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: 2022-B-107 Selpercatinib

Stand: August 2022

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

Selpercatinib
[zur Behandlung des fortgeschrittenen, medullären Schilddrüsenkarzinoms mit RET-Mutation]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	**Beschluss über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V:** - Cabozantinib: Beschluss vom 22.01.2015 - Vandetanib: Beschluss vom 05.09.2013 und 06.07.2017 - 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 **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Selpercatinib L01EX22 Retsevmo®	Anwendungsgebiet: Retsevmo® als Monotherapie wird angewendet zur Behandlung von Erwachsenen und Jugendlichen ab 12 Jahren mit fortgeschrittenem RET-mutiertem medullärem Schilddrüsenkarzinom (MTC).
Proteinkinaseinhibitoren	
Cabozantinib L01XE26 COMETRIQ®	COMETRIQ ist indiziert für die Behandlung des medullären Schilddrüsenkarzinoms bei erwachsenen Patienten mit progredienter, nicht resektabler, lokal fortgeschrittener oder metastasierter Erkrankung. Bei Patienten, deren Rearranged during Transfection-(RET)-Mutationsstatus unbekannt oder negativ ist, sollte vor der Entscheidung über die individuelle Behandlung ein möglicherweise geringerer Nutzen berücksichtigt werden (siehe wichtige Informationen in den Abschnitten 4.4 und 5.1).
Selpercatinib L01EX22 Retsevmo®	Retsevmo als Monotherapie wird angewendet zur Behandlung von Erwachsenen und Jugendlichen ab 12 Jahren mit fortgeschrittenem RET-mutierten medullären Schilddrüsenkarzinom (MTC), die eine systemische Therapie nach einer Behandlung mit Cabozantinib und/oder Vandetanib benötigen.
Vandetanib L01XE12 Caprelsa®	Caprelsa ist indiziert für die Behandlung eines aggressiven und symptomatischen medullären Schilddrüsenkarzinoms (MTC) bei Patienten mit nicht resektabler, lokal fortgeschrittener oder metastasierter Erkrankung. Caprelsa ist angezeigt für Erwachsene sowie Jugendliche und Kinder im Alter von 5 Jahren und älter. Bei Patienten, deren Rearranged during Transfection-(RET-)Mutationsstatus nicht bekannt oder negativ ist, sollte vor der Entscheidung über eine individuelle Behandlung ein möglicherweise geringerer Nutzen berücksichtigt werden (siehe wichtige Informationen in den Abschnitten 4.4 und 5.1).

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2022-B-107/108 (Selpercatinib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	14. Juni 2022

Inhaltsverzeichnis

Abkürzungsverzeichnis

AE	Adverse Events
ATA	American Thyroid Association
ATEs	Arterial Thromboembolic Events
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
DTC	Differentiated Thyroid Cancer
ECRI	ECRI Guidelines Trust
FTC	Follicular Thyroid Cancer
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
MTC	Medullary Thyroid Cancer
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
OS	Overall Survival
PFS	Progression-Free Survival
PTC	Papilliary Thyroid Cancer
RET	Rearranged during Transfection
RR	Relatives Risiko
RR-DTC	Radioiodine Refractory Differentiated Thyroid Carcinoma
SIGN	Scottish Intercollegiate Guidelines Network
TKI	Tyrosine Kinase Inhibitors
TRAEs	Treatment-Related Adverse Events
TRIP	Turn Research into Practice Database
VTEs	Venous Thromboembolic Events
WHO	World Health Organization

1 Indikation

Behandlung von Erwachsenen mit einem fortgeschrittenen Schilddrüsenkarzinom.

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.google.com/*) 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 11.05.2022 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 1152 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 5 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.2 Systematische Reviews

James DL et al., 2021 [2].

Radioiodine Remnant Ablation for Differentiated Thyroid Cancer: A Systematic Review and Meta-analysis

Fragestellung

Is treatment with low-activity radioactive iodine (RAI) comparable with high-activity RAI regarding recurrence rates in well-differentiated thyroid carcinoma?

Methodik

Population:

- Patients with low-and intermediate-risk DTC

Intervention:

- was low-activity (≤3GBq) RAI remnant ablation

Komparator:

- highactivity (>3 GBq) RAI remnant ablation

Endpunkte:

- The primary outcome was disease recurrence at a follow-up period ofat least 12 months, and secondary outcomes included successful remnant ablation, adverse events, length of hospital stay, and quality of life (QOL).

Recherche/Suchzeitraum:

- Cochrane Library, Medline, Embase, Scopus, and Google Scholar electronic databases.
- The latest search was performed in March 2020

Qualitätsbewertung der Studien:

- RCTs: Cochrane risk of bias tool.
- The quality of RCTs and observational studies was also assessed using the Jadad scale and the Newcastle-Ottawa scale (NOS), respectively.

Ergebnisse

Anzahl eingeschlossener Studien:

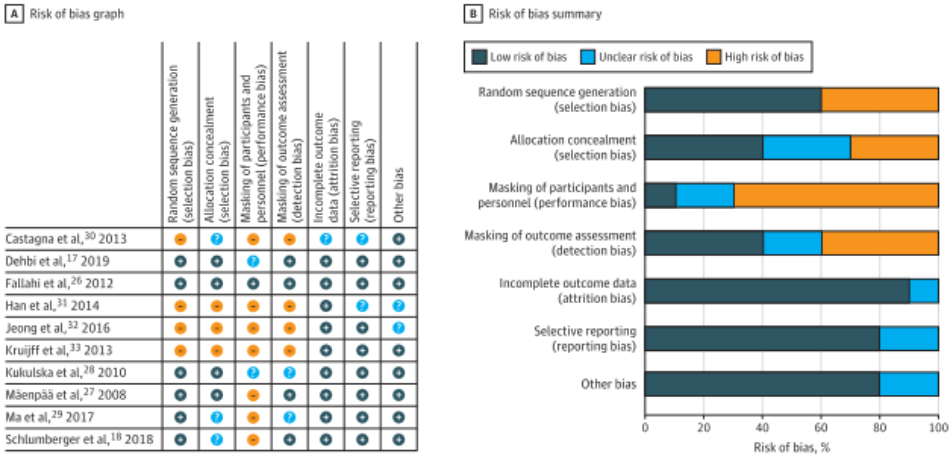
- Ten studies that included 3821 patients met inclusion criteria, including 6 RCTs and 4 observational studies.

Charakteristika der Population:

- The population comprised patients with primary low- and intermediate-risk DTC as defined by the ATA (defined as either PTC or FTC variants) who were undergoing primary total or near-total thyroidectomy.

Qualität der Studien:

- A Jadad scale score of 3 or more or a NOS score of 7 or more represented studies of high quality.



Studienergebnisse:

- Recurrence Rates
  - All 10 studies described recurrence data.
  - There was no heterogeneity (I2 = 0%; P = .48), so a fixed-effects model was used.
  - No statistical difference was observed for long-term cure recurrence rates between low- and high-RAI activities (RR,0.88; 95% CI, 0.62-1.27; P = .50)
- Successful Ablation
  - All 10 studies were included in this analysis.
  - While there was a trend favoring high- vs low-activity RAI in achieving successful ablation (71.5% vs 67.4%), meta-analysis demonstrated no significant difference in successful ablation between RAI activities (RR, 0.95; 95% CI, 0.87-1.03; P = .20; I2 = 79%)
- Length of Stay Three
  - RCTs reported data concerning LOS.
  - There was no difference in LOS between the different RAI activities (weighted mean difference, −3.91; 95% CI, −25.90 to 18.08; P = .73; I2 = 99%)

Anmerkung/Fazit der Autoren

In this systematic review and meta-analysis, low-activity RAI was comparable with high-activity RAI regarding successful ablation and recurrence rates. This suggests that low-activity RAI is preferable to high-activity in low- and intermediate-risk DTC because of its similar efficacy but reduced morbidity.

Kommentare zum Review

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Liu JW et al., 2018 [3].

Tyrosine kinase inhibitors for advanced or metastatic thyroid cancer: a meta-analysis of randomized controlled trials

Fragestellung

To evaluate the effectiveness and safety of tyrosine kinase inhibitors (TKIs) for advanced or metastatic thyroid cancer treatment.

Methodik

Population:

- patients with locally advanced, unresectable, or metastatic thyroid cancer

Intervention/Komparator:

- Sorafenib vs. Placebo, Cabozantinib vs. Placebo, Vandetanib vs. Placebo, Lenvatinib vs. Placebo

Endpunkte:

- Primary outcomes: overall survival (OS) and progression-free survival (PFS)
- Secondary outcomes: complete and partial RRs and adverse events (AEs)

Recherche/Suchzeitraum:

- PubMed, EMBASE, Scopus, and Cochrane databases were electronically searched for relevant studies published until April 2017

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Six RCTs (n=1,615)

Charakteristika der Population:

- Four trials were initially RCTs, but if independent radiologic review confirmed disease progression, the patients who were receiving the placebo could elect to enter the open-label experimental drug phase [9,10,12,18.]
- Three trials enrolled patients with advanced or metastatic DTC [10,12,18,] and two other trials recruited unresectable, advanced, or metastatic MTC patients [10,17].
- Among all DTCs, 486 patients with papillary thyroid cancer and 125 patients with follicular thyroid cancer were included

Table 1. Characteristics of the included randomized controlled trials.

First author (year)	Inclusion criteria	Cancer type	No. of patients (% male)	Age, y	Intervention
Brose (2014)[18]	Age ≥18 y; advanced or metastatic radioiodine-refractory DTC	PTC/FTC/Hurthle cell/poorly differentiated/others	S: 207 (50.2) P: 210 (45.2)	S: 63 (24–82) P: 63 (30–87)	S: Sorafenib 400 mg twice P: Placebo
Elisei (2013)[17]	Adult; unresectable, advanced or metastatic MTC	MTC	C: 219 (68.9) P: 111 (63.1)	C: 55 (20–86) P: 55 (21–79)	C: Cabozantinib 140 mg qd P: Placebo
Leboulleux (2012)[9]	Age ≥18 y; advanced or metastatic DTC	PTC/FTC/poorly differentiated	V: 72 (54) P: 73 (53)	V: 63 (29–81) P: 64 (23–87)	V: Vandetanib 300 mg qd P: Placebo
Schlumberger (2015)[12]; Kiyota (2015)[13]	Age ≥18 y; radioiodine-refractory DTC	PTC/FTC/poorly differentiated	L: 261 (48) P: 131 (57)	L: 64 (27–89) P: 61 (21–81)	L: Lenvatinib 24 mg qd P: Placebo
Wells (2012)[10]	Adult; unresectable or metastatic MTC	MTC	V: 231 (58) P: 100 (56)	V: 50.7[a] P: 53.4	V: Vandetanib 300 mg qd P: Placebo

Abbreviations. C, cabozantinib; DTC, differentiated thyroid cancer; FTC, follicular thyroid cancer; L, lenvatinib; MTC, medullary thyroid cancer; P, placebo; PTC, papillary thyroid cancer; S, sorafenib; V, vandetanib; y, years.
Data presented as median (range) except where [a]indicates the mean.

Qualität der Studien:

Table 2. Methodological quality assessment of included studies.

First author (year)	Allocation generation	Allocation concealment	Blinding of patients and assessors	Data analysis	Lost to follow-up (%)	Selective reporting	Other bias
Brose (2014)[18]	Computer generated	Unclear	Double blinded	ITT	1.2	Low risk	Industry funded
Elisei (2013)[17]	Unclear	Unclear	Double blinded	ITT	5	Low risk	Industry funded; 20.6% patients took TKIs before the study
Leboulleux (2012)[9]	Computer generated	Unclear	Double blinded	ITT	0	Low risk	Industry funded; majority of patients discontinued vandetanib before data cutoff
Schlumberger (2015)[12]; Kiyota (2015)[13]	Computer generated	Unclear	Double blinded	ITT	0	Low risk	Industry funded; only 47% patients continued to receive study drug at data cutoff point
Wells (2012)[10]	Unclear	Unclear	Double blinded	ITT	0.30	Low risk	Industry funded

Risk of bias was assessed according to the method recommended by the Cochrane Collaboration.
Abbreviation. ITT, intention-to-treat.

Studienergebnisse:

- OS:

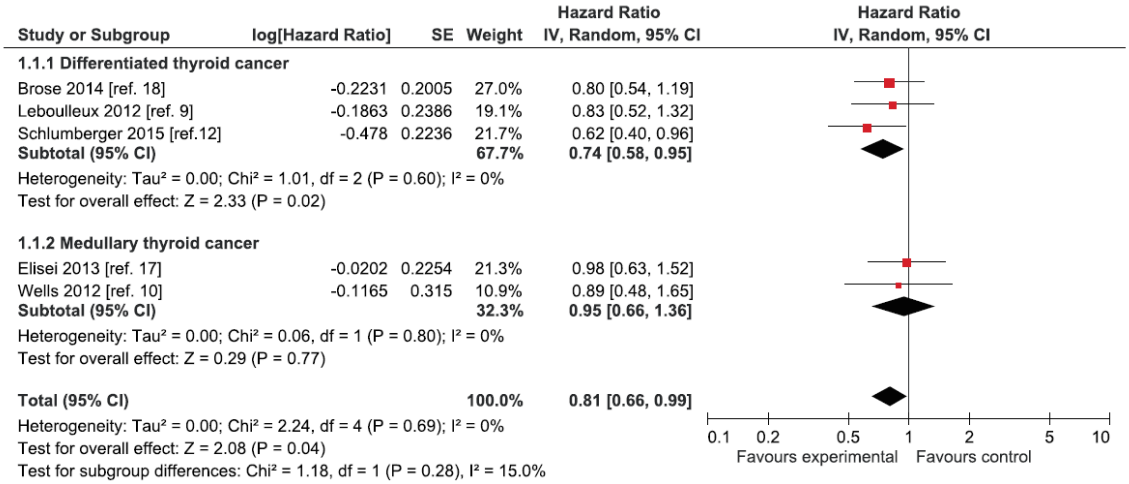

Figure 2. Forest plot of the comparison of the hazard ratio of overall survival between the tyrosine kinase inhibitor treatment and control groups: 1.1.1 differentiated thyroid cancer and 1.1.2 medullary thyroid cancer.

  - Among three TKIs, only lenvatinib showed a significantly higher OS (HR=0.62; 95% CI, 0.40–0.96) than the control group (Figure 2, 1.1.1 DTC).

- PFS

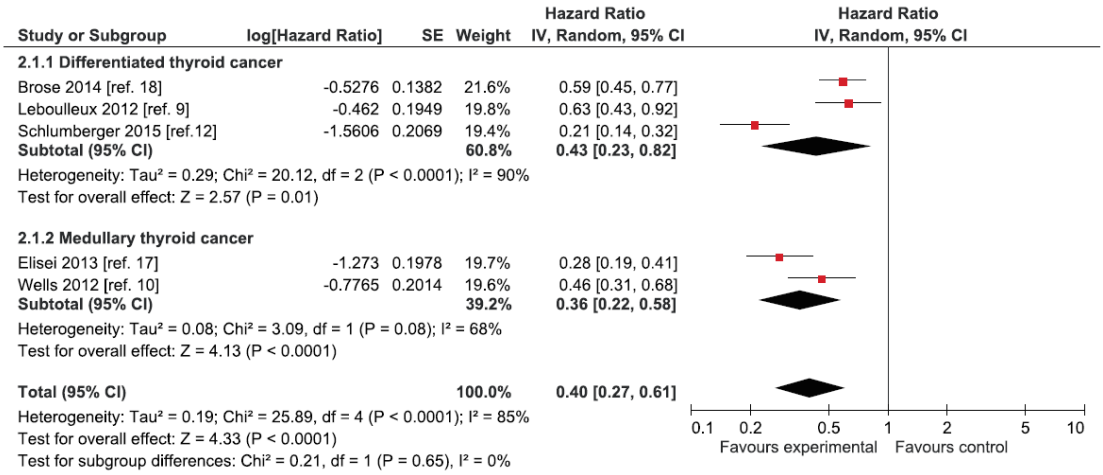

Figure 3. Forest plot of the comparison of the hazard ratio of progression-free survival between the tyrosine kinase inhibitor treatment and control groups: 2.1.1 differentiated thyroid cancer and 2.1.2 medullary thyroid cancer.

- AEs:
  - All trials reported significantly more AEs of any grade in the TKI treatment group than in the control group (hypertension: risk ratio=5.42; 95% CI, 3.53–8.34; alopecia: risk ratio=6.20; 95% CI, 2.92–13.16; rash: risk ratio=3.91; 95% CI, 2.51–6.10; diarrhea: risk ratio=3.45; 95% CI, 2.13–5.60; nausea: risk ratio=2.10; 95% CI, 1.70–2.60).
  - TKI treatment group also exhibited significantly more grade 3+ AEs than the control group did (hypertension: risk ratio=8.96; 95% CI, 3.46–23.17; rash: risk ratio=4.20; 95% CI, 1.11–15.87; diarrhea: risk ratio=7.63; 95% CI, 3.55–16.40).
- Response rate:

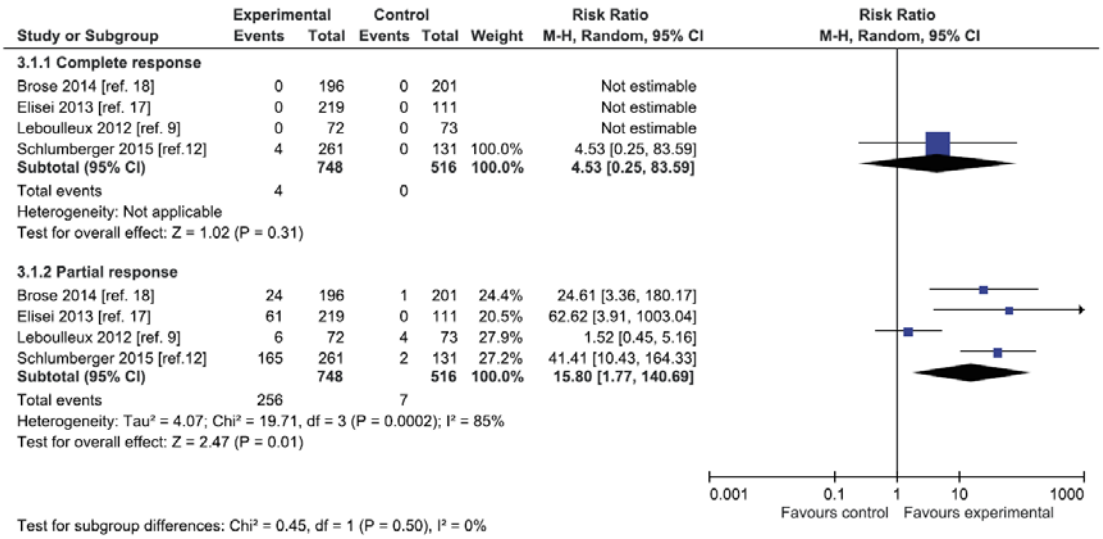

Figure 4. Forest plot of the comparison of the risk ratio of the objective response rate between the tyrosine kinase inhibitor treatment and control groups: 3.1.1 complete response and 3.1.2 partial response.

Anmerkung/Fazit der Autoren

In conclusion, our meta-analysis revealed that TKI target therapy is promising for patients with radioiodine-refractory advanced or metastatic DTC or MTC. The use of TKIs significantly improved the PFS and RR, and thus prolonged the life expectancy of the patients. Our results indicate that lenvatinib is the most effective but has the highest toxicity among all included TKIs. The optimal choice of TKIs for treatment of patients with advanced or metastatic DTC or MTC must be thoroughly investigated through additional RCTs. However, clinical physicians should consider the high incidence of AEs. The

preferences of patients regarding TKI treatments should be discussed with physicians to ensure the most favorable outcome.

Kommentare zum Review

Among the included studies, Schlumberger et al. and Kiyota et al. analyzed patient outcomes from the same trial (the phase 3 SELECT trial)[12,13]. However, Kiyota et al. mainly focused on analyzing the outcome of TKI treatment in Japanese patients[13].

Bai Y et al., 2019 [1].

Risk of venous and arterial thromboembolic events associated with tyrosine kinase inhibitors in advanced thyroid cancer: a meta-analysis and systematic review

Fragestellung

To assess the incidence and risk of arterial and venous thromboembolic events (ATEs and VTEs) associated with tyrosine kinase inhibitors (TKIs) in advanced thyroid cancer patients.

Methodik

Population:

- Advanced thyroid cancer patients

Intervention/Komparator:

- Sorafenib vs. Placebo, Cabozantinib vs. Placebo, Vandetanib vs. Placebo, Lenvatinib vs. Placebo (Axitinib vs. Placebo, Sunitinib vs. Placebo = nicht relevant für AWG)

Endpunkte:

- ATEs/VTEs: thrombosis/ thrombus/embolism (excluded vascular access relatedthrombosis if reported separately), arterial thrombosis, cerebral infarct, cerebral ischemia, cerebrovascular accident, myocardial infarction and myocardial ischemia.

Recherche/Suchzeitraum:

- Pubmed, Embase, and Cochrane Library electronic databases up to August 2017

Qualitätsbewertung der Studien:

- Jadad Scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 12 studies (n=1,781 patients were available for the meta-analysis)
- Four RCTs, eight phase II trials

Charakteristika der Population:

Table 1: Baseline characteristics of 12 included trials

authors	phase	total	treatment arms	median age (years)	median PFS	No. for analysis
Lam E.T. et al. 2010 [40]	II	16	sorafenib 400 mg bid po	60	17.9	16
Wells Jr S.A. et al. 2012 [39]	III	331	vandetanib 300 mg qd po	50.7	30.5	231
			placebo	53.4	19.3	100
Savvides P. et al. 2013 [37]	II		sorafenib 400 mg bid po	59	1.9	20
Elisei R. et al. 2013 [38]	III	330	cabozantinib 140 mg qd po	55	11.4	214
			placebo	55	4	109
Brose M.S. et al. 2014 [36]	III	416	sorafenib 400 mg bid po	63	10.8	207
			placebo	63	5.8	209
Cohen E.E.W. et al. 2014 [35]	II	60	axitnib 5 mg bid po	59	15	60
Cabanillas M.E. et al. 2015 [30]	II	58	lenvatinib 24 mg qd po	63	12.6	58
Schlumberger M. et al. 2015 [31]	III	392	lenvatinib 24 mg qd po	64	18.3	261
			placebo	61	3.6	131
Bikas A. et al. 2016 [32]	II	23	sunitnib 50 mg qd	61	8	23
Schlumberger M. et al. 2016 [33]	II	59	lenvatinib 24 mg qd po	51.6	9	59
Cabonillas M.E. et al. 2017 [34]	II	25	cabozantinib 140 mg qd po	64	12.7	25
Ravaud A. et al. 2017 [29]	II	71	sunitinib 50 mg qd	66	13.1	71

Abbreviation: PFS, progression-free survival.

Qualität der Studien:

- The quality of the four randomized controlled trials was high. All of these trials were double-blinded, placebo-controlled trials, thus had a Jadad score of 5.

Studienergebnisse:

- Peto OR of high-grade ATEs in TKIs versus placebo arms was 4.72 (95% CI 1.18–18.95; P = 0.029). The test for heterogeneity was not significant (I^2 = 0%, p = 0.73).
- Peto OR of VTEs in TKIs versus placebo arms was non-significant 1.36 (95% CI 0.51–3.64; P = 0.54). The test for heterogeneity was not significant (I^2 = 0%, P = 0.70).

Anmerkung/Fazit der Autoren

In conclusion, this study demonstrates that TKIs treatment in advanced TCs patients is associated with a significant increase of high-grade ATEs, but not for VTEs. Given the increasing use of TKIs in TCs patients, it is important for physicians and patients to be aware of the risk of ATEs and prevent accordingly, especially those caused by cardiac toxicity, to maximize the clinical benefits of TKIs in these patients.

Kommentare zum Review

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Yu S et al., 2019 [5].

Treatment-related adverse effects with TKIs in patients with advanced or radioiodine refractory differentiated thyroid carcinoma: a systematic review and meta-analysis

Fragestellung

To explore the frequency of severe adverse effects in advanced or radioiodine refractory differentiated thyroid carcinoma (RR-DTC) patients treated with sorafenib and lenvatinib.

Methodik

Population:

- Patients ≥18 years with advanced or RR-DTC

Intervention/Komparator:

- Sorafenib vs. Placebo; Lenvatinib vs. Placebo

Endpunkte:

- Adverse events (AEs)

Recherche/Suchzeitraum:

- A comprehensive search of computerized databases to include relevant studies published in English between January 2008 and May 2018 was performed, including PubMed, Web of Science, Ovid, EMASE, and the Cochrane Library, encompassing the period from the drugs' inspection on July 2018

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Seven studies (n=657 patients)

Charakteristika der Population:

Table S1 Baseline characteristics of enrolled studies

Study	Year	Treatment	Number of patients evaluated for toxicity	Number of patients experienced toxicity (grade ≥3)/all grade													
				Hand-foot syndrome	Weight loss	Diarrhea	Rash	Mucositis	Hypocal-cemia	Hyper-tension	Nausea	Fatigue	Anorexia	Voice change	Vomiting	Increased ALT	Increasing AST
Schneider et al[1]	2012	Sorafenib	31	7/22	3/18	2/16	5/17	3/16	0/15	5/15	0/3	NA	NA	NA	NA	NA	NA
Brose et al[2]	2014	Sorafenib	207	42/158	0/97	12/142	10/104	2/48	19/39	20/84	0/43	12/103	5/66	1/25	1/23	6/26	2/23
Cabanillas et al[3]	2015	Lenvatinib	58	NA	7/40	6/39	NA	1/18	NA	6/44	0/29	5/35	1/30	0/25	0/22	NA	NA
Schlumberger et al[4]	2015	Lenvatinib	261	9/83	25/121	21/155	1/42	11/93	7/18	109/177	6/107	24/154	12/131	3/63	5/74	0/1	0/1
Berdelou et al[5]	2017	Lenvatinib	75	0/21	0/44	1/34	NA	2/18	NA	26/50	0/14	6/46	1/27	0/1	0/5	NA	NA
Nervo et al[6]	2018	Lenvatinib	12	2/11	2/11	5/8	NA	1/7	NA	5/9	1/9	1/7	NA	0/3	1/4	NA	NA
Balmelli et al[7]	2018	Lenvatinib	13	0/1	NA	2/4	NA	1/4	NA	1/2	NA	2/6	1/3	0/1	NA	NA	NA

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; NA, not available.

Qualität der Studien:

Table S2 Risk of bias in enrolled studies

Study	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free selective reporting	Free of other bias
Schneider et al[1]	Yes	No	Yes	No	No	No
Brose et al[2]	Yes	Yes	Yes	No	No	No
Cabanillas et al[3]	Yes	No	Yes	No	No	No
Schlumberger et al[4]	Yes	Yes	Yes	No	No	No
Berdelou et al[5]	Yes	No	No	No	No	No
Nervo et al[6]	Yes	No	No	No	No	No
Balmelli et al[7]	Yes	No	No	No	No	No

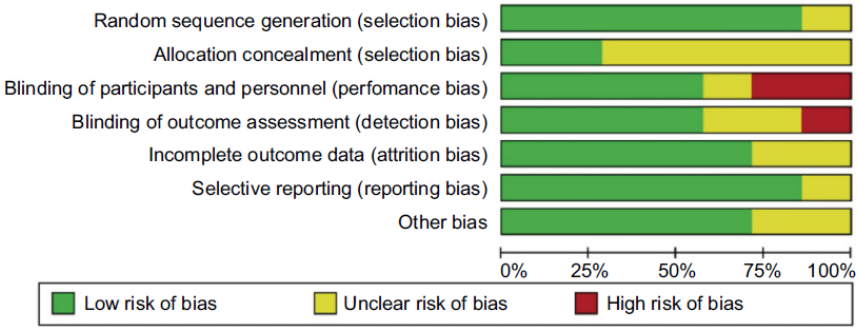


Figure S1 Risk of bias graph.

Studienergebnisse:

Frequency of all-grade treatment-related AEs (TRAEs)

- Significant higher OR of all grade TRAEs in sorafenib vs. lenvatinib
  - All grade handfoot syndrome: OR=6.56, 95% CI=4.53–9.48, P<0.0001
  - All grade hypocalcemia: OR=3.96, 95% CI=2.25–6.98, P<0.0001
  - All grade rash: OR=5.39, 95% CI=3.56–8.18, P<0.0001
- Significant lower OR of all grade TRAEs in sorafenib vs. lenvatinib
  - All grade voice change: OR=0.49, 95% CI=0.30–0.79, P=0.003
  - All grade hypertension: OR=0.31, 95% CI=0.23–0.42, P<0.0001
  - All grade nausea: OR=0.40, 95% CI=0.27–0.57, P<0.0001
- No significant differences for other all grade TRAEs, including diarrhea, weight loss, anorexia, fatigue, and mucositis

Frequency of severe TRAEs (grade ≥3)

- Significant higher OR of Grade ≥3 TRAEs in sorafenib vs. lenvatinib:
  - Grade ≥3 hand-foot syndrome: OR=8.25, 95% CI=4.19–16.24, P<0.0001
  - Severe hypocalcemia: OR=3.15, 95% CI=1.30–7.63, P=0.009
- Significant lower OR of Grade ≥3 TRAEs in sorafenib vs. lenvatinib
  - Grade ≥3 hypertension: OR=0.22, 95% CI=0.14–0.34, P<0.0001
  - Severe nausea: OR=0.11, 95% CI=0.01–2.09, P<0.05
- No significant differences for grade ≥3 diarrhea, mucositis and anorexia

Anmerkung/Fazit der Autoren

Our study has shown that different TKI drugs are associated with a highly increased risk of treatment-related toxicity in advanced or RR-DTC. Early interventions and management of

TRAEs based on which TKI drugs are applied can minimize the impacts on patients' QoL, better deploying medical resources. Overall, patients and physicians should be familiar with the risks of TRAEs and early management of their side effects to promote patients' QoL.

Kommentare zum Review

/

3.3 Leitlinien

National Comprehensive Cancer Network (NCCN), 2022 [4].

Thyroid Carcinoma. version 2.2022

Zielsetzung/Fragestellung

Leitlinien-Update

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- Literature Search Criteria and Guidelines Update Methodology Prior to the update of this version of the NCCN Guidelines for Thyroid Carcinoma, an electronic search of the PubMed database was performed to obtain key literature since the previous Guidelines update, using the following search term: thyroid carcinoma. The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.34
- NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. When citing data and recommendations from other organizations, the terms men, male, women, and female will be used to be consistent with the cited sources.

LoE

- All recommendations are category 2A unless otherwise indicated.

The specific definitions of the NCCN categories for recommendations are included below:

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

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

GoR

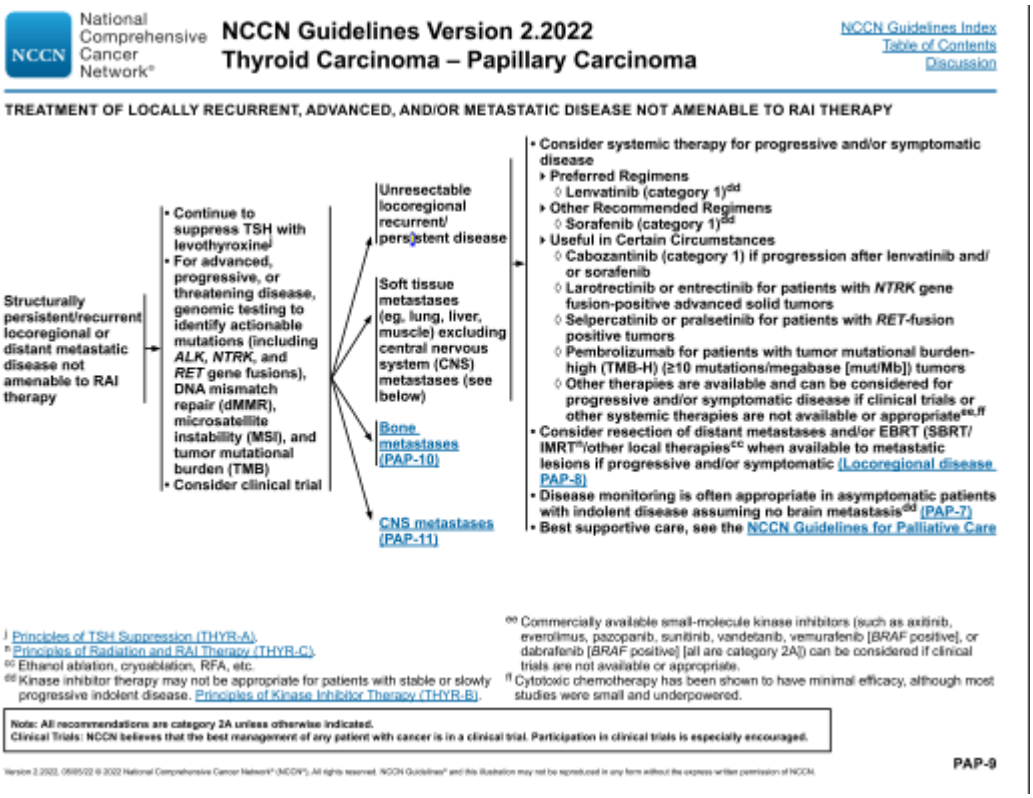
- Keine Angaben

Sonstige methodische Hinweise

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz für alle Formen des Schilddrüsenkrebses (differenziert, medullär und undifferenziert), wird die LL jedoch ergänzend dargestellt.

Empfehlungen

Papillary Carcinoma



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TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY[gg]

Bone metastases

- Consider surgical palliation and/or EBRT/SBRT/other local therapies[cc] 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/EBRT/IMRT in select cases
- Consider intravenous bisphosphonate or denosumab[hh]
- Disease monitoring may be appropriate in asymptomatic patients with indolent diseasedd (PAP-7)
- Consider systemic therapy for progressive and/or symptomatic disease
  - Preferred Regimens
    - Lenvatinib (category 1)[dd]
  - Other Recommended Regimens
    - Sorafenib (category 1)[dd]
  - Useful in Certain Circumstances
    - Cabozantinib (category 1) 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*-fusion positive tumors
    - Pembrolizumab or patients with TMB-H (≥10 mut/Mb) tumors
    - 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[dd,ee,ff]
- Best supportive care, see the NCCN Guidelines for Palliative Care

[cc] Ethanol ablation, cryoablation, RFA, etc.
[dd] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. Principles of Kinase Inhibitor Therapy (THYR-B).
[ee] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [*BRAF* positive], or dabrafenib [*BRAF* positive] [all are category 2A]) can be considered if clinical trials are not available or appropriate.
[ff] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.
[gg] RAI therapy is an option in some patients with bone metastases and RAI-sensitive disease.
[hh] 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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY[gg]

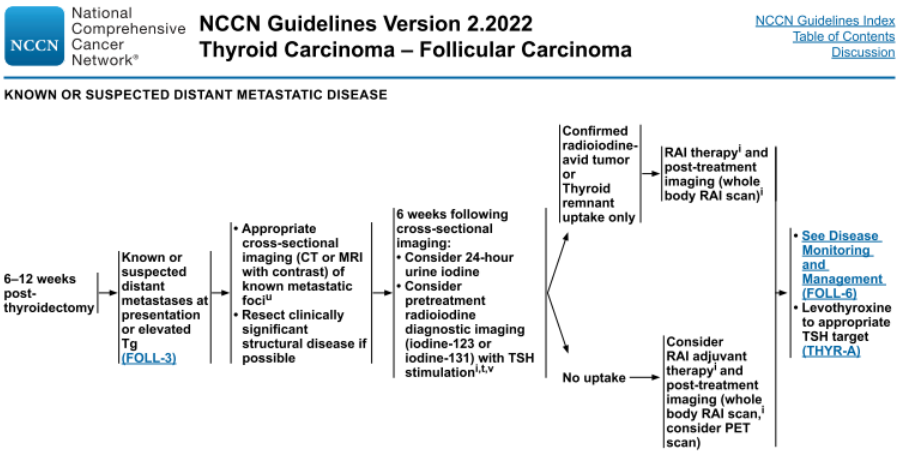
CNS metastases

- For solitary CNS lesions, either neurosurgical resection or stereotactic radiosurgery[ii] is preferred or
- For multiple CNS lesions, consider radiotherapy, including whole brain radiotherapy or stereotactic radiosurgery,[ii] and/or resection in select cases
  and/or
- Consider systemic therapy for progressive and/or symptomatic disease
  - Preferred Regimens
    - Lenvatinib (category 1)[dd,ii,jj]
  - Other Recommended Regimens
    - Sorafenib (category 1)[dd,ii,jj]
  - Useful in Certain Circumstances
    - Cabozantinib (category 1) 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*-fusion positive tumors
    - Pembrolizumab for patients with TMB-H (≥10 mut/Mb) tumors
      and/or
    - 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[dd,ee,ff,hh]
- Best supportive care, see the NCCN Guidelines for Palliative Care

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

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

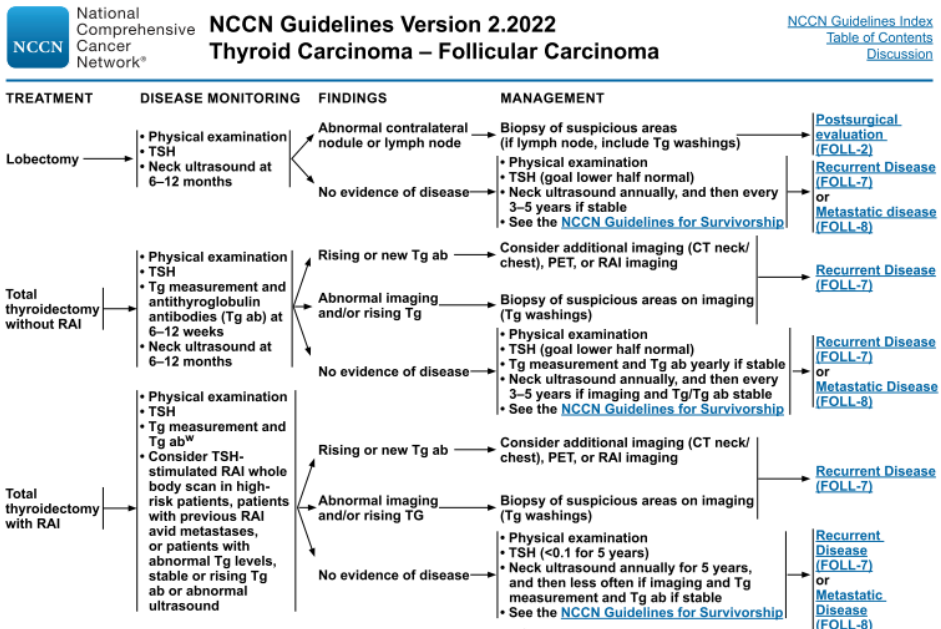
Follicular Carcinoma



[i] Principles of Radiation and RAI Therapy (THYR-C).
[t] While pre-ablation diagnostic scans in this setting are commonly done at NCCN Member Institutions the panel recommends selective use of pre-ablation diagnostic scans based on pathology, postoperative Tg, intraoperative findings, and available imaging studies. Furthermore, dosimetry studies are considered in patients at high risk of having RAI-avid distant metastasis. Empiric RAI doses may exceed maximum tolerable activity levels in patients with decreased GFR. Patients on dialysis require special handling.
[u] To evaluate macroscopic metastatic foci for potential alterative therapies (such as surgical resection and/or external beam radiation) to prevent invasion/compression of vital structures or pathologic fracture either as a result of disease progression or TSH stimulation.
[v] Thyrotropin alfa may be used for elderly patients for whom prolonged hypothyroidism may be risky.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

FOLL-5



[w] In selected patients who may be at higher risk for residual/recurrent disease (eg, N1 patients), obtain a stimulated Tg and consider concomitant diagnostic RAI imaging.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

FOLL-6

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RECURRENT DISEASE

- Rising or newly elevated Tg and negative imaging
- Non-resectable tumors
- Non-radioiodine responsive[x]

→ Suppress TSH with levothyroxine[f] → Continue surveillance with unstimulated Tg, ultrasound, and other imaging as clinically indicated (FOLL-6)

Progressively rising Tg (basal or stimulated) Scans (including PET) negative →
Consider radioiodine therapy with ≥100 mCi
and
Post-treatment iodine-131 imaging (category 3); additional RAI treatments should be limited to patients who responded to previous RAI therapy (minimum of 6–12 months between RAI treatments)

Locoregional recurrence → Consider preoperative iodine total body scan →
Surgery (preferred) if resectable[y]
and
Consider radioiodine treatment,[z] if postoperative radioiodine imaging positive
or
Disease monitoring for non-progressive disease that is stable and distant from critical structures
or
For select patients with unresectable, non–radioiodine-avid, and progressive disease, consider:
- EBRT (IMRT/SBRT)[i]
  and/or
- Systemic therapies (Treatment of Metastatic Disease FOLL-8)

or
For select patients with limited burden nodal disease, consider local therapies when available (eg, ethanol ablation, RFA)

Metastatic disease →
RAI therapy for iodine-avid disease[i]
and/or
Local therapies when available[aa]
and/or
If not amenable to RAI FOLL-8

[f] See Principles of TSH Suppression (THYR-A).
[i] See Principles of Radiation and RAI Therapy (THYR-C).

[x] 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 mo 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.

[y] Preoperative vocal cord assessment, if central neck recurrence.

[z] The administered activity of RAI therapy should be adjusted for pediatric patients. See Principles of Radiation and RAI Therapy (THYR-C).

[aa] Ethanol ablation, cryoablation, RFA, etc.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

FOLL-7

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

Structurally persistent/recurrent locoregional or distant metastatic disease not amenable to RAI therapy →
- Continue to suppress TSH with levothyroxine[f]
- For advanced, progressive, or threatening disease, genomic testing to identify actionable mutations (including *ALK*, *NTRK*, and *RET* gene fusions), dMMR, MSI, and TMB
- Consider clinical trial

→ **Unresectable locoregional recurrent/ persistent disease**
Soft tissue metastases (eg, lung, liver, muscle) excluding CNS metastases (see below)
Bone metastases (FOLL-9)
CNS metastases (FOLL-10)

→
- Consider systemic therapy for progressive and/or symptomatic disease
  - Preferred Regimens
    - ◊ Lenvatinib (category 1)[bb]
  - Other Recommended Regimens
    - ◊ Sorafenib (category 1)[bb]
  - 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*-fusion positive tumors
    - ◊ Pembrolizumab for patients with tumor mutational burden-high (TMB-H) (≥10 mutations/megabase [mut/Mb]) tumors
    - ◊ 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[cc,dd]
- Consider resection of distant metastases and/or EBRT (SBRT/IMRT)[i]/other local therapies[aa] when available to metastatic lesions if progressive and/or symptomatic. (Locoregional disease FOLL-7)
- Disease monitoring is often appropriate in asymptomatic patients with indolent disease assuming no brain metastasis.[dd] (FOLL-6)
- Best supportive care, see the See NCCN Guidelines for Palliative Care

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

[cc] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [*BRAF* positive], or dabrafenib [*BRAF* positive] [all are category 2A]) can be considered if clinical trials are not available or appropriate.
[dd] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

FOLL-8

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TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY[ee]

Bone metastases →

- **Consider surgical palliation and/or EBRT/SBRT/other local therapies[aa] 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/EBRT/IMRT in select cases[i]**
- **Consider intravenous bisphosphonate or denosumab[ff]**
- **Disease monitoring may be appropriate in asymptomatic patients with indolent disease[bb] (FOLL-6)**
- **Consider systemic therapy for progressive and/or symptomatic disease**
  - **Preferred Regimens**
    - **Lenvatinib (category 1)[bb]**
  - **Other Recommended Regimens**
    - **Sorafenib (category 1)[bb]**
  - **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*-fusion positive tumors**
    - **Pembrolizumab for patients with TMB-H (≥10 mut/Mb) tumors**
    - **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[bb,cc,dd]**
- **Best supportive care, see the NCCN Guidelines for Palliative Care**

[i] See Principles of Radiation and RAI Therapy (THYR-C).
[aa] Ethanol ablation, cryoablation, RFA, etc.
[bb] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Kinase Inhibitor Therapy (THYR-B).
[cc] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [*BRAF* positive], or dabrafenib [*BRAF* positive] [all are category 2A]) can be considered if clinical trials are not available or appropriate.
[dd] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.
[ee] RAI therapy is an option in some patients with bone metastases and RAI-sensitive disease.
[ff] 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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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Discussion

TREATMENT OF METASTATIC DISEASE NOT AMENABLE TO RAI THERAPY[ee]

CNS metastases →

- **For solitary CNS lesions, either neurosurgical resection or stereotactic radiosurgery is preferred**
  or
- **For multiple CNS lesions, consider radiotherapy,[i] including whole brain radiotherapy or stereotactic radiosurgery,[i] and/or resection in select cases**
  and/or
- **Consider systemic therapy for progressive and/or symptomatic disease**
  - **Preferred Regimens**
    - **Lenvatinib (category 1)[bb,gg,hh]**
  - **Other Recommended Regimens**
    - **Sorafenib (category 1)[bb,gg,hh]**
  - **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*-fusion positive tumors**
    - **Pembrolizumab for patients with TMB-H (≥10 mut/Mb) tumors**
      and/or
    - **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[bb,cc,dd,ff]**
- **Best supportive care, see the NCCN Guidelines for Palliative Care**

[i] Principles of Radiation and RAI Therapy (THYR-C).
[aa] Ethanol ablation, cryoablation, RFA, etc.
[bb] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. Principles of Kinase Inhibitor Therapy (THYR-B).
[cc] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [*BRAF* positive], or dabrafenib [*BRAF* positive] [all are category 2A]) can be considered if clinical trials are not available or appropriate.
[dd] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.
[ee] RAI therapy is an option in some patients with bone metastases and RAI-sensitive disease.
[ff] 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.
[gg] After consultation with neurosurgery and radiation oncology; data on the efficacy of lenvatinib or sorafenib for patients with brain metastases have not been established.
[hh] TKI therapy should be used with caution in otherwise untreated CNS metastases due to bleeding risk.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Medullary Carcinoma

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RECURRENT OR PERSISTENT LOCOREGIONAL DISEASE — **TREATMENT**

Locoregional →

- Surgical resection is the preferred treatment modality
- EBRT/IMRT can be considered for unresectable disease or, less commonly, after surgical resection
- Consider systemic therapy[s] for unresectable disease that is symptomatic or progressing by RECIST criteria[t,u]
  - Preferred Regimens
    - ◊ Vandetanib[v] (category 1)
    - ◊ Cabozantinib (category 1)
    - ◊ Selpercatinib (*RET* mutation-positive)[w]
    - ◊ Pralsetinib (*RET* mutation-positive)[w]
  - Useful in Certain Circumstances
    - ◊ Pembrolizumab (TMB-H [≥10 mut/Mb])[w]
- Disease monitoring

→ Recurrent or Persistent Disease; Distant Metastases (MEDU-7)

[s] Increasing tumor markers, in the absence of structural disease progression, are not an indication for treatment with systemic therapy.
[t] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. Principles of Kinase Inhibitor Therapy in Advanced Thyroid Carcinoma (THYR-B).
[u] Treatment with systemic therapy is not recommended for increasing calcitonin/CEA alone.
[v] Only health care professionals and pharmacies certified through the vandetanib Risk Evaluation and Mitigation Strategy (REMS) program, a restricted distribution program, will be able to prescribe and dispense the drug.
[w] Genomic testing including TMB or *RET* somatic genotyping in patients who are germline wild-type or germline unknown.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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RECURRENT OR PERSISTENT DISEASE DISTANT METASTASES

Asymptomatic disease →

- Disease monitoring
- Consider resection (if possible), ablation (eg, RFA, embolization, other regional therapy)
- Systemic therapy[s] if not resectable and progressing by RECIST criteria[t,u]
  - Preferred Regimens
    - ◊ Vandetanib[t,v] (category 1)
    - ◊ Cabozantinib (category 1)
    - ◊ Selpercatinib (*RET* mutation-positive)[w]
    - ◊ Pralsetinib (*RET* mutation-positive)[w]
  - Useful in Certain Circumstances
    - ◊ Pembrolizumab (TMB-H [≥10 mut/Mb])[w]

→ Progressive disease, see pathway below

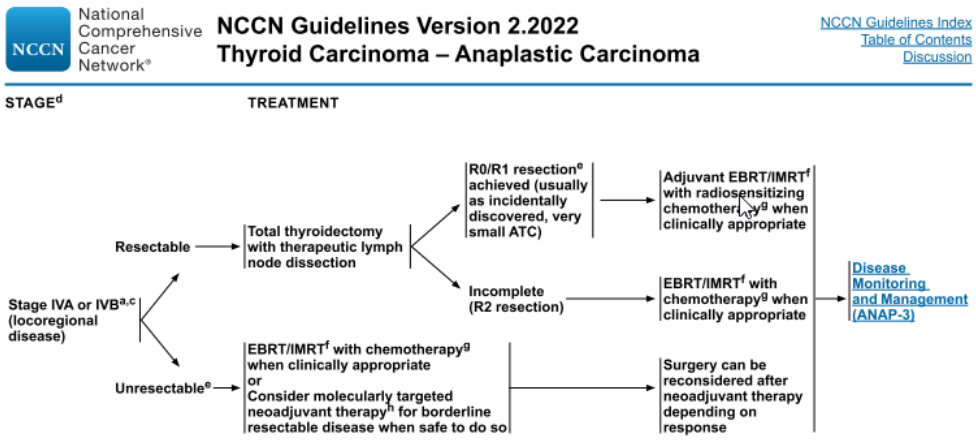
Symptomatic disease or Progression[t] →

- Systemic therapy or clinical trial
  - Preferred Regimens
    - ◊ Vandetanib (category 1)[x]
    - ◊ Cabozantinib (category 1)[x]
    - ◊ Selpercatinib (*RET* mutation-positive)[w]
    - ◊ Pralsetinib (*RET* mutation-positive)[w]
  - Other Recommended Regimens
    - ◊ Consider other small-molecule kinase inhibitors[y]
    - ◊ Dacarbazine (DTIC)-based chemotherapy[z]
  - Useful in Certain Circumstances
    - ◊ Pembrolizumab (TMB-H [≥10 mut/Mb])[w]
- EBRT/IMRT for local symptoms
- Consider intravenous bisphosphonate or denosumab[aa] therapy for bone metastases
- Consider palliative resection, ablation (eg, RFA, embolization, other regional therapy), or other regional treatment
- Best supportive care, see the NCCN Guidelines for Palliative Care

[s] Increasing tumor markers, in the absence of structural disease progression, are not an indication for treatment with systemic therapy.
[t] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. Principles of Kinase Inhibitor Therapy in Advanced Thyroid Carcinoma (THYR-B).
[u] Treatment with systemic therapy is not recommended for increasing calcitonin/CEA alone.
[v] Only health care professionals and pharmacies certified through the vandetanib Risk Evaluation and Mitigation Strategy (REMS) program, a restricted distribution program, will be able to prescribe and dispense the drug.
[w] Genomic testing including TMB or *RET* somatic genotyping in patients who are germline wild-type or germline unknown.
[x] Clinical benefit can be seen in both sporadic and familial MTC.
[y] While not FDA-approved for treatment of medullary thyroid cancer, other commercially available small-molecule kinase inhibitors (such as sorafenib, sunitinib, lenvatinib, or pazopanib) can be considered if clinical trials or preferred systemic therapy options are not available or appropriate, or if the patient progresses on preferred systemic therapy options.
[z] Doxorubicin/streptozocin alternating with fluorouracil/dacarbazine or fluorouracil/dacarbazine alternating with fluorouracil/streptozocin.
[aa] Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

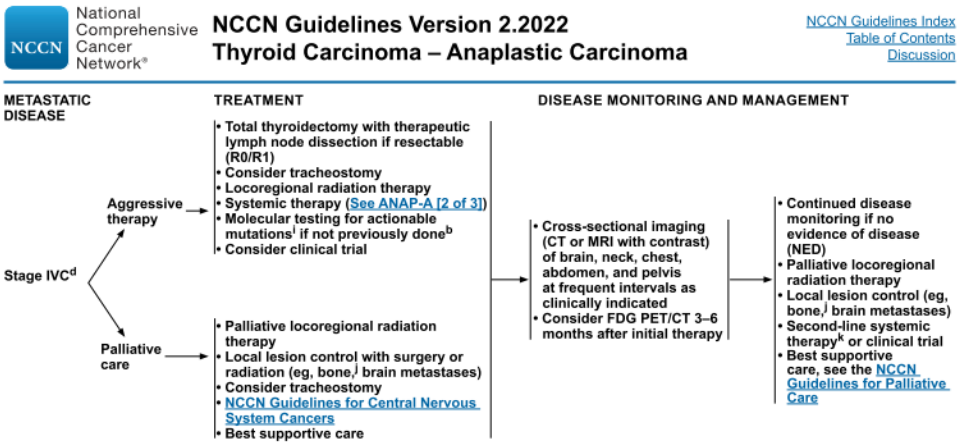
Anaplastic Carcinoma



[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, squamous cell carcinoma, 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. 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-fusion positive tumors; and larotrectinib or entrectinib for patients with *NTRK* gene fusion-positive tumors.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ANAP-2



[b] Molecular testing should include *BRAF, NTRK, ALK, RET, MSI, dMMR*, and tumor mutational burden.
[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. Presented at the Annual Meeting of the European Society for Medical Oncology in Barcelona, Spain; September 27-October 1, 2019. Oral presentation.); 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]).

Note: All recommendations are category 2A unless otherwise indicated.
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ANAP-3

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NCCN Guidelines Version 2.2022
Thyroid Carcinoma – Anaplastic Carcinoma

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SYSTEMIC THERAPY

Adjuvant/Radiosensitizing Chemotherapy Regimens[1]		
Other Recommended Regimens		
Paclitaxel/carboplatin	Paclitaxel 50 mg/m², carboplatin 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 Therapies for Metastatic Disease ANAP-A (2 of 3)

[1] Bible KC, Kebebew E, Brierley J, et al. 2021 American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. Thyroid 2021;31:337-386.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Thyroid Carcinoma – Anaplastic Carcinoma

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SYSTEMIC THERAPY

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* fusion positive)	400 mg PO	Once daily
Selpercatinib[6] (*RET* 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, carboplatin AUC 2 IV or Paclitaxel 135–175 mg/m², 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 pegfilgrastim) 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[7] (TMB-H [≥10 mut/Mb])	200 mg IV or 400 mg IV	Every 3 weeks Every 6 weeks

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

References

SYSTEMIC THERAPY REFERENCES

[1] Smallridge RC, Ain KB, Asa SL, et al. American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. Thyroid 2012;22:1104-1139.
[2] Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib and trametinib treatment in patients with locally advanced or metastatic BRAF V600-mutant anaplastic thyroid cancer. J Clin Oncol 2018;36:7-13.
[3] Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018;378:731-739.
[4] Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:271-282.
[5] Subbiah V, Hu MI, Gainor JF, et al. Clinical activity of the RET inhibitor pralsetinib (BLU-667) in patients with RET fusion+ solid tumors. Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 29-31, 2020.
[6] Wirth L, Sherman E, Drilon A, et al. Registrational results of LIBRETTO-001: a phase 1/2 trial of selpercatinib (LOXO-292) in patients with RET-altered thyroid cancers. Presented at the Annual Meeting of the European Society for Medical Oncology; September 27-October 1, 2019; Barcelona, Spain. Oral presentation.
[7] Marabelle A, Fakih MG, Lopez J, et al. Association of tumor mutational burden with outcomes in patients with select advanced solid tumors treated with pembrolizumab in KEYNOTE-158. Presented at the Annual Meeting of the European Society for Medical Oncology; September 30, 2019; Barcelona, Spain.
[8] Bible KC, Kebebew E, Brierley J, et al. 2021 American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. Thyroid 2021;31:337-386.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 5 of 12, Monat 2022) am 11.05.2022

#	Suchfrage
1	[mh "thyroid neoplasms"]
2	[mh "adenocarcinoma, papillary"]
3	[mh "adenocarcinoma, follicular"]
4	[mh "thyroid carcinoma, anaplastic"]
5	[mh "multiple endocrine neoplasia type 2a"]
6	[mh "multiple endocrine neoplasia type 2b"]
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
8	((struma maligna) OR (papillary AND adenocarcinoma*) OR (follicular AND adenocarcinoma*) OR (("multiple endocrine neoplasia") AND (2 OR 2a OR 2b OR II OR IIa OR IIb))):ti,ab,kw
9	((thyroid) AND (cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesion* OR malignan*)):ti,ab,kw
10	#8 OR #9
11	#7 OR #10
12	#11 with Cochrane Library publication date from May 2017 to May 2022

Systematic Reviews in PubMed am 11.05.2022

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 02.01.2020.

#	Suchfrage
1	thyroid neoplasms[mh]
2	adenocarcinoma, papillary[mh]
3	adenocarcinoma, follicular[mh]
4	"thyroid carcinoma, anaplastic"[mh]
5	"multiple endocrine neoplasia type 2a"[mh]
6	"multiple endocrine neoplasia type 2b"[mh]
7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6) AND therapy[sh]
8	"thyroid cancer, hurthle cell"[nm] OR "familial medullary thyroid carcinoma"[nm] OR "thyroid cancer, medullary"[nm] OR "thyroid carcinoma, nonmedullary 1"[nm] OR "nonmedullary thyroid carcinoma, with or without cell oxyphilia"[nm] OR "thyroid cancer, follicular"[nm] OR “thyroid carcinoma, papillary, with papillary renal neoplasia”[nm]
9	“struma maligna”[tiab] OR (papillary[tiab] AND adenocarcinoma*[tiab]) OR (follicular[tiab] AND adenocarcinoma*[tiab]) OR (“multiple endocrine neoplasia”[tiab] AND (2[tiab] OR 2a[tiab] OR 2b[tiab] OR II[tiab] OR IIa[tiab] OR Iib[tiab]))
10	thyroid[tiab]
11	(((((((((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]
12	#10 AND #11

#	Suchfrage
13	#8 OR #9 OR #12
14	(#13) AND ((treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab]))
15	#7 OR #14
16	(#15) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
17	((#16) AND ("2017/05/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
18	(#17) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in PubMed am 11.05.2022

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[majr]
2	adenocarcinoma, papillary[majr]
3	adenocarcinoma, follicular[majr]

#	Suchfrage
4	"thyroid carcinoma, anaplastic"[majr]
5	"multiple endocrine neoplasia type 2a"[majr]
6	"multiple endocrine neoplasia type 2b"[majr]
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
8	"thyroid cancer, hurthle cell"[nm] OR "familial medullary thyroid carcinoma"[nm] OR "thyroid cancer, medullary"[nm] OR "thyroid carcinoma, nonmedullary 1"[nm] OR "nonmedullary thyroid carcinoma, with or without cell oxyphilia"[nm] OR "thyroid cancer, follicular"[nm] OR “thyroid carcinoma, papillary, with papillary renal neoplasia”[nm]
9	“struma maligna”[tiab] OR (papillary[tiab] AND adenocarcinoma*[tiab]) OR (follicular[tiab] AND adenocarcinoma*[tiab]) OR (“multiple endocrine neoplasia”[tiab] AND (2[tiab] OR 2a[tiab] OR 2b[tiab] OR II[tiab] OR IIa[tiab] OR Iib[tiab]))
10	thyroid[ti]
11	(((((((((tumor[ti]) OR tumors[ti]) OR tumour*[ti]) OR carcinoma*[ti]) OR adenocarcinoma*[ti]) OR neoplas*[ti]) OR sarcoma*[ti]) OR cancer*[ti]) OR lesion*[ti]) OR malignan*[ti]
12	#10 AND #11
13	#7 OR #8 OR #9 OR #12
14	(#13) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
15	(((#14) AND ("2017/05/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
16	(#15) NOT (retracted publication [pt] OR retraction of publication [pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am TT.MM.20JJ

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Nationale VersorgungsLeitlinien (NVL)

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

- *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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[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

Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

2022-B-107

Kontaktdaten

Fachgesellschaften:

Deutsche Gesellschaft für Endokrinologie (DGE)

Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)

Deutsche Gesellschaft für Nuklearmedizin (DGN)

Indikation gemäß Beratungsantrag

Behandlung von Erwachsenen und Jugendlichen ab 12 Jahren mit fortgeschrittenem RET-mutiertem medullärem Schilddrüsenkarzinom, die nicht bereits mit einem RET-Inhibitor behandelt wurden

Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Zusammenfassung

Das medulläre Schilddrüsenkarzinom (MTC) ist ein seltener, von den C-Zellen der Schilddrüsen ausgehender Tumor. MTC machen etwa 5% aller neu diagnostizierten Schilddrüsenkarzinome aus. Eine zentrale Rolle in der Pathogenese des MTC spielt das *RET* Protoonkogen. *RET* Mutationen sind bei etwa 95% der Patient*innen mit genetischer Prädisposition nachweisbar. Beim sporadischem MTC sind *RET* Mutationen in mehr als der Hälfte der Patient*innen nachweisbar, bei 85% als Mutation *M918T*.

Standard in der Erstlinie ist die Therapie mit einem der beiden zugelassenen Multikinase-Inhibitoren Cabozantinib oder Vandetanib. Bei Erwachsenen und Jugendlichen ab 12 Jahren mit fortgeschrittenem RET-mutiertem medullärem Schilddrüsenkarzinom gilt diese Empfehlung:

1. Nach systemischer Therapie mit einem der zugelassenen TKI:
    - nach Therapie mit Cabozantinib Selpercatinib oder Vandetanib
    - nach Therapie mit Vandetanib Selpercatinib oder Cabozantinib.

Fragestellung

Die Fragestellung wirkt unvollständig. Es fehlt ein Hinweis auf den Krankheits- und Therapiestatus: unvorbehandelt, rezidiviert/refraktär? Diese Faktoren sind relevant für eine gezielte, gutachterliche Expertise.

Kontaktdaten

Fachgesellschaften:

Deutsche Gesellschaft für Endokrinologie (DGE)

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Deutsche Gesellschaft für Nuklearmedizin (DGN)

Indikation gemäß Beratungsantrag

Behandlung von Erwachsenen und Jugendlichen ab 12 Jahren mit fortgeschrittenem RET-mutiertem medullärem Schilddrüsenkarzinom, die nicht bereits mit einem RET-Inhibitor behandelt wurden

Stand des Wissens

Das medulläre Schilddrüsenkarzinom (MTC) ist ein seltener, von den C-Zellen der Schilddrüsen ausgehender Tumor. MTC machen etwa 5% aller neu diagnostizierten Schilddrüsenkarzinome aus. Die Zahl an Schilddrüsenkarzinom Neuerkrankten in Deutschland wird für das Jahr 2022 auf 5.000 Frauen und 2.200 Männer geschätzt [1]. Bei 20-25% der MTC Patient*innen besteht eine genetische Prädisposition.

Die Therapie erfolgt stadienabhängig. Im lokal begrenzten Stadium besteht eine hohe Heilungschance durch frühzeitige Operation. Der individuelle Krankheitsverlauf von MTC-Patient*innen mit fortgeschrittener Erkrankung ist sehr variabel. Eine zytotoxische Chemotherapie ist lediglich bei aggressiven Verläufen im fortgeschrittenen Stadium eine Therapieoption (off label) auf Basis kleiner Fallserien. Die Remissionsraten liegen unter 20% [2-5].

Eine zentrale Rolle in der Pathogenese des MTC spielt das *RET* Protoonkogen. *RET* Mutationen sind bei etwa 95% der Patient*innen mit genetischer Prädisposition nachweisbar. Beim sporadischem MTC sind *RET* Mutationen in mehr als der Hälfte der Patient*innen nachweisbar, bei 85% als Mutation *M918T*. Neben *RET*- spielen auch *RAS*-Mutationen eine wichtige Rolle in der Pathogenese des medullären Schilddrüsenkarzinoms. Beim fortgeschrittenen medullären Schilddrüsenkarzinom liegen *RET*-Mutationen in bis zu 90% der Fälle vor [6]. Die Aktivierung weiterer Tyrosinkinasen ist relevant für Progression und Metastasierung [7].

Bei etwa 10% der Patient*innen besteht bereits bei Erstdiagnose eine metastasierte Erkrankung. Bei weiteren 20-40% treten Metastasen im weiteren Krankheitsverlauf auf. Ein sensitiver und spezifischer Parameter in der Nachsorge ist die Bestimmung von Calcitonin im Serum.

Die Therapiesituation beim fortgeschrittenen und metastasierten MTC hat sich in den letzten 10 Jahren durch die Zulassung der beiden Multikinase-Inhibitoren Cabozantinib und Vandetanib deutlich verbessert [8-10]. Ihr Einsatz erfolgt unabhängig vom Vorliegen einer *RET*-Mutation. Für Cabozantinib wurde ein objektives Ansprechen unabhängig vom Vorliegen einer *RET*- oder *HRAS*-Mutation gezeigt. Gegenüber Placebo wurde eine statistisch signifikante Verlängerung des Gesamtüberlebens lediglich in der Gruppe der Patient*innen mit einer *RETM918T* Mutation nachgewiesen [11].

Für Patient*innen, die nur einen der zugelassenen MTKIs erhalten haben, wurde bis 2021 in der klinischen Praxis die sequentielle Therapie mit dem alternativen zugelassenen MTKI durchgeführt. In einer deutschen

Kontaktdaten

Fachgesellschaften:

Deutsche Gesellschaft für Endokrinologie (DGE)

Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)

Deutsche Gesellschaft für Nuklearmedizin (DGN)

Indikation gemäß Beratungsantrag

Behandlung von Erwachsenen und Jugendlichen ab 12 Jahren mit fortgeschrittenem RET-mutiertem medullärem Schilddrüsenkarzinom, die nicht bereits mit einem RET-Inhibitor behandelt wurden

Registerstudie [12] erhielten 63% der Patient*innen zwei, 21% der Patient*innen mehr als zwei MTKI-Therapien (einschließlich off label use).

Die Behandlungssituation nach Vorbehandlung hat sich durch die Zulassung von Selpercatinib im Februar 2021 geändert. Selpercatinib ist zugelassen bei Erwachsenen und Jugendlichen (ab 12 Jahre) mit fortgeschrittenem MTC, Nachweis einer *RET*-Mutation im Tumorgewebe oder in der Keimbahn, und Vorbehandlung mit Cabozantinib und/oder Vandetanib. In der einarmigen Zulassungsstudie führte Selpercatinib bei etwa zwei Drittel der Patient*innen zu einer objektiven Remission. Die mediane progressionsfreie Überlebensrate nach 24 Monaten lag bei etwa 70%, die Gesamtüberlebensrate nach 24 Monaten bei etwa 80%. Die Rate schwerer Nebenwirkungen war niedriger als bei Therapie mit Cabozantinib oder Vandetanib. Selpercatinib hat auch eine hohe Wirksamkeit bei ZNS Metastasen [13].

Wie bei anderer Gelegenheit ausgeführt, ist für die Bewertung von Selpercatinib als Zweitlinientherapie beim *RET*-mutierten MTC der Vergleich mit einem der beiden zugelassenen TKI erforderlich.

Andere Multikinase-Inhibitoren wie Lenvatinib, Pazopanib, Sorafenib oder Sunitinib erzielen ebenfalls Remissionen, wurden aber nicht in größeren Studien getestet und sind in dieser Indikation nicht zugelassen [14].

Selpercatinib wird auch bei Kindern und Jugendlichen eingesetzt. Ergebnisse werden im GPOH-MET Registers dokumentiert. Aktuell wird Selpercatinib bei fortgeschrittenem MTC auch ohne vorherige Therapie mit anderen TKI eingesetzt. Die erkrankten Kinder/Jugendlichen werden über das Kindertumorregister Heidelberg in die LOXO-RET-18036-Studie (LIBRETTO-121) eingeschlossen. Darüber hinaus wird findet Selpercatinib auch im Rahmen der LIBRETTO-531-Studie in der ersten Linie eine Anwendung. Hier erfolgt eine Randomisierung in einen Therapiearm, der Selpercatinib erhält und in einen Therapiearm, der entweder Cabozantinib oder Vandetanib erhält (Entscheidung der behandelnden Ärzt*innen).

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von „*fortgeschrittenem RET-mutiertem medullärem Schilddrüsenkarzinom, das nicht bereits mit einem RET-Inhibitor behandelt wurde*“ die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Ja, siehe oben: Anmerkungen zur Fragestellung.

Kontaktdaten

Fachgesellschaften:

Deutsche Gesellschaft für Endokrinologie (DGE)

Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)

Deutsche Gesellschaft für Nuklearmedizin (DGN)

Indikation gemäß Beratungsantrag

Behandlung von Erwachsenen und Jugendlichen ab 12 Jahren mit fortgeschrittenem RET-mutiertem medullärem Schilddrüsenkarzinom, die nicht bereits mit einem RET-Inhibitor behandelt wurden

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