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-046-z Selpercatinib

Stand: April 2024

| 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>- Cabozantinib: Beschluss vom 01.12.2022<br>- Lenvatinib: Beschluss vom 15.12.2015 und 15.08.2019<br>- Selpercatinib: Beschluss vom 02.09.2021 |
| 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 | Zugelassenes Anwendungsgebiet:<br>Selpercatinib 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) |
| **Zytostatika** | |
| Doxorubicin<br>L01DB01<br>generisch | - […]<br>- fortgeschrittenes papilläres/follikuläres Schilddrüsenkarzinom<br>- anaplastisches Schilddrüsenkarzinom |
| **Proteinkinaseinhibitoren** | |
| Cabozantinib<br>L01EX07<br>Caprelsa | Differenziertes Schilddrüsenkarzinom (differentiated thyroid carcinoma, DTC)<br>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>L01XE29<br>Lenvima | LENVIMA ist indiziert als Monotherapie 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>L01XE05<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 nach § 35a SGB V

# Vorgang: 2024-B-046z (Selpercatinib)

| | |
|---|---|
| Auftrag von: | Abt. AM |
| Bearbeitet von: | Abt. FB Med |
| Datum: | 12. März 2024 |

# Inhaltsverzeichnis

# Abkürzungsverzeichnis

| | |
|---|---|
| ATA | American Thyroid Association |
| ATC | Anaplastic Thyroid Cancer |
| AWG | Anwendungsgebiet |
| AWMF | Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften |
| CNS | Central Nervous System |
| CR | Complete Response |
| CYP | Children and Young People |
| dMMR | Mismatch Repair Deficient |
| DTC | Differentiated Thyroid Cancer |
| EBRT | External Beam Radiation Therapy |
| ECRI | ECRI Guidelines Trust |
| ETA | European Thyroid Association |
| FDA | Food and Drug Administration |
| FNA | Fine-Needle Aspiration |
| FTC | Follicular Thyroid Carcinoma |
| G-BA | Gemeinsamer Bundesausschuss |
| GDG | Guideline Development Group |
| GIN | Guidelines International Network |
| GoR | Grade of Recommendations |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| HR | Hazard Ratio |
| IHC | Immunohistochemistry |
| IMRT | Intensity-Modulated Radiation Therapy |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen |
| ITT | Intention-To-Treat |
| KI | Konfidenzintervall |
| LCR | Local Control Rate |
| LoE | Level of Evidence |
| MDT | Multidisciplinary Team |
| MKI | Multi-Kinase Inhibitor |
| MSI(-H) | Microsatellite Instability(-High) |
| MTC | Medullary Thyroid Cancer |
| NCCN | National Comprehensive Cancer Network |
| NCDB | National Cancer Database |

| | |
|---|---|
| NICE | National Institute for Health and Care Excellence |
| OR | Odds Ratio |
| ORR | Overall Response Rate |
| OS | Overall Survival |
| PD | Progressive Disease |
| PDTC | Poorly Differentiated Thyroid Cancer |
| PFS | Progression-Free Survival |
| PR | Partial Response |
| PS | Performance Status |
| PTC | Papillary Thyroid Carcinoma |
| RAI(-rDTC) | Radioiodine (-refractory Differentiated Thyroid Cancer) |
| RCT | Randomized Controlled Trial |
| RFA | Radiofrequency Ablation |
| RR | Relatives Risiko |
| RT | Radiotherapie |
| SBRT | Stereotactic Body Radiotherapy |
| SEER | Surveillance, Epidemiology, and End Results |
| SIGN | Scottish Intercollegiate Guidelines Network |
| SRS | Stereotactic Radiosurgery |
| TEAE | Treatment-Emergent Adverse Event |
| Tg (ab) | (Anti)thyroglobulin (Antibodies) |
| TKI | Tyrosinkinase-Inhibitor |
| TMB(-H) | Tumor Mutational Burden(-High) |
| TRIP | Turn Research into Practice Database |
| TSH | Thyroid-Stimulating Hormone |
| US | Ultrasound |
| VEGF | Vascular Endothelial Growth Factor |
| WBRT | Whole Brain Radiation Therapy |
| WBS | Whole-Body Scan |
| WHO | World Health Organization |

# 1 Indikation

Behandlung von Erwachsenen und Jugendlichen ab 12 Jahren mit einem fortgeschrittenen Schilddrüsenkarzinom, das refraktär gegenüber einer Radiojodtherapie ist (wenn eine Radiojodtherapie geeignet ist).

*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 *Schilddrüsenkarzinom* 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.ecosia.org/) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 26.02.2024 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 1120 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 7 Referenzen eingeschlossen. Es erfolgte 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

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**Su J et al., 2022 [6].**

Efficacy and safety of multi-kinase inhibitors in patients with radioiodine-refractory differentiated thyroid cancer: a systematic review and meta-analysis of clinical trials

➔ Siehe auch
- **Su J et al., 2023 [5].**
- **Yu J et al., 2024 [7].**

**Fragestellung**

Radioiodine-refractory differentiated thyroid cancer (RAI-rDTC) has frequently been associated with poor prognosis. We conducted a meta-analysis of published randomized controlled trials to evaluate multi-kinase inhibitors' efficacy and safety profile treatment.

**Methodik**

Population:
- Radioiodine-refractory differentiated thyroid cancer (RAI-rDTC)
- Aged 18 and above
- trials were excluded if they included anaplastic thyroid cancer (ATC) or medullary thyroid cancer (MTC);

Intervention:
- Apatinib, Cabozantinib, **Lenvatinib, Sorafenib,** Vandetanib

Komparator:
- Placebo

Endpunkte:
- Progression-free survival in RAI-rDTC, Overall survival in RAI-rDTC
- Overall survival in papillary thyroid carcinoma (PTC) or follicular thyroid carcinoma (FTC)
- Adverse events

Recherche/Suchzeitraum:
- using PubMed, Embase, Cochrane, and Medline databases
- up to 20 December 2021

Qualitätsbewertung der Studien:
- Cochrane Risk of Bias tool

## Ergebnisse

Anzahl eingeschlossener Studien:

- six articles, all of which were double-blinded, randomized controlled trials.

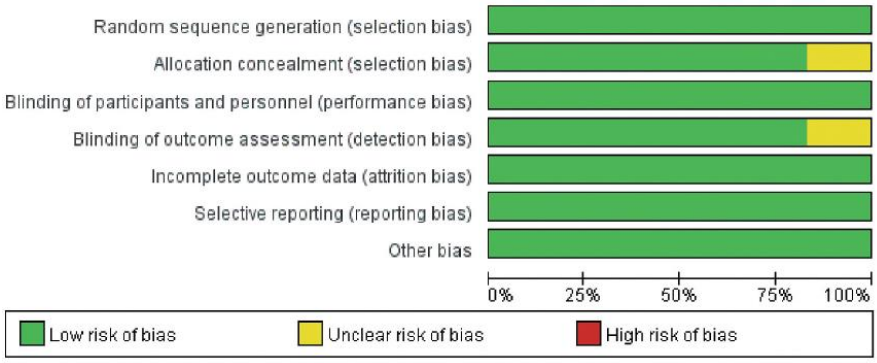
Charakteristika der Population/Studien:

- A total of 1384 patients were included in six studies

Table 1. Overview of literature characteristics.

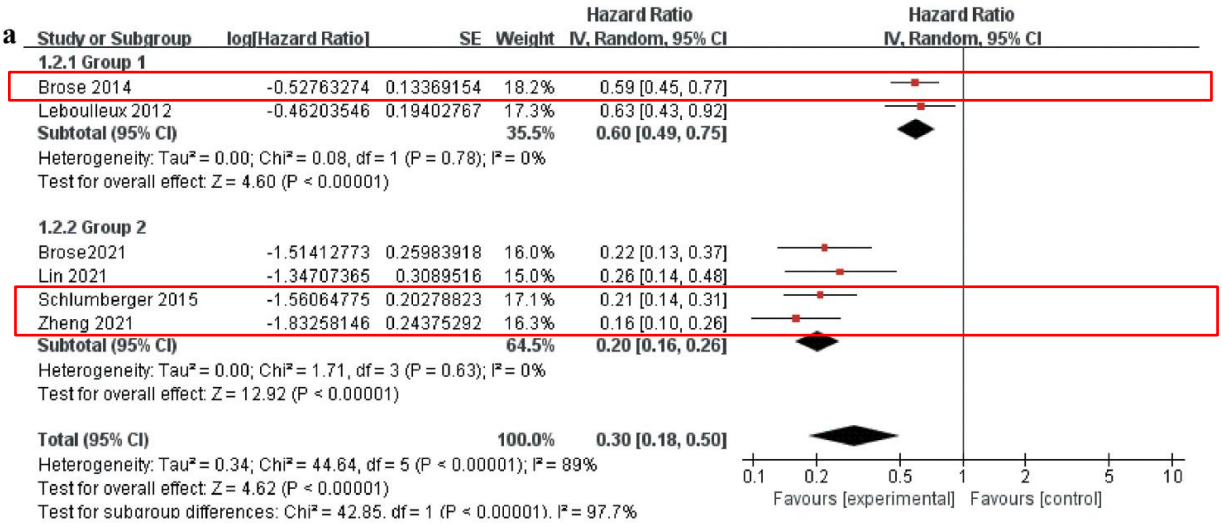
| References | Study design | MKIs name | Mean age Sample size | Previous treatment |
|---|---|---|---|---|
| Leboulleux 2012 [8] | randomized, double-blind, phase II trial | Vandetanib | 63.5 years 145 patients | 6 patients one TKIs<br>20 patients' chemotherapy |
| Brose 2014 [9] | randomized, double-blind, phase III trial | Sorafenib | 63.0 years 417 patients | None |
| Schlumberger 2015 [10] | randomized, double-blind, phase III trial | Lenvatinib | 63.0 years 392 patients | 72 patients sorafenib<br>8 patients sunitinib<br>5 patients pazopanib<br>8 patients other TKIs |
| Brose 2021 [11] | randomized, double-blind, phase III trial | Cabozantinib | 65.3 years 187 patients | 69 patients sorafenib<br>74 patients lenvatinib<br>44 patients both TKIs |
| Zheng 2021 [12] | randomized, double-blind, phase III trial | Lenvatinib | 60.0 years 151 patients | 38 patients one TKIs |
| Lin 2021 [13] | randomized, double-blind, phase III trial | Apatinib | 57.7 years 92 patients | 4 patients sorafenib<br>4 patients donafenib<br>3 patients' chemotherapy |

Qualität der Studien:




Studienergebnisse:

### Progression-free survival/Overall Survival in RAI-rDTC



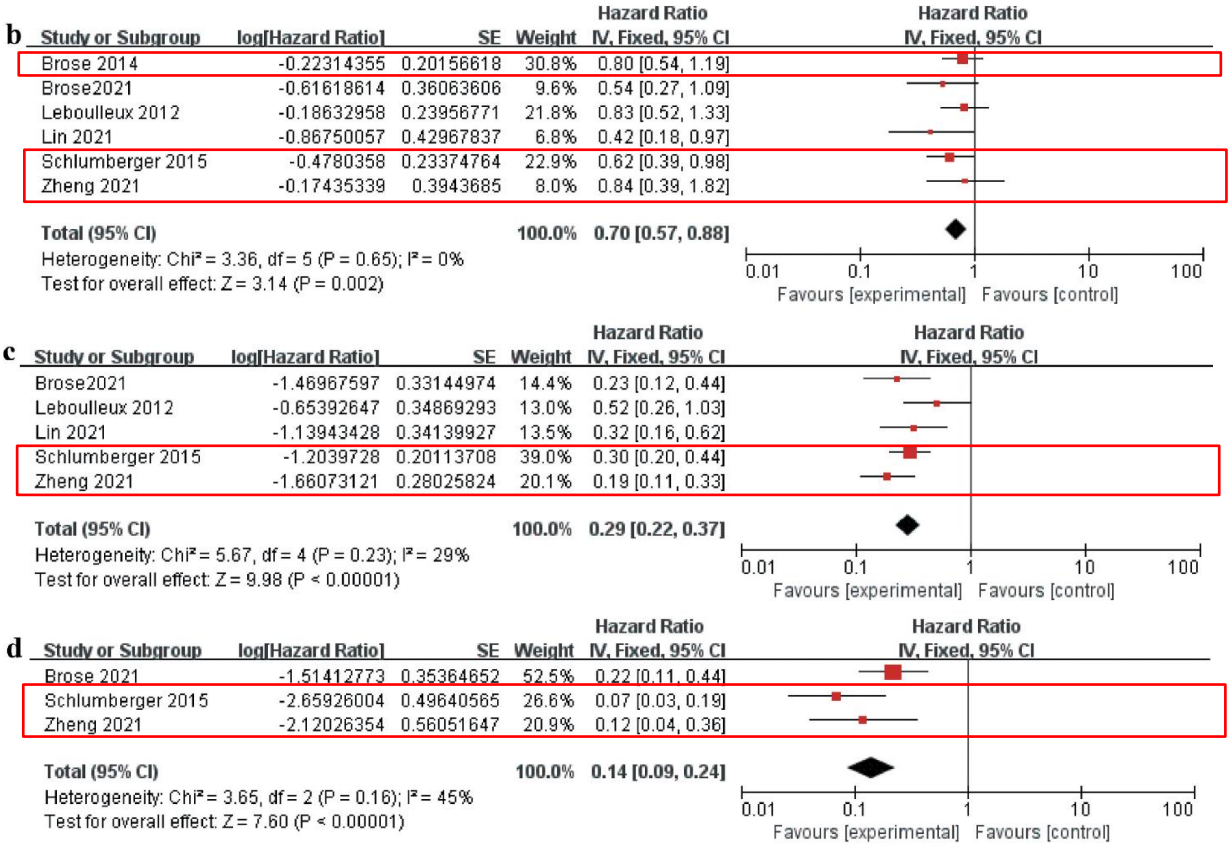
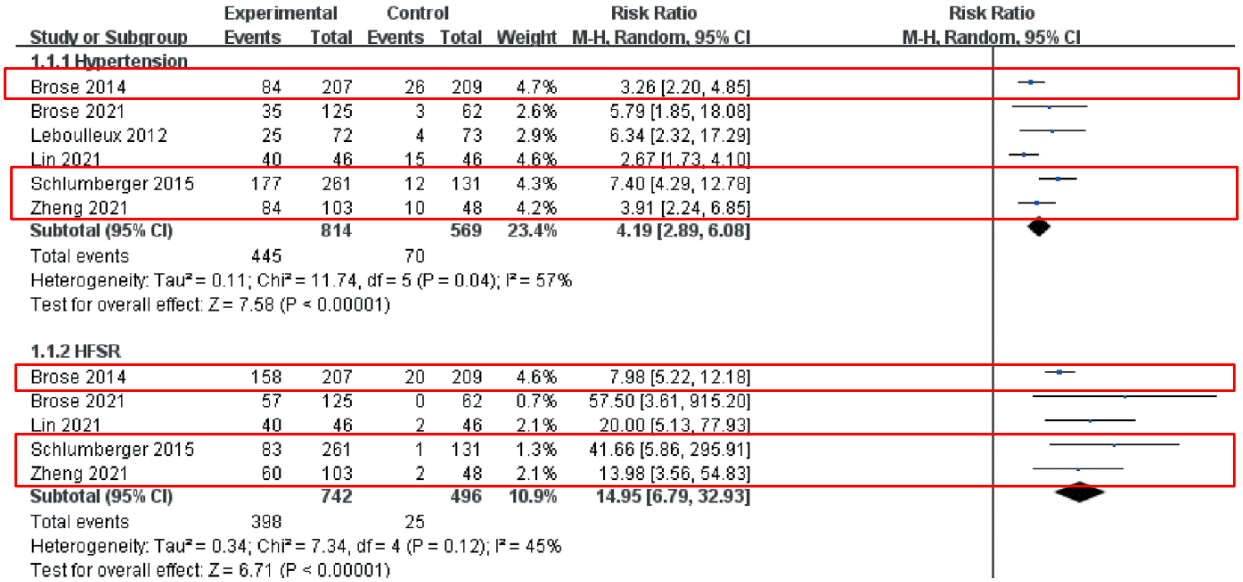



Figure 4. (a) Meta-analysis of the median PFS in patients with RAI-rDTC. (b) Meta-analysis of the OS in patients with RAI-rDTC. (c) Meta-analysis of the median PFS in patients with PTC. (d) Meta-analysis of the median PFS in patients with FTC.

## Adverse events



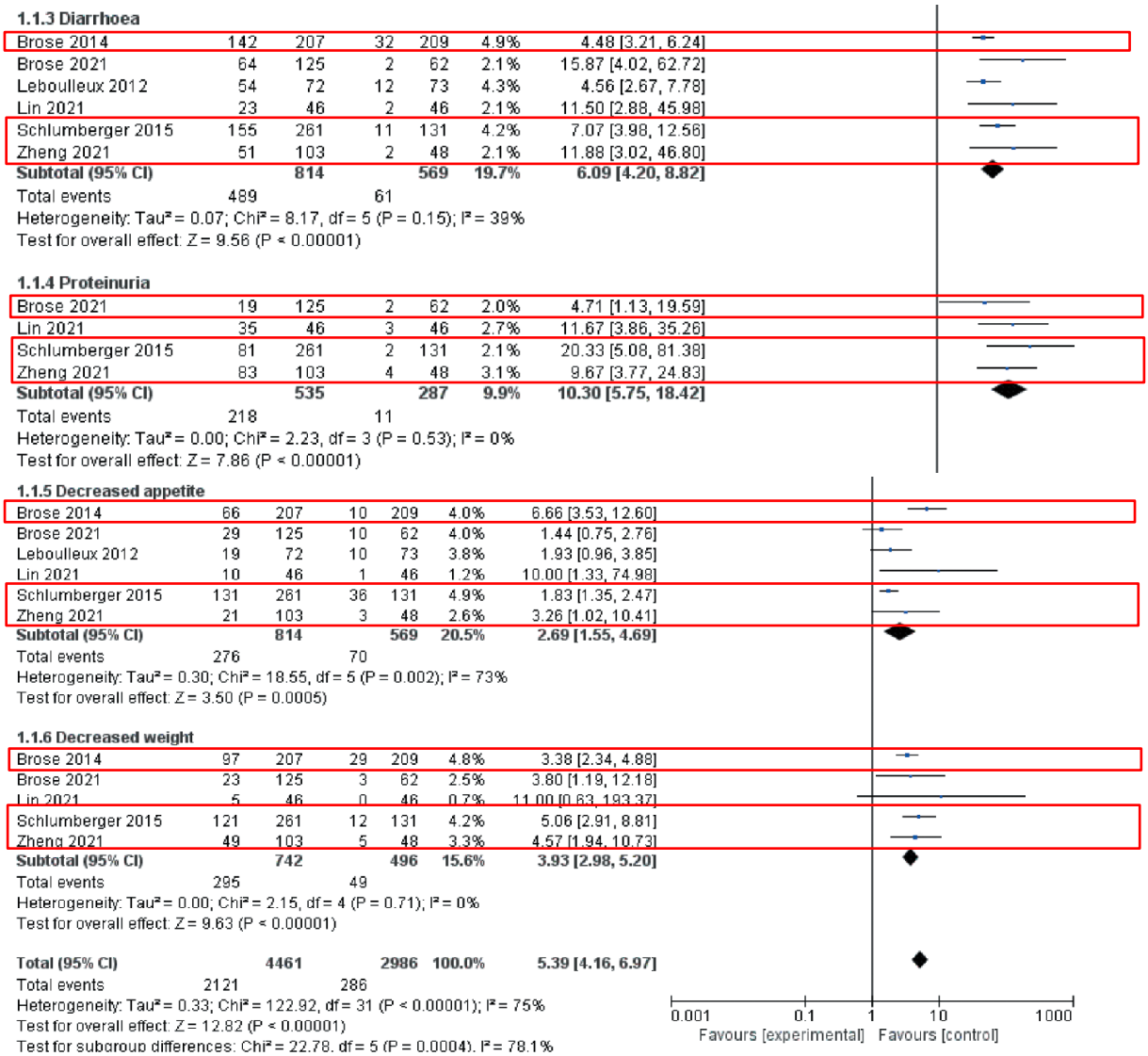



Figure 5. Six of the most common AEs in MKIs.

## Anmerkung/Fazit der Autoren

MKIs are a promising treatment for patients with RAI-rDTC. Currently, MKIs are the preferred treatment for RAI-rDTC patients, the use of MKIs can significantly improve PFS and OS ($P < 0.01$). Both PTC and FTC patients can use MKIs, but it is necessary to pay attention to the side effects of related medications and choose medications based on their economic and health status. To achieve the optimal outcome, the goal of treatment is to improve the patient's quality of life. To achieve a long-term sustainable outcome, efforts should also be made to manage adverse events and focus on specific efficacy, with ongoing research.

*Kommentare zum Review*

- Es wurden auch Patienten eingeschlossen, die bereits eine Vorbehandlung erhalten hatten (z.B. Chemotherapie oder Tyrosinkinase-Inhibitoren).

## 3.3 Leitlinien

**National Comprehensive Cancer Network, 2024 [4].**

Thyroid Carcinoma; Version 1.2024

### Zielsetzung/Fragestellung

This guideline covers diagnosis and management of thyroid cancer in people aged 16 and over. It aims to reduce variation in practice and increase the quality of care and survival for people with thyroid cancer.

### Methodik

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

Grundlage der Leitlinie

Aktuelles Update der Leitlinie, Erstveröffentlichung unklar.

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

Recherche/Suchzeitraum:

- PubMed database
- articles from additional sources deemed as relevant […] as discussed by the panel

LoE/GoR

- GRADE

| 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). |

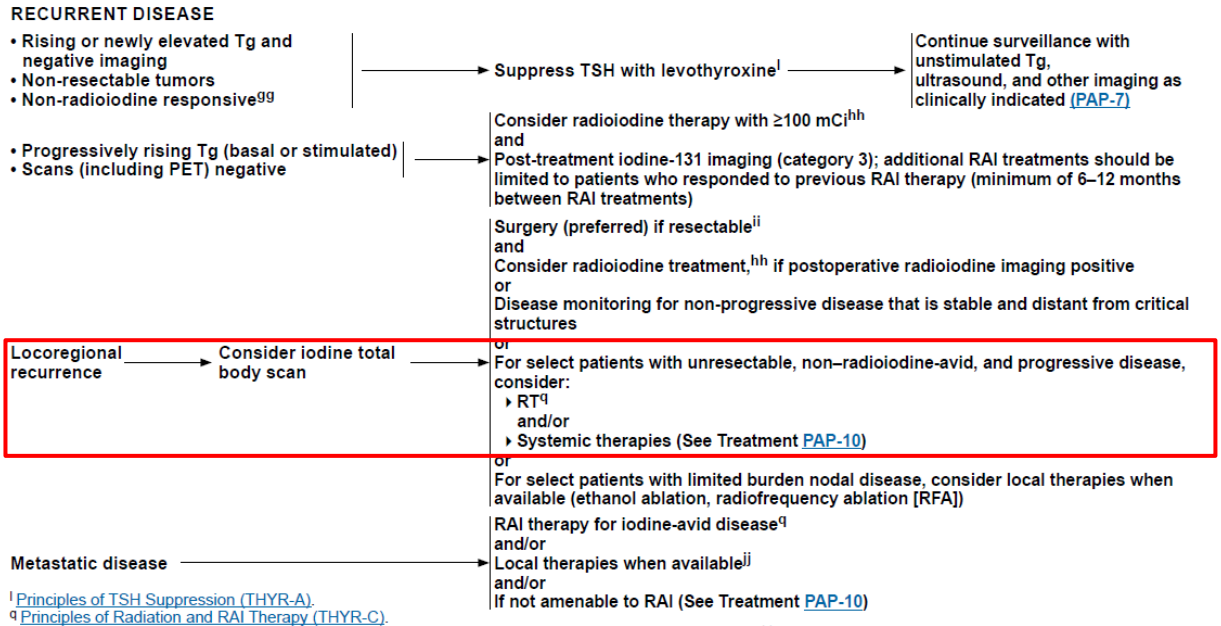
All recommendations are considered appropriate.

Sonstige methodische Hinweise

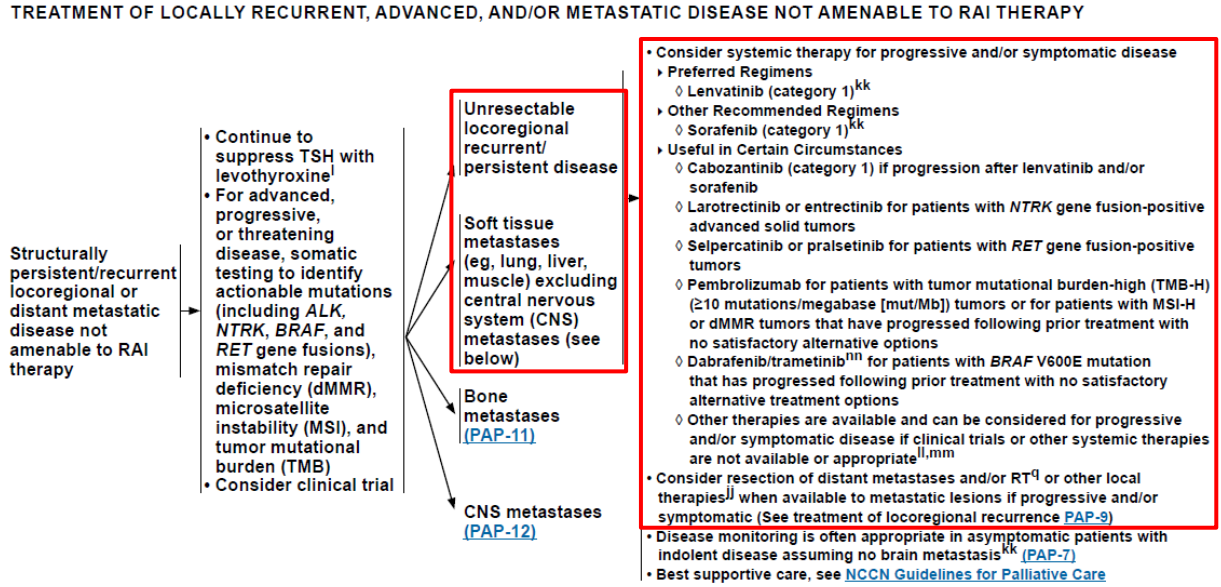
- Es wurde kein Suchzeitraum für die Literaturrecherche angegeben.
- Alle Empfehlungen entsprechen der Evidenz-Kategorie 2A, sofern nicht anders angegeben.

## Empfehlungen

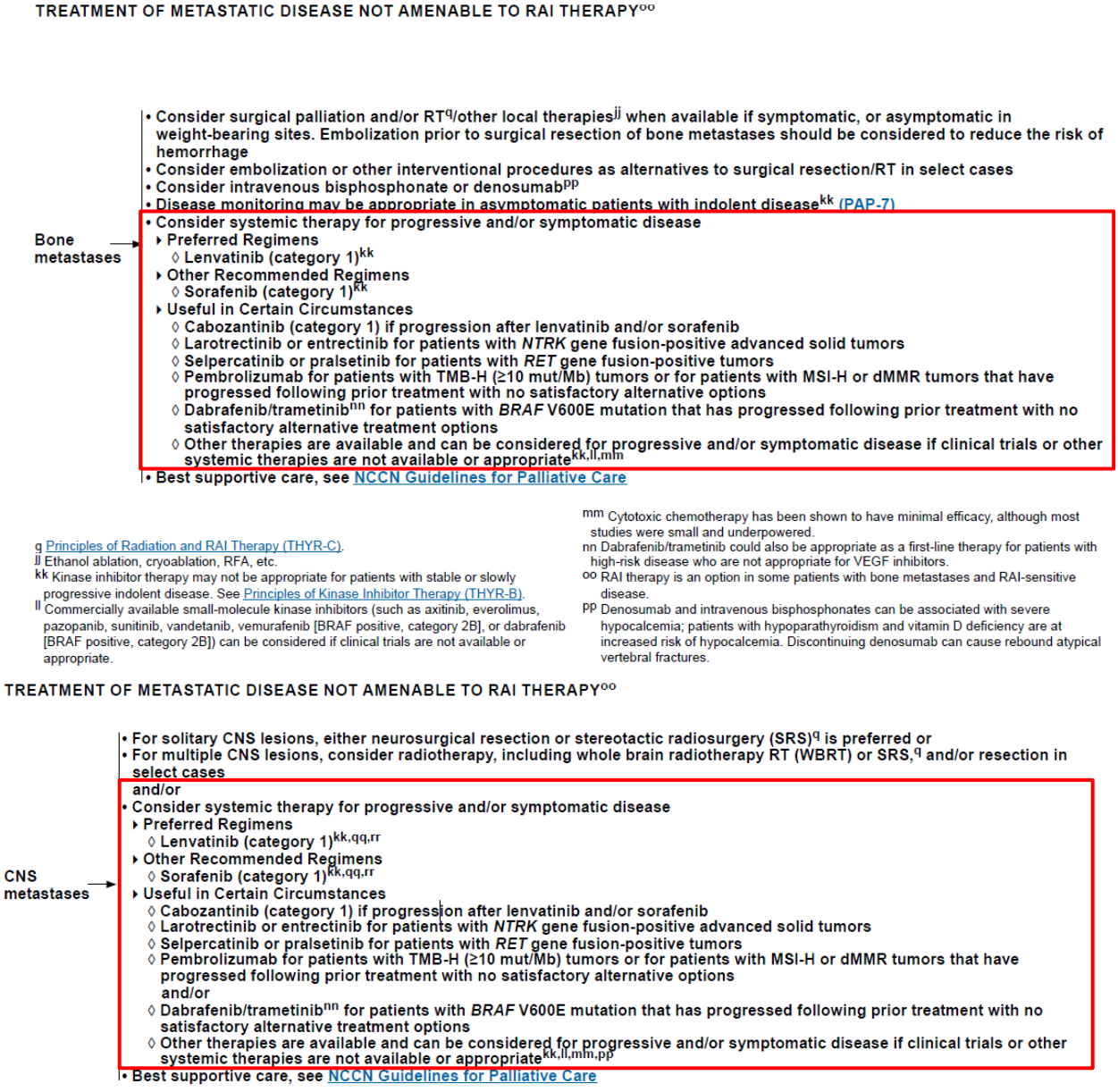
### Papillary Carcinoma




[l] Principles of TSH Suppression (THYR-A).
[q] Principles of Radiation and RAI Therapy (THYR-C).
[gg] Generally, a tumor is considered iodine-responsive if follow-up iodine-123 or low-dose iodine-131 (1–3 mCi) whole body diagnostic imaging done 6–12 months after iodine-131 treatment is negative or shows decreasing uptake compared to pre-treatment scans. It is recommended to use the same preparation and imaging method used for the pre-treatment scan and therapy. Favorable response to iodine-131 treatment is additionally assessed through change in volume of known iodine-concentrated lesions by CT/MRI, and by decreasing unstimulated or stimulated Tg levels.
[hh] The administered activity of RAI therapy should be adjusted for pediatric patients. See Principles of Radiation and RAI Therapy (THYR-C).
[ii] Preoperative vocal cord assessment, if central neck recurrence.
[jj] Ethanol ablation, cryoablation, RFA, etc.




[l] 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 Kinase Inhibitor Therapy (THYR-B).
[ll] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [BRAF positive, category 2B], or dabrafenib [BRAF positive, category 2B] ) can be considered if clinical trials are not available or appropriate.
[mm] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.
[nn] Dabrafenib/trametinib could also be appropriate as a first-line therapy for patients with high-risk disease who are not appropriate for VEGF inhibitors.







Hintergrundinformation:

**Recurrent Disease**

The NCCN Panel agrees that surgery is the preferred therapy for locoregional recurrent disease if the tumor is resectable (see Recurrent Disease in the NCCN Guidelines for Papillary [Thyroid] Carcinoma). Cervical ultrasound, including the central and lateral compartments, is the principal imaging modality when locoregional recurrence is suspected.[3] Cross-sectional imaging with CT or MRI may also be valuable for evaluation and surgical planning, especially when reliable high-resolution diagnostic ultrasound is unavailable and/or there is suspicion of invasion into the aerodigestive tract. In most cases, lesions suspicious for locoregional recurrence, which are amenable to needle biopsy, should be interrogated with

FNA biopsy before surgery. Tg washout assay may be a useful adjunct to FNA biopsy in these cases, particularly if cytology is negative. Iodine whole body scan can be used to guide subsequent use of RAI or other follow-up approach.

Clinically significant nodal recurrence in a previously undissected nodal basin should be treated with a formal compartmental resection.[3] In the central neck, this is usually achieved through a unilateral level VI dissection and, occasionally, a level VII dissection. In the lateral compartment, a formal modified radical neck dissection—including levels II, III, IV, and Vb—should be performed. Extending the dissection field into levels I or Va may be necessary when these levels are clinically involved. Selective dissection of individual nodal metastases (cherry picking) is not considered adequate surgery for nodal disease in a previously undissected field, and is not recommended in the NCCN Guidelines for Thyroid Carcinoma. Clinically significant nodal recurrence detected in a previously dissected nodal basin may be treated with a more focused dissection of the region containing the metastatic disease. For example, a level II recurrence detected in a patient who underwent a modified radical neck dissection as part of the primary treatment may only require selective dissection of level II. Likewise, a central neck recurrence detected in a patient who underwent a central neck dissection as part of the primary treatment may only require a focused resection of the region of recurrence.

For unresectable locoregional recurrence, RAI treatment and RT are recommended if the iodine-131 imaging is positive.[390] Local therapies, such as ethanol ablation or RFA, are also an option if available.[391] RT alone is another option in the absence of iodine-131 uptake for select patients not responsive to other therapies.[297,392] EBRT improves local control in patients with gross residual non-RAI–avid disease following surgery.[290] When recurrent disease is suspected based on progressively rising Tg values (basal or stimulated) and negative imaging studies (including PET scans), RAI therapy can be considered using an empirically determined dose of greater than or equal to 100 mCi of iodine- 131 (see Recurrent Disease in the NCCN Guidelines for Papillary [Thyroid] Carcinoma). The NCCN Panel had a major disagreement (category 3) about recommending post-treatment iodine-131 imaging in this setting, because some do not feel that these patients should have imaging. No study has shown a decrease in morbidity or mortality in patients treated with iodine-131 on the basis of increased Tg measurements alone. In a long-term follow-up study, no survival advantage was associated with empiric high-dose RAI in patients with negative imaging.[393] Further, potential long-term side effects (ie, xerostomia, nasolacrimal duct stenosis, bone marrow and gonadal compromise, the risk of hematologic and other malignancies) may negate any benefit.[394,395] Active surveillance may be considered for patients with low-volume disease that is stable and distant from critical structures.

**Metastatic Disease**

**For clinically progressive or symptomatic disease, systemic therapy should be considered**. Recommended systemic therapy options include: 1) lenvatinib (preferred) or sorafenib;[319,325] 2) clinical trials; 3) other small-molecule kinase inhibitors if a clinical trial is not available; or 4) resection of distant metastases and/or EBRT or IMRT.[406,407] Lenvatinib and sorafenib are category 1 options in this setting based on phase 3 randomized trials.[319,325] The NCCN Panel feels that lenvatinib is the preferred agent in this setting based on a response rate of 65% for lenvatinib when compared with 12% for sorafenib, although these agents have not been directly compared.[317,319,325] The decision to use lenvatinib or sorafenib should be individualized for each patient based on likelihood of response and comorbidities. The efficacy of lenvatinib or sorafenib for patients with brain metastases has not been established; therefore, consultation with neurosurgeons and radiation oncologists is recommended. Kinase inhibitors have been used as second-line therapy for thyroid cancer.[320,408]

Lenvatinib was compared with placebo in patients with metastatic differentiated thyroid cancer that was refractory to RAI in a phase 3 randomized trial.[319] Patients receiving lenvatinib had a PFS of 18.3 months compared with 3.6 months for those receiving placebo (HR, 0.21; 99% CI, 0.14–0.31; P < .001). Six treatment-related deaths occurred in the lenvatinib group. A prespecified subset analysis of this trial found that the PFS benefit of lenvatinib compared to placebo was maintained regardless of age (using a cut-off of 65 years). Furthermore, a longer median OS was observed in older patients treated with lenvatinib compared to placebo (HR, 0.27; 95% CI, 0.31–0.91; P = .20), although patients >65 years also had higher rates of grade 3 and greater adverse effects from treatment. A retrospective analysis of a phase 3 trial demonstrated that patients receiving lenvatinib with ECOG performance status (PS) 0 at baseline had improved PFS (HR, 0.52; 95% CI, 0.35–0.77; P = .001), OS (HR, 0.42; 95% CI, 0.26–0.69; P = .0004), and response rate (overall response rate [ORR], 3.51; 95% CI, 2.02–6.10; P < .0001) compared with patients with a baseline ECOG PS 1.[409] Any-grade treatment-emergent adverse events (TEAEs) occurred in nearly all patients who received lenvatinib, irrespective of ECOG PS at baseline (ECOG PS 0, TEAEs in 100%; ECOG

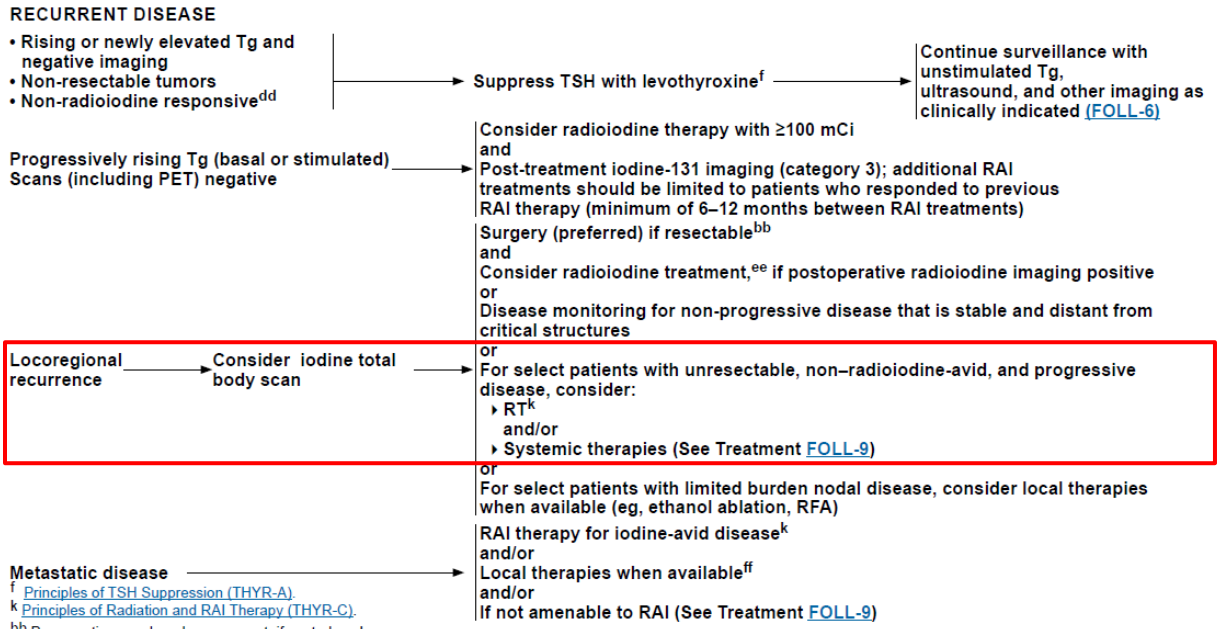
PS 1, TEAEs in 99%). Taken together, these results suggest that lenvatinib is an appropriate treatment option for patients of any age with RAI-refractory differentiated thyroid cancer.[410]

Another phase 3 randomized trial compared sorafenib with placebo in patients with RAI-refractory metastatic differentiated thyroid cancer.[325] Patients receiving sorafenib had a PFS of 10.8 months compared with 5.8 months for those receiving placebo (HR, 0.59; 95% CI, 0.45–0.76; P < .0001). One treatment-related death occurred in the sorafenib group. Hand-foot syndrome is common with sorafenib and may require dose adjustments.

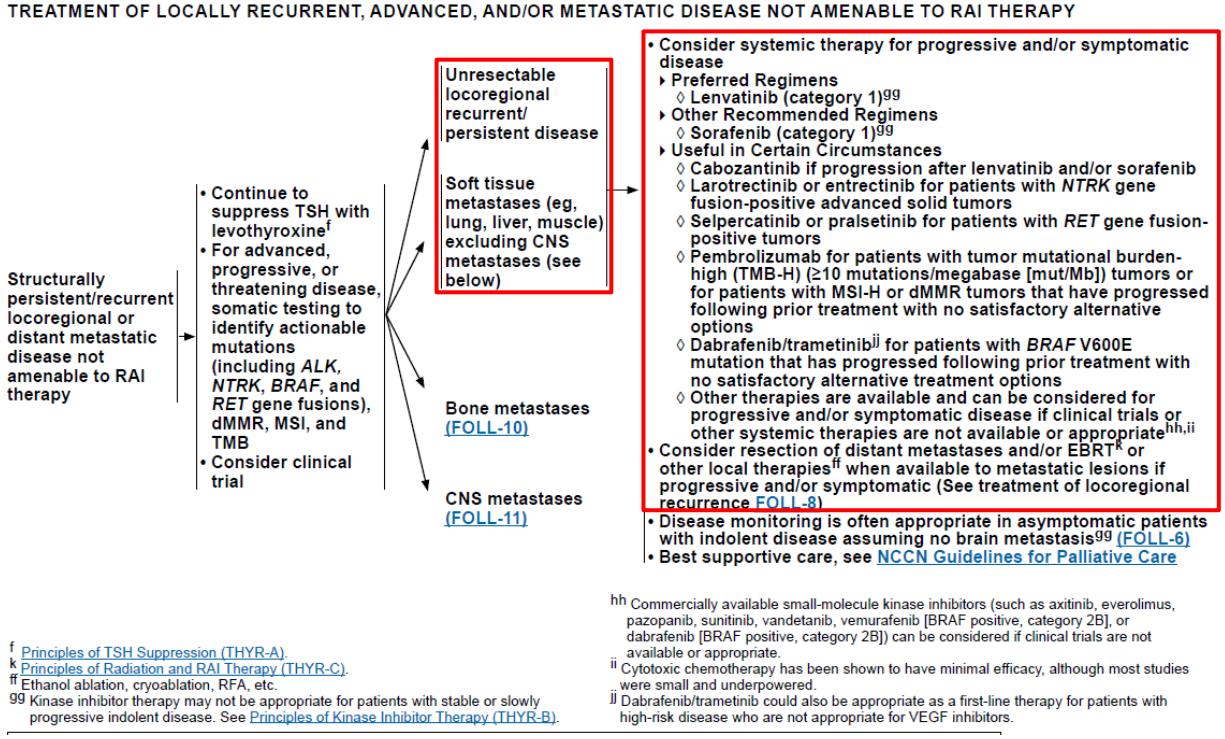
A phase 3 randomized trial compared cabozantinib to placebo in patients with RAI-refractory differentiated thyroid cancer that progressed during or after treatment with one or two VEGFR TKIs (including lenvatinib and sorafenib).[357] Interim analyses of the intention-to-treat (ITT) population (n = 187) showed that the median PFS was not reached in patients receiving cabozantinib, compared with 1.9 months for those receiving placebo (HR, 0.22; 99% CI, 0.13–0.36; P < .0001). Serious treatment-related adverse events occurred in 16% of patients in the cabozantinib arm, compared with 2% in the placebo arm, though no treatment-related deaths occurred. At time of extended follow-up, median PFS continued to favor the cabozantinib arm over the placebo arm (11.0 months vs. 1.9 months, respectively; HR, 0.22; 95% CI, 0.15–0.32; P < .0001).[411] ORR was 11.0% for the cabozantinib arm, compared to 0% in the placebo arm (P = .0003). Cabozantinib is a category 1 option for patients with disease progression after lenvatinib and/or sorafenib.

Other commercially available small-molecule kinase inhibitors may also be considered for progressive and/or symptomatic disease if a clinical trial is not available—including dabrafenib/trametinib (for BRAF-positive disease), larotrectinib or entrectinib (for NTRK gene fusion-positive disease), selpercatinib or pralsetinib (for RET fusion-positive disease), axitinib, everolimus, pazopanib, sunitinib, vandetanib, or cabozantinib—although some of these have not been approved by the FDA for differentiated thyroid cancer (see Principles of Kinase Inhibitor Therapy in Advanced Thyroid Carcinoma in the NCCN Guidelines for Thyroid Carcinoma). Note that kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease,[319,325,359,412,413] and caution should be used in patients with untreated CNS metastases due to the associated bleeding risk.[414] The anti-PD-1 antibody pembrolizumab is also an option for patients with TMB-high (TMB-H) (≥10 mutations/megabase [mut/Mb]) disease[348] and for MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory treatment options.[349] Active surveillance is often appropriate for asymptomatic patients with indolent disease and no brain metastasis.[320,359] Palliative care is recommended as indicated for patients with advanced and progressive disease (see the NCCN Guidelines for Palliative Care, available at www.NCCN.org).

## Follicular Carcinoma




[f] Principles of TSH Suppression (THYR-A).
[k] Principles of Radiation and RAI Therapy (THYR-C).
[bb] Preoperative vocal cord assessment, if central neck recurrence.
[dd] Generally, a tumor is considered iodine-responsive if follow-up iodine-123 or low-dose iodine-131 (1–3 mCi) whole body diagnostic imaging done 6–12 months after iodine-131 treatment is negative or shows decreasing uptake compared to pre-treatment scans. It is recommended to use the same preparation and imaging method used for the pre-treatment scan and therapy. Favorable response to iodine-131 treatment is additionally assessed through change in volume of known iodine-concentrated lesions by CT/MRI, and by decreasing unstimulated or stimulated Tg levels.
[ee] The administered activity of RAI therapy should be adjusted for pediatric patients. See Principles of Radiation and RAI Therapy (THYR-C).
[ff] Ethanol ablation, cryoablation, RFA, etc.




[f] Principles of TSH Suppression (THYR-A).
[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 Kinase Inhibitor Therapy (THYR-B).
[hh] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [BRAF positive, category 2B], or dabrafenib [BRAF positive, category 2B]) can be considered if clinical trials are not available or appropriate.
[ii] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.
[jj] Dabrafenib/trametinib could also be appropriate as a first-line therapy for patients with high-risk disease who are not appropriate for VEGF inhibitors.

**TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY[kk]**

**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[ll]
- Disease monitoring may be appropriate in asymptomatic patients with indolent disease[gg] (FOLL-6)
- Consider systemic therapy for progressive and/or symptomatic disease
  - Preferred Regimens
    - ◊ Lenvatinib (category 1)[gg]
  - Other Recommended Regimens
    - ◊ Sorafenib (category 1)[gg]
  - Useful in Certain Circumstances
    - ◊ Cabozantinib if progression after lenvatinib and/or sorafenib
    - ◊ Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors
    - ◊ Selpercatinib or pralsetinib for patients with *RET* gene fusion-positive tumors
    - ◊ Pembrolizumab for patients with TMB-H (≥10 mut/Mb) tumors or for patients with MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory alternative options
    - ◊ Dabrafenib/trametinib[jj] for patients with *BRAF* V600E mutation that has progressed following prior treatment with no satisfactory alternative treatment options
    - ◊ Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate[gg,hh,ii]
- Best supportive care, see NCCN Guidelines for Palliative Care

k Principles of Radiation and RAI Therapy (THYR-C).
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jj Dabrafenib/trametinib could also be appropriate as a first-line therapy for patients with high-risk disease who are not appropriate for VEGF inhibitors.
kk RAI therapy is an option in some patients with bone metastases and RAI-sensitive disease.
ll 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.

**TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY[kk]**

**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
  - Preferred Regimens
    - ◊ Lenvatinib (category 1)[gg,mm,nn]
  - Other Recommended Regimens
    - ◊ Sorafenib (category 1)[gg,mm,nn]
  - Useful in Certain Circumstances
    - ◊ Cabozantinib if progression after lenvatinib and/or sorafenib
    - ◊ Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors
    - ◊ Selpercatinib or pralsetinib for patients with *RET* gene fusion-positive tumors
    - ◊ Pembrolizumab for patients with TMB-H (≥10 mut/Mb) tumors or for patients with MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory alternative options
      and/or
    - ◊ Dabrafenib/trametinib[jj] for patients with *BRAF* V600E mutation that has progressed following prior treatment with no satisfactory alternative treatment options
    - ◊ Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate[gg,hh,ii,ll]
- Best supportive care, see NCCN Guidelines for Palliative Care

k Principles of Radiation and RAI Therapy (THYR-C).
gg Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Kinase Inhibitor Therapy (THYR-B).
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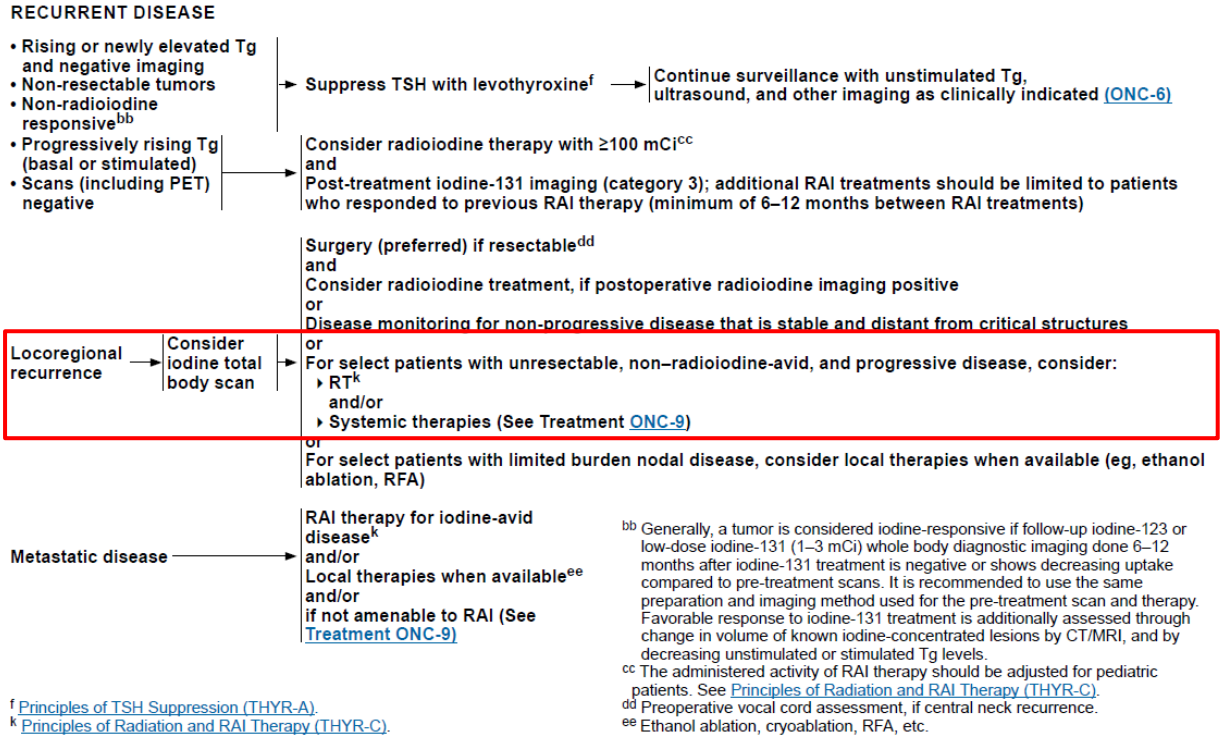
ii Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.
jj Dabrafenib/trametinib could also be appropriate as a first-line therapy for patients with high-risk disease who are not appropriate for VEGF inhibitors.
kk RAI therapy is an option in some patients with bone metastases and RAI-sensitive disease.
ll 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.
mm After consultation with neurosurgery and radiation oncology; data on the efficacy of lenvatinib or sorafenib for patients with brain metastases have not been established.
nn TKI therapy should be used with caution in otherwise untreated CNS metastases due to bleeding risk.

Hintergrundinformation

The diagnosis and treatment of papillary and follicular thyroid carcinoma are similar; therefore, only the important differences in the management of follicular carcinoma are highlighted. […]

*Methodikeranmerkung: Für das vorliegende AWG werden keine relevanten Unterschiede in der Behandlung zwischen dem follikulärem und papillärem Schilddrüsenkarzinom beschrieben.*

## Oncocytic Carcinoma




[f] Principles of TSH Suppression (THYR-A).
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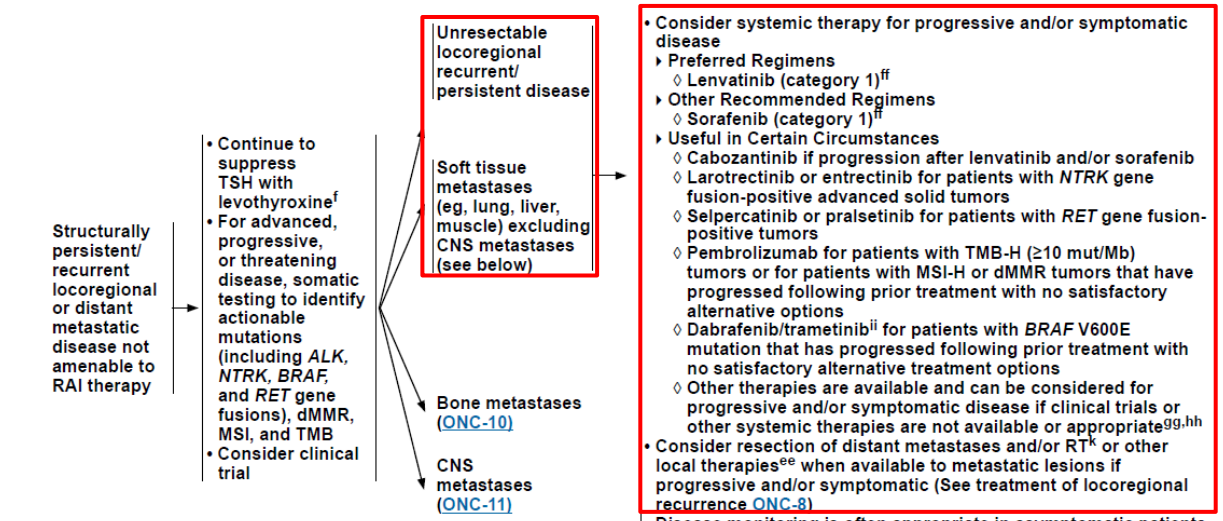
[bb] Generally, a tumor is considered iodine-responsive if follow-up iodine-123 or low-dose iodine-131 (1–3 mCi) whole body diagnostic imaging done 6–12 months after iodine-131 treatment is negative or shows decreasing uptake compared to pre-treatment scans. It is recommended to use the same preparation and imaging method used for the pre-treatment scan and therapy. Favorable response to iodine-131 treatment is additionally assessed through change in volume of known iodine-concentrated lesions by CT/MRI, and by decreasing unstimulated or stimulated Tg levels.
[cc] The administered activity of RAI therapy should be adjusted for pediatric patients. See Principles of Radiation and RAI Therapy (THYR-C).
[dd] Preoperative vocal cord assessment, if central neck recurrence.
[ee] Ethanol ablation, cryoablation, RFA, etc.

### TREATMENT OF LOCALLY RECURRENT, ADVANCED, AND/OR METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY




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

[gg] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [BRAF positive, category 2B], or dabrafenib [BRAF positive, category 2B]) can be considered if clinical trials are not available or appropriate.
[hh] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.
[ii] Dabrafenib/trametinib could also be appropriate as a first-line therapy for patients with high-risk disease who are not appropriate for VEGF inhibitors.

**TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY[jj]**

**Bone metastases →**

- Consider surgical palliation and/or RT[k]/other local therapies[ee] 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[kk]
- Disease monitoring may be appropriate in asymptomatic patients with indolent disease[ff] (ONC-6)
- Consider systemic therapy for progressive and/or symptomatic disease
  - Preferred Regimens
    - ◊ Lenvatinib (category 1)[ff]
  - Other Recommended Regimens
    - ◊ Sorafenib (category 1)[ff]
  - Useful in Certain Circumstances
    - ◊ Cabozantinib if progression after lenvatinib and/or sorafenib
    - ◊ Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors
    - ◊ Selpercatinib or pralsetinib for patients with *RET* gene fusion-positive tumors
    - ◊ Pembrolizumab for patients with TMB-H (≥10 mut/Mb) tumors or for patients with MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory alternative options
    - ◊ Dabrafenib/trametinib[ii] for patients with *BRAF* V600E mutation that has progressed following prior treatment with no satisfactory alternative treatment options
    - ◊ Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate[ff,gg,hh]
- Best supportive care, see NCCN Guidelines for Palliative Care

[k] Principles of Radiation and RAI Therapy (THYR-C).
[ee] Ethanol ablation, cryoablation, RFA, etc.
[ff] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Kinase Inhibitor Therapy (THYR-B).
[gg] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [BRAF positive, category 2B], or dabrafenib [BRAF positive, category 2B]) can be considered if clinical trials are not available or appropriate.
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[jj] RAI therapy is an option in some patients with bone metastases and RAI-sensitive disease.
[kk] 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.

**TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY[jj]**

**CNS metastases →**

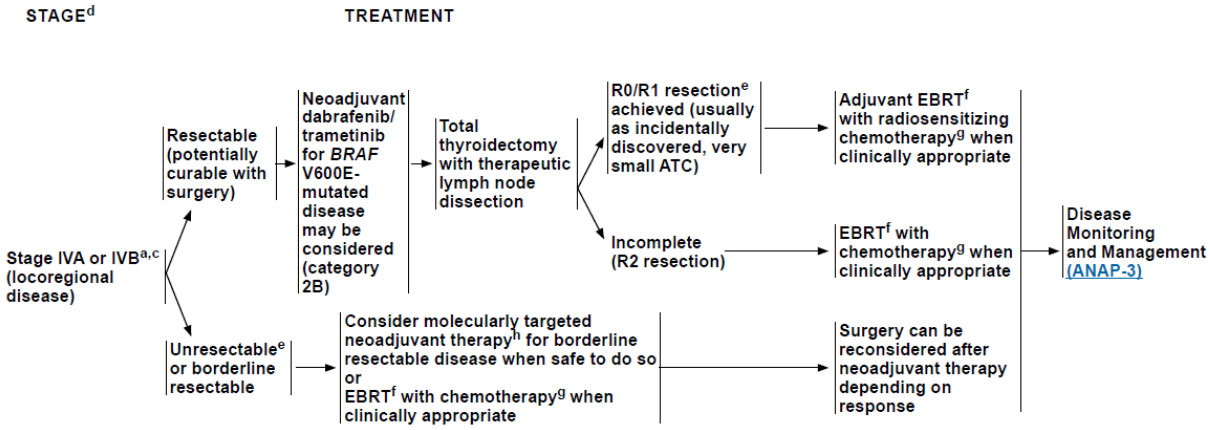
- For solitary CNS lesions, either neurosurgical resection or SRS[k] is preferred
  or
- For multiple CNS lesions, consider radiotherapy, including WBRT or SRS,[k] and/or resection in select cases
- Consider systemic therapy For progressive and/or symptomatic disease
  - Preferred Regimens
    - ◊ Lenvatinib (category 1)[ff,ll,mm]
  - Other
    - ◊ Sorafenib (category 1)[ff,ll,mm]
  - Useful in Certain Circumstances
    - ◊ Cabozantinib if progression after lenvatinib and/or sorafenib
    - ◊ Larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive advanced solid tumors
    - ◊ Selpercatinib or pralsetinib for patients with *RET* gene fusion-positive tumors
    - ◊ Pembrolizumab for patients with TMB-H (≥10 mut/Mb) tumors or for patients with MSI-H or dMMR tumors that have progressed following prior treatment with no satisfactory alternative options
      and/or
    - ◊ Dabrafenib/trametinib[ii] for patients with *BRAF* V600E mutation that has progressed following prior treatment with no satisfactory alternative treatment options
    - ◊ Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate[ff,gg,hh,kk]
- Best supportive care, see NCCN Guidelines for Palliative Care

[k] Principles of Radiation and RAI Therapy (THYR-C).
[ff] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. Principles of Kinase Inhibitor Therapy (THYR-B).
[gg] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [BRAF positive, category 2B], or dabrafenib [BRAF positive, category 2B]) can be considered if clinical trials are not available or appropriate.
[hh] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.
[ii] Dabrafenib/trametinib could also be appropriate as a first-line therapy for patients with high-risk disease who are not appropriate for VEGF inhibitors.
[jj] RAI therapy is an option in some patients with bone metastases and RAI-sensitive disease.
[kk] 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.
[ll] After consultation with neurosurgery and radiation oncology; data on the efficacy of lenvatinib or sorafenib for patients with brain metastases have not been established.
[mm] TKI therapy should be used with caution in otherwise untreated CNS metastases due to bleeding risk.

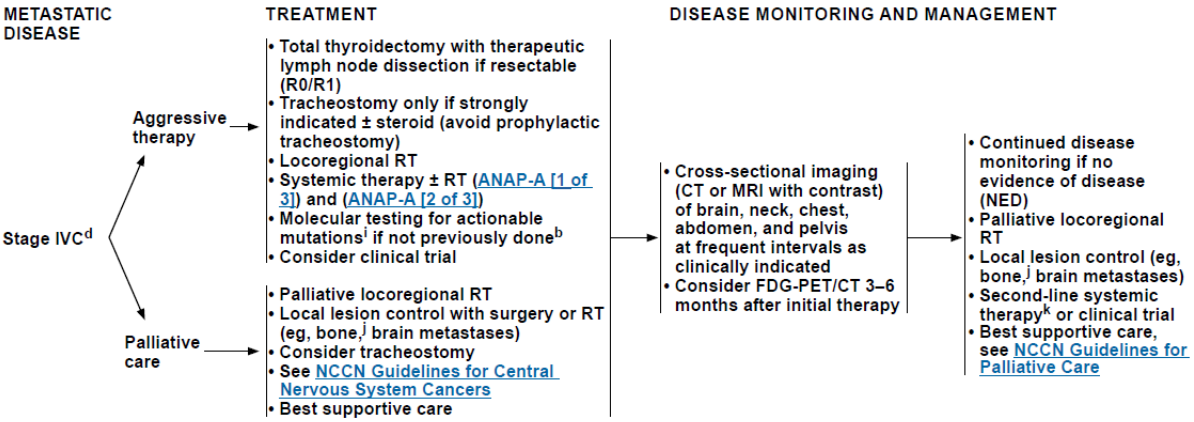
Hintergrundinformation:

> […] The surgical management of oncocytic carcinoma is almost identical to follicular thyroid carcinoma, except that 1) locoregional nodal metastases are more common, and therefore therapeutic lymph node dissections of the affected compartment are needed for clinically apparent biopsy-proven disease; and 2) metastatic oncocytic carcinoma is less likely to concentrate iodine-131 (see Papillary Thyroid Carcinoma: Surgical Therapy in this Discussion).[419] Molecular testing may indicate a benign nodule, thus suggesting that observation without surgical intervention may be appropriate. Postoperative EBRT can be considered for: 1) unresectable primary oncocytic carcinomas that do not concentrate iodine-131 if disease is threatening vital structures; and 2) unresectable locoregional recurrence (see Postsurgical Evaluation and Recurrent Disease in the NCCN Guidelines for Oncocytic [Thyroid] Carcinoma), similar to the management for follicular thyroid carcinoma. […]

## Anaplastic Carcinoma




[a] Consider core or open biopsy if FNA is "suspicious" for ATC or is not definitive. Morphologic diagnosis combined with immunohistochemistry is necessary to exclude other entities such as poorly differentiated thyroid cancer, medullary thyroid cancer, and lymphoma.
[c] Preoperative evaluations need to be completed as quickly as possible and involve integrated decision-making in a multidisciplinary team and with the patient. Consider referral to multidisciplinary high-volume center with expertise in treating ATC.
[d] Staging (ST-1).
[e] Resectability for locoregional disease depends on extent of involved structures, potential morbidity, and mortality associated with resection. In most cases, there is no indication for a debulking surgery. See Staging (ST-1) for definitions of R0/R1/R2.
[f] Principles of Radiation and RAI Therapy (THYR-C).
[g] Adjuvant/Radiosensitizing Chemotherapy Regimens for Anaplastic Thyroid Carcinoma (ANAP-A [1 of 3]).
[h] Regimens that may be used for neoadjuvant therapy include dabrafenib/trametinib for *BRAF* V600E mutations; selpercatinib or pralsetinib for RET gene fusion-positive tumors; and larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive tumors.




[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).
[i] Consider dabrafenib/trametinib if *BRAF* V600E mutation positive (Subbiah V, et al. J Clin Oncol 2018;36:7-13); larotrectinib or entrectinib if *NTRK* gene fusion positive (Drilon A, et al. N Engl J Med 2018;378:731-739; Doebele RC, et al. Lancet Oncol 2020;21:271-282); selpercatinib or pralsetinib if *RET* fusion positive (Wirth L, et al. Oral presentation at the Annual Meeting of the European Society for Medical Oncology in Barcelona, Spain; September 27-October 1, 2019.); or pembrolizumab for TMB-H (Marabelle A, et al. Presented at the Annual Meeting of ESMO in Barcelona, Spain; September 30, 2019).
[j] 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.
[k] Systemic Therapy Regimens for Metastatic Disease (ANAP-A [2 of 3]).

SYSTEMIC THERAPY

| Adjuvant/Radiosensitizing Chemotherapy Regimens[1] | | |
|---|---|---|
| Other Recommended Regimens | | |
| Paclitaxel/carboplatin | Paclitaxel 50 mg/m² IV, carboplatin area under the curve (AUC) 2 IV | Weekly |
| Docetaxel/doxorubicin | Docetaxel 20 mg/m² IV, doxorubicin 20 mg/m² IV | Weekly |
| Paclitaxel | 30–60 mg/m² IV | Weekly |
| Docetaxel | 20 mg/m² IV | Weekly |

| Systemic Therapy Regimens for Metastatic Disease | | |
|---|---|---|
| Preferred Regimens | | |
| Dabrafenib/trametinib[2] (*BRAF* V600E mutation positive) | Dabrafenib 150 mg PO and Trametinib 2 mg PO | Twice daily Once daily |
| Larotrectinib[3] (*NTRK* gene fusion positive) | 100 mg PO | Twice daily |
| Entrectinib[4] (*NTRK* gene fusion positive) | 600 mg PO | Once daily |
| Pralsetinib[5] (*RET* gene fusion-positive) | 400 mg PO | Once daily |
| Selpercatinib[6] (*RET* gene fusion-positive) | 120 mg PO (<50 kg) or 160 mg PO (≥50 kg) | Twice daily |
| Other Recommended Regimens | | |
| Paclitaxel[8] | 60–90 mg/m² IV or 135–200 mg/m² | Weekly Every 3–4 weeks |
| Doxorubicin[8] | 20 mg/m² IV or 60–75 mg/m² IV | Weekly Every 3 weeks |
| Paclitaxel/carboplatin[1] (category 2B) | Paclitaxel 60–100 mg/m² IV, carboplatin AUC 2 IV or Paclitaxel 135–175 mg/m² IV, carboplatin AUC 5–6 IV | Weekly Every 3–4 weeks |
| Docetaxel/doxorubicin[1] (category 2B) | Docetaxel 60 mg/m² IV, doxorubicin 60 mg/m² IV (with G-CSF) or Docetaxel 20 mg/m² IV, doxorubicin 20 mg/m² IV | Every 3–4 weeks Weekly |
| Useful in Certain Circumstances | | |
| Doxorubicin/cisplatin[8] | Doxorubicin 60 mg/m² IV, cisplatin 40 mg/m² IV | Every 3 weeks |
| Pembrolizumab[a,7] | 200 mg IV or 400 mg IV | Every 3 weeks Every 6 weeks |
| Pembrolizumab/lenvatinib[9] | Pembrolizumab 200 mg IV (or 400 mg IV every 6 weeks) + Lenvatinib 20–24 mg PO daily | Every 3 weeks |
| Nivolumab[10,11] | 240 mg IV or 480 mg IV | Every 2 weeks Every 4 weeks |

Hintergrundinformation:

ATCs are aggressive undifferentiated tumors, with a disease-specific mortality approaching 100%.[497] Patients with anaplastic carcinoma are older than those with differentiated carcinomas, with a mean age at diagnosis of approximately 71 years.[498] Fewer than 10% of patients are <50 years, and 60% to 70% of patients are AFAB.[110,498] The incidence of ATC is decreasing because of better management of differentiated thyroid cancer and because of increased iodine in the diet.[497,499] As previously mentioned, anaplastic carcinoma is the least common type of thyroid carcinoma. An average of 63,229 patients/year were diagnosed with thyroid carcinoma between 2010 to 2014. Of these 63,229 patients, only 514 patients (0.8%) had anaplastic carcinoma.[31]

Approximately 50% of patients with ATC have either a prior or coexistent differentiated carcinoma. Anaplastic carcinoma develops from more differentiated tumors as a result of one or more dedifferentiating steps, particularly loss of the p53 tumor suppressor protein.[500] No precipitating events have been identified, and the mechanisms leading to anaplastic transformation of differentiated carcinomas are uncertain. Differentiated thyroid carcinomas can concentrate iodine, express TSH receptor, and produce Tg, whereas undifferentiated carcinomas typically do not. Therefore, iodine-131 imaging and therapy cannot be used.

Patients with ATC may present with symptoms such as rapidly enlarging neck mass, dyspnea, dysphagia, neck pain, Horner syndrome, stroke, and hoarseness due to vocal cord paralysis.[501] Patients with ATC present with extensive local invasion, and distant metastases are found at initial disease presentation in 15% to 50% of patients.[502,503] The lungs and pleura are the most common sites of distant metastases (≤90% of patients with distant disease). About 5% to 15% of patients have bone metastases; 5% have brain metastases; and a few have metastases to the skin, liver, kidneys, pancreas, heart, and adrenal glands.

**Treatment.** ATC has a very poor prognosis and responds poorly to conventional therapy. RAI treatment is not effective in these patients.[504] The role of palliative and supportive care is paramount and should be initiated early in the disease.[504] At the outset of the diagnosis, it is critical that conversations about end-of-life care be initiated so that a clear understanding of how to manage the airway is undertaken, which is clear to the family and all providers. Tracheostomy is often a morbid and temporary treatment of the airway and may not be the option a patient would choose.[509,515]

**Surgery.** Once the diagnosis of ATC is confirmed, it is essential to rapidly determine whether local resection is an option.[497] Before resection is attempted, the extent of disease—particularly with disease potentially involving the larynx, trachea, esophagus, pharynx, carotid artery, and other neck structures— should be accurately assessed by an experienced surgeon who is capable of complex neck surgery, if necessary. However, most patients with ATC have unresectable or metastatic disease. The patency of the airway should be assessed throughout the patient's course of treatment.[509] If the patient appears to have resectable disease, an attempt at total thyroidectomy with complete gross tumor resection should be made, with resection of all involved local or regional structures and nodes.[504] Total thyroidectomy with attempted complete tumor resection has not been shown to prolong survival except for the few patients whose tumors are small and confined entirely to the thyroid or readily excised structures.[508,510,516,517] Patients need to receive levothyroxine if total thyroidectomy is done. Tracheostomy may be considered in patients with stage IVc disease.

**Radiation Therapy.** EBRT can increase survival in some patients; EBRT can also improve local control and can be used for palliation (eg, to prevent asphyxiation).[457,497,504,512,518-522] Adjuvant RT, especially when combined with concurrent chemotherapy, is associated with improved survival.[523] Higher RT dose is associated with OS in patients with unresected ATC.[524] For solitary brain lesions, either neurosurgical resection or RT is recommended. Once brain metastases are diagnosed, disease-specific mortality is very high, with a reported median survival of 1.3 months. For unresected or incompletely resected disease, RT, usually with concurrent chemotherapy, should commence as quickly as possible. For R0 or R1 resection, adjuvant RT, usually with concurrent chemotherapy, should begin as soon as the patient has sufficiently recovered from surgery, ideally 2 to 3 weeks postoperatively. IMRT technique is encouraged. Enteral nutrition may be useful for some patients who have difficulty swallowing (see Principles of Nutrition: Management and Supportive Care in the NCCN Guidelines for Head and Neck Cancer, available at www.NCCN.org). If enteral feeding is considered, a careful conversation should occur with the patient about their wishes. For guidance regarding appropriate treatment volumes for use of RT for ATC, see the Principles of Radiation and Radioactive Iodine Therapy: External Beam Radiation Therapy in the NCCN Guidelines for Thyroid Carcinoma.

**Systemic Therapy.** Systemic therapy recommendations are described in the algorithm (see Systemic Therapy for Anaplastic Thyroid Carcinoma in the NCCN Guidelines for Anaplastic [Thyroid] Carcinoma). When systemic therapy is indicated, targeted therapy options are preferred. Dabrafenib plus trametinib combination is an option for BRAF V600E mutation-positive tumors,[525] larotrectinib or entrectinib are options for NTRK gene fusionpositive tumors,[344,345,526] selpercatinib or pralsetinib are options for RET fusion-positive disease,[346,347] and pembrolizumab is an option for TMB-H (≥10 mut/Mb) disease.[348] Other recommended regimens include paclitaxel and doxorubicin monotherapies.[504] Doxorubicin combined with cisplatin is an option based on a small randomized trial.[527] Paclitaxel combined with carboplatin and docetaxel combined with doxorubicin are also systemic therapy options for patients with metastatic ATC, but these are category 2B options based on low-quality evidence[504] and less panel consensus.

The NCCN Panel recommends molecular testing to help inform decisions regarding systemic therapy and to determine eligibility for clinical trials. The dosage and frequency of administration of all the recommended systemic therapy agents are provided in the algorithm. Either concurrent chemoradiation or chemotherapy alone regimens may be used depending on the clinical setting; however, chemoradiation is generally more toxic. If using chemoradiation, the ATA Guidelines recommend using weekly chemotherapy regimens.[504]

A phase 2, open-label trial of 16 patients with BRAF V600E-mutated ATC evaluated the efficacy and safety of dabrafenib 150 mg, twice daily, in combination with trametinib 2 mg, once daily.[525] The confirmed ORR was 69% (95% CI, 41%–89%), with seven responses ongoing. An updated analysis including 36 patients showed an ORR of 56% (95% CI, 38.1%– 72.1%), including 3 complete responses, and 12-month duration of response was 50%.528 Median PFS and OS were 6.7 months and 14.5 months, respectively.[528] Twelve-month OS and PFS rates were 43.2% and 51.7%, respectively.[528] The combination was found to be well-tolerated as evaluated in 100 patients across seven rare tumor types; common adverse events included fatigue (38%), pyrexia (37%), and nausea (35%).[525] Based on these data, the FDA approved dabrafenib/trametinib for ATC with BRAF V600E mutation in 2018.

A pooled analysis of three 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 seven patients with thyroid cancer of which one patient had ATC.[344,529] For the whole population, the ORR was 75% (95% CI, 61%–85%) by independent review and 80% (95% CI, 67%– 90%) by investigator assessment.[344,529] One hundred percent of the thyroid cancers in this study responded to larotrectinib, with one complete response and four partial responses.[529] Larotrectinib was found to be welltolerated, as the majority (93%) of adverse events were grades 1 or 2 and no treatment-related adverse events of grades 3 or 4 occurred in more than 5% of patients.[344] A pooled analysis from a phase II trial and two phase I trials including 54 patients with NTRK gene fusion-positive cancer (9% having thyroid cancer) showed an objective response rate of 57.4% for entrectinib, another TRK inhibitor.[345] Based on these data, the FDA approved larotrectinib and entrectinib for treatment of patients with NTRK gene fusion-positive tumors, and the panel also recommends NTRK therapy options such as larotrectinib or entrectinib for patients with NTRK gene fusion-positive metastatic ATC.

The phase I–II LIBRETTO-001 study evaluated the efficacy of the RET inhibitor selpercatinib in 19 patients with previously treated RET fusion-positive thyroid cancer (2 patients with anaplastic disease).[346] The ORR was 79% (95% CI, 54%–94%), and 1-year PFS was 64% (95% CI, 37%– 82%). In the ongoing phase I–II ARROW study, pralsetinib, another RET inhibitor, is being evaluated in patients with RET fusion-positive disease (NCT03037385). In an analysis including 9 patients with RET fusionpositive thyroid cancer, the ORR was 89% (95% CI, 52%–100%) with durable responses (100% disease control rate [DCR]).[347] In 2020, the FDA approved both of these RET inhibitors for RAI-refractory RET fusionpositive thyroid cancer requiring systemic therapy.

The FDA approved the anti-PD-1 antibody pembrolizumab for treatment of previously treated TMB-H (≥10 mut/Mb) solid tumors in 2020 based on results of the phase II KEYNOTE-158 trial, which included two patients with thyroid cancer.[348] For the whole sample, the ORR was 29% (95% CI, 21%–39%). Grade 3–5 treatment-related adverse events were reported in 15% of the patients. A phase II study evaluated another anti-PD-1 antibody, spartalizumab, in 42 patients with locally advanced or metastatic ATC.[530] The ORR was 19% (95% CI, 8.6%–34.1%), but was higher for patients with PD-L1–positive disease (29%; 95% CI, 13.2%–48.7%) and highest in patients with PD-L1 greater than 50% (35%; 95% CI, 14.2%– 61.7%).

Treatment with anthracyclines and taxanes is generally not very effective for advanced anaplastic disease, although some patients may show disease response or have stable disease.[504,522] Single-agent doxorubicin is approved by the FDA for ATC. A randomized trial including 84 patients with advanced thyroid cancer (not limited to ATC) showed an 11.6% complete response rate in patients who received doxorubicin combined with cisplatin, compared to a complete response in 0 patients who received single-agent doxorubicin.[527] ORR did not differ significantly between the study arms (26% vs. 17%, respectively). Single-agent paclitaxel may benefit some patients with newly diagnosed ATC; increased survival has been reported in patients with stage IVB disease.[531-533] If weekly paclitaxel is used, the ATA Guidelines[504] recommend using paclitaxel at 60 to 90 mg/m2 IV weekly and not the dose previously reported in the study by Ain et al.[533]

Given the poor outcome with current standard therapy, all patients— regardless of surgical resection—should be considered for clinical trials. Previous clinical trials for ATC have tested therapies including fosbretabulin (and its parent drug, combretastatin A4 phosphate [CA4P], and crolibulin [EPC2407], which are vascular disrupting agents), efatutazone (an oral PPAR gamma agonist), and novel multitargeted therapies including bevacizumab with doxorubicin, sorafenib, sunitinib, imatinib, and pazopanib.[334,534-542] A trial in 80 patients (FACT) reported that the addition of fosbretabulin—to a carboplatin/paclitaxel regimen—resulted in a nonsignificant increase in median survival (5.2 vs. 4.0 months).[534,543] Preliminary data suggest that ALK inhibitors may be effective in a subset of patients with PTC who have ALK gene fusions; however, these ALK gene fusions are rarely reported in patients with ATC.[350-353]

Hyperfractionated EBRT, combined with radiosensitizing doses of doxorubicin, may increase the local response rate to about 80%, with a subsequent median survival of 1 year.[544] Distant metastases then become the leading cause of death.[545] Similar improvement in local disease control has been reported with a combination of hyperfractionated RT and doxorubicin-based regimens, followed by debulking surgery in responsive patients or other multimodality approaches.[522,546-548] IMRT may be useful to reduce toxicity.[457,504,549-553] However, the addition of larger doses of other chemotherapeutic drugs has not been associated with improved control of distant disease or with improved survival. Other radiosensitizing agents that may be considered include docetaxel and paclitaxel with or without carboplatin.[531,533,550,554] Although optimal results have been reported with hyperfractionated EBRT combined with chemotherapy, the NCCN Panel acknowledges that considerable toxicity is associated with such treatment and that prolonged remission is uncommonly reported.[555]

Multimodality therapy is recommended in patients with locally resectable disease (see Treatment in the NCCN Guidelines for Anaplastic [Thyroid] Carcinoma).[504,534,549,556-560] Small retrospective studies have reported that patients with ATC who receive trimodal therapy including surgery, radiation, and systemic therapy demonstrate improved survival compared to those who undergo less aggressive treatment approaches.[561-563] In a case series, complete surgical resection without tracheostomy or radical re-resection was achieved in six patients with initially unresectable BRAF V600E-mutated ATC who received neoadjuvant dabrafenib/trametinib.[564] One-year OS was 83%, and the local control rate (LCR) was 100%. Two patients eventually died from distant metastasis, but the treatment response continued to be durable in the remaining four patients.

**PRINCIPLES OF KINASE INHIBITOR THERAPY IN ADVANCED THYROID CARCINOMA1-7**

Oral kinase inhibitors demonstrate clinically significant activity in randomized, placebo-controlled clinical trials in locally recurrent unresectable and metastatic MTC and in radioiodine-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.

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**Lebbink CA et al., 2022 [3].**

*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 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: 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 [2].**

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 wird die LL ergänzend dargestellt.*

Grundlage der Leitlinie

- 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.

Recherche/Suchzeitraum:

- […] 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.

LoE/GoR

- 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: 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%**)

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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**Bible KC et al., 2021 [1].**

*American Thyroid Association*

2021 American Thyroid Association Guidelines for Management of Patients with Anaplastic Thyroid Cancer

**Zielsetzung/Fragestellung**

Anaplastic thyroid cancer (ATC) is a rare but highly lethal form of thyroid cancer. Since the guidelines for the management of ATC by the American Thyroid Association were first published in 2012, significant clinical and scientific advances have occurred in the field. The aim of these guidelines is to inform clinicians, patients, and researchers on published evidence relating to the diagnosis and management of ATC.

**Methodik**

Grundlage der Leitlinie

Vollständige Überarbeitung der ursprünglich 2012 veröffentlichen Leitlinie.

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

Recherche/Suchzeitraum:

- Databases were searched from inception to the date of the search (February 15, 2017, initially and updated in May 11, 2020)
- 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.

LoE

- 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**)
- […] there are four categories of quality of evidence: **high quality, moderate quality, low quality, and very low quality**.
- **High-quality evidence** on therapeutic interventions **requires one or more studies at low risk of bias** (e.g., randomized-controlled trials [RCTs] without important limitations), that have consistent results and precise estimates.
- **Very low-quality evidence derives from studies at high risk of bias** (e.g., observational), or inconsistent and imprecise results across studies.

GoR

- **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
- Along with the **quality of the body of evidence**, the authors considered a **balance between benefits, risks, and burdens of interventions** as an important factor in deciding the strength of the recommendation.
- When the authors deemed that there was a large body of indirect evidence to support the benefit of a recommendation, and in which the evaluation of alternatives in clinical trials would be unproductive and unnecessary, the authors provided **good practice statements** […] **based on the authors' expert opinion** […].

Sonstige methodische Hinweise

- "Good practice statements" sind ausschließlich konsensbasiert.
- „Values Statements" (informiert durch die Patientenvertretung) schildern wichtige Abwägungen bezüglich der Empfehlung und der Evidenz (über das hinaus, was in der Empfehlung und im Text zur Evidenzbasis für die Empfehlung beschrieben wurde).

**Empfehlungen: RADIOTHERAPY AND SYSTEMIC CHEMOTHERAPY IN LOCOREGIONALLY CONFINED (STAGES IVA AND IVB) ATC: PRINCIPLES AND APPROACHES**

Radiotherapy after complete/near-complete (R0 or R1) resection.

RECOMMENDATION 14

Following R0 or R1 resection, we recommend that good performance status patients with no evidence of metastatic disease who wish an aggressive approach should be offered standard fractionation IMRT with concurrent systemic therapy.

**Strength of Recommendation: Strong**

**Quality of Evidence: Low**

GOOD PRACTICE STATEMENT 8

Radiation therapy should begin no later than 6 weeks after surgery.

GOOD PRACTICE STATEMENT 9

Patient goals of care, medical and psychosocial fitness for therapy, potential toxicities, financial considerations, and robustness of social support must be prominently considered in the decision to proceed with aggressive multimodal therapy.

GOOD PRACTICE STATEMENT 10

Cytotoxic chemotherapy can be initiated within 1 week of surgery, providing sufficient healing, in anticipation of subsequent chemoradiation.

Hintergrundinformation:

The best outcomes in terms of both local control and survival in IVA/IVB ATC based upon consistent results from multiple studies appear to be associated with complete/near-complete surgical resection followed by radiotherapy, often administered in combination with chemotherapy; studies are summarized in Supplemental Data S4. Unfortunately, there is inconsistency in outcomes measured, reporting of effectiveness of local control, and in terminology used; multimodality often is also sometimes used to describe surgery and postoperative radiotherapy without chemotherapy. In published reports, there is furthermore always an element of case selection bias; invariably, patients with better performance status, younger age, and less extensive disease receive more aggressive combination therapy. Nevertheless, unselected Surveillance, Epidemiology, and End Results (SEER) data detailing 516 patients revealed in a multivariate analysis that, along with age, only the combined use of surgical resection and radiotherapy

was identified as an independent predictor of survival (224). Given large patient numbers and the fact that this was a population-based study, these data provide the strongest and least biased evidence presently available. That the combination of surgery and radiotherapy is important is also supported in the form of another smaller population-based study from British Columbia analyzing 75 patients; survival was better in patients who had more extensive surgery and had high-dose radiotherapy with or without chemotherapy (203). Moreover, a meta-analysis of 17 retrospective studies that included 1147 patients also concluded that postoperative radiotherapy reduces the risk of death compared with surgery alone (237).

More recently, although not population based, there have been three analyses of NCDB data obtained from U.S. cancer centers. In one study, longer survival was associated with doses of radiotherapy >59.4Gy—but not with lower doses. There was a survival of 38% at 2 years (median 16 months) in patients who received high-dose radiotherapy after a thyroidectomy—but these accounted for only 5% of the study population, suggesting selection bias (212). In another analysis of patients who had unresected disease, again, a higher radiotherapy dose was associated with greater survival, but so was an ''intermediate dose'' (defined as 45–59.9 Gy) in patients with unresectable ATC (238). In a third analysis of NCDB data (239), a small survival benefit was found from trimodality treatment.

In general, most single-institution studies also report improved results due to the combination of surgery and radiotherapy (4,66,95,97,200–202,204,206,207,218,240–244). In a multicenter study from Korea (245) involving 329 patients, median survival was 15 months (84 patients) with a 1-year survival of 50% among patients undergoing surgery and radiotherapy compared with 5 months without surgery (50 patients) but with radiotherapy or chemoradiotherapy alone—and only 2 months with no treatment (81 patients).

Assessing the incremental additional contribution of systemic therapy to that of radiotherapy and surgery has been less well studied, but available retrospective data suggest benefit. In patients with stage IVA disease, trimodality treatment was associated with a longer median survival than surgery and radiotherapy without chemotherapy (11.2 months vs. 9.3 months, $p < 0.001$) The difference was maintained in stage IVB patients (9.9 months vs. 5.9 months, $p < 0.001$) and even in patients with metastatic disease (4.9 months vs. 3.5 months, $p < 0.001$).

Most studies report survival only, but those reporting local control generally show improvement with multimodality treatment. For instance, Liu et al. reported a 2-year local control rate of 43% with postoperative radiotherapy compared with 7% in surgery alone in patients without distant metastases (201,206,207,240,246,247). In a recent series from Prasongsook et al., local control was 90% for the lifetime of patients treated with combination chemotherapy and concurrent radiotherapy (248).

In the majority of series, radiotherapy is given after surgery; however, in a few, preoperative radiotherapy has been given. In some series, radiotherapy is ''sandwiched'' pre- and postoperatively (95,97). For instance, Tennvall et al. initially used a ''sandwich'' approach with preoperative chemoradiotherapy followed by surgery then further chemoradiotherapy—but subsequently instead administered preoperative chemoradiation then surgery, then adjuvant chemotherapy without radiation (220). In their latest series, 17 out of 23 patients were able to undergo some form of surgery, 2 with gross residual disease. Despite this approach, the median survival was only 2 months (220); this approach has not been adopted by other centers, although some have utilized preoperative chemotherapy alone (219,221).

In a recent series comparing outcomes from an intensive combined modality approach (surgery, when feasible, followed by chemo-intensity-modulated radiotherapy [IMRT] using taxanes) versus historical pre-IMRT approaches combined with doxorubicin, all-stage overall survival at 1 year improved from 10% to 43% (248). In comparing stage-specific outcomes, however, differences in overall survival among patients receiving the most intensive trimodal therapy were only statistically significant among stages IVA and IVB patients.

In patients with initially resectable disease, there does not appear to be any substantive evidence that preoperative radiotherapy is preferable to postoperative radiotherapy. Surgical resection may therefore reasonably be performed first, with postoperative chemoradiotherapy given subsequently. However, in patients with initially unresectable disease, chemoradiotherapy may rarely enable subsequent resection and should be considered in patients with good performance status and without significant metastatic disease. However, the potential benefit in a few must be weighed against the risk of toxicity in a population

of patients, the majority of whom still have poor survival. It is unclear if patients with incidentally detected ATC after thyroidectomy benefit from radiotherapy (249).

**Toxicities from radiotherapy and chemoradiotherapy, risks versus benefits.** The reported benefits from aggressive bi- or trimodal therapy, however, must be carefully balanced with patient goals of care and expected negative impacts on short- and long-term quality of life. Quality-of-life data are completely lacking. However, historical data reporting toxicities from prior approaches exist, but must also be viewed in light of current use of IMRT, which reduces toxicities to normal adjacent structures. It is nevertheless clear that short-term toxicities from multimodal therapy in the setting of ATC are extreme, but confounded by issues arising from the cancer itself. For example, Prasongsook et al. reported a 60% hospitalization rate and a temporary requirement for feeding tube placement in 60% among ATC patients undergoing trimodal therapy (248). Prasongsook et al. also reported a 3% mortality rate during multimodal therapy in ATC (248). Chronic problems such as lymphedema, limited neck range of motion, and chronic dry mouth are also common and irreversible. Hence, it is imperative to discuss such complications with patients so as to insure their informed decision-making.

There are few specific data on radiation toxicity in patients being treated for ATC. The available data are outlined above. In general, it can be assumed that toxicity is similar to that seen in the treatment of other head and neck cancers but is dependent on the volume being treated and the radiation dose prescribed and if concurrent chemoradiation is given. Serious complications are rare following well-planned external beam radiation therapy. Acute toxicity at the end of a course of radiation therapy includes skin erythema and moist desquamation and mucositis of the esophagus, trachea, and larynx and also xerostomia. Late toxicity includes skin telangiectasias, skin pigmentation, soft tissue fibrosis, and mild lymphedema, usually appearing just below the chin. Esophageal stenosis can usually be treated by dilatation, but gastric tube (G-tube) dependency. Tracheal stenosis is rare.

Two large series on the use of external beam radiation therapy without concurrent chemotherapy in DTC reported no Radiation Therapy Oncology Group grade IV toxic effects (250,251). However, in a series of 12 ATC patients, 23% experienced acute or chronic morbidity requiring hospitalization, and 2 out of 5 long-term survivors who were treated with concurrent chemoradiation had esophageal stenosis (one required a permanent G-tube) (244).

**Timing and sequencing of perioperative radiotherapy and/or systemic chemotherapy**. There are no definitive data to indicate when radiotherapy and chemotherapy should start or how they should be sequenced. Some physicians may prefer sequential therapy. However, given that ATC grows very rapidly, it is probably prudent to start therapy as soon as feasible. Radiotherapy can generally begin after postoperative healing has transpired and when the patient has recovered sufficiently to lie supine and tolerate immobilization. In particular, radiation treatment planning should begin expeditiously when postoperative swelling has diminished, ~2 to 3 weeks after surgery. Depending on the time required for treatment planning, treatment may start with a parallel opposed pair beam arrangement until the final treatment plan is available, which should be less than 5 business days. In terms of time of initiation of systemic therapy if elected, this too should begin expeditiously. However, systemic chemotherapy can often be initiated more quickly after surgery than can radiotherapy, as less postoperative healing is required for its safe administration. In a single-institution series, Prasongsook et al. reported a median time from surgery to chemotherapy of 19 days, and median time from surgery to radiotherapy initiation of 27 days (248).

## Radiotherapy and/or chemotherapy in patients with unresectable or gross residual locoregionally confined disease

### RECOMMENDATION 15

We recommend that patients who have undergone R2 resection or have unresectable but nonmetastatic disease with good performance status and who wish an aggressive approach be offered standard fractionation IMRT with systemic therapy. Alternatively, in BRAFV600E-mutated ATC, combined BRAF/MEK inhibitors can be considered in this context.

**Strength of Recommendation: Strong**

**Quality of Evidence: Low**

RECOMMENDATION 16

In patients with unresectable disease during initial evaluation in whom radiotherapy and/or systemic (chemotherapy or combined BRAF/MEK inhibitors) therapy render the tumor potentially resectable, we recommend reconsideration of surgical resection.

**Strength of Recommendation: Strong**

**Quality of Evidence: Low**

RECOMMENDATION 17

Among patients who are to receive radiotherapy for unresectable thyroid cancer or in the postoperative setting, IMRT is recommended.

**Strength of Recommendation: Strong**

**Quality of Evidence: Low**

RECOMMENDATION 18

The use of cytotoxic chemotherapy involving a taxane (paclitaxel or docetaxel), administered with or without anthracyclines (doxorubicin) or platin (cisplatin or carboplatin), is recommended in patients treated with definitive-intention radiation.

**Strength of Recommendation: Strong**

**Quality of Evidence: Low**

GOOD PRACTICE STATEMENT 11

In patients of poor performance status, palliative or preventative (no residual disease present) locoregional radiotherapy over high-dose radiotherapy is suggested.

Hintergrundinformation:

Even among patients who do not have resectable disease, or who have an R2 resection, radiotherapy can achieve local control; several series, however, show a radiation dose/response relationship with outcomes. These data must be interpreted with caution as all such studies are retrospective with selection bias; patients with less extensive disease and better performance status and better expected outcomes are more likely to be given high-dose radiotherapy. Levendag et al. Reported that patientswho received <30 Gy had a median survival of 1 month compared with 3.3 months if >30 Gy was given (225). Pierie et al. reported that ATC patients who had ≥45 Gy had better survival (200). Swaak-Kragten et al. reported that median survival was 5.4 months if given >40 Gy but only 1.7 months if less <40 Gy was given (201). Wang et al. reported a median survival was 3 months if <40 Gy and 11 months if >40 Gy was administered (226). In a recent report on the experience with radiotherapy and weekly doxorubicin, a median survival of 6 months was reported, but a radiotherapy dose ≥50 Gy was associated with amedian survival of 8.4 months, and, if >60 Gy was given, the median survival was highest at 14months (252). These studies collectively suggest that higher dose radiotherapy is associated with longer survival and moreover that IMRT should be used to deliver these doses safely and effectively.

How to most appropriately select patients for aggressive multimodal therapy remains uncertain, but patients with good performance status and no metastases should probably be offered high-dose tumor bed radiotherapy. There is, however, also the suggestion that patients with limited metastatic disease may benefit from an aggressive approach to the local and regional disease to ensure local tumor control. Levendag et al. reported that median survival in patients with metastatic disease was improved if local control was achieved (8 months vs. 2 months) (225).

In the analysis of data from the NCDB discussed above, patients with stage IVC disease had slightly better survival after trimodality treatment than after bimodal therapy (surgery and radiotherapy, IVC 4.9 months vs. 3.5 months, $p < 0.001$). In contrast, both Liu et al. and Prasongsook et al. reported no survival benefit from multimodality treatment in patients with clearly metastatic disease at diagnosis. Thus, enthusiasm for aggressive therapies must be tempered in consideration of the overall poor survival of patients with metastatic disease and in light of patient wishes.

For patients with poor performance status who decline—or who would not be expected to tolerate—high-dose radiotherapy, low-dose radiotherapy may be of palliative benefit with respect to control of local disease/symptoms, but there are few supporting data. Juror and associates reported a 40% CR rate from radiotherapy, and a 42% PR rate for an overall RR of 82%, and a trend to increased survival with higher doses. Higher doses of radiotherapy, however, were not associated with improved RRs (doses of less than 20 Gy were excluded) (205). Thus, there is probably a reasonable chance of transient response to palliative radiotherapy using modest doses. However, in the analysis of NCDB data, by Glaser et al., a survival benefit was only seen in patients who re received greater than 59.4 Gy (212). In contrast, in the series of patients with unresected ATC from the NCDB, Pezzi et al. showed no survival benefit from <45 Gy compared with no radiotherapy; however, there was improved survival associated with 45–59.9 Gy compared with less or no radiotherapy (238). Importantly, outcome measures included survival and not symptom or local control, and so, a palliative effect of low-dose radiation (often given in large fractions such as 3 Gy times 10 (30 Gy) or 4 Gy times 5 (20 Gy) is uncertain. There are few data on quality-of-life impacts in these patients. Lessened toxicity in response to a palliative radiotherapy program could therefore prompt consideration of such an approach in symptomatic patients not considered appropriate for high-dose radiotherapy because of considerations such as performance status, widespread metastatic disease, or patient wishes.

**Radiotherapy treatment volume and techniques** (conventional, altered fractionation, IMRT, adaptive radiotherapy, proton therapy). The radiotherapy treatment volume required to optimally treat either unresected or postoperative ATC is generally very large (thyroid gland or operative bed, bilateral level II–V cervical nodes, level VI central neck nodes, and upper mediastinal nodes to the carina), with an element of compromise therefore required in efforts to achieve acceptable toxicity. A variety of conventional two-dimensional and three-dimensional planning techniques have been used over the years; however, with IMRT, it is possible to generate concave dose distributions and dose gradients with narrow margins so as to enable treatment of complex treatment volumes minimizing dose to adjacent normal structures such as spinal cord, larynx, esophagus, brachial plexus, and salivary glands. In the rare instance that chemoradiotherapy produces a rapid reduction in the tumor volume, there may also be a role for adaptive radiotherapy and replanning radiotherapy to ensure adequate treatment of the tumor volume while avoiding higher doses to organs at risk and to treat a smaller high-dose tumor volume and potentially reduce toxicities.

There is strong evidence of the benefit of IMRT in improving outcomes and reducing toxicity in other head and neck cancers (253,254). Although there is insufficient evidence in a systematic review to propose evidence-based recommendations for ATC, given the dosimetric advantages and potential reduction in toxicity, IMRT should be offered to patients with ATC as an alternative to conventional treatment planning (255). The availability of intensity-modulated proton therapy may offer an advantage over IMRT in reducing radiotherapy dose to normal structures such as the larynx, esophagus, and salivary glands—but evidence of incremental clinical benefit over IMRT is presently lacking.

Using hyperfractionation may also increase radiotherapy RRs, at the cost of increased physical toxicity and financial burden—but with the advantage of shorter overall treatment time compared with conventional radiotherapy (which theoretically can reduce the risk of tumor cell repopulation). This latter effect may be important in rapidly growing ATC, and has been used in combination with chemotherapy in several studies. In a study of radiotherapy alone, Wang et al. found that hyperfractionated radiotherapy resulted in longer median survival compared with conventional fractionation (13.6 months vs. 10.3 months), although the difference was not statistically significant (226). In a small number of patients, Kobayashi et al. reported better local control with postoperative hyperfractionated radiotherapy than conventional radiotherapy (242). In contrast, Dandekar et al. reported that a hyperfractionated accelerated protocol with larger fraction sizes than usually given conferred significant toxicity but no survival advantage (256). One study used high-dose, short-course hypofractionated radiotherapy to complete radiotherapy in a shorter time and reported it to be effective with comparable local control and toxicity compared with conventional fractionation (257).

**Role of chemotherapy combined with radiotherapy as neo/adjuvant therapy in locoregionally confined (stages IVA or IVB) ATC.** In the past, when chemoradiotherapy was given for thyroid cancer, radiotherapy was most often combined with doxorubicin, reported in a series of single-institutional studies. Although these reports have not shown consistent benefit, there is increasing evidence that taxanes, which are also radiosensitizing agents, may be more effective chemotherapeutic agents than those traditionally used in ATC (218,244,258). Kawada et al. (259) alternatively reported a discouraging RR of only 14% to docetaxel monotherapy in advanced ATC. Encouraging results, however, have been reported when taxanes are combined with radiotherapy. Troch et al. reported four CR and two PR among six patients treated with combined docetaxel and IMRT, with five of six patients surviving >21 months (260). Similarly, among 10

consecutively treated IVA and IVB ATC patients with locoregional disease, Foote et al. (230) reported that five patients were alive and cancer-free having been followed >32 months with a median overall survival of 60 months (overall survival at 1 and 2 years was 70% and 60%, respectively) in response to IMRT combined with adjuvant and radiosensitizing chemotherapy, including docetaxel plus doxorubicin. In an updated report examining 30 patients receiving multimodal therapy and 18 treated with palliative intention, median overall survival was 21 months compared with 3.9 months in the pooled multimodal therapy versus palliative intention groups (HR, 0.32; p = 0.0006). Among patients with stage IVB disease, median overall survival was 22.4 months among multimodal therapy, versus 4 months among palliative intention patients (OR 0.12; [CI 0.03–0.44]; p = 0.0001), with 68% multimodal therapy versus 0% palliative intention patients alive at 1 year; however, the cohort size was small, all multimodal therapy patients received both chemotherapy and IMRT, and the study was historical and not randomized. Hence, although this study suggests improved outcomes in response to multimodal therapy in IVA/IVB ATC, it does not specifically clarify the incremental value of the addition of chemotherapy to IMRT. Among patients with stage IVC cancer, overall survival did not differ by therapy in the same study (248), suggesting also that improved outcomes are concentrated in patients without distant metastases. In a small series of 18 patients from Egypt, debulking surgery followed by concurrent chemoradiotherapy with docetaxel and further chemotherapy was shown to be feasible and effective (261).

Altered fractionation can be combined with chemotherapy (referred to as concurrent chemotherapy), but with the risk of increased toxicity. Altered fractionation does not prevent the initiation of chemotherapy after completion, and, as overall treatment time is reduced with altered fractionation schedules, chemotherapy may be started sooner than after conventional radiotherapy.

To date, there has been no comparison of altered fractionation radiotherapy alone or combined with chemotherapy compared with conventional chemoradiotherapy, and either may be considered depending on institutional preferences.

## SYSTEMIC THERAPEUTIC APPROACHES TO LOCALLY ADVANCED UNRESECTABLE AND/OR METASTATIC DISEASE

### Systemic therapy for unresectable stage IVB and stage IVC patients

#### RECOMMENDATION 19

Among ATC patients with unresectable or advanced disease wishing aggressive therapy, we suggest early initiation of cytotoxic chemotherapy as an initial and potentially bridging approach until mutational interrogation results and/or mutationally specified therapies might be available, and if appropriate.

**Strength of Recommendation: Conditional**

**Quality of Evidence: Low**

Hintergrundinformation:

In advanced disease, decisions related to the timing and administration of systemic therapies relative to palliative local therapies depend greatly on the following: the patient's goals of care, the burden of distant metastatic disease and threat(s) imposed by said disease, the patency and stability of the airway, prior therapies, the availability of attractive therapeutic options including clinical trials, patient clinical condition and comorbidities, and whether the patient's tumor harbors a targetable mutation in which personalized targeted therapy is readily available and affordable. Figures 1 and 2 illustrate in broad strokes approaches to patients with locally advanced or metastatic disease taking these factors into account. Because of the paucity of data indicating comparative efficacies of various candidate systemic therapies in this context, and the critical need for better data in this context, clinical trials should be prominently considered if available and feasible. Inclusion criteria for clinical trials can be rigid; thus, if a clinical trial is an option for the patient, this should be considered early on and be expeditious. Critically, many clinical trials require good performance status and commonly also the ability of patients to swallow intact tablets/capsules, thus excluding the sickest ATC patients from studies and from potentially life-extending therapies, and in the process having the potential to bias study results to have uncertain relevance to many ATC patients.

**Expeditious therapy initiation**. Given the very aggressive nature of ATC and imminent threat from disease progression, expeditious treatment initiation is critical among patients wishing an aggressive approach. As described below, anthracyclines (doxorubicin) and taxanes (paclitaxel, docetaxel) have modest and often

disappointing and only transient clinical activity in advanced ATC. While awaiting molecular information or targeted drug approval, radiotherapy and/or the expeditious initial use of these cytotoxic chemotherapy drugs as ‘‘bridging’’ chemotherapy are prudent among patients wishing aggressive treatment (Table 6). Furthermore, productively targetable alterations may not exist in a particular tumor, or targeted therapy may not be available, making cytotoxic chemotherapy the only viable systemic therapeutic option. Consequently, the early application of ‘‘bridging’’ cytotoxic chemotherapy has been used in clinical practice, reported in the literature (263), and is being used in at least one first-line ATC therapeutic clinical trial (NCT03181100), so as to ensure that a potentially effective therapy is not withheld or delayed. This is a strategy of strong consideration in clinical practice and in other trial designs.

Systemic therapy: targeted approaches

RECOMMENDATION 20

In BRAFV600E-mutated IVC and in unresectable IVB ATC patients who decline radiation therapy, initiation of BRAF/MEK inhibitors (dabrafenib plus trametinib) is recommended over other systemic therapies if available.

**Strength of Recommendation: Strong**

**Quality of Evidence: Low**

Values Statement regarding Recommendation 20

The authors—including patient advocates—for this recommendation placed a high value on available and emerging data indicating the potential for profound benefit from using this approach in a setting where little hope had previously existed, supporting the strong recommendation made in the presence of low-quality evidence.

RECOMMENDATION 21

In BRAFV600E-mutated unresectable stage IVB ATC in which radiation therapy is feasible, chemoradiotherapy or neoadjuvant dabrafenib/trametinib represents alternatives to initial therapy.

**Strength of Recommendation: Conditional**

**Quality of Evidence: Low**

Hintergrundinformation:

Mutation-guided individualized targeted therapeutic strategies are now increasingly finding application, especially in advanced or initially unresectable ATC. Retrospective assessments of outcomes observed from using this strategy are now being published, with emerging evidence to support a potential survival advantage to the use of targeted therapy in ATC in one recent study (HR in response to use versus nonuse of targeted therapy, 0.49; [CI 0.39–0.63]; $p < 0.001$) (264).

**$BRAF_{V600E}$-mutated ATC**. Because targetable somatic mutations in ATC may suggest potentially efficacious personalized therapeutics, most centers with ATC expertise interrogate tumors for mutations early on so as to define later candidate opportunities that may exist in this space. Among ATCs, $BRAF_{V600E}$ is the most commonly encountered productively actionable mutation, seen in 50–70% of cases (74–76). When PTC coexists in the pathology specimen with ATC, over 90% may harbor a $BRAF_{V600E}$ mutation (126). In May 2018, the BRAF/MEK inhibitor combination, dabrafenib plus trametinib, was approved by the U.S. FDA for ATC patients harboring a $BRAF_{V600E}$ (but not other) mutation. BRAF-directed therapy can induce prompt and impressive tumor regression in these patients, and therefore, use of these drugs in stage IVC patients is recommended in $BRAF_{V600E}$- mutated patients. In $BRAF_{V600E}$-mutated ATC patients with unresectable stage IVB disease, however, consideration of upfront chemoradiation is the current standard. Alternatively, when upfront chemoradiation may be contraindicated or not desired by the patient, systemic therapy with BRAF-directed therapy can be considered. Neoadjuvant use of dabrafenib plus trametinib is also being explored as a way to convert an unresectable primary tumor to resectable (221,222). Moreover, there are now emerging data to suggest that surgical resection following favorable response to neoadjuvant BRAF inhibitory therapy can lead to prolonged survival (94% 1-year overall survival, n = 20) (264).

In particular, dabrafenib (150mg twice daily) combined with trametinib (2mg daily) was studied in a prospective, nonrandomized clinical trial of patients with $BRAF_{V600E}$-mutated ATC (116). Data presented to the FDA on 23 evaluable patients showed an overall RR of 61% [CI 39–80%]; CR was seen in 4% and PR in 57%. Response duration was ≥6 months in 64% of responding patients and overall survival was 80% at 1 year. In this clinical trial, all patients had an Eastern Cooperative Oncology Group performance status of 0–1 and patients who were unable to swallow pills were excluded; thus, patients enrolled in this trial may have had a lessor tumor burden and could have biased results. Recently updated results presented at the European Society of Medical Oncology 2018 (265) indicated that that median overall survival was 86 weeks [CI 35 weeks–not estimable], and median progression-free survival was 60 weeks by investigator assessment [CI 20 weeks–not estimable]; the study, however, included some IVA and IVB patients. Single-agent BRAF inhibitor therapy alternatively using vemurafenib was studied in seven BRAF-mutated ATC patients, with two responses noted (266). Vemurafenib/cobimetinib (MEK inhibitor) in combination with immunotherapy is currently also being studied in a prospective clinical trial (NCT03181100). There is consensus that at least $BRAF_{V600E}$ mutational analysis should be undertaken early-on and urgently in ATCs. Rapid BRAF testing can be performed by IHC (33) if there is available and viable tissue, or potentially by cfDNA blood-based ''liquid biopsy'' testing of peripheral blood (113) as alternatives to more comprehensive and definitive, but time-consuming, mutational interrogation.

RECOMMENDATION 22

In BRAF nonmutated patients, radiation therapy with concurrent chemotherapy should be considered in an effort to maintain the airway in patients with low burden of metastatic disease.

**Strength of Recommendation: Strong**

**Quality of Evidence: Low**

Hintergrundinformation:

**BRAF-nonmutated ATC**. In patients whose tumors do not harbor a BRAFV600E therapeutically targetable mutation or where mutational status is unknown, patient goals of care, disease extent, and threats imposed by disease should together especially inform the election and timing of the application of systemic therapy. In cases in which the patient is stage IVB or stage IVC with a low burden of distant metastatic disease and/or symptomatic or imminently threatening locoregional disease that can be treated with radiation therapy to the neck, external beam radiation therapy +/- concomitant chemotherapy should be a priority to reduce risk of asphyxiation. If radiation is intended, a more definitive IMRT course is preferable, best with coadministration of cytotoxic chemotherapy such as a taxane with or without cis- or carbo-platinum or with doxorubicin (e.g., docetaxel plus doxorubicin), with restaging scans performed midway through any longer IMRT course so as to assess for early distant disease progression. If there is rapid progression of distant metastatic disease, immediate change of systemic therapy should be offered. Clinical trials, particularly those that are mutation targeted, should be considered in patients who are healthy enough to participate, given some success in targeting the BRAFV600E oncogene in ATC. Molecular testing, to include fusion testing, and referral to trials should be made very early on in the diagnosis so as to minimize delay in initiation of systemic therapy, also realizing that other potentially productively targetable mutations may present therapeutic opportunities beyond those involving cytotoxic chemotherapy, as discussed in the following sections.

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**

Hintergrundinformation:

**NTRK, RET, and ALK fusions in ATC.** 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 patients 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.

**Antiangiogenic drugs**. In patients without a BRAFV600E mutation, or in the setting of patients who do not respond to—or who progress through—personalized targeted therapy, there are few data to support the use of any one class of drug. Historically, cytotoxic chemotherapy has been used, but responses to these are often very short-lived. Thus, interest in targeted molecular therapy with antiangiogenic drugs in ATC has resulted in several clinical trials (272–274). Only one antiangiogenic drug, lenvatinib, a multikinase inhibitor of VEGFR 1–3, FGFR 1–4, PDGFR, RET, and kit (FDA approved for DTC) has shown efficacy in a prospective clinical trial done in Japan, and on this basis is approved for use in Japan (245). Of 17 ATC patients, 4 (24%) responded, with a median overall survival of 10.6 months. Other retrospective studies have shown some efficacy in ATC (263,275). However, an intended confirmatory phase 2 trial of lenvatinib undertaken in ATC through the International Thyroid Oncology Group was closed at interim analysis due to lack of efficacy. Sorafenib, axitinib, gefinitnib, and pazopanib used as a single agent have not shown promising results, suggesting that kinase inhibitors may collectively have little activity in ATC (276–279).

One of the major limitations of using antiangiogenic drugs in ATC patients is the risk of bleeding in this patient population where disease often invades the trachea, esophagus, and great vessels. Rapid tumor shrinkage could alternatively lead to bleeding and/or fistula when these structures are invaded with tumor (280–283). Patients who are being treated with potent antiangiogenic drugs should be warned about these potential risks.

## Immunotherapy

### RECOMMENDATION 24

In IVC ATC patients with high PD-L1 expression, checkpoint (PD-L1, PD1) inhibitors can be considered first-line therapy in the absence of other targetable alterations or as later line therapy, preferably in the context of a clinical trial.

**Strength of Recommendation: Conditional**

**Quality of Evidence: Low**

Hintergrundinformation:

Immunotherapy for patients with ATC is also currently under investigation. Small studies have shown that ATC tumors express immune markers such as PD-L1 and immune infiltration is a hallmark of this disease (284,285). While checkpoint inhibitors are approved across a variety of solid tumors, none is FDA approved specifically for ATC.

Spartalizumab, an anti-PD-1/PD-2 immunotherapy drug, has been studied in ATC (286). The primary objective of the phase 2 portion of this trial was to determine the overall RR by RECIST v1.1. The RR was 19% (five PR and three CR observed). Twelve BRAFV600E-mutated ATC patients participated in this trial and the RR in this group was only 8% (1 of 12 BRAFV600E-mutated patients obtained a PR). The median overall survival in the entire cohort was 5.9 months, with 40% of patients alive at 1 year. The median progressionfree survival was 1.7 months. Interestingly, those patients with PD-L1 expression of <1% had a median overall survival of 1.6 months and there were no responses in this group; however, those with PD-L1 expression of 1–49% and ≥50% had a median overall survival that had not been reached and an overall RR of 18% (2/11) and 35% (6/17). It should be noted that at the time of the writing of these guidelines, spartalizumab is not FDA approved and is not commercially available.

Several clinical trials using immunotherapy in combination with other systemic agents or with radiation are underway (NCT03181100; NCT03122496; NCT02239900; NCT02404441). There are anecdotal reports of combination therapy involving immunotherapy showing responses in ATC (287). In addition, there are now retrospective data to also indicate apparently improved ATC outcomes when immunotherapy is added to targeted therapy in ATC (OR 0.58, [CI 0.36–0.94], p = 0.03) (264).

## mTOR inhibitors

*Methodikeranmerkung: Es wurde keine Empfehlung formuliert.*

Hintergrundinformation:

**mTOR inhibitors**. Everolimus is a rapamycin analogue that inhibits mTOR. Three clinical trials with everolimus have included patients with ATC (288–290). All three of these trials included fewer than 10 ATC patients and none had more than one responder. However, in two of these studies, one patient in each trial had a dramatic response to everolimus. The trial by Hanna et al. included molecular analysis of thyroid cancer patient tumors. It was noted that although the median progression-free survival was short in the ATC group, in the larger cohort of thyroid cancer, those with a mutation in the PI3K/mTOR/AKT pathway had a median progression-free survival of 15.2 months. One patient had a TSC2 mutation and had a PR that lasted nearly 18 months. Wagle et al. (121) describe this case in great detail in a separate publication. Another ATC patient had an NF1 mutation and had SD that lasted for 26 months. Thus, patient selection for PI3K/mTOR/AKT pathway mutations may be important in ATC, although a larger trial with selected patients is needed. A second-generation mTOR inhibitor trial was recently completed with results currently unavailable (NCT02244463).

## Vascular disrupting agents

*Methodikeranmerkung: Es wurde keine Empfehlung formuliert.*

Hintergrundinformation

**Vascular disrupting agents.** Fosbretabulin, a prodrug of the investigational antimicrotuble disrupting agent combretastatin, was assessed in a phase 2 trial in ATC, producing no PR or CR in ATC patients. However, SD was seen in 7 of 26 patients with a median survival of 4.7 months and 23% of patients surviving 1 year (291). This drug is not presently commercially available.

## Systemic therapy: cytotoxic chemotherapy

### GOOD PRACTICE STATEMENT 12

Patients with BRAF wild-type (BRAF ‘‘negative’’ or unknown mutation status) IVB unresectable or metastatic ATC wishing an aggressive approach and not receiving chemoradiation should be encouraged to participate in clinical trials given the rarity of ATC, the paucity of data in support of improved survival or quality of life from any systemic therapeutics, and the need to develop evidence-based safe and effective therapeutic approaches in advanced ATC.

RECOMMENDATION 25

In metastatic ATC patients lacking other therapeutic options including clinical trials, we suggest cytotoxic chemotherapy including a taxane and/or an anthracycline or taxane with or without cis- or carboplatin.

**Strength of Recommendation: Conditional**

**Quality of Evidence: Low**

Hintergrundinformation:

**Taxanes**. A nonrandomized multicenter clinical trial conducted by Ain et al. demonstrated that the taxane paclitaxel administered weekly or every 3 weeks resulted in transient disease regression in 53% of 19 evaluable patients, with anecdotal evidence suggestive that weekly therapy may be superior to every 3-week 96-hour infusional therapy (258). However, reported dosages of paclitaxel (225 mg/m2 IV weekly) were incorrect (Kenneth Ain, pers. comm.), as paclitaxel dosages should instead be 60–90 mg/m2 IV weekly to assure safety. The WHO criteria were used to determine response, but maintenance of response was required for only 2, rather than the typical 4 weeks utilized in the RECIST criteria, making study results difficult to interpret in the context of studies using RECIST response criteria. The median overall survival was 24 weeks.

Anecdotal experience, however, suggests that single-agent paclitaxel can have disease-modifying effects in some patients and may impact survival in a subset of treated patients. Furthermore, a recent report indicated also that docetaxel at a dosage of 60 mg/m2 IV administered as a single agent every 3 weeks can occasionally also even produce CR—but more commonly stabilize disease for a period of time (259). In this study, one of seven patients had a CR lasting 50 weeks, but median time to progression was only 6 weeks.

**Anthracyclines and platins.** Published studies of the application of doxorubicin in ATC generally discuss its use in combination with surgery and radiotherapy, making assessment of RRs and impact on survival uncertain in advanced disease (220,292). However, in a trial conducted by the Eastern Cooperative Oncology Group (293) from 1976 to 1982, 84 patients with advanced progressive thyroid cancer of all histotypes (not specifically ATC) were randomized to receive doxorubicin alone (60 mg/m2 IV every 3 weeks) or doxorubicin plus cisplatin (60 mg/m2 IV doxorubicin, 40 mg/m2 cisplatin IV every 3 weeks). In 37 patients with ATC on this study, doxorubicin alone produced no CR and 1 PR in 21 treated ATC patients, while doxorubicin plus cisplatin yielded 3 each CR and PR of 18 treated ATC patients (PR+CR: 5% vs. 33%; $p < 0.03$). Median survival in ATC was only 2.7 months, but two responses to doxorubicin plus cisplatin were durable at 41.3 and 34.7 months, suggesting a possible impact on survival in select patients with ATC. Doxorubicin, 20 mg/m2 IV weekly or 60–75 mg/m2 IV every 3 weeks, is the only cytotoxic chemotherapy specifically approved by the FDA for use in ATC.

## APPROACHES TO BRAIN METASTASES

RECOMMENDATION 26

In ATC patients considering therapy, we recommend brain MRI assessing the presence of brain metastases at time of diagnosis as a part of initial staging and when symptoms otherwise prompt concern.

**Strength of Recommendation: Strong**

**Quality of Evidence: Low**

Hintergrundinformation:

Clinically apparent brain metastases at presentation are relatively unusual in ATC, occurring in *1–5% of patients, but they are associated with worse prognosis (41,66,199,294,295). Chiu et al. (295) studied 47 cases of all types of thyroid cancer that had metastatic disease to the brain. Brain metastases were most commonly detected during the monitoring of the patient after the original diagnosis of thyroid cancer, but were the initial manifestation of thyroid cancer in 15%. Patients with brain metastases tended to be older and had more aggressive disease; 11 of the 47 (23%) had ATC. In ATC patients with brain metastases, 56% had locoregional invasion, and 89% had locoregional cervical node involvement. The median time interval from ATC diagnosis to brain metastases diagnosis was 0.7 years, with median time from diagnosis of brain lesions to death being 1.3 months; disease-specific mortality was 100%. Salvati et al. (294) reported solitary

brain metastases in 12 patients with thyroid cancer, 5 of whom had ATC; median size of brain metastases in the ATC patients was 4 cm. All patients were treated with surgical removal and radiotherapy. The median survival of the five patients with ATC was 9 months (individual survival in months: 7, 8, 9, 10, 10).

Brain MRI and CT scans are more sensitive in detecting brain lesions than FDG PET scans, with evidence suggesting that brain MRI is more sensitive than CT (294,296); therefore, MRI should ideally be performed before initiating systemic therapy as a part of initial ATC staging.

RECOMMENDATION 27

In ATC patients with neurologic brain compressive symptoms or signs, we recommend dexamethasone (4–16 mg/day).

**Strength of Recommendation: Strong**

**Quality of Evidence: Low**

RECOMMENDATION 28

In ATC patients with brain metastases, referral to neurosurgery/radiation oncology should be made.

**Strength of Recommendation: Strong**

**Quality of Evidence: Low**

GOOD PRACTICE STATEMENT 15

Patients with brain metastases may be expected to be at increased risk if operating motor vehicles or if placed in a situation in which they may jeopardize themselves or others and therefore should be appropriately counseled.

Hintergrundinformation:

Salvati et al. (294) found a statistically significant improvement in survival (p = 0.03) among ATC patients undergoing gross total removal of brain metastases compared with patients undergoing subtotal removal. Surgical treatment resulted in improvement in quality of life and improvement in neurological symptoms. However, the number of patients studied was small, being three for total removal (survival 9, 10, and 10 months) and two for subtotal removal (survival 7 and 8 months), and selection bias may be a significant issue in this study.

There are insufficient data to make a recommendation for or against stereotactic radiotherapy in patients with ATC and brain metastases versus resection (295), but the poor prognosis of ATC and the logistical advantages of stereotactic radiotherapy make it preferable to surgery in most patients. Carefully to be considered in the decision-making process, however, is whether other systemic diseases are imminently threatening, coupled with consideration of the patient goals of care. Multiple lesions not amenable to stereotactic radiotherapy should instead be treated with whole-brain radiation therapy, else the patient should be referred to hospice care.

There is no published evidence that systemic therapy is effective in treating brain metastases from ATC, however, dabrafenib does cross the blood/brain barrier. Although VEGF-R-directed kinase inhibitors penetrate the central nervous system, it should be noted that they may be detrimental by increasing risk of bleeding into brain metastases in the case of untreated brain metastases (297,298).

Ryken et al. (299) published guidelines for patients with brain metastases from a variety of different tumors, recommending that patients with brain metastases with mass effect be treated with 4–8 mg/day of dexamethasone as the initial dose. Patients with moderate to severe cranial symptoms should be considered to receive 16 mg/day (generally 4 mg, four times daily) (299). It is recommended that there be discussion of the long-term issues regarding corticosteroid administration, and pneumocystis carinii pneumonia prophylaxis may be a consideration.

Mikkelsen et al. (300) provided guidelines that did not recommend routine prophylactic use of antiseizure medications for adult patients with brain metastases who have not yet had a seizure. There is a paucity of relevant controlled studies. A single underpowered RCT did not detect a statistically significant difference

in seizure activity in patients who prophylactically received antiseizure medication and those who did not (301), but further clarity is needed on this issue.

**APPROACHES TO BONE METASTASES**

RECOMMENDATION 29

In patients with ATC with symptomatic or threatening bone metastases—but without structural compromise or threatened spinal cord compression in need of surgical remediation—we recommend palliative radiotherapy.

**Strength of Recommendation: Strong**

**Quality of Evidence: Low**

RECOMMENDATION 30

In patients with ATC with bone metastasis causing structural compromise in a weight-bearing region or threatening spinal cord compression, we recommend orthopedic fixation before initiation of palliative radiotherapy.

**Strength of Recommendation: Strong**

**Quality of Evidence: Low**

RECOMMENDATION 31

In patients with ATC with bone metastasis, we suggest periodic intravenous bisphosphonate infusions or subcutaneous RANK ligand inhibitor.

**Strength of Recommendation: Conditional**

**Quality of Evidence: Low**

Hintergrundinformation:

ATC metastasizes to bone in 5–15% of cases, usually in the presence of multiple other sites of distant metastases (41,66,199,302). With regard to therapy for symptomatic or threatening bony metastases, surgery or radiotherapy should be considered and tailored to the situation. Radiation therapy is preferred unless surgery is required either to preserve, or to treat loss of function (e.g., actual or imminent spinal cord compression, pathological long bone fracture). Interventional radiology palliation, such as via cryoablation, may also have a role, especially in patients in whom surgery and radiotherapy are contraindicated (303). Other approaches such as vertebroplasty may also be appropriate in selected cases, and consultation with the local expert spinal and orthopedic teams should be considered.

Once bone metastases are noted, assessment for additional metastases should be undertaken. Since 99mTc methylene diphosphonate bone scan mainly detects osteoblastic lesions, this technique has less sensitivity and specificity than 18F FDG PET scan (304). MRI and CT scans are excellent for identifying bone lesions in a specific site of concern, but are less useful for general skeletal screening, but whole-body MRI may be used for this purpose (305). Although a skeletal survey with plain radiographs to also include long bones may also be used to screen the skeleton, it is time-consuming and it may be distressing and trigger pain among patients with symptomatic metastases (305). As an alternative to general skeletal screening and/or FDG PET imaging, an expectant approach with symptomatic monitoring triggering therapy directed to symptomatic disease may be preferable in patients electing a less aggressive approach or best supportive care.

In addition to pharmacological pain palliation, bone pain from metastases can be effectively alleviated with a course of palliative radiotherapy, typically performed over 1–2 weeks with 5–10 equal daily fractions of 300–400 cGy to a total dose of 2000–3000 cGy. A single fractionation of 800 cGy may also be an appropriate alternative fractionation. In the setting of metastases involving weight-bearing bones causing structural weakness, orthopedic fixation should be considered (306). Palliative radiotherapy can be administered usually after orthopedic fixation to further promote pain relief and also after surgical decompression of spinal cord compression is existent. A randomized trial has shown that direct decompressive surgery plus postoperative radiotherapy is superior to radiotherapy alone in the treatment of spinal cord compression secondary to metastatic disease (307,308).

For patients experiencing progression of bone metastases despite systemic therapy, there may be a role for bisphosphonates (e.g., zoledronic acid/Zometa, 4mg IV every 3 months in patients with normal renal function), as bisphosphonates have been shown to be effective in preventing, inhibiting, and delaying cancer-associated skeletal complications. Denosumab, an inhibitor of receptor activator of nuclear factor B ligand (RANK ligand), is also effective in decreasing skeletal events in patients with metastatic cancer to the bones, and in some settings is more effective than IV bisphosphonates (309). In parallel with administration of antiresorptive agents, calcium and vitamin D supplementation is essential, and calcium levels must be assessed before each cycle of antiresorptive therapy to assure safe administration; in the case of zoledronic acid, dosage is also reduced proportionate to reductions in renal function.

## APPROACHES TO OTHER SITES OF METASTASES

*Methodikeranmerkung: Es wurde keine Empfehlung formuliert.*

Hintergrundinformation:

Thyroid cancers including ATCs can metastasize to any site. Systemic therapy as described above is the first line of treatment, but if a particular metastasis is symptomatic or has progressed despite systemic therapy, treatment may be individualized to metastatic locations, much as would be the case for other malignancies.

For example, lung metastases are quite common in advanced ATC; in patients who develop symptomatic metastases to pleura/chest wall, these can be palliated using radiotherapy. Occasionally, central mediastinal nodal metastases arise that compress bronchi and threaten post-obstructive pneumonia. Under such circumstances, palliative radiotherapy should be considered. Endobronchial lesions causing hemoptysis can be palliated using endobronchial therapy such as laser or by radiotherapy. Hence, the approach to other metastatic disease sites must be thoughtfully individualized in the context of the threat posed by individual lesions relative to that posed by other and more diffuse multicentric metastatic diseases, also considered in the context of patient goals of care.

## APPROACHES TO OLIGOPROGRESSIVE METASTATIC DISEASE

GOOD PRACTICE STATEMENT 16

In patients on systemic therapy who develop oligo-progressive disease, local tumor-directed therapy may be considered to postpone the need to change otherwise beneficial systemic therapy.

Hintergrundinformation

In patients on systemic therapy who are fortunate to have a good response, resistant clones develop, resulting in progression of metastatic disease. This usually results in a change in systemic therapy or, if there are no alternative systemic therapies, cessation of treatment. If, however, progression occurs in a small number of metastases (conventionally 5 or less), then the disease is said to be oligo-progressive (310). Local therapy such as SBRT or radiofrequency ablation (RFA) directed to the oligo-progressive disease sites may control this disease, allowing the patient to stay on otherwise effective therapy, delaying the need to change systemic management for a time. Hypothetically, such therapy may also initiate an immunological cascade and a potential abscopal effect on other disease sites. Surgery, however, is usually not appropriate in ATC patients with multiple known other sites of metastatic disease, but can be considered on a case-by-case basis, depending on the morbidity of the involved surgery. The addition of pembrolizumab at the time of progression has been described anecdotally.

There is currently little prospective evidence available to definitively support the application of ablative therapy in oligo-progressive cancer patients (311,312), but there is evidence that treatment of oligo-metastatic disease can be curative in some malignancies (such as colorectal cancer and soft tissue sarcoma (313,314). Thus, it seems reasonable to consider local therapy such as SBRT or RFA for oligo-progressive metastases in ATC patients who have otherwise had a good response to systemic therapies and who wish a continued aggressive approach. Additional prospective data are needed to prove that therapy directed at oligo-progressive disease is of benefit to patients in terms of survival or quality of life in ATC; realizing that such data are challenging to generate in ATC, data available for more common cancers may serve as a guide in ATC.

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# 4 Detaillierte Darstellung der Recherchestrategie

**Cochrane Library - Cochrane Database of Systematic Reviews (Issue 02 of 12, February 2024) am 23.02.2024**

| # | Suchfrage |
|---|---|
| 1 | MeSH descriptor: [Thyroid Neoplasms] explode all trees |
| 2 | MeSH descriptor: [Thyroid Cancer, Papillary] explode all trees |
| 3 | MeSH descriptor: [Adenocarcinoma, Follicular] explode all trees |
| 4 | MeSH descriptor: [Carcinoma, Papillary, Follicular] explode all trees |
| 5 | MeSH descriptor: [Thyroid Carcinoma, Anaplastic] explode all trees |
| 6 | thyroid:ti,ab,kw |
| 7 | (cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesion* OR malignan*):ti,ab,kw |
| 8 | #6 AND #7 |
| 9 | #1 OR #2 OR #3 OR #4 OR #5 OR #8 |
| 10 | #9 with Cochrane Library publication date from Feb 2019 to present, in Cochrane Reviews |

**Systematic Reviews in PubMed am 23.02.2024**

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

| # | Suchfrage |
|---|---|
| 1 | Thyroid Neoplasms[mh] |
| 2 | Thyroid cancer, papillary[mh] |
| 3 | Thyroid cancer, follicular [Supplementary Concept] |
| 4 | Thyroid cancer, Hurthle cell [Supplementary Concept] |
| 5 | Adenocarcinoma, Follicular[mh] |
| 6 | Carcinoma, Papillary, Follicular[mh] |
| 7 | Thyroid cancer, medullary[Supplementary Concept] |
| 8 | Familial medullary thyroid carcinoma[Supplementary Concept] |
| 9 | Thyroid Carcinoma, Anaplastic[mh] |
| 10 | (((((Papillary[tiab]) OR Hurthle cell[tiab]) OR follicular[tiab]) OR differentiated[tiab]) OR nonmedullary[tiab]) |
| 11 | (((medullary[tiab]) OR C-cell*[tiab]) OR calcitonin[tiab]) OR anaplastic[tiab] |
| 12 | #10 OR #11 |
| 13 | thyroid[tiab] |

| # | Suchfrage |
|---|---|
| 14 | (((((((((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] |
| 15 | #12 AND #13 AND #14 |
| 16 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #15 |
| 17 | (#16) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab]) |
| 18 | (#17) AND ("2019/02/01"[PDAT] : "3000"[PDAT]) |
| 19 | (#18) NOT "The Cochrane database of systematic reviews"[Journal] |
| 20 | (#19) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt]) |

**Leitlinien in PubMed am 23.02.2024**

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

| # | Suchfrage |
|---|---|
| 1 | Thyroid Neoplasms[mh] |
| 2 | Thyroid cancer, papillary[mh] |
| 3 | Thyroid cancer, follicular [Supplementary Concept] |
| 4 | Thyroid cancer, Hurthle cell [Supplementary Concept] |
| 5 | Adenocarcinoma, Follicular[mh] |

| # | Suchfrage |
|---|---|
| 6 | Carcinoma, Papillary, Follicular[mh] |
| 7 | Thyroid cancer, medullary[Supplementary Concept] |
| 8 | Familial medullary thyroid carcinoma[Supplementary Concept] |
| 9 | Thyroid Carcinoma, Anaplastic[mh] |
| 10 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 |
| 11 | Thyroid[ti] |
| 12 | (((((Papillary[ti]) OR Hurthle cell[ti]) OR follicular[ti]) OR differentiated[ti]) OR nonmedullary[ti]) |
| 13 | (((medullary[ti]) OR C-cell*[ti]) OR calcitonin[ti])OR anaplastic[ti] |
| 14 | thyroid[tiab] |
| 15 | (((((((((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] |
| 16 | #11 AND #15 |
| 17 | (#12 OR #13) AND #14 AND #15 |
| 18 | #10 OR #16 OR #17 |
| 19 | (#18) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti]) |
| 20 | (#19) AND ("2019/02/01"[PDAT] : "3000"[PDAT]) |
| 21 | (#20) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt]) |

**Iterative Handsuche nach grauer Literatur, abgeschlossen am 26.02.2024**

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

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

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

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

## Referenzen


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[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021

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