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: 2026-B-071-z Selpercatinib

Stand: Mai 2026

| I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA | |
|---|---|
| **Selpercatinib<br>[zur Behandlung des fortgeschrittenen Schilddrüsenkarzinoms mit RET-Fusion]** | |
| **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. | - Strahlentherapie |
| Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen | **Beschluss über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V:**<br>- Lenvatinib: Beschluss vom 15.12.2015 und 15.08.2019<br>- Selpercatinib: Beschluss vom 02.09.2021<br>- Cabozantinib: Beschluss vom 01.12.2022<br>- Selpercatinib: Beschluss vom 07.11.2024 |
| 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**<br>**ATC-Code**<br>**Handelsname** | **Anwendungsgebiet**<br>(Text aus Fachinformation) |
|---|---|
| Zu bewertendes Arzneimittel: | |
| Selpercatinib<br>L01EX22<br>Retsevmo | Anwendungsgebiet:<br>Selpercatinib als Monotherapie wird angewendet zur Behandlung von Erwachsenen und **Kindern ab 2 Jahren** mit:<br>- fortgeschrittenem RET-Fusions-positiven Schilddrüsenkarzinom, das refraktär für radioaktives Jod ist (wenn radioaktives Jod angemessen ist) |
| **Zytostatika** | |
| Doxorubicin<br>L01DB01<br>generisch | - […]<br>- fortgeschrittenes oder rezidiviertes papilläres/follikuläres Schilddrüsenkarzinom<br>- anaplastisches Schilddrüsenkarzinom<br>- […] |
| **Proteinkinaseinhibitoren** | |
| Cabozantinib<br>L01EX07<br>Cabometyx | CABOMETYX ist als Monotherapie für die Behandlung von Erwachsenen mit lokal fortgeschrittenem oder metastasiertem differenziertem Schilddrüsenkarzinom (DTC) indiziert, die refraktär gegenüber Radiojod (RAI) sind oder dafür nicht in Frage kommen und bei denen während oder nach einer vorherigen systemischen Therapie eine Progression aufgetreten ist. |
| Lenvatinib<br>L01EX08<br>Lenvima | <u>Differenziertes Schilddrüsenkarzinom (DTC)</u><br>LENVIMA als Monotherapie ist indiziert für die Behandlung von erwachsenen Patienten mit progressivem, lokal fortgeschrittenem oder metastasiertem differenziertem (papillärem/follikulärem/Hürthle-Zell-) Schilddrüsenkarzinom (DTC), das nicht auf eine Radiojodtherapie (RAI) angesprochen hat.<br>[…] |
| Selpercatinib<br>L01EX22<br>Retsevmo | Retsevmo als Monotherapie wird angewendet zur Behandlung von Erwachsenen und Jugendlichen ab 12 Jahren mit:<br>- fortgeschrittenem RET-Fusions-positiven Schilddrüsenkarzinom, das refraktär für radioaktives Jod ist (wenn radioaktives Jod angemessen ist)<br>[…] |

| II. Zugelassene Arzneimittel im Anwendungsgebiet | |
|---|---|
| Sorafenib<br>L01EX02<br>Nexavar | <u>Differenziertes Schilddrüsenkarzinom</u><br>Nexavar ist angezeigt zur Behandlung von Patienten mit progressivem, lokal fortgeschrittenem oder metastasiertem, differenziertem (papillärem/follikulärem/Hürthle-Zell-) Schilddrüsenkarzinom, welches gegenüber radioaktivem Jod refraktär ist.<br>[…] |

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

## Abteilung Fachberatung Medizin

# Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie

# Vorgang: 2026-B-071z (Beratung nach § 35a SGB V) Selpercatinib

| | |
|---|---|
| Auftrag von: | Abt. AM |
| Bearbeitet von: | Abt. FB Med |
| Datum: | 28. April 2026 |

# Inhaltsverzeichnis

# Abkürzungsverzeichnis

| | |
|---|---|
| ATA | American Thyroid Association |
| ATC | Anaplastic Thyroid Cancer |
| AWG | Anwendungsgebiet |
| AWMF | Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften |
| CYP | Children and Young People |
| dMMR | Mismatch repair deficient |
| DTC | Differentiated Thyroid Cancer |
| ECRI | Emergency Care Research Institute |
| FTC | Follicular Thyroid Carcinoma |
| G-BA | Gemeinsamer Bundesausschuss |
| GIN | Guidelines International Network |
| GoR | Grade of Recommendations |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| HR | Hazard Ratio |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen |
| KI | Konfidenzintervall |
| LoE | Level of Evidence |
| MTC | Medullary Thyroid Cancer |
| NICE | National Institute for Health and Care Excellence |
| OR | Odds Ratio |
| PTC | Papillary Thyroid Carcinoma |
| RAI | Radiojodtherapie |
| RET-PV | RET-Fusions-positives Schilddrüsenkarzinom (RET pathogenic variant) |
| RR | Relatives Risiko |
| SIGN | Scottish Intercollegiate Guidelines Network |
| TKI | Tyrosinkinase-Inhibitor |
| TMB | Tumormutationslast (Tumor Mutational Burden) |
| TRIP | Turn Research into Practice Database |
| WHO | World Health Organization |

# 1 Indikation

Behandlung von fortgeschrittenem RET-Fusions-positivem Schilddrüsenkrebs, die auf radioaktives Jod nicht ansprechen (sofern die Behandlung mit radioaktivem Jod indiziert ist) bei Kindern ab 2 Jahren und Jugendlichen bis 12 Jahren.

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

# 2 Systematische Recherche

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

Der Suchzeitraum der systematischen Literaturrecherche wurde auf die letzten fünf Jahre eingeschränkt und die Recherchen am 10.04.2026 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Auflistung durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 1483 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. Dabei wurde für systematische Reviews, inkl. Meta-Analysen, ein Publikationszeitraum von 2 Jahren und für Leitlinien von 5 Jahren betrachtet. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Alle eingeschlossenen Referenzen wurden im Volltext beschafft. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen im Volltext gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 3 Referenzen eingeschlossen. Es erfolgt eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

# 3 Ergebnisse

## 3.1 Cochrane Reviews

Es wurden keine geeigneten Cochrane Reviews im vorliegenden AWG identifiziert.

## 3.2 Systematische Reviews

Es wurden keine geeigneten systematischen Reviews im vorliegenden AWG identifiziert.

## 3.3 Leitlinien

**National Comprehensive Cancer Network (NCCN), 2025 [3].**

Thyroid carcinoma: version 1.2025

**Methodik**

*Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz hinsichtlich der Fragestellung wird die LL ergänzend dargestellt.*

Grundlage der Leitlinie

- Repräsentatives Gremium: unklar;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt; unklar
- Systematische Suche: keine Angaben zum Suchzeitraum, Literatursuche nur in Pubmed
- Auswahl und Bewertung der Evidenz: trifft teilweise zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: unklar;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft teilweise zu;
- Regelmäßige Überprüfung der Aktualität gesichert: All active NCCN Guidelines are reviewed and updated at least annually

Recherche/Suchzeitraum:

- Prior to the update of this version of the NCCN Guidelines for Thyroid Carcinoma, an electronic search of the PubMed database was performed to obtain key literature since the previous Guidelines update, using the following search term: thyroid carcinoma. The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature

LoE/GoR

| NCCN Categories of Evidence and Consensus | |
|---|---|
| **Category 1** | Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate. |
| **Category 2A** | Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate. |
| **Category 2B** | Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) 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.

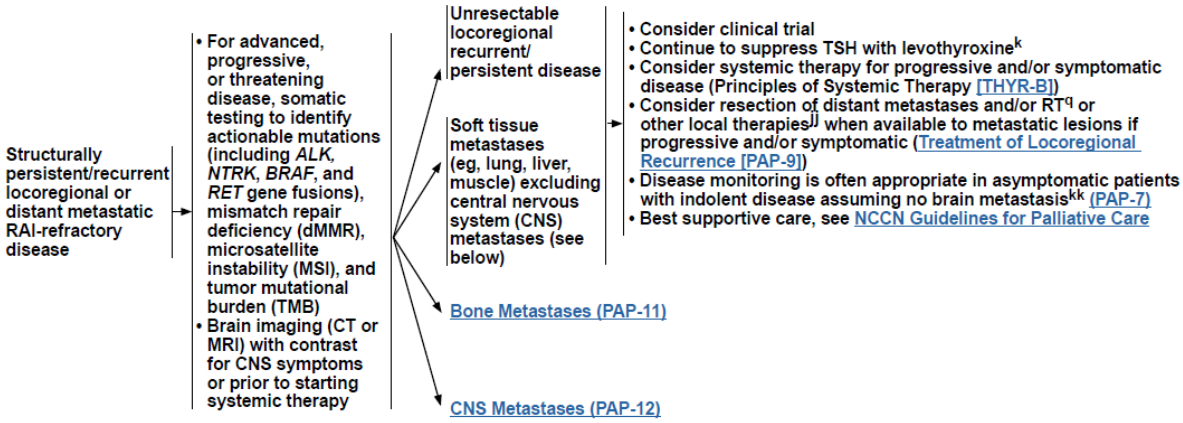
| NCCN Categories of Preference | |
|---|---|
| **Preferred intervention** | Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability. |
| **Other recommended intervention** | Other interventions that may be somewhat less efficacious, more toxic, or 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

## Papillary Carcinoma

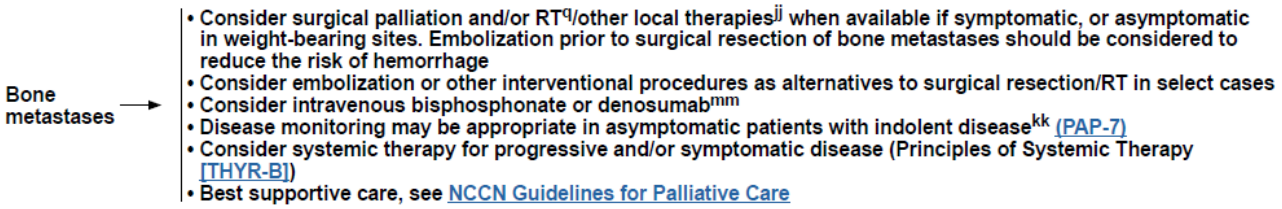
TREATMENT OF LOCALLY RECURRENT, ADVANCED, AND/OR METASTATIC RAI-REFRACTORY DISEASE




[k] Principles of TSH Suppression (THYR-A).
[q] Principles of Radiation and RAI Therapy (THYR-C).
[jj] Ethanol ablation, cryoablation, RFA, etc.
[kk] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Systemic Therapy (THYR-B).

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

TREATMENT OF METASTATIC RAI-REFRACTORY DISEASE [ll]




[q] Principles of Radiation and RAI Therapy (THYR-C).
[jj] Ethanol ablation, cryoablation, RFA, etc.
[kk] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Systemic Therapy (THYR-B).
[ll] RAI therapy is an option in some patients with bone metastases and RAI-sensitive disease.
[mm] Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk of hypocalcemia. Discontinuing denosumab can cause rebound atypical vertebral fractures. An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.

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

TREATMENT OF METASTATIC RAI-REFRACTORY DISEASE

CNS metastases →
- For solitary CNS lesions, either neurosurgical resection or stereotactic radiosurgery (SRS)[q] is preferred or
- For multiple CNS lesions, consider radiotherapy, including whole brain radiotherapy RT (WBRT) or SRS,[q] and/or resection in select cases
and/or
- Consider systemic therapy for progressive and/or symptomatic disease (Principles of Systemic Therapy [THYR-B])
- Best supportive care, see NCCN Guidelines for Palliative Care

[q] Principles of Radiation and RAI Therapy (THYR-C).

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

## Follicular Carcinoma

TREATMENT OF LOCALLY RECURRENT, ADVANCED, AND/OR METASTATIC RAI-REFRACTORY DISEASE

Structurally persistent/recurrent locoregional or distant metastatic RAI-refractory disease →
- For advanced, progressive, or threatening disease, somatic testing to identify actionable mutations (including *ALK*, *NTRK*, *BRAF*, and *RET* gene fusions),[hh] dMMR, MSI, and TMB
- Brain imaging (CT or MRI) with contrast for CNS symptoms or prior to starting systemic therapy

→ Unresectable locoregional recurrent/ persistent disease
→ Soft tissue metastases (eg, lung, liver, muscle) excluding CNS metastases (see below)

→
- Consider clinical trial
- Consider systemic therapy for progressive and/ or symptomatic disease (Principles of Systemic Therapy [THYR-B])
- Continue to suppress TSH with levothyroxine[f]
- Consider resection of distant metastases and/or EBRT[k] or other local therapies[ff] when available to metastatic lesions if progressive and/or symptomatic (Treatment of Locoregional Recurrence [FOLL-8])
- Disease monitoring is often appropriate in asymptomatic patients with indolent disease assuming no brain metastasis[gg] (FOLL-6)
- Best supportive care, see NCCN Guidelines for Palliative Care

→ Bone metastases (FOLL-10)

→ CNS metastases (FOLL-11)

[f] Principles of TSH Suppression (THYR-A).
[k] Principles of Radiation and RAI Therapy (THYR-C).
[ff] Ethanol ablation, cryoablation, RFA, etc.

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

[gg] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Systemic Therapy (THYR-B).
[hh] *BRAF* V600E mutation in follicular carcinoma is rare. If this mutation is present in a case of follicular carcinoma, pathology diagnosis should be questioned.

TREATMENT OF METASTATIC RAI-REFRACTORY DISEASE [ii]

Bone metastases →
- Consider surgical palliation and/or RT[k]/other local therapies[ff] when available if symptomatic, or asymptomatic in weight-bearing sites. Embolization prior to surgical resection of bone metastases should be considered to reduce the risk of hemorrhage
- Consider embolization or other interventional procedures as alternatives to surgical resection/RT in select cases
- Consider intravenous bisphosphonate or denosumab[jj]
- Disease monitoring may be appropriate in asymptomatic patients with indolent disease[gg] (FOLL-6)
- Consider systemic therapy for progressive and/or symptomatic disease (Principles of Systemic Therapy [THYR-B])
- Best supportive care, see NCCN Guidelines for Palliative Care

[k] Principles of Radiation and RAI Therapy (THYR-C).
[ff] Ethanol ablation, cryoablation, RFA, etc.
[gg] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Systemic Therapy (THYR-B).
[ii] RAI therapy is an option in some patients with bone metastases and RAI-sensitive disease.
[jj] Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk of hypocalcemia. Discontinuing denosumab can cause rebound atypical vertebral fractures. An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.

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

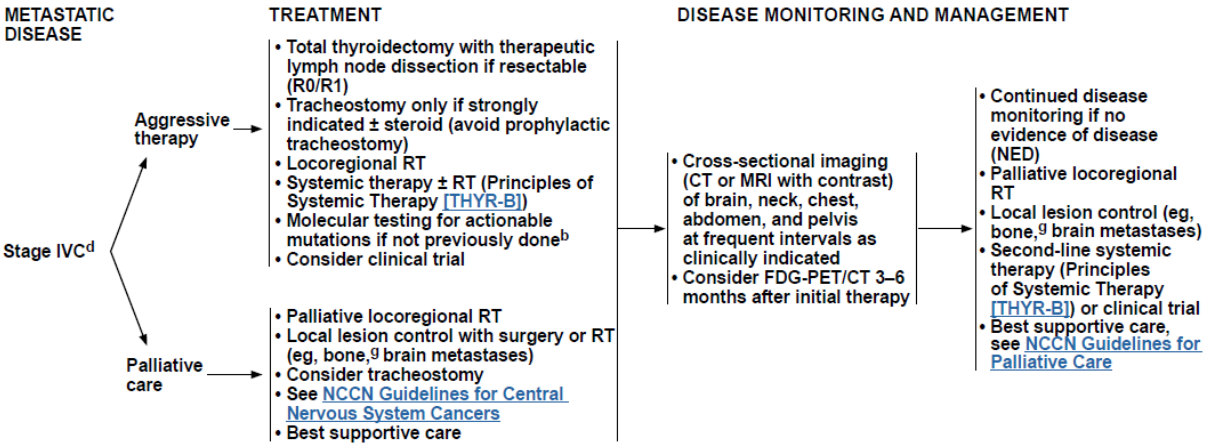
**TREATMENT OF METASTATIC RAI-REFRACTORY DISEASE**

**CNS metastases →**
- For solitary CNS lesions, either neurosurgical resection or SRS is preferred
  or
- For multiple CNS lesions, consider radiotherapy, including WBRT or SRS[k], and/or resection in select cases
  and/or
- Consider systemic therapy for progressive and/or symptomatic disease (Principles of Systemic Therapy [THYR-B])
- Best supportive care, see NCCN Guidelines for Palliative Care

[k] Principles of Radiation and RAI Therapy (THYR-C).

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

## Anaplastic Carcinoma




[b] Molecular testing should include *BRAF, NTRK, ALK, RET*, MSI, dMMR, and tumor mutational burden. BRAF IHC testing is recommended due to faster turnaround compared to genetic testing.
[d] Staging (ST-1).
[g] Consider use of intravenous bisphosphonates or denosumab. Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk. An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.

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

## Principles of Systemic Therapy

PRINCIPLES OF SYSTEMIC THERAPY

| Differentiated Thyroid Cancer (RAI-refractory papillary carcinoma, RAI-refractory follicular carcinoma, oncocytic carcinoma): Progressive and/or symptomatic disease | | |
|---|---|---|
| **Preferred regimen** | **Other recommended regimen** | **Useful in certain circumstances** |
| Lenvatinib (category 1)[a,b,c] | Sorafenib (category 1)[a,b,c] | • Cabozantinib if progression after lenvatinib and/or sorafenib (category 1 for papillary carcinoma; category 2A for follicular carcinoma and oncocytic carcinoma)<br>• Dabrafenib/trametinib[e] for *BRAF* V600E mutation that has progressed following prior treatment with no satisfactory alternative treatment options<br>• Pembrolizumab/lenvatinib if disease progression on lenvatinib<br>• Pemetrexed/carboplatin if disease progression following prior treatment<br>• *NTRK* gene fusion-positive advanced solid tumors<br>▸ Entrectinib<br>▸ Larotrectinib<br>▸ Repotrectinib<br>• *RET* gene fusion-positive tumors<br>▸ Pralsetinib<br>▸ Selpercatinib[d]<br>• Pembrolizumab[g] for TMB-H [≥10 [mut/Mb]] or for MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory alternative options<br>• Consider if clinical trials or other systemic therapies are not available or appropriate[f]:<br>▸ Axitinib<br>▸ Everolimus<br>▸ Pazopanib<br>▸ Sunitinib<br>▸ Vandetanib<br>▸ Dabrafenib (if *BRAF* positive) (category 2B)<br>▸ Vemurafenib (if *BRAF* positive) (category 2B) |

[a] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease.
[b] After consultation with neurosurgery and radiation oncology, data on the efficacy of lenvatinib or sorafenib for patients with brain metastases have not been established.
[c] Tyrosine kinase inhibitor (TKI) therapy should be used with caution in otherwise untreated CNS metastases due to bleeding risk.
[d] Selpercatinib is also FDA approved for pediatric patients 2 years of age or older.
[e] Dabrafenib/trametinib could also be appropriate as a first-line therapy for patients with high-risk disease who are not appropriate for VEGF inhibitors.
[f] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.
[g] See the NCCN Guidelines for Immunotherapy-Related Toxicities for treatment of toxicity from immunotherapy.

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

THYR-B

| Anaplastic Carcinoma: Systemic Therapy Regimens for Metastatic Disease | | |
|---|---|---|
| **Preferred regimens** | **Other recommended regimens** | **Useful in certain circumstances** |
| • *BRAF* V600E mutation positive<br>▸ Dabrafenib/trametinib[2]<br>• *NTRK* gene fusion-positive tumors<br>▸ Entrectinib[4]<br>▸ Larotrectinib[3]<br>▸ Repotrectinib[5]<br>• *RET* gene fusion-positive tumors<br>▸ Pralsetinib[7]<br>▸ Selpercatinib[6,d] | • Doxorubicin[8]<br>• Paclitaxel[8]<br>• Carboplatin/paclitaxel[1] (category 2B)<br>• Docetaxel/doxorubicin[1] (category 2B) | • Cisplatin/doxorubicin[8]<br>• Nivolumab[11,12,g,l]<br>• Pembrolizumab[9,g,m]<br>• Pembrolizumab/lenvatinib[10,g]<br>• Pemetrexed/carboplatin if disease progression following prior treatment[23] |

[a] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease.
[d] Selpercatinib is also FDA approved for pediatric patients 2 years of age and older.
[g] See NCCN Guidelines for Immunotherapy-Related Toxicities for treatment of toxicity from immunotherapy.
[l] Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.
[m] Pembrolizumab is FDA approved for patients with TMB-H [≥10 mut/mb] disease.

References

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

THYR-B

## KINASE INHIBITOR THERAPY IN ADVANCED THYROID CARCINOMA[13-22]

- **Oral kinase inhibitors demonstrate clinically significant activity in randomized, placebo-controlled clinical trials in locally recurrent unresectable and metastatic MTC and in RAI-refractory differentiated thyroid cancer (DTC).**

- **When considering kinase inhibitor therapy for individual patients, several factors should be considered.**
  - **Kinase inhibitor therapy can be associated with improved progression-free survival, but is not curative.**
  - **Kinase inhibitor therapy is expected to cause side effects that may have a significant effect on quality of life.**
  - **The natural history of MTC and DTC is quite variable with rates of disease progression ranging from a few months to many years.**

- **The pace of disease progression should be factored into treatment decisions. Patients with very indolent disease who are asymptomatic may not be appropriate for kinase inhibitor therapy, particularly if the side effects of treatment will adversely affect the patient's quality of life, whereas patients with more rapidly progressive disease may benefit from kinase inhibitor therapy, even if they have drug-induced side effects.**

- **Optimal management of kinase inhibitor side effects is essential. Where available, guidelines outlining the management of the dermatologic, hypertensive, and gastrointestinal side effects of kinase inhibitors can be used; side effects have been fatal. In addition, dose modification may be required, including dose holds and dose reductions.**

- **Molecular testing has been shown to be beneficial when making targeted therapy decisions, particularly related to drug therapies or clinical trial participation. In addition, the presence of some mutations may have prognostic importance.**

## REFERENCES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[2] Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib and trametinib treatment in patients with locally advanced or metastatic BRAF V600-mutant anaplastic thyroid cancer. J Clin Oncol 2018;36:7-13.
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[4] 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.
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[9] Marabelle A, Fakih MG, Lopez J, et al. Association of tumor mutational burden with outcomes in patients with select advanced solid tumors treated with pembrolizumab in KEYNOTE-158. Presented at the Annual Meeting of the European Society for Medical Oncology; September 30, 2019; Barcelona, Spain.
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*European Thyroid Association*

2022 European Thyroid Association Guidelines for the management of pediatric thyroid nodules and differentiated thyroid carcinoma

**Zielsetzung/Fragestellung**

At present, no European recommendations for the management of pediatric thyroid nodules and differentiated thyroid carcinoma (DTC) exist. Differe nces in clinical, molecular, and pathological characteristics between pediatric and adult DTC emphasize the need for specific recommendations for the pediatric population. […] The present guideline provides guidance for healthcare professionals to make well-considered decisions together with patients and parents regarding diagnosis, treatment, and follow-up of pediatric thyroid nodules and DTC.

**Methodik**

*Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund fehlender höherwertiger Evidenz hinsichtlich der Fragestellung wird die LL ergänzend dargestellt.*

Grundlage der Leitlinie

Die „ATA Pediatric Guideline“ aus 2015 diente als Rahmen für die vorliegende Leitlinie.

- Repräsentatives Gremium, Patientenvertretung jedoch nicht ersichtlich;
- Interessenkonflikte und finanzielle Abhängigkeiten dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse nicht explizit beschrieben, externes Begutachtungsverfahren nicht dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist über den Hintergrundtext dargestellt;
- Regelmäßige Überprüfung der Aktualität unklar.

Recherche/Suchzeitraum:

- For each clinical question, a systematic literature search was performed using Pubmed (last search date: May 2020)
- If all expert panel members agreed on a recommendation of the 2015 ATA Pediatric Guideline (8), no specific search was performed.

LoE

- modified Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to grade the quality of evidence
- Quality of evidence was scored as
- **level 1: high** (randomized controlled trial (RCT) evidence/meta-analysis – high-quality evidence (⊕⊕⊕⊕));
- **level 2: moderate** (intervention short of RCT or large observational studies –moderate-quality (⊕⊕⊕⊖));

- **level 3: low quality** (case–control studies, case series – low quality (⊕⊕⊖⊖));
- **level 4: very low quality** (case reports, expert opinion – very low quality (⊕⊖⊖⊖))
- If all expert panel members agreed on a recommendation of the 2015 ATA Pediatric Guideline […] the grade of quality of evidence, as had been assigned by the ATA working group, was assumed. The statements based on recommendations of the 2015 ATA Pediatric Guideline are considered as 'expert opinion' (level 4).

GoR

- The strength of each statement was scored as **strong (S, a recommendation)** or **weak (W, a suggestion – not a recommendation)**, depending on the clinical significance and weight of opinion favoring the statement.
- **Strong recommendations** are clinically important best practice and **should be applied to most patients in most circumstances. Strong statements are associated with the phrase 'we recommend'.**
- In contrast, **weak statements should be considered** by the clinician and will be applicable to best practice only to certain patients or under certain circumstances. […] **weak statements are associated with the phrase 'we suggest'**.

Sonstige methodische Hinweise

- Die Leitlinie bezieht sich auf Kinder und Jugendliche bis 18 Jahre.
- Falls Konsens bestand, wurden Empfehlungen und deren Evidenzgraduierung von der 2015 ATA Leitlinie übernommen und in der vorliegenden Leitlinie als Expertenmeinung gekennzeichnet.
- Die Kennzeichnung „4W" spiegelt einen Vorschlag („suggestion") mit Evidenzgrad 4 wider, also einen schwachen Empfehlungsgrad (mit W für „weak").

**Empfehlungen**

*Hinweis: Die Leitlinie enthält keine Empfehlungen speziell für fortgeschrittenen RET-Fusions-positiven Schilddrüsenkrebs im vorliegenden Anwendungsgebiet.*

**C9. Targeted therapy in the management of pediatric DTC**

Suggestion 17:

**We suggest** that, in specific cases, treatment with targeted therapy may be considered, but this should preferably only be given in the setting of clinical trials (4W).

Hintergrundinformation

Pediatric DTC commonly presents with advanced disease at diagnosis with a high prevalence of cervical lymph node metastases and lung metastases, usually identified on the whole-body scan performed after I-131 treatment. However, the outcome of these cases is good, and death-related events are very rare. The major reason for this good outcome is the responsiveness of the metastatic lesions to I-131 therapy. **Very rarely, children with metastatic thyroid cancer require therapies other than I-131. It is however interesting to recall that childhood PTC has a high prevalence of RET/PTC rearrangements as well as NTRK fusions (116).** This information is particularly relevant since new tyrosine kinase inhibitors directed against either RET or TRK alterations (117, 118) are under development and have already reached the approval of FDA and EMA for adult patients. The expert panel searched the outcome of DTC in children treated with surgery and I-131 vs those treated with different treatment modalities (Appendix A [Q18], B). Mahajan et al. reported three cases for whom lenvatinib was given (119). Two patients remained clinically stable on lenvatinib 11 and 23 months after initiation of therapy. The third patient transitioned to a tumor-specific targeted therapy after 1 month. Waguespack et al. have reported one 14-year-old female treated with sorafenib who showed significant improvement in lung metastases 67 days after start of treatment (120).

Based on these case reports, **the expert panel agreed that targeted therapy may play a role in the management of disease in very rare cases of pediatric progressive I-131-refractory PTC, for whom no**

**standard therapy exists (Appendix C). There is currently no consensus on the absolute definition or criterion that defines that a patient has I-131-refractory DTC.** Each patient should be managed individually with a thorough understanding of the many factors that enter the appraisal of the likelihood that a tumor will be refractory to I-131, as well as weighing the patient's specific clinical scenario and the risks and benefits of I-131 therapy. **Pediatric progressive I-131-refractory PTC may be suspected in cases with presence of more than one metastatic lesion with at least one lesion without I-131 uptake in the post-therapy scan, structural progression of tumors after I-131 therapy despite the presence of iodine uptake in the post-therapy scan, or significant uptake on FDG PET/CT (121, 122)**.

## D7. Radioiodine refractory disease

Suggestion 27A:

**We suggest** that, when radioiodine refractory disease is suspected, its presence should be thoroughly investigated and confirmed before considering systemic targeted therapy. An observation or wait-and-see strategy may be appropriate (**4W**).

Suggestion 27B:

**We suggest** that targeted therapy should be reserved only for patients with large-volume disease which is significantly progressing on TSH-suppressive therapy and not amenable to surgical approach and should preferably be given in a research setting (**4W**).

**Hintergrundinformation**

In pediatric DTC patients, metastatic disease is well differentiated and often characterized by intense iodine uptake on post-therapeutic I-131 WBS. Responses to I-131 in this setting are good and patients often achieve complete remission after repeated I-131 therapeutic courses (103, 105). In the pediatric population, I-131 refractory disease is rare (109). In the setting of radioiodine refractory thyroid cancer not amenable to surgical resection, **systemic therapy with TKIs may be considered. However, although TKIs have been largely and successfully used in adult patients, molecularly targeted therapy has not been applied in a large cohort of DTC pediatric patients and only few case report or series are available in literature (119, 120). Although encouraging results have been reported, a long duration of treatment with TKI could significantly influence the quality of life and should be reserved only for specific patients as I-131 refractory pediatric DTC patients usually do well on TSH-suppressive levothyroxine therapy alone (156).** In this clinical setting, the definition of I-131 refractory disease is of primary importance considering that very few pediatric patients will not respond to I-131 and even in this setting, may remain stable or without symptoms over the years (122).

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**Howard SR et al., 2022 [1].**

Paediatric differentiated thyroid carcinoma: a UK National Clinical Practice Consensus Guideline

**Zielsetzung/Fragestellung**

This guideline is written as a reference document for clinicians presented with the challenge of managing paediatric patients with **differentiated thyroid carcinoma up to the age of 19 years**. Care of paediatric patients with differentiated thyroid carcinoma differs in key aspects from that of adults, and there have been several recent developments in the care pathways for this condition; this guideline has sought to identify and attend to these areas. It addresses the presentation, clinical assessment, diagnosis, management (both surgical and medical), genetic counselling, follow-up and prognosis of affected patients. […] It is intended as an evidence base for future optimal management and to improve the quality of clinical care of paediatric patients with differentiated thyroid carcinoma.

**Methodik**

*Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund fehlender höherwertiger Evidenz hinsichtlich der Fragestellung wird die LL ergänzend dargestellt.*

<u>Grundlage der Leitlinie</u>

- Repräsentatives Gremium, Patientenvertretung unklar;
- Interessenkonflikte und finanzielle Abhängigkeiten dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist über den Hintergrundtext dargestellt;
- Regelmäßige Überprüfung der Aktualität nicht beschrieben.

<u>Recherche/Suchzeitraum:</u>

- […] using the Ovid MEDLINE database (1990 – March 2015), the Cochrane Library, TRIP and the EMBASE database […]
- A further search was added for papers published March 2015 – August 2020 using the same databases and methodology to ensure the most up to date literature was included.

<u>LoE/GoR</u>

- The quality of evidence and risk of bias was assessed using the **GRADE** approach.
- The strength of the recommendation was determined by the **trade-off between the potential benefits and potential harms of the recommendation**, taking into account the quality of the underpinning evidence.
- Where an evidence base to formulate recommendations was lacking (i.e., no evidence, contradictory evidence or very low-quality evidence), an **expert consensus** was necessary (**70% or more of the Delphi respondents**)
- We followed a consistent NICE terminology, using the verbs **'offer' and 'consider' for strong and less strong interventions** / actions, respectively and the verbs **'should' for strong** and **'may' and 'consider' for moderate** recommendations.

**Empfehlungen**

*Hinweis: Die Leitlinie enthält keine Empfehlungen speziell für fortgeschrittenen RET-Fusions-positiven Schilddrüsenkrebs im vorliegenden Anwendungsgebiet.*

**Differentiated thyroid cancer: metastatic, recurrent or persistent disease**

53. Consider further surgical resection for persistent local structural disease (**Moderate Recommendation, GDG Consensus**)

Hintergrundinformation: Structural disease refers to a definite abnormality on imaging, identifying that cancer has infiltrated anatomical structures such as jugular vein, trachea or oesophagus, or metastatic lymph nodes. If structural disease is detected on the neck US, MDT discussion about the role of further surgery is recommended.

57. Consider the use of palliative targeted therapy in CYP with progressing radioiodine refractory DTC (**Moderate Recommendation, Moderate- Quality Evidence**)

Hintergrundinformation: Radioiodine refractory disease includes either the presence of at least one lesion that does not take up I-131 or clinical evidence that I-131 is no longer providing benefit. There is no evidence that traditional chemotherapeutic agents are an effective treatment of radioiodine refractory DTC in CYP. **Targeted agents, sorafenib and lenvatinib, have been licensed more generally for the treatment of radioiodine refractory disease in adults but have not been proven in the paediatric population. In young adults over the age of 16 with progressing (i.e., with radiographic evidence of disease progression), radioiodine refractory DTC, sorafenib and lenvatinib can be considered as per marketing approval and based on phase III data from DECISION (Brose et al. 2014) and SELECT (Schlumberger et al. 2015) trials, respectively.** These drugs should be administered under the supervision of clinicians with experience in managing these drugs and associated toxicities (Brose et al. 2012).
The use of next-generation sequencing to identify gene alterations, including BRAF mutations, RET, ALK and NTRK gene fusions, depends on the availability of such testing and NHS England is currently establishing a national test directory service over seven genomic hubs UK-wide to carry out cancer genomic testing by next-generation sequencing and interpret all results. Currently, the service offers testing in paediatric DTC via a multi-target next-generation sequencing panel for RET small and structural variants and NTRK1/2/3 structural variants (https://www. england.nhs.uk/publication/national-genomic-test-directories/). Future studies in CYP will likely help to direct targeted therapies for the treatment of individuals with particular somatic point mutations and fusion genes (Nies et al. 2021).
NICE has recommended the use of Larotrectinib (https://www.nice.org.uk/guidance/ta630) within the Cancer Drugs Fund as an option for treating NTRK fusion-positive solid tumours in adults and children if the disease is locally advanced or metastatic, or surgery could cause severe health problems and they have no satisfactory treatment options. Entrectinib has been recommended for use under similar circumstances in children over 12 years of age if they have not had treatment with an NTRK inhibitor previously (https://www.nice.org.uk/guidance/ ta644). Clinical trials of RET inhibitors are ongoing.
**In the rare situation where CYP are not cured of their DTC, palliative care teams should be involved in care at an early stage. Symptom control may include palliative radiotherapy,** in a similar manner to as described above in Recommendation 55. **Other locally ablative treatment modalities such as surgery, radiofrequency ablation and vertebroplasty can be considered** to treat deposits of disease that are causing specific symptoms.

58. Consider the use of external beam radiotherapy for symptom control in the palliative setting (**Moderate Recommendation, Low-Quality Evidence, Delphi Consensus 73%**)

Hintergrundinformation: External beam radiotherapy is very rarely indicated in CYP with DTC in the primary or adjuvant setting because their disease is usually very iodine avid and sensitive so there is no benefit from the addition of external beam radiotherapy (Hay et al. 2010). External beam radiotherapy to the neck can be of use in the palliative setting for symptom control, for example in cases of unresectable disease invading the larynx, trachea or oesophagus, where uncontrolled growth of the disease will cause life-threatening or distressing symptoms. There may also be a role in palliating the effects of more distant metastases for example painful bone metastases, bleeding or obstructing deposits of tumour or brain

metastases. Any external beam radiotherapy administered should be delivered in a dedicated paediatric radiotherapy centre (Landau et al. 2000).

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# 4 Detaillierte Darstellung der Recherchestrategie

**Cochrane Library - Cochrane Database of Systematic Reviews (Issue 4 of 12, April 2026) am 08.04.2026**

| # | Suchschritt |
|---|---|
| 1 | [mh "Thyroid Neoplasms"] |
| 2 | [mh "Adenocarcinoma, Papillary"] |
| 3 | [mh "Adenocarcinoma, Follicular"] |
| 4 | [mh "thyroid carcinoma, anaplastic"] |
| 5 | thyroid:ti,ab,kw |
| 6 | (cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesion* OR malignan*):ti,ab,kw |
| 7 | #5 AND #6 |
| 8 | #1 OR #2 OR #3 OR #4 OR #7 |
| 9 | #8 with Cochrane Library publication date from Apr 2021 to present, in Cochrane Reviews |

**Leitlinien und systematische Reviews in PubMed am 08.04.2026**

verwendete Suchfilter für Leitlinien:
*Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 20.03.2026*

verwendeter Suchfilter für systematische Reviews:
*Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 01.01.2026.*

| # | Suchschritt |
|---|---|
| | **Leitlinien** |
| 1 | Thyroid Neoplasms[mh] |
| 2 | Adenocarcinoma, Papillary [mh] |
| 3 | Adenocarcinoma, Follicular[mh] |
| 4 | Thyroid Carcinoma, Anaplastic[mh] |
| 5 | #1 OR #2 OR #3 OR #4 |
| 6 | Thyroid[ti] OR multiple endocrine[ti] |
| 7 | (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]) |
| 8 | #6 AND #7 |
| 9 | (((((papillary[tiab]) OR Hurthle cell*[tiab]) OR follicular[tiab]) OR differentiated[tiab]) OR nonmedullary[tiab]) |
| 10 | (((medullary[tiab]) OR C-cell*[tiab]) OR calcitonin[tiab]) OR anaplastic[tiab] |
| 11 | thyroid[tiab] |

| # | Suchschritt |
|---|---|
| 12 | (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]) |
| 13 | (#9 OR #10) AND #11 AND #12 |
| 14 | #5 OR #8 OR #13 |
| 15 | (#14) AND (Guideline[pt] OR Practice Guideline[pt] OR Consensus Statement [pt] OR Consensus Development Conference, NIH[pt] OR guideline*[ti] OR recommendation*[ti] OR ((consensus[ti] OR position[ti]) AND (expert[ti] OR delphi[ti] OR statement*[ti] OR paper*[ti] OR document*[ti] OR report*[ti]))) |
| 16 | (#15) AND ("2021/04/01"[PDAT] : "3000"[PDAT]) |
| 17 | (#16) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "preprint"[pt]) |
| | **systematische Reviews** |
| 18 | (#14) AND ("systematic review"[pt] OR "meta-analysis"[pt] OR "network meta-analysis"[pt] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR (("evidence-based medicine"[mh] OR evidence synthes*[tiab]) AND "review"[pt]) OR ((("evidence based"[tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR "technical report"[pt] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab]) |
| 19 | (#18) AND ("2021/04/01"[PDAT] : "3000"[PDAT]) |
| 20 | (#19) NOT "The Cochrane database of systematic reviews"[Journal] |
| 21 | (#20) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "preprint"[pt]) |
| | **systematische Reviews ohne Leitlinien** |
| 22 | (#21) NOT (#17) |
| 23 | (#22) AND ("2024/04/01"[PDAT] : "3000"[PDAT]) |
| 24 | #22 NOT #23 |

**Iterative Handsuche nach grauer Literatur, abgeschlossen am 10.04.2026**

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- American Society of Clinical Oncology (ASCO)
- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

## Referenzen


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Gemeinsamer Bundesausschuss

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

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