicin Ifosfamide Irinotecan Melphalan Oxaliplatin Paclitaxel Paclitaxel, albumin bound Pemetrexed Vinorelbine Targeted Therapy Niraparib/bevacizumab (category 2B)[k,26] Niraparib (category 3)[v,27] Olaparib (category 3)[w,28] Pazopanib (category 2B)[29] Rucaparib (category 3)[x,30] Hormone Therapy Aromatase inhibitors (anastrozole, exemestane, letrozole) Goserelin acetate Leuprolide acetate Megestrol acetate Tamoxifen[j]	For mucinous carcinoma: • 5-FU/leucovorin/oxaliplatin ± bevacizumab (category 2B for bevacizumab)[k,s] • Capecitabine/oxaliplatin ± bevacizumab (category 2B for bevacizumab)[k,s] Carboplatin/paclitaxel (for age >70)[9,y] Carboplatin/paclitaxel, albumin bound (for confirmed taxane hypersensitivity) Irinotecan/cisplatin (for clear cell carcinoma)[31] Targeted Therapy Dabrafenib + trametinib (for *BRAF* V600E-positive tumors)[z,32] Entrectinib or larotrectinib or repotrectinib[33] (for *NTRK* gene fusion-positive tumors)[z] Mirvetuximab soravtansine-gynx/bevacizumab (for FRα-expressing tumors) (category 2B)[k,34] Selpercatinib (for *RET* gene fusion-positive tumors)[z,35] For low-grade serous carcinoma: • Trametinib[36] • Binimetinib (category 2B)[37,38] Hormone Therapy Fulvestrant (for low-grade serous carcinoma) Immunotherapy Dostarlimab-gxly (for dMMR/MSI-H recurrent or advanced tumors)[z,39] Pembrolizumab (for MSI-H or dMMR solid tumors, or patients with TMB-H tumors ≥10 mutations/megabase)[z,40]

PRINCIPLES OF SYSTEMIC THERAPY
Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)[p]/Fallopian Tube/Primary Peritoneal Cancer[q]

Recurrence Therapy for Platinum-Resistant Disease (alphabetical order)

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Cytotoxic Therapy Cyclophosphamide (oral)/ bevacizumab[k,41] Docetaxel[42] Etoposide (oral)[43] Gemcitabine[44,45] Liposomal doxorubicin[44,45] Liposomal doxorubicin/ bevacizumab[k,s,46] Paclitaxel (weekly)[g,47] Paclitaxel (weekly)/ bevacizumab[g,k,s,46] Topotecan[48,49] Topotecan/bevacizumab[k,s,46] Targeted Therapy (single agents) Bevacizumab[k,s,21,22] Mirvetuximab soravtansine-gynx (for FRα-expressing tumors [≥75% positive tumor cells])(category 1)[z,50,51]	Cytotoxic Therapy[u] Capecitabine Carboplatin[*] Carboplatin/docetaxel[*] Carboplatin/paclitaxel (weekly)[g,*] Carboplatin/gemcitabine[14] ± bevacizumab[k,s,t,15,*] Carboplatin/liposomal doxorubicin[16] ± bevacizumab[k,s,17,*] Carboplatin/paclitaxel[g,18] ± bevacizumab[k,s,t,19,*] Cyclophosphamide Cyclophosphamide (oral)/pembrolizumab/bevacizumab[k,53,54] Doxorubicin Gemcitabine/bevacizumab[k,55] Gemcitabine/cisplatin[20,*] Ifosfamide Irinotecan Ixabepilone/bevacizumab (category 2B)[k,aa,56] Melphalan Oxaliplatin Paclitaxel Paclitaxel, albumin bound Pemetrexed Sorafenib/topotecan[51] Vinorelbine Targeted Therapy (single agents) Niraparib (category 3)[v,27] Olaparib (category 3)[w,28] Pazopanib (category 2B)[29] Rucaparib (category 3)[x,30] Hormone Therapy Aromatase inhibitors (anastrozole, exemestane, letrozole) Goserelin acetate Leuprolide acetate Megestrol acetate Tamoxifen[j]	Carboplatin/paclitaxel (for age >70)[g,y,*] Carboplatin/paclitaxel, albumin bound (for confirmed taxane hypersensitivity)[*] Immunotherapy Dostarlimab-gxly (for dMMR/MSI-H recurrent or advanced tumors)[z,39] Pembrolizumab (for patients with MSI-H or dMMR solid tumors, or TMB-H tumors ≥10 mutations/megabase)[z,40] Hormone Therapy Fulvestrant (for low-grade serous carcinoma) Targeted Therapy Dabrafenib + trametinib (for *BRAF* V600E-positive tumors)[z,32] Entrectinib or larotrectinib or repotrectinib[33] (for *NTRK* gene fusion-positive tumors)[z] Fam-trastuzumab deruxtecan-nxki (for HER2-positive tumors [IHC 3+ or 2+])[57] Mirvetuximab soravtansine-gynx/bevacizumab (for FRα-expressing tumors)[k,z,34,58,59] Selpercatinib (for *RET* gene fusion-positive tumors)[z,35] For low-grade serous carcinoma: • Trametinib[36] • Binimetinib (category 2B)[37,38]

*33 Solomon BJ, Drilon A, Lin JJ, et al. Repotrectinib in patients with NTRK fusionpositive advanced solid tumors, including non-small cell lung cancer: update from the phase 1/2 TRIDENT-1 trial. Ann Oncol. 2023;34:S787-S788.

NCCN, 2024 [19].

National Comprehensive Cancer Network

Uterine Neoplasms, vers. 3.2024

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie, Recherche/Suchzeitraum, LoE / GoR ist der zuvor dargestellten NCCN-LL „Central Nervous System Cancers „[7] zu entnehmen

Empfehlungen

The NCCN Panel also recommends larotrectinib or entrectinib for NTRK gene fusion-positive endometrial tumors as a category 2B subsequent therapy option.

SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

RECURRENT DISEASE[i,j]

First-Line Therapy for Recurrent Disease[k]	Second-Line or Subsequent Therapy
Preferred • Carboplatin/paclitaxel (category 1 for carcinosarcoma)[l,7] • Carboplatin/paclitaxel/pembrolizumab (except for carcinosarcoma) (category 1)[c,d,m,8] • Carboplatin/paclitaxel/dostarlimab-gxly (category 1)[c,d,m,9] • Carboplatin/paclitaxel/durvalumab (for dMMR tumors only) (category 1)[c,d,m,10] • Carboplatin/paclitaxel/trastuzumab[d,h] (for HER2-positive uterine serous carcinoma)[g,11] • Carboplatin/paclitaxel/trastuzumab[d,h] (for HER2-positive carcinosarcoma)[g,11] **Other Recommended Regimens** • Carboplatin/docetaxel[n] • Carboplatin/paclitaxel/bevacizumab[d,o,12,13] **Useful in Certain Circumstances (Biomarker-directed therapy: after prior platinum-based therapy including neoadjuvant and adjuvant)** • MMR-proficient (pMMR) tumors ‣ Lenvatinib/pembrolizumab (category 1)[c,14] • TMB-H tumors[p] ‣ Pembrolizumab[c,15] • MSI-H/dMMR tumors[q] ‣ Pembrolizumab[c,16] ‣ Dostarlimab-gxly[c,17]	**Other Recommended Regimens** • Cisplatin/doxorubicin[18] • Cisplatin/doxorubicin/paclitaxel[r,18] • Cisplatin/gemcitabine[19] • Cisplatin • Carboplatin • Doxorubicin • Liposomal doxorubicin • Paclitaxel[20] • Albumin-bound paclitaxel[s] • Topotecan • Bevacizumab[o,t,21] • Temsirolimus[22] • Cabozantinib • Docetaxel (category 2B) • Ifosfamide (for carcinosarcoma) • Ifosfamide/paclitaxel (for carcinosarcoma)[23] • Cisplatin/ifosfamide (for carcinosarcoma) **Useful in Certain Circumstances (Biomarker-directed therapy)** • pMMR tumors ‣ Lenvatinib/pembrolizumab (category 1)[c,14] • TMB-H tumors[p,15] ‣ Pembrolizumab[c] • MSI-H/dMMR tumors[q] ‣ Pembrolizumab[c,16] ‣ Dostarlimab-gxly[c,17] ‣ Avelumab[c] ‣ Nivolumab[c,24] • HER2-positive tumors (IHC 3+ or 2+) ‣ Fam-trastuzumab deruxtecan-nxki[25] • *NTRK* gene fusion-positive tumors ‣ Larotrectinib ‣ Entrectinib

SYSTEMIC THERAPY FOR UTERINE SARCOMA[a]
(Clinical trials strongly recommended)

Advanced, Recurrent/Metastatic or Inoperable Disease	
First-Line Therapy[b]	Second-Line or Subsequent Therapy
Preferred Regimens • Doxorubicin • Docetaxel/gemcitabine • Doxorubicin/trabectedin (for LMS)[1] • Doxorubicin/ifosfamide • Doxorubicin/dacarbazine **Useful in Certain Circumstances** • Biomarker-directed therapy ‣ *NTRK* gene fusion-positive tumors ◊ Larotrectinib ◊ Entrectinib ‣ IMT with ALK translocation ◊ Crizotinib[2] ◊ Ceritinib[3] ◊ Brigatinib[4,5] ◊ Lorlatinib ◊ Alectinib • PEComa ‣ Albumin-bound sirolimus	**Preferred Regimens** • Trabectedin[c] **Other Recommended Regimens** • Gemcitabine/dacarbazine • Gemcitabine/vinorelbine • Dacarbazine • Gemcitabine • Epirubicin • Ifosfamide • Liposomal doxorubicin • Pazopanib • Temozolomide • Eribulin (category 2B) **Useful in Certain Circumstances** • Biomarker-directed therapy ‣ TMB-H tumors[d] ◊ Pembrolizumab ‣ Consider PARP inhibitors for *BRCA*-altered LMS[e,6,7-9] ◊ Olaparib[10] ◊ Rucaparib ◊ Niraparib • PEComa ◊ Sirolimus ◊ Everolimus ◊ Temsirolimus

NCCN, 2024 [8].

National Comprehensive Cancer Network

Cervical cancer, vers. 4.2024

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie, Recherche/Suchzeitraum, LoE / GoR ist der zuvor dargestellten NCCN-LL „Central Nervous System Cancers „[7] zu entnehmen

Empfehlungen

SYSTEMIC THERAPY FOR CERVICAL CANCER[a]

Squamous Cell Carcinoma, Adenocarcinoma, or Adenosquamous Carcinoma		
Chemoradiation[b]	Recurrent or Metastatic Disease	
	First-line Therapy[b,f]	Second-line or Subsequent Therapy[j]
Preferred Regimens • Cisplatin[c,d,1] • Carboplatin if patient is cisplatin intolerant[c,d] Other Recommended Regimens[e] (if cisplatin and carboplatin are unavailable) • Capecitabine/mitomycin[2] • Gemcitabine[3] • Paclitaxel[4,5]	Preferred Regimens • PD-L1–positive tumors ‣ Pembrolizumab + cisplatin/paclitaxel ± bevacizumab (category 1)[d,g,h,i,6] ‣ Pembrolizumab + carboplatin/paclitaxel ± bevacizumab (category 1)[d,g,h,i,6] • Cisplatin/paclitaxel/bevacizumab[d,g,7] (category 1) • Carboplatin/paclitaxel/bevacizumab[d,g] Other Recommended Regimens • Cisplatin/paclitaxel (category 1)[8,9] • Carboplatin/paclitaxel[10,11] (category 1 for patients who have received prior cisplatin therapy) • Topotecan/paclitaxel/bevacizumab[d,g,7,12] (category 1) • Topotecan/paclitaxel[12] • Cisplatin/topotecan[12] • Cisplatin[9] • Carboplatin[13,14]	Preferred Regimens • Pembrolizumab for TMB-H tumors[h,k] or PD-L1–positive[i] or MSI-H/dMMR tumors[h,15] • Tisotumab vedotin-tftv[16] • Cemiplimab[h,17] Other Recommended Regimens • Bevacizumab[g] • Paclitaxel[14,18] • Albumin-bound paclitaxel • Docetaxel • Fluorouracil • Gemcitabine • Pemetrexed • Topotecan • Vinorelbine • Irinotecan Useful in Certain Circumstances • PD-L1–positive tumors ‣ Nivolumab[h,i,19] • HER2-positive tumors (IHC 3+ or 2+) ‣ Fam-trastuzumab deruxtecan-nxki[20] • RET gene fusion-positive tumors ‣ Selpercatinib • *NTRK* gene fusion-positive tumors ‣ Larotrectinib ‣ Entrectinib

Hintergrund:
NTRK gene fusions are found in about 1% of all solid tumors. An integrated efficacy and safety analysis of patients with metastatic or locally advanced solid tumors harboring oncogenic NTRK1, NTRK2, and NTRK3 gene fusions treated with entrectinib in three ongoing, early-phase trials (ALKA-372–001, STARTRK-1, and STARTRK-2) showed durable and clinically meaningful responses with manageable safety profile.[150] The efficacy-evaluable population comprised of 54 adults with advanced or metastatic NTRK fusion-positive solid tumors comprising ten different tumor types and 19 different histologies, including one patient with cervical sarcoma. Out of 54 patients, 31 (57%; 95% CI, 43.2–70.8) patients had an objective response, of which four (7%) were complete responses and 27 (50%) were partial responses. Median duration of response (DoR) was 10 months (95% CI, 7.1 – not estimable [NE]). In a long-term efficacy and safety analysis in 121 patients at median follow-up of 25.8 months, 61% reported complete or partial responses, median DoR was 20 months (95% CI, 10.1–19.9) and median PFS was 13.8 months (95% CI, 10.1–19.9).[151] In another primary analysis, the efficacy and safety of larotrectinib was reported in 55 patients enrolled in three clinical studies who had locally advanced or metastatic tumors with NTRK gene fusions and had progressed on standard chemotherapy received previously. The three clinical trials included a phase 1 dose-finding study in adults, phase 1–2 dose-finding study in a pediatric population, and a phase 2, single-arm, basket trial.[152] The overall response rate of Larotrectinib in these patients was 75% (95% CI, 61%–85%) with 13% complete response (CR) and 62% partial responses with median DoR and PFS not reached at the time. In a long-term follow-up analysis, out of 153 patients, 121 patients (79%; 95% CI, 72–85) had objective response with 16% having a CR, 63% with partial response, and 12% with a stable disease. The median DoR was 35.2 months (22.8 – NE) and the median PFS was 28.3 months.[153] Both larotrectinib and entrectinib are FDA-approved for NTRK gene fusion solid tumors for patients who have progressed following treatment or have no satisfactory standard therapy.[154,155]

Referenzen:
150. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients withadvanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:271-282. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31838007.
151. Demetri GD, De Braud F, Drilon A, et al. Updated Integrated Analysis of the Efficacy and Safety of Entrectinib in Patients With NTRK Fusion-Positive Solid Tumors. Clin Cancer Res 2022;28:1302-1312. Available at:https://www.ncbi.nlm.nih.gov/pubmed/35144967.
152. 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.
153. Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. Lancet Oncol 2020;21:531-540. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32105622.
154. Marcus L, Donoghue M, Aungst S, et al. FDA Approval Summary:
Entrectinib for the Treatment of NTRK gene Fusion Solid Tumors. Clin Cancer Res 2021;27:928-932. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32967940.

155. Scott LJ. Larotrectinib: First Global Approval. Drugs 2019;79:201-206. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30635837

NCCN, 2024 [20].

National Comprehensive Cancer Network

Vulvar cancer, vers. 4.2024

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie, Recherche/Suchzeitraum, LoE / GoR ist der zuvor dargestellten NCCN-LL „Central Nervous System Cancers „[7] zu entnehmen

Empfehlungen

SYSTEMIC THERAPY[a,1]

Chemoradiation	Advanced or Recurrent/Metastatic Disease	
	First-line Therapy[c]	Second-line or Subsequent Therapy
Preferred Regimens • Cisplatin • Carboplatin if patient is cisplatin intolerant Other Recommended Regimens • Cisplatin/fluorouracil • If cisplatin or carboplatin are unavailable:[b] ‣ Capecitabine/mitomycin[2] ‣ Gemcitabine[3] ‣ Paclitaxel[4,5]	Preferred Regimens • Cisplatin/paclitaxel/bevacizumab[d] • Cisplatin/paclitaxel • Carboplatin/paclitaxel • Carboplatin/paclitaxel/bevacizumab (category 2B)[d] Other Recommended Regimens • Cisplatin • Carboplatin	Other Recommended Regimens • Paclitaxel • Cemiplimab[e,6,7] • Erlotinib (category 2B)[8] • Cisplatin/gemcitabine (category 2B) Useful in Certain Circumstances (Biomarker directed therapy) • TMB-high (TMB-H) ‣ Pembrolizumab[e,f,9] • PD-L1–positive ‣ Pembrolizumab[e,g] • MSI-high (MSI-H)/MMR deficient (dMMR) tumors[10] ‣ Pembrolizumab[e,10] • HER2-positive tumors (IHC 3+ or 2+) ‣ Fam-trastuzumab deruxtecan-nxki[11] • HPV-related tumors ‣ Nivolumab[e,12] • *NTRK* gene fusion-positive tumors ‣ Larotrectinib ‣ Entrectinib

Hintergrund:
NTRK gene fusions lead to constitutively active tropomyosin receptor kinases (TRKs), which in turn promote development and progression of cancer. Approximately 0.3% of solid tumors express NTRK gene fusions, although expression varies widely by cancer type.[170] Entrectinib and larotrectinib are broadly active TRK inhibitors that are effective in patients with a variety of advanced or metastatic NTRK fusion-positive solid tumors.[170-172] In a primary analysis, the efficacy and safety of larotrectinib was reported in 55 patients enrolled in three clinical studies who had locally advanced or metastatic tumors with NTRK gene fusions and had progressed on standard chemotherapy received previously.[171] The three clinical trials included a phase 1 dose-finding study in adults, phase 1/2 dose-finding study in the pediatric population, and a phase 2, single-arm, basket trial. The ORR of larotrectinib in these patients was 75% (95% CI, 61%–85%), with 22% complete response and 53% partial response with median duration of response and PFS not reached at the time. In a longterm follow-up analysis, out of 153 patients, 121 patients (79%; 95% CI, 72–85) had objective response with 16% having a complete response, 63% having a partial response, and 12% having stable disease. The median duration of response was 35.2 months (22.8–NE) and the median PFS was 28.3 months.[173] Similarly, entrectinib showed a durable and clinically meaningful response in 54 patients with advanced/metastatic NTRK gene fusion tumors enrolled in three phase 1/2 clinical trials with 57.4% ORR, 10.4-month median duration of response, and 11.2-month median PFS.[170] In a long-term efficacy and safety analysis in 121 patients at median follow-up of 25.8 months, 61% reported complete or partial responses, and median duration of response was 20 months (95% CI, 10.1–19.9). Both larotrectinib and entrectinib are FDA-approved for NTRK gene fusion solid tumors for patients who have progressed following treatment or have no satisfactory standard therapy. The NCCN Guidelines for Vulvar Cancer recommend larotrectinib and entrectinib as a secondline or subsequent, useful in certain circumstances option for NTRK gene fusion-positive tumors and recently changed the category of evidence from category 2B to category 2A.

Referenzen:
170. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:271-282. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31838007.
171. 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.
172. Hong DS, Bauer TM, Lee JJ, et al. Larotrectinib in adult patients with solid tumours: a multi-centre, open-label, phase I dose-escalation study. Ann Oncol 2019;30:325-331. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30624546.
173. Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. Lancet Oncol 2020;21:531-540. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32105622.

NCCN, 2024 [13].

National Comprehensive Cancer Network

Occult Primary (Cancer of Unknown Primary [CUP]), vers. 2.2025

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie, Recherche/Suchzeitraum, LoE / GoR ist der zuvor dargestellten NCCN-LL „Central Nervous System Cancers „[7] zu entnehmen

Empfehlungen

PRINCIPLES OF SYSTEMIC THERAPY

Selected Systemic Therapy for Occult Primaries: Adenocarcinoma[a]

Regimens are listed in alphabetical order by category of preference.

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Carboplatin and paclitaxel[1,2] • Cisplatin and gemcitabine[3] **Preferred Regimens for Presumed GI Primary Site** • CapeOX[4] • FOLFIRI[b,5-9] • mFOLFOX6[b,4,10]	• Capecitabine[c,d,11,12] • Docetaxel and carboplatin[13] • Docetaxel and cisplatin[14] • Fluorouracil[b,c,d,15-18] • Gemcitabine and carboplatin[19] • Gemcitabine and docetaxel[20] • Irinotecan and carboplatin[21]	**Biomarker-Driven Therapy** ***BRAF* V600E mutation-positive tumors** • Dabrafenib + trametinib[e,22] **dMMR/MSI-H tumors** • Dostarlimab-gxly[f,g,23] • Pembrolizumab[f,24-26] ***NTRK* gene fusion-positive tumors** • Entrectinib[h,27] • Larotrectinib[h,28] • Repotrectinib[h,29] **TMB-high (TMB-H) (≥10 mut/Mb) tumors** • Pembrolizumab[f,24-26,30] **HER2-positive (IHC 3+) tumors** • Fam-trastuzumab deruxtecan-nxki[i,31] ***RET* gene fusion-positive tumors** • Selpercatinib[j,32] **Cytotoxic Chemotherapy** • FOLFIRINOX [b,c,k,33] • Irinotecan and gemcitabine[l,34] • mFOLFIRINOX[b,c,k,35,36] • Paclitaxel, carboplatin, and etoposide[k,37]

[a] Consider programmed death ligand 1 (PD-L1) testing for patients with recurrent, progressive, or metastatic disease.
[b] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin.
[c] For patients with presumed gastrointestinal (GI) primary site.
[d] These regimens can be given with concurrent radiation.
[e] For patients with *BRAF* V600E mutation-positive unresectable or metastatic solid tumors that have progressed following prior treatment and have no satisfactory alternative treatment options.
[f] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[g] For patients with recurrent or advanced tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options. Note, patients who had received prior immune checkpoint inhibitor therapy were excluded from the dostarlimab-gxly clinical trial.
[h] For patients with *NTRK* gene fusion-positive tumors without a known acquired resistance mutation, that are metastatic or where surgical resection is likely to result in severe morbidity, and that have no satisfactory alternative treatments or that have progressed following treatment.
[i] For patients with advanced or metastatic solid tumors that progressed on or following prior systemic treatment and who have no satisfactory alternative treatment options.
[j] For patients with advanced or metastatic solid tumors that progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.
[k] Only for patients with PS ECOG 0–1.
[l] For patients ineligible to receive platinum-based chemotherapy.

Note: All recommendations are category 2A unless otherwise indicated.

For Squamous Cell Carcinoma see OCC-B 8 of 14

References on OCC-B 13 of 14

OCC-B

PRINCIPLES OF SYSTEMIC THERAPY

Selected Systemic Therapy for Occult Primaries: Squamous Cell Carcinoma[a]

Regimens are listed in alphabetical order by category of preference.

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Carboplatin and paclitaxel[1,2] • mFOLFOX6[b,4,10]	• Capecitabine[d,11,12] • Cisplatin and fluorouracil[d,38-40] • Docetaxel and carboplatin[41] • Docetaxel and cisplatin[14,42] • Fluorouracil[b,d,15-18] • Gemcitabine and carboplatin[19] • Gemcitabine and cisplatin[3] • Paclitaxel and cisplatin[43]	**Biomarker-Driven Therapy** ***BRAF* V600E mutation-positive tumors** • Dabrafenib + trametinib[e,22] ***NTRK* gene fusion-positive tumors** • Entrectinib[h,27] • Larotrectinib[h,28] • Repotrectinib[h,29] **HER2-positive (IHC 3+) tumors** • Fam-trastuzumab deruxtecan-nxki[i,31] ***RET* gene fusion-positive tumors** • Selpercatinib (category 2B)[j,32] **dMMR/MSI-H tumors or TMB-H (≥10 mut/Mb) tumors** • Pembrolizumab[f,24-26,30] **Cytotoxic Chemotherapy** • Docetaxel, cisplatin, and fluorouracil[k,44]

[a] Consider programmed death ligand 1 (PD-L1) testing for patients with recurrent, progressive, or metastatic disease.
[b] Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin.
[d] These regimens can be given with concurrent radiation.
[e] For patients with *BRAF* V600E mutation-positive unresectable or metastatic solid tumors that have progressed following prior treatment and have no satisfactory alternative treatment options.
[f] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[h] For patients with *NTRK* gene fusion-positive tumors without a known acquired resistance mutation, that are metastatic or where surgical resection is likely to result in severe morbidity, and that have no satisfactory alternative treatments or that have progressed following treatment.
[i] For patients with advanced or metastatic solid tumors that progressed on or following prior systemic treatment and who have no satisfactory alternative treatment options.
[j] For patients with advanced or metastatic solid tumors that progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.
[k] Only for patients with PS ECOG 0–1.
[l] For patients ineligible to receive platinum-based chemotherapy.

Note: All recommendations are category 2A unless otherwise indicated.

Continued on OCC-B 9 of 14
References on OCC-B 13 of 14
OCC-B

*27 Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:271-282. Erratum in Lancet Oncol 2020;21:e70; Lancet Oncol 2020;21:e341; Lancet Oncol 2020;21:e372; and Lancet Oncol 2021;22:e428.
28 Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusionpositive cancers in adults and children. N Engl J Med 2018;378:731-739.
29 Solomon BJ, Drilon A, Lin JJ, et al. Repotrectinib in patients with NTRK fusionpositive advanced solid tumors, including non-small cell lung cancer: update from the phase 1/2 TRIDENT-1 trial [abstract]. Eur Soc Med Onc Congress 2023;34(Suppl 2):Abstract 1372P.

Hintergrund:
Entrectinib and larotrectinib (TRK-directed TKIs), and repotrectinib (a nextgeneration ROS1 and TRK-directed TKI), are used as single agents in patients with NTRK gene fusion-positive tumors without a known acquired resistance mutation, that are metastatic or where surgical resection is likely to result in severe morbidity, and that have no satisfactory alternative treatments or that have progressed following treatment. A pooled analysis of three clinical trials (two phase 1 trials [ALKA-372–001 and STARTRK-1] and one phase 2 trial [STARTRK-2]) evaluated the activity of entrectinib in 54 patients aged ≥18 years with NTRK gene fusion-positive solid tumors.[45] Thirty one participants (57%; 95% CI 43.2–70.8]) had an objective response, of which 4 (7%) and 27 (50%) had a complete response and partial response, respectively. The average duration of response was 10 months. To evaluate the efficacy of larotrectinib on NTRK gene fusionpositive solid tumors, 55 patients were enrolled in one of three protocols: a phase 1 study involving adults, a phase 1–2 study involving children, or a phase 2 study involving adolescents and adults.[44] ORR was 75% (95% CI, 61–85) at the primary data cutoff date. Seven (13%) patients had a complete response, 34 (62%) had a partial response, and 7 (13%) had stable disease. At 1 year, 71% of participants continued to have a response and 55% remained progression free. The ongoing phase I/II TRIDENT-1 trial evaluated the safety and efficacy of repotrectinib in TKInaïve and TKI-pretreated ROS1 and NTRK gene fusion-positive locally advanced or metastatic solid tumors.[185] Of the total participants in the study (TKI-naïve: n = 40; TKI-pretreated: n = 48), one (n =1) had CUP in the TKI-pretreated cohort. The primary endpoint of TRIDENT-1 was confirmed ORR and results showed an ORR of 50% (95% CI, 35-65) in the TKI-pretreated cohort (Clinical Trial ID: NCT03093116).

Referenzen:
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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 12 of 12, December 2024) am 02.12.2024

#	Suchfrage
1	secretory:ti,ab,kw
2	[mh "breast neoplasms"[mj]]
3	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesion* OR malignan*):ti,ab,kw
4	#1 AND (#2 OR #3)
5	[mh "fibrosarcoma"]
6	(DFSP OR dermatofibrosarcoma OR fibrosarcoma*):ti,ab,kw
7	#5 OR #6
8	[mh "nevus, spindle cell"]
9	((pigmented AND spindle) OR reed) AND (nevus OR neve* OR nevi):ti,ab,kw
10	#8 OR #9
11	[mh "adenoma, pleomorphic"]
12	#3 AND (pleomorphic adenoma* OR salivary gland):ti,ab,kw
13	#11 OR #12
14	[mh "thyroid cancer, papillary"]
15	#3 AND (thyroid AND papillary):ti,ab,kw
16	#14 OR #15
17	[mh "thyroid neoplasms"[mj]]
18	#3 AND (thyroid AND differentiated):ti,ab,kw
19	#17 OR #18
20	[mh "nephroma, mesoblastic"]
21	(mesoblastic AND nephroma*):ti,ab,kw
22	#20 OR #21
23	[mh glioma[mj]]
24	glioma:ti,ab,kw
25	((high OR III OR 3 OR IV OR 4) AND grade*):ti,ab,kw
26	(#23 OR #24) AND #25
27	[mh "carcinoma, mucoepidermoid"]
28	mucoepidermoid*:ti,ab,kw
29	#27 OR #28
30	(solid tumor OR solid tumors OR solid tumour*):ti,ab,kw
31	((agnostic OR independent) AND (tumor OR tumors OR tumour* OR tissue OR histology)):ti,ab,kw
32	#30 OR #31
33	[mh "oncogene proteins, fusion"]
34	((oncogen* OR oncoprotein*) AND (driv* OR fusion*)):ti,ab,kw
35	[mh "receptor, trkA"]
36	[mh "receptor, trkB"]
37	[mh "receptor, trkC"]

38	[mh "TFG protein, human"]
39	((*TRK* OR ((neurotrophic AND tyrosine AND receptor* AND kinase*) AND (fusion* OR alteration* OR fused OR gene* OR rearrange*)))):ti,ab,kw
40	(*TRK* AND (fusion OR fused)):ti,ab,kw
41	(((Proto-Oncogene* AND trk) OR c-trk Protein* OR BDNF OR Brain Derived Neurotrophic Factor)):ti,ab,kw
42	#3 AND (#33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41)
43	#4 OR #7 OR #10 OR #13 OR #16 OR #19 OR #22 OR #26 OR #29 OR #32 OR #42
44	#43 with Cochrane Library publication date from Dec 2019 to present, in Cochrane Reviews

Systematic Reviews und Leitlinien in PubMed am 02.12.2024

verwendeter Suchfilter für Systematic Reviews ohne Änderung:

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

verwendeter Suchfilter für Leitlinien ohne Änderung:

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

#	Suchschritt
	Leitlinien
1	secretory breast carcinoma[nm]
2	mammary analogue secretory carcinoma[mh]
3	secretory[tiab] 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 lesion*[ti] OR malignan*[ti])
4	#1 OR #2 OR #3
5	fibrosarcoma[majr]
6	DFSP[ti] OR dermatofibrosarcoma[ti] OR fibrosarcoma*[ti]
7	#5 OR #6
8	(nevus, spindle cell[majr] AND skin neoplasms[mh]) OR (nevus, spindle cell[mh] AND skin neoplasms[majr])
9	((pigmented[tiab] AND spindle[tiab]) OR reed[tiab]) AND (nevus[tiab] OR neve*[tiab] OR nevi[tiab])
10	#8 OR #9
11	(adenoma, pleomorphic[majr] AND salivary gland neoplasms[mh]) OR (adenoma, pleomorphic[mh] AND salivary gland neoplasms[majr])

#	Suchschritt
12	(pleomorphic adenoma*[tiab] OR salivary gland[tiab]) 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 lesion*[ti] OR malignan*[ti])
13	#11 OR #12
14	thyroid cancer, papillary[majr]
15	(thyroid[tiab] AND papillary[tiab]) 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 lesion*[ti] OR malignan*[ti])
16	#14 OR #15
17	(thyroid neoplasms[majr] AND cell differentiation[mh]) OR (thyroid neoplasms[mh] AND cell differentiation[majr])
18	(thyroid[tiab] AND differentiated[tiab]) 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 lesion*[ti] OR malignan*[ti])
19	#17 OR #18
20	nephroma, mesoblastic[mh]
21	mesoblastic[tiab] AND nephroma*[tiab]
22	#20 OR #21
23	glioma[majr]
24	glioma*[ti]
25	(high[tiab] OR III[tiab] OR 3[tiab] OR IV[tiab] OR 4[tiab]) AND grade*[tiab]
26	(#23 OR #24) AND #25
27	carcinoma, mucoepidermoid[majr]
28	mucoepidermoid*[ti]
29	low[tiab] AND grade*[tiab]
30	(#27 OR #28) AND #29
31	solid tumor[tiab] OR solid tumors[tiab] OR solid tumour*[tiab]
32	(agnostic[ti] OR independent[ti]) AND (tumor[ti] OR tumors[ti] OR tumour*[ti] OR tissue[ti] OR histology[ti])
33	#31 OR #32
34	"oncogene proteins, fusion"[mh]
35	(oncogen*[tiab] OR oncoprotein*[tiab]) AND (driv*[tiab] OR fusion*[tiab])
36	"receptor, trkA"[mh]
37	"receptor, trkB"[mh]
38	"receptor, trkC"[mh]
39	"TFG protein, human"[nm]

#	Suchschritt
40	((NTRK*[tiab] OR (neurotrophic[tiab] AND tyrosine[tiab] AND receptor*[tiab] AND kinase*[tiab])) AND (fusion*[tiab] OR alteration*[tiab] OR fused[tiab] Or gene*[tiab] OR rearrange*[tiab]))
41	TRK[tiab] AND (fusion[tiab]OR fused[tiab])
42	TRKA[tiab] OR TRKB[tiab] OR TRKC[tiab] OR (Proto-Oncogene*[tiab] AND trk[tiab]) OR c-trk Protein*[tiab] OR BDNF[tiab] OR Brain Derived Neurotrophic Factor[tiab]
43	#34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42
44	(#43) AND (tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR neoplas*[tiab] OR sarcoma*[tiab] OR cancer*[tiab] OR lesion*[tiab] OR malignan*[tiab])
45	#4 OR #7 OR #10 OR #13 OR #16 OR #19 OR #22 OR #26 OR #30 OR #33 OR #44
46	(#45) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
47	(((#46) AND ("2019/12/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
48	(#47) NOT (retracted publication [pt] OR retraction of publication [pt])
	Systematische Reviews
49	(#45) AND ((treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab]))
50	(#49) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR

#	Suchschritt
	reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
51	(((#50) AND ("2019/12/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp])))
52	#51 NOT ("retracted publication"[Publication Type] OR "retraction of publication"[Publication Type] OR "preprint"[Publication Type])
	Systematische Reviews ohne Leitlinien
53	#52 NOT #48

Iterative Handsuche nach grauer Literatur, abgeschlossen am 04.12.2024

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)

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

- ECRI Guidelines Trust (ECRI)
- Trip Medical Database

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