Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2020-B-005 Selpercatinib

Stand: März 2020

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

Selpercatinib
[zur Behandlung des fortgeschrittenen Schilddrüsenkarzinoms mit RET-Fusion]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	• Strahlentherapie • Radiojodtherapie
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:** • Lenvatinib: Beschluss vom 15.12.2015 und 15.08.2019
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. N.N.	Geplantes Anwendungsgebiet: Retsevmo als Monotherapie wird angewendet zur Behandlung von Erwachsenen mit fortgeschrittenem RET-Fusions-positivem Schilddrüsenkarzinom, die eine systemische Therapie nach einer Behandlung mit Sorafenib und/oder Lenvatinib benötigen.
Zytostatika	
Doxorubicin L01DB01 generisch	• […] • fortgeschrittenes papilläres/follikuläres Schilddrüsenkarzinom • anaplastisches Schilddrüsenkarzinom
Proteinkinase-Inhibitoren	
Lenvatinib L01XE29 Lenvima®	LENVIMA ist indiziert als Monotherapie für die Behandlung von erwachsenen Patienten mit progressivem, lokal fortgeschrittenem oder metastasiertem differenziertem (papillärem/follikulärem/Hürthle-Zell-) Schilddrüsenkarzinom (DTC), das nicht auf eine Radiojodtherapie (RAI) angesprochen hat. […]
Sorafenib L01XE05 Nexavar®	<u>Differenziertes Schilddrüsenkarzinom</u> Nexavar ist angezeigt zur Behandlung von Patienten mit progressivem, lokal fortgeschrittenem oder metastasiertem, differenziertem (papillärem/follikulärem/Hürthle-Zell-) Schilddrüsenkarzinom, welches gegenüber radioaktivem Jod refraktär ist. […]

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2020-B-001/005 (Selpercatinib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	11. Februar 2020

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

Fortgeschrittenes 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 *Schilddrüsenkarzinom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 14.01.2020 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, 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 950 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 10 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2017 [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 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, 2016 [2].

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 5. September 2013 / 4. August 2016 – Vandetanib

gültig bis: 01.10.2020

Anwendungsgebiet

Caprelsa® ist indiziert für die Behandlung von aggressivem und symptomatischem medullärem Schilddrüsenkarzinom (MTC) bei Patienten mit nicht resektabler, lokal fortgeschrittener oder metastasierter Erkrankung.

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.

Zweckmäßige Vergleichstherapie

Die zweckmäßige Vergleichstherapie für Vandetanib zur Behandlung von aggressivem und symptomatischem medullärem Schilddrüsenkarzinom (MTC) bei Patienten mit nicht resektabler, lokal fortgeschrittener oder metastasierter Erkrankung ist Best-Supportive-Care.

Als Best-Supportive-Care wird die Therapie verstanden, die eine bestmögliche, patientenindividuell optimierte, unterstützende Behandlung zur Linderung von Symptomen und Verbesserung der Lebensqualität gewährleistet (z. B. Bisphosphonate bei schmerzhaften Knochenmetastasen, externe Strahlentherapie).

Ausmaß des Zusatznutzens gegenüber Best-Supportive-Care (BSC):

Anhaltspunkt für einen geringen Zusatznutzen

G-BA, 2019 [5].

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: 01.11.2020

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

G-BA, 2019 [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 15. August 2019 – Lenvantinib

Anwendungsgebiet (laut Zulassung vom 20. August 2018):

LENVIMA ist indiziert als Monotherapie für die Behandlung von erwachsenen Patienten mit progressivem, lokal fortgeschrittenem oder metastasiertem differenziertem (papillärem/ follikulärem/Hürthle-Zell-) Schilddrüsenkarzinom (DTC), das nicht auf eine Radiojodtherapie (RAI) angesprochen hat.

Zweckmäßige Vergleichstherapie

Sorafenib

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

3.2 Cochrane Reviews

Es wurden eine relevanten Cochrane Reviews identifiziert.

3.3 Systematische Reviews

Liu JW et al., 2018 [6].

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:

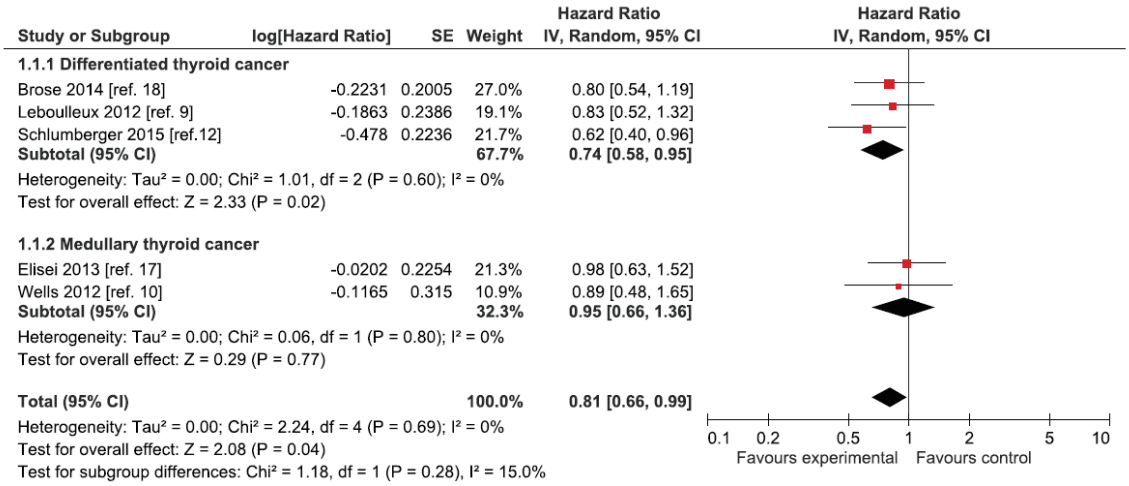

Figure 2. Forest plot of the comparison of the hazard ratio of overall survival between the tyrosine kinase inhibitor treatment and control groups: 1.1.1 differentiated thyroid cancer and 1.1.2 medullary thyroid cancer.

- 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:

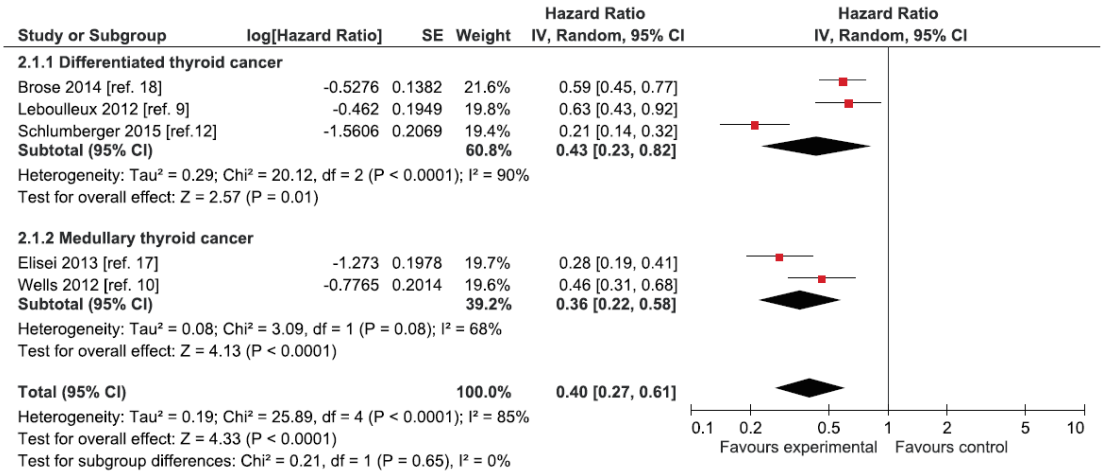

Figure 3. Forest plot of the comparison of the hazard ratio of progression-free survival between the tyrosine kinase inhibitor treatment and control groups: 2.1.1 differentiated thyroid cancer and 2.1.2 medullary thyroid cancer.

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:

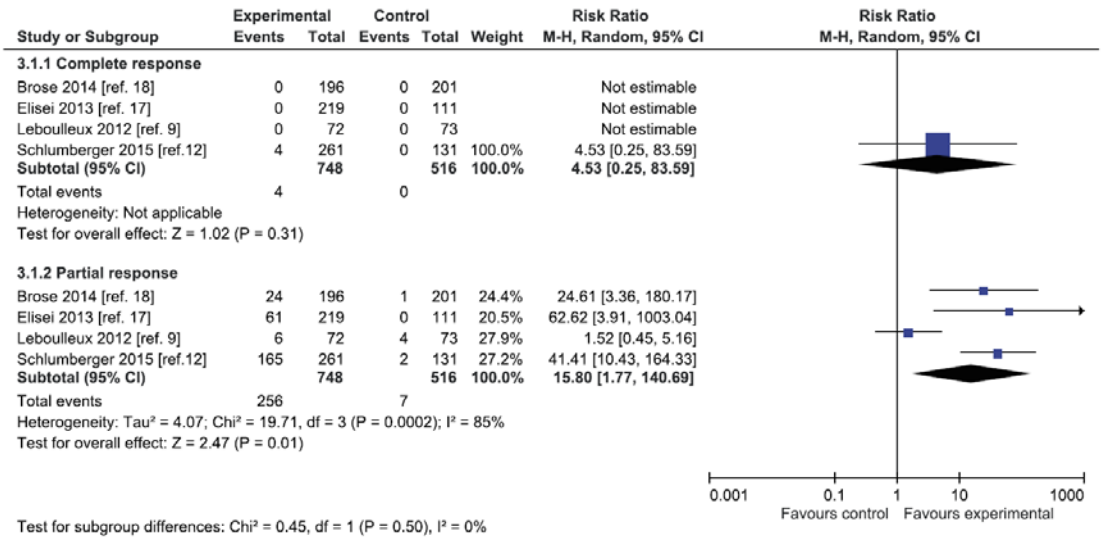

Figure 4. Forest plot of the comparison of the risk ratio of the objective response rate between the tyrosine kinase inhibitor treatment and control groups: 3.1.1 complete response and 3.1.2 partial response.

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].

Siehe auch:

Yimaer W et al., 2016 [9].

Metaanalyse derselben fünf RCTs, zeigt gleiche Ergebnisse zu OS, PFS und AEs.

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 [10].

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

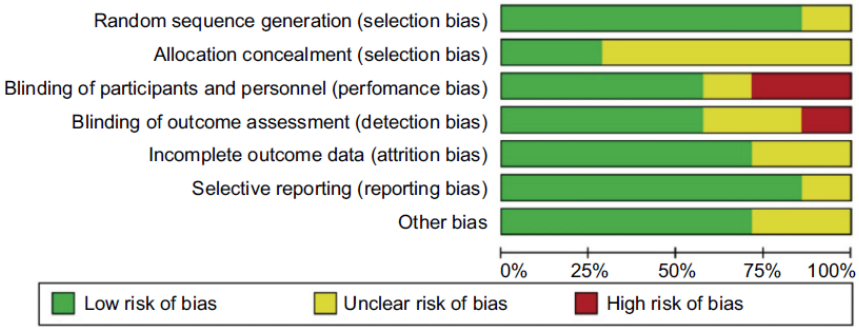

Figure S1 Risk of bias graph.

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

Wells SA et al., 2015 [8].

The American Thyroid Association Guidelines Task Force on Medullary Thyroid Carcinoma

Revised American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma

Leitlinienorganisation/Fragestellung

In 2007 the American Thyroid Association (ATA) assembled a group of expert clinicians and basic scientists to evaluate published papers and to recommend evidence-based guidelines for the diagnosis and management of patients with medullary thyroid carcinoma (MTC).

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: trifft teilweise zu, keine Patientenvertreter;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche
- Keine Qualitätsbewertung der Primärstudien;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert: unklar.

Recherche/Suchzeitraum:

- The Task Force identified relevant articles by searching MEDLINE/PubMed from January 1980 to April 2014

LoE/GoR

- The Task Force members graded recommendations using criteria adapted from the United States Preventive Services Task Force, Agency for Healthcare Research and Quality (Table 3) as were used in the previous MTC guidelines.

TABLE 3. STRENGTH OF RECOMMENDATIONS BASED ON AVAILABLE EVIDENCE

Rating	*Definition*
A	**Strongly recommends.** The recommendation is based on good evidence that the service or intervention can improve important health outcomes. Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.
B	**Recommends.** The recommendation is based on fair evidence that the service or intervention can improve important health outcomes. The evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes.
C	**Recommends.** The recommendation is based on expert opinion.
D	**Recommends against.** The recommendation is based on expert opinion.
E	**Recommends against.** The recommendation is based on fair evidence that the service or intervention does not improve important health outcomes or that harms outweigh benefits.
F	**Strongly recommends against.** The recommendation is based on good evidence that the service or intervention does not improve important health outcomes or that harms outweigh benefits.
I	**Recommends neither for nor against.** The panel concludes that the evidence is insufficient to recommend for or against providing the service or intervention because evidence is lacking that the service or intervention improves important health outcomes, the evidence is of poor quality, or the evidence is conflicting. As a result, the balance of benefits and harms cannot be determined.

Adapted from the U.S. Preventive Services Task Force, Agency for Healthcare Research and Quality.

Sonstige methodische Hinweise

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

Empfehlungen

[V] SYSTEMIC THERAPY

RECOMMENDATION 63

The use of single agent or combinatorial cytotoxic chemotherapeutic regimens should not be administered as first-line therapy in patients with persistent or recurrent MTC given the low response rates and the advent of promising new treatment options.

Grade D Recommendation

RECOMMENDATION 64

Treatment with radiolabeled molecules or pretargeted radio-immunotherapy may be considered in selected patients, ideally in the setting of a well-designed clinical trial.

Grade C Recommendation

Hintergrundinformationen:

Single agent or combination cytotoxic chemotherapeutic regimens administered to patients with MTC are characterized by low response rates (15%–20%) of short duration, although they may be indicated in selected patients. The most effective regimens are combination therapy with doxorubicin and another agent, or 5-fluorouracil and dacarbazine (331–333).

There is limited experience with radiolabeled molecules delivering high radiation dose to cancers. Response, survival, and long-term safety of systemic [90Y-DOTA]-TOC were evaluated in a phase II clinical trial of patients with advanced MTC, increasing serum Ctn levels, and tumor uptake on 111Inoctreoscan (334). Of 31 patients, 18 (58.1%) had a posttherapeutic prolongation of the serum Ctn doubling time of at least 100%. Only 9 (29%) of the 31 patients, however, experienced reduction of serum Ctn levels and were designated responders. The responders had a significantly longermedian survival from the time of treatment compared to nonresponders, 74.5 months (range, 15.7–107 months) compared to 10.8 months (range, 1.4–85 months; p = 0.02). Thirteen percent of patients developed hematologic toxicities, and 23% developed renal toxicities. The degree of 111In-octreoscan tumor uptake was not associated with treatment response or improvement in survival (334).

The efficacy of pretargeted radio-immunotherapy with bispecific monoclonal antibody and 131I-labeled bivalent hapten has shown promising results in early studies of patients with advanced MTC; however, there have been no prospective, randomized trials comparing this therapy to other therapies or a placebo (335,336). Treatment with 131IMIBG is generally

regarded as ineffective in patients with MTC, although some reports have described partial tumor remission or stability (337,338). At present treatment with radioisotope-based therapy should only be considered in the context of a clinical trial.

[V-1] The basis for targeted therapy with TKIs

RECOMMENDATION 65

In patients with significant tumor burden and symptomatic or progressive metastatic disease according to RECIST treatment with TKIs targeting both RET and VEGFR tyrosine kinases should be considered as systemic therapy. The TKIs vandetanib or cabozantinib can be used as single- agent first-line systemic therapy in patients with advanced progressive MTC.

Grade A Recommendation

Hintergrundinformationen:

Germline RET mutations are present in virtually all patients with MEN2A and MEN2B. Approximately half of the patients with sporadic MTC have somatic RET mutations, and 18%–80% of patients without somatic RET mutations have somatic RAS mutations. Also, vascular endothelial growth factor (VEGF) receptors (VEGFR-1 [FLT-1] and VEGFR-2 [FLK-1, KDR]) are often overexpressed in MTC, both in tumor cells and in the supporting vascular endothelium (339). Many agents that target VEGFR-2 kinase also target RET kinase. In recent years several TKIs (axitinib, cabozantinib, gefitinib, imatinib, motesanib, sorafenib, sunitinib, and vandetanib) have been evaluated in phase I, II, and III clinical trials of patients with advanced MTC (340– 350). In phase II clinical trials partial response rates ranged from 0% to 50%, with a large number of patients demonstrating prolonged stable disease. On the basis of recently completed phase III clinical trials the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved two orally administered TKIs, vandetanib (2011) and cabozantinib (2012), for the treatment of patients with advanced progressive MTC.

[V-1-1] Clinical trials of vandetanib in patients with advanced MTC

A phase II clinical trial with vandetanib, targeting the RET, EGFR, and VEGFR kinases, was evaluated at a maximal tolerated dose (300 mg/d) in 30 patients with hereditary MTC. Partial responses were observed in 10 patients, among whom six had a confirmed partial response, and another 16 patients had stable disease longer than 24 weeks (347). Another phase II trial with vandetanib (100 mg/d) included 19 patients with hereditary MTC. A partial response was observed in three patients and stable disease longer than 24 weeks was seen in another 10 patients. However, it was not clear whether there was a relationship between dose and efficacy or between dose and toxicity (348).

A prospective, randomized, double blind, phase III trial (National Clinical Trial [NCT]00322452) of 331 patients with symptomatic or progressing locally advanced or metastatic MTC compared PFS in patients treated with vandetanib (300 mg/d) or placebo (349). The median PFS was significantly prolonged from 19.3 months in the placebo arm to a predicted median of 30.5 months (median not yet reached) in the vandetanib arm (hazard ratio [HR], 0.46; $p < 0.0001$). Partial responses were observed in 45% of patients treated with vandetanib, with a predicted median duration of response of 22 months. The improvement in quality of life, pain reduction, and diarrhea allowed several patients in the vandetanib arm to resume a normal social life. All subgroups of patients, with regard to tumor burden, progression rate, or symptoms, experienced significant PFS benefits from treatment. Also, PFS benefits were observed both in patients with a RET mutation and those without a RET mutation. In 41% of patients the RET status was unknown due to the inability to sequence all RET exons. Adverse events, including diarrhea, fatigue, rash and folliculitis, photosensitization, hypertension, and prolongation of the QTc interval, were mainly grade 1 or 2. Twelve percent of patients receiving vandetanib discontinued treatment due to toxicity and 35%required dose reductions because of an adverse event (349). The FDA approved vandetanib in April 2011 with Risk Evaluation and Mitigation Strategies (REMS), and the EMA approved vandetanib in November 2011 for the treatment of aggressive and symptomatic MTC in patients with unresectable locally advanced or metastatic disease. However, the EMA approval was conditional, and there was a request for the company marketing vandetanib to provide more evidence regarding benefit in patients with and without the RET mutation in their tumor.

[V-1-2] Clinical trials of cabozantinib in patients with advanced MTC

A phase I/II trial with cabozantinib, targeting the kinases of RET, c-MET, and VEGFR, included 35 evaluable MTC patients. Seventeen patients had a partial response, and in 10 of them a partial response was confirmed (344). Partial responses were observed regardless of somatic RET mutation status in both treatment-naı¨ve patients and in those who had been treated previously with another kinase inhibitor, suggesting the absence of cross-resistance with other compounds. In a randomized, prospective phase III trial of 330 patients with progressive, metastatic, or locally advanced MTC (NCT00704730), treatment with cabozantinib (140 mg/ d) was compared to placebo (350). Median PFS was significantly improved from 4.0 months (placebo) compared to 11.2 months (cabozantininb) (HR, 0.28; $p < 0.0001$). Benefits in PFS were observed in all subgroups studied. The overall response rate was 28% (350). Side effects were significant and included diarrhea, abdominal discomfort, fatigue, hypertension, palmo-plantar erythrodysesthesia, and gastrointestinal

fistulas. In fact, 16% of patients receiving cabozantinib discontinued treatment due to toxicity, and 79% required dose reductions because of an adverse event (350). A recent analysis demonstrated benefits of cabozantinib treatment in patients with either RET or RAS mutated tumors (351). On the basis of the results of the phase III clinical trial, the FDA and the EMA approved cabozantinib for the treatment of patients with advanced disease.

In the two phase III trials thus far completed, vandetanib and cabozantinib have shown the potential to provide high rates of disease control with durable responses and a highly significant improvement of PFS. However, the drugs have to be given daily and chronically to maintain tumor control. Short-term toxicity is significant, with dose reduction or treatment withdrawal in a significant proportion of patients. Also, there are few data on long-term toxicity and no data on overall survival. Currently, treatment with the drugs is indicated only in patients with significant tumor burden and documented tumor progression.

Patients treated with TKIs for advanced MTC require careful monitoring because they are at increased risk for developing hypothyroidism, characterized by elevated serum TSH levels despite normal serum levels of free triiodothyronine triiodothyronine and thyroxine (340). Although the mechanism for this metabolic complication is unclear, it has recently been shown that the TKI sorafenib induces alteration in triiodothyronine and thyroxine clearance probably by inducing type 3- deiodinase activity (352,353).

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Thyroid Carcinoma. version 2.2019

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:

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.[31]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN webpage.

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:

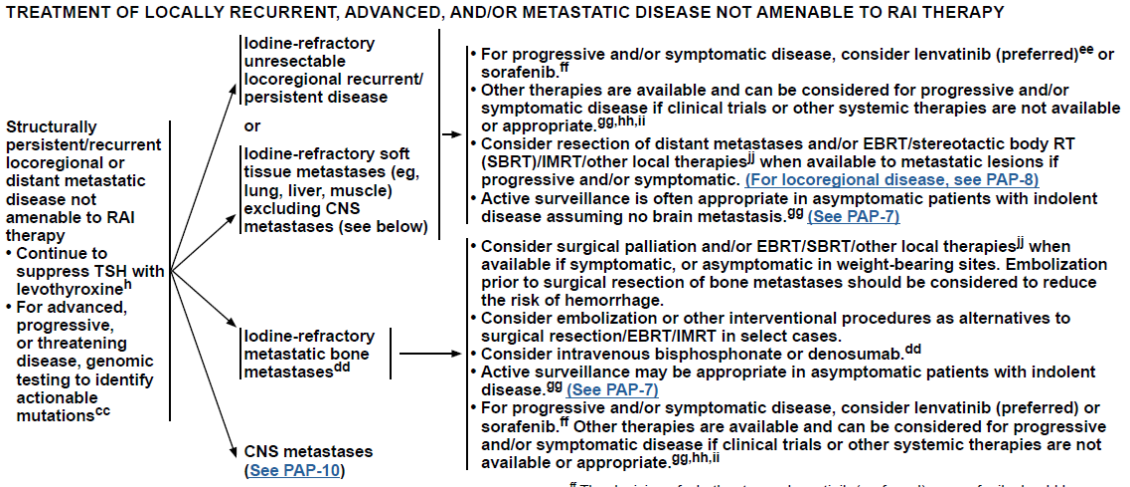
- Keine Angaben

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

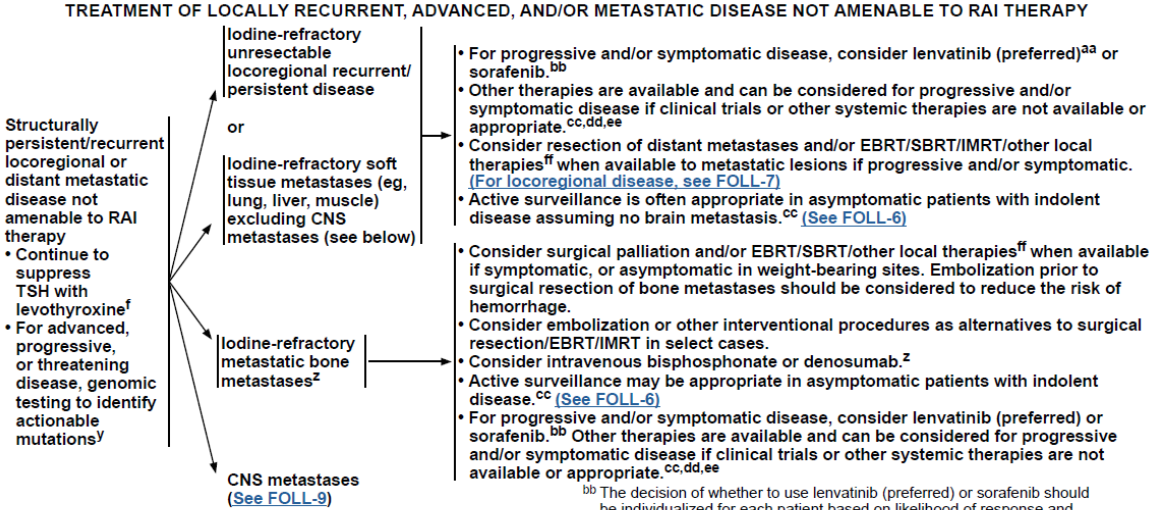
Papillary Carcinoma



[h] See Principles of TSH Suppression (THYR-A).
[cc] Larotrectinib and entrectinib are FDA approved for patients with *NTRK* gene fusion-positive advanced solid tumors.
[dd] Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk.
[ee] In a subset of patients (older than 65 years of age), lenvatinib showed an overall survival benefit compared to placebo. Brose MS, Worden FP, Newbold KL, et al. Effect of age on the efficacy and safety of lenvatinib in radioiodine-refractory differentiated thyroid cancer in the phase III SELECT trial. J Clin Oncol 2017;35:2692-2699.
[ff] The decision of whether to use lenvatinib (preferred) or sorafenib should be individualized for each patient based on likelihood of response and comorbidities.
[gg] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Kinase Inhibitor Therapy (THYR-B).
[hh] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [*BRAF* positive], dabrafenib [*BRAF* positive], or cabozantinib [all are category 2A]) can be considered if clinical trials are not available or appropriate.
[ii] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.
[jj] 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.

Follicular Carcinoma



[f] See Principles of TSH Suppression (THYR-A).
[y] Larotrectinib and entrectinib are FDA approved for patients with *NTRK* gene fusion-positive advanced solid tumors.
[z] Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk.
[aa] In a subset of patients (older than 65 years of age), lenvatinib showed an overall survival benefit compared to placebo. Brose MS, Worden FP, Newbold KL, et al. Effect of age on the efficacy and safety of lenvatinib in radioiodine-refractory differentiated thyroid cancer in the phase III SELECT trial. J Clin Oncol 2017;35:2692-2699.
[bb] The decision of whether to use lenvatinib (preferred) or sorafenib should be individualized for each patient based on likelihood of response and comorbidities.
[cc] Kinase inhibitor therapy may not be appropriate for patients with stable or slowly progressive indolent disease. See Principles of Kinase Inhibitor Therapy (THYR-B).
[dd] Commercially available small-molecule kinase inhibitors (such as axitinib, everolimus, pazopanib, sunitinib, vandetanib, vemurafenib [*BRAF* positive], dabrafenib [*BRAF* positive], or cabozantinib [all are category 2A]) can be considered if clinical trials are not available or appropriate.
[ee] Cytotoxic chemotherapy has been shown to have minimal efficacy, although most studies were small and underpowered.
[ff] 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.

Medullary Carcinoma

RECURRENT OR PERSISTENT DISEASE TREATMENT
LOCOREGIONAL DISEASE

Locoregional →

- **Surgical resection is the preferred treatment modality**
  or
- **EBRT/IMRT can be considered for unresectable disease or, less commonly, after surgical resection**
  or
- **Consider vandetanib[q,r] (category 1, preferred) or cabozantinib (category 1, preferred)[q] for unresectable disease that is symptomatic or progressing by RECIST criteria[s,t]**
  or
- **Active surveillance**

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

[q] Increasing tumor markers, in the absence of structural disease progression, are not an indication for treatment with vandetanib or cabozantinib.
[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] 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).
[t] 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.

RECURRENT OR PERSISTENT DISEASE
DISTANT METASTASES

Asymptomatic disease →

- **Active surveillance**
  or
- **Consider resection (if possible), ablation (eg, RFA, embolization, other regional therapy),**
  or
- **Vandetanib[q,r] (category 1, preferred) or cabozantinib[q] (category 1, preferred) if not resectable and progressing by RECIST criteria[s,t]**

→ **Progressive disease, see pathway below**

Symptomatic disease or progression[s] →

- **Systemic therapy or clinical trial**
  - **Preferred Regimens**
    - **Vandetanib (category 1, preferred)[u]**
    - **Cabozantinib (category 1, preferred)[u]**
  - **Other Recommended Regimens**
    - **Consider other small-molecule kinase inhibitors[v]**
    - **Dacarbazine (DTIC)-based chemotherapy[w]**
- **EBRT/IMRT for local symptoms**
- **Consider intravenous bisphosphonate or denosumab[x] therapy for bone metastases**
- **Consider palliative resection, ablation (eg, RFA, embolization, other regional therapy), or other regional treatment**
- **Best supportive care**

[q] Increasing tumor markers, in the absence of structural disease progression, are not an indication for treatment with vandetanib or cabozantinib.
[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] 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).
[t] Treatment with systemic therapy is not recommended for increasing calcitonin/CEA alone.
[u] Clinical benefit can be seen in both sporadic and familial MTC.
[v] 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, vandetanib, or cabozantinib are not available or appropriate, or if the patient progresses on vandetanib or cabozantinib.
[w] Doxorubicin/streptozocin alternating with fluorouracil/dacarbazine or fluorouracil/dacarbazine alternating with fluorouracil/streptozocin.
[x] Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk.

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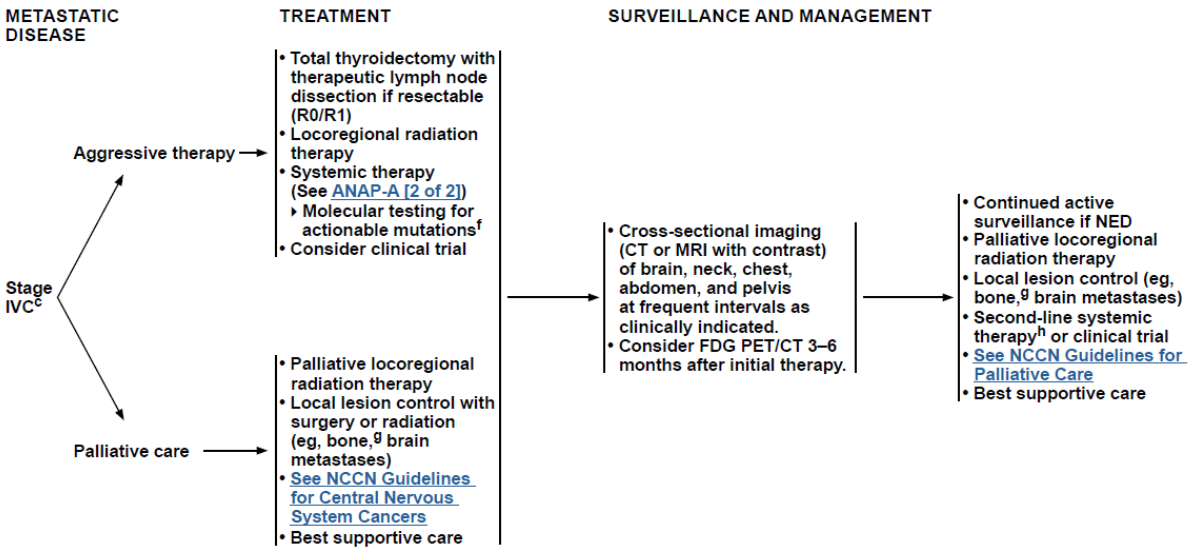
Anaplastic Carcinoma



[c] See Staging (ST-1).
[f] Consider dabrafenib/trametinib combination therapy if *BRAF* V600E mutation positive (Subbiah V, et al. Dabrafenib and trametinib treatment in patients with locally advanced or metastatic *BRAF* V600-mutant anaplastic thyroid cancer. J Clin Oncol 2018;36(1):7-13) or consider larotrectinib or entrectinib if *NTRK* gene fusion positive (Drilon A, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018;378(8):731-739, Demetri GD, Paz-Ares L, Farago AF, et al. Efficacy and safety of entrectinib in patients with NTRK fusion-positive tumours: pooled analysis of STARTRK-2, STARTRK-1 and ALKA-372-001. Presented at the European Society for Medical Oncology Meeting in Munich, Germany; October 12-23, 2018. Oral Presentation).
[g] Consider use of intravenous bisphosphonates or denosumab. Denosumab and intravenous bisphosphonates can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk.
[h] See Systemic Therapy Regimens for Metastatic Disease (ANAP-A [2 of 2]).

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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.

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)	Larotrectinib 100 mg PO	Twice daily
Other Recommended Regimens		
Entrectinib[4] (*NTRK* gene fusion positive)	Entrectinib 600 mg PO	Once daily
Paclitaxel/carboplatin[1]	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]	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
Paclitaxel[1]	60–90 mg/m² IV or 135–200 mg/m² IV	Weekly Every 3–4 weeks
Doxorubicin[1]	60–75 mg/m² IV or 20 mg/m² IV	Every 3 weeks Weekly
Useful in Certain Circumstances		
Lenvatinib[5] (if not tolerating or no response to recommended agents in patients without curative option)	24 mg PO	Daily

[1] Adapted with permission from Mary Ann Liebert, Inc., Smallridge RC, et al. American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. Thyroid 2012;22:1121.
[2] Subbiah V, et al. Dabrafenib and trametinib treatment in patients with locally advanced or metastatic BRAF V600-mutant anaplastic thyroid cancer. J Clin Oncol 2018;36(1):7-13.
[3] Drilon A, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018;378(8):731-739.
[4] Demetri GD, Paz-Ares L, Farago AF, et al. Efficacy and safety of entrectinib in patients with NTRK fusion-positive tumours: pooled analysis of STARTRK-2, STARTRK-1 and ALKA-372-001. Presented at the European Society for Medical Oncology Meeting in Munich, Germany; October 12-23, 2018. Oral Presentation.
[5] Tahara M, Kiyota N, Yamazaki T, et al. Lenvatinib for anaplastic thyroid cancer. Front Oncol 2017;7:25.

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.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 1 of 12, January 2020) am 13.01.2020

#	Suchfrage
#1	MeSH descriptor: [Thyroid Neoplasms] explode all trees
#2	MeSH descriptor: [Adenocarcinoma, Papillary] explode all trees
#3	MeSH descriptor: [Adenocarcinoma, Follicular] explode all trees
#4	MeSH descriptor: [Thyroid Carcinoma, Anaplastic] explode all trees
#5	MeSH descriptor: [Multiple Endocrine Neoplasia Type 2a] explode all trees
#6	MeSH descriptor: [Multiple Endocrine Neoplasia Type 2b] explode all trees
#7	{OR #1-#6}
#8	(struma maligna"):ti,ab,kw OR (papillary AND adenocarcinoma*):ti,ab,kw OR (follicular AND adenocarcinoma*):ti,ab,kw OR ("Multiple Endocrine Neoplasia" AND (2 OR 2a OR 2b OR II OR IIa OR IIb)):ti,ab,kw"
#9	(thyroid):ti,ab,kw AND (cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesions* OR malignan*):ti,ab,kw
#10	{OR #7-#9}
#11	#10 with Cochrane Library publication date Between Jan 2015 and Jan 2020

Systematic Reviews in Medline (PubMed) am 13.01.2020

#	Suchfrage
1	"thyroid neoplasms/therapy"[MeSH Terms]
2	"adenocarcinoma, papillary/therapy"[MeSH Terms]
3	"adenocarcinoma, follicular/therapy"[MeSH Terms]
4	"thyroid carcinoma, anaplastic/therapy"[MeSH Terms]
5	"multiple endocrine neoplasia type 2a/therapy"[MeSH Terms]
6	"multiple endocrine neoplasia type 2b/therapy"[MeSH Terms]
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
8	"Thyroid cancer, Hurthle cell"[Supplementary Concept] OR "Familial medullary thyroid carcinoma"[Supplementary Concept] OR "Thyroid cancer, medullary"[Supplementary Concept] OR "Thyroid Carcinoma, Nonmedullary 1"[Supplementary Concept] OR "Nonmedullary thyroid carcinoma, with or without cell oxyphilia"[Supplementary Concept] OR "Thyroid cancer, follicular"[Supplementary Concept] OR "Thyroid Carcinoma, Papillary, With Papillary Renal Neoplasia"[Supplementary Concept]
9	"struma maligna"[Title/Abstract] OR (papillary[Title] AND adenocarcinoma*[Title]) OR (follicular[Title] AND adenocarcinoma*[Title]) OR ("Multiple Endocrine Neoplasia"[Title/Abstract] AND (2[Title/Abstract] OR 2a[Title/Abstract] OR 2b[Title/Abstract] OR II[Title/Abstract] OR IIa[Title/Abstract] OR IIb[Title/Abstract]))
10	thyroid[Title/Abstract]
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 lesions*[tiab]) OR malignan*[tiab]

12	#10 AND #11
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 ("2015/01/01"[PDAT] : "3000"[PDAT])
18	(#17) NOT "The Cochrane database of systematic reviews"[Journal]
19	(#18) NOT retracted publication[ptyp]

Leitlinien in Medline (PubMed) am 14.01.2020

#	**Suchfrage**
1	thyroid neoplasms[MeSH Major Topic]
2	adenocarcinoma, papillary[MeSH Major Topic]
3	adenocarcinoma, follicular[MeSH Major Topic]
4	"thyroid carcinoma, anaplastic"[MeSH Major Topic]
5	"multiple endocrine neoplasia type 2a"[MeSH Major Topic]

6	"multiple endocrine neoplasia type 2b"[MeSH Major Topic]
7	"Thyroid cancer, Hurthle cell"[Supplementary Concept] OR "Familial medullary thyroid carcinoma"[Supplementary Concept] OR "Thyroid cancer, medullary"[Supplementary Concept] OR "Thyroid Carcinoma, Nonmedullary 1"[Supplementary Concept] OR "Nonmedullary thyroid carcinoma, with or without cell oxyphilia"[Supplementary Concept] OR "Thyroid cancer, follicular"[Supplementary Concept] OR "Thyroid Carcinoma, Papillary, With Papillary Renal Neoplasia"[Supplementary Concept]
8	"struma maligna"[Title/Abstract] OR (papillary[Title] AND adenocarcinoma*[Title]) OR (follicular[Title] AND adenocarcinoma*[Title]) OR ("Multiple Endocrine Neoplasia"[Title/Abstract] AND (2[Title/Abstract] OR 2a[Title/Abstract] OR 2b[Title/Abstract] OR II[Title/Abstract] OR IIa[Title/Abstract] OR IIb[Title/Abstract]))
9	thyroid[Title]
10	(((((((((tumor[ti) OR tumors[ti]) OR tumour*[ti]) OR carcinoma*[ti]) OR adenocarcinoma*[ti]) OR neoplas*[ti]) OR sarcoma*[ti]) OR cancer*[ti]) OR lesions*[ti]) OR malignan*[ti]
11	#9 AND #10
12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #11
13	(#12) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
14	(#13) AND ("2015/01/01"[PDAT] : "3000"[PDAT])
15	(#14) NOT retracted publication[ptyp]

Referenzen

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treatment of advanced thyroid cancer: a meta-analysis of randomized controlled trials. Onco Targets Ther 2016;9:1167-1173.

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