Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2021-B-009-z Selpercatinib

Stand: Februar 2021

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
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 N.N. Retsevmo	Anwendungsgebiet laut positive Opinion: Retsevmo as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib.
Proteinkinase-Inhibitoren	
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).
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: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2021-B-009z (Selpercatinib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	22. Januar 2021

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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 des fortgeschrittenes medulläres Schilddrüsenkarzinom, bei dem eine systemische Therapie angezeigt ist.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation medulläres Schilddrüsenkarzinom durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 21.01.2021 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 372 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 7 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2017 [4].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 6. Juli 2017 - Vandetanib (neues Anwendungsgebiet: Schilddrüsenkarzinom, Patienten ab 5 Jahren).

Anwendungsgebiet

Vandetanib ist indiziert für Jugendliche und Kinder im Alter von 5 Jahren und älter für die Behandlung eines aggressiven und symptomatischen medullären Schilddrüsenkarzinoms (MTC) bei Patienten mit nicht resektabler, lokal fortgeschrittener oder metastasierter Erkrankung.

Zweckmäßige Vergleichstherapie

Best-Supportive-Care

Ausmaß des Zusatznutzens gegenüber Best-Supportive-Care:

Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen auf der Grundlage der Übertragung von Evidenz auf eine pädiatrische Population, vergleichende Daten für die pädiatrische Population liegen nicht vor.

G-BA, 2020 [2].

Siehe auch: (G-BA, 2019 [3])

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 22. Januar 2015 / 6. Juni 2019 – Cabozantinib

gültig bis: 01.07.2021

Anwendungsgebiet

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.

Vergleichstherapie

- Nicht erforderlich -

Ausmaß des Zusatznutzens

Cabozantinib ist zugelassen als Arzneimittel zur Behandlung eines seltenen Leidens nach der Verordnung (EG) Nr. 141/2000 des Europäischen Parlaments und des Rates vom 16.

Dezember 1999 über Arzneimittel für seltene Leiden. Gemäß § 35a Absatz 1 Satz 10 SGB V gilt der medizinische Zusatznutzen durch die Zulassung als belegt.

Der Gemeinsame Bundesausschuss (G-BA) bestimmt gemäß 5. Kapitel § 12 Absatz 1 Nummer 1 Satz 2 der Verfahrensordnung des G-BA (VerfO) das Ausmaß des Zusatznutzens für die Anzahl der Patienten und Patientengruppen, für die ein therapeutisch bedeutsamer Zusatznutzen besteht. Diese Quantifizierung des Zusatznutzens erfolgt am Maßstab der im 5. Kapitel § 5 Absatz 7 Nummer 1 bis 4 VerfO festgelegten Kriterien.

Ausmaß des Zusatznutzens:

Gering

3.2 Cochrane Reviews

Es wurden eine relevanten Cochrane Reviews identifiziert.

3.3 Systematische Reviews

Liu JW et al., 2018 [5].

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:

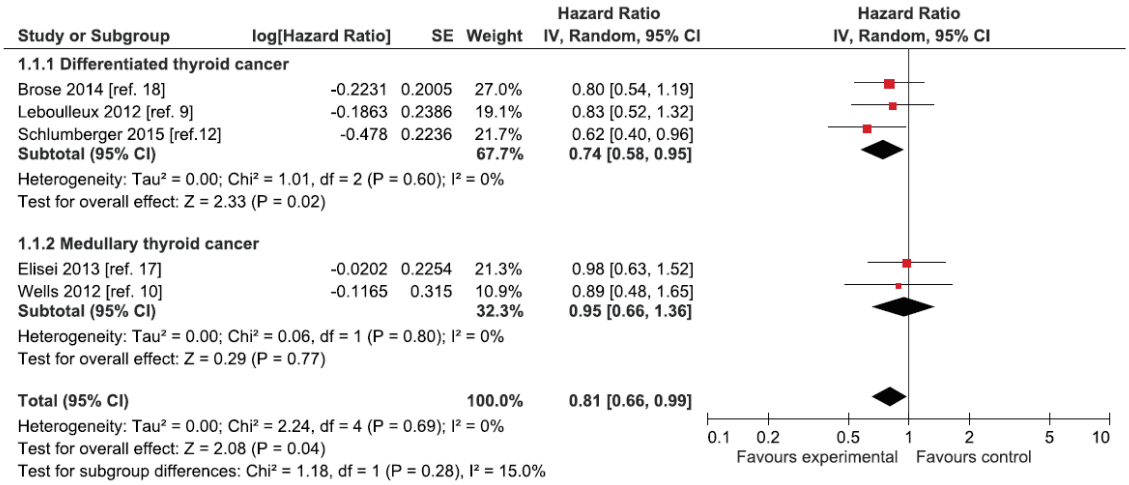


Figure 2. Forest plot of the comparison of the hazard ratio of overall survival between the tyrosine kinase inhibitor treatment and control groups: 1.1.1 differentiated thyroid cancer and 1.1.2 medullary thyroid cancer.

- 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:

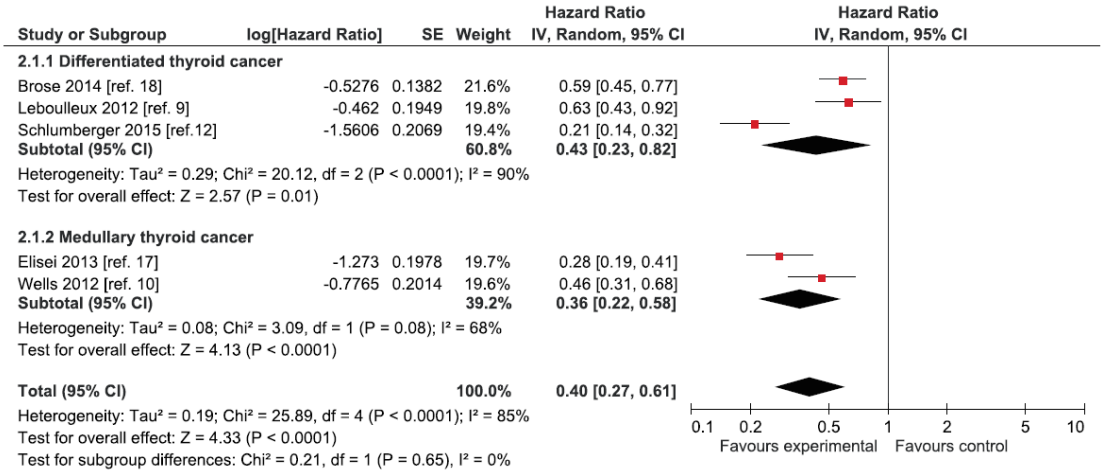


Figure 3. Forest plot of the comparison of the hazard ratio of progression-free survival between the tyrosine kinase inhibitor treatment and control groups: 2.1.1 differentiated thyroid cancer and 2.1.2 medullary thyroid cancer.

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:

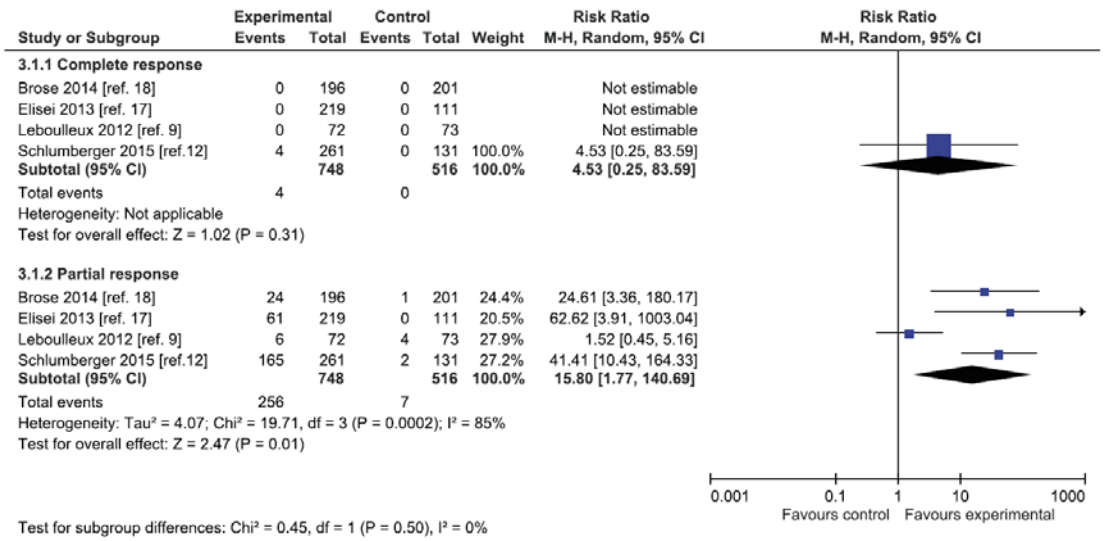


Figure 4. Forest plot of the comparison of the risk ratio of the objective response rate between the tyrosine kinase inhibitor treatment and control groups: 3.1.1 complete response and 3.1.2 partial response.

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 (nur für die vier RCTs dargestellt):

- 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.

Yu S et al., 2019 [7].

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

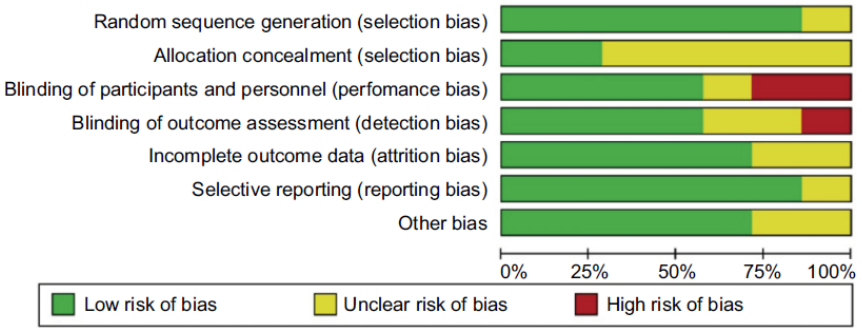


Figure S1 Risk of bias graph.

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.

3.4 Leitlinien

National Comprehensive Cancer Network (NCCN), 2020 [6].

Thyroid Carcinoma. Version 2.2020

Leitlinienorganisation/Fragestellung

Leitlinien-Update

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: unklar;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- 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:

- PubMed. Suchezeitraum k.A.

LoE:

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.

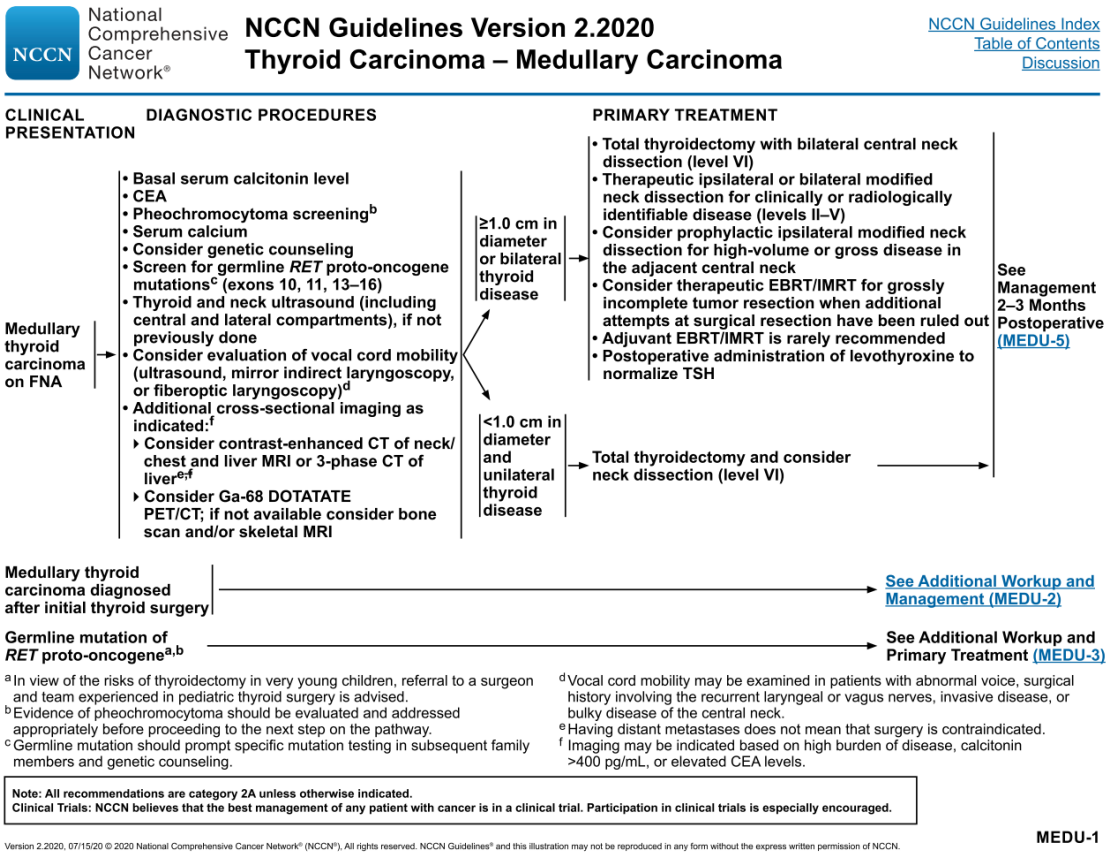
NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly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

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

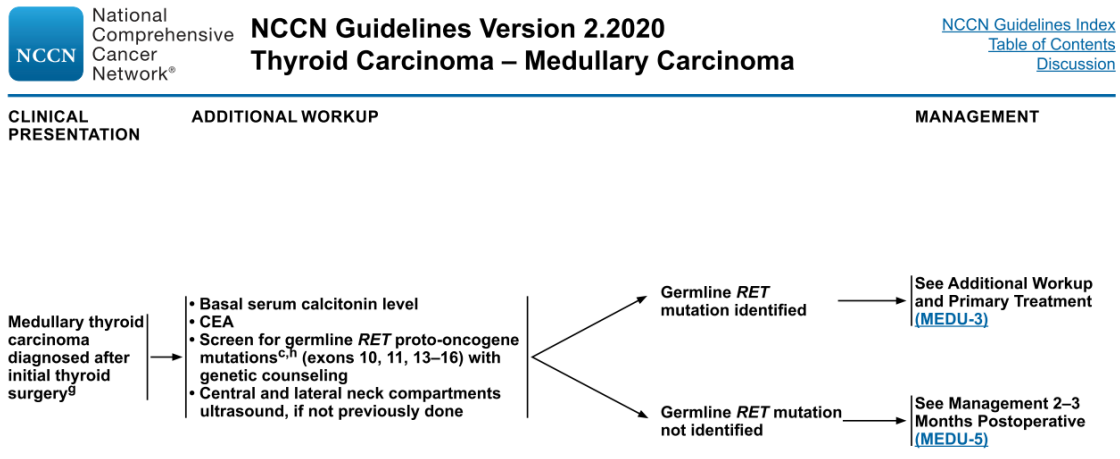
Empfehlungen



[a] In view of the risks of thyroidectomy in very young children, referral to a surgeon and team experienced in pediatric thyroid surgery is advised.
[b] Evidence of pheochromocytoma should be evaluated and addressed appropriately before proceeding to the next step on the pathway.
[c] Germline mutation should prompt specific mutation testing in subsequent family members and genetic counseling.
[d] Vocal cord mobility may be examined in patients with abnormal voice, surgical history involving the recurrent laryngeal or vagus nerves, invasive disease, or bulky disease of the central neck.
[e] Having distant metastases does not mean that surgery is contraindicated.
[f] Imaging may be indicated based on high burden of disease, calcitonin >400 pg/mL, or elevated CEA levels.

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.

MEDU-1



[c] Germline mutation should prompt specific mutation testing in subsequent family members and genetic counseling.
[g] If initial thyroid surgery was less than a total thyroidectomy, additional surgical intervention (eg, completion thyroidectomy ± central neck dissection) may not be necessary unless there is a positive germline RET mutation or radiographic evidence of disease (ie, biopsy-proven residual neck disease).
[h] Prior to germline testing, all patients should be offered genetic counseling either by their physician or a genetic counselor.

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.

MEDU-2

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2020
Thyroid Carcinoma – Medullary Carcinoma

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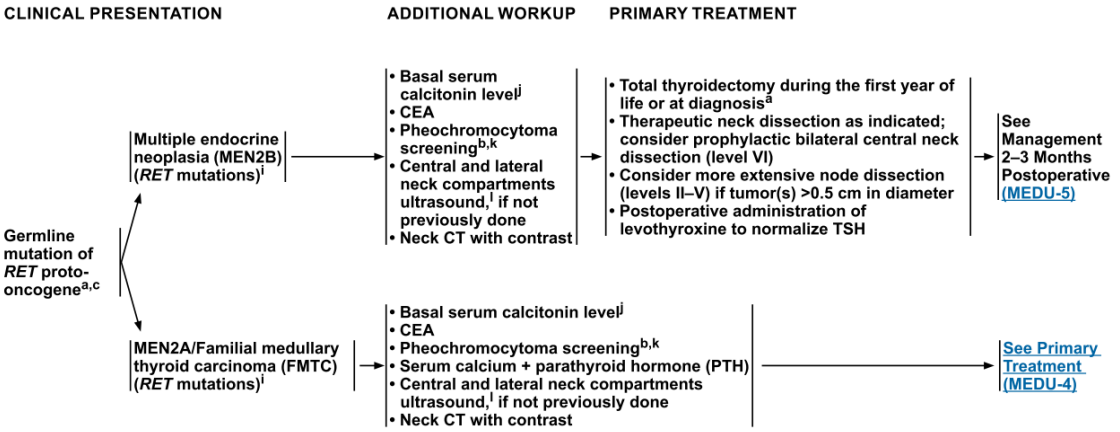

[a] In view of the risks of thyroidectomy in very young children, referral to a surgeon and team experienced in pediatric thyroid surgery is advised.
[b] Evidence of pheochromocytoma should be evaluated and treated appropriately before proceeding to the next step on the pathway.
[c] Germline mutation should prompt specific mutation testing in subsequent family members and genetic counseling.
[i] The timing of prophylactic thyroidectomy generally depends on the aggressiveness of the inherited *RET* mutation. Codon M918T mutations are considered highest risk and codon 634 and A883F mutations are considered high risk, with MTC usually presenting at a younger age, whereas other RET mutations associated with MEN2A or FMTC are generally moderate risk. Prophylactic thyroidectomy may be delayed in patients with less high-risk *RET* mutations that have later onset of MTC, provided the annual basal calcitonin measurement is normal, the annual ultrasound is unremarkable, there is no history of aggressive MTC in the family, and the family is in agreement. (Brandi ML, et al. J Clin Endocrinol Metab 2001;86(12):5658-5671 and American Thyroid Association Guidelines Task Force. Wells SA, et al. Thyroid 2015;25(6):567-610.)
[j] Normal calcitonin ranges have not been established for very young children.
[k] Screening for pheochromocytoma (MEN2A and MEN2B) and hyperparathyroidism (MEN2A) should be performed annually. For some RET mutations (codons 768, 790, 804, or 891), less frequent screening may be appropriate.
[l] In addition to ultrasound, parathyroid imaging may include sestamibi scan with SPECT or 4D-CT depending on institutional practice/protocol.

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.

MEDU-3

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2020
Thyroid Carcinoma – Medullary Carcinoma

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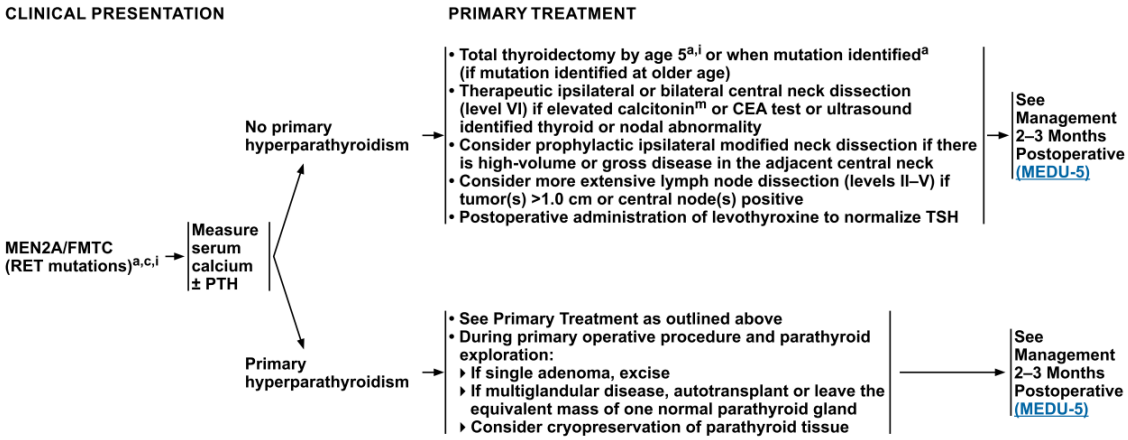
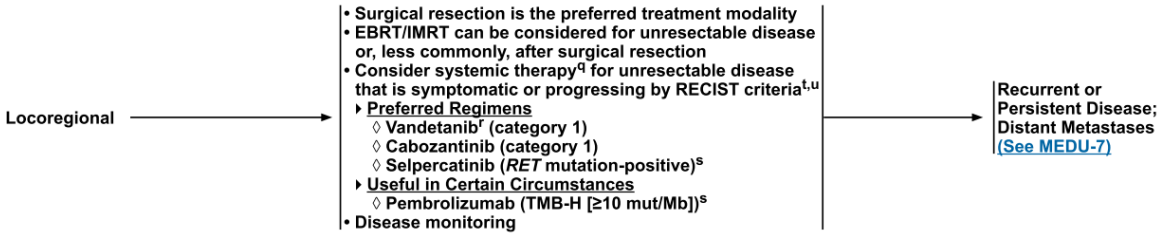


[a] In view of the risks of thyroidectomy in very young children, referral to a surgeon and team experienced in pediatric thyroid surgery is advised.
[c] Germline mutation should prompt specific mutation testing in subsequent family members and genetic counseling.
[i] The timing of prophylactic thyroidectomy generally depends on the aggressiveness of the inherited *RET* mutation. Codon M918T mutations are considered highest risk and codon 634 and A883F mutations are considered high risk, with MTC usually presenting at a younger age, whereas other RET mutations associated with MEN2A or FMTC are generally moderate risk. Prophylactic thyroidectomy may be delayed in patients with less high-risk *RET* mutations that have later onset of MTC, provided the annual basal calcitonin measurement is normal, the annual ultrasound is unremarkable, there is no history of aggressive MTC in the family, and the family is in agreement. (Brandi ML, et al. J Clin Endocrinol Metab 2001;86:5658-5671 and American Thyroid Association Guidelines Task Force. Wells SA, et al. Thyroid 2015;25:567-610.)
[m] Prophylactic neck dissection may not be required if serum calcitonin is less than 40 ng/mL, because lymph node metastases are unlikely with minor calcitonin elevations in this setting.

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.

MEDU-4

RECURRENT OR PERSISTENT DISEASE TREATMENT
LOCOREGIONAL DISEASE

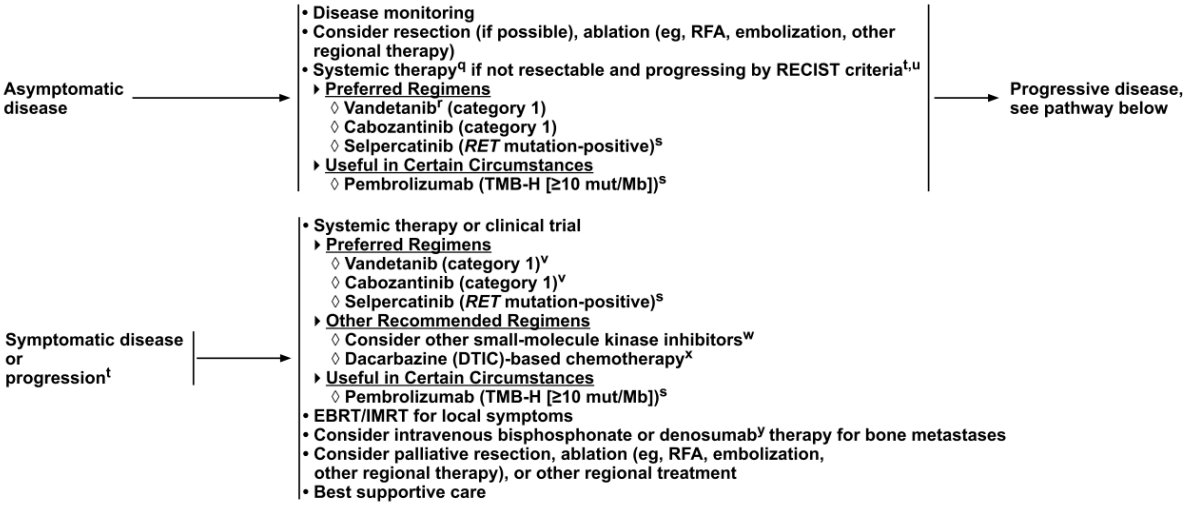


[q] Increasing tumor markers, in the absence of structural disease progression, are not an indication for treatment with systemic therapy.
[r] Only health care professionals and pharmacies certified through the vandetanib Risk Evaluation and Mitigation Strategy (REMS) program, a restricted distribution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

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.

MEDU-6

RECURRENT OR PERSISTENT DISEASE
DISTANT METASTASES



[q] Increasing tumor markers, in the absence of structural disease progression, are not an indication for treatment with systemic therapy.
[r] Only health care professionals and pharmacies certified through the vandetanib REMS program, a restricted distribution program, will be able to prescribe and dispense the drug.
[s] Genomic testing including tumor mutational burden (TMB) or *RET* somatic genotyping in patients who are germline wild-type or germline unknown.
[t] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See 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] Clinical benefit can be seen in both sporadic and familial MTC.
[w] 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
[x] Doxorubicin/streptozocin alternating with fluorouracil/dacarbazine or fluorouracil/dacarbazine alternating with fluorouracil/streptozocin.
[y] 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.

MEDU-7

4 Detaillierte Darstellung der Recherchestrategie

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

#	Suchfrage
1	MeSH descriptor: [Thyroid Neoplasms] explode all trees
2	MeSH descriptor: [Carcinoma, Neuroendocrine] explode all trees
3	MeSH descriptor: [Carcinoma, Medullary] explode all trees
4	#1 OR #2 OR #3
5	(thyroid AND neuroendocrine):ti,ab,kw
6	(thyroid AND (MTC OR medullary)):ti,ab,kw
7	#5 OR #6
8	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesions* OR malignan*):ti,ab,kw
9	#7 AND #8
10	#4 OR #9
11	MeSH descriptor: [Multiple Endocrine Neoplasia Type 2a] explode all trees
12	MeSH descriptor: [Multiple Endocrine Neoplasia Type 2b] explode all trees
13	(("multiple endocrine") AND (neoplasia OR neoplasms) AND (2 OR 2a OR 2b OR iia OR iib)) OR (pheochromocytoma AND amyloid AND medullary AND thyroid) OR sipple* OR (neuromata* AND mucosal AND endocrine*) OR wagenmann-froboese*:ti,ab,kw
14	#11 OR #12 OR #13
15	#10 OR #14
16	#15 with Cochrane Library publication date from Jan 2016 to present

Systematic Reviews in Medline (PubMed) am 19.01.2021

#	Suchfrage
1	carcinoma, neuroendocrine[mh:noexp] AND (thyroid neoplasms[mh] OR thyroid gland[mh])
2	carcinoma, medullary[mh:noexp] AND (thyroid neoplasms[mh] OR thyroid gland[mh])
3	thyroid cancer, medullary[nm]
4	#1 OR #2 OR #3
5	thyroid[tiab] AND neuroendocrine[tiab]
6	thyroid[tiab] AND (MTC[tiab] OR medullary[tiab])
7	#5 OR #6
8	(((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesions*[tiab]) OR malignan*[tiab]
9	#7 AND #8
10	#4 OR #9
11	multiple endocrine neoplasia type 2a[mh]

12	multiple endocrine neoplasia type 2b[mh]
13	("multiple endocrine"[tiab] AND (neoplasia[tiab] OR neoplasms[tiab]) AND (2[tiab] OR 2a[tiab] OR 2b[tiab] OR iia[tiab] OR iib[tiab])) OR (pheochromocytoma[tiab] AND amyloid[tiab] AND medullary[tiab] AND thyroid[tiab]) OR sipple*[tiab] OR (neuromata*[tiab] AND mucosal[tiab] AND endocrine*[tiab]) OR wagenmann-froboese*[tiab]
14	#11 OR #12 OR #13
15	#10 OR #14
16	familial medullary thyroid carcinoma[nm]
17	#15 OR #16
18	(#17) 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]))))))
19	(#18) AND ("2016/01/01"[PDAT] : "3000"[PDAT])
20	(#19) NOT "The Cochrane database of systematic reviews"[Journal]
21	(#20) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 19.01.21

#	Suchfrage
1	thyroid neoplasms[mh]
2	carcinoma, neuroendocrine[mh:noexp]
3	carcinoma, medullary[mh:noexp]
4	multiple endocrine neoplasia[mh:noexp]
5	multiple endocrine neoplasia type 2a[mh]
6	multiple endocrine neoplasia type 2b[mh]
7	thyroid cancer, medullary[nm]
8	familial medullary thyroid carcinoma[nm]
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10	thyroid[tiab] AND neuroendocrine[tiab]
11	thyroid[tiab] AND (MTC[tiab] OR medullary[tiab])
12	thyroid[ti]
13	#10 OR #11 OR #12
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 lesions*[tiab]) OR malignan*[tiab]
15	#13 AND #14
16	#9 OR #15
17	("multiple endocrine"[tiab] AND (neoplasia[tiab] OR neoplasms[tiab]) AND (2[tiab] OR 2a[tiab] OR 2b[tiab] OR iia[tiab] OR iib[tiab])) OR (pheochromocytoma[tiab] AND amyloid[tiab] AND medullary[tiab] AND thyroid[tiab]) OR sipple*[tiab] OR (neuromata*[tiab] AND mucosal[tiab] AND endocrine*[tiab]) OR wagenmann-froboese*[tiab]
18	#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 ("2016/01/01"[PDAT] : "3000"[PDAT])
21	(#N) NOT (retracted publication [pt] OR retraction of publication [pt])

Referenzen

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4. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 6. Juli 2017 - Vandetanib (neues Anwendungsgebiet: Schilddrüsenkarzinom, Patienten ab 5 Jahren) [online]. Berlin (GER): G-BA; 2017. [Zugriff: 21.01.2021]. URL: https://www.g-ba.de/downloads/91-1385-273/2017-07-06_Geltende-Fassung_Vandetanib_nAWG_D-270.pdf.
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